Inertial Manifolds
in Biological Systems

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I, Pasquale Iannelli, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis

Abstract

The focus of this thesis is biological systems whose dynamics present an interesting feature: only some dimensions drive the whole system. In our examples, the dynamics is expressed as ODEs, such that the i^{th} equation depends on all the variables $\dot{x}_i = f(x_1, \ldots, x_i, x_{i+1}, \ldots)$, so that they cannot be solved by classical methods.

The authors in the literature found that one could express the variable of order bigger than N as a function of the first N variables, thus closing the differential equations; the approximations obtained were exponentially close to the non-approximated result.

In Nonlinear Dynamics, such functions are called Inertial Manifolds. They are defined as manifolds that are invariant under the flow of the dynamical system, and attract all trajectories exponentially.

The first example gives rise to a generalisation of a theorem which, in the literature, is proved for the PDE $\dot{u} = -Au + V(u)$. We prove existence for the most general case $\dot{u} = -A(u)u + V(u)$ and consider the validity of the results for the biological parameters. We also present a theoretical discussion, by providing examples.

The second example arises from Statistics applied to population biology. The infinite number of differential equations for the moments are approximated using a Moment Closure technique, that is expressing moments of order higher than N as a function of the first moments, generally using the function valid for the normal distribution. The example shows exceptional approximation. Though this technique is often used, there is no complete mathematical justification.

We examine the relation between the Moment Closure technique and Inertial Manifolds. We prove that the approximated system can be seen as a *perturbation* of the original system, that it admits an Inertial Manifold, which is close to the original one for $\epsilon \to 0$ and $t \to \infty$.

Contents

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We have used the following notations:

- A Glossary in chapter **4** contains the definitions of all terms and concepts
- Chapters are numbered starting from 1, and beginning with the introduction
- Sections are numbered starting from 1, resetting the counter inside of each chapter
- Sub-sections are numbered starting from 1, resetting the counter inside of each section
- **3.2.1** refers to chapter **3**, section **2**, sub-section **1**; in the text we refer to it either with *"as in section* **3.2.1***"* or with *"as in* **3.2.1***"*
- equations are numbered starting from 1, resetting the counter inside of each chapter
- E.4.5 refers to equation 5 in chapter 4; in the text we refer to it either with *"as in equation E.4.5"* or with *"as in E.4.5"*
- Similarly, T.1.2 refers to theorem 2 in chapter 1, L.3.4 refers to lemma 4 in chapter 3, D.5.6 refers to definition 6 in chapter 5; they all share the same counter, which is reset inside of each chapter
- $\mathcal{M}$ is always an Inertial Manifold
- u is always a time dependent variable of a differential equation in a Banach or Hilbert space
- m_i are always moments and κ_i are always cumulants
- $\mathbb{0}$ is used for the null element in a Banach or Hilbert space, and in general in a function space; 0 is used for the null scalar
- the rest of the notation is specific to the chapter or section

Chapter 1

Introduction

We give an overview of the thesis, including its origins, motivations, the research programme, the original results and a perspective of the published work in the field.

1 Introduction

Our aim in this introductory section is to give an overview of the work included in the thesis, with the following objectives:

– to identify the motivations, mathematically speaking, that led us to choose this subject as an appealing one for a PhD thesis;

– to present an account of the results by themselves;

– to describe their relevance to the framework of the published research in the field.

One fact, that might seem to be contingent, has influenced the three arguments above in a variety of ways: I have interrupted my course of study for about 8 years, just before undertaking the writing up of the thesis. Thanks to this pause, the mathematical results here presented are not the same that would have been presented 8 years ago.

In the next section, we shall briefly indicate the effects of this interruption, and then relate a more classical mathematical introduction in the following sections.

1.1 Genesis

My PhD studies started back in 1996, and continued until 1999. During this period, I was involved in a number of projects, all of which have originated from applications to Biology. They had the same mathematical motivation, which is the understanding of the simplification of complex dynamical systems.

I started with the investigation of Inertial Manifolds in a biological system describing the dynamics of Gap Junctions, which is a dynamical form of cell-to-cell communication, described in [1-BAI-1997]. The totality of the research I did under the guidance of Professor Stark and Dr Baigent was published in [47-IAN-1998]; it consists of a generalisation of a standard theorem about the existence of Inertial Manifolds. This theorem applies to systems like $\dot{u} = -Au + V(u)$ and gives conditions on the eigenvalues of a linear operator A and the Lipschitz constant of V for an Inertial Manifold to exist. We generalised to a family of linear operators $A(u)$. Briefly, an Inertial Manifold can be thought of as yielding a slaving principle, stating that the coordinates u can be split into two sets of coordinates $u = (s, \varphi)$ such that φ can be expressed as a function of s.

When I finally decided to resume the writing up of my thesis, I found out that, in the 10 years since the publication of this paper, almost no research had been published in the meantime on generalisations of these sort of theorems.

Thus, when confronting the task of composing my thesis, it seemed natural to extend the results originally published to include a proof of existence under very general conditions. These results are included in section **2.4.4**.

The other main subject I approached in 1998 and 1999, was the study of the dynamics of the moments of a probability generating function for a parasite-host problem described in [72-ISH-1995]. The Moment Closure technique was used, and it gave, surprisingly enough for the author, a very good approximation. With Moment Closure technique, we refer to a class of methods that express the moments of high order as functions of those of lower order; a slaving principle as in the Inertial Manifold theory. The surprise came because it was not always possible to justify in [72-ISH-1995] such an approximation from a statistical or biological point of view. Furthermore, in the literature this method is widely used, though, no general theoretical account of why it works is given from a dynamical perspective.

Thus, I researched on the subject and found that the system, for the particular values of the parameters, possesses an Inertial Manifold. I also found that there was a relation between the function used in the Moment Closure and the one defining the Inertial Manifold. The results I obtained at that time were published in [48-STA-2001]. Eight years later, I present a version with all the mathematical details and a sound functional setting for an infinite dimensional set of differential equations. In fact, we decided to use a different structure and organisation so as to aim at a broader audience, possibly without a dynamical systems and functional analysis mathematical background.

Once again, when I finally decided to complete my PhD thesis, I found that almost no work had been published on the path I pursued; I was unable to find any reference or published paper dedicated to understanding, using a dynamic perspective, why Moment Closure functions work so well and if they hold any relation to Inertial Manifolds at all.

Thus, the most obvious line of investigation was to further develop the example above; the results from this completely new piece of research, which I would not have pursued in year 2000, are included in sections **3.3.4** and **3.3.5**. The main finding is that the normal approximation defines a manifold which tends coordinate-wise to the original Inertial Manifold, though in a peculiar sense, that is for $t \to \infty$ and $\epsilon \to 0$, where ϵ is a small parameter present in the biological model being studied.

As I have shown above, apart from the original results that I achieved before year 2000, this 8-year lapse of time has contributed to directing my interest into the finding of original results:

– the proof of a more general theorem of existence of Inertial Manifolds,

– an elucidation on the relation of Moment Closure and Inertial Manifolds.

On the other hand, during the last 8 years, though I worked in a mathematical related subject, I had somehow reduced my contacts with the day-to-day usage of mathematics. This is why I felt the urgent need to first understand and then explain in detail all the features of Inertial Manifold I started investigating so long ago. This gave rise to a series of improved proofs with detailed calculations made explicit, correction of mistakes and a complete new series of examples.

Improvements:

- detailed proof of Gronwall's inequalities, used in the proof of the existence of the Inertial Manifold;
- clarified description of Evolution Operator, including a correction of the proof of its Lipschitz Property;
- clarification of the relation between the Gap Condition and the Strong Squeezing Property for our generalisation;
- formal definition of all used Hilbert and Banach Spaces, including quoting the correct theorems that prove existence and uniqueness of solution to the associated PDEs.

Examples and new proofs:

- an example of a dynamical system, which does not satisfy the Cone Condition, but nevertheless has an Inertial Manifold;
- example of the approximating flow for an Inertial Manifold that is asymptotically complete;
- an example of Inertial Manifold that is not asymptotically complete;
- proof that the system I originally studied is asymptotically complete;
- relation between different Moment Closure approximations and the corresponding rate of attraction;
- the proof that the Moment Closure used in [72-ISH-1995] is an Inertial Manifold for a *perturbation* of the original system.

1.2 What are Inertial Manifolds?

As we have seen so far, the basic topic of this thesis can be described as "understanding how Inertial Manifold can be used to simplify complex biological models". Before we proceed to explain how we do this, it is then important that we give an account of what Inertial Manifolds are.

We shall assume that the reader is familiar with the essentials of Function Analysis, in particular with Banach and Hilbert spaces, and Semi-Group Theory. Good classical references are given in **5.2.1** and **5.3.1**.

Furthermore, we shall see that we derive differential equations from statistical models, so that a basic understanding of Probability theory is assumed, especially the definition of moments, cumulants, and of the most important generating functions: probability, moment and cumulant generating functions. Nevertheless, a profound knowledge of this field is neither assumed nor necessary.

A glossary in chapter **4** contains the definitions of all terms and concepts used in the thesis.

Inertial Manifolds could be classified as a sub-topic of Dynamical Systems theory. A good, not too technical introduction to the broad field of Dynamical Systems can be found in [29-GLE-1994], and a more formal one in the books [39-TEM-1998] and [37-ROB-2001]. One could roughly define it as the study of those dynamical equations $\dot{u} = F(u)$ where for every time t $u(t)$ belongs to a Banach space V, $\dot{u}$ to the Banach space L, and F is a function from $V \to L$. In such cases, many different behaviours can be observed. One of the most famous is what is called chaos. This is a system which appears to behave randomly, though what really is happening is that the dynamics are fully determined by the initial conditions u_0 and a small perturbation of u_0 changes the solution completely; this means that a chaotic system is sensitive to initial conditions, in the sense that two points might be arbitrarily close and nevertheless the two trajectories starting at those points will be significantly different in the future.

Clearly not all nonlinear dynamical systems are chaotic, and thus much effort has been dedicated to identifying the conditions under which one can safely predict the behaviour of a nonlinear dynamical system. In fact, many dynamical systems found in Nature are dissipative, that is, if it were not for some driving force, they would stop evolving. This means that typically two forces, the dissipative one and the driving one, will interact so to drive the system to its normal behaviour. This does not mean that the system is driven to a steady state, but just that, no matter what the initial conditions are, usually the dynamics can be reduced to that of a subset of the whole phase space. This subset is called the attractor. In the informal words of Wikipedia, *"an attractor is a set to which a dynamical system evolves after a long enough time"*. For a very formal definition one can refer to the books quoted above. An attractor A can be semi-formally defined as a set that is invariant under the dynamics, and for which there exists a non-empty set $B(A)$ consisting of the points that in the limit enter A.

Attractors can contain any type of dynamics, fixed points, loops, tori or a chaotic behaviour. Their importance is that they describe the dynamics of the system after a long enough time.

A few basic questions can be asked: How long do we have to wait before entering the attractor? What shape has it got? Does the attractor change under small perturbations like $\dot{u} = F(u) + \epsilon G(u)$?

The study of the third question is the leitmotiv of Perturbation Theory, with its branches of Singular and Non-Singular Perturbation Theory. A comprehensive introduction is to be found in [22-BER-2001].

A review in [31-GUT-1998] of the Moon-Earth-Sun dynamics gives an interesting historical account of all the major techniques used in the study of Dynamical Systems, especially nonlinear ones.

DEFINITION D.1.1 Dynamical System *Formally, a dynamical system is defined by a triplet $(\mathcal{U}, \mathcal{T}, \mathcal{S})$ where $\mathcal{U}$ is a state space, $\mathcal{T}$ a set of times, and $\mathcal{S}$ a rule for evolution, $\mathcal{S} : \mathcal{U} \times \mathcal{T} \to \mathcal{U}$, that gives the consequent(s) to a state $u \in \mathcal{U}$.*

This definition is taken from [35-MEI-2007]. A dynamical system is a model describing the temporal evolution of a system: given a $u \in \mathcal{U}$, the rule $\mathcal{S}$ tells us where u will be after a time $t \in \mathcal{T}$. Though one can study discrete times $\mathcal{T}$, we deal only with the continuous $\mathcal{T} = \mathbb{R}$, and $\mathcal{U}$ will be a Banach or Hilbert space. Our rule will be the semigroup $S(t)$ associated to a differential equation: $\mathcal{S}(u, t) = S(t)u$. This is often called the trajectory and when u is the solution of a differential equation it is also indicated as $u(t)$, and if one wants to make explicit the dependency on the initial condition u_0, then it may be indicated as $S(t)u_0$ or as $u_{u_0}(t)$.

We use the formal definition of global attractors given in [37-ROB-2001].

DEFINITION D.1.2 ***Global Attractor*** *Given a semigroup $S(t)$, a global attractor $\mathcal{A}$ is the maximal compact invariant set such that*

$$S(t)\mathcal{A} = \mathcal{A} \qquad \forall \qquad t \geq 0$$

and the minimal set that attracts all bounded sets:

$$\mathrm{dist}(S(t)X, \mathcal{A}) \to 0 \qquad \textit{as} \qquad t \to \infty$$

for all bounded sets $X \in U$.

In proposition 10.14 at page 276 of [37-ROB-2001], the author proves that given a trajectory $u(t) = S(t)u_0$, $\epsilon > 0$ and $T > 0$, then there exists a time $\tau = \tau(\epsilon, T)$ and a point $v_0 \in \mathcal{A}$ such that

$$|u(\tau + t) - S(t)v_0| \leq \epsilon \qquad \forall \quad 0 \leq t \leq T. \tag{E.1.1}$$

Equation E.1.1 means that at any time T there exists a trajectory u on the manifold that approximates $S(t)u_0$ for small times.

In this sense, one can think of the attractor as describing the whole dynamics: though a trajectory may never actually be in the attractor itself, there is always a point close to it in the sense of E.1.1.

As remarked by Robinson, one cannot say that the trajectory $S(t)v_0$ is the one that best approximates $u(t)$; this is because equation E.1.1 is only valid between 0 and T; thus if one wants to follow $u(t)$ on the attractor for a longer time, we will have, in general, to switch to another trajectory starting at another point $v_1 \in \mathcal{A}$.

At this point we introduce Inertial Manifolds. For an up-to-date review, one can also consult [56-REG-2005].

These are simply defined as invariant manifolds that attract exponentially all the trajectories of the flow defined by the dynamical system. An Inertial Manifold $\mathcal{M}$ is then defined as follows.

DEFINITION D.1.3 ***Inertial Manifold*** ***A finite dimensional Lipschitz manifold $\mathcal{M}$ is an Inertial Manifold if***

- ***$\mathcal{M}$ is forward invariant, that is for any point $m \in \mathcal{M}$, and for any time $t \geq 0$, the flow starting at m will belong to $\mathcal{M}$ at every time t; in the language of semi-groups, if $S(t)$ is the semigroup associated to the dynamics:***

$$\forall m \in \mathcal{M}, \quad \forall t \geq 0, \qquad S(t)m \in \mathcal{M};$$

- ***for any point $m \notin \mathcal{M}$, the distance between the flow starting at m and $\mathcal{M}$ will decrease exponentially:***

$$\forall m \notin \mathcal{M}, \quad \text{dist}\,(S(t)m, \mathcal{M}) \leq Ce^{-\alpha t};$$

where α is an appropriate positive constant depending on the dynamical system and C is a constant depending on the initial condition.

Having defined Inertial Manifolds in this way it is clear that, while on the one hand they contain the global attractor, on the other hand they provide a much nicer way of reducing the study of dynamical systems. There are a number of reasons why this is so.

First of all, they attract all dynamics exponentially; this means that no matter what the initial condition, after a very short transient the flow will be very close to the Inertial Manifold; this is in contrast with E.1.1, from which we only know that the distance goes to zero, but nothing is said about the rate of attraction. As remarked in [39-TEM-1998] in its introduction to chapter 8 about Inertial Manifolds, *"we can construct attractors which attract the orbits at an arbitrary slow speed"*.

Secondly, not included in the definition of Inertial Manifold, is that usually they are proved to be asymptotically complete; this is defined as follows.

DEFINITION D.1.4 ***Asymptotically Complete Inertial Manifold*** ***An Inertial Manifold is asymptotically complete if for any point $m \notin \mathcal{M}$ there exists a point $n \in \mathcal{M}$ such that the distance between the flow starting at m and the flow starting at n decreases exponentially:***

$$\text{dist}\,(S(t)m, S(t)n) \leq Ce^{-\alpha t}.$$

This is indeed a very pleasant property. In fact, not only we know that no matter where we started from, we end up quickly on the manifold, we also know that the flow can be reproduced after a transient to an extreme degree of accuracy (exponential accuracy) with a flow completely contained on the Inertial Manifold; in fact, if $n \in \mathcal{M} \Rightarrow S(t)n \in \mathcal{M}$. This is what, with perhaps a bit too much of passion, is defined in [56-REG-2005] as "completely describing the long term dynamics *without error*". Clearly there is an error, though exponentially small.

Note that this is a much stronger requirement than E.1.1: here we find a unique trajectory for all positive times on the Inertial Manifold that approximates the original trajectory, with the additional property of the approximation having an exponentially small error.

A third reason is that they are Lipschitz manifolds, and so at least C^0; usually they are proved to be at least C^1 with a Lyapunov-Perron proof, while a geometric type of proof gives only C^0 and Lipschitz; however, the assumptions for both are the same or very similar, and so C^1 is usually expected. Notice that attractors are not required to be regular, and in fact they can even be of fractal dimension.

Last but not least, the Inertial Manifold is finite dimensional, while an attractor can even be of fractal dimension. This means that with an Inertial Manifold we can reduce the study of an infinite dimensional dynamical system, described by a PDE, to the study of a finite dimensional differential equation, described by an ODE. As everybody knows, ODEs are much easier to deal with than PDEs, therefore this feature of Inertial Manifolds is of great utility, especially in numerical computations.

We see how this is usually done before turning to the next section. First of all, note that the vast majority of the known Inertial Manifolds are given as graphs of functions; though see section **2.5.3** for one that is not such in all coordinates systems. That is, the variable of the dynamical system $\dot{u} = F(u)$ can be split into two parts, $u = (p, q)$ where p belongs to a finite dimensional subspace H' of H, and $q \in Q = H - H'$. Then there exists a function $h : H' \to Q$ such that the set of points $\mathcal{M} = \{p, h(p)\}$ is the Inertial Manifold. Then, the finite dimensional ODE is given by

$$\dot{p} = PF(p + h(p)), \qquad \text{E.1.2}$$

where PF denotes the projection on the subspace H' of the function F.

The importance of equation E.1.2 is reflected in the following definition.

DEFINITION D.1.5 ***<u>Inertial Form</u>*** ***Given a dynamical system $\dot{u} = F(u)$, where $u \in V$, which admits an Inertial Manifold expressed as a graph of a function $h : \mathbb{R}^n \to V - \mathbb{R}^n$, the inertial form is***

$$\dot{p} = PF(p + h(p)).$$

Sometimes, we might speak of a function h being an Inertial Manifold; in this case we mean that the graph of the function h is an Inertial Manifold. For example, we use this shorter nomenclature in chapter **3**; here we study whether a moment closure function is an Inertial Manifold, that is whether the graph of such a function is or not an Inertial Manifold.

Before proceeding any further, we wish to emphasise the relation between Inertial Manifolds and slow manifolds. Following [22-BER-2001], in the dynamical system

$$\begin{aligned} \dot{x} &= f(x, y) \\ \dot{y} &= \epsilon g(x, y) \end{aligned} \qquad \text{E.1.3}$$

where ϵ is a small parameter, y is called the slow variable and x the fast variable. This is because for small ϵ one expects the changes in the y coordinate to be smaller that those along the x coordinates. We give a slightly more formal argument following [22-BER-2001].

Taking the limit for $\epsilon \to 0$ one obtains the limiting system

$$\begin{aligned} \dot{x} &= f(x, y) \\ \dot{y} &= constant \end{aligned} \qquad \text{E.1.4}$$

where y plays the role of a parameter. The perturbed system in the form E.1.3 can be thought of as a modification of the associated system E.1.4 in which the parameter y changes slowly in time. Rescaling time and writing $s = \frac{t}{\epsilon}$ one can rewrite E.1.3 as

$$\begin{aligned} \epsilon\dot{x} &= f(x, y) \\ \dot{y} &= g(x, y) \end{aligned} \qquad \text{E.1.5}$$

and now taking the limit for $\epsilon \to 0$ one obtains a mixed algebraic-differential system

$$\begin{aligned} 0 &= f(x, y) \\ \dot{y} &= g(x, y) \end{aligned} \qquad \text{E.1.6}$$

Using the appropriate implicit function theorem, from $0 = f(x, y)$ one can get x as a function y, $x = x^*(y)$. In [22-BER-2001] one observes that the set of points $x = x^*(y)$, or $0 = f(x, y)$, is a set of equilibrium points, such that the orbits are attracted to it, under certain conditions. One can then split the attraction to the slow manifold into two components, the component along the x coordinate and one along the y coordinate. The rate of attraction along the x component is much faster than the rate along the y coordinate.

Thus slow manifolds are very similar to Inertial Manifolds.

DEFINITION D.1.6 ***Slow Manifold*** *Slow manifolds are invariant manifolds, which locally can be given as the graph of a function $x = x^*(y)$ towards which trajectories are attracted and the rate of attraction is faster in the x direction than in the y direction.*

An Inertial Manifold improves on this, as it is a Lipschitz finite manifold, the slow variable y is finite, the rate of attraction in the fast direction x is exponential, and is usually given as a global graph of a function.

In the next section we shall discuss the utility of Inertial Manifolds for the biological models we took as a starting point for our research. In the following sections we present the conditions under which Inertial Manifolds exist in our examples. In section **1.5** we shall review how they are employed in the Literature and what are the conditions most commonly used for an Inertial Manifold to exist.

1.3 Why Inertial Manifolds in our examples?

In the examples we will treat in this thesis, biological assumptions and observed data give clue to the presence of an Inertial Manifold. Though the aim of this section is not to give an account of the modelling of such biological system, which is left to later sections, we review here, briefly and under general terms, why we decided to investigate Inertial Manifolds in these examples.

Let us follow a chronological order and start by the gap junction example; the complete details of this examples are given in chapter **2**, and the original biological model was studied in [1-BAI-1997]. In this model, two variables are studied; s represents the state of the gap junctions, that is of the mechanism of communication amongst cells, and φ represents the concentration of the various chemical species being exchanged. We will show that the system is driven by the following differential equations:

$$\begin{aligned} \dot{s} =& \epsilon g(s, \varphi) \\ \dot{\varphi} =& - B(s)\varphi + w. \end{aligned}$$

We see here one of the features of Inertial Manifolds that we shall see again later: the two differential equations are coupled, that is each one depends on the other.

Now, if $\epsilon = 0$, s is a constant and φ is uniquely determined. As ϵ is a small parameter, one might ask if the system behaves not too differently when ϵ remains small but different from 0. This is what Perturbation Theory is about, that is to identify whether this is true or not. Though we shall not follow this road, as explained in detail in chapter **2**, one of the main results one could possibly draw from this theory, is the existence of an invariant manifold, persistent under small perturbations, towards which the dynamics of φ is attracted. This is very similar to the result one obtains if an Inertial Manifold was proved to exist.

The other model arises from Statistics applied to population biology, is treated in chapter **3** and is about a host-parasite system; it studies the growth of a population of hosts under the influence of parasites. This model possesses Moment Closure functions which have a strict relation with Inertial Manifolds.

The model uses a random variable N representing the number of individuals in the population and derive differential equations for the probability, moment and cumulant generating functions. From these, one obtains an infinite number of ordinary differential equations for the moments m_i, which are of the form

$$\dot{m}_i = f(m_1, \ldots, m_i, m_{i+1}). \qquad \text{E.1.7}$$

Again we note that each equation in the system depends on all the others.

A difference with the previous model immediately catches the eye: there is no explicit ϵ here; there are no coordinates that can be initially thought of as slow, that is with a small derivative, as in the case of $\dot{s} = \epsilon g(s, \varphi)$. However, in this case one or more functions are introduced to close the system. The most notable of them is the so called normal approximation. This is usually based on the biological assumption that the observed random variables are approximately normal. The normal approximation states that all the cumulants from the third on can be approximated by zero, that is one can *"neglects all cumulants of orders greater than the second"*, as Whittle says in [84-WHI-1957]. This means that we can use the relation $m_3 = 3m_1m_2 - 2m_1^3$ to close the first two equations of E.1.7:

$$\dot{m}_1 = f(m_1, m_2),$$

$$\dot{m}_2 = f(m_1, m_2, m_3) = f(m_1, m_2, 3m_1m_2 - 2m_1^3).$$

The other moments are then given by a function of the first two moments. This means that again we have a new dynamics on a finite dimensional manifold $\mathcal{M} = \{m_1, m_2, H(m_1, m_2)\}$, where H is the function defining the normal approximation, whose first component, corresponding to the third coordinate of $\mathcal{M}$, is $3m_1m_2 - 2m_1^3$.

In the example we treat, experimental data show that these approximations are good, in the sense that the steady state obtained by using the approximation is close to the exact steady state of the original equation. One important feature of the model in [72-ISH-1995] is that the transient time before convergence of the approximated moments to the true ones is small, this suggesting exponential attraction.

We wish to make a further remark about the meaning that is usually given to the words "good approximation" in most of the papers dealing with Moment Closure. The focus here is not always about the whole dynamics and global attraction, as in Inertial Manifolds theory or more generally speaking in Dynamical Systems Theory; sometimes the centre of attention in Statistics seems to be the steady states, independently of the dynamics. For example, this is the case in [78-MAT-1996] and [80-NÅS-2003], where the attention is focused only on the stationary distribution and the corresponding steady-state solutions and equilibrium values. On the other hand, Isham in [72-ISH-1995] states that an argument justifying the use of the normal approximation *"would have to be an asymptotic one"*, that is an argument based on the behaviour of the dynamics as time $t \to \infty$.

Most times, a biological and statistical assumption completely justifies the use of the normal approximation. In the words of Keeling, in [74-KEE-2000], *"this technique relies on the assumption that the first few moments capture the distribution of population size"*.

However, in [72-ISH-1995] the author explicitly states that *"there is no suggestion in the paper that N is, even approximately, normally distributed"*. Nevertheless, the results obtained by using this approximation are very satisfactory, *"even in cases where the normal distribution is a wholly inappropriate approximation to the true distribution"*. We wish to examine if Inertial Manifolds are behind this surprising fact.

In brief, we were drawn to investigate the presence of an Inertial Manifold by various considerations: the normal approximation gives very good, exponential approximations, the differential equations are coupled, the approximation are expressed as a function which can be used to uncouple the equations. In short, all the features of Inertial Manifolds appear to be present.

Recapitulating, we wanted to answer the following questions: do the dynamical systems given in the examples have an Inertial Manifold? If so, does the Inertial Manifold explain the biological observed data?

1.4 The Inertial Manifolds in our examples

Having reviewed the definition of Inertial Manifolds and the motivations we had in believing that this mathematical object was behind the biological models we were dealing with, it is now time to take a look at the results we obtained.

While we proved existence of an Inertial Manifold for the gap junction model and that it explained the biological observed data through an extension and generalisation of a standard theorem, we proved that the normal approximation is not an Inertial Manifold in the other population biology model. On the other hand, we did prove that it admits an Inertial Manifold, and that the normal approximation is a function that is close to the true Inertial Manifold; so we were able to give an explanation on why it works well.

How did we do it? Here is a brief mathematical account of the above mentioned results and the techniques we used to prove them.

1.4.1 The generalisation

As we said before, the dynamics of the variables $s \in \mathbb{R}^n$ and $\varphi \in \mathbb{R}^m$ describing the Gap Junction biological system are the solution of the differential equations:

$$\begin{aligned} \dot{s} &= \epsilon g(s, \varphi) \\ \dot{\varphi} &= -B(s)\varphi + w \end{aligned} \qquad \text{E.1.8}$$

where g is a Lipschitz function, w is a constant vector and $B(s)$ is a definite positive matrix depending on s, that is a family of positive definitive linear operators from $\mathbb{R}^m \to \mathbb{R}^m$.

In the previous section **1.3**, we have seen that the biological system represented by E.1.8 is likely to have an Inertial Manifold. What are then the conditions that guarantee existence for an Inertial Manifold, as stated in the standard theorems one finds in the literature? Are they satisfied by our example?

As we have said, most dynamical systems studied in the literature in relation to Inertial Manifolds are expressed as

$$\dot{u} = -Au + V(u) \qquad \text{E.1.9}$$

where u belongs to a Banach or Hilbert space and A is a linear operator in such space. The most common hypothesis used to prove the existence of an Inertial Manifold for such a system is the so-called “gap condition”. This is satisfied if A is a self-adjoint positive operator which has two successive eigenvalues whose difference is sufficiently large relative to the Lipschitz constant of V. We can certainly write our system E.1.8 in the form of E.1.9 by setting $u = (s, \varphi)$ and $B(s) = B_0 + B_1(s)$, so that

$$\begin{pmatrix} \dot{s} \\ \dot{\varphi} \end{pmatrix} = -\begin{pmatrix} \mathbb{0} & \mathbb{0} \\ \mathbb{0} & B_0 \end{pmatrix}\begin{pmatrix} s \\ \varphi \end{pmatrix} + \begin{pmatrix} \epsilon g(s, \varphi) \\ -B_1(s)\varphi + w \end{pmatrix}$$

and A would then be given by

$$A = \begin{pmatrix} \mathbb{0} & \mathbb{0} \\ \mathbb{0} & B_0 \end{pmatrix}.$$

The gap of the spectrum of A is therefore given by the size of the smallest eigenvalue of B_0. In fact, in the particular biological model we are dealing with, B_0 is a symmetric positive matrix. Hence, in order to satisfy the gap condition we require the Lipschitz constant of $B_1(s)\varphi$ to be small relative to this gap (and also ϵ to be small). In the case of our model of gap junction dynamics, we have no biological justification for such an assumption.

The main result in chapter **2** is therefore the generalisation of standard techniques to show that systems of the form

$$\begin{pmatrix} \dot{s} \\ \dot{\varphi} \end{pmatrix} = -\begin{pmatrix} \mathbb{0} & \mathbb{0} \\ \mathbb{0} & B(s) \end{pmatrix}\begin{pmatrix} s \\ \varphi \end{pmatrix} + \begin{pmatrix} \epsilon g(s, \varphi) \\ f(s, \varphi) \end{pmatrix} \qquad \text{E.1.10}$$

possess an Inertial Manifold if ϵ and the Lipschitz constant of f are small by comparison to the smallest eigenvalue b of $B(s)$. In the above equation we have introduced the family $A(s)$ of positive definite operators

$$A(s) = \begin{pmatrix} \mathbb{0} & \mathbb{0} \\ \mathbb{0} & B(s) \end{pmatrix}.$$

Note that in the case of a symmetric positive operator, b is defined as the minimum over s of the minimum eigenvalue $\lambda(s)$ of $B(s)$. Since in our biological model E.2.4, $f = w$ which is constant, this immediately implies the existence of an Inertial Manifold for this system for small ϵ. Furthermore, we shall give explicit estimates of the size of ϵ.

Our assumptions on the family of operators $B(s)$ will be that their spectrum is discrete and that there exist a $b > 0$ such that $\langle \frac{1}{2}(B(s) + B^*(s))\varphi, \varphi\rangle > b\,|\varphi|^2$ for all s and φ, where $B^*(s)$ is the adjoint operator of $B(s)$. Notice that in the case of a symmetric positive family of operators, b is then given by the smallest eigenvalue $\lambda(s)$ of $B(s)$.

We point out that systems of the form E.1.10 with non-constant f are more general than required to deal with system E.2.2 (page 59), where this term is fixed. Also, instead of setting E.1.10 in a finite Hilbert space $\mathbb{R}^n$, we deal with a general Hilbert space H. The reasons we include these generalisations are twofold. On the one hand, the modifications required to treat them are minimal and require only a small additional effort which is mostly algebraic and not conceptual; one thus gets the more general result almost for free. On the other hand, a non-constant f gives rise to a number of biological additional applications and extensions of the system that were not initially included in [1-BAI-1997]. Firstly, such an extension permits us to treat the more realistic case in which membrane permeability is a nonlinear function of φ. This has been observed in some experiments, and it is useful to know that the existence of an Inertial Manifold does not depend on linear membrane properties. Secondly, the general form of our theorem allows us to consider the case where the molecules transferred between cells are relatively large. The roles of s and φ are then reversed so that φ becomes the slow variable and we obtain an Inertial Manifold that is the graph of a function of φ.

It is also worth mentioning that though $A(s)$ depends only on s and not on φ, one can extend the same proof to a very general family of operators $A(u)$ defined as

$$A(u) = \begin{pmatrix} B_{ss}(s,\varphi) & B_{s\varphi}(s,\varphi) \\ B_{\varphi s}(s,\varphi) & B_{\varphi\varphi}(s,\varphi) \end{pmatrix}, \qquad \text{E.1.11}$$

where the subscripts are not derivatives but merely labels. Full details on this extension are given in section **2.4.4**.

What is then the method we use? It is the Lyapunov-Perron method, which goes back to the work in [34-LYA-1947] and [36-PER-1929], and is about 100 years old. It is a rather general method used in Nonlinear Dynamics for proofs related to the existence of all sorts of invariant manifolds. For example, the classical book [23-CAR-1981] uses this method in relation to centre manifolds. Briefly, given a dynamical system as

$$\begin{aligned} \dot{x} &= Ax + f(x,y) \\ \dot{y} &= By + g(x,y) \end{aligned} \qquad \text{E.1.12}$$

where, amongst all the other conditions found in [23-CAR-1981], all the eigenvalues of the matrix A have zero real parts and all the eigenvalues of the matrix B have negative real parts,

f and g are sufficiently smooth and $f(0,0) = g(0,0) = 0$; a centre manifold is defined as an invariant manifold $y = h(x)$ for E.1.12, where h is a function defined for small x with $h(0) = 0$ and $Dh(0) = 0$. It is not surprising then that, in complete analogy with what happens with an Inertial Manifold, the dynamics of y follows the dynamics of x and one may say that x enslaves the variable y. One of the major differences between centre manifolds and Inertial Manifolds is that one theory is local and the other one is global.

This method, sometimes also called the analytic method, is widely used in Inertial Manifold theory: [39-TEM-1998], [53-MAL-1988], [41-CHO-1992], and most of the papers quoted in the bibliographic section **5.3.3** use this method of proof. Nevertheless it is not the only one, the most notable example is the geometric proof in [57-ROB-1995]; the same author gives a comparison of the two methods in [58-ROB-1993].

We also remark that the geometrical approach to Inertial Manifolds is through the use of cone conditions and in particular the strong squeezing property (see [57-ROB-1995] or the glossary in chapter **4** for a definition). Just a few years before I first started my research activities, [59-ROB-1994] proved that this is sufficient to ensure the existence of a Lipschitz Inertial Manifold. It is easy to show that our system E.1.10 satisfies this condition for sufficiently small ϵ. Unfortunately, Robinson's proof only yields a Lipschitz manifold, and hence if we require the Inertial Manifold to be C^1, we need another approach, such as the one used here.

The main motivation for requiring the Inertial Manifold to be C^1 is that this ensures that the reduced dynamics on the manifold is also C^1. This allows us to apply all of the standard techniques of low-dimensional Nonlinear Dynamics to the reduced system. Thus, for instance, in [1-BAI-1997], the authors used Dulac's test and the Poincaré-Bendixson theorem to show that no oscillations are possible in the two-cell system. It is much more straightforward to employ such methods in their standard setting of C^1 systems. Furthermore, when we come to do bifurcation analysis and consider the behaviour of eigenvalues of equilibrium points, C^1 is absolutely essential. We also point out that we expect this type of biological system to behave smoothly, and it would be rather strange if our reduced model exhibited non-smooth features.

A standard approach to the Lyapunov-Perron method, which is used for example in [23-CAR-1981], [32-HEN-1981] or [39-TEM-1998], is to derive a formal equation, via the variation of constants formula, which the Inertial Manifold should satisfy if it exists. From this, an operator T on an appropriate space of functions is defined and one proves that T has a fixed point; this fixed point is an Inertial Manifold. Note that the Inertial Manifold may not be unique.

We first reproduce this approach in the following lines for the case $\dot{u} = -Au + V(u)$, and then indicate the modifications needed in the general case $\dot{u} = -A(u)u + V(u)$.

To define T, first we split the Hilbert space H into two orthogonal subspaces H' and $H - H'$: the first one corresponds to the enslaving coordinates s and the other to the enslaved coordinates φ. Denote now the projection onto H' by P, and the projection onto its orthogonal complement by Q. Let X be the space of bounded Lipschitz functions from $H' = PH$ to QH. An element in H' will be denoted by p, and it corresponds to our s, similarly $q \in QH$ corresponds to φ. Fix $h \in X$ and let $p_{p_0,h}$ be the solution with initial value $p(0) = p_0$ of the equation

$$\dot{p} = -PAp + PV(p + h(p)). \qquad \text{E.1.13}$$

This solution exists by classical results on ordinary differential equations and is continuous. For example, the hypothesis of Picard-Lindelöf theorem are valid for any time $t \in \mathbb{R}$, stated in the glossary in chapter **4**. We wish to make explicit that the solution for E.1.13 exists for any time, not just for positive times. In fact, since the function PV is *globally* Lipschitz on PH, the solution $p_{p_0,h}(t)$ with $p_{p_0,h}(0) = p_0$ exists for all $t \in \mathbb{R}$ and is unique.
Equation E.1.13 is also referred to as **Inertial Form**, as stated in definition **D.1.5** (page 19).

An Inertial Manifold must then be a function $\overline{h} \in X$ such that the function $q(t) = \overline{h}(p_{p_0,\overline{h}}(t))$ satisfies the equation

$$\dot{q} = -QAq + QV(p + \bar{h}(p)). \qquad \text{E.1.14}$$

where p indicates $p_{p_0,\bar{h}}(t)$. This is because the variable $\bar{u}(t) = (p_{p_0,\bar{h}}(t), \bar{h}(p_{p_0,\bar{h}}(t))$ is then a solution to the original equation $\dot{u} = -Au + V(u)$.

At this point, we note that once p_0 and h are fixed, one defines the function

$$\tilde{V}(t) = QV(p_{p_0,h}(t) + h(p_{p_0,h}(t)))$$

and it is not difficult to prove (see [39-TEM-1998]) that there exists a unique function $q(t)$ which is the solution of

$$\dot{q} = -QAq + \tilde{V}(t).$$
$$q(0) = h(p_0) \qquad \text{E.1.15}$$
$$t \in \mathbb{R}$$

Obviously q depends on p_0 and h.

Via the variation of constants formula, one can easily check that $q(t)$ is a solution of E.1.15 if and only if

$$q(t) = \int_{-\infty}^{t} e^{QA(\tau - t)} QV(p_{p_0,h}(\tau) + h(p_{p_0,h}(\tau)))d\tau,$$

which is equivalent to

$$q(0) = \int_{-\infty}^{0} e^{QA(\tau)} QV(p_{p_0,h}(\tau) + h(p_{p_0,h}(\tau)))d\tau. \qquad \text{E.1.16}$$

The equivalence of the above equations is shown by applying E.1.16 to $p_{p_0,h}(t)$ and then applying a change of coordinates $\sigma = t + \tau$, as we do for our more general case in chapter **2.4.1**. Also notice that A is positive, so that the eigenvalues of $-A$ are negative and thus the term $\exp\{-At\}$ vanishes in the variation of constants method at $-\infty$.

The right-hand side of E.1.16 is evidently an operator T on the space X: to each function h is assigned another function Th, the value of which at p_0 is defined as follows:

$$Th(p_0) = \int_{-\infty}^{0} e^{QA(\tau)} QV(p_{p_0,h}(\tau) + h(p_{p_0,h}(\tau)))d\tau. \qquad \text{E.1.17}$$

Thus, a function $\bar{h}$ is an invariant manifold if and only if it is a fixed point of T.

As previously mentioned, the most obvious approach to applying this method to systems of the form E.1.8 is to decompose $B(s)$ as $B(s) = B_0 + B_1(s)$ so that E.1.8 can be written in the form

$$\begin{pmatrix} \dot{s} \\ \dot{\varphi} \end{pmatrix} = -\begin{pmatrix} \mathbb{0} & \mathbb{0} \\ \mathbb{0} & B_0 \end{pmatrix}\begin{pmatrix} s \\ \varphi \end{pmatrix} + \begin{pmatrix} \epsilon g(s,\varphi) \\ -B_1(s)\varphi + w \end{pmatrix}.$$

The space H' then corresponds to the variable s, and in the case of a symmetric positive operator the gap in the spectrum of A is simply the smallest eigenvalue of B_0. As already described, the disadvantage of this approach is that to prove the existence of an Inertial

Manifold, we need to place restrictions on the Lipschitz constant of $B_1(s)\varphi$, something for which we have no biological justification in our particular model.

Although the above delineated method is not directly applicable to our case, we shall follow it quite closely. We denote by $s_{s_o,h}$ the unique solution of the following finite dimensional equation:

$$\dot{s} = \epsilon g(s, h(s))$$
$$s(0) = s_0 \qquad \text{E.1.18}$$
$$t \in \mathbb{R}$$

with initial value s_0. Note that this is the inertial form equivalent to E.1.13, and thus $s_{s_o,h}(t)$ exists for all times $t \in \mathbb{R}$.

Then we shall show that, for fixed s_0 and h, there exists a unique solution, which is continuous, for the following equation, equivalent to E.1.15:

$$\dot{\varphi} = -B(s_{s_o,h})\varphi + f(s_{s_o,h}, h(s_{s_o,h})). \qquad \text{E.1.19}$$

Unfortunately, since $QA(u) = B(s)$ depends on time, via the function s, it does not generate a semigroup, or in other words $e^{Bt}\varphi$ is not the solution of $\dot{\varphi} = B(s)\varphi$. We thus need to replace e^{Bt} in the variation of constants formula by a more general evolution operator $U_s(t,\tau)$ as in [18-AHM-1991] or [20-PAZ-1983]. This is a generalisation of the concept of a semigroup to the case where the generator B depends on time. It is defined in such a way that the function $y(t) = U_s(t,\tau)\zeta$ is the solution of

$$\dot{y} = -B(s(t))y$$
$$y(\tau) = \zeta. \qquad \text{E.1.20}$$
$$\tau \geq t$$

When B is a scalar, U is thus given by

$$U_s(t, t_0) = \exp\left(\int_{t_0}^{t} B(s(\tau))\mathrm{d}\tau\right).$$

However, in higher dimensions where B is a matrix, no such closed form is possible.

The operator T will now be defined by

$$Th(s_0) = \int_{-\infty}^{0} U_s(0,\tau) f(s_{s_0,h}, h(s_{s_0,h}))\mathrm{d}\tau, \qquad \text{E.1.21}$$

which is the equivalent of E.1.17. Having defined T, the proof of existence of an Inertial Manifold for sufficiently small ϵ is straightforward. We first show that T is well defined on X, maps X into X and is a contraction. It thus has unique fixed point $\varphi_\epsilon^\star$ which is an invariant manifold, and which is Lipschitz by construction.

As remarked in [58-ROB-1993] in the case of a symmetric positive operator one heavily uses the relations between the eigenvalues of $B(s)$, the Lipschitz constants of f and ϵ in proving the properties of T. This is how we can give explicit estimates on ϵ and conclude that the biological constants satisfy the conditions for the existence of an Inertial Manifold.

In order to prove differentiability, we introduce a second operator T_h^1, which for every fixed h maps the space of linear functionals on PH to itself. T_h^1 is obtained formally by differentiating under the sign of the integral of the definition of T. This operator is shown to be a contraction and its fixed point to be the derivative of our invariant manifold. Note that this approach is similar to that used by [41-CHO-1992] to prove differentiability of Inertial Manifolds for systems of the form E.1.9 satisfying a standard gap condition.

Finally, we use the differentiability and invariance of $\bar{h}$, the fixed point of T, to show directly that its graph is exponentially attracting.

The full proofs of the properties of T are given in section **2.4.1** and those of T_h^1 in section **2.4.2**. In this introduction, we wish to present just a hint of the flavour of these proofs, and we do this by quickly reviewing the proof of the fact that T is a contraction, proved in Lemma **L.2.9** (page 83).

We wish to prove that there exists a constant $\xi < 1$ such that

$$|Th_1(s_0) - Th_2(s_0)| \leq \xi \, \|h_1 - h_2\| \qquad \text{E.1.22}$$

for any two given functions $h_1, h_2 \in X$. Thus one wishes to analyse the difference $|Th_1(s_0) - Th_2(s_0)|$. We use the Lipschitz condition on f and g, a series of properties of the evolution operator U, and a few Gronwall's inequalities to derive an inequality like E.1.22. The constant ξ is given as an expression of ϵ, the Lipschitz constants of f and g

and the eigenvalues of $B(s)$, when $B(s)$ is a family of symmetric positive operators. By imposing that $\xi < 1$, which is a condition on ϵ, one proves that T is a contraction. The whole process of proof consists then in determining analytical inequalities satisfied by U and the appropriate Gronwall's inequalities that guarantee the properties of T.

By the definition E.1.21 of T, adding and summing to the difference $|Th_1(s_0) - Th_2(s_0)|$ the same term

$$U_{s_{h_2}}(0,\tau)f(s_{h_1}(\tau), h_1(s_{h_1}(\tau)),$$

we obtain that

$$\begin{aligned}|Th_1(s_0) - Th_2(s_0)| & \\ \le & \int_{-\infty}^{0} \left|\left(U_{s_{h_1}}(0,\tau) - U_{s_{h_2}}(0,\tau)\right) f(s_{h_1}(\tau), h_1(s_{h_1}(\tau)))\right| \mathrm{d}\tau \\ & + \int_{-\infty}^{0} \left|U_{s_{h_2}}(0,\tau)\left[f(s_{h_1}(\tau), h_1(s_{h_1}(\tau))) - f(s_{h_2}(\tau), h_2(s_{h_2}(\tau)))\right]\right| \mathrm{d}\tau.\end{aligned}$$

In section **2.3** we prove some bounds on $U_{s_h}(0,\tau)$ that are useful in constructing the final bound of E.1.22. One of these bounds relates the difference $(U_{s_{h_1}} - U_{s_{h_2}})$ to the difference $(s_{h_1} - s_{h_2})$; here is where we need to prove a Gronwall's inequality. Each of these inequalities is proved in a series of lemmas just before they are needed.

For example, we use the following inequalities

$$\begin{aligned}\left|U_{s_{h_1}} - U_{s_{h_2}}\right| &\le \beta e^{-b\tau} \int_{\tau}^{0} \left|s_{h_1}(\sigma) - s_{h_2}(\sigma)\right| \mathrm{d}\sigma, \\ \left|s_{h_1}(t) - s_{h_2}(t)\right| &< \frac{\|h_1 - h_2\|}{p_1 + 1}\left[e^{-\epsilon\gamma(p_1+1)t} - 1\right] \\ \left|U_{s_{h_1}}\right| &\le e^{b\tau}\end{aligned}$$

and the Lipschitz property of f to obtain that

$$\begin{aligned}&|Th_1(s_0) - Th_2(s_0)| \\ &\qquad \le \|h_1 - h_2\| \frac{b^2\theta(p_1+1) + b\beta F - \beta F[b - \epsilon\gamma(p_1+1)]}{b^2(b - \epsilon\gamma(p_1+1))(p_1+1)}.\end{aligned}$$

The bound on ϵ consists in imposing

$$\frac{b^2\theta(p_1+1) + b\beta F - \beta F[b - \epsilon\gamma(p_1+1)]}{b^2(b - \epsilon\gamma(p_1+1))(p_1+1)} < 1.$$

Analysing our usage of the Lyapunov-Perron method, we see that the principal difference between the results presented here and standard Inertial Manifold theorems is that we allow the operator A to depend on u , thereby incorporating some of the nonlinearity of the problem into A. In effect, we can think of the form $-Au + r(u)$ as an expansion about $u = 0$, which gives little control over the dynamics for large u, while by writing $-A(u)u + V(u)$, we are in some sense linearizing locally about each u, and hence have far more information about local contraction rates throughout the whole of phase-space.

In terms of the proof of our results the most significant effect of this change is to replace the operator e^{Bt} in the variation of constants formula by a more general evolution operator $U_s(t, \tau)$, which gives the solution of the equation $\dot{\varphi} = B(s(t))\varphi$ (see section **2.3** for more details).

Full details can be found in chapter **2**, which is structured in the following way.

- **2.1 - The biological model**: a description of the construction of the biological dynamical system;
- **2.2 - The functional settings**: the functional setting for our dynamical system;
- **2.3 - Preliminary results**: proofs of the preliminary results related to the evolution operator U;
- **2.4 - The Inertial Manifold**: the existence of a C^1 Lipschitz Inertial Manifold, subdivided into:
  - **2.4.1 - Existence**: proofs of the properties of the operator T;
  - **2.4.2 - Smoothness**: proofs of the properties of the operator T_h^1;
  - **2.4.3 - Exponential attraction and asymptotic completeness**: proof of the fact the $\mathcal{M}$ is exponentially attracting and asymptotically complete;
  - **2.4.4 - Further generalisation**: the proof for the more general dynamical system $\dot{u} = -A(u)u + V(u)$ with $A(u)$ defined in E.1.11 (page 26).
  - **2.4.5 - The gap condition and the strong squeezing property**: an account of the relation between the condition $(1-k)b > \theta$ and the classical Gap Condition;

– **2.5 - Examples**: examples clarifying asymptotic completeness property, an Inertial Manifold that is not asymptotically complete, and a dynamical system that has an Inertial Manifold even though it does not satisfy the Strong Squeezing Property.
– **2.6 - Application to the biology**: the application of our results to the Gap Junction example of [1-BAI-1997].

1.4.2 The similarity

When trying to describe a natural phenomenon in mathematical terms, often the first decision the scholar has to take is whether to use a deterministic or a stochastic approach. However the two are not seen as being in contradiction, rather deterministic models are viewed as "first degree" approximations to the stochastic models describing the same phenomenon, even if sometimes they yield different results.

One could say that one of the questions, with which this thesis is concerned, is under which conditions and up to what extent a deterministic model can be considered a good approximation of a stochastic one. However, we do not approach the question under a very general theoretical framework; rather, we are interested in contributing a little to this important subject.

We do this by studying if, when the *dynamics* describing the evolution of the moments of a probability distribution function can be well approximated by using a deterministic or normal approximation, this can be explained by some dynamical properties of the dynamical system, like Inertial Manifolds.

In fact, usually one of the major problems encountered when dealing with stochastic models is that the variables, generally the moments of a probability function, are in infinite number and thus, when studying a time-dependent problem, one obtains an infinite system of differential equations.

In the simplest cases, e.g. when the transition probabilities are linear functions of the random variables, the system can be solved recursively, that is the equation for the first moment first, and so on, as the equation for the moment of order k involves only the moments of order $1, \ldots, k$.

In many other cases, as stated in [14-BAI-1964], generally when the transition probabilities are non-linear functions of the random variables, one obtains equations which cannot be resolved recursively, as the equation for the moment of order k involves moments of higher order.

However it is commonly assumed that the first few coordinates actually carry more "information" than the others and often a very good description of a phenomenon is given by ignoring the other coordinates. A system which is approximated by the equations involving the first moment only is sometimes called a "deterministic approximation", which suggests a strong relation to a deterministic "equivalent" model.

This and other approximations can be obtained by assuming suitable relations among the moments, which, if substituted into the equations, can simplify the system. For example, from the differential equation in the first two moments m_1 and m_2

$$\dot{m}_1 = F_1(m_1, m_2),$$

one can assume a relation $\sigma^2 = m_2 - m_1^2 = 0$ to obtain

$$\dot{m}_1 = F_1(m_1, m_1^2)$$

and thus close the equation and reduce the dimension of the system.

This is the deterministic approximation and is obtained by setting to zero the variance σ^2, that is a mathematical measure of how one "expects" the phenomenon to vary from one observation to another. Another commonly used approximation is the "normal approximation", which consists in assuming that the distribution is approximately normal and thus that the relation $m_3 = 3m_1\sigma^2 + m_1^3$ holds. What is common to the deterministic and normal approximation is that, in a sense, all the higher moments are ignored. As we saw in section **1.3**, for the example in [72-ISH-1995], this behaviour makes one initially suspect the existence of an Inertial Manifold.

As we shall see below, the methods of the proofs contained in chapter **3** are not so sophisticated as the Lyapunov-Perron method described before. Mostly, they rely on a correct algebraic manipulation of the variables and on the adequate analysis and breakdown of mathematical facts. This is a very complicated sentence just to say that the method of proof does not matter here at all, and what matters are the contents and the basic mathematical reasoning on which they are built. Not much deep, sound knowledge of any particular branch of mathematics is needed to follow them, just a mathematical spirit.

The equations governing the dynamics of the factorial moments g_k of the population dynamics in [72-ISH-1995] are originally nonlinear:

$$\dot{g}_k = h_k + \sum_{i=1}^{k-1} \binom{k}{i} h_{k-i} g_i + \alpha g_1 g_k - \alpha g_{k+1} - (\alpha + \mu) k g_k.$$

Nevertheless, we show in section **3.2.1** that, with an appropriate change of coordinates, we can express the same dynamics with linear differential equations:

$$\dot{\rho}_k = h_k - \alpha \rho_{k+1} - (\alpha + \mu) k \rho_k. \qquad \text{E.1.23}$$

where the ρ_k are the factorial cumulants, treated in section **3.2.2**. The deterministic approximation $\sigma^2 = 0$ is expressed in the ρ_k coordinates as $\rho_1 + \rho_2 = 0$ and the normal approximation as $\rho_3 + 3\rho_2 + \rho_1 = 0$.

In a suitable function space L, the above equation admits a unique steady point $\bar{R} = \{\bar{\rho}_k\}$ which is also exponentially attracting (theorem **T.3.2**). Here it suffices to say that $\bar{R}$ is such that

$$\bar{\rho}_1 = \frac{h_1}{\alpha + \mu} - \frac{\alpha h_2}{2(\alpha + \mu)^2} + \mathcal{O}\left(\frac{\alpha^2}{(\alpha + \mu)^3}\right),$$

and

$$\bar{\sigma}^2 = \rho_1 + \rho_2 = \frac{h_1}{\alpha + \mu} + \frac{\mu h_2}{2(\alpha + \mu)^2} + \mathcal{O}\left(\frac{\alpha^2}{(\alpha + \mu)^3}\right),$$

where α/μ is small.

Next, we introduce the deterministic and normal approximation in the dynamics E.1.23, so that we obtain two closed linear dynamical systems. One corresponds to the deterministic approximation and is obtain introducing $\rho_2 = -\rho_1$ into equation E.1.23 for $k = 1$. We thus obtain one linear equation in one variable ρ_1:

$$\dot{\rho}_1 = h_1 - \mu \rho_1. \qquad \text{E.1.24}$$

Similarly, the other dynamical system, corresponding to the normal approximation, gives us two linear equations in two variables:

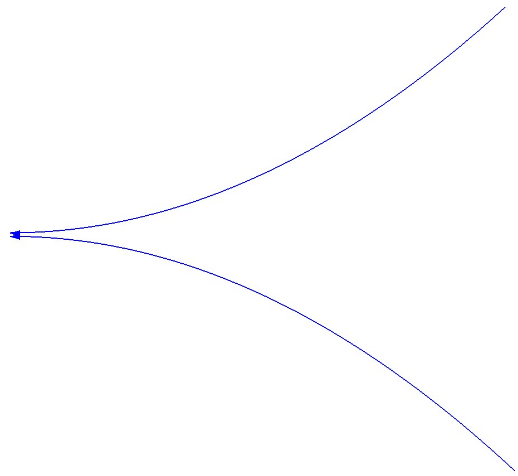
$$\begin{aligned} \dot{\rho}_1 &= h_1 - \alpha \rho_2 - (\alpha + \mu) \rho_1 \\ \dot{\rho}_2 &= h_2 + \alpha \rho_1 - (2\mu - \alpha) \rho_2 \end{aligned} \qquad \text{E.1.25}$$

One then shows easily in section **3.3** that E.1.24 admits a unique steady point $\tilde{\rho}_1 = h_1/\mu$. Equation E.1.25 also admits a unique globally attracting steady point $(\hat{\rho}_1, \hat{\rho}_2)$.

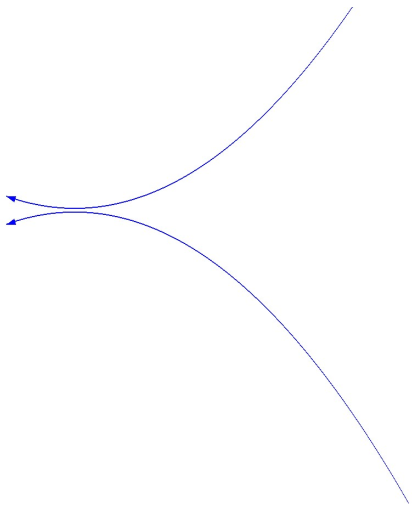
We demonstrate that if we assume that $\alpha = \epsilon\mu$, that is that $\alpha \ll \mu$, and we let $\epsilon \to 0$, then $(\bar{\rho}_1 - \tilde{\rho}_1) \to 0$ as $\epsilon \to 0$. Similarly, the distances $(\bar{\rho}_1 - \hat{\rho}_1)$ and $(\bar{\sigma}^2 - \hat{\sigma}^2)$ go to 0 as $\epsilon \to 0$.

Section **3.3.3** is then concerned with the fact that the original fixed point $\overline{R}$ and the fixed points of the approximated dynamical systems are close. This is one of the reasons why using the approximations gives good results. Nevertheless, this is not an explanation that takes into account the global dynamics of the whole system.

From a dynamical point of view one would want that each fixed point attract the dynamics like this:



rather than like this:



The second graphic is an example of a dynamical system where two flows tend at infinity to two points that are very close, but the distance between the two flows does not decrease and does not go to zero. To this situation we prefer one where the two flows, apart from tending to two points that are close, will get closer and closer, and the distance between the two decreases.

Also note that in the above argument extracted from section **3.3.3** we never express any relation between the higher coordinates and the first one (for the deterministic approximation) or the first two (for the normal approximation). We just state that the first coordinates of the fixed points are close. From the viewpoint of Inertial Manifolds, this is a serious limitation. In fact, an Inertial Manifold is a finite dimensional manifold that can express the dynamics of all the higher coordinates in terms of a finite set of coordinates. This is clearly seen when the Inertial Manifold is given as graph of a function, which is the most common case. Therefore if the deterministic or normal approximation, which are functions, were Inertial Manifolds, one would expect that all high coordinates can be expressed in terms of the first coordinate (deterministic) or the first two coordinates (normal).

The very definition of an Inertial Manifold h for systems like

$$\dot{u} = F(u) \qquad \text{E.1.26}$$

implies that for any initial condition $u_0 = (p_0, q_0)$ we have that $h(p_{p_0}(t))$ is exponentially close to $q_{u_0}(t)$, where $p_{p_0}(t)$ is the solution of the inertial form E.1.2 (page 18) starting at p_0 and $q_{u_0}(t)$ is the q coordinate of the solution of E.1.26 starting at u_0 (see sections **1.2**, **2.4.3** and **2.5.1** for further details).

This means that the higher coordinates of any trajectory starting at any initial point are exponentially approximated by a curve on the Inertial Manifold. Said otherwise, Inertial Manifold theory is concerned with the reduction of the dimension of the dynamical system, i.e. the main result one obtains from the existence of an Inertial Manifold is that one can solve the ODE defined by the inertial form E.1.2 for the first few coordinates and then obtain an approximated result for all the other coordinates by the function defining the Inertial Manifold.

On the other hand, the focus of a moment closure technique is quite different. Generally speaking, a moment closure function will be a function from $\mathbb{R}^n$ to $H - \mathbb{R}^n$, so that each coordinate m_j for $j > n$ can be expressed as $m_j = h_j(m_1, \ldots, m_n)$.

Thus equation

$$\dot{m}_i = f_i(m_1, \ldots, m_i, m_{i+1}, \ldots)$$

is reproduced with a small error by the ODE

$$\begin{aligned} m_1 &= f_1(m_1, \ldots, m_n, h_{n+1}(m_1, \ldots, m_n), \ldots) \\ &\ldots \\ m_n &= f_n(m_1, \ldots, m_n, h_{n+1}(m_1, \ldots, m_n), \ldots) \end{aligned} \qquad \text{E.1.27}$$

The main object of interest when using such a technique is the set of equations E.1.27; these are then used to prove that the first n true moments are close to the first n approximated moments. This is in contrast with the use of an Inertial Manifold; in fact no study of the distance between the higher true moments and the higher approximated moments is usually given via a moment closure function. On the other hand, the existence of an Inertial Manifold does not by itself give any clue on the distance between the true first coordinates and the approximated first coordinates, which is at the basis of the definition of an asymptotically complete Inertial Manifold.

Recapitulating, both an Inertial Manifold and a moment closure function are represented by a function H from $\mathbb{R}^n$ to $H - \mathbb{R}^n$, that is a relation between the first n coordinates and all the others; thus H can be expressed as

$$H = \{h_{n+1}(m_1, \ldots, m_n), h_{n+2}(m_1, \ldots, m_n), \ldots, h_{n+k}(m_1, \ldots, m_n), \ldots\}$$

They both are used to approximate the solutions $m_1, \ldots, m_i, \ldots$ of an infinite dynamical system

$$\dot{m}_i = f_i(m_1, \ldots, m_i, m_{i+1}, \ldots). \qquad \text{E.1.28}$$

Thus we can use H to define the inertial form:

$$\begin{aligned} m_1 &= f_1(m_1, \ldots, m_n, h_{n+1}(m_1, \ldots, m_n), \ldots) \\ &\ldots \\ m_n &= f_n(m_1, \ldots, m_n, h_{n+1}(m_1, \ldots, m_n), \ldots) \end{aligned} \qquad \text{E.1.29}$$

Let us denote by $\bar{m}_j$, $1 \leq j \leq n$ the solution of E.1.29 and by m_k, $k \geq 1$ the solution of E.1.28.

The difference between the two is then that an Inertial Manifold guarantees that the distance between $m_k(t)$ and $h_k(\bar{m}_1(t), \ldots, \bar{m}_n(t))$ goes to zero exponentially for $k > n$ as $t \to \infty$; on the contrary a moment closure approximation is used to study the distance between $m_j(t)$ and $\bar{m}_j(t)$ for $1 \leq j \leq n$.

In many statistical applications the function f_i depends only on $m_1, \ldots, m_{i+1}$, so that in order to close the equations of system E.1.28, one only needs to use h_{n+1}; in the case of the normal approximation, this corresponds to setting the variance equal to zero. This usage of the deterministic and normal approximations to obtain equations E.1.29 is so predominant that some times authors just state that *"the approximation to the mean is obtained by setting $\sigma^2 = 0$"* as in [72-ISH-1995]. However we stress that this is just a consequence of the assumption of the normal approximation, which is equivalent to assuming that *"the cumulants of order higher than 2 are small"* as in [80-NÅS-2003] and [84-WHI-1957].

For our purposes, it is extremely important to stress that when authors use the deterministic and normal approximations, they are actually defining an infinite dimensional function, though they might only use the equations $\sigma^2 = 0$ or $\kappa_3 = 0$, respectively. Otherwise, we would not be able to make any comparison at all between the normal approximation and an Inertial Manifold.

Thus, to complete the study of the dynamical system treated in [72-ISH-1995] and [48-STA-2001] from a dynamical perspective, we cannot limit ourselves to the observation in section **3.3.3** that the functions defining the deterministic and normal approximations give fixed points whose first coordinates are close to those defined by the true Inertial Manifold. That is, the fact that the distances $(\bar{\rho}_1 - \tilde{\rho}_1)$, $(\bar{\rho}_1 - \hat{\rho}_1)$ and $(\bar{\sigma}^2 - \hat{\sigma}^2)$ go to 0 as $\epsilon \to 0$ is not telling us anything about whether the moment closure is an Inertial Manifold or not.

To see this, we have to prove some stronger results relating the higher moments of the original Inertial Manifold and the approximated ones. That is, in the case of the deterministic approximation, we have to study if $\hat{\rho}_j$ for $j \geq 2$ is close or not to $\bar{\rho}_j$. For the normal approximation one just takes $j \geq 3$. Remember that the normal approximation defines each $\hat{\rho}_j$; in fact the normal approximation states that all the higher cumulants are equal to 0; we shall find a relation in section **3.3.5** between the cumulants and the factorial cumulants, so that setting to zero cumulant j is equivalent to define a relation between ρ_j and $\rho_1, \ldots, \rho_{j-1}$.

Thus in order to find a justification based on a dynamical system perspective, we resort to the arguments of section **3.3.4**. Here we reproduce the arguments proved in this section, but adapted to the deterministic approximation. In section **3.3.4** we prove the same results also for the normal approximation and for a general Moment Closure function satisfying certain conditions.

In words, we use the moment closure function to define a set of differential equations for all the higher coordinates. This is an extension of the standard use of a moment closure, where, as we have remarked, the focus is a set of equations E.1.27 which gives an approximation for the first n moments. Then, we shall prove that this new set of equations admits an Inertial Manifold, given by the moment closure function, and that this system can be regarded, in a peculiar sense, as a "perturbed" dynamical system and that the "perturbed" and true Inertial Manifolds are close.

Formally, we take L a suitable function space, and we notice that the function Φ:

$$\Phi : \mathbb{R} \to L - \mathbb{R},$$

$$\Phi : \rho_1 \mapsto \Phi(\rho_1) = \{\bar{\rho}_2, \bar{\rho}_3, \ldots\}.$$

defines a one dimensional Inertial Manifold for E.1.23:

$$\mathcal{M} = \{\rho_1, \Phi(\rho_1)\} = \{\rho_1, \bar{\rho}_2, \bar{\rho}_3, \ldots\}.$$

Then we take the function $\widetilde{\Phi}(\rho_1) = \rho_1$; note that this functions defines the deterministic approximation in the sense that this approximation is defined by $\rho_2 + \widetilde{\Phi}(\rho_1) = 0$. Thus we introduce a change of coordinates $\widetilde{\rho}_2 = \rho_2 + \widetilde{\Phi}(\rho_1) - \bar{\rho}_2$ and create a new dynamical system

$$\begin{aligned}
&\dot{\rho}_1 = h_1 - \alpha(\widetilde{\rho}_2 + \bar{\rho}_2 - \rho_1) - (\alpha + \mu)\rho_1 = h_1 - \alpha\bar{\rho}_2 - \alpha\widetilde{\rho}_2 - \mu\rho_1 \\
&\dot{\widetilde{\rho}}_2 = \dot{\rho}_2 + \dot{\rho}_1 \\
&\dot{\rho}_k = h_k - \alpha\rho_{k+1} - k(\alpha + \mu)\rho_k \qquad \text{for } k \geq 3.
\end{aligned} \tag{E.1.30}$$

We prove that the manifold $\widetilde{\mathcal{M}} = \{\rho_1, \widetilde{\Phi}(\rho_1), \bar{\rho}_3, \ldots\}$ is an Inertial Manifold for E.1.30.

Given two set of points $\mathcal{N} = \{n_1, n_2, \ldots\} \in L$ and $\bar{\mathcal{N}} = \{\bar{n}_1, \bar{n}_2, \ldots\} \in L$, their difference in our functional space L (see section **3.2.3**) is given by

$$\mathrm{dist}\left(\mathcal{N}, \bar{\mathcal{N}}\right) = \sum_{i=1}^{\infty} |n_i - \bar{n}_i|^2 .$$

With this definition, we finally prove that the distance between $\widetilde{\mathcal{M}}$ and $\mathcal{M}$ goes to zero as $t \to \infty$ and $\epsilon \to 0$. In fact, these two manifolds are equal on all coordinates, except the second one (in the case of the deterministic approximation). Then, on the one hand we prove that

$$\widetilde{\Phi}(\bar{\rho}_1) \to \bar{\rho}_2 \qquad \text{as } \epsilon \to 0,$$

while on the other hand

$$\forall \epsilon > 0 \qquad \widetilde{\Phi}(\rho_1(t)) \to \widetilde{\Phi}(\bar{\rho}_1) \qquad \text{as } t \to \infty$$

This is the condition a Moment Closure function has to verify in order to be a good approximation from a Dynamical System perspective. As we remark in section **3.3.4**, one can then view $\widetilde{\rho}_2$ as a *perturbation* of ρ_2; in fact we can introduce $\delta(\epsilon, t) = \widetilde{\Phi}(\rho_1(t)) - \bar{\rho}_2$ which goes to zero as $\epsilon \to 0$ and $t \to \infty$ and then, by definition, $\widetilde{\rho}_2 = \rho_2 + \delta(\epsilon, t)$.

Thus we can say that the deterministic and normal approximations are Inertial Manifold for a *perturbed* dynamical system, and that the *perturbed* Inertial Manifolds are close to the Inertial Manifold for the *non-perturbed* dynamical system.

Notice that we use the term *perturbation* in a peculiar way, and that is why we use a slanted font for it. First of all, notice that the manifolds we have defined, $\mathcal{M}$ and $\widetilde{\mathcal{M}}$ are both hyperplanes, and thus they cannot be a good approximation one of the other for all times. These two manifolds are defined by two attracting points $\overline{R}$ and $\widetilde{R}$, which are close for small values of ϵ. Notice now that the dynamics of E.1.23 (page 36) tends to $\overline{R}$ as $t \to \infty$ and that of E.1.30 tends to $\widetilde{R}$ as $t \to \infty$. Thus, when both $t \to \infty$ and $\epsilon \to 0$, the two dynamics are close.

A limitation of the above argument is that it uses the Moment Closure function only to define one component of $\widetilde{\mathcal{M}}$, the second one for the deterministic approximation and the third one for the normal approximation. In section **3.3.5** we overcome this limitation by adapting the arguments above to a manifold $\bar{\mathcal{M}}$ which is defines as

$$\bar{\mathcal{M}} = \{\rho_1, \rho_2, \Psi_3(\rho_1, \rho_2), \Psi_4(\rho_1, \rho_2), \ldots, \Psi_n(\rho_1, \rho_2), \},$$

where Ψ_n is the function defining the normal approximation for the n^{th} factorial cumulant. We are able to show again that this manifold is an Inertial Manifold for a *perturbation* of E.1.23. The interesting result is that $\Psi_n(\bar{\rho}_1, \bar{\rho}_2)$ is close to $\bar{\rho}_n$, and so we can prove that for $\epsilon \to 0$ and $t \to \infty$ the normal approximation is approximating closely the Inertial Manifold for the original system for each coordinate. Note that we do not prove that the distance between the manifolds $\mathcal{M}$ and $\widetilde{\mathcal{M}}$ goes to 0, we only prove that the difference between each pair of coordinates goes to 0; stated otherwise, we prove that

$$|\Psi_n(\bar{\rho}_1, \bar{\rho}_2) - \bar{\rho}_n| \to 0$$

but we do **not** prove that

$$\operatorname{dist}\left(\mathcal{M}, \widetilde{\mathcal{M}}\right) = \sum_{n=3}^{\infty} |\Psi_n(\bar{\rho}_1, \bar{\rho}_2) - \bar{\rho}_n|^2 \to 0.$$

Notice that this particular example admits an exponentially attracting fixed point, and thus all trajectories are Inertial Manifold. Why do we then consider in sections **3.3.4** and **3.3.5** very special Inertial Manifold, that is hyperplanes? The fact, is that in a sense we are using Inertial Manifold to find a slow manifold in the sense of definition **D.1.6** (page 20), and we are interested in the *slowest* manifold. As we prove in section **3.3.2**, given the hyperplanes $\mathcal{M}_n$ defined as

$$\mathcal{M}_n = \{\rho_1, \ldots, \rho_n, \bar{\rho}_{n+1}, \bar{\rho}_{n+2}, \ldots\},$$

then the hyperplane $\mathcal{M}_{n+1}$ is a slower manifold than the hyperplane $\mathcal{M}_n$, that is the rate of attraction along the fast coordinates is faster for $\mathcal{M}_{n+1}$ than for $\mathcal{M}_n$.

From the perspective of biologically interpreting the results, our conclusions are that all observed data are fully justified by the mathematical properties of the model: For example, the short transient for convergence of the approximated moments is justified by global exponential attraction in time for small ϵ and the fact that the convergence of $\widetilde{\mathcal{M}}$ to the true Inertial Manifold is coordinate-wise and not global is in complete accordance with the reiterated observation in Isham's paper that the random variable being studied is not normally distributed, though the normal approximation is good.

Full details can be found in chapter **3**, which is structured in the following way.

- **3.1 - The biological model**: derivation of the differential equations for the biological model, as in [72-ISH-1995];
- **3.2 - The functional settings**: describes the functional spaces in which equation E.1.23 makes sense, and the factorial cumulants;
- **3.3 - Almost an Inertial Manifold**: the proof that the normal approximation is almost an Inertial Manifold;
  - **3.3.1 - The fixed point and Inertial Manifolds**: the fixed point of E.1.23 defines various Inertial Manifolds;
  - **3.3.2 - The best Inertial Manifold**: a study of the rate of attraction explains why the normal approximation is better than the deterministic one;
  - **3.3.3 - Comparison of the steady states for the full and approximated models**: from a steady state point of view, the first and second approximated moments are close to the original one;
  - **3.3.4 - Perturbations of the Inertial Manifold**:the deterministic and normal approximations can be seen as *perturbations* of the Inertial Manifold;
  - **3.3.5 - Higher factorial cumulants for the normal approximation**: the normal approximation is close to the Inertial Manifold, coordinate-wise;
- **3.4 - Our choice of coordinates**: explains why we chose to use the factorial cumulants, though they are not the most familiar set of coordinates;
- **3.5 - Interpreting the results**: why our results explain the observed features of the biological example.

1.5 Inertial Manifolds in the Literature

Rather than presenting a strict and arid chronological review of Inertial Manifolds, we prefer to focus on some of the main issues and deal with each one separately. The topics we wish to treat are:

- some of the equations for which Inertial Manifold have been proven to exist; we shall see that nearly all are expressed in the form $\dot{u} = -Au + V(u)$;
- a review of other methods of proof and a brief comparison with the Lyapunov-Perron method.

1.5.1 Generalisations

Let us then begin with the review of some examples. The Kuramoto-Sivashinsky equation, a modified Navier-Stokes equation, and the Ginzburg-Landau equation are both treated in [39-TEM-1998] and in [37-ROB-2001]. In both, the equations are proved to satisfy the Gap Condition, and thus possess an Inertial Manifold. The difference between the two books is the method they use to prove the existence of an Inertial Manifold when the Gap Condition is satisfied; Temam uses the Lyapunov-Perron method and Robinson the Geometric proof. What is of concern to us is that all these equations can be expressed in an appropriate function space H as

$$\dot{u} = -Au + V(u). \qquad \text{E.1.31}$$

More references dealing with the same equations, and to which the two books refer back, can also be found in section **5.3.3**.

Equation E.1.31 is the most typical equation that one deals with, up to the point that in the review in [56-REG-2005] dedicated to methods of dimension reduction it is the only equation dealt with.

However, we were able to find a couple of references that treat the nonautonomous differential equations

$$\dot{u} = -A(t)u + V(t,u). \qquad \text{E.1.32}$$

The authors Koksch and Siegmund have published a number of papers on the subject; we quote only [50-KOK-2002] and [51-KOK-2003], which contain enough material for our purposes. In fact, in this thesis we deal only with autonomous differential equations, and thus our interest in E.1.32 is limited to curiosity and background material. The main point we wish to note is that in the two papers [50-KOK-2002] and [51-KOK-2003] the authors assume that $V(t, u)$ is continuous in time and satisfies a Lipschitz-type condition in u, and $A(t)$ is a family of linear operators from $X \to Z$, with X and Z two Banach spaces, such that the linear evolution equation

$$\begin{aligned} \dot{u} =& - A(t)u \\ u(0) =& u_0 \end{aligned} \qquad \text{E.1.33}$$

admits a unique solution. Clearly one will not be able to use semigroups to define the solution of E.1.33 and one has to resort to evolution operators, as we do in section **2.3.2** but for different reasons. In fact the solution to E.1.33 is defined as that evolution operator $U(t, \tau) : \mathbb{R}^2 \to \mathcal{L}(Z, Z)$ such that for $t \geq \tau$

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t}U(t,\tau) =& - A(t)U(t,\tau) \\ U(\tau,\tau) =& \mathbb{I} \end{aligned}$$

where $\mathbb{I}$ is the identity operator from Z to Z. Also note that the evolution operator satisfies a series of conditions that bound its norm, and that are similar to equation E.2.18 that we prove in section **2.3.3**.

Finally, in [50-KOK-2002] and [51-KOK-2003] the squeezing property and cone invariance are proved to hold for equation E.1.32; it is important to note that the form in which these two properties are expressed in [50-KOK-2002] and [51-KOK-2003] is different from our definitions, as it is an extension to the nonautonomous case.

This leads us to remark that in this thesis generalisation to equations like

$$\dot{u} = -A(u)u + V(u) \qquad \text{E.1.34}$$

does not bring in new definitions of any concepts; this is not surprising at all, as most of the times the same differential equation can be expressed either as E.1.34 or as E.1.31; this is a matter of choice and convenience. On the other hand, a nonautonomous differential equation corresponds to a completely different problem, of a completely different nature.

Another interesting paper is the one by Shao in [65-SHA-1998]. This paper was published in 1998; it deals with an equation very similar to E.1.34. Nevertheless, the conditions assumed in [65-SHA-1998] are different from those we deal with.

The setting of the differential equations for the dynamics studied in [65-SHA-1998] are as follows:

- there are two Hilbert Spaces H_1 and H_2, $u \in H_1$ and $v \in H_2$;
- H_1 can be divided into two orthogonal subspaces P and Q, where P is finite dimensional; as usual $u = (p, q)$ where $p \in P$ and $q \in Q$;
- the differential equations are

$$\begin{aligned} \dot{p} =& F(p, q, v) \\ \dot{q} =& -Cq + G(p, q, v) \\ \dot{v} =& -D(p, q)v + H(p, q). \end{aligned} \qquad \text{E.1.35}$$

- C is a positive, self-adjoint linear operator from $Q \to Q$ and generates the semigroup e^{-Ct};
- D is a uniformly positive and bounded operator on H_2, that is there exist positive constants γ and Γ such that

$$\gamma \|v\|^2 \leq \langle v, D(p, q)v \rangle \leq \Gamma \|v\|^2$$

  for all $u = (p, q) \in H_1$ and $v \in H_2$; D is also assumed to be Lipschitz in (p, q) in the operator norm;
- the functions F, G and H are all assumed to be bounded and Lipschitz.

If one now introduces the product Hilbert space $\mathcal{H} = H_1 \times H_2$, then E.1.35 might seem to be very similar to ours. In fact $P \subseteq \mathcal{H}$ and we could expect an Inertial Manifold from $P \to \mathcal{H} - P$. In such a case, we could introduce the variable $w \in \mathcal{H}$ and consider that $w = (p, y)$ where $y = (q, v)$. Thus our system

$$\begin{aligned} \dot{s} =& \epsilon g(s, \varphi) \\ \dot{\varphi} =& -B(s)\varphi + f(s, \varphi). \end{aligned}$$

would be similar to E.1.35 with $s = p, \varphi = y, \epsilon g = F$ and substituting $B(s)$ with

$$\widetilde{B}(p, y) = \begin{pmatrix} C & \mathbb{0} \\ \mathbb{0} & D(p, q) \end{pmatrix}$$

and $f(s, \varphi)$ with

$$\tilde{f} = \begin{pmatrix} G(p, q, v) \\ H(p, q) \end{pmatrix}.$$

We immediately see one difference, that is that the operator $\tilde{B}$ depends on q, and not only on the finite coordinates p. One might then hope that one could apply our theory to the generalisation, which we treat in section **2.4.4**, where we consider a family of operators like this:

$$A(u) = \begin{pmatrix} B_{ss}(s, \varphi) & B_{s\varphi}(s, \varphi) \\ B_{\varphi s}(s, \varphi) & B_{\varphi\varphi}(s, \varphi) \end{pmatrix}.$$

However, the theorem proved in [65-SHA-1998] does not prove the existence of an Inertial Manifold $\mathcal{M} : P \rightarrow \mathcal{H} - P$. It proves the existence of a Lipschitz, globally exponentially attracting manifold $\mathcal{M}$ defined as the graph of a function $\Phi : P \otimes H_2 \rightarrow H_1$. The big difference with the theorems generally proved about Inertial Manifolds is that in [65-SHA-1998] Φ and thus $\mathcal{M}$ is not finite dimensional. In fact, H_2 is only required to be a Hilbert separable space; L^2 is separable and is not finite dimensional.

The main assumption in Shao's paper is that the Strong Squeezing property holds. The method of proof is the graph transform method of Hadamard, which we will explain in the next section.

One last remark: the two examples [65-SHA-1998] and [50-KOK-2002] are the only ones we were able to trace in the literature that deal with systems different from E.1.31.

1.5.2 Methods of proof

Apart from the Lyapunov-Perron method used in this thesis, we can distinguish the following other methods:

- the graph transform method of Hadamard, used for example in [53-MAL-1988], [37-ROB-2001], [58-ROB-1993] and [65-SHA-1998];
- the Cauchy method of [25-CON-1989] and simplified in [57-ROB-1995];
- the elliptic method of [42-FAB-1991].

The following methods all apply to the evolution equation

$$\dot{u} = -Au + V(u), \tag{E.1.36}$$

though we have seen that they can be applied to generalisations.

Notice that the notion of an invariant manifold was first introduced by Lyapunov in 1892 in [34-LYA-1947], along with the method named after him. Since then, many methods have been used to prove existence of various types of invariant manifolds, as for example Centre Manifolds. These methods have been so successful that they have been adapted to prove existence of Inertial Manifolds, and these adaptations resulted in the methods that we review here. A good comparison of the various methods of proofs can be found in section 6 of the paper [58-ROB-1993], where special attention is dedicated to the use of the gap condition in the various methods of proof.

In the following we present a brief survey of methods for proving existence of Inertial Manifolds.

The graph transform method or the Hadamard method

This method is based on the idea of taking one Lipschitz manifold and following its evolution under the flow of E.1.36; if an Inertial Manifold exists, then this initial manifold will converge to the Inertial Manifold, at least under certain assumptions such as the strong squeezing property.

We reproduce closely the description of this method given in [53-MAL-1988]. The strategy for constructing the Inertial Manifold $\mathcal{M}$ in the graph transform method is the following: one begins with finite dimensional set $\mathcal{M}_0 = \mathcal{P} \times \{\mathbb{0}\}$, where $\mathcal{P}$ is the finite dimensional subspace of our Hilbert space H; let us denote the projection on $\mathcal{P}$ by P and the projection on $\mathcal{Q} = H - P$ by Q. Next one lets the dynamics of E.1.36 act on $\mathcal{M}_0$ for $t > 0$. This yields the set $\mathcal{M}_t \subseteq H$, which is defined to be the image of $\mathcal{M}_0$ under the flow at time t. One then shows that for each $t > 0$ there is a Lipschitz function $\Phi_t : \mathcal{P} \to H - \mathcal{P}$ such that $\mathcal{M}_t = \text{graph}\,(\Phi_t)$. In addition, one shows that for each t , the function Φ_t is Lipschitz, and the limit $\Phi_t \to \Phi$ as $t \to \infty$ will exist with a uniform exponential rate. The desired invariant manifold $\mathcal{M}$ will be given as the graph of this limiting function.

The geometric method or the Cauchy method

The geometric construction in [57-ROB-1995] starts by defining some set Ω as the support of the function V in E.1.36. In the case that there exists an absorbing ball for E.1.36, then clearly the dynamical system E.1.36 can be modified so that V is then zero outside of a sphere Ω of radius ρ. Then one takes the boundary of the projection of the sphere on the finite dimensional subspace $\mathcal{P} \subseteq H$, $\Gamma = \partial(\mathcal{P}\Omega)$ and the set Σ defined by

$$\Sigma = \overline{\bigcup_{t \geq 0} S(t)\Gamma}$$

where $S(t)$ is the semigroup generated by E.1.36. Σ is the closure of the union of the forward trajectories starting on Γ.

The first step is to show that Σ is the graph of a Lipschitz function. This is done using the cone condition. Σ is invariant and finite dimensional by definition. One then introduces the manifold

$$\mathcal{M} = \Sigma \cup \left\{ u : u \in \mathcal{P}, |u| \geq \rho \right\},$$

that is the union of Σ with the part of the subspace $\mathcal{P}$ that lies outside Ω. Notice that $\mathcal{M}$ is invariant by definition and is Lipschitz because so is Σ. To show that $\mathcal{M}$ is exponentially attracting one considers the set $V(u)$ given by the intersection of $\mathcal{M}$ with the complement of the invariant cone from the strong squeezing property; $V(u)$ depends on the trajectory u chosen:

$$V(u) = \left\{ v \in \mathcal{M} : |Q(v-u)| \geq |P(v-u)| \right\}.$$

$V(u)$ is a compact finite dimensional set, and then one constructs a sequence of points in $V(u)$ that approximate $u(t)$ exponentially, using the squeezing property. Notice that this method conveys easily a numerical algorithm to compute an approximation of any trajectory $u(t)$.

The elliptic regularisation method

Finally, the last method we review is the “elliptic regularisation” of [42-FAB-1991]. The elliptic regularisation method, introduced by Sacker in [63-SAC-1965], has the same starting point as the method of Lyapunov-Perron and that of Hadamard. One begins with a finite dimensional subspace $\mathcal{P} \subseteq H$ and its orthogonal $\mathcal{Q} = H - \mathcal{P}$. Then, as we have already seen, an Inertial Manifold h is the graph of a function $h : \mathcal{P} \to \mathcal{Q}$; on the one hand one has that

$$\frac{\mathrm{d}h(p(t))}{\mathrm{d}t} = -Ah(p) + QV(p, h(p))$$

and on the other that

$$\frac{\mathrm{d}h(p(t))}{\mathrm{d}t} = Dh(-Ap + PV(p, h(p))),$$

so that one can prove that h is invariant if and only if it is a solution of

$$Dh(-Ap + PV(p, h(p))) = -Ah(p) + QV(p, h(p)). \qquad \text{E.1.37}$$

The method of elliptic regularisation consists in replacing E.1.37 with

$$-\epsilon\Delta h_\epsilon + Dh_\epsilon(-Ap + PV(p, h_\epsilon(p))) + Ah_\epsilon(p) = QV(p, h_\epsilon(p)) \qquad \text{E.1.38}$$

for $\epsilon > 0$ and to construct h by taking the limit of h_ϵ as $\epsilon \to 0$. Δ is the Laplacian operator on $\mathcal{P}$, which can guarantee that E.1.38 has a unique, sufficiently regular solution.

Notice that the elliptic regularisation method can be used to give a direct approximating algorithm for the Inertial Manifold.

A comparison with the Lyapunov-Perron method

A couple of basic differences immediately catch the eye: firstly, the Hadamard and Cauchy methods are more geometric in nature, and the other two are more analytic. Secondly, the Cauchy method and the elliptic regularisation method can immediately provide numerical algorithms for computing an approximating trajectory or the Inertial Manifold itself.

The Lyapunov-Perron method shares an interesting feature with the Hadamard method. In the first method, we define an operator T in a suitable function space X of Lipschitz functions from PH to QH and we prove that it is a contraction. Being a contraction, we can choose any $h_0 \in X$ and define the iterative sequence $h_n = T(h_{n-1})$ and $h_n \to \bar{h}$, the fixed point of T. The Hadamard method follows the evolution of a particular function in X, that is the function $\tilde{h}$ defining the hyperplane PH. Thus, if we take the initial function

$h_0 = \tilde{h}$, then we would be arriving to the same Inertial Manifold, though using two different approximations. Notice that the similarity ends here, as the mapping of the operator T does not hold immediate relation to the flow of the dynamical system used in the Hadamard method.

Notice that the sequence h_n could be used to approximate the Inertial Manifold, if we were able to solve numerically the integral defining T.

1.6 Moment Closure and Inertial Manifolds in the Literature

In this second section dedicated to the literature, we review very briefly Moment Closure and Dynamical Systems techniques applied to Statistics, especially in biological modelling; we also review when the Moment Closure technique is used successfully and when not. It is important to emphasise that we do not present a review of Moment Closure as this departs from the subject of this thesis. Notice that although the study of Moment Closure functions and their relation with Dynamical Systems was first studied by Maxwell around 1866 for the kinetics theory of gas motion, there are few applications to biological models.

Moment closure approximations have been around for a very long time now; since Whittle's paper [84-WHI-1957] they have been justified, some way or the other, by referring back most of the times to some statistical properties of the system being studied. For example, in [73-ISH-2005], the author says that the good results given by the moment closure method *"can sometimes be attributed to central limit effects"*, though at the same time the normal approximation might work well even when there is no statistical justification that the population distribution is *"even approximately normal"*, as stated in [72-ISH-1995]. At the same time, as emphasised in [79-MAT-1999], there are not yet any **general** studies that *"investigate the general accuracy of the cumulant function approximations"*.

Actually, the normal approximation and Moment Closure techniques in general do not always provide good approximations. In [69-BER-1995] there are a couple of examples where Moment Closure methods give very large errors and convergence *"may not occur at all"*. For example, some moments were known to have finite value and yet according to the moment closure function they exploded even if a finite element numerical method could compute. In [81-NEW-2007] the authors study the mean and variance of the extinction time for the stochastic logistic process using and comparing a few methods, one of which is the moment closure approximation. This approximation fails to give correct predictions.

To sum up, Lloyd in [76-LLO-2004] says that *"We do not yet have a simple criterion for determining the validity of the solutions of the moment equations without recourse to generating model realisations"*. In other words, the underlying question being asked by Lloyd is the same we are concerned with. We found that it is not possible to determine a general criterion based solely on Inertial Manifolds. Notice that [76-LLO-2004] is one of the two papers where [48-STA-2001] is actually quoted, the other being [73-ISH-2005], another paper by Isham. This might just not be a coincidence, as these two authors seem to me to be making more commentaries regarding the importance of producing a rigourous statement of why some dimension reduction techniques work better than others.

A technique different from moment closure and that relies on more dynamical aspects is the aggregation technique, found for example in [68-AUG-2000]. This technique is applicable when the biological system being studied can be divided into two levels of organisation, as for example individuals and population. The individual level is more detailed, containing micro-variables, and is subject to a fast dynamics, while the population level is a slow dynamics and contains the macro-variables. The paper [68-AUG-2000] is a review of how one can obtain the population dynamics from the individual dynamics using the aggregation method. For example, Auger presents a model that investigates the effect of individual decisions of preys and predators on the global stability of the community in the long run.

What is of interest to us is that the concept of slow-fast dynamics is used here to reduce the "dimension" of the dynamical system. However, this is not a projection of the dynamics on a subspace, and thus it is not to be understood as in the theory of Inertial Manifolds. In fact, here the authors construct from a dynamical system with many micro-variables a new dynamical system with fewer variables (the macro-variables) so that the two systems are not in any functional relationship but rather *"a sort of approximate relationship can be demonstrated"*.

For a comparison of other techniques as linearisation and simulation with moment closure, one can refer to [77-MAR-2000]. Here a case is presented where local linearisation outperforms the normal approximation.

It is important to stress that though we were not able to find any reference studying the relationship between Inertial Manifolds and Moment Closure, there have been other authors that have applied nonlinear dynamical techniques to the study of complex biological stochastic systems. For example, [75-KEE-2001] studies the global attractor of the dynamics of an epidemiological model.

A review of how nonlinear dynamics techniques have been applied to a number of biological systems can be found in the introduction in [82-ROH-2002]. In this paper, deterministic and stochastic effects are identified; the deterministic ones are shown to move the dynamics towards the attractor, whilst the stochastic ones move it away from it. In

[70-CUS-1998] a population dynamics is shown to have a stable manifold and an unstable one.

1.7 A short conclusion

Recapitulating, whilst on the one hand the normal approximation is not always a good approximation, on the other hand we present an example where it is a good approximation because it is related to Inertial Manifolds.

Summing up these facts, we feel that one general, broad conclusion we might draw from this research is that, instead of studying whether the normal approximation is good or not for a particular example, a more appropriate way of finding a simplification of the problem, at least from a dynamical point of view, would be to study the existence of an Inertial Manifold for that particular problem.

Furthermore in this thesis we have shown that, in order to check existence of an Inertial Manifold, one might use the gap condition or a generalisation of it, and depending on how one decides to represent the differential equation, the gap condition might be verified or not. That is, we have presented the scientists with a broader choice for modelling their problems from Nature, and thus more ways of studying the existence of an Inertial Manifold for a particular problem.

Chapter 2

Gap Junctions a generalisation

From a model arising from cell-to-cell communication, we present a generalisation of a theorem of existence of Inertial Manifold for such dynamical systems as $\dot{u} = -A(u)u + V(u)$. Examples and applications to the biological system are also described, as well as a elucidation on the role of the Gap Condition and the Strong Squeezing Property.

2 Gap Junctions: a generalisation

In this chapter of the thesis, we shall investigate the existence of an Inertial Manifold in a dynamical system derived from the study of a network of biological cells. We shall use the Lyapunov-Perron method applied to a very general class of systems of the form

$$\dot{u} = -A(u)u + V(u), \qquad \text{E.2.1}$$

where $A(u)$ is a family of bounded, positive linear operators in a Hilbert space. We do have to stress the fact that in the literature, Inertial Manifolds are studied nearly only for the case of a constant bounded linear operator, that is for the equation $\dot{u} = -Au + V(u)$; nevertheless, the semigroup (or rather the evolution operator) of an equation like E.2.1 is studied in [20-PAZ-1983] and [18-AHM-1991].

Effective intercellular communication is essential for the proper functioning of any multicellular organism. In many tissues, an important intercellular link is provided by the exchange of ions and small molecules through such junctions. In this fashion, biological signals may be relayed from one cell to a distant neighbour via a chain of intervening cells and gap junctions. Gap junctions are dynamic structures whose permeability is sensitive to changes in the configuration of neighbouring cells. In particular, many types of gap junction respond to changes in electrical potential, tending to become more impermeable as the potential across the junction is increased. Furthermore, such changes are not instantaneous, but generally occur with an exponential transient. It is possible to measure such changes experimentally, but only in isolated cells, or pairs of cells. Given such information, it is difficult to predict directly the behaviour of even a moderate number of coupled cells. To address such questions requires the development of mathematical models of such networks of cells. A class of such models has been previously developed in [1-BAI-1997], based on detailed data taken from electrophysiological experiments carried out on early Xenopus embryos. These describe the movement of chemical species through gap junctions linking the cells that make up the embryo. As it was done in the original paper [47-IAN-1998], we shall restrict ourselves to the case of a single chemical species, but the generalisation to an arbitrary number is straightforward. The concentration of the chemical species in each cell is denoted by a vector φ and the configuration of various gap junctions by a vector s.

The dynamics of these two variables is coupled and may be written in the form

$$\begin{aligned} \dot{s} &= \epsilon g(s, \varphi) \\ \dot{\varphi} &= -B(s)\varphi + w. \end{aligned} \qquad \text{E.2.2}$$

Here, g represents the dynamic response of the junctions to changes in the state of adjoining cells, $B(s)$ is a positive definite matrix representing the permeabilities of the gap junctions and w is a constant vector representing the membrane resting potentials of the cells. In the case of Xenopus embryo the dynamics of the gap junctions are much slower than that of the chemical concentrations of small ions and hence ϵ is small; see section **2.6.2** for detailed numerical values of the biological constants.

If we hold s fixed (i.e. set $\epsilon = 0$), it is clear that φ will converge to a unique globally attracting equilibrium $\varphi^\star(s)$. The principal aim of this section of the thesis and of the published paper on the same subject [47-IAN-1998] is to investigate the behaviour of the system when we incorporate the dynamics of s. This falls within the realms of singular perturbation theory, and since we are interested in global results it is most appropriate to use the techniques of geometric singular perturbation theory; see [27-FEN-1971], [28-FEN-1979], [38-SAK-1990]. Recall that these are based on the concept of Normal Hyperbolicity. In particular, one can prove that, under certain conditions, the graph of $\varphi^\star$ is a normally hyperbolic invariant manifold and hence persists for small perturbations. Hence the system E.2.2 for small ϵ has an attracting invariant manifold $\mathcal{M}$, which is the graph of a function $\varphi^\star$.

Suppose that $\mathcal{M}$ is in fact globally attracting so that all trajectories converge to it. Then the asymptotic dynamics of E.2.2 can be reduced to the dynamics on $\mathcal{M}$, which can be written in terms of s only:

$$\dot{s} = \epsilon g(s, \varphi_\epsilon^\star(s)).$$

The function $\varphi_\epsilon^\star$ then "slaves" the dynamics of φ to that of s. After an initial transient during which φ rapidly converges to $\varphi_\epsilon^\star$, the dynamics of the whole system is therefore determined by the dynamics of the gap junctions. This suggests that perhaps rather than the conventional view of cells coupled by gap junctions, we should think of the system as gap junctions coupled by cells.

Unfortunately, for our purposes, there would be two drawbacks if we were to choose an approach based on Normal Hyperbolicity or Singular Perturbation Theory such as Tikhonov theorem. Firstly, since this is a local theory, none of the standard theorems address the question of whether or not $\mathcal{M}$ is globally attracting. In fact, for our particular system, this is easy to verify once $\mathcal{M}$ has been constructed. More seriously, such standard results do not give any explicit estimates of the size of ϵ required to ensure the existence of $\mathcal{M}$. This makes it impossible to confirm whether such an invariant manifold exists for physiologically relevant parameter values. One could, in principle, refine the proofs of such theorems to keep track of the sizes of relevant quantities and hence obtain the required estimates. In practice, this is not an attractive proposition.

A more promising approach, and the one adopted here, is to apply techniques from the theory of Inertial Manifolds. Recall that an Inertial Manifold is defined to be a globally attracting invariant manifold. It is normally constructed as the graph of a function from one subset of variables to another, and hence, as described in the chapter **1**, represents a "slaving" principle between these subsets. Inertial Manifolds have been the subject of intense interest in recent years, especially in the 80s and 90s, particularly in the context of certain classes of partial differential equations, where they permit the reduction of the asymptotic dynamics to finite dimensions; see [23-CAR-1981], [44-FOI-1988], [32-HEN-1981], [49-JON-1996] and [57-ROB-1995] and the review in [67-TEM-1990]. Note also that, usually an Inertial Manifold determines the dynamics of the whole system, in the sense that for any trajectory v in the phase-space there exists a trajectory v_m on the manifold which exponentially attracts ν. This property is known as exponential tracking or asymptotic completeness (see [60-ROB-1996] and section **2.4.3**).

Although the construction of Inertial Manifolds is closely related to the proofs of persistence of normally hyperbolic manifolds (and indeed of most other classes of invariant manifolds) the assumptions made are normally somewhat stronger, leading to simpler proofs. The framework for such results is usually that of a general evolution equation on a Hilbert space

$$\dot{u} = -Au + V(u), \qquad \text{E.2.3}$$

where A is a positive linear operator and V a Lipschitz function. A common hypothesis used to prove the existence of an Inertial Manifold for such a system is the so-called "gap condition".

As we saw in the introductory section 1.4.1, the main result in this section of the thesis is therefore the generalisation of standard techniques to show that systems of the form

$$\begin{pmatrix} \dot{s} \\ \dot{\varphi} \end{pmatrix} = -\begin{pmatrix} \mathbb{0} & \mathbb{0} \\ \mathbb{0} & B(s) \end{pmatrix} \begin{pmatrix} s \\ \varphi \end{pmatrix} + \begin{pmatrix} \epsilon g(s,\varphi) \\ f(s,\varphi) \end{pmatrix} \qquad \text{E.2.4}$$

possess an Inertial Manifold if ϵ and the Lipschitz constant of f are small by comparison to the smallest eigenvalue of $B(s)$. Since in our biological model E.2.4, $f = w$ which is constant, this immediately implies the existence of an Inertial Manifold for this system for small ϵ. Furthermore, we shall give explicit estimates of the size of ϵ. We have then substituted the linear operator A in E.2.3 with a family $A(s)$ of linear operators:

$$A(s) = \begin{pmatrix} \mathbb{0} & \mathbb{0} \\ \mathbb{0} & B(s) \end{pmatrix} \qquad \text{E.2.5}$$

Before proving the main theorem of existence of the Inertial Manifold, we describe in the next section the biological model originally presented in [1-BAI-1997].

2.1 The biological model

The biological model developed in [1-BAI-1997] describes the movement of an arbitrary number of chemical species throughout a network of M cells connected by gap junctions. Here we shall restrict ourselves to a single species, and denote its electrochemical potential in the k^{th} cell by φ_k. Cells are connected by gap junction channels. In the model, each such channel is controlled by gates which may be open or closed. It is assumed that each gap junction has the same number N of gating configurations. Denote by s^i_{lk} the fraction of gap junction channels connecting cells l and k which are in state i. The probability per unit time of the transition from state i to state j is given by α^{ij}. This is assumed to depend on the difference $\varphi_l - \varphi_k$ of the electrochemical potentials of the chemical species in cells l and k. The dynamics of gating states may then be expressed as

$$\frac{\mathrm{d}}{\mathrm{d}t} s^j_{lk} = \sum_{i=1}^{N} \left(\alpha^{ij}(\varphi_l - \varphi_k) s^i_{lk} \right) - \left[\sum_{i=1}^{N} \alpha^{ji}(\varphi_l - \varphi_k) \right] s^j_{lk}. \qquad \text{E.2.6}$$

Since $\sum_{i=1}^{N} s^i_{lk} = 1$, we can eliminate one of the gating states from the dynamics, and write E.2.6 in the form

$$\frac{\mathrm{d}}{\mathrm{d}t} s = b(\varphi) - \tilde{g}(\varphi) s, \qquad \text{E.2.7}$$

where both $\tilde{g}$ and b depend on the potential φ via the difference $\varphi_l - \varphi_k$ between cells labled l and k. In fact

$$\begin{aligned} \sum_{i=1}^{N} \left(\alpha^{ij}(\varphi_l - \varphi_k) s^i_{lk} \right) = & \sum_{i=1}^{N-1} \left(\alpha^{ij}(\varphi_l - \varphi_k) s^i_{lk} \right) \\ & + \alpha^{Nj}(\varphi_l - \varphi_k) s^N_{lk} \\ = & \ \alpha^{Nj}(\varphi_l - \varphi_k) \\ & + \sum_{i=1}^{N-1} \left[\alpha^{ij}(\varphi_l - \varphi_k) - \alpha^{Nj}(\varphi_l - \varphi_k) \right] s^i_{lk}. \end{aligned}$$

Define now $b(\varphi)$ as the vector function with elements $b_j(\varphi) = \alpha^{Nj}(\varphi_l - \varphi_k)$ and $\tilde{g}(\varphi)$ as the matrix with elements $\tilde{g}_{ij}(\varphi) = \alpha^{ij}(\varphi_l - \varphi_k) - \alpha^{Nj}(\varphi_l - \varphi_k)$; this lets us finally write the system E.2.6 as E.2.7.

Turning now to the dynamics of φ, this is given by

$$C_k \frac{\mathrm{d}}{\mathrm{d}t} \varphi_k = I^g_k + I^m_k + I^p_k,$$

where C_k is a generalisation of capacitance; I_k^g indicates the flux through the gap junction, I_k^m through the membrane and I_k^p through the active pumping. The last of these is assumed to be constant and I_k^m is given by $-\rho_k(\varphi_k - \tilde{\varphi})$, where ρ_k is the permeability of the membrane in cell k and $\tilde{\varphi}$ is the constant uniform extracellular electrochemical potential. Finally

$$I_k^g = \sum_{l \in N_k} P_{lk}(\varphi_l - \varphi_k),$$

where P_{lk} is the permeability of the gap junction channels connecting cells l and k and N_k, is the set of indices of cells connected to cell k. This is given by

$$P_{lk} = \sum_{i=1}^{N} \rho_{lk}^i s_{lk}^i,$$

where ρ_{lk}^i is the permeability of state i. Combining these equations gives

$$\begin{aligned} \dot{s} &= b(\varphi) - \tilde{g}(\varphi)s \\ \dot{\varphi} &= -B(s)\varphi + w, \end{aligned} \qquad \text{E.2.8}$$

where the matrix B has components

$$B_{kl} = \begin{cases} -\dfrac{P_{lk}}{C_k} & \text{if } l \neq k \\ \dfrac{\rho_k}{C_k} + \displaystyle\sum_{j \in N_k} \dfrac{P_{jk}}{C_k} & \text{if } l = k \end{cases}$$

and w is a constant vector given by

$$w_k = \frac{\rho_k \tilde{\varphi} + I_k^p}{C_k}.$$

In our biological model all cells are identical. This means that the capacitance is the same, i.e. $C_k = C$. On the other hand, if a gap junction connects cell l and cell k, then the permeability P_{lk} must be equal to P_{kl}; this follows from the definition of P_{lk}. Though these two facts make the matrix B symmetric, we shall only use the fact that this matrix is positive definite. Indeed the fact that B is symmetric is never used anywhere in the proof of our main theorem; we only use it to show that the particular biological system from which we started our investigation satisfies all the hypothesis of our theorem, including the fact that B is positive definite.

2.2 The functional settings

Rewriting the system E.2.8 in the form

$$\begin{pmatrix} \dot{s} \\ \dot{\varphi} \end{pmatrix} = -\begin{pmatrix} \mathbb{0} & \mathbb{0} \\ \mathbb{0} & B(s) \end{pmatrix}\begin{pmatrix} s \\ \varphi \end{pmatrix} + \begin{pmatrix} \epsilon g(s,\varphi) \\ w \end{pmatrix},$$

where w is still a constant, allows us to introduce the variable $u = (s, \varphi)$ in the space $\mathbb{R}^{n+m}$, where n is the dimension of s and m of φ. Although $\mathbb{R}^{n+m}$ is a finite dimensional space, we shall work under the assumption that u belongs to a general Hilbert space, possibly infinite. In fact our proof is completely valid in a general Hilbert space; the most important fact is that this general Hilbert space can be divided into two orthogonal spaces, one being finite, corresponding in our case to the space of s, and that dominates the whole dynamics. The fact that the space spanned by the first eigenvalues dominates the whole dynamics is actually included in the so called "gap condition", or the similar condition we are dealing with.

The functional settings for this chapter are then the following. Let H be a Hilbert space, and let $u \in H$. Let $A(u)$ be a family of linear bounded operators from H to H; this means that for each $u \in H$, $A(u)$ is a bounded linear operator. We assume that A is Lipschitz with respect to u and thus continuous. Let V be a Lipschitz bounded function from H to H.

We can split the space H into two orthogonal subspaces $H' = PH$ and $QH = H - PH$. We denote s the elements of H' and φ the elements of QH. H' is finite dimensional and QH may be infinite dimensional, though this is not required by the biological model in [1-BAI-1997].

We now consider the system of the form

$$\dot{u} = -A(u)u + V(u). \qquad \text{E.2.9}$$

In our particular case we have

$$A(u) = \begin{pmatrix} \mathbb{0} & \mathbb{0} \\ \mathbb{0} & B(s) \end{pmatrix} \qquad \text{E.2.10}$$

and

$$V(u) = \begin{pmatrix} \epsilon g(s,\varphi) \\ w \end{pmatrix}.$$

Note that in our case $A(u)$ depends only on the first dimensions, so that the division of the space H into two looks natural. Also, in general the second component of $V(u)$ is not a constant but a function:

$$V(u) = \begin{pmatrix} \epsilon g(s,\varphi) \\ f(s,\varphi) \end{pmatrix}.$$

In the reminder of this chapter we shall use the following notation for norms.

- $|\cdot|$ is the norm in H, $|u|_H = |s|_{PH} + |\varphi|_{QH}$. We drop the subscripts, as always $|s|$ is a norm in the finite subspace PH and $|\varphi|$ is always the norm in QH.
- $\|\cdot\|$ is an operator norm, that is, it is always associated to the norm of an operator in a function space. The subscript will indicate to which function space we refer, when confusion may arise.

2.3 Preliminary results

In this section we present a series of results that we shall need during the course of the proof.

- First of all, we assume that an absorbing ball exists. We shall prove this result for our particular biological model in **2.6.1**.
- Secondly, we show how we can modify our system outside the absorbing ball, in such a way that we can follow trajectories backwards in time. In other words, we study a different system that coincides with the original one inside the absorbing ball and has nice properties outside. Thus the Inertial Manifold for the modified system coincides with an Inertial Manifold for the original one inside the absorbing ball.
- Finally, we define the evolution operator $U_s(t,\tau)$, study some of its properties, prove that it is C^1 and that our biological system admits a well-defined evolution operator.

2.3.1 The cut-off function

In order to prove the existence of an Inertial Manifold, we need to follow trajectories backwards in time. In doing so, trajectories leave the absorbing ball. Unfortunately, we have little control over the system outside this region. We therefore follow the standard approach of modifying the system using a cut-off function outside the absorbing ball in such a way that f and g are globally bounded and Lipschitz, and so that B is positive definite everywhere. The system is not modified inside the absorbing ball and hence an Inertial Manifold for the modified system is also an Inertial Manifold for the original system in the absorbing ball, as required. Unfortunately, we cannot use the standard cut-off function, since this would modify the inequality for ϵ given in the statement of the theorem. Instead, we proceed as follows.

Let r_s be the radius of the absorbing ball on the coordinate s and r_φ the radius on the coordinate φ; given $\delta > 0$ we can always find a function $\psi_s(s)$ such that

$$\psi_s(s) = \begin{cases} s & \text{if } |s| \leq r_s \\ \text{smooth, increasing} & \text{if } r_s \leq |s| \leq r_s + 2\delta \\ r_s + \delta & \text{if } |s| \geq r_s + 2\delta \end{cases}$$

We can also find a function $\psi_\varphi(\varphi)$ which is defined similarly for φ, using the same δ. We choose the smooth parts in such a way that all these functions have Lipschitz constants equal to 1.

We now define a modified system using

$$\begin{aligned} \tilde{f} &= f(\psi_s(s), \psi_\varphi(\varphi)) \quad \text{instead of} \quad f(s,\varphi), \\ \tilde{g} &= g(\psi_s(s), \psi_\varphi(\varphi)) \quad \text{instead of} \quad g(s,\varphi), \\ \tilde{B} &= B(\psi_s(s)) \quad \text{instead of} \quad B(s). \end{aligned}$$

Denote the compact set where $|s| \leq r_s + 2\delta$ and $|\varphi| \leq r_\varphi + 2\delta$ by $\Omega(\delta)$. Let $F(\delta)$ and $G(\delta)$ be the maxima of f and g on $\Omega(\delta)$ and $b(\delta)$ the largest b satisfying $\left|\varphi^T B(s)\varphi\right| > b\,|\varphi|^2$ on $\Omega(\delta)$. Similarly, let $\tilde{F}(\delta)$, $\tilde{G}(\delta)$, $\tilde{b}(\delta)$ be analogous maxima for the modified system on the whole of H. Since $|\psi_s(s)| \leq |s|$ and $\left|\psi_\varphi(\varphi)\right| \leq |\varphi|$, it is clear that $F(\delta) = \tilde{F}(\delta)$, $G(\delta) = \tilde{G}(\delta)$ and $b(\delta) = \tilde{b}(\delta)$. Furthermore, $F(\delta)$, $G(\delta)$ and $b(\delta)$ are continuous in δ and hence $\tilde{F}(\delta) \to F(0) = F$ as $\delta \to 0$, and similarly for $\tilde{G}(\delta)$ and $\tilde{b}(\delta)$.

Next, let $\theta(\delta)$ be the Lipschitz constant for f on $\Omega(\delta)$ and $\tilde{\theta}(\delta)$ be the corresponding constant for $\tilde{f}$ on the whole of $\mathbb{R}^n$. Note that

$$\left|D_s\tilde{f}(s,\varphi)\right| = \left|D_s f(\psi_s(s), \psi_\varphi(\varphi))\right| |D_s\psi_s(s)| \leq \left|D_s f(\psi_s(s), \psi_\varphi(\varphi))\right|,$$

where D_s is the derivation operator with respect to s and similarly for differentiation with respect to φ. Since the Lipschitz constant is the maximum of the derivatives with respect to s and φ, it is clear that $\tilde{\theta}(\delta) \leq \theta(\delta)$. On the other hand, since f and $\tilde{f}$ are identical on $\Omega(0)$, we have $\theta(0) \leq \tilde{\theta}(\delta)$. Finally $\theta(\delta)$ is continuous in δ, and hence $\tilde{\theta}(\delta) \to \theta(0) = \theta$ as $\delta \to 0$. Similarly, if we define $\gamma(\delta)$ and $\tilde{\gamma}(\delta)$ as the corresponding Lipschitz constants for g and $\tilde{g}$ respectively, we get $\tilde{\gamma}(\delta) \to \gamma$ as $\delta \to 0$. The same argument also applies to β.

We can now proceed as follows. We shall show that if for some δ the modified system satisfies

$$\epsilon \leq \frac{k\tilde{b}(\delta)}{2\tilde{\gamma}(\delta)} \frac{(1-k)^2\tilde{b}(\delta)^2 - 2(1-k)\tilde{b}(\delta)\tilde{\theta}(\delta)}{\tilde{\beta}(\delta)\tilde{F}(\delta) + (1-k)^2\tilde{b}(\delta) - (1-k)\tilde{b}(\delta)\tilde{\theta}(\delta)}, \qquad \text{E.2.11}$$

then it possesses an Inertial Manifold $\mathcal{M}(\delta)$. Since the original and the modified systems are the same inside the absorbing ball, we can conclude that there exists an Inertial Manifold $\mathcal{M}'$ for the unmodified system, equal to $\mathcal{M}(\delta)$ inside the absorbing ball. But the right-hand side of E.2.11 is continuous at $\delta = 0$ and hence if ϵ satisfies

$$\epsilon < \frac{kb}{2\gamma} \frac{(1-k)^2 b^2 - 2(1-k)b\theta}{\beta F + (1-k)^2 b^2 - (1-k)b\theta} \qquad \text{E.2.12}$$

then it satisfies E.2.11 for all sufficiently small $\delta > 0$. Hence, if E.2.12 is satisfied, the unmodified system has an Inertial Manifold in the absorbing ball, as required. Note that the Inertial Manifolds $\mathcal{M}(\delta)$ for different δ are not necessarily identical (which is why the Inertial Manifold $\mathcal{M}'$ is not necessarily unique), so we do not try to take the limit of the $\mathcal{M}(\delta)$ as $\delta \to 0$. Instead we just pick one fixed δ which is sufficiently small.

We will continue by proving the theorem for the modified system, but without using the $\tilde{f}$ notation; i.e. we drop the tilde for notational convenience.

2.3.2 The evolution operator: definition

Before we continue, we shall introduce the evolution operator associated to the matrix $C_s(t) = -B(s(t))$, which appears in equation E.1.19 (page 30):

$$\dot{\varphi} = -B(s_{s_o,h})\varphi + f(s_{s_o,h}, h(s_{s_o,h})).$$

We will follow the notations and methods in [18-AHM-1991] and [20-PAZ-1983]; although in the original paper [47-IAN-1998] we restricted our discussion to the finite dimensional case, in this thesis we will use the same arguments adapted to a general Hilbert space.

The evolution operator is the generalisation of a semigroup of operators to the case in which the generator depends on time, say via a function of time, such as the solution of the system itself. That is, given $s(t)$ any function of the time t and given the equation defined in the Hilbert space H

$$\begin{aligned} \dot{y} &= C_s(t)y \\ y(\tau) &= z \end{aligned} \qquad \text{E.2.13}$$

the evolution operator might be defined as the solution $y(t) = U_s(t,\tau)z$ of the above system.

More formally, let $C_s(t)$ be a family of operators depending on time t and on a bounded, Lipschitz function $s(t)$, such that, for each time t and for each bounded, Lipschitz function $s(t)$, $C_s(t)$ is the infinitesimal generator of a continuous semigroup $S_{t,s}(\tau)$ on the space H.

We note now that in the original paper [47-IAN-1998] we cited incorrectly some results from the books [18-AHM-1991] and [20-PAZ-1983] to prove a series of results on the evolution operator $U_s(t,\tau)$, especially the Lipschitz property of U. We explain this incorrect interpretation in detail.

On the one hand, we interpreted correctly that the operator $C_s(t)$ does not depend on the variable y: if we recapitulate the procedure we follow in the proof, we first find a solution $s_{s_0,h}(t)$ to the inertial form:

$$\dot{s} = \epsilon g(s, h(s)), \tag{E.2.14}$$

and then we plug this function of time into

$$\dot{\varphi} = -B(s_{s_o,h})\varphi + f(s_{s_o,h}, h(s_{s_o,h})); \tag{E.2.15}$$

at this point it is clear that we are interested in an evolution operator which depends only upon time and not on the variable of the differential equation. That is, $-B(s_{s_o,h})$ depends on time through the function of time $s(t)$ and not on φ.

On the other hand, we were mislead by the presence of s in the definition of $B(s)$ and we quoted lemma 5.3.10 in [18-AHM-1991], page 176. This theorem refers to an evolution operator associated to the differential equation

$$\dot{x} = C(t,x)x + f(t,x),$$

and here the operator C depends both on time and on the variable. We have seen this is not our case.

In our case the operator C depends on time through a function: $C = C(s(t))$. This means that, though we can still use all those results proved in [18-AHM-1991] and [20-PAZ-1983] for operators depending only on time, we will have to provide an original proof for those results that use explicitly the dependency of C on a function of time:

- the evolution operator U_s is Lipschitz with respect to s,
- the evolution operator U_s is differentiable with respect to s.

2.3.3 The evolution operator: properties

In this section we consider the operator $C_s(t)$ as a family of operators depending on time t, each being the infinitesimal generator of a continuous semigroup $S_{t,s}(\tau)$ on the space H. Suppose that there exist two real numbers $M \geq 1, \omega \in \mathbb{R}$ such that the resolvents of the family $\{C_s(t)\}$ contain the set (ω, ∞) for every (t, s) and if for every finite non-decreasing sequence $0 \leq t_1 \leq \ldots \leq t_n \leq T$ the norm of the product

$$\prod_{j=1}^{n} S_{t_j, s(t_j)}(\tau_j) \leq M \exp\left\{\omega \sum_{j=1}^{n} \tau_j\right\} \qquad \text{E.2.16}$$

whenever the τ_j are positive; then there exists an operator valued function $U_s(t, \tau)$, sometimes called the evolution operator associated to C_s, such that $U_s(t,t) = \mathbb{I}$, where $\mathbb{I}$ is the identity operator, and $U_s(t,r)U_s(r,\tau) = U_s(t,\tau)$, as one would expect from the fact that $U_s(t,\tau)$ is the 'solution' of E.2.13.

Let us recall that the resolvent set of an operator A is the set of all those λ such that the operator $\lambda\mathbb{I} - A$ is invertible. Also, if $T(t)$ is the semigroup generated by A, then the inverse $R(\lambda)$ of $\lambda\mathbb{I} - A$ is given by

$$R(\lambda)x = \int_0^\infty e^{-\lambda t} T(t) x \mathrm{d}t, \qquad \text{E.2.17}$$

where x is any element of the Hilbert space over which A is defined.

Under these assumptions, theorem 5.2.26 (page 163) of [18-AHM-1991] and theorem 3.1 (page 135) of [20-PAZ-1983] prove that if for every time such that $0 \leq \tau \leq t \leq T < \infty$ the operator C_s is strongly continuous, then there exist a unique evolution operator U_s for the equation E.2.13, which also admits a unique solution $y(t) = U_s(t,\tau)z$, and the evolution operator satisfies the following properties:

$$\|U_s(t,\tau)\| \leq M \exp\{\omega(t-\tau)\}, \qquad \text{E.2.18}$$

$$\frac{\partial}{\partial t} U_s(t,\tau) = C_s(t) U_s(t,\tau), \qquad \text{E.2.19}$$

$$\frac{\partial}{\partial \tau} U_s(t,\tau) = -U_s(t,\tau) C_s(\tau). \qquad \text{E.2.20}$$

Clearly the fact that $C_s(t)$ depends upon time through a function $s(t)$ is irrelevant.

2.3.4 The evolution operator: Lipschitz

We shall now consider the fact that the operator C_s depends on time through a function of time. We are interested in studying how the evolution operator U_s varies when s changes. We shall prove a sort of Lipschitz condition on the evolution operator, as stated in the following Lemma.

LEMMA L.2.1 *If the operator C_s is Lipschitz with respect to s with Lipschitz constant ζ, then*

$$\left\| U_{s_1}(t,\tau) - U_{s_2}(t,\tau) \right\| \leq M^2 \zeta e^{\omega(t-\tau)} \int_\tau^t |s_1(\sigma) - s_2(\sigma)| \, d\sigma. \qquad \text{E.2.21}$$

Proof The proof is very simple. First of all, thanks to E.2.19 and E.2.20, the following holds:

$$\frac{\partial}{\partial \sigma}\Big[U_{s_1}(t,\sigma)U_{s_2}(\sigma,\tau)\Big] = U_{s_1}(t,\sigma)\Big[-C_{s_1}(\sigma) + C_{s_2}(\sigma)\Big]U_{s_2}(\sigma,\tau).$$

If we now integrate the left hand side of this equation between τ and t, we obtain that

$$\begin{aligned}\int_\tau^t \frac{\partial}{\partial \sigma}\Big[U_{s_1}(t,\sigma)U_{s_2}(\sigma,\tau)\Big] \mathrm{d}\sigma &= U_{s_1}(t,t)U_{s_2}(t,\tau) - U_{s_1}(t,\tau)U_{s_2}(\tau,\tau) \\ &= U_{s_2}(t,\tau) - U_{s_1}(t,\tau).\end{aligned}$$

Now we can take the norm of this expression:

$$\begin{aligned}\left\| U_{s_1}(t,\tau) - U_{s_2}(t,\tau) \right\| \leq & \int_\tau^t \left\| \frac{\partial}{\partial \sigma}\Big[U_{s_1}(t,\sigma)U_{s_2}(\sigma,\tau)\Big] \right\| \mathrm{d}\sigma \\ = & \int_\tau^t \left\| U_{s_1}(t,\sigma)\Big[-C_{s_1}(\sigma) + C_{s_2}(\sigma)\Big]U_{s_2}(\sigma,\tau) \right\| \mathrm{d}\sigma \\ & \text{using E.2.18} \\ \leq & \int_\tau^t M e^{\omega(t-\sigma)} M e^{\omega(\sigma-\tau)} \left\| C_{s_1}(\sigma) - C_{s_2}(\sigma) \right\| \mathrm{d}\sigma \\ \leq & M^2 e^{\omega(t-\tau)} \int_\tau^t \zeta \, |s_1(\sigma) - s_2(\sigma)| \, \mathrm{d}\sigma.\end{aligned}$$

With this, the proof is complete.

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2.3.5 The evolution operator: differentiability

In this section we shall show an original result regarding the differentiability of U_s, not included in neither [18-AHM-1991] nor [20-PAZ-1983].

LEMMA L.2.2 *If C_s is Fréchet differentiable with respect to s so is $U_s(t,\tau)$ and its derivative is given by*

$$\frac{\partial}{\partial s}U_s(t,\tau)\delta = \int_\tau^t U_s(t,\sigma)\frac{\partial}{\partial s}C_s(\sigma)\delta U_s(\sigma,\tau)\mathrm{d}\sigma. \qquad \text{E.2.22}$$

Proof First of all, as we saw in the previous lemma

$$\frac{\partial}{\partial\sigma}\Big[U_{s+\delta}(t,\sigma)U_s(\sigma,\tau)\Big] = U_{s+\delta}(t,\sigma)\Big[C_s(\sigma) - C_{s+\delta}(\sigma)\Big]U_s(\sigma,\tau).$$

Integrating it over the interval $[\tau, t]$ and multiplying both sides by -1:

$$U_{s+\delta}(t,\tau) - U_s(t,\tau) = \int_\tau^t U_{s+\delta}(t,\sigma)\Big[C_{s+\delta}(\sigma) - C_s(\sigma)\Big]U_s(\sigma,\tau)\mathrm{d}\sigma. \qquad \text{E.2.23}$$

By definition of Fréchet differentiability, we now want to show that the following norm goes to zero as $\|\delta\|$ goes to zero

$$\left\| U_{s+\delta}(t,\tau) - U_s(t,\tau) - \frac{\partial}{\partial s}U_s(t,\tau)\delta \right\| |\delta|^{-1}.$$

To do this, we first use the above formula for $U_{s+\delta}(t,\tau) - U_s(t,\tau)$, and then add and subtract the term $\int U_{s+\delta}(t,\sigma)\frac{\partial}{\partial s}C_s(\sigma)\delta U_s(\sigma,\tau)$. So we obtain the following chain of inequalities:

$$\begin{aligned}
&\left\| U_{s+\delta}(t,\tau) - U_s(t,\tau) - \frac{\partial}{\partial s}U_s(t,\tau)\delta \right\| \|\delta\|^{-1} \\
&= |\delta|^{-1} \left\| \int_\tau^t \Big[U_{s+\delta}(t,\sigma)C_{s+\delta}(\sigma) - U_{s+\delta}(t,\sigma)C_s(\sigma)\Big]U_s(\sigma,\tau) \right. \\
&\qquad \left. - U_s(t,\sigma)\frac{\partial}{\partial s}C_s(\sigma)\delta U_s(\sigma,\tau)\mathrm{d}\sigma \right\| \\
&\le M\,|\delta|^{-1}\int_\tau^t \left\| U_{s+\delta}(t,\sigma)C_{s+\delta}(\sigma) - U_{s+\delta}(t,\sigma)C_s(\sigma) \right. \\
&\qquad \left. - U_{s+\delta}(t,\sigma)\frac{\partial}{\partial s}C_s(\sigma)\delta \right\| e^{\omega(\sigma-\tau)}\mathrm{d}\sigma \\
&\quad + M\,|\delta|^{-1}\int_\tau^t \left\| U_{s+\delta}(t,\sigma)\frac{\partial}{\partial s}C_s(\sigma)\delta - U_s(t,\sigma)\frac{\partial}{\partial s}C_s(\sigma)\delta \right\| e^{\omega(\sigma-\tau)}\mathrm{d}\sigma
\end{aligned}$$

$$\leq \quad M\,|\delta|^{-1}\int_{\tau}^{t}\|U_{s+\delta}(t,\sigma)\|\left\|C_{s+\delta}(\sigma)-C_s(\sigma)-\frac{\partial}{\partial s}C_s(\sigma)\delta\right\|e^{\omega(\sigma-\tau)}\mathrm{d}\sigma$$
$$+\,M\,|\delta|^{-1}\int_{\tau}^{t}\|U_{s+\delta}(t,\sigma)-U_s(t,\sigma)\|\left\|\frac{\partial}{\partial s}C_s(\sigma)\delta\right\|e^{\omega(\sigma-\tau)}\mathrm{d}\sigma.$$

It is clear at this point that as U_s is continuous with respect to s and C_s is Fréchet differentiable with respect to s, the above norm goes to zero as $\|\delta\|\to 0$ and the theorem holds.

//////

We also note that the norm of the derivative of U_s is bounded by

$$M^2 e^{\omega(t-\tau)}\left\|\frac{\partial C_s}{\partial s}\right\|(t-\tau). \qquad \text{E.2.24}$$

2.3.6 The evolution operator of our system

In this section we shall show that the theory just described can be applied to our problem by identifying $C_s(t) = -B(s(t))$. We shall prove that indeed for any function $s(t)$ the hypothesis defined in 2.3.3holds with $M = 1$, $\omega = -b$ and $\zeta = \beta$.

First of all, we use theorem 5.1 at page 127 of [20-PAZ-1983] to show that indeed $C_s(t) = -B(s(t))$ is the infinitesimal generator of an evolution operator. The only conditions for this to be true is that for every t, $C_s(t)$ is a bounded linear operator, which is true, and that the function $t \to C_s(t)$ be continuous in the uniform operator topology.

This is true if for every $\epsilon > 0$ there exists a $\delta > 0$ such that for every $|\tau| < \delta$ we have that $\|C_s(t+\tau) - C_s(t)\| < \epsilon$. B being by hypothesis Lipschitz, one has

$$\|C_s(t+\tau)-C_s(t)\| = \|B(s(t+\tau))-B(s(t))\| \leq \beta\,|s(t+\tau)-s(t)|$$

where β is the Lipschitz constant of B; thanks to the fact that s is continuous in time, one has that $C_s(t)$ is continuous in the uniform operator topology.

Now we want to show that the resolvent of $C_s(t) = -B(s(t))$ is contained in the set $(-b,\infty)$ for all s and t. Using E.2.17 (page 70) and the fact that for fixed s and t the semigroup associated to $-B(s(t))$ is given by $\exp\{-B(s(t))\tau\}$, we can write

$$\begin{aligned}\|R(\lambda)\| &= \left\| \int_0^\infty e^{-\lambda\tau} e^{-B(s(t))\tau} \mathrm{d}\tau \right\| \\ &\leq \int_0^\infty e^{-\lambda\tau} e^{-b\tau} \mathrm{d}\tau \\ &= \frac{1}{\lambda + b}\end{aligned}$$

which is finite for $\lambda > -b$. Note that we have used the fact that $B(s)$ is a bounded linear operator, thus generating a uniformly continuous semigroup.

In order to show that E.2.16 (page 70) holds it suffices to show that (using theorem 2.2 at page 131 of [20-PAZ-1983])

$$\left\| \prod_{j=1}^{k} R(\lambda_j : C_s(t_j)) \right\| \leq M \prod_{j=1}^{k} \frac{1}{\lambda_j - \omega}.$$

This follows again by using the formula E.2.17:

$$\begin{aligned}\left\| \prod_{j=1}^{k} R(\lambda_j : C_s(t_j)) \right\| &= \left\| \prod_{j=1}^{k} \int_0^\infty e^{-\lambda_j t} e^{-B(s(t_j))t} \mathrm{d}t \right\| \\ &\leq \prod_{j=1}^{k} \int_0^\infty e^{-\lambda_j t} e^{-bt} \mathrm{d}t \\ &= \prod_{j=1}^{k} \frac{1}{\lambda_j + b}.\end{aligned}$$

Thus now equation E.2.18 is:

$$\|U_s(t,\tau)\| \leq e^{-b(t-\tau)},$$

equation E.2.21 is:

$$\left\| U_{s_1}(t,\tau) - U_{s_2}(t,\tau) \right\| \leq \beta e^{-b(t-\tau)} \int_\tau^t |s_1(\sigma) - s_2(\sigma)| \, \mathrm{d}\sigma,$$

and equation E.2.24 is:

$$\left\| \frac{\partial U_s}{\partial s} \right\| \leq e^{-b(t-\tau)} \left\| \frac{\partial C_s}{\partial s} \right\| (t - \tau).$$

2.4 The Inertial Manifold

As we saw in section 2.3.1, we assume that our system has an absorbing, bounded region where B is definite positive. This fact will be proved in section **2.6.1** for our particular model. We then modify B in the usual way using a “bump” function to assure that it is positive-definite everywhere.

We define b as the maximum value for which the following inequality holds for every s and every φ:

$$\langle \varphi, B(s)\varphi \rangle \geq b\,|\varphi|^2 . \qquad \text{E.2.25}$$

The main result in this section is as follows.

THEOREM T.2.3 ***If for the system E.2.4 (page 61), there exists an absorbing ball where $B(s)$ is definite positive, b is defined by E.2.25, the derivative of $B(s)$ with respect to s has norm β, f and g are Lipschitz bounded differentiable functions with Lipschitz derivative, the maxima of f and g are F and G and the Lipschitz constants are θ and γ respectively and if there exists a constant $k \in (0,1)$ such that $(1-k)b > 2\theta$, then for small positive ϵ the system E.2.4 admits an Inertial Manifold which is the graph of a function $h(s)$ which is Lipschitz, bounded, differentiable and with Lipschitz derivative.***

The bound on ϵ is

$$\epsilon < \frac{kb}{2\gamma}\frac{(1-k)^2b^2 - 2(1-k)b\theta}{\beta F + (1-k)^2b^2 - (1-k)b\theta}. \qquad \textbf{E.2.26}$$

It may be worth noting that since the first eigenvalues of $A(u)$ are zero, when A is given in the form E.2.5 (page 61) used throughout the proof, the condition $(1-k)b > 2\theta$ could be erroneously regarded as the classical gap condition. This is not the case. In fact the classical definitions of the gap condition (see glossary), for example the one given in [39-TEM-1998], compare the difference of two eigenvalues of A (in this case b and 0) with the Lipschitz constant of all the nonlinear parts, that is in our case the sum of β and θ. Thus the condition $(1-k)b > 2\theta$ is not the classical gap condition but a weaker form of it, clearly implied by the former but different from it (see section **2.4.5** for details).

Also note that E.2.4 (page 61) admits an Inertial Manifold although the classical gap condition is not satisfied, which seems to be a rather rare case. See also [53-MAL-1988] for another result in this direction.

2.4.1 Existence

Before proceeding, we want to prove that equation E.2.15 (page 69) admits one and only one solution. In the system originally treated in [47-IAN-1998], the existence is immediate since we were dealing with the finite dimensional case only.

To prove uniqueness, consider φ_1 and φ_2 two solutions of E.2.15, but corresponding to the same initial value $\varphi_1(0) = \varphi_2(0)$. Then let $\varphi = \varphi_1 - \varphi_2$. It obviously satisfies

$$\dot{\varphi} = -B(s_{s_0,h})\varphi.$$

By multiplication by φ^T we obtain

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}|\varphi|^2 \leq -b\,|\varphi|^2\,,$$

which readily implies $\varphi = 0$ (since $\varphi(0) = 0$) and hence uniqueness.

In this thesis, where we are dealing with the general case of a possibly infinite Hilbert space, existence and uniqueness are provided by the results in [18-AHM-1991] and [20-PAZ-1983] that we quoted in section 2.3.3.

We shall use the set X consisting of all those bounded Lipschitz functions from PH to its orthogonal QH, bounded by p and with Lipschitz constant p_1. Notice that $X \subseteq L^\infty$, the space of all essentially bounded functions, which is proved to be a Banach space in many text books, such as [37-ROB-2001] or [8-RUD-1987]. The L^∞ norm, that is the norm of all essentially bounded functions, is given by

$$\|h\|_\infty = \sup_{x\in H} |h(x)|\,.$$

We will apply the Banach fixed point theorem to X, thus we need X to be a closed set, which we prove in the following lemma:

LEMMA L.2.4 *Every Cauchy sequence $\{h_n\}$ in X in the L^∞ norm converges to an element $h \in X$.*

Proof Take a Cauchy sequence $\{h_n\}$ in X in the L^∞ norm. L^∞ being a Banach space, there exists $h \in L^\infty$ to which h_n converges.
By theorem 3.12 of [8-RUD-1987], there exists a subsequence that converges point-wise to $h(x)$ almost everywhere, thus $\|h\|_\infty \leq p$.

By considering the following

$$\forall x, y \in PH \quad \forall n \in \mathbb{N} \qquad \frac{|h_n(x) - h_n(y)|}{|x - y|} \leq p_1, \qquad \text{E.2.27}$$

and taking the limit for $n \to \infty$ in E.2.27 proves that the Lipschitz constant of h is less than p_1.

We have thus proved that $h \in X$ and thus X is a closed subset of L^∞.

//////

Consider now the operator T, obtained with the variation of constants formula as earlier, mapping X to X, given by

$$Th(s_0) = \int_{-\infty}^{0} U_{s_0,h}(0,\tau) f(s_{s_0,h}(\tau), h(s_{s_0,h}(\tau)))\mathrm{d}\tau,$$

where $U_{s_0,h}$ is the evolution operator associated to the equation E.2.15 for a fixed s_o and $h \in X$.

We claim that this operator is well defined and that it is a contraction for certain ranges of values of ϵ, p, p_1. Moreover, its fixed point is an Inertial Manifold for E.2.4 (page 61). This is because, from the definition of the operator T, its fixed point is an invariant manifold and it is exponentially attracting.

It is easy to see that the fixed point of T is an invariant manifold by following the method used in [32-HEN-1981] or in [41-CHO-1992]. In fact, any fixed point of T will satisfy for any $\xi \in PH$ the relation $h(\xi) = (Th)(\xi)$; so taking now the solution $\xi(t) = s_{s_0,h}(t)$ of the inertial form E.2.14 (page 69), for any time t we have that

$$h(s_{s_0,h}(t)) = \int_{-\infty}^{0} U_{[s_{s_0,h}(t)],h}(0,\tau) f(s_{[s_{s_0,h}(t)],h}(\tau), h(s_{[s_{s_0,h}(t)],h}(\tau)))\mathrm{d}\tau, \qquad \text{E.2.28}$$

where $s_{[s_{s_0,h}(t)],h}(\tau)$ is the solution of the inertial form E.2.14 starting at time $\tau = 0$ at the point $s_{s_0,h}(t)$, and evaluated at time τ. Clearly, by using basic properties of semi-groups, this solution is the same as $s_{s_0,h}(t + \tau)$ that is the solution of E.2.14 starting at point s_0 and evaluated at time $t + \tau$. Also, the evolution operator $U_{[s_{s_0,h}(t)],h}(0,\tau)$ corresponds to the solution of E.2.15 that at time τ starts at the point $s_{s_0,h}(t)$, and this corresponds to the evolution operator starting at time $t + \tau$ at point s_0. So we can re-write E.2.28 as

$$h(s_{s_0,h}(t)) = \int_{-\infty}^{0} U_{s_0,h}(0, t+\tau) f(s_{s_0,h}(t+\tau), h(s_{s_0,h}(t+\tau)))\mathrm{d}\tau. \qquad \text{E.2.29}$$

Now we can introduce the change of variable $\sigma = t + \tau$ and obtain:

$$\varphi(t) = h(s_{s_0,h}(t)) = \int_{-\infty}^{t} U_{s_0,h}(t,\sigma) f(s_{s_0,h}(\sigma), h(s_{s_0,h}(\sigma)))\mathrm{d}\sigma.$$

An easy differentiation shows that the fixed point of T is indeed invariant. In fact, using E.2.19 (page 70):

$$\begin{aligned}\dot{\varphi}(t) =& \int_{-\infty}^{t} C_s(t) U_{s_0,h}(t,\tau) f(s_{s_0,h}(\tau), h(s_{s_0,h}(\tau)))\mathrm{d}\tau \\ &+ U_{s_0,h}(t,t) f(s_{s_0,h}(t), h(s_{s_0,h}(t))) \\ =& C_s(t)\varphi(t) + f(s_{s_0,h}(t), h(s_{s_0,h}(t))),\end{aligned} \qquad \text{E.2.30}$$

where $C_s(t)$ comes out of the integral because we are integrating in $\mathrm{d}\tau$.

LEMMA L.2.5 *The operator T maps the space of functions bounded by p to itself.*

Proof To simplify the notation we shall write s_{s_0} instead of $s_{s_0,h}(t)$. Then

$$\begin{aligned}\left|Th(s_{s_0})\right| &\le \int_{-\infty}^{0} \left|U_{s_{s_0}}(0,\tau) f(s_{s_0}, h(s_{s_0}))\right| \mathrm{d}\tau \\ &\le \int_{-\infty}^{0} e^{b\tau} F \mathrm{d}\tau = \frac{F}{b},\end{aligned}$$

where F is the maximum of f. Thus, when $p \ge F/b$, we have that $\left|Th(s_{s_0})\right| \le p$.

//////

LEMMA L.2.6 *Gronwall's inequality applied to E.2.14 gives the following inequality for $t < 0$, whenever g has Lipschitz constant γ and h has Lipschitz constant p_1*

$$\left|s_{s_0}(t) - s_{s_1}(t)\right| < |s_0 - s_1| \, e^{-\epsilon\gamma(p_1+1)t}. \qquad \text{E.2.31}$$

Proof The solution $s_{s_0}(t)$ of the system E.2.14 (page 69) corresponding to the initial value s_0 satisfies the equality

$$s_{s_0}(0) - s_{s_0}(t) = s_0 - s_{s_0}(t) = \int_{t}^{0} \epsilon g(s_{s_0}(\sigma), h(s_{s_0}(\sigma)))\mathrm{d}\sigma. \qquad \text{E.2.32}$$

Now, if we get two initial values s_0 and s_1 and their corresponding solutions s_{s_0} and s_{s_1} and subtract the two equations E.2.32 term by term we have that

$$
\begin{aligned}
\left|s_{s_0}(t) - s_{s_1}(t)\right| &= \left|s_0 - s_1 + \epsilon \int_t^0 g(s_{s_0}(\sigma), h(s_{s_0}(\sigma))) - g(s_{s_1}(\sigma), h(s_{s_1}(\sigma)))\mathrm{d}\sigma\right| \\
&\leq |s_0 - s_1| + \epsilon \int_t^0 \left|g(s_{s_0}(\sigma), h(s_{s_0}(\sigma))) - g(s_{s_1}(\sigma), h(s_{s_1}(\sigma)))\right| \mathrm{d}\sigma \\
&\leq |s_0 - s_1| + \epsilon \int_t^0 \gamma\Big[\left|s_{s_0}(\sigma) - s_{s_1}(\sigma)\right| + \left|h(s_{s_0}(\sigma)) - h(s_{s_1}(\sigma))\right| \Big]\mathrm{d}\sigma \\
&\leq |s_0 - s_1| + \epsilon \int_t^0 \gamma\Big[\left|s_{s_0}(\sigma) - s_{s_1}(\sigma)\right| + p_1 \left|s_{s_0}(\sigma) - s_{s_1}(\sigma)\right| \Big]\mathrm{d}\sigma \\
&= |s_0 - s_1| + \epsilon\gamma(p_1 + 1) \int_t^0 \left|s_{s_0}(\sigma) - s_{s_1}(\sigma)\right| \mathrm{d}\sigma.
\end{aligned}
$$

Gronwall's lemma (see glossary) states that if we have two positive functions of time a and b and a constant c such that

$$a(t_1) \leq c + \int_{t_0}^{t_1} b(s)a(s)\mathrm{d}s$$

then

$$a(t_1) \leq c \exp\left(\int_{t_0}^{t_1} b(s)\mathrm{d}s\right).$$

We can thus apply Gronwall's lemma with $t_1 = 0$, $t_0 = t$, $a(t) = \left|s_{s_0}(t) - s_{s_1}(t)\right|$, $b(t) = \epsilon\gamma(p_1 + 1)$ and $c = |s_0 - s_1|$, to obtain that

$$\left|s_{s_0}(t) - s_{s_1}(t)\right| \leq |s_0 - s_1| e^{\int_t^0 \epsilon\gamma(p_1+1)\mathrm{d}s} = |s_0 - s_1| e^{-\epsilon\gamma(p_1+1)t}.$$

//////

LEMMA L.2.7 *For sufficiently small ϵ the operator T maps the space of p_1 Lipschitz functions to itself.*

Proof First of all we shall simplify the notation and suppress the explicit dependency on time and on h and we shall write s_{s_0} for $s_{s_0,h}(\tau)$, $h(s_{s_0})$ for $h(s_{s_0,h}(\tau))$, and similarly for s_{s_1} and $h(s_{s_1})$.

Secondly, we shall use the fact that f is Lipschitz with constant θ and that h is Lipschitz with constant p_1, so that we have the following inequality:

$$
\begin{aligned}
\left|f(s_{s_0}, h(s_{s_0})) - f(s_{s_1}, h(s_{s_1}))\right| &\leq \theta\Big[\left|s_{s_0} - s_{s_1}\right| + \left|h(s_{s_0}) - h(s_{s_1})\right| \Big] \\
&\leq \theta\Big[\left|s_{s_0} - s_{s_1}\right| + p_1 \left|s_{s_0} - s_{s_1}\right| \Big] \\
&= \theta(p_1 + 1) \left|s_{s_0} - s_{s_1}\right|.
\end{aligned}
$$

This inequality will be used throughout this chapter, although we explicitly mention it only here.

Using E.2.21 (page 71) and adding and subtracting the term $U_{s_{s_1}}(0,\tau)f(s_{s_0},h(s_{s_0}))$, we have

$$
\begin{aligned}
&|Th(s_0) - Th(s_1)| \\
&\quad\leq \int_{-\infty}^{0} \left| U_{s_{s_0}}(0,\tau)f(s_{s_0},h(s_{s_0})) - U_{s_{s_1}}(0,\tau)f(s_{s_1},h(s_{s_1}))\right| \mathrm{d}\tau \\
&\quad\leq \int_{-\infty}^{0} \left|\left[U_{s_{s_0}}(0,\tau) - U_{s_{s_1}}(0,\tau)\right] f(s_{s_0},h(s_{s_0}(\tau)))\right| \mathrm{d}\tau \\
&\quad\quad + \int_{-\infty}^{0} \left| U_{s_{s_1}}(0,\tau)\left[f(s_{s_0},h(s_{s_0})) - f(s_{s_1},h(s_{s_1}))\right]\right| \mathrm{d}\tau \\
&\quad\leq \int_{-\infty}^{0} \beta F e^{b\tau}\left[\int_{\tau}^{0} \left|s_{s_0}(\sigma) - s_{s_1}(\sigma)\right| \mathrm{d}\sigma \right] \mathrm{d}\tau \\
&\quad\quad + \int_{-\infty}^{0} e^{b\tau}\theta(p_1+1)\left|s_{s_0}(\tau) - s_{s_1}(\tau)\right| \mathrm{d}\tau,
\end{aligned}
\qquad \text{E.2.33}
$$

where β is the Lipschitz constant of B.

Using lemma **L.2.6** we have that equation E.2.33 is dominated by

$$
\begin{aligned}
&\int_{-\infty}^{0} \frac{\beta F}{\epsilon\gamma(p_1+1)}\left(e^{b\tau-\epsilon\gamma(p_1+1)\tau} - e^{b\tau}\right)|s_0 - s_1|\,\mathrm{d}\tau \\
&\qquad + \int_{-\infty}^{0} \theta(p_1+1)e^{b\tau-\epsilon\gamma(p_1+1)\tau}|s_0 - s_1|\,\mathrm{d}\tau \\
&\qquad = \frac{\beta F}{\epsilon\gamma(p_1+1)}\left(\frac{1}{(b-\epsilon\gamma(p_1+1))} - \frac{1}{b}\right)|s_0 - s_1| \\
&\qquad + \theta(p_1+1)\frac{1}{(b-\epsilon\gamma(p_1+1))}|s_0 - s_1| \\
&\qquad = \left\{\frac{\beta F}{b(b-\epsilon\gamma(p_1+1))} + \frac{\theta(p_1+1)}{(b-\epsilon\gamma(p_1+1))}\right\}|s_0 - s_1|
\end{aligned}
\qquad \text{E.2.34}
$$

where, in order to obtain finite integrals, we impose that

$$
\epsilon \leq k\frac{b}{\gamma(p_1+1)} \qquad \text{E.2.35}
$$

with k a number between 0 and 1, which will be chosen later. Using E.2.35 one can write

$$
b - \epsilon\gamma(p_1+1) = (1-k)b + kb - \epsilon\gamma(p_1+1) \geq (1-k)b. \qquad \text{E.2.36}
$$

Thus we have that the right hand side of E.2.34 is dominated by

$$
\left\{\frac{\beta F}{b(1-k)b} + \frac{\theta(p_1+1)}{(1-k)b}\right\}|s_0 - s_1|\,.
$$

We shall now impose that the above term be less than $p_1 |s_0 - s_1|$, so that finally

$$|Th(s_0) - Th(s_1)| \leq p_1 |s_0 - s_1|$$

and Th is a Lipschitz function with constant p_1.

Imposing that

$$\frac{\beta F}{b(1-k)b} + \frac{\theta(p_1+1)}{(1-k)b} \leq p_1$$

is equivalent to

$$\beta F + b\theta \leq p_1((1-k)b^2 - b\theta)$$

which can also be written as

$$p_1 \geq \frac{\beta F + b\theta}{(1-k)b^2 - b\theta}. \qquad \text{E.2.37}$$

//////

So, thanks to Lemmas **L.2.5** and **L.2.7**, the operator T is well defined in the space of functions X, provided E.2.37 holds and $p \geq F/b$.

LEMMA L.2.8 *Gronwall's inequality applied to E.2.14 gives the following inequality for* $t < 0$, *whenever* g *has Lipschitz constant* γ *and* h_1, h_2 *have Lipschitz constant* p_1

$$\left|s_{h_1}(t) - s_{h_2}(t)\right| < \frac{\|h_1 - h_2\|_\infty}{p_1 + 1}\left[e^{-\epsilon\gamma(p_1+1)t} - 1\right]. \qquad \text{E.2.38}$$

Proof In order to simplify the notation, we suppress again the explicit dependency on time and the initial condition and we denote by s_{h_1} and s_{h_2} the two solutions of E.2.14 (page 69) corresponding to the same initial value s_0 but to two different functions h_1 and h_2. We also suppress the dt variable of integration.

As we did in the proof of **L.2.6** we subtract the two integral equations corresponding to the two solutions s_{h_1} and s_{h_2}.

$$\begin{aligned}\left|s_{h_1}(t) - s_{h_2}(t)\right| &= \left|s_{h_1}(0) - s_{h_2}(0) + \int_t^0 \epsilon g(s_{h_1}, h_1(s_{h_1})) - \epsilon g(s_{h_2}, h_2(s_{h_2}))\right| \\ &\leq \int_t^0 \epsilon \left|g(s_{h_1}, h_1(s_{h_1})) - g(s_{h_2}, h_2(s_{h_2}))\right| \\ &\leq \int_t^0 \epsilon\gamma\Big[\left|s_{h_1} - s_{h_2}\right| + \left|h_1(s_{h_1}) - h_2(s_{h_2})\right|\Big]\end{aligned}$$

$$
\begin{aligned}
&\leq \int_t^0 \epsilon\gamma\Big[\,\big|s_{h_1} - s_{h_2}\big| + \big|h_1(s_{h_1}) - h_1(s_{h_2})\big| + \big|h_1(s_{h_2}) - h_2(s_{h_2})\big|\,\Big] \\
&\leq \int_t^0 \epsilon\gamma\Big[\,\big|s_{h_1} - s_{h_2}\big| + p_1\,\big|s_{h_1} - s_{h_2}\big| + \big|h_1(s_{h_2}) - h_2(s_{h_2})\big|\,\Big] \\
&\leq \int_t^0 \epsilon\gamma\Big[(p_1+1)\,\big|s_{h_1} - s_{h_2}\big| + \|h_1 - h_2\|_\infty\Big] \\
&= \int_t^0 \epsilon\gamma(p_1+1)\Big[\,\big|s_{h_1} - s_{h_2}\big| + \frac{\|h_1 - h_2\|_\infty}{p_1+1}\Big]
\end{aligned}
$$

where $\|h_1 - h_2\|_\infty$ is the L^∞ norm, i.e. the sup on s of $|h_1(s) - h_2(s)|$, which is finite as both $h_1, h_2 \in X$.

Now add the term $\|h_1 - h_2\|_\infty / (p_1 + 1)$ to both terms of the above inequality:

$$
\begin{aligned}
&\big|s_{h_1}(t) - s_{h_2}(t)\big| + \frac{\|h_1 - h_2\|_\infty}{p_1+1} \\
&\qquad\leq \frac{\|h_1 - h_2\|_\infty}{p_1+1} + \int_t^0 \epsilon\gamma(p_1+1)\Big[\,\big|s_{h_1} - s_{h_2}\big| + \frac{\|h_1 - h_2\|_\infty}{p_1+1}\Big].
\end{aligned}
$$

We are ready to apply Gronwall's lemma with

$$
\begin{aligned}
a(t) &= \big|s_{h_1}(t) - s_{h_2}(t)\big| + \frac{\|h_1 - h_2\|_\infty}{p_1+1} \\
b(t) &= \epsilon\gamma(p_1+1) \\
c &= \frac{\|h_1 - h_2\|_\infty}{p_1+1}
\end{aligned}
$$

to obtain

$$
\big|s_{h_1}(t) - s_{h_2}(t)\big| + \frac{\|h_1 - h_2\|_\infty}{p_1+1} \leq \frac{\|h_1 - h_2\|_\infty}{p_1+1} e^{-\epsilon\gamma(p_1+1)t}
$$

which is exactly the inequality stated in the lemma.

//////

The existence of a fixed point, which we prove in the next lemma using a contraction principle, could be also proved using the Schauder fixed point theorem. This theorem states that if T is a continuous mapping from a closed convex subset K of a Banach space to itself, then T has at least one fixed point.

Unfortunately so far we have only proved that T is well defined and not that it is continuous. In fact, so far we have only considered for a fixed $h \in X$ the value of $\|Th\|$ and the value of $|Th(s_0) - Th(s_1)|$. In order to prove continuity one has to evaluate the difference $\|Th_1 - Th_2\|$ which is essentially what we do in the next lemma.

LEMMA L.2.9 *The operator $T : X \to X$ is a contraction for sufficiently small ϵ.*

Proof As we have done until now, we will suppress some of the notation; we write s_{h_1} for $s_{s_0,h_1}(\tau)$ and $U_{s_{h_1}}$ for $U_{s_{s_0.h_1}}(0,\tau)$.

We must prove that for any $h_1, h_2 \in X$ the following relation holds for a constant $\delta \in (0,1)$

$$\|Th_1 - Th_2\|_\infty \le \delta \|h_1 - h_2\|_\infty ;$$

which is equivalent to proving that for any $s_0 \in H$ the following holds

$$|Th_1(s_0) - Th_2(s_0)| \le \delta \|h_1 - h_2\|_\infty .$$

Given h_1 and h_2 in X and any point s_0 in $\mathbb{R}^n$ we can write

$$\begin{aligned} |Th_1(s_0) - Th_2(s_0)| \le & \int_{-\infty}^{0} \left|\left(U_{s_{h_1}} - U_{s_{h_2}}\right) f(s_{h_1}, h_1(s_{h_1}))\right| \mathrm{d}\tau \\ & + \int_{-\infty}^{0} \left|U_{s_{h_2}}\left[f(s_{h_1}, h_1(s_{h_1})) - f(s_{h_2}, h_2(s_{h_2}))\right]\right| \mathrm{d}\tau \\ \le & \int_{-\infty}^{0} \beta F e^{b\tau} \left(\int_{\tau}^{0} \left|s_{h_1}(\sigma) - s_{h_2}(\sigma)\right| \mathrm{d}\sigma\right) \mathrm{d}\tau \\ & + \int_{-\infty}^{0} e^{b\tau}\theta\left[(p_1+1)\left|s_{h_1} - s_{h_2}\right| + \|h_1 - h_2\|_\infty\right] \mathrm{d}\tau. \end{aligned} \quad \text{E.2.39}$$

Now, applying lemma **L.2.8** to E.2.39 and using E.2.35 (page 80) to obtain finite integrals, yields

$$\begin{aligned} & \left|Th_1(s_0) - Th_2(s_0)\right| \\ & \quad \le \int_{-\infty}^{0} \beta F e^{b\tau} \left(\int_{\tau}^{0} \frac{\|h_1 - h_2\|_\infty}{p_1+1}\left[e^{-\epsilon\gamma(p_1+1)\sigma} - 1\right] \mathrm{d}\sigma\right) \mathrm{d}\tau \\ & \quad + \int_{-\infty}^{0} e^{b\tau}\theta \|h_1 - h_2\|_\infty \left[e^{-\epsilon\gamma(p_1+1)\tau} - 1\right] \mathrm{d}\tau + \frac{\theta}{b}\|h_1 - h_2\|_\infty \\ & \quad = \int_{-\infty}^{0} \beta F \frac{\|h_1 - h_2\|_\infty}{\epsilon\gamma(p_1+1)^2} e^{b\tau}\left[e^{-\epsilon\gamma(p_1+1)\tau} - 1\right] \mathrm{d}\tau \\ & \quad + \int_{-\infty}^{0} \beta F \frac{\|h_1 - h_2\|_\infty}{(p_1+1)} e^{b\tau}\tau \mathrm{d}\tau \\ & \quad + \frac{\theta}{(b - \epsilon\gamma(p_1+1))}\|h_1 - h_2\|_\infty \\ & \quad = \|h_1 - h_2\|_\infty \frac{b^2\theta(p_1+1) + b\beta F - \beta F[b - \epsilon\gamma(p_1+1)]}{b^2(b - \epsilon\gamma(p_1+1))(p_1+1)}, \end{aligned} \quad \text{E.2.40}$$

where we have used the fact that

$$\int_{-\infty}^{0} e^{\lambda r} r \mathrm{d}r = -\frac{1}{\lambda^2}.$$

Using E.2.36 (page 80) again to find a bound on E.2.40 yields the inequality:

$$|Th_1(s_0) - Th_2(s_0)| \leq \|h_1 - h_2\|_\infty \frac{b\theta(p_1+1) + \beta F - \beta F(1-k)}{b^2(1-k)(p_1+1)}. \qquad \text{E.2.41}$$

Now the right-hand side of E.2.41 is less than $\alpha \|h_1 - h_2\|_\infty$ for some $0 < \alpha < 1$, this yielding the Lipschitz condition for T, if and only if

$$p_1 > \frac{k\beta F}{(1-k)b^2 - b\theta} - 1. \qquad \text{E.2.42}$$

This last inequality is proved by imposing that the constant in right hand side of E.2.41 be strictly less than 1:

$$\frac{b\theta(p_1+1) + \beta F - \beta F(1-k)}{b^2(1-k)(p_1+1)} < 1$$

which is equivalent to

$$b\theta(p_1+1) + k\beta F < b^2(1-k)(p_1+1),$$

and grouping p_1 on one side gives exactly the inequality E.2.42.

//////

Thus only three conditions E.2.35, E.2.37, E.2.42, plus $p \geq F/b$ guarantee that T is a contraction in the space X. In the next section we shall show that its fixed point is also differentiable with continuous derivative.

2.4.2 Smoothness

To show that the invariant manifold is C^1, that is continuously differentiable, we shall introduce an operator on the space $X^1_{p_1}$, which in a sense is a space of derivatives. This space is defined as follows:

$$X^1_{p_1} = \Big\{\Delta : PH \mapsto \mathcal{L}(PH, QH); \quad \|\Delta\|_{X^1} = \sup_s \|\Delta(s)\|_{\mathcal{L}} \leq p_1\Big\}.$$

In the biological model $PH = \mathbb{R}^n$ and $QH = \mathbb{R}^m$. We define an operator T_h^1, depending on $h \in X$, which maps $X_{p_1}^1$ to itself. We show that for every $h \in X$ it is a contraction in $X_{p_1}^1$; then we take the fixed point $\bar{\Delta}$ corresponding to the fixed point $\bar{h}$ of T and we show that it is indeed the derivative of $\bar{h}$.

In words, $\mathcal{L}(PH, QH)$ is the function space of all the linear operators from PH to QH; $X_{p_1}^1$ is the space of all functions from PH to $\mathcal{L}(PH, QH)$ with bounded norm; to each element in PH it associates a linear operator. This is a derivative, something that one can see thinking about the scalar case: to each element in $\mathbb{R}$ we associate the slope of the tangent to a function, the slope being nothing less than a scalar, which can be viewed as a linear operator.

Finally T_h^1 is a function that to each function in $X_{p_1}^1$ associates another function.

Thus, if we have $s, \eta \in PH$, the notation $T_h^1 \Delta(s)\eta$ will have to be read as follows:

- Δ is a function in $X_{p_1}^1$;
- $T_h^1 \Delta$ is the function in $X_{p_1}^1$ associated to Δ by T_h^1; lets denote $T_h^1(\Delta)$ by Θ;
- $T_h^1 \Delta(s) = \Theta(s)$ is an operator in $\mathcal{L}(PH, QH)$, and is the operator associated to s by the function $\Theta = T_h^1(\Delta)$; lets denote it by $\mathcal{A}$
- $T_h^1 \Delta(s)\eta = \Theta(s)\eta = \mathcal{A}\eta$ is an element in QH, and is the element associated to η by $\mathcal{A}$, which is a linear operator;
- thus the norm of $T_h^1 \Delta(s)\eta$ will be indicated by $|\cdot|$, as it is an element in $QH \subseteq H$.

Before proceeding with the proof of the theorem, we shall show that $X_{p_1}^1$ is a closed subset of a Banach space.

LEMMA L.2.10 *The space of functions $X^1 = \{\Delta : PH \mapsto \mathcal{L}(PH, QH)\}$ is a Banach space when provided with the following norm*

$$\|\Delta\|_{X^1} = \sup_s \|\Delta(s)\|_{\mathcal{L}} .$$

Proof We will use the notation $\mathcal{L} = \mathcal{L}(PH, PQ)$.

First we show that X^1 is closed under linear operations, then that $\|\Delta\|_{X^1}$ is a norm, and finally that X^1 is complete.

To show that X^1 is closed under linear operations, we get $\Delta_1, \Delta_2 \in X^1$ and $\lambda \in \mathbb{R}$, and we show that $\Delta_1 + \lambda\Delta_2$ is well defined in X^1.

By definition of X^1, $\forall s \in PH$ we have that $\Delta_1(s) \in \mathscr{L}$ and $\Delta_2(s) \in \mathscr{L}$. Using the fact that $\mathscr{L}(PH, PQ)$ is well defined under linear operations, it follows that $\forall s \in PH$ we have that $[\Delta_1(s) + \lambda\Delta_2(s)] \in \mathscr{L}$.

Thus $\Delta_1 + \lambda\Delta_2$ is defined for each $s \in PH$ as $\Delta_1(s) + \lambda\Delta_2(s)$, and thus $\Delta_1 + \lambda\Delta_2 \in X^1$.

Now we prove that $\|\Delta\|_{X^1}$ is a norm.

First we show that if $\|\Delta\|_{X^1} = 0$ then $\Delta = \mathbb{0}$. By definition, $\|\Delta\|_{X^1} = 0$ implies that $\forall s \in PH$ $\|\Delta(s)\|_{\mathscr{L}} = 0$. $\mathscr{L}$ being a normed space, this implies that $\forall s \in PH \quad \Delta(s) = \mathbb{0}$.

Now we show that $\|\Delta_1 + \lambda\Delta_2\|_{X^1} \leq \|\Delta_1\|_{X^1} + |\lambda| \, \|\Delta_2\|_{X^1}$. Once again we use the fact that $\mathscr{L}$ is a normed space:

$$\begin{aligned} \|\Delta_1 + \lambda\Delta_2\|_{X^1} &= \sup_s \|\Delta_1(s) + \lambda\Delta_2(s)\|_{\mathscr{L}} \\ &\leq \sup_s \left\{ \|\Delta_1(s)\|_{\mathscr{L}} + |\lambda| \, \|\Delta_2(s)\|_{\mathscr{L}} \right\} \\ &\leq \sup_s \|\Delta_1(s)\|_{\mathscr{L}} + |\lambda| \sup_s \|\Delta_2(s)\|_{\mathscr{L}} \\ &= \|\Delta_1\|_{X^1} + |\lambda| \, \|\Delta_2\|_{X^1} \, . \end{aligned}$$

We need only to show that X^1 is complete. Take then a sequence Δ_n which is a Cauchy sequence. By definition $\forall \epsilon > 0$ there exist N such that for $n, m > N$,

$$\|\Delta_n - \Delta_m\|_{X^1} = \sup_s \|\Delta_n(s) - \Delta_m(s)\|_{\mathscr{L}} < \epsilon.$$

This means that for every s the sequence $\Delta_n(s)$ is Cauchy in $\mathscr{L}$. $\mathscr{L}$ being a complete space, for every s there exist the limit $\Delta(s) = \lim_{n\to\infty} \Delta_n(s) \in \mathscr{L}$. We can now define Δ as the function from $PH \to \mathscr{L}$ given by $\Delta(s)$ for every $s \in PH$.

We thus just need showing that $\Delta \in X^1$ and $\Delta_n \to \Delta$ in the X^1 norm. By definition of Cauchy sequence we have:

$$\forall \epsilon > 0 \quad \exists N; \quad \forall n, m > N \quad \sup_s \|\Delta_m(s) - \Delta_n(s)\|_{\mathscr{L}} < \epsilon.$$

Now let $m \to \infty$ and obtain that

$$\forall \epsilon > 0 \quad \exists N; \quad \forall n > N \quad \sup_s \|\Delta(s) - \Delta_n(s)\|_{\mathscr{L}} < \epsilon, \qquad \text{E.2.43}$$

which shows that $\Delta_n \to \Delta$ in the X^1 norm.

Also, by applying the triangular inequality $|a| - |b| \leq |a - b|$ valid in any Banach space to E.2.43 we have that

$$\|\Delta\|_{X^1} \leq \|\Delta_n\|_{X^1} + \epsilon < \infty,$$

which shows that $\Delta \in X^1$.

//////

Clearly the ball $X^1_{p_1}$ of radius p_1 is closed in X^1.

In order to define the operator T^1_h we shall consider the linearisation of E.2.14 (page 69). First of all, fix $s_0 \in PH$ and $h \in X$, then consider a solution $s_{s_0,h}$ of E.2.14 corresponding to s_0 and h. Finally the linearised differential equation is expressed in terms of the variable η and is

$$\begin{aligned} \dot{\eta} &= \epsilon Dg(s_{s_0,h}, h(s_{s_0,h}))(\eta + \Delta(s_{s_0,h})\eta) \\ \eta(0) &= \eta_0 \end{aligned} \qquad \text{E.2.44}$$

Suppressing some notation and writing s for $s_{s_0,h}$ the above equation might be more readable:

$$\dot{\eta} = \epsilon Dg(s, h(s))(\eta + \Delta(s)\eta).$$

Notice that the linearisation corresponds simply to applying the chain rule of derivation.

η being finite dimensional, it is immediate from classical results that this equation admits a unique solution that we shall call $\eta_{\eta_0,\Delta}$. Suppressing the explicit dependency on time and writing $s_{s_0,h}$ for $s_{s_0,h}(\tau)$, we can define the operator

$$\begin{aligned} T^1_h \Delta(s_0)\eta_0 = &\int_{-\infty}^{0} U_{s_{s_0,h}} Df(s_{s_0,h}, h(s_{s_0,h})) \left[\eta_{\eta_0,\Delta} + \Delta(s_{s_0,h})\eta_{\eta_0,\Delta}\right] \mathrm{d}\tau \\ &+ \int_{-\infty}^{0} DU_{s_{s_0,h}} \eta_{\eta_0,\Delta} f(s_{s_0,h}, h(s_{s_0,h})) \mathrm{d}\tau \end{aligned}$$

where DU indicates the Fréchet derivative of U with respect to s, which exists thanks to lemma **L.2.2** (page 72). Notice that T^1_h is obtained by formally calculating the derivative of T.

LEMMA L.2.11 *Gronwall's inequality applied to E.2.44 gives the following inequality for $t < 0$, whenever g has Lipschitz constant γ and $\Delta \in X^1_{p_1}$*

$$\left|\eta_{\eta_0,\Delta}(t)\right| \leq |\eta_0| \, e^{-\epsilon\gamma(p_1+1)t}. \qquad \text{E.2.45}$$

Proof We suppress explicit dependency on time, initial condition and h, so that we can write s for $s_{s_0,h}(\tau)$.

Integrating E.2.44 between t and 0 we have that

$$\begin{aligned}\left|\eta_{\eta_0,\Delta}(t)\right| &= \left|\eta_0 + \int_t^0 \epsilon Dg(s,h(s))(\eta_{\eta_0,\Delta} + \Delta(s)\eta_{\eta_0,\Delta})\right| \\ &\leq |\eta_0| + \int_t^0 \left|\epsilon Dg(s,h(s))(\eta_{\eta_0,\Delta} + \Delta(s)\eta_{\eta_0,\Delta})\right| \\ &\leq |\eta_0| + \int_t^0 \epsilon \left|Dg(s,h(s))\right| \left|(\eta_{\eta_0,\Delta} + \Delta(s)\eta_{\eta_0,\Delta})\right| \\ &\leq |\eta_0| + \int_t^0 \epsilon\gamma \left|\eta_{\eta_0,\Delta}\right| (1+p_1).\end{aligned}$$

We can now apply Gronwall's lemma with

$$a(t) = \eta_{\eta_0,\Delta}(t)$$

$$b(t) = \epsilon\gamma(1+p_1)$$

$$c = |\eta_0|$$

and thus obtain the inequality stated in the lemma.

//////

LEMMA L.2.12 *For small ϵ the operator T_h^1 is well defined.*

Proof First, we notice that for every s_0, h, the operator $T_h^1\Delta(s_0)\eta_0$ is linear in η_0. To see that T_h^1 is well defined, we just need to show that the norm $\left\|T_h^1\Delta\right\|_\infty$ is bounded by p_1.

As usual we simplify the notation. In the following text, s indicates $s_{s_0,h}$ and $f(s) = f(s_{s_0,h}, h(s_{s_0,h}))$; also U_s is evaluated at $(0,\tau)$.

$$\begin{aligned}\left|T_h^1\Delta(s_0)\eta_0\right| &\leq \int_{-\infty}^0 \|U_s\| \, |Df(s)| \left|\eta_{\eta_0,\Delta} + \Delta(s)\eta_{\eta_0,\Delta}\right| + \|DU\| \left|\eta_{\eta_0,\Delta}\right| |f(s)| \\ &\quad \text{using E.2.18 (page 70) and E.2.24 (page 73)} \\ &\leq \int_{-\infty}^0 e^{b\tau} \left[\theta(p_1+1) - \tau\beta F\right] \left|\eta_{\eta_0,\Delta}\right|.\end{aligned} \qquad \text{E.2.46}$$

Using E.2.45 we obtain that

$$\begin{aligned}\left|T_h^1\Delta(s_0)\eta_0\right| &\leq \int_{-\infty}^0 e^{b\tau-\epsilon\gamma(p_1+1)\tau} \left[\theta(p_1+1) - \tau\beta F\right] |\eta_0| \\ &= \left(\frac{\theta(p_1+1)}{b-\epsilon\gamma(p_1+1)} + \frac{\beta F}{[b-\epsilon\gamma(p_1+1)]^2}\right) |\eta_0|,\end{aligned} \qquad \text{E.2.47}$$

where again we have used E.2.35 (page 80). Now using E.2.36 the constant multiplying η_0 on the right hand side of E.2.47 is bounded by:

$$\frac{\theta(p_1+1)}{(1-k)b} + \frac{\beta F}{(1-k)^2 b^2}$$

which is less than p_1 if and only if

$$(1-k)b\theta p_1 + (1-k)b\theta + \beta F \leq (1-k)^2 b^2 p_1,$$

which is equivalent to

$$p_1 \geq \frac{\beta F + (1-k)b\theta}{(1-k)^2 b^2 - (1-k)b\theta}. \qquad \text{E.2.48}$$

Now remember that the norm of a linear operator is defined as the smallest number c such that $\|Lx\| \leq c\,\|x\|$. We have just proved that for any Δ, s_0, η_0

$$\left|T_h^1 \Delta(s_0)\eta_0\right| \leq p_1 \left|\eta_0\right|$$

and so the norm of the linear operator $T_h^1 \Delta(s_0)$ is certainly smaller than p_1. Now the norm of $T_h^1 \Delta$ in X^1 is the sup on s_0 of the operator norms. This shows that the norm in X^1 is always less than p_1. Thus T_h^1 is well defined if E.2.35 and E.2.48 hold.

//////

LEMMA L.2.13 *Gronwall's inequality applied to E.2.44 gives the following inequality for $t < 0$, whenever g has Lipschitz constant γ and $\Delta_1, \Delta_2 \in X^1_{p_1}$*

$$\left|\eta_{\Delta_1}(t) - \eta_{\Delta_2}(t)\right| \leq \frac{\|\Delta_1 - \Delta_2\|_{X^1}}{p_1+1} \left|\eta_0\right| e^{-2\epsilon\gamma(p_1+1)t}. \qquad \text{E.2.49}$$

Proof As usual, we suppress some notation and in this case we write s for $s_{s_0,h}(\tau)$; we also suppress the dτ notation under the sign of integral.

We fix $h \in X, s_0, \eta_0 \in PH$ and take $\Delta_1, \Delta_2 \in X^1_{p_1}$. Now consider η_1 the solution of E.2.44 corresponding to Δ_1 and η_2 the solution corresponding to Δ_2. Integrating the two corresponding equations and subtracting them we have:

$$
\begin{aligned}
|\eta_1(t) - \eta_2(t)| &\leq \int_t^0 \epsilon \, |Dg(s)(\eta_1 + \Delta_1(s)\eta_1) - Dg(s)(\eta_2 + \Delta_2(s)\eta_2)| \\
&\leq \epsilon\gamma \int_t^0 |\Delta_1(s)\eta_1 - \Delta_2(s)\eta_2| + |\eta_1 - \eta_2| \\
&\leq \epsilon\gamma \int_t^0 |\Delta_1(s)\eta_2 - \Delta_2(s)\eta_2| + |\Delta_1(s)\eta_1 - \Delta_1(s)\eta_2| + |\eta_1 - \eta_2| \\
&\leq \epsilon\gamma \int_t^0 \|\Delta_1(s) - \Delta_2(s)\|_{\mathcal{L}} \, |\eta_2| + p_1 \, |\eta_1 - \eta_2| + |\eta_1 - \eta_2|
\end{aligned}
$$

where we used the definition of the operator norm as the smallest number c such that $\|Lx\| \leq c\,|x|$ applied to the operator $\Delta_1(s) - \Delta_2(s)$.

Now, we can also use the definition of the norm in X_1 as

$$
\|\Delta_1 - \Delta_2\|_{X^1} = \sup_s \left\{ \|\Delta_1(s) - \Delta_2(s)\|_{\mathcal{L}} \right\}.
$$

We now suppress the X^1 in the notation of the norm in X_1 and write $\|\Delta\|$ for $\|\Delta\|_{X_1}$.

We apply **L.2.11** to η_2 in the above equation and obtain

$$
\begin{aligned}
|\eta_1(t) - \eta_2(t)| &\leq \int_t^0 \epsilon\gamma \, \|\Delta_1 - \Delta_2\| \, |\eta|_2 + \epsilon\gamma(p_1 + 1) \, |\eta_1 - \eta_2| \\
&\leq \int_t^0 \epsilon\gamma \, \|\Delta_1 - \Delta_2\| \, |\eta_0| \, e^{-\epsilon\gamma(p_1+1)\tau} + \int_t^0 \epsilon\gamma(p_1 + 1) \, |\eta_1 - \eta_2| \\
&= \epsilon\gamma \, \|\Delta_1 - \Delta_2\| \, |\eta_0| \left[\frac{e^{-\epsilon\gamma(p_1+1)t} - 1}{\epsilon\gamma(p_1 + 1)} \right] + \int_t^0 \epsilon\gamma(p_1 + 1) \, |\eta_1 - \eta_2| \\
&\leq \frac{\|\Delta_1 - \Delta_2\|}{(p_1 + 1)} \, |\eta_0| \, e^{-\epsilon\gamma(p_1+1)t} + \int_t^0 \epsilon\gamma(p_1 + 1) \, |\eta_1 - \eta_2| \, .
\end{aligned}
$$

Now multiply both sides of the inequality by the strictly positive function $e^{\epsilon\gamma(p_1+1)t}$:

$$
\begin{aligned}
&|\eta_1(t) - \eta_2(t)| e^{\epsilon\gamma(p_1+1)t} \\
&\quad \leq \frac{\|\Delta_1 - \Delta_2\|}{(p_1 + 1)} \, |\eta_0| + e^{\epsilon\gamma(p_1+1)t} \int_t^0 \epsilon\gamma(p_1 + 1) \, |\eta_1 - \eta_2| \, .
\end{aligned}
\tag{E.2.50}
$$

As we are integrating in $[t, 0]$ for negative times, we have that for each $\tau \geq t$, $e^{\epsilon\gamma(p_1+1)t} \leq e^{\epsilon\gamma(p_1+1)\tau}$. Thus

$$
\begin{aligned}
e^{\epsilon\gamma(p_1+1)t} \int_t^0 \epsilon\gamma(p_1 + 1) \, |\eta_1 - \eta_2| &= \int_t^0 e^{\epsilon\gamma(p_1+1)t} \epsilon\gamma(p_1 + 1) \, |\eta_1 - \eta_2| \\
&\leq \int_t^0 e^{\epsilon\gamma(p_1+1)\tau} \epsilon\gamma(p_1 + 1) \, |\eta_1 - \eta_2|
\end{aligned}
$$

and using this inequality in E.2.50 we have that

$$|\eta_1(t) - \eta_2(t)|e^{\epsilon\gamma(p_1+1)t} \leq \frac{\|\Delta_1 - \Delta_2\|}{(p_1+1)} |\eta_0| + \int_t^0 \epsilon\gamma(p_1+1) |\eta_1 - \eta_2| e^{\epsilon\gamma(p_1+1)\tau}. \qquad \text{E.2.51}$$

We can apply Gronwall's lemma to

$$a(t) = |\eta_1(t) - \eta_2(t)| e^{\epsilon\gamma(p_1+1)t}$$

$$b(t) = \epsilon\gamma(p_1+1)$$

$$c = \frac{\|\Delta_1 - \Delta_2\|}{(p_1+1)} |\eta_0|$$

to obtain

$$|\eta_1(t) - \eta_2(t)| e^{\epsilon\gamma(p_1+1)t} \leq \frac{\|\Delta_1 - \Delta_2\|_{X^1}}{(p_1+1)} |\eta_0| e^{-\epsilon\gamma(p_1+1)t}$$

and by multiplying both sides by $e^{-\epsilon\gamma(p_1+1)t}$ we prove the lemma.

//////

LEMMA L.2.14 *For small ϵ and for fixed h the operator T_h^1 is a contraction.*

Proof In the following computation, we fix $h \in X, s_0, \eta_0 \in PH$. As usual we simplify the notation. In the following text, s indicates $s_{s_0,h}$ and $f(s) = f(s_{s_0,h}, h(s_{s_0,h}))$; also U_s is evaluated at $(0,\tau)$.

$$\begin{aligned}
&\left|T_h^1 \Delta_1(s_0)\eta_0 - T_h^1 \Delta_2(s_0)\eta_0\right| \\
&\leq \int_{-\infty}^0 \left|U_s Df(s)(\eta_{\Delta_1} + \Delta_1\eta_{\Delta_1} - \eta_{\Delta_2} - \Delta_2\eta_{\Delta_2})\right| \\
&\quad + \int_{-\infty}^0 \left|DU_s\eta_{\Delta_1} f(s) - DU_s\eta_{\Delta_2} f(s)\right| \\
&\quad \text{using E.2.18} \\
&\leq \int_{-\infty}^0 e^{b\tau}\theta \left|\eta_{\Delta_1} + \Delta_1\eta_{\Delta_1} - \eta_{\Delta_2} - \Delta_2\eta_{\Delta_2}\right| \\
&\quad + \int_{-\infty}^0 \left|DU_s\eta_{\Delta_1} f(s) - DU_s\eta_{\Delta_2} f(s)\right| \\
&\quad \text{adding and subtracting } \Delta_1\eta_{\Delta_2} \text{ and using E.2.24} \\
&\leq \int_{-\infty}^0 e^{b\tau}\theta \left|\eta_{\Delta_1} - \eta_{\Delta_2}\right| \\
&\quad + \int_{-\infty}^0 e^{b\tau}\theta \left|\Delta_1\eta_{\Delta_1} - \Delta_1\eta_{\Delta_2}\right| + \int_{-\infty}^0 e^{b\tau}\theta \left|\Delta_1\eta_{\Delta_2} - \Delta_2\eta_{\Delta_2}\right|
\end{aligned}$$

$$
\begin{aligned}
& - \int_{-\infty}^{0} e^{b\tau} \beta \tau F \left| \eta_{\Delta_1} - \eta_{\Delta_2} \right| \\
\leq \; & \int_{-\infty}^{0} e^{b\tau} (\theta(p_1 + 1) - \tau \beta F) \left| \eta_{\Delta_1} - \eta_{\Delta_2} \right| \\
& + \int_{-\infty}^{0} e^{b\tau} \theta \left| \eta_{\Delta_1} \right| \| \Delta_1 - \Delta_2 \|_{X^1} .
\end{aligned} \qquad \text{E.2.52}
$$

From now on we shall also write $\|\Delta_1 - \Delta_2\|$ for $\|\Delta_1 - \Delta_2\|_{X^1}$. Thus, using **L.2.11** and **L.2.13**, E.2.52 reads as

$$
\begin{aligned}
& \left| T_h^1 \Delta_1(s_0) \eta_0 \; - T_h^1 \Delta_2(s_0) \eta_0 \right| \\
& \quad \leq \int_{-\infty}^{0} e^{b\tau - 2\epsilon\gamma(p_1+1)\tau} \left[\theta(p_1 + 1) - \tau \beta F \right] \frac{\|\Delta_1 - \Delta_2\|}{p_1 + 1} |\eta_0| \\
& \quad + \int_{-\infty}^{0} e^{b\tau - \epsilon\gamma(p_1+1)\tau} \theta \, |\eta_0| \, \|\Delta_1 - \Delta_2\| \\
& \quad = \|\Delta_1 - \Delta_2\| \, |\eta_0| \\
& \quad \times \left[\frac{\beta F}{[b - 2\epsilon\gamma(p_1 + 1)]^2 (p_1 + 1)} + \frac{\theta}{b - \epsilon\gamma(p_1 + 1)} \right] \\
& \quad + \|\Delta_1 - \Delta_2\| \, |\eta_0| \, \frac{\theta}{b - 2\epsilon\gamma(p_1 + 1)} .
\end{aligned} \qquad \text{E.2.53}
$$

Now we substitute E.2.35 (page 80) with the following, which implies E.2.35 and all the previous lemmas derived from E.2.35:

$$
\epsilon \leq \frac{k}{2} \frac{b}{\gamma(p_1 + 1)} . \qquad \text{E.2.54}
$$

Thus the right hand side of E.2.53 is bounded by

$$
\|\Delta_1 - \Delta_2\| \, |\eta_0| \left[\frac{\beta F}{(1 - k)^2 b^2 (p_1 + 1)} + \frac{2\theta}{(1 - k) b} \right] .
$$

We now impose that the above formula be strictly dominated by $\|\Delta_1 - \Delta_2\| \, |\eta_0|$, that is that the constant multiplying this factor be strictly less than one, which is the definition of T_h^1 being a contraction. Thus we have that

$$
\frac{\beta F}{(1 - k)^2 b^2 (p_1 + 1)} + \frac{2\theta}{(1 - k) b} < 1
$$

if and only if

$$
p_1 > \frac{\beta F + 2(1 - k) b \theta - (1 - k)^2 b^2}{(1 - k)^2 b^2 - 2(1 - k) b \theta} . \qquad \text{E.2.55}
$$

We note that $2(1-k)b\theta - (1-k)^2b^2$ is strictly negative if and only if $2\theta - (1-k)b$ is strictly negative. Thus provided that $(1-k)b > 2\theta$ we have that if

$$p_1 > \frac{\beta F}{(1-k)^2b^2 - 2(1-k)b\theta} \quad \text{E.2.56}$$

then E.2.55 holds and T^1_h is a contraction.

//////

Now we would like to show that the fixed point $\overline{\Delta}$ of T^1_h is the derivative of the fixed point $\bar{h}$ of T. To do so, first we have to show that for any $h \in X \bigcap C^1$ we have $DTh = T^1_h Dh$. Once this is done, the rest is trivial. In fact, if we take a Lipschitz function $h_0 \in C^1$. Obviously, $h_0 \in X$ and $\Delta_0 = Dh_o \in X^1$. We define

$$h_n = Th_{n-1}$$

$$\Delta_n = Dh_n = T^1_{h_{n-1}} Dh_{n-1}$$

Now h_n converges to the fixed point $\bar{h}$ of T and Δ_n to the fixed point $\overline{\Delta}$ of T^1_h, and since the convergence is uniform in X and X^1, it follows from elementary properties of sequences of functions that $\bar{h} \in C^1$ and $\overline{\Delta} = D\bar{h}$.

LEMMA L.2.15 *The derivative of Th is $T^1_h Dh$.*

Proof We show that for every $\zeta > 0$ there exists $\mu > 0$ such that, if $|\sigma| < |\mu|$, then

$$\left\| Th(s_0+\sigma) - Th(s_0) - T^1_h Dh(s_0)\sigma \right\| < \zeta$$

which is the definition of a Fréchet derivative.

Thus, simplifying the notation and summing and subtracting the term $U_{s_{s_0}+\sigma} f(s_{s_0})$, we have:

$$\begin{aligned}
\| Th(s_0+\sigma) \; & - Th(s_0) - T^1_h Dh(s_0)\sigma \| \\
& \le \int_{-\infty}^{0} \left| U_{s_{s_0}+\sigma} f(s_{s_0+\sigma}) - U_{s_{s_0}} f(s_{s_0}) \right| \\
& \quad + \left\| T^1_h Dh(s_0)\sigma \right\| \\
& \le \int_{-\infty}^{0} \left| U_{s_{s_0}+\sigma} f(s_{s_0+\sigma}) - U_{s_{s_0}+\sigma} f(s_{s_0}) \right| \\
& \quad + \int_{-\infty}^{0} \left| U_{s_{s_0}+\sigma} f(s_{s_0}) - U_{s_{s_0}} f(s_{s_0}) \right| \\
& \quad + \left\| T^1_h Dh(s_0)\sigma \right\| .
\end{aligned}$$

Use now the results E.2.18 (page 70) to E.2.21 on the evolution operator U and equation E.2.47 (page 88) for the bound of $\left\| T_h^1 Dh(s_0)\sigma \right\|$ and obtain:

$$\begin{aligned} \| Th(s_0+\sigma) \; &- Th(s_0) - T_h^1 Dh(s_0)\sigma \| \\ &\leq \int_{-\infty}^{0} e^{b\tau}\theta(p_1+1)\left|s_{s_0+\sigma}(\tau) - s_{s_0}(\tau)\right| \\ &\quad + \int_{-\infty}^{0} \beta F e^{b\tau} \int_{\tau}^{0} \left|s_{s_0+\sigma}(r) - s_{s_0}(r)\right| \mathrm{d}r \\ &\quad + \left[\frac{\theta(p_1+1)}{b-\epsilon\gamma(p_1+1)} + \frac{\beta F}{[b-\epsilon\gamma(p_1+1)]^2}\right]|\sigma| \end{aligned}$$

Now we shall use again **L.2.6** (page 78) applied to $\left|s_{s_0+\sigma} - s_{s_0}\right|$ to obtain that

$$\begin{aligned} \| Th(s_0+\sigma) \; &- Th(s_0) - T_h^1 Dh(s_0)\sigma \| \\ &\leq \int_{-\infty}^{0} e^{b\tau}\theta(p_1+1)\left|s_0+\sigma-s_0\right| e^{-\epsilon\gamma(p_1+1)\tau} \\ &\quad + \int_{-\infty}^{0} \beta F e^{b\tau} \int_{\tau}^{0} \left|s_0+\sigma-s_0\right| e^{-\epsilon\gamma(p_1+1)r} \mathrm{d}r \\ &\quad + \left[\frac{\theta(p_1+1)}{b-\epsilon\gamma(p_1+1)} + \frac{\beta F}{[b-\epsilon\gamma(p_1+1)]^2}\right]|\sigma| \\ &= \int_{-\infty}^{0} \theta(p_1+1)\left|\sigma\right| e^{(b-\epsilon\gamma(p_1+1))\tau} \\ &\quad + \int_{-\infty}^{0} \beta F e^{b\tau}\left|\sigma\right|\left[\frac{1}{\epsilon\gamma(p_1+1)}e^{-\epsilon\gamma(p_1+1)\tau} - \frac{1}{\epsilon\gamma(p_1+1)}\right] \\ &\quad + \left[\frac{\theta(p_1+1)}{b-\epsilon\gamma(p_1+1)} + \frac{\beta F}{[b-\epsilon\gamma(p_1+1)]^2}\right]|\sigma| \end{aligned}$$

Solving the integrals:

$$\begin{aligned} \| Th(s_0+\sigma) \; &- Th(s_0) - T_h^1 Dh(s_0)\sigma \| \\ &\leq \frac{\theta(p_1+1)}{b-\epsilon\gamma(p_1+1)}\left|\sigma\right| \\ &\quad + \frac{\beta F}{\epsilon\gamma(p_1+1)\left(b-\epsilon\gamma(p_1+1)\right)}\left|\sigma\right| \\ &\quad - \frac{\beta F}{\epsilon\gamma(p_1+1)b}\left|\sigma\right| \\ &\quad + \left[\frac{\theta(p_1+1)}{b-\epsilon\gamma(p_1+1)} + \frac{\beta F}{[b-\epsilon\gamma(p_1+1)]^2}\right]|\sigma| \end{aligned}$$

and being $b > b - \epsilon\gamma(p_1+1)$ we have that the right hand side of the above equation is bounded by a strictly positive constant L multiplying $|\sigma|$. It is thus immediate that we can satisfy the condition for the Fréchet derivative to exist. In fact, for every $\zeta > 0$ there exists a $\mu > 0$ such that $\forall\,|\sigma| < \mu$ one has $\left\| Th(s_0+\sigma) - Th(s_0) - T_h^1 Dh(s_0)\sigma \right\| < \zeta$; just put $\mu = \zeta/L$.

//////

At this point, we note that E.2.54 (page 92) and

$$p_1 > \frac{\beta F + (1-k)b\theta}{(1-k)^2b^2 - 2(1-k)b\theta} \qquad \text{E.2.57}$$

imply the previous lemmas, since they imply E.2.37 (page 81), E.2.42 (page 84), E.2.48 (page 89) and E.2.56 (page 93). First of all note that

$$\begin{aligned}\frac{\beta F + (1-k)b\theta}{(1-k)^2b^2 - 2(1-k)b\theta} &= \frac{1}{(1-k)}\ \frac{\beta F + (1-k)b\theta}{(1-k)b^2 - 2b\theta}\\ &= \frac{1}{(1-k)}\ \frac{\beta F}{(1-k)b^2 - 2b\theta} + \frac{b\theta}{(1-k)b^2 - 2b\theta}.\end{aligned}$$

We now use the above equality to show each implication.

−E.2.57 ⇒ E.2.37 because $0 < k < 1$ and

$$\begin{aligned}p_1 &> \frac{\beta F + (1-k)b\theta}{(1-k)^2b^2 - 2(1-k)b\theta}\\ &> \frac{\beta F}{(1-k)b^2 - 2b\theta} + \frac{b\theta}{(1-k)b^2 - 2b\theta}\\ &> \frac{\beta F + b\theta}{(1-k)b^2 - b\theta};\end{aligned}$$

−E.2.57 ⇒ E.2.42 because $0 < k < 1$ and

$$\begin{aligned}p_1 &> \frac{\beta F + (1-k)b\theta}{(1-k)^2b^2 - 2(1-k)b\theta}\\ &> \frac{\beta F}{(1-k)b^2 - 2b\theta} + \frac{b\theta}{(1-k)b^2 - 2b\theta}\\ &> \frac{k\beta F}{(1-k)b^2 - b\theta} + 0\\ &> \frac{k\beta F}{(1-k)b^2 - b\theta} - 1;\end{aligned}$$

−E.2.57 ⇒ E.2.48 is straightforward:

$$\begin{aligned}p_1 &> \frac{\beta F + (1-k)b\theta}{(1-k)^2b^2 - 2(1-k)b\theta}\\ &> \frac{\beta F + (1-k)b\theta}{(1-k)^2b^2 - (1-k)b\theta};\end{aligned}$$

−E.2.57 ⇒ E.2.56 because $(1-k)b-\theta > 0$ and

$$\begin{aligned} p_1 &> \frac{\beta F + (1-k)b\theta}{(1-k)^2b^2 - 2(1-k)b\theta} \\ &> \frac{\beta F}{(1-k)^2b^2 - 2(1-k)b\theta}. \end{aligned}$$

To obtain a bound on ϵ simply substitute E.2.57 in E.2.54:

$$\epsilon \leq \frac{kb}{2\gamma} \frac{(1-k)^2b^2 - 2(1-k)b\theta}{\beta F + (1-k)^2b^2 - (1-k)b\theta}. \qquad \text{E.2.58}$$

2.4.3 Exponential attraction and asymptotic completeness

In this section we shall present results regarding the rate of attraction of the trajectories of system E.2.4 (page 61) to the invariant manifold $\mathcal{M}$ obtained as the graph of a function. In fact, so far we have just proved the existence of a C^1 invariant manifold, and in order for the manifold to be "inertial" we have to show that all trajectories are attracted to it in an exponential fashion. In the next lemma, originally proved in [47-IAN-1998], we show that this is indeed the case; additionally we shall then prove a stronger result, not proved in [47-IAN-1998], i.e. the asymptotic completeness of the Inertial Manifold. Recall that according to the definition **D.1.4** (page 17) an Inertial Manifold is asymptotically complete if any trajectory $v(t)$ of the dynamical system can be exponentially approximated by a trajectory $\bar{v}(t)$ completely contained in the Inertial Manifold. In order to prove asymptotic completeness of our Inertial Manifold, we shall use the technique and results developed in [60-ROB-1996].

Before proceeding with the actual proofs of the lemmas contained in this section, we would like to make some comments on one equation that an invariant manifold satisfies:

$$\frac{\mathrm{d}}{\mathrm{d}t} h(s(t)) = -B(s)h(s) + f(s, h(s)). \qquad \text{E.2.59}$$

We proved it with equation E.2.30 (page 78), when s is the solution of the inertial form. In order to prove that it is valid for a solution $s(t)$ of E.2.4, we follow [39-TEM-1998], page 550.

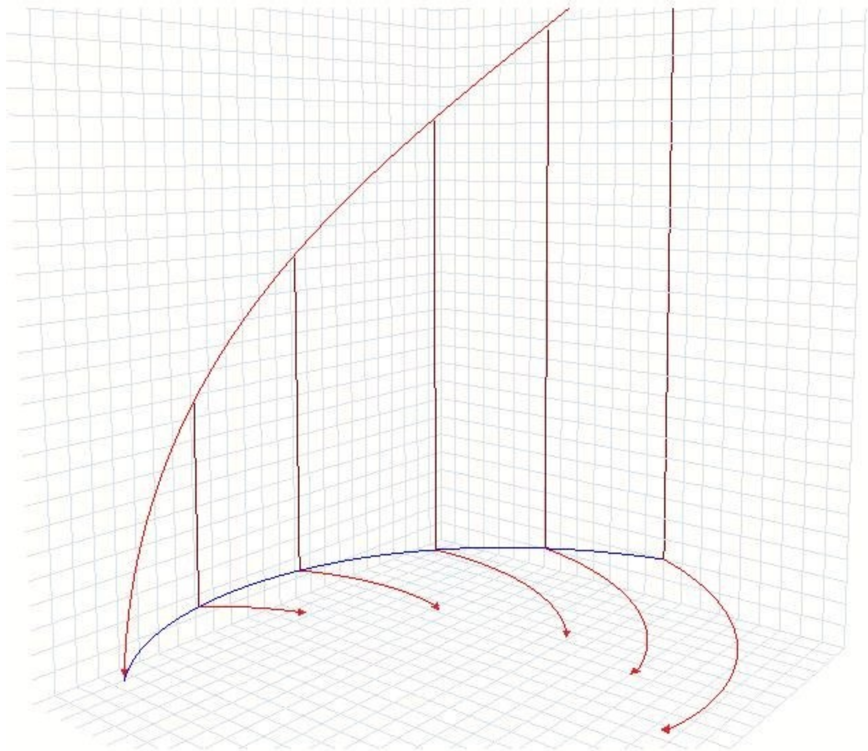
Take now any initial condition $Z_0 = (s_0, \varphi_0)$ and the solution $(s(t), \varphi(t))$ of E.2.4 (page 61) associated to Z_0. It is clear that $(s(t), h(s(t)))$ belongs to the Inertial Manifold;

nevertheless it is not the solution of E.2.4; it is just a curve, given by the projection on the Manifold of the flow starting outside the Manifold. If if it were a solution of E.2.4, then all Inertial Manifolds would be asymptotically complete, which is just not the case as we show in section **2.5.2**.

Define now for any time t the solution $\tilde{s}_{s(t),h}(\tau)$ of the inertial form E.2.14 (page 69) starting at time $\tau = 0$ at point $s(t)$. Using equation E.2.59 applied to $\tilde{s}_{s(t),h}(\tau)$, given any time t and for any time τ, one has that (without suppressing any notation)

$$\frac{\mathrm{d}}{\mathrm{d}\tau}h(s_{s(t),h}(\tau)) = -B(s_{s(t),h}(\tau))h(s_{s(t),h}(\tau)) + f(s_{s(t),h}(\tau), h(s_{s(t),h}(\tau))).$$

which is true also for $\tau = 0$, which proves that E.2.59 is true for any solution $s(t)$ of E.2.4. We can see the curve represented by $(s(t), h(s(t)))$ in the next graphic:



This graphic corresponds to the dynamical system in cylindrical coordinates:

$$\begin{aligned}\dot{z} &= -z,\\ \dot{r} &= 1 - r,\\ \dot{\theta} &= 1 - r + z,\end{aligned} \qquad \text{E.2.60}$$

which will be extensively studied in section **2.5.1**. Here it just suffices to know that the hyperplane $\mathcal{Z} = \{z = 0\}$ is an Inertial Manifold. We have drawn in red 6 flows of E.2.60. The one descending towards the hyperplane $\mathcal{Z}$ is the solution corresponding to the initial condition $z_0 = 3, r_0 = 2, \theta_0 = \pi$, and is the equivalent of the flow $(s(t), \varphi(t))$. The other five are solutions lying on $\mathcal{Z}$ and corresponding to the initial conditions starting from the projection of the flow onto the manifold at different times. We have then drawn in blue the curve represented by $(s(t), h(s(t))$: this curve is the projection on the Inertial Manifold of the flow starting outside the Inertial Manifold. We can see graphically that this curve does not correspond to a flow on the Manifold.

Let us now continue by showing the next lemma.

LEMMA L.2.16 *The invariant manifold is exponentially attracting.*

Proof We follow the method of proof given in [41-CHO-1992], [64-SEL-1992] and [61-ROD-2007] and [39-TEM-1998].

Given any solution $(s(t), \varphi(t))$ of the system E.2.4 for any initial condition, we want to evaluate the difference

$$z(t) = \varphi(t) - h(s(t)).$$

First of all, note that the fact that h is invariant, means that, as we have just seen above, it satisfies the equation

$$\frac{\mathrm{d}}{\mathrm{d}t} h(s(t)) = -B(s)h(s) + f(s, h(s)). \tag{E.2.61}$$

Notice that the derivative of $h(s(t))$, apart from E.2.61, also satisfies the equation

$$\frac{\mathrm{d}}{\mathrm{d}t} h(s(t)) = \frac{\mathrm{d}h}{\mathrm{d}s}\frac{\mathrm{d}s}{\mathrm{d}t} = (Dh)(\epsilon g(s, h(s)));$$

and thus the following relation holds:

$$\epsilon Dhg(s, h(s)) = -B(s)h(s) + f(s, h(s)). \tag{E.2.62}$$

In the following we shall write h for $h(s)$. Now we can differentiate $z(t)$ and obtain

$$\begin{aligned}
\dot{z} &= \dot{\varphi} - Dh\dot{s} \\
&= -B(s)\varphi + f(s,\varphi) - \epsilon Dhg(s,\varphi) \\
&= -B(s)z - B(s)h + f(s,z+h) - \epsilon Dhg(s,z+h) \\
&\quad \text{using E.2.62} \\
&= -B(s)z + \epsilon Dhg(s,h) - f(s,h) + f(s,z+h) - \epsilon Dhg(s,z+h) \\
&= -B(s)z + \epsilon\Big(Dhg(s,h) - Dhg(s,z+h)\Big) + f(s,z+h) - f(s,h).
\end{aligned} \qquad \text{E.2.63}$$

We now take the scalar product of equation E.2.63 with z to obtain

$$\begin{aligned}
\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}|z|^2 = -\langle z, B(s)z\rangle + \epsilon\langle z, Dhg(s,h) - Dhg(s,z+h)\rangle \\
+ \langle z, f(s,z+h) - f(s,h)\rangle.
\end{aligned}$$

Now

$$\langle z, Dh\big(g(s,h) - g(s,z+h)\big)\rangle \le |z|^2\, p_1\gamma$$

and

$$\langle z, f(s,z+h) - f(s,h)\rangle \le \theta\,|z|^2\,.$$

Hence, since $\langle z, Bz\rangle \ge b\,|z|^2$, we have

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}|z|^2 \le (-b + \epsilon p_1\gamma + \theta)\,|z|^2\,. \qquad \text{E.2.64}$$

If

$$\epsilon < \frac{b-\theta}{p_1\gamma} \qquad \text{E.2.65}$$

then $(-b + \epsilon p_1\gamma + \theta)$ is negative, permitting us to conclude that z tends to 0 exponentially.

The following short and simple computation shows that E.2.54 (page 92) and $(1-k)b > 2\theta$ imply E.2.65.

Consider $(1-k)b > 2\theta$; this is equivalent to $kb/2 < b/2 - \theta$, which implies $kb/2 < b - \theta$. On the other hand for any $\epsilon, \gamma, p_1 \ge 0$ we have that $\epsilon\gamma p_1 \le \epsilon\gamma(p_1+1)$; by E.2.54 the right hand side is in turn less than $kb/2$. Chaining all the inequalities we have

$$\epsilon\gamma p_1 \le \epsilon\gamma(p_1+1) \le \frac{kb}{2} < b - \theta$$

which is exactly E.2.65.

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We have thus completed the proof of theorem **T.2.3** (page 75), that is, we have shown the existence of an invariant manifold which attracts exponentially all orbits.

We now proceed to show the asymptotic completeness of our Inertial Manifold.

LEMMA L.2.17 *The Inertial Manifold is asymptotically complete.*

Proof As in [60-ROB-1996] and [41-CHO-1992] we consider an initial condition $u_0 = (s_0, \varphi_0)$ and both the solution $u(t) = (s(t), \varphi(t))$ of E.2.2 (page 59), and any solution $\bar{u}(t) = (\bar{s}(t), h(\bar{s}(t)))$ on the Inertial Manifold, where $\bar{s}(t)$ is any solution of E.2.14 (page 69). Let's calculate the distance between $u(t)$ and $\bar{u}(t)$. By our choice of norm:

$$\begin{aligned} |u(t) - \bar{u}(t)| &\leq |s(t) - \bar{s}(t)| + |\varphi(t) - h(\bar{s}(t))| \\ &\leq |s(t) - \bar{s}(t)| + |\varphi(t) - h(s(t))| + |h(s(t)) - h(\bar{s}(t))| \\ &\leq (p_1 + 1)\,|s(t) - \bar{s}(t)| + |\varphi(t) - h(s(t))|\,. \end{aligned} \qquad \text{E.2.66}$$

From the previous lemma we know that $|\varphi(t) - h(s(t))| \leq C_0 e^{-\varsigma t}$, where C_0 is a constant depending on the initial condition, that is $C_0 = |\varphi(0) - h(s(0))|$. Clearly the difference between $s(t)$ and $\bar{s}(t)$ will not tend to zero, as $\bar{s}(t)$ is just any solution of E.2.14. However if we show that $|s(t) - \bar{s}(t)|$ tends to zero exponentially for some *particular* solution $\bar{s}(t)$, then we have proved our lemma. In fact for a given initial condition u_0 take this particular solution of the inertial form and call it $\bar{s}$; then the inequalities in E.2.66 show us that $|u(t) - \bar{u}(t)|$ tends to zero exponentially.

We note that we shall not prove this result directly, rather we shall use some of the results in [60-ROB-1996].

First of all we rewrite the equation for $s(t)$ as

$$\begin{aligned} \dot{s} &= \epsilon g(s, \varphi) \\ &= \epsilon g(s, \varphi) - \epsilon g(s, h(s)) + \epsilon g(s, h(s)) \\ &= \epsilon g(s, h(s)) + \delta(t, s_0, \varphi_0) \end{aligned}$$

where $\delta(t, s_0, \varphi_0) = \epsilon g(s, \varphi) - \epsilon g(s, h(s))$.

Note that we have rewritten the equation for $s(t)$ as a perturbation of the inertial form. After we have shown that the term δ tends to zero exponentially, we shall use theorem 3.2 in [60-ROB-1996] to show that under these conditions, there exists a solution $\bar{s}(t)$ that tends exponentially to $s(t)$.

This theorem in [60-ROB-1996] is stated for a general ODE of the form

$$\dot{x} = r(x) \qquad \text{E.2.67}$$

so that, setting $x = s$ and $r = \epsilon g$, our equation $\dot{s} = \epsilon g(s, h(s))$ is of the form in E.2.67 and we can use these results directly. Robinson then compares this system with a perturbation

$$\dot{x} = R(x). \qquad \text{E.2.68}$$

Theorem 3.2 of [60-ROB-1996] states that, given an ODE of the form E.2.67 and given a perturbation of it of the form E.2.68, such that for any $x(t)$ solution of E.2.68 $|R(x) - r(x)| \le Be^{-\mu t}$ for some $\mu > 0$, with $r(x)$ Lipschitz and such that any two solutions x_1 and x_2 of E.2.67 satisfy

$$|x_1(t) - x_2(t)| \le C\,|x_1(0) - x_2(0)|\,e^{-\nu t}$$

where $0 < \nu < \mu$, then for any solution $x(t)$ of E.2.68 there exists a solution $y(t)$ of E.2.67 such that

$$|x(t) - y(t)| \le De^{-\mu t}.$$

Notice that $y(t)$ does not necessarily start at $x(0)$, that is the approximating flow does not necessarily start at the projection of the the flow on the manifold, as we saw in the introduction of this section. More of this will be seen in section **2.5.1**.

In our case, setting $x = s$, we can write

$$r(x) = \epsilon g(x, h(x)),$$

$$R(x) = \epsilon g(x, h(x)) + \delta(t, x_0).$$

First we show that $|R(x) - r(x)| \leq Be^{-\mu t}$:

$$\begin{aligned} |R(s) - r(s)| &= |\delta(t, s_0)| \\ &= |\epsilon g(s, \varphi) - \epsilon g(s, h(s))| \\ &\leq \epsilon\gamma \left[|s - s| + |\varphi - h(s)|\right] \\ &\leq \epsilon\gamma C_0 e^{-\varsigma t}, \end{aligned}$$

where we have used the result of lemma **L.2.16** (page 98). Thus the first condition of the theorem holds with $B = \epsilon\gamma C_0$ and $\mu = \varsigma = b - \epsilon p_1 \gamma - \theta$. Now note that the second condition of the theorem is exactly lemma **L.2.6** (page 78), with $\nu = \epsilon\gamma(p_1 + 1)$. The condition $\nu < \mu$ is thus $\epsilon\gamma(p_1+1) < b - \epsilon p_1 \gamma - \theta$, which is true if $\epsilon\gamma(p_1+1) < (b-\theta)/2$. At this point note that the conditions E.2.54 (page 92) and $(1-k)b > \theta$ imply

$$\epsilon\gamma(p_1 + 1) < \frac{1}{2}kb < \frac{1}{2}(b - \theta),$$

and the proof is complete.

//////

2.4.4 Further generalisation

As we have seen so far, one of the major contributions of our paper [47-IAN-1998] has been to generalise results for the existence of Inertial Manifold to dynamical systems of the form

$$\dot{u} = -A(u)u + f(u).$$

Nevertheless, this generalisation so far has been confined to a particular case, namely a system where $A(u)$ is of the form E.2.5 (page 61)

$$A(u) = \begin{pmatrix} \mathbb{0} & \mathbb{0} \\ \mathbb{0} & B(s) \end{pmatrix}.$$

In this section we shall proceed to present more general results. Indeed we shall show how one can easily adapt not only the Lyapunov-Perron method of proof employed so far, but also the detailed proof itself. In fact, there are just a few points where one has to take care of some algebraic details in order for the proof to hold unchanged. Thus, rather than repeating the whole proof, we prefer to indicate for each step the changes one has to make.

First of all, we shall just consider a family of operators like this:

$$A(u) = \begin{pmatrix} B_{ss}(s,\varphi) & B_{s\varphi}(s,\varphi) \\ B_{\varphi s}(s,\varphi) & B_{\varphi\varphi}(s,\varphi) \end{pmatrix},$$

where the subscripts are not derivatives but merely labels, and a dynamical system like

$$\begin{pmatrix} \dot{s} \\ \dot{\varphi} \end{pmatrix} = -\begin{pmatrix} B_{ss}(s,\varphi) & B_{s\varphi}(s,\varphi) \\ B_{\varphi s}(s,\varphi) & B_{\varphi\varphi}(s,\varphi) \end{pmatrix}\begin{pmatrix} s \\ \varphi \end{pmatrix} + \begin{pmatrix} g(s,\varphi) \\ f(s,\varphi) \end{pmatrix}, \tag{E.2.69}$$

where we have incorporated the ϵ term into the function g. We do this, as we have now shifted our focus from the fact that g is a small function, to a general relation among the various eigenvalues and Lipschitz constants.

We shall assume that E.2.69 admits an absorbing ball, so that we can modify all our functions as in section 2.3.1. This way, we can assume that we say Lipschitz for globally Lipschitz, and bounded for globally bounded.

In such a case the inertial form equivalent to E.2.14 (page 69) is given by

$$\dot{s} = -B_{ss}(s,h(s))s - B_{s\varphi}(s,h(s))h(s) + g(s,h(s)). \tag{E.2.70}$$

We can now introduce the function $g_1(s,\varphi) = -B_{s\varphi}(s,h(s))\varphi + g(s,\varphi)$, which is bounded and Lipschitz if $B_{s\varphi}$, h and g are Lipschitz. So E.2.70 looks like

$$\dot{s} = -B_{ss}(s,h(s))s + g_1(s,h(s)). \tag{E.2.71}$$

If we assume that B_{ss} is Lipschitz with Lipschitz constant β_{ss}, then for any Lipschitz function h classical results guarantee that E.2.71 admits a unique solution for any initial condition. We shall call $s_{s_0,h}$ such a solution.

Consider now the dynamics:

$$\dot{\varphi} = -B_{\varphi s}(s_{s_0,h},h(s_{s_0,h}))s_{s_0,h} - B_{\varphi\varphi}(s_{s_0,h},h(s_{s_0,h}))\varphi + f(s_{s_0,h},h(s_{s_0,h})),$$

and introduce the function $f_1(s,\varphi) = -B_{\varphi s}(s,\varphi)s + f(s,\varphi)$ so that we can rewrite the above equation as

$$\dot{\varphi} = -B_{\varphi\varphi}(s_{s_0,h},h(s_{s_0,h}))\varphi + f_1(s_{s_0,h},h(s_{s_0,h})). \tag{E.2.72}$$

Once again, f_1 is a bounded Lipschitz function if so are $B_{\varphi s}$, h and f. Thus we have *diagonalised* our equation E.2.69 to this form

$$\begin{pmatrix} \dot{s} \\ \dot{\varphi} \end{pmatrix} = -\begin{pmatrix} B_{ss}(s,\varphi) & \mathbb{O} \\ \mathbb{O} & B_{\varphi\varphi}(s,\varphi) \end{pmatrix} \begin{pmatrix} s \\ \varphi \end{pmatrix} + \begin{pmatrix} g_1(s,\varphi) \\ f_1(s,\varphi) \end{pmatrix}. \qquad \text{E.2.73}$$

Remember that the system has been appropriately prepared, so that the following constants make sense:

- Φ_M as the radius of the attracting ball in the φ coordinates,
- S_M as the radius of the attracting ball in the s coordinates.
- $\beta_{\varphi\varphi}$ the Lipschitz constant of $B_{\varphi\varphi}$,
- β_{ss} the Lipschitz constant of B_{ss},
- $\mathcal{B}_{ss}$ as the superior limit on (s,φ) of the maximum eigenvalue of B_{ss}, in case B_{ss} is self-adjoint and positive, and as the biggest positive constant such that $\langle B_{ss}(u)s, s\rangle \leq \mathcal{B}_{ss}\,|s|^2$,
- $\mathcal{B}_{\varphi\varphi}$ as the inferior limit on (s,φ) of the minimum eigenvalue of $B_{\varphi\varphi}$,in case B_{ss} is self-adjoint and positive, and as the smallest positive constant such that $\langle B_{\varphi\varphi}(u)\varphi, \varphi\rangle \geq \mathcal{B}_{\varphi\varphi}\,|\varphi|^2$,
- γ_1 the Lipschitz constant of g_1,
- F_1 the maximum of f_1,
- θ_1 the Lipschitz constant of f_1,

We can now consider the evolution operator, depending on time, defined by $C_s(t) = B_{\varphi\varphi}(s(t), h(s(t)))$. This operator satisfies the same hypothesis as the evolution operator defined in section 2.3.6. The only thing we have to prove that $C_s(t)$ is uniformly continuous with respect to t. This is true if for every $\epsilon > 0$ there exists a $\delta > 0$ such that for every $|\tau| < \delta$ we have that $\|C_s(t+\tau) - C_s(t)\| < \epsilon$. As by hypothesis $B_{\varphi\varphi}$ and h are Lipschitz, one has

$$\|C_s(t+\tau) - C_s(t)\| = \left\|B_{\varphi\varphi}(s(t+\tau), h(s(t+\tau))) - B_{\varphi\varphi}(s(t), h(s(t)))\right\|$$

$$\leq \beta_{\varphi\varphi}(p_1+1)\,|s(t+\tau) - s(t)|$$

where p_1 is the Lipschitz constant of h; thus $C_s(t)$ is continuous in the uniform operator topology.

Again, as we saw in section 2.3.2, note that $C_s(t)$ depends on time through a function of time and not on the variable of differentiation.

This example of the use of the Lipschitz constants of $B_{\varphi\varphi}$ and h is really clarifying. It is telling us that whenever in the proof of theorem **T.2.3** (page 75) we find the Lipschitz constant β we shall just substitute it with $\beta_{\varphi\varphi}(p_1+1)$. In fact, the family of operators $C_s(t) = -B_{\varphi\varphi}(s, h(s))$ is Lipschitz with respect to s with Lipschitz constant $\beta_{\varphi\varphi}(p_1+1)$.

Clearly we can now simply define the operator T using the same formula as before:

$$Th(s_0) = \int_{-\infty}^{0} U_{s_{0,h}}(0,\tau) f_1(s_{0,h}(\tau), h(s_{0,h}(\tau)))\mathrm{d}\tau.$$

We want to prove that T maps the space X of bounded, Lipschitz functions to itself and that it is a contraction. Then we shall take its fixed point and prove that it is invariant and exponentially attracting.

The fact that a fixed point of T is invariant can be proved using **exactly** the same method we used in section 2.4.1.

It is immediate that this operator maps functions bounded by p to functions bounded by p, as the proof of lemma **L.2.5** (page 78) holds without any change at all.

In order for us to prove that T maps Lipschitz functions to Lipschitz functions, we can rewrite equation E.2.33 (page 80):

$$\begin{aligned}
|Th(s_0) - Th(s_1)| \le\ & \int_{-\infty}^{0} \left| U_{s_{s_0}}(0,\tau) f_1(s_{s_0}, h(s_{s_0})) - U_{s_{s_1}}(0,\tau) f_1(s_{s_1}, h(s_{s_1}))\right| \mathrm{d}\tau \\
\le\ & \int_{-\infty}^{0} \left|\left[U_{s_{s_0}}(0,\tau) - U_{s_{s_1}}(0,\tau)\right] f_1(s_{s_0}, h(s_{s_0}(\tau)))\right| \mathrm{d}\tau \\
& + \int_{-\infty}^{0} \left| U_{s_{s_1}}(0,\tau)\left[f_1(s_{s_0}, h(s_{s_0})) - f_1(s_{s_1}, h(s_{s_1}))\right]\right| \mathrm{d}\tau \\
\le\ & \int_{-\infty}^{0} \beta_{\varphi\varphi}(p_1+1) F_1 e^{\beta_{ss}\tau} \left[\int_{\tau}^{0} \left|s_{s_0}(\sigma) - s_{s_1}(\sigma)\right| \mathrm{d}\sigma\right] \mathrm{d}\tau \\
& + \int_{-\infty}^{0} e^{\beta_{ss}\tau} \theta_1(p_1+1) \left|s_{s_0}(\tau) - s_{s_1}(\tau)\right| \mathrm{d}\tau,
\end{aligned}$$

where we have substituted β with $\beta_{\varphi\varphi}(p_1+1)$. This is because E.2.21 (page 71) holds with the Lipschitz constant of C_s with respect to s, that is with $\beta_{\varphi\varphi}(p_1+1)$. It is clear from this point on, that the rest of the proof of Lemma **L.2.7** (page 79) will be exactly the same, if one can find an equivalent equation E.2.31 given in **L.2.6**.

As in the proof of **L.2.6**, we shall evaluate the difference of two solutions of the inertial form E.2.71.

$$
\begin{aligned}
\left|s_{s_0}(t) - s_{s_1}(t)\right| \le & |s_0 - s_1| + \int_t^0 \gamma_1(p_1+1)\left|s_{s_0}(\sigma) - s_{s_1}(\sigma)\right| \mathrm{d}\sigma \\
& + \int_t^0 \left|B_{ss}(s_{s_0}, h(s_{s_0}))s_{s_0} - B_{ss}(s_{s_1}, h(s_{s_1}))s_{s_1}\right| \mathrm{d}\sigma \\
\le & |s_0 - s_1| + \int_t^0 \gamma_1(p_1+1)\left|s_{s_0}(\sigma) - s_{s_1}(\sigma)\right| \mathrm{d}\sigma \\
& + \int_t^0 \left|B_{ss}(s_{s_0}, h(s_{s_0}))s_{s_0} - B_{ss}(s_{s_0}, h(s_{s_0}))s_{s_1}\right| \mathrm{d}\sigma \\
& + \int_t^0 \left|B_{ss}(s_{s_0}, h(s_{s_0}))s_{s_1} - B_{ss}(s_{s_1}, h(s_{s_1}))s_{s_1}\right| \mathrm{d}\sigma \\
\le & |s_0 - s_1| + \int_t^0 \gamma_1(p_1+1)\left|s_{s_0}(\sigma) - s_{s_1}(\sigma)\right| \mathrm{d}\sigma \\
& + \int_t^0 \mathcal{B}_{ss}\left|s_{s_0}(\sigma) - s_{s_1}(\sigma)\right| + S_M\beta_{ss}(p_1+1)\left|s_{s_0}(\sigma) - s_{s_1}(\sigma)\right| \mathrm{d}\sigma
\end{aligned}
$$

Is is clear now that E.2.31 holds with the following formulation:

$$
\left|s_{s_0}(t) - s_{s_1}(t)\right| < |s_0 - s_1|\, e^{-\tilde{\gamma}t}.
$$

where $\tilde{\gamma} = \gamma_1(p_1+1) + \mathcal{B}_{ss} + S_M\beta_{ss}(p_1+1)$.

We have thus demonstrated that the operator T is well defined. In fact one can simply take the proof of lemma **L.2.7** and substitute $\tilde{\gamma}$ for $\epsilon\gamma$ and $\beta_{\varphi\varphi}(p_1+1)$ for β and obtain equivalent constraints of all the various constants. As we said before, in this section we are not interested in solving the actual algebra, but *just* in showing that the theory of Inertial Manifolds can be extended with some little efforts to a larger class of functions than those generally studied in the literature. The *only* difficulty would reside neither in the method of proof, nor in the actual algebra involved in the proof, but in representing a dynamical system in the form E.2.69 in such a way that the various Lipschitz constants and the constants $\mathcal{B}_{ss}$ and $\mathcal{B}_{\varphi\varphi}$ satisfy the condition given by the proof. One can think of this condition as an extended "Gap Condition"; in fact, it will represent a relation between these constants, though not in a simple form as the standard gap condition, as it will incorporate the Lipschitz constants of both $B_{\varphi\varphi}$ and B_{ss}. We will speak about the gap condition more extensively in section **2.4.5**.

We now continue with the proof of the fact that T is a contraction. Again, if we look at equation E.2.39 (page 83), we have to substitute β with $\beta_{\varphi\varphi}(p_1+1)$. The other thing to prove is an inequality similar to E.2.38. As in the proof of Lemma **L.2.8**, we take the difference of two solutions corresponding to the same initial condition, but to two different functions $h_1, h_2 \in X$, for negative times:

$$\begin{aligned}
\left|s_{h_1}(t) - s_{h_2}(t)\right| \leq & \int_t^0 \left|B_{ss}(s_{h_1}, h_1(s_{h_1}))s_{h_1} - B_{ss}(s_{h_2}, h_2(s_{h_2}))s_{h_2}\right| \\
& + \int_t^0 \left|g_1(s_{h_1}, h_1(s_{h_1})) - g_1(s_{h_2}, h_2(s_{h_2}))\right| \\
\leq & \int_t^0 \left|B_{ss}(s_{h_1}, h_1(s_{h_1}))s_{h_1} - B_{ss}(s_{h_1}, h_1(s_{h_1}))s_{h_2}\right| \\
& + \int_t^0 \left|B_{ss}(s_{h_1}, h_1(s_{h_1}))s_{h_2} - B_{ss}(s_{h_2}, h_2(s_{h_2}))s_{h_2}\right| \\
& + \int_t^0 \gamma_1(p_1+1)\Big[\left|s_{h_1} - s_{h_2}\right| + \frac{\|h_1 - h_2\|}{p_1+1}\Big] \\
\leq & \int_t^0 \mathcal{B}_{ss}\left|s_{h_1} - s_{h_2}\right| \\
& + \int_t^0 (S_M\beta_{ss} + \gamma_1)(p_1+1)\Big[\left|s_{h_1} - s_{h_2}\right| + \frac{\|h_1 - h_2\|}{p_1+1}\Big] \\
\leq & \int_t^0 \Big[\mathcal{B}_{ss} + (S_M\beta_{ss} + \gamma_1)(p_1+1)\Big]\Big[\left|s_{h_1} - s_{h_2}\right| + \frac{\|h_1 - h_2\|}{p_1+1}\Big]
\end{aligned}$$

and we get the same inequality E.2.38:

$$\left|s_{h_1}(t) - s_{h_2}(t)\right| < \frac{\|h_1 - h_2\|}{p_1+1}\left[e^{-\tilde{\gamma}t} - 1\right]$$

where $\tilde{\gamma} = \mathcal{B}_{ss} + (S_M\beta_{ss} + \gamma_1)(p_1+1)$.

Before proceeding to prove that the fixed point is indeed exponentially attracting, we shall prove that it is C^1. Note that there are two reasons why we want this. The first one is that this result is mathematically interesting on its own. The second one is that we need C^1 to use exactly the same technique of section 2.4.3 to prove that the fixed point is exponentially attracting.

We remember that in order to prove this result, we looked for a solution of E.2.44 (page 87), that is the linearised equation of the inertial form. As we have done so far, we study the equation equivalent to E.2.44:

$$\begin{aligned}
&\dot{\eta} = -B_{ss}(s_{s_0,h}, h(s_{s_0,h}))\eta + Dg_1(s_{s_0,h}, h(s_{s_0,h}))(\eta + \Delta(s_{s_0,h})\eta) \\
&\eta(0) = \eta_0
\end{aligned} \qquad \text{E.2.74}$$

where $s_0 \in PH$ is an initial condition, $h \in X$ is a Lipschitz bounded function, $s_{s_0,h}$ is a solution of the inertial form E.2.71 corresponding to s_0 and h, and $\Delta \in X^1$ is a function from PH to $\mathcal{L}(PH, PQ)$, and so $\Delta(s_{s_0,h}(t))$ is a the linear functional from PH to QH for every time t.

Let us recall the definition of the operator T_h^1, which, for a given $h \in X$ is an operator from $X^1 \to X^1$, which we shall prove to be well defined and a contraction:

$$T_h^1 \Delta(s_0)\eta_0 = \int_{-\infty}^{0} U_{s_{s_0,h}} Df(s_{s_0,h}, h(s_{s_0,h})) \left[\eta_{\eta_0,\Delta} + \Delta(s_{s_0,h})\eta_{\eta_0,\Delta}\right] \mathrm{d}\tau + \int_{-\infty}^{0} DU_{s_{s_0,h}} \eta_{\eta_0,\Delta} f(s_{s_0,h}, h(s_{s_0,h}))\mathrm{d}\tau$$

where now $\eta_{\eta_0,\Delta}$ is the solution of E.2.74. Reviewing the proofs that T_h^1 is well defined, is a contraction and that $DTh = T_h^1 Dh$, one can see that they only depend on properties of f and $U_{s_{s_0,h}}$ which are the same, independently of whether $B(u)$ is a function only of s or both of s and φ; the only algebra that actually changes is the one depending on the estimates on $\eta_{\eta_0,\Delta}$.

The proofs for lemmas **L.2.12**, **L.2.14** and **L.2.15** remain untouched and we shall just have to substitute the recurrent term $\epsilon\gamma(1 + p_1)$ with some other $\bar{\gamma}$ derived by the appropriate Gronwall's inequality.

Let us now indicate how the Gronwall's inequalities E.2.45 (page 87) and E.2.49 (page 89) are modified. Regarding E.2.45, let us simply note that

$$\left|\eta_{\eta_0,\Delta}(t)\right| = |\eta_0| + \int_t^0 |B_{ss}(s, h(s))\eta| + \int_t^0 \left|Dg_1(s, h(s))(\eta_{\eta_0,\Delta} + \Delta(s)\eta_{\eta_0,\Delta})\right| \leq |\eta_0| + \int_t^0 (\gamma_1 + \mathcal{B}_{ss})(1 + p_1) \left|\eta_{\eta_0,\Delta}\right|,$$

so that in this case $\bar{\gamma} = \gamma_1(1 + p_1) + \mathcal{B}_{ss}$.

As for the second Gronwall's inequality, the one regarding two different $\Delta_1, \Delta_2 \in X^1$, here goes the modification:

$$\begin{aligned} |\eta_1(t) - \eta_2(t)| \leq & \int_t^0 |B_{ss}(s, h(s))(\eta_1 - \eta_2)| \\ & + \int_t^0 |Dg_1(s)(\eta_1 + \Delta_1(s)\eta_1) - Dg_1(s)(\eta_2 + \Delta_2(s)\eta_2)| \\ \leq & \int_t^0 \mathcal{B}_{ss} |\eta_1 - \eta_2| \\ & + \int_t^0 \gamma_1 |\Delta_1(s)\eta_1 - \Delta_2(s)\eta_2| + \gamma_1 |\eta_1 - \eta_2| \\ \leq & \int_t^0 \gamma_1 \|\Delta_1(s) - \Delta_2(s)\|_{\mathcal{L}} |\eta_2| + (\gamma_1(1 + p_1) + \mathcal{B}_{ss}) |\eta_1 - \eta_2| \end{aligned}$$

and from this point of the proof we can use the same $\bar{\gamma} = \gamma_1(1 + p_1) + \mathcal{B}_{ss}$.

We now proceed to show that the invariant fixed point is exponentially attracting. As in lemma **L.2.16** (page 98) we take $z(t) = \varphi(t) - h(s(t))$; writing h for $h(s)$, we obtain that on the one hand

$$\frac{\mathrm{d}}{\mathrm{d}t} h(s(t)) = \frac{\mathrm{d}h}{\mathrm{d}s}\frac{\mathrm{d}s}{\mathrm{d}t} = (Dh)(-B_{ss}(s, h)s + g_1(s, h)),$$

and on the other, h being an invariant manifold,

$$\frac{\mathrm{d}}{\mathrm{d}t} h(s(t)) = -B_{\varphi\varphi}(s, h)h + f_1(s, h),$$

and thus the following relation holds:

$$-B_{\varphi\varphi}(s, h)h = -DhB_{ss}(s, h)s + Dhg_1(s, h)) - f_1(s, h). \qquad \text{E.2.75}$$

So we can differentiate $z(t)$ and obtain the analogous of E.2.63 (page 99)

$$\begin{aligned} \dot{z} =& \dot{\varphi} - Dh\dot{s} \\ =& - B_{\varphi\varphi}(s, \varphi)\varphi + f_1(s, \varphi) - Dh[-B_{ss}(s, \varphi))s + g_1(s, \varphi)] \\ =& - B_{\varphi\varphi}(s, z + h)z - B_{\varphi\varphi}(s, z + h)h + f_1(s, z + h) \\ & + DhB_{ss}(s, z + h))s - Dhg_1(s, z + h)]. \end{aligned} \qquad \text{E.2.76}$$

Analysing the calculations in E.2.63, we note that we substituted the term corresponding to $B_{\varphi\varphi}(s, z + h)h$, that is $-B(s)h$, with the result corresponding to E.2.75. We must now note that this is not directly possible in our case, as the actual expression in E.2.75 does not depend on φ as $B_{\varphi\varphi}(s, z+h)h$ does. We shall then add and subtract this term to E.2.75 and obtain thus the following

$$\begin{aligned}-B_{\varphi\varphi}(s, z+h)h =& - B_{\varphi\varphi}(s, z+h)h \\ &+ B_{\varphi\varphi}(s, h)h - DhB_{ss}(s, h)s + Dhg_1(s, h) - f_1(s, h).\end{aligned} \tag{E.2.77}$$

We can now substitute this value in E.2.76 and rearranging the terms to bring together the similar ones:

$$\begin{aligned}\dot{z} =& - B_{\varphi\varphi}(s, z+h)z \\ &+ B_{\varphi\varphi}(s, h)h - B_{\varphi\varphi}(s, z+h)h \\ &+ Dhg_1(s, h) - Dhg_1(s, z+h) \\ &+ f_1(s, z+h) - f_1(s, h) \\ &+ DhB_{ss}(s, z+h))s - DhB_{ss}(s, h)s.\end{aligned}$$

We can now take the scalar product with z and obtain

$$\begin{aligned}\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}|z|^2 =& - \langle z, B_{\varphi\varphi}(s, z+h)z\rangle \\ &+ \langle z, \left(B_{\varphi\varphi}(s, h) - B_{\varphi\varphi}(s, z+h)\right)h\rangle \\ &+ \langle z, Dhg_1(s, h)) - Dhg_1(s, z+h)\rangle \\ &+ \langle z, f_1(s, z+h) - f_1(s, h)\rangle \\ &+ \langle z, (DhB_{ss}(s, z+h) - DhB_{ss}(s, h))\, s\rangle.\end{aligned}$$

It is clear now that by using the facts that

- the system is dissipative,
- h and s are bounded,
- $B_{\varphi\varphi}$, B_{ss}, f_1 and g_1 are all Lipschitz functions,
- $\mathcal{B}_{\varphi\varphi}$ is strictly positive,

we can prove again that z tends to zero as it satisfies the following inequality

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}|z|^2 \leq \left(-\mathcal{B}_{\varphi\varphi} + \beta_{\varphi\varphi}\Phi_M + \gamma_1 + \theta_1 p_1 + \beta_{ss}S_M\right)|z|^2 ,$$

which will be negative for appropriate values of the constants.

To conclude this section, we refer again to the original biological dynamical system E.2.6 (page 62). Remember that the dynamics of gating states may then be expressed as

$$\frac{\mathrm{d}}{\mathrm{d}t}s^j_{lk} = \sum_{i=1}^{N}\left(\alpha^{ij}(\varphi_l - \varphi_k)s^i_{lk}\right) - \left[\sum_{i=1}^{N}\alpha^{ji}(\varphi_l - \varphi_k)\right]s^j_{lk}$$

and, eliminating one of the gating states, as

$$\frac{\mathrm{d}}{\mathrm{d}t}s = b(\varphi) - \tilde{g}(\varphi)s.$$

It is clear now, that one could have written the dynamics of the s part of the system with $B_{ss}(s,\varphi) = \tilde{g}(\varphi)s$ and $g_1(s,\varphi) = b(\varphi)$ so to apply the more general theory presented in this section:

$$\dot{s} = -B_{ss}(s,\varphi)s + g_1(s,\varphi) \qquad \text{E.2.78}$$

Note that even if one knows that the system admits an Inertial Manifold, it does not necessarily mean that the representation of the system as given in E.2.78 satisfies the inequalities among the various eigenvalues and Lipschitz constant that guarantee the existence of an Inertial Manifold for the given representation. In fact, the whole of this research was originated from the fact that the standard Gap Condition could not be proven for the system represented as $\dot{u} = -Au + f(u)$. This is a clear example of the multiple choices the scientist has to make when deciding how to best represent the system in order to prove the existence of an Inertial Manifold; with the development of a more general theory, many more possibilities can arise and not all of them will give rise to the appropriate inequalities.

2.4.5 The gap condition and the strong squeezing property

In this section we shall study the relation between the condition $(1-k)b > \theta$, the classical Gap Condition and the Strong Squeezing Property, as stated for example in [39-TEM-1998]. This condition is always stated as a relation between the difference of two consecutive eigenvalues of the linear operator A of the system E.2.3 (page 61) and the Lipschitz constant of the nonlinear part V of E.2.3. Usually this condition is used to prove that the strong squeezing property holds and subsequently that an Inertial Manifold exists. In fact it was shown by Robinson in [57-ROB-1995] that the strong squeezing property is sufficient for an Inertial Manifold to exist. However, as we stated earlier, this proof only yields a Lipschitz manifold and not a differentiable one.

The strong squeezing property is defined as a two part property for the dynamics under the flow of E.2.3. The first part is often called the cone invariance property, and it says that if a point u_1 belongs to the cone of radius χ centred in the point u_2, i.e. if

$$|Q(u_1 - u_2)| \leq \chi \, |P(u_1 - u_2)|$$

then the flow $u_1(t)$ starting at u_1 will always belong to the cone centred in $u_2(t)$, i.e. for every $t \geq 0$

$$|Q(u_1(t) - u_2(t))| \leq \chi \, |P(u_1(t) - u_2(t))| \, .$$

The second part is often called the squeezing property and states that if a point u_1 does not belong to the cone of radius χ centred in the point u_2, then only two things can occur: either $u_1(t)$ will eventually enter the cone centred in $u_2(t)$, and thus it will remain there, or the distance between $u_1(t)$ and $u_2(t)$ will decay to zero exponentially:

$$|Q(u_1(t) - u_2(t))| \leq |Q(u_1 - u_2)| \, e^{-\kappa t}$$

for some $\kappa > 0$.

In our case the system E.2.4 does not satisfy the classical gap condition. However we have proved that an Inertial Manifold exists. We shall now prove that our system satisfies the strong squeezing property.

LEMMA L.2.18 *For small ϵ and with $(1-k)b > \theta$, the Strong Squeezing Property holds for E.2.4.*

Proof We shall follow the proof given in [39-TEM-1998] to show that the Gap Condition implies the Strong Squeezing Property.

To show the Cone Property, it will suffice to show that if the trajectory starting at $u_1(0)$ would leave the cone of radius χ centred in $u_2(0)$, then there would be a time $t > 0$

such that $u_1(t) = (s_1(t), \varphi_1(t))$ belongs to the boundary of the cone of radius χ centred in $u_2(t) = (s_2(t), \varphi_2(t))$. Showing that whenever a trajectory reaches the boundary of the cone, the trajectory is pushed back into the cone shows that no trajectory can ever leave the cone. This is equivalent to showing that at such time t the quantity

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(q^2(t) - \chi^2 p^2(t)\right)$$

is strictly negative, where $q(t) = |\varphi_2(t) - \varphi_1(t)|$ and $p(t) = |s_2(t) - s_1(t)|$.

Let us write down the equation for $p'(t)$, writing p for $p(t)$, q for $q(t)$ and $\tilde{p} = s_2(t) - s_1(t)$:

$$\begin{aligned}\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}p^2 = \langle \tilde{p}, \frac{\mathrm{d}}{\mathrm{d}t}\tilde{p}\rangle &= \langle \tilde{p}, \epsilon\left(g(s_2,\varphi_2) - g(s_1,\varphi_1)\right)\rangle \\ &\geq -p\epsilon\gamma\,(p+q) \\ &= -\epsilon\gamma\left(p^2 + pq\right)\end{aligned}$$

where we used the fact that in any Hilbert space $|\langle a, b\rangle| \leq |a|\,|b|$.

Now we write down the equation for $q'(t)$, writing $\tilde{q} = \varphi_2(t) - \varphi_1(t)$:

$$\begin{aligned}\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}q^2 =& \langle \tilde{q}, \frac{\mathrm{d}}{\mathrm{d}t}\tilde{q}\rangle = \langle \tilde{q}, -B(s_2)\varphi_2 + B(s_1)\varphi_1 + f(s_2,\varphi_2) - f(s_1,\varphi_1)\rangle \\ =& \langle \tilde{q}, -B(s_2)\varphi_2 + B(s_2)\varphi_1 - B(s_2)\varphi_1 + B(s_1)\varphi_1 + f(s_2,\varphi_2) - f(s_1,\varphi_1)\rangle \\ =& \langle \tilde{q}, -B(s_2)\varphi_2 + B(s_2)\varphi_1\rangle + \langle \tilde{q}, -B(s_2)\varphi_1 + B(s_1)\varphi_1\rangle \\ &+ \langle \tilde{q}, f(s_2,\varphi_2) - f(s_1,\varphi_1)\rangle \\ \leq& -bq^2 + \beta qp\,|\varphi_1| + \theta(qp + q^2)\end{aligned}$$

where we have used E.2.25 (page 75). Remembering that we are dealing with a modified system for which $|\varphi_1| < r_\varphi$ (see section 2.3.1):

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}q^2 \leq -bq^2 + \beta r_\varphi qp + \theta(qp + q^2). \qquad \text{E.2.79}$$

We can now evaluate the expression

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\left(q^2 - \chi^2 p^2\right) \leq -bq^2 + \beta r_\varphi qp + \theta(qp + q^2) + \chi^2\epsilon\gamma\left(p^2 + pq\right).$$

Now if $u_2(t)$ belongs to the boundary of the cone at a point t, then by definition of the cone at this point $q(t) = \chi p(t)$ and

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\left(q(t)^2 - \chi^2 p(t)^2\right) \leq \left(-b + \frac{\beta r_\varphi}{\chi} + \frac{\theta}{\chi} + \theta + \epsilon\gamma + \chi\epsilon\gamma\right) q^2$$

which is strictly negative if

$$\chi^2\epsilon\gamma + \chi(-b + \epsilon\gamma + \theta) + \beta r_\varphi + \theta < 0. \qquad \text{E.2.80}$$

This is a second degree inequality in χ which admits real solutions if and only if its discriminant is positive, that is if and only if $(-b + \epsilon\gamma + \theta)^2 > 4\epsilon\gamma(\beta r_\varphi + \theta)$, which is certainly true for small ϵ. Thus we have proved that the Cone Condition holds for a cone of radius χ, where χ is any real positive number satisfying

$$\frac{b - \epsilon\gamma - \theta - \sqrt{\Delta}}{2\epsilon\gamma} < \chi < \frac{b - \epsilon\gamma - \theta + \sqrt{\Delta}}{2\epsilon\gamma}, \qquad \text{E.2.81}$$

whenever $\Delta = (-b + \epsilon\gamma + \theta)^2 - 4\epsilon\gamma(\beta r_\varphi + \theta) > 0$.

Now we shall prove that the squeezing property holds. Assume that for all positive times the orbit of u_2 never enters the cone, that is $q(t) > \chi p(t)$. Substituting this in E.2.79 we obtain

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}q^2 \leq \left(-b + \frac{\beta r_\varphi}{\chi} + \theta + \frac{\theta}{\chi}\right) q^2$$

which, together with the fact that $b > (1-k)b > \theta$, gives exponential decay for

$$\chi > \frac{\beta r_\varphi + \theta}{b - \theta}. \qquad \text{E.2.82}$$

It is clear that for small ϵ there exists a χ satisfying both E.2.81 and E.2.82. This is not surprising as E.2.82 is the same condition as E.2.80 when $\epsilon = 0$. In fact, we have that any solution of E.2.80 satisfies

$$0 < \chi^2\epsilon\gamma < \chi(b - \epsilon\gamma - \theta) - \beta r_\varphi - \theta,$$

so that

$$\chi > \frac{\beta r_\varphi + \theta}{b - \epsilon\gamma - \theta} > \frac{\beta r_\varphi + \theta}{b - \theta}.$$

/////

As we have already said, the condition $(1-k)b > \theta$ is not the classical gap condition, as the Lipschitz constant γ does not appear in the equation.

Furthermore, we would like to point out that as stated in [39-TEM-1998], the radius χ of the cone appears explicitly in the gap condition, in a form similar to E.2.82. Once again, we have to stress the fact that E.2.82 is not the classical gap condition, if not for anything else, at least because there appears the Lipschitz constant β of $B(s)$, which cannot possibly appear in the classical gap condition as the operator used in such systems does not depend neither on time nor on the variable u as it is in our case.

Finally, we would like to point out that in **L.2.16** (page 98) we have used inequalities quite similar to those used in proving the Strong Squeezing Property.

2.5 Examples

In this section we develop a few examples:

- the first example is about an Inertial Manifold that is asymptotically complete, and the difference between the flow of the complete dynamics, the approximating flow of the reduced dynamics and the projection of the original flow on the P subspace;
- the second one is about an Inertial Manifold that is not asymptotically complete, i.e. that does not admit an approximating flow;
- the third one is about a dynamical system that has an Inertial Manifold even though it does not satisfy the Strong Squeezing Property.

2.5.1 The approximating projected flow

We begin with some remarks on the difference between a manifold being exponentially attracting and one being asymptotically complete.

Though it is self-evident that being asymptotically complete is a stronger requirement than just exponentially attracting, we want to point out that finding the flow on the manifold that is the actual approximation of a general flow is not really straightforward. In fact, one might think that given any initial condition $(s_0, \varphi_0) \in H$, the approximating flow on the manifold is the one starting at $(s_0, h(s_0))$. This is not always the case, as the following example will demonstrate. Additionally, remember that in the proof of lemma **L.2.17** (page 100) we used Theorem 3.2 of [60-ROB-1996] to find an approximation of the flow, and in this theorem the approximated flow was not required to start at the projection of the initial value on the manifold. Also remember the introduction to section 2.4.3, where we saw the difference between the projection of the flow on the Inertial Manifold and a flow on the Inertial Manifold starting at a point projected on the Manifold.

Let's consider the dynamics in cylindrical coordinates in $\mathbb{R}^3$ given by the solution to the differential equation:

$$\begin{aligned}\dot{z} &= -z,\\ \dot{r} &= 1 - r,\\ \dot{\theta} &= 1 - r + z,\end{aligned} \qquad \text{E.2.83}$$

where r and θ are polar coordinates.

Given an initial condition (z_0, r_0, θ_0), the solution of E.2.83 is given by

$$\begin{aligned} z(t) =& z_0 e^{-t}, \\ r(t) =& (r_0 - 1)e^{-t} + 1, \\ \theta(t) =& \theta_0 - (1 - r_0 + z_0)e^{-t} + (1 - r_0 + z_0). \end{aligned} \quad \text{E.2.84}$$

This system is dissipative, as everything is attracted to the unit circle on the hyperplane $\mathcal{Z} = \{z = 0\}$. Considering that z is exponentially attracted to the hyperplane $\mathcal{Z} = \{z = 0\}$, it is clear that $\mathcal{Z}$ satisfies all the conditions of the definition of an Inertial Manifold: it is a Lipschitz, invariant, finite dimensional manifold, exponentially attracting. In this example, the coordinate s is given by the two coordinates (r, θ) and φ by the coordinate z.

We now show that it is also asymptotically complete, by explicitly finding for any trajectory $\zeta(t)$ starting at any initial condition (z_0, r_0, θ_0) a correspondent trajectory $\tilde{\zeta}$ on $\mathcal{Z}$ starting at $(\tilde{r}_0, \tilde{\theta}_0)$ that approximates exponentially ζ.
On the Inertial Manifold the dynamics is reduced to

$$\begin{aligned} \dot{r} =& 1 - r, \\ \dot{\theta} =& 1 - r, \end{aligned} \quad \text{E.2.85}$$

which has the unique solution

$$\begin{aligned} r(t) =& (r_0 - 1)e^{-t} + 1, \\ \theta(t) =& \theta_0 - (1 - r_0)e^{-t} + (1 - r_0). \end{aligned} \quad \text{E.2.86}$$

For ζ satisfying E.2.84 we have that the various coordinates tend to the following values exponentially:

$$\begin{aligned} & z(t) \to 0, \\ & r(t) \to 1, \\ & \theta(t) \to \theta_0 + (1 - r_0 - z_0). \end{aligned}$$

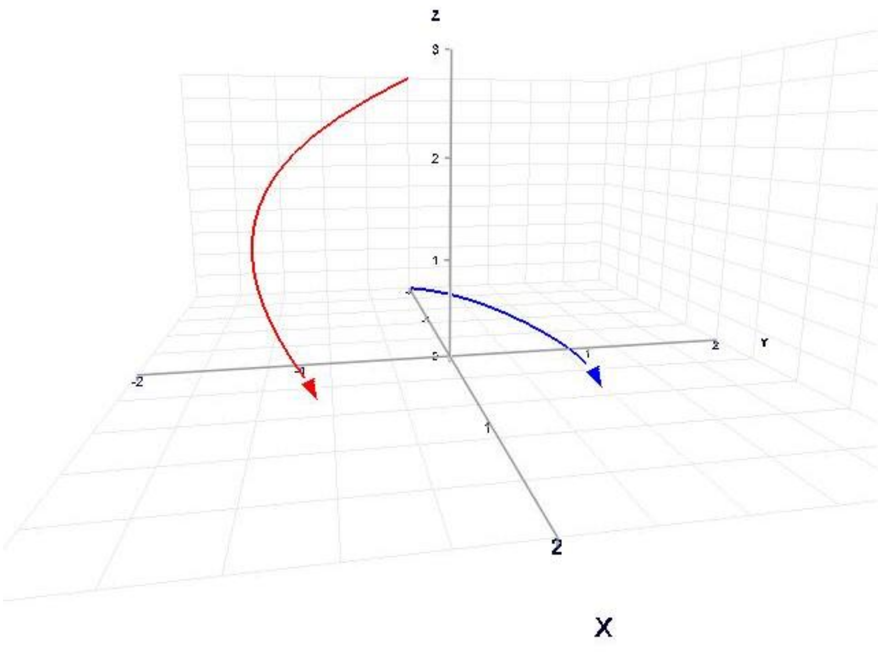
For $\tilde{\zeta}$ we have

$$r(t) \to 1,$$

$$\theta(t) \to \tilde{\theta}_0 + (1 - \tilde{r}_0),$$

It is now clear that the trajectory starting at $\tilde{r}_0 = r_0$ and $\tilde{\theta}_0 = \theta_0 + z_0$ is a trajectory $\tilde{\zeta}(t)$ that approximates exponentially $\zeta(t)$.

We are now ready to show that for this example one cannot take the trajectory on the Inertial Manifold starting at $(s_0, h(s_0))$ as the one that approximates exponentially the trajectory starting at (s_0, φ_0). In fact, for our example E.2.83, this would correspond to taking the flow starting at $(0, r_0, \theta_0)$. Now, θ will tend to $\theta_0 + 1 - r_0$ which is different from $\theta_0 + (1 - r_0 + z_0)$ unless $z_0 = 0$. It is also remarkable that the two dynamics can be very different indeed. For example, for $r_0 = 2$ and $z_0 = 3$, one has that $\dot{\theta}(t) = 2e^{-t} + 2$ and so $\theta(t)$ grows clockwise, while for $r_0 = 2$ and $z_0 = 0$ the behaviour of θ is quite different, as $\dot{\theta}(t) = -e^{-t} - 1$ and $\theta(t)$ decreases anticlockwise. We show the two curves in the next picture; the red line corresponds to the curve starting at $(z_0 = 3, r_0 = 2, \theta_0 = \pi)$ and the blue line to the curve starting at $(z_0 = 0, r_0 = 2, \theta_0 = \pi)$.



We would like now to give some indications on how one can define generally the approximating trajectory. Both in the paper [60-ROB-1996] and in [41-CHO-1992], one can find *constructive* proofs of when an Inertial Manifold is asymptotically complete. The two methods are slightly different, but following the proof, one can define an approximating trajectory on the Inertial Manifold through a definition of the difference between the two trajectories as the solution of a new differential equation.

For example, in [41-CHO-1992] the authors study a system like

$$\dot{u} = -Au + f(u), \qquad \text{E.2.87}$$

where A is a positive definite bounded linear operator on a Hilbert space H to which u belongs. The space H is then split into the two usual orthogonal spaces PH and QH, and we denote $p = Pu$ and $q = Qu$. Then the solution approximating a trajectory starting at (p_0, q_0) is given by a solution of the inertial form starting at $(p_0 + \delta_0, h(p_0 + \delta_0))$ where

$$\delta_0 = -\int_0^{\infty} e^{PAs} \left[Pf(p, h(p) + r) - Pf(p + \delta, h(p + \delta))\right] \mathrm{d}s$$

where h is the Inertial Manifold, $(p(t), q(t))$ is the solution of E.2.87, $r = q - h(p)$, and δ is the solution of

$$\dot{\delta} = -PA\delta + Pf(p, h(p) + r) - Pf(p + \delta, h(p + \delta)).$$

2.5.2 An Inertial Manifold not asymptotically complete

We wish to continue by remarking that there exist Inertial Manifolds that are not asymptotically complete. In the paper [60-ROB-1996] one finds an example of an invariant manifold which is attracting (though not exponentially attracting) but not asymptotically complete. In the same paper a sufficient condition for an Inertial Manifold to be asymptotically complete is given, whilst in the paper [52-LAN-1999] this condition is extended to a sufficient condition for an invariant, attracting manifold to be complete, and the rate of attraction of the approximating trajectory is the same as the rate of attraction to the manifold.

We present the example in [60-ROB-1996], and then construct from this an example of an Inertial Manifold which is not asymptotically complete. Take the differential equation

$$\begin{aligned} \dot{z} &= -\mu z\,|z| \\ \dot{r} &= 0, \\ \dot{\theta} &= (1 + z)w(r) \end{aligned} \qquad \text{E.2.88}$$

where $w(r)$ is a function such that $w(1) = 1$. The hyperplane $\mathcal{Z} = \{z = 0\}$ is an invariant attracting manifold, though it is not an Inertial Manifold because it is not exponentially attracting. The solution to E.2.88 for an initial condition $(1, \theta_0, z_0)$ is:

$$z(t) = \frac{z_0}{1 + \mu |z_0| t}$$

$$r(t) = 1$$

$$\theta(t) = \theta_0 + t + \frac{1}{\mu} \ln(1 + \mu |z_0| t)$$

and the difference between the trajectory $\theta(t)$ and the trajectory $\tilde{\theta}(t)$ laying on the invariant manifold $\mathcal{Z}$ and starting at $(1, \tilde{\theta}_0, 0)$ is given by

$$\begin{aligned} \left|\theta(t) - \tilde{\theta}(t)\right| &= \left|\theta_0 + t + \frac{1}{\mu} \ln(1 + \mu |z_0| t) - \tilde{\theta}_0 - t - \frac{1}{\mu} \ln(1)\right| \\ &= \left|\theta_0 - \tilde{\theta}_0 + \frac{1}{\mu} \ln(1 + \mu |z_0| t)\right| \end{aligned}$$

which is an expression that for $\forall\ \theta_0, \tilde{\theta}_0, z_0$ tends to infinity and not to zero.

We now give an example of a dynamical system that admits an Inertial Manifold but is not asymptotically complete. We base our example on the idea presented in [60-ROB-1996], that is we find a $z(t)$ that converges to 0, this time exponentially, and a $y(t)$ that depends on $z(t)$ in such a way that the term depending on z_0 diverges to ∞ unless $z_0 = 0$. We will consider the following dynamical system

$$\begin{aligned} \dot{z} &= -z \\ \dot{x} &= 2x, \\ \dot{y} &= \frac{zx}{1 + zx} \end{aligned} \qquad \text{E.2.89}$$

which admits the hyperplane $\mathcal{Z} = \{z = 0\}$ as an Inertial Manifold. In fact the solution of E.2.89 for the initial condition (z_0, x_0, y_0) is given by

$$z(t) = z_0 e^{-t}$$

$$x(t) = x_0 e^{2t}$$

$$y(t) = y_0 + \ln\left(1 + z_0 x_0 e^t\right) - \ln(1 + z_0 x_0)$$

while on the hyperplane $\mathcal{Z}$, the solution corresponding to $(\tilde{x}_0, \tilde{y}_0)$ is

$$x(t) = \tilde{x}_0 e^{2t},$$

$$y(t) = \tilde{y}_0;$$

again the difference between the trajectory $(z(t), x(t), y(t))$ and any trajectory $(\tilde{x}(t), \tilde{y}(t))$ starting at $(0, \tilde{x}_0, \tilde{y}_0)$ is given by

$$\begin{aligned} |x(t) - \tilde{x}(t)| &= \left| x_0 e^{2t} - \tilde{x}_0 e^{2t} \right|, \\ |y(t) - \tilde{y}(t)| &= \left| y_0 - \tilde{y}_0 + \ln\left(1 + z_0 x_0 e^{t}\right) - \ln\left(1 + z_0 x_0\right) \right|. \end{aligned} \qquad \text{E.2.90}$$

Note now that $\forall\ z_0, x_0, y_0$ not belonging to the hyperplane $\mathcal{Z} = \{z = 0\}$, the expressions in E.2.90 tend both to zero if and only if

$$\tilde{x}_0 = x_0 = 0,$$

$$\tilde{y}_0 = y_0;$$

while in any other case they both tend to infinity. We have thus constructed a dynamical system that admits an Inertial Manifold that is not asymptotically complete, as there exist trajectories that cannot be approximated by any other trajectory completely on the Inertial Manifold, these trajectories being all those that start at any point with $z_0 \neq 0$ and $x_0 \neq 0$.

2.5.3 An Inertial Manifold without squeezing property

In the literature one usually finds a great deal of references to various forms of the gap condition, how it implies the strong squeezing property and finally a series of proofs (and explanations) on why the strong squeezing property implies the existence of an Inertial Manifold. For example, one could look at the book by Temam [39-TEM-1998], or [37-ROB-2001] by Robinson, and a number of papers like [59-ROB-1994].

Nevertheless, the literature does not seem to be deeply concerned about counterexamples. Indeed we were able to find only two papers that present counterexamples concerning the existence of Inertial Manifolds; they are [54-MAL-1992], where examples are given of Inertial Manifold for systems that do not satisfy the spectral gap condition but satisfy the strong squeezing property, and [62-ROM-2000], where one can find examples of various dynamical systems that, in spite of being dissipative, do not have an Inertial Manifold. Yet we were not able to find any reference of counterexamples of dynamical systems that possess an Inertial Manifold without possessing the strong squeezing property.

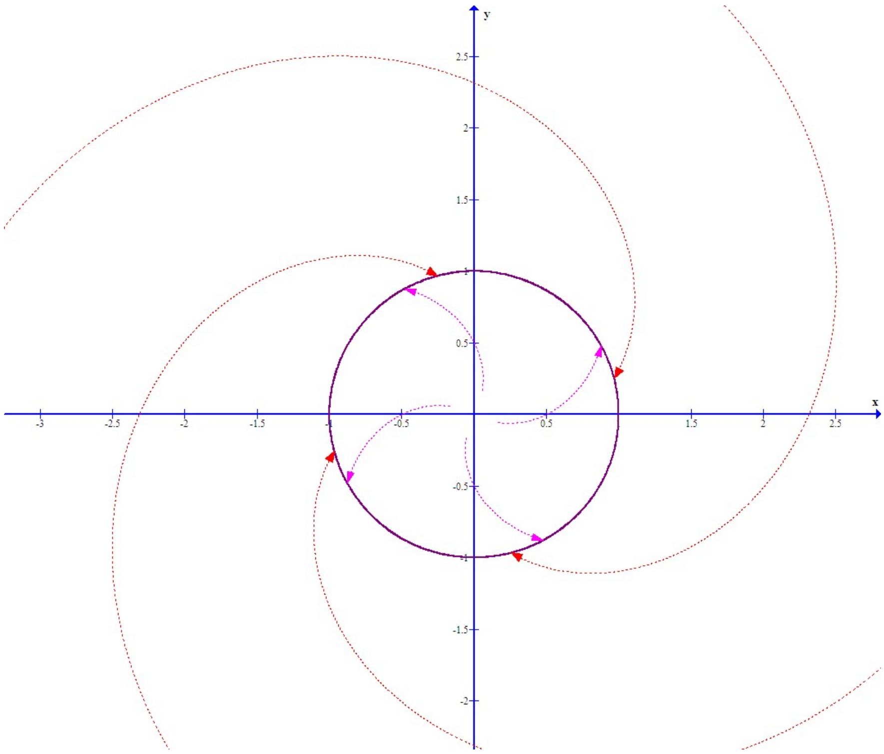
Before proceeding, we shall recall that the gap condition implies the strong squeezing property, and that this is composed of the cone invariance (things in the cone will remain in the cone) plus the squeezing property (things outside the cone will get exponentially closer to the cone). For full definitions, refer to the glossary in chapter **4**.

As we have seen, our dynamical system E.2.4 (page 61) satisfies the strong squeezing property and has an Inertial Manifold, though at the time of first writing the paper more than 10 years ago we did not realise that this was the case; indeed we were quite happy about our results, because it seemed to be the counterexample we are now talking about. Now, 10 years later, we appreciate the fact that we were dealing with an example of a system that does not satisfy the classical gap condition but at the same time does satisfy the strong squeezing property.

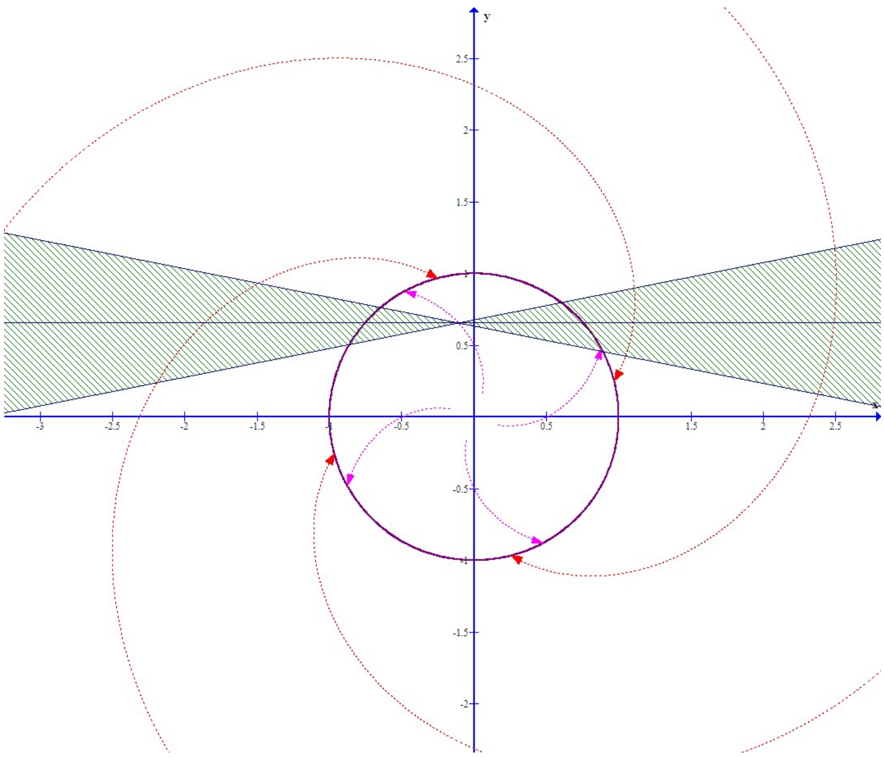
Thus now the question arises about the existence of a dynamical system with an Inertial Manifold that does not satisfy the strong squeezing property. As a result of carefully pondering the meaning of the cone condition part of the strong squeezing property, we were able to find such a counterexample and thus illustrate the fact that the strong squeezing property is not necessary for a dynamical system to have an Inertial Manifold.

As we have seen in section 2.4.5, the first part of the strong squeezing property is usually called the cone invariance property and it says that if a point u_1 belongs to the cone of radius χ centred in the point u_2, then the flow $u_1(t)$ starting at u_1 will always belong to the cone centred in $u_2(t)$. As explained in [39-TEM-1998] and [37-ROB-2001], this property means in a way that if two flows start together (inside the cone), then they will always stay together. Thus we concentrated in finding a dynamics which has flows attracted (exponentially) to the same manifold but from two different directions.

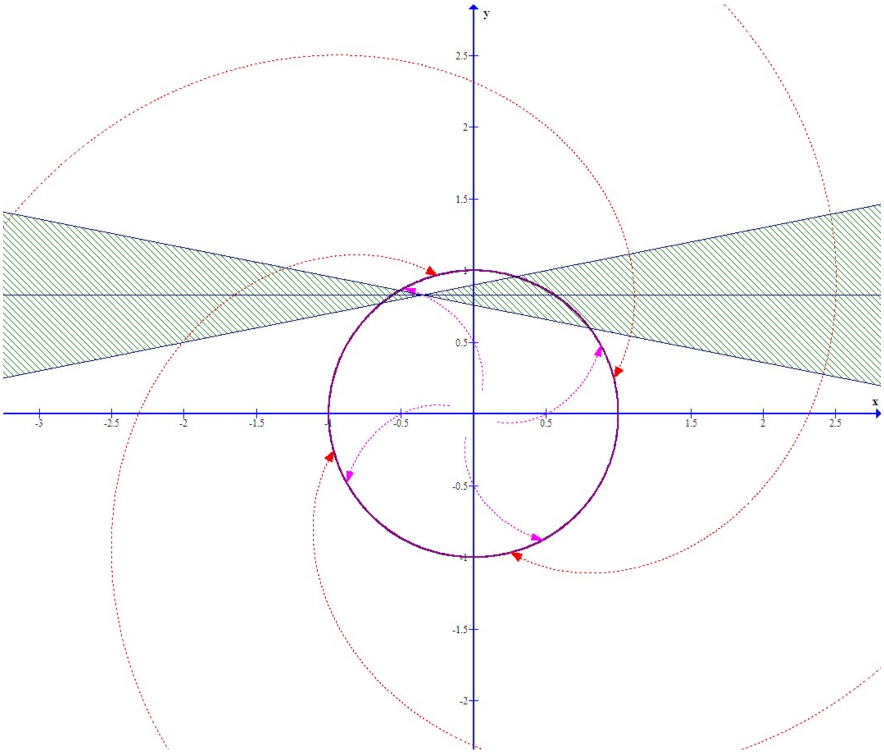
In order to get such a flow, the first thing that one can think about is a flow that is attracted to a closed curve, like the unit circle $\mathcal{C}$, and such that it flows clockwise inside $\mathcal{C}$ and anticlockwise outside $\mathcal{C}$, as we show in the following figure:



Thus, one can see in a graphic way that, no matter how large we create a cone, there will always be points that start inside the cone, but will end up leaving the cone. We can see this graphically in the following image



and then, observing the same picture after some time has elapsed:



In the three pictures above we have drawn the unit circle, 4 trajectories starting inside the unit circle and 4 other trajectories starting outside it; additionally in the second picture we present a cone centred at point p on one of the internal trajectories, and in the third one we finally draw the same cone, with the same radius, but centred on the same trajectory but after a certain time t has elapsed.

We now proceed to present the counterexample formally and with detailed analytical results.

First of all, note that the fact that a flow grows clockwise or anticlockwise simply means that in polar coordinates the angle of the flow increases or decreases. Thus polar coordinates seem to be a natural choice for our example, as we can say that the flow is clockwise or anticlockwise by simply telling the sign of the derivative of the angle. So, we want to find a differential equation which represents the graphics above and satisfies the following properties:

– the flow is continuous,

– the flow is dissipative,

– the differential equations for the radius r and the angle θ are not independent,

– the radius converges to 1,

– the derivative of the angle is negative outside the unit circle $\mathcal{C}$ and positive inside the unit circle $\mathcal{C}$.

A system that has these properties is:

$$\begin{aligned} \dot{r} &= 1 - r \\ \dot{\theta} &= 1 - r \end{aligned} \qquad \text{E.2.91}$$

which clearly satisfies all the above properties.

We now give the explicit solution to E.2.91 for the initial condition (r_0, θ_0):

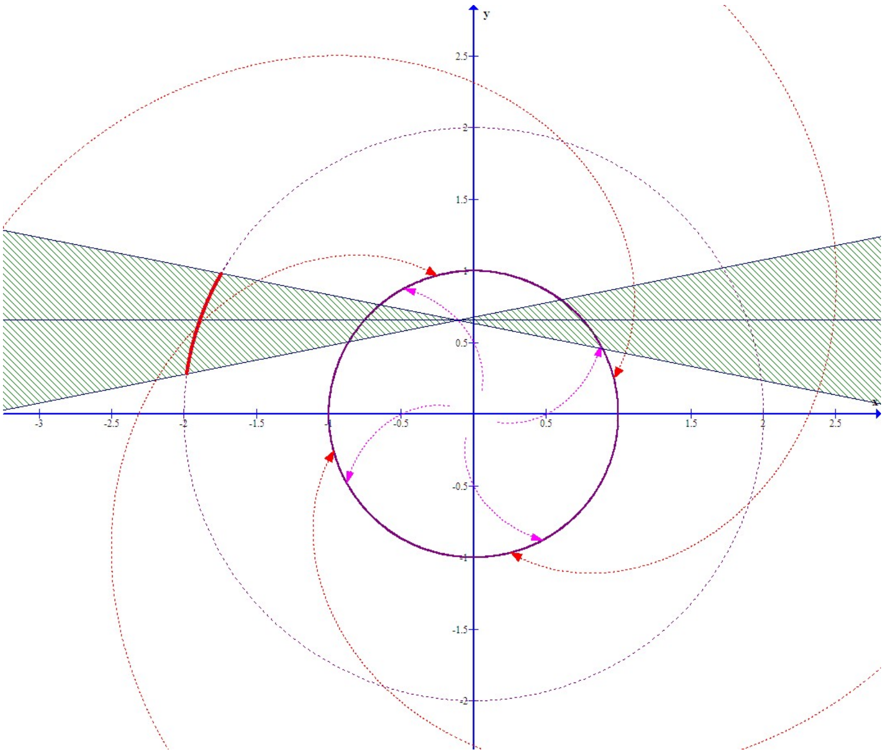
$$\begin{aligned} r(t) &= (r_0 - 1)e^{-t} + 1, \\ \theta(t) &= \theta_0 + (r_0 - 1)e^{-t} - (r_0 - 1). \end{aligned} \qquad \text{E.2.92}$$

Note that $\mathcal{C}$ is composed of fixed points, as both $\dot{r} = \dot{\theta} = 0$, that is it is an invariant manifold; furthermore all points are exponentially attracted to it, as r tends to 1 exponentially and θ tends to $\theta_0 - (r_0 - 1)$ also exponentially. That is, the unit circle $\mathcal{C}$ is an Inertial Manifold.

We now want to show that no two points on the same circle (inside or outside the $\mathcal{C}$) tend to the same point on the unit circle $\mathcal{C}$, and that given a circle C_{r_0} (inside or outside $\mathcal{C}$) and any point $\bar{p}$ on $\mathcal{C}$ then there exists a point p_0 on C_{r_0} so that p_0 tends to $\bar{p}$. In fact, given two different points on C_{r_0}, they will have the same radius, r_0 but two different angles θ_1 and θ_2. The first point will tend to the point on $\mathcal{C}$ with angle $\bar{\theta} = \theta_1 - r_0 + 1$ and the second one to the point with angle $\bar{\theta} = \theta_2 - r_0 + 1$, which are different as $\theta_1 \neq \theta_2$. The same argument shows that given a point $\bar{p}$ on $\mathcal{C}$ with angle $\bar{\theta}$, the flow starting at angle $\bar{\theta} - 1 + r_0$ will tend to $\bar{p}$.

The above argument, together with the fact that the flow is invariant under rotation, means that we can prove any property for any point we like and then that property will apply to all points with the same radius. Thus we shall restrict our study of the cone invariance property to just one point. Again, we shall also restrict to the study of cones whose axis is parallel to the x axis; in fact, the dynamical system being invariant under rotation, we can always rotate any cone to the one with the same angle but with axis parallel to the x axis.

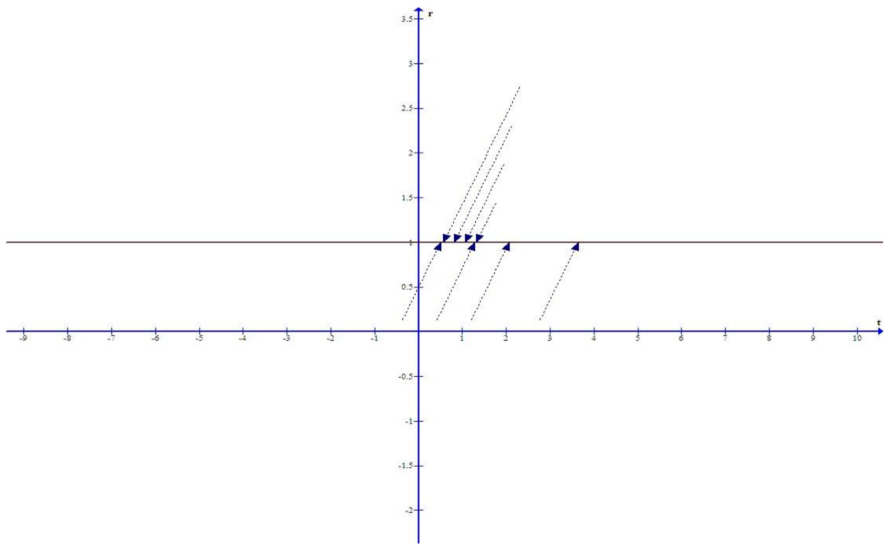
It is now geometrically easy to understand that the cone condition does not hold. We shall use a reductio ad absurdum proof. Suppose that the cone condition holds and take the cone centred at a point p inside the unit circle $\mathcal{C}$. The vertex of the cone does then evolve towards a point $\bar{p}$ on the unit circle. Take now the section of circle outside $\mathcal{C}$, as show in the figure below.



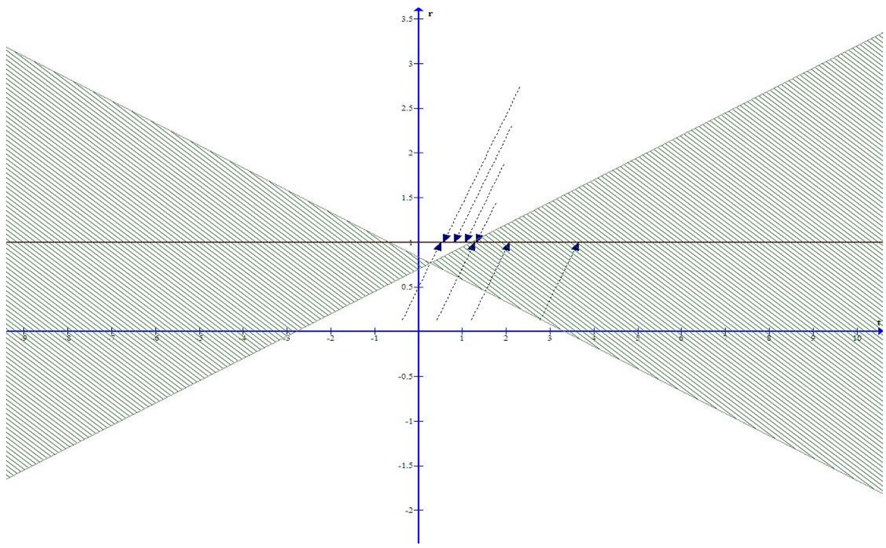
On the one hand, these points are all attracted to the Inertial Manifold $\mathcal{C}$, and are all attracted to different points of the Inertial Manifold. On the other hand, if the cone invariance property holds, then they must remain inside the cone, and at infinity, the segment of the unit circle inside the cone will reduce to a single point, that is the point $\bar{p}$, which is a contradiction. This result holds for any angle of the cone.

So we have found an example of a continuous dissipative system that admits an Inertial Manifold but not the cone invariance property. One could argue that generally Inertial Manifolds are given as graph of functions and not loops, and that the strong squeezing property holds an Inertial Manifold that is the graph of a function; and so our argument would not be really complete. Nevertheless, we can add a third dimension to the system, with the equation $\dot{z} = -z$ which has a solution $z(t) = z_0 e^{-t}$ which is exponentially attracted to the plane described by r and θ, and that does not change our argument about the cone property not holding. Yet this system has an Inertial Manifold which is the graph of a function, the plane $\mathcal{Z} = \{z = 0\}$.

We point out that if we were to consider the coordinates r, θ as coordinates in the Banach space $\mathbb{R}^2$, then the Inertial Manifold is indeed the graph of a function, $r = 1$:



and a cone in this new coordinate system would look like this:



In the two pictures above we have again drawn a trajectory $r = 1$, corresponding to the polar coordinates unit circle, and 4 trajectories starting below the straight line $r = 1$ (corresponding to polar coordinates inside the unit circle) and 4 other trajectories starting above it (corresponding to polar coordinates outside the unit circle); additionally in the second picture we present a cone centred at point p on one of trajectories below.

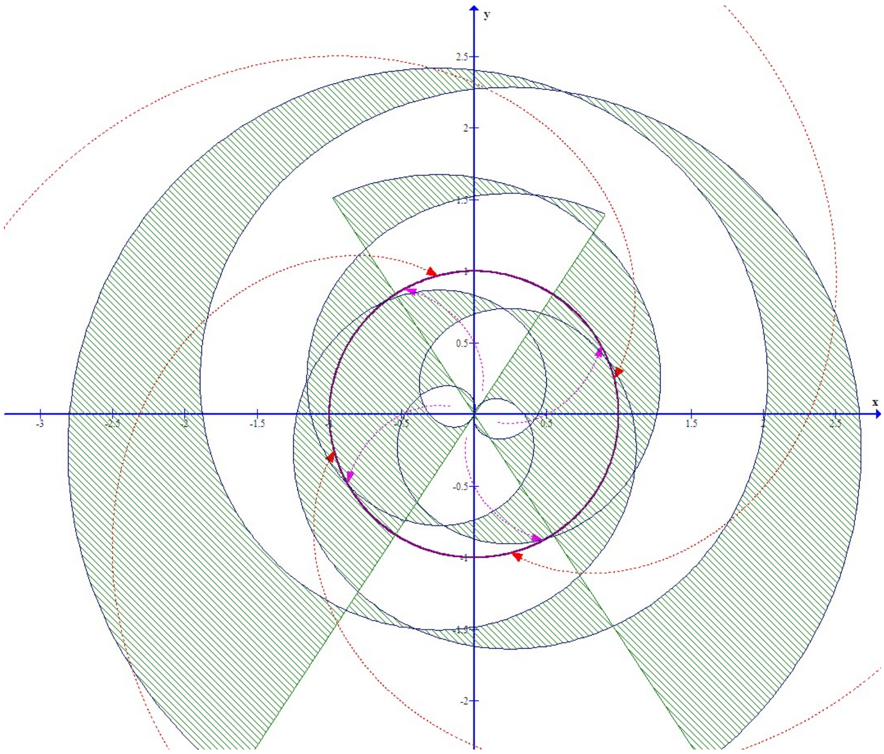
This shows that the section of the Inertial Manifold spanned by this cone eventually includes the whole Inertial Manifold, and thus the cone invariance property holds. This is not surprising at all, as if we interpret the polar coordinates as coordinates of a Banach space, the equation can be represented as

$$\dot{u} = -Au + f(u)$$

where $u = (r, \theta)$, $f(u)$ is the constant function $(1, 1)$ and

$$A = \begin{pmatrix} 1 & 0 \\ 1 & 0 \end{pmatrix}.$$

Now, f has Lipschitz constant equal to 0 and A has two real eigenvalues 0 and 1. Thus the gap condition holds and the system admits an Inertial Manifold. Obviously there is no contraction, as the cone in the (r, θ) coordinates looks nothing like a cone in standard coordinates:



In the picture above we have drawn the image in the (x, y) coordinates of a standard cone in the (r, θ) coordinates. Here, the cone in the (r, θ) coordinates is $r = \pm t/4 + 0.7$ which in the (x, y) coordinates is the region delimited by the two lines parameterised by the parameter t:

$$x(t) = (\pm t/4 + 0.7)\sin t,$$

$$y(t) = (\pm t/4 + 0.7)\cos t.$$

2.6 Application to the biology

In this section, we will consider the application of **T.2.3** (page 75) to a dynamical system which models the evolution of a network of cells connected by gap junctions. In other words, the objective of this section is to mathematically justify an intuitively obvious result, that is the fact that the dynamics of φ is much faster than that of s; we do this by proving that the parameters defining the equation for the concrete example satisfy the condition of our theorem.

Since our experimental data were derived from electrophysiological experiments, we will only consider a specific approximation of the model in which the intercellular concentrations are assumed constant. Thus the electrochemical potential reduces to the electrical potential.

Although we will prove that the general form of gating dynamics E.2.6 (page 62) has bounded solutions, we will be applying our theory to the specific gating mechanism described in [1-BAI-1997] which consists of three states with fractional populations s^1, s^2 and $s^0 = 1 - s^1 - s^2$. For this case, equations E.2.6 become

$$\begin{aligned}\frac{\mathrm{d}s^1}{\mathrm{d}t} &= \beta(u) - [\alpha(u) + \beta(u)]s^2 - \beta(u)s^1 \\ \frac{\mathrm{d}s^2}{\mathrm{d}t} &= \beta(-u) - [\alpha(-u) + \beta(-u)]s^1 - \beta(-u)s^2\end{aligned} \qquad \text{E.2.93}$$

where α and β are the transition rates given by

$$\begin{aligned}\alpha(u) &= \lambda \exp[-A_\beta(u - v_0)] \\ \beta(u), &= \lambda \exp[A_\beta(u - v_0)].\end{aligned} \qquad \text{E.2.94}$$

Here v_0 is the transjunctional voltage for which the channel opening rate equals the channel closing rate, u is the transjunctional electrochemical difference $\varphi_l - \varphi_k$ between cells labled l and k and λ, A_α and A_β are positive constants. We will assume that the gap junctions are identical in structure, so that their transition rates are equal. The permeability of the channels in populations s^1_{lk}, s^2_{lk} will be denoted by g_{min} and the permeability of those channels in the remaining population will be denoted by g_{max}. The conductance of each gap junction is then given by $R_{lk} = g_{min} + (g_{min} - g_{max})(s^1_{lk} + s^2_{lk})$. For each gap junction linking cell l to cell k, equations E.2.93 and E.2.94 take the compact form

$$\frac{\mathrm{d}}{\mathrm{d}t}s_{lk} = g_{lk}(s, \varphi) = b_{lk}(\varphi) - \tilde{g}_{lk}(\varphi)s_{lk} \qquad \text{E.2.95}$$

where $s_{lk} = (s^1_{lk}, s^2_{lk})^T$, $b_{lk} = (\beta(\varphi_l - \varphi_k), \beta(\varphi_k - \varphi_l))^T$ and

$$\tilde{g}_{lk} = \begin{pmatrix} \alpha(\varphi_l - \varphi_k) + \beta(\varphi_l - \varphi_k) & \beta(\varphi_l - \varphi_k) \\ \beta(\varphi_k - \varphi_l) & \alpha(\varphi_k - \varphi_l) + \beta(\varphi_k - \varphi_l) \end{pmatrix}. \qquad \text{E.2.96}$$

Note that we can rewrite this in matrix notation as

$$\dot{s} = b(\varphi) - G(\varphi)s$$

which is useful for applying the result of our theorem to the case of transfer of larger charged molecules.

2.6.1 Boundedness of the solution

To show that the dynamics E.2.8 (page 63) has an absorbing set, we first show that the dynamics of the gating of each gap junction, as given by E.2.6 (page 62), is bounded. Thus, we consider a gating mechanism of the general form

$$\frac{\mathrm{d}s^j}{\mathrm{d}t} = \sum_{i=1}^{N} \alpha^{ij}(u)s^i - \left[\sum_{i=1}^{N} \alpha^{ij}(u)\right] s^j \qquad \text{E.2.97}$$

where $0 \leq s^j \leq 1$, $\sum_{i=1}^N s^i = 1$, and each rate constant $\alpha^{ij}(u)$ is positive for all transjunctional electrochemical differences u.

Let $\sum_N$ denote the simplex $\{s \in R^N_+ : \sum_{i=1}^N s^i = 1\}$. Note that we require all initial data for s to lie in $\sum_N$, since we are dealing with fractional populations. If $s^j = 0$, then, since we assume that $\alpha^{ij}(u) > 0$, $\dot{s}^j = \sum_{i=1}^N \alpha^{ij}(u)s^i > 0$, and thus all such boundary points of $\sum_N$ will move inwards under the dynamics. In other words, we have proved that if a trajectory were to meet an hyperplane at a time $\bar{t}$, that is one the coordinate $s^j(\bar{t}) = 0$, then its derivative would be strictly positive at that instant $\bar{t}$, and thus s^j would be still be positive in a neighbourhood of $\bar{t}$.

Furthermore, summing E.2.97 over j we obtain

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t}\sum_{j=1}^{N} s^j &= \sum_{j=1}^{N}\sum_{i=1}^{N} \alpha^{ij}(u)s^i - \sum_{j=1}^{N}\left[\sum_{i=1}^{N} \alpha^{ji}(u)\right] s^j \\ &= \sum_{j=1}^{N}\sum_{i=1}^{N} \alpha^{ij}(u)s^i - \sum_{j=1}^{N}\sum_{i=1}^{N} \alpha^{ji}(u)s^j = 0 \end{aligned}$$

and so $\sum_{i=1}^{N} s^i(t) = 1$ for all $t > 0$ (provided $s(0) \in \sum_N$). Hence the dynamics E.2.97 leaves the simplex $\sum_N$ invariant. Note that this result is true regardless of the functional form of the rate constants α^{ij}; it is sufficient that they be positive.

Now this result combined with the fact that all coordinates will always remain non-negative for $t > 0$, implies that all s^j are bounded. Grouping the gap junction dynamics together shows that s evolves in the set $\left(\sum_N\right)^{n_g}$, where n_g is the number of gap junctions.

The next step is to show that the matrix $B(s)$ is positive definite, which is crucial to the proof of **T.2.3** (page 75). We will do this by showing that each eigenvalue λ of $B(s)$ is positive. First note that $B(s)$ has real eigenvalues because it is real and symmetric; in particular it is symmetric because we are supposing that all cells are equal, thus they have the same capacitance, that is $\forall i,\ C_i = C$. Notice again that the fact that B is symmetric is never used in the proof of our theorem, and thus it is not necessary for our theory to hold. We only mention it it here because it is a convenient way of proving that the matrix B of the biological system satisfies the condition of the theorem.

Now decompose the matrix $B(s) = D - F$ where D is the diagonal matrix with i^{th} diagonal element

$$d_{ii} = \frac{\rho_i}{C} + \sum_{l \in N_i} \frac{R_{li}}{C}$$

and F has zeros along the diagonal with $f_{ij} = R_{ij}/C$ if $j \in N_i$ (N_i is the set of the indexes of the cells connected to cell i) and $f_{ij} = 0$ otherwise. Then using Gerschgorin's circle theorem, all eigenvalues of $B(s)$ must lie in the union of circles $\bigcup W_i$ where

$$W_i = \left\{ z \in \mathbb{C} : |z - d_{ii}| \leq \sum_{j \neq i} |f_{ij}| \right\}.$$

In our case

$$W_i = \left\{ z \in \mathbb{R} : \left| z - \frac{\rho_i}{C} - \sum_{l \in N_i} \frac{R_{li}}{C} \right| \leq \sum_{j \in N_i} \frac{R_{ij}}{C} \right\}.$$

Now using the inequality $|a - b| \geq |a| - |b|$ and the fact that $R_{ij} = R_{ji}$ we have that if $z \in W_i$ then

$$\sum_{j\in N_i} \frac{R_{ij}}{C} \geq \left| z - \frac{\rho_i}{C} - \sum_{l\in N_i} \frac{R_{li}}{C} \right|$$
$$\geq |z| - \left| \frac{\rho_i}{C} + \sum_{l\in N_i} \frac{R_{li}}{C} \right|$$
$$= |z| - \frac{\rho_i}{C} - \sum_{l\in N_i} \frac{R_{li}}{C}$$

and thus

$$|z| \leq \frac{\rho_i}{C} + 2\sum_{j\in N_i} \frac{R_{ij}}{C}.$$

We can also use the inequality $|b-a| = |a-b| \geq |a| - |b|$ to write that if $z \in W_i$ then

$$\sum_{j\in N_i} \frac{R_{ij}}{C} \geq \left| \frac{\rho_i}{C} + \sum_{l\in N_i} \frac{R_{li}}{C} \right| - |z|$$
$$= \frac{\rho_i}{C} + \sum_{l\in N_i} \frac{R_{li}}{C} - |z|$$

which can then we written again as

$$|z| \geq \frac{\rho_i}{C}.$$

This shows that each eigenvalue λ_k satisfies

$$0 < \min_i \frac{\rho_i}{C} \leq \lambda_k \leq \max_i \left(\frac{\rho_i}{C} + 2\sum_{j\in N_i} \frac{R_{ij}}{C} \right)$$

and so $B(s)$ is positive-definite.

From E.2.8 (page 63), we have

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}|\varphi|_2^2 = -\varphi^T B(s)\varphi + \varphi^T w$$

where $|\cdot|_2$ denotes the usual Euclidean norm. Now, B being positive definitive we have that

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}|\varphi|_2^2 \leq -b|\varphi|^2 + |w||\varphi| = |\varphi|(-b|\varphi| + |w|)$$

where b is the minimum eigenvalue of $B(s)$. Now clearly the right hand side is negative for all $|\varphi| > R_0 = |w|/b$. This shows that all components $\varphi(t)$ of solutions of E.2.8 (page 63) eventually enter the set Ω_0 defined by $|\varphi| \leq R_0$.

2.6.2 Evaluation of constants

In this section, we evaluate the various constants used in the bounds stated in Theorem **T.2.3** (page 75).

First note that in our application $f(s,\varphi) = w$, a constant vector, and, since we may assume that the extracellular potential is zero and that the C_k are all equal to a constant C:

$$F = \max_k |w/C_k|_\infty = \max_k \left| \frac{I_k^p}{C} \right| .$$

The Lipschitz constant of f is clearly $\theta = 0$. The condition $(1-k)b > 2\theta$ is trivially satisfied for $k \in (0,1)$.

In the previous section we proved that $b \geq \min_k \rho_k / C$, where b is the minimum on s of the minimum eigenvalue of $B(S)$.

Now, recalling that $g = \epsilon^{-1}(b(\varphi) - \tilde{g}(\varphi)s)$, we calculate

$$\begin{aligned} G &= \max_{l,k} |g_{lk}|_\infty \\ &= \epsilon^{-1} \max_{l,k} |b_{lk} - \tilde{g}_{lk} s_{lk}|_\infty \\ &\leq \epsilon^{-1} \max_u |\alpha(u) + \beta(u)| . \end{aligned}$$

Similarly, the Lipschitz constant for g is

$$\begin{aligned} \gamma &= \max_{l,k} |Dg_{lk}|_\infty \\ &= \max_{l,k} \max \left\{ \left| D_\varphi g_{lk} \right|_\infty , |D_s g_{lk}|_\infty \right\} \\ &\leq \epsilon^{-1} \max_{l,k} \max \left\{ |\tilde{g}_{lk}|_\infty , A_\alpha |\alpha|_\infty + A_\beta |\beta|_\infty \right\} \\ &\leq 2\epsilon^{-1} G \end{aligned}$$

since $A_\alpha, A_\beta < 1$. Finally, we need the norm of the derivative of the matrix $B(s)$. This is

$$\begin{aligned} \beta &= |B_s|_\infty \\ &= \max_{l,k} |D_s Bkl|_\infty \\ &= \max_k \left| \sum_{j \in N_k} \left(\frac{g_{min} - g_{max}}{C_k} \right) (1,1)^T \right|_\infty \\ &\leq (g_{min} - g_{max}) \max_k \left(\frac{|N_k|}{C_k} \right) . \end{aligned}$$

We are now in a position to check that the conditions of Theorem **T.2.3** are satisfied when the model is fitted with experimentally determined parameter values for small ion transfer [1-BAI-1997]. In the first instance, we will assume that the cells are identical. This provides a sensible base from which we may study the results of varying the parameters. Thus we assume the following typical parameter values as derived from recent electrophysiological experiments on Xenopus cell pairs. These are as follows.

$$\rho_k = \rho_0 \approx 10^{-7}\text{mho}, \qquad C_k = C_0 \approx 1.0 \times 10^{-10}\text{F}$$

$$g_{min} = 0.05 \times 10^{-7}\text{mho}, \qquad g_{max} = 1.0 \times 10^{-7}\text{mho},$$

$$\lambda = 0.3\text{s}^{-1}, \qquad u_0 = 0.014\text{V}^{-1}, \qquad A_\alpha = 80\text{V}^{-1}, \qquad A_\beta = 140\text{V}^{-1},$$

Using these parameters we estimate

$$b = 10^3, \qquad \beta = 10^3\bar{N}, \qquad G = 15\epsilon^{-1}, \qquad \gamma = 2\epsilon^{-1}G = \epsilon^{-2}30,$$

where $\bar{N}$ is the typical number of cells joined to a given cell, and we suppose $\bar{N} = 4$. (For the estimation of G see Fig A1 in [1-BAI-1997].)

With these parameter values, we check the validity of inequality E.2.26. For $\theta = 0$

$$\epsilon\gamma < \frac{kb}{2}\frac{(1-k)^2b^2}{\beta F + (1-k)^2b^2}. \qquad \text{E.2.98}$$

Here we are free to choose k between 0 and 1 to get the estimate. Setting $\epsilon = 1$ and using the parameters just obtained, we have for $b = \bar{b}$

$$\epsilon\gamma = 20 < \frac{k}{2}500\frac{1}{1 + 0.004(1-k)^2}. \qquad \text{E.2.99}$$

A simple calculation, performed with Mathematica, shows that the right-hand side is maximised at $k = 0.66$, and that the maximum is 245. Hence, the left-hand side of E.2.99 being non-decreasing in b, and b being greater than $\bar{b}$, E.2.99 holds also for b defined in E.2.25 (page 75).

Thus, for the parameters chosen, we do satisfy the conditions of the existence theorem.

2.6.3 Interpreting the results

Observe that for a fixed s, the dynamics of φ is a gradient system, which has a unique attracting equilibrium state $\varphi^\star = B(s)^{-1}w$. Furthermore, with respect to small ions the capacitance of typical cells is small, so that $(C_k)^{-1}$ is several orders of magnitude larger than that of $\tilde{g}$, in other words the φ dynamics is much faster than the s dynamics. For large molecules, the reverse is true: $(C_k)^{-1}$ is much smaller than $\tilde{g}$. Our data, given the experimentally observed size of $(C_k)^{-1}$, are likely to correspond to currents composed of small ions. Since data measuring the intercellular transfer of larger charged molecules are not yet available, here we will focus on the case $(C_k)^{-1} \gg 1$, although as we will demonstrate in our discussion, the case $(C_k)^{-1} \ll 1$ can also be dealt with using our theory.

We thus expect φ to move rapidly towards $\varphi^\star(s)$ and then to track $\varphi^\star(s)$ closely in response to the much slower changes in s. This informal description is made rigourous by proving the existence of an Inertial Manifold for the system. If we write $g(s,\varphi) = \epsilon^{-1}[b(\varphi) - \tilde{g}((\varphi)s]$, this will follow from our general result on the existence of such manifolds for systems of the form given by E.2.2 (page 59).

Finally, we discuss two extensions of this model which can immediately be treated by the theory developed in this chapter. The first is the case of nonlinear membrane permeability. This is obtained by perturbing ρ_k to $\rho_k + f$. The theorem then tells us that an Inertial Manifold can be found provided that the Lipschitz constant of f is sufficiently small when compared to the smallest eigenvalue b, or in biological terms, the membrane nonlinearity is sufficiently weak. This gives us an indication of the strength of feedback required to produce a network of cells with additional properties, such as excitability.

The second is the case when the molecules transferred are no longer ions but larger charged molecules, such as cyclic AMP. In this case the system E.2.4 (page 61) is replaced by

$$\dot{s} = g(s,\varphi)$$

$$\dot{\varphi} = \mu\left[-B(s)\varphi + f(s,\varphi)\right]$$

where $\mu \ll 1$. The actual form of g, given in detail in section **2.1**, is

$$g(s,\varphi) = -G(\varphi)s + b(\varphi)$$

where G is a block diagonal matrix whose diagonal elements consist of 2 x 2 positive-definite matrices, so that G itself is positive definite. Hence Theorem **T.2.3** can be applied to the new system for which φ is now the slow variable, s the fast variable and G plays the role of B. The theorem shows that for certain parameter ranges an Inertial Manifold exists, so that the system will rapidly approach a dynamical regime in which the gap junctions are slaved to the cell potentials.

Chapter 3

Stochastic Processes a similarity

As they appear to have much in common, we study the similarity of Moment Closure techniques and Inertial Manifolds. In our example, they are almost the same, the Moment Closure functions being a "perturbation" of the original Inertial Manifold for $t \to \infty$ and $\epsilon \to 0$. The Moment Closure is proved to be close to the Inertial Manifold, at least coordinate-wise.

3 Stochastic Processes: a similarity

Since the publication of Whittle's classic paper [84-WHI-1957] about the use of normal approximation, which is just one of the many Moment Closure methods nowadays used in the literature, this technique of dimension reduction has been extensively used in many areas of Statistics; naturally the method has been extended to include a larger class of Moment Closure methods, as for example in [80-NÅS-2003] the two methods of setting the third or the fourth cumulant equal to zero have been compared; in [79-MAT-1999] the fifth cumulant is set to zero and in [83-SIN-2007] a nonstandard Moment Closure technique is used, that is a function $\Phi(m_1, \ldots, m_k) = \prod m_j$.

As Isham says in [73-ISH-2005], *"the success of the moment closure method can sometimes be attributed to central limit effects"*, and thus often there will be a biological/statistical assumption such as that the random variables are normally distributed, as in Whittle's paper.

As we saw in the introductory chapter **1**, we were not able to find much published work where an explanation of the good results provided by Moment Closure methods in biological examples would be based on a purely dynamical perspective.

In fact, we are not aware of any other paper, apart from ours [48-STA-2001], on the parallel between the Moment Closure methods and Inertial (invariant) Manifolds. We personally think that it is worthwhile to continue this line of investigation, and so we decided to analyse this relationship through the study of the example in [72-ISH-1995]. Notice however that in kinetic theory much work has been carried out since Maxwell theory of thermodynamics at the end of the 19^{th} century. See for example [30-GOR-2005] for references and an up-to-date review and state-of-the-art research on the subject of invariant manifolds applied to physical and chemical kinetics.

The aim of this chapter of the thesis is thus to investigate the similarity between these two mathematical phenomena, between the phenomenon of constraining higher moments (Moment Closure) and the one of constraining higher coordinates (Inertial Manifold).

We will pursue our aim by studying a concrete example found in [72-ISH-1995]. The author of [72-ISH-1995] considers the differential equation obtained for the probability generating function for a stochastic model describing the interaction between macroparasites and their hosts. The parasite load within a single host is investigated. The author obtains exact algebraic results and presents a method of approximating the moments of the probability generating function for the parasite load. Since the author has exact results for the probability generating function one can easily compare these results with those produced by using a deterministic or normal approximation. Isham also notes that the normal approximation gives better approximation. Notice that the model in [72-ISH-1995] is a simple one and a more extended version was studied in [71-HER-2000]. However, for sake of simplicity we just treat the case of [72-ISH-1995].

In the introductory chapter 1 we detail the reasons why we believe that the normal approximation might be similar to Inertial Manifolds, at least for the example we treat in this thesis. We will show that the deterministic and normal approximation used in [72-ISH-1995] are actually very close to being Inertial Manifolds.

Let us take a dynamical system like

$$\dot{u} = F(u) \qquad \text{E.3.1}$$

where u belongs to a (possible infinite dimensional) Hilbert space H, that can be split into two spaces, one finite dimensional H', and the other $Q = H - H'$. Then u can be represented as $u = (p, q)$, where p indicates an element of H' and q an element of Q. An Inertial Manifold is then a Lipschitz function from $H' \to Q$ such that all the trajectories of E.3.1 are exponentially attracted to $(p, h(p))$ and the dynamics of E.3.1 can be reproduced, with an exponentially small error, by the ODE

$$\dot{p} = PF(p + h(p)). \qquad \text{E.3.2}$$

In a very similar fashion, a Moment Closure approximation starts from an infinite dynamical system of differential equations

$$\dot{m}_i = f_i(m_1, \dots, m_i, m_{i+1}, \dots) \qquad \text{E.3.3}$$

where $\mu = \{m_i\}$ belongs to some Hilbert space H and the introduction of a function h from $\mathbb{R}^n$ to $H - \mathbb{R}^n$, so that each coordinate m_j for $j > n$ can be expressed as $m_j = h_j(m_1, \dots, m_n)$ and equation E.3.2 is reproduced with a small error by the ODE

$$\begin{aligned} m_1 &= f_1(m_1, \dots, m_n, h_{n+1}(m_1, \dots, m_n), \dots) \\ &\dots \\ m_n &= f_n(m_1, \dots, m_n, h_{n+1}(m_1, \dots, m_n), \dots) \end{aligned} \qquad \text{E.3.4}$$

In both cases a non closed infinite dimensional system is well approximated using a relation (the function h) that can express the "non-important" coordinates in terms of the "important" ones and that closes the system formed by the first n equations.

Remember, as we remarked in section 1.4.2 at page 38, that the moment closure technique is aimed at providing an approximated solution $\bar{m}_j$ close to the solution m_j of the full system E.3.2 for $1 \leq j \leq n$, in contrast with what happens with an Inertial Manifold, which is used to show that $h_j(\bar{m}_1, \dots, \bar{m}_n)$ is close to m_j for $j > n$.

This is why we do not limit ourselves to the study of the steady states of section **3.3.3**, but wish to give a more dynamical account for all higher coordinates in sections **3.3.4** and **3.3.5**. Thus the statement that "the deterministic and normal approximation are close to being Inertial Manifolds", can be interpreted in two ways:

– steady state result: the first one or two coordinates of the steady points of the approximated system are close to the steady point of the full system, which in turn is an Inertial Manifold;

– dynamical system result: all the moments m_j for $j \geq 3$ obtained by the function defining the moment closure are close to those of the Inertial Manifold of the full system.

Notice that in the actual example we will treat here, the functions f_i depend only on the first $i + 1$ coordinates, that is equation E.3.3 is given by

$$\dot{m}_i = f_i(m_1, \ldots, m_i, m_{i+1}).$$

3.1 The biological model

We reproduce here some of the results from the paper [72-ISH-1995] that originated the research in this section.

Isham is interested in modelling host-macroparasite interaction, which is a particular case of host-parasite interaction. Macroparasites are those parasites whose lifecycle is external to the host so that the host's parasite load only builds up through reinfection. See the references in [72-ISH-1995] for an account on the literature on the mathematical modelling of such problems.

In a general model the state of the host is described by the 3 variables $I(a)$, $L(a)$ and $M(a)$, where $I(a)$ represents the host's immunity level and $L(a)$ is the number of parasite larvae and $M(a)$ of those mature parasites, all evaluated at the host's age a. Thus $M(a)$ is the number of parasites present in an individual host of age a. Isham's paper deals with a simplified case where one does not distinguish between mature and larvae stages of parasites, and no immune reaction is provoked by the parasites, in the sense that they neither induce an increased host mortality rate nor stimulate immune reaction.

Thus, Isham considers a model where the only non trivial variable is $M(a)$. In particular, she assumes that at birth the host is free of parasites, that is $M(0) = 0$; then the host will acquire a random number C of parasites at time points modelled by a Poisson process. C is described by its probability generating function $\bar{h}(z) = \sum_{c=0}^{\infty} h_c z^c$. The author makes some assumptions on the parasite, in particular that the parasites level in the environment is constant.

The death rate at age a of the host in the absence of parasites is given by $\mu_H(a)$; when parasites are present, this rate is increased by an amount α for each parasite present. Parasites die at rate μ_M per parasite. The exposure to parasites is is model by a Poisson process of rate $\Phi(a)$.

We can now calculate the possible transitions for a host that has survived to age a. If the number of parasites infecting the host is $M(a) = m$, then the host can:

- increase its parasite load, to $m + c$ at rate $\Phi(a)h_c$ for $c = 1, 2 \ldots$;
- decrease its parasite load, to $m - 1$ at rate $\mu_M m$; as the probability of the parasites dying is μ_M and the number of parasites is m;
- the host may die, at rate $\mu_H(a) + \alpha m$.

The probability $p_m(a)$ is defined as the probability that the host survives to age a and has parasite load $M(a) = m$. We now proceed to derive the differential equation governing p_m. Notice that the following calculations is not directly given in [72-ISH-1995], the likely reason being that they are quite trivial given the above rates. Nevertheless, I feel the need to explicitly give them, as I am more familiar with the Functional Analysis and Nonlinear Dynamics areas of mathematics than with Statistics or Probability.

According to the above transitions, the rate of change of probability $p_m(a)$ will be given by a sum of terms, which are derived in the following lines:

$$\frac{\mathrm{d}p_m(a)}{\mathrm{d}a} = \varrho_1 + \varrho_2 + \varrho_3 + \varrho_4 + \varrho_5$$

According to the first transition, if the host had a load of $m - c$, then it will reach load m with rate $\Phi(a)h_c$, that is

$$\varrho_1 = +\Phi(a) \sum_{c=1}^{m} p_{m-c}(a) h_c;$$

similarly, if the host has load m, then it will go to any other load $m + c$, with rate $\Phi(a)h_c$; this means that the only case it will not increase its load is if it stays the same, which it does with rate $(1 - h_0)\Phi(a)$:

$$\varrho_2 = -(1 - h_0)\Phi(a) p_m(a).$$

The second transition means that the probability of a host remaining with a load m will decrease, as it will have $m - 1$ with a rate proportional to $\mu_M m$:

$$\varrho_3 = -\mu_M m p_m(a);$$

similarly, the probability of reaching parasite load m will increase if the load was $m + 1$:

$$\varrho_4 = +\mu_M (m + 1) p_{m+1}(a).$$

Finally, if a host has survived to age a, then the probability rate at which it will die is $(\mu_H(a) + \alpha m) p_m(a)$; thus $\dot{p}_m$ must be decreased by such a term:

$$\varrho_5 = -(\mu_H(a) + \alpha m) p_m(a).$$

Finally, adding all terms together:

$$\begin{aligned}\frac{\mathrm{d}p_m(a)}{\mathrm{d}a} =& \varrho_1 + \varrho_2 + \varrho_3 + \varrho_4 + \varrho_5 \\ =& -\left\{\mu_H(a) + \alpha m + (1-h_0)\Phi(a) + \mu_M m\right\} p_m(a) \\ &+ \mu_M(m+1)p_{m+1}(a) + \Phi(a)\sum_{c=1}^{m} p_{m-c}(a)h_c.\end{aligned} \quad \text{E.3.5}$$

We derive the differential equation satisfied by the probability generating function $R(a,z) = \sum_{m=0}^{\infty} p_m z^m$. This equation is obtained by explicitly deriving the series defining the probability generating function, substituting the term $\dot{p}_m$ with E.3.5 and rearranging the terms. Remember that $\frac{\partial R(a,z)}{\partial z} = \sum_{m=0}^{\infty} m p_m(a) z^{m-1}$.

$$\begin{aligned}\frac{\partial R(a,z)}{\partial a} =& \sum_{m=0}^{\infty} \frac{\mathrm{d}p_m}{\mathrm{d}a} z^m \\ =& \sum_{m=0}^{\infty} \Bigg\{ -\Big(\mu_H(a) + (1-h_0)\Phi(a)\Big) p_m(a) + \Phi(a)\sum_{c=1}^{m} p_{m-c}(a)h_c \\ & - (\alpha m + \mu_M m)p_m(a) + \mu_M(m+1)p_{m+1}(a) \Bigg\} z^m \\ =& -\mu_H(a)\sum_{m=0}^{\infty} p_m(a) z^m \\ & + \Phi(a)\sum_{m=0}^{\infty}\left(\sum_{c=0}^{m} p_{m-c}(a)h_c\right) z^m - \Phi(a)\sum_{m=0}^{\infty} p_m(a)z^m \\ & - (\alpha + \mu_M)\sum_{m=0}^{\infty} m p_m(a) z^m + \mu_M \sum_{m=0}^{\infty}(m+1)p_{m+1}(a)z^m \\ =& -\Big\{\mu_H(a) - \Phi(a)\left[\bar{h}(z) - 1\right]\Big\} R(a,z) \\ & - \left\{(\alpha + \mu_M)z - \mu_M\right\}\frac{\partial R(a,z)}{\partial z}.\end{aligned}$$

Now, the probability of the host surviving to age a, is given by the function $S(a) = R(a,1)$. Remembering that $\bar{h}(z)$ is a probability generating function, so $\bar{h}(1) = 1$, we can derive the equation for $S(a)$:

$$\begin{aligned}\frac{\mathrm{d}S(a)}{\mathrm{d}a} =& -\Big\{\mu_H(a) - \Phi(a)\left[\bar{h}(1) - 1\right]\Big\} R(a,1) \\ & - \left\{(\alpha + \mu_M)1 - \mu_M\right\}\frac{\partial R(a,1)}{\partial z}. \\ =& -\mu_H(a)S(a) - \alpha m_M(a)S(a),\end{aligned}$$

where m_M is the expected value of $M(a)$. We follow Isham in emphasising that the parasite load $M(a)$ is conditional upon survival of the host to age a; this is important for probability generating function Q, we are going to define next, to make sense.

We are finally ready to give the equation that was studied in [72-ISH-1995] using the normal and deterministic approximations, those same approximations that we shall prove to be related to an Inertial Manifold. Consider the probability generating function $Q(a,z) = R(a,z)/S(a)$, that is the probability for loads given survival to age a. The differential equation for Q is obtained in the following calculations:

$$\begin{aligned}\frac{\partial Q(a,z)}{\partial a} =&\frac{\partial R(a,z)}{\partial a}\frac{1}{S(a)} - \frac{R(a,z)}{S^2(a)}\frac{\partial S(a)}{\partial a}\\ =&-\left\{\mu_H(a) - \Phi(a)\left[\bar{h}(z)-1\right]\right\}\frac{R(a,z)}{S(a)}\\ &-\left\{(\alpha+\mu_M)z-\mu_M\right\}\frac{\partial R(a,z)}{\partial z}\frac{1}{S(a)}\\ &-\frac{R(a,z)}{S^2(a)}\Big(-\mu_H(a)S(a)-\alpha m_M(a)S(a)\Big)\\ =&\left\{\Phi(a)\left[1-\bar{h}(z)\right]+\alpha m_M\right\}Q(a,z)\\ &-\left\{(\alpha+\mu_M)z-\mu_M\right\}\frac{\partial Q(a,z)}{\partial z}.\end{aligned} \qquad \text{E.3.6}$$

This is the equation we are interested in.

3.2 The functional settings

In this section we present the differential equation we will study, the coordinate system we shall be working in, and formal functional analysis settings under which the equation makes sense.

3.2.1 The dynamical system

In the following we will substitute the notation a for age by t for time, as usual in Functional Analysis.

Given a probability measure $\mathscr{P}$ on the positive integers which is time dependent, so that the measure of the set $\{m\}$ at time t is given by $l_m(t)$, we can define the probability generating function associated to this measure as the power series

$$Q(t, Z) = \sum_m l_m(t) Z^m,$$

which is defined at least for $Z \in [0, 1]$. Note that $Q(t, 1) = \sum_m l_m(t) \equiv 1$ at any time t by definition of probability measure.

$$m_k(t) = \sum_m M^k l_m = E(M^k(t)),$$

where $E(M^k)$ is the expected value (or integral) of the polynomial M^k with respect to the measure $\mathscr{P}$. It is a well known result (see [14-BAI-1964] at page 7) that the expected value of the polynomials $v_k(M) = (M)(M-1)\dots(M-k+1)$ are given by the k^{th} derivative of Q with respect to z and evaluated at $z = 1$. In symbols:

$$g_k = E(v_k) = D_z^k Q(t, Z)|_{z=1}.$$

They are also called the factorial moments.

In [72-ISH-1995] the author studies equation E.3.6, under the assumptions that follow. First of all, $\Phi(t)$ is assumed a constant, so that the term $\Phi(t)[1 - \bar{h}(z)]$ is a function only of z, and we shall denoted it from now on by $h(z)$. Secondly, remember that m_M is the expectation of $M(t)$, so that it is also equal to the derivative of Q with respect to z evaluated at $z = 1$. Thus we can re-write equation E.3.6 as

$$\frac{\partial Q}{\partial t} = F(Q) = \left\{ h(z) + \alpha \frac{\partial Q}{\partial z}(z = 1) \right\} Q - \left\{ (\alpha + \mu) z - \mu \right\} \frac{\partial Q}{\partial z}. \qquad \text{E.3.7}$$

The methodology we should follow is the following:

– first we should find a differential equation for the moments $\mathfrak{M} = (m_k(t))$, $\dot{\mathfrak{M}} = f(\mathfrak{M})$,

– then study the space of co-ordinates m_k, and see if there exists an Inertial Manifold.

Let us notice first of all that, while the derivation of an equation for the vector of factorial moments $G(t) = (g_k(t))$ is straightforward, the derivation of the equation for M is quite complicated and laborious. However, as the moment of order k is an invertible linear combination of $g_1, g_2, \ldots, g_k$, it follows that any relation between the moments can be translated into a relation between the factorial moments and vice-versa.

In order to find the differential equation for the g_k it is sufficient to derive both members of E.3.7 with respect to z k times and then put $z = 1$. After some algebra E.3.7 gives

$$\dot{g}_k = h_k + \sum_{i=1}^{k-1} \binom{k}{i} h_{k-i} g_i + \alpha g_1 g_k - \alpha g_{k+1} - (\alpha + \mu) k g_k. \qquad \text{E.3.8}$$

where $h_k = D_z^k h(z)|_{z=1}$.

This equation is not linear, due to the term $\alpha g_1 g_k$, and its study could be quite cumbersome. However it is possible to use a different set of co-ordinates which gives a linear differential equation. We shall find that establishing the existence of a relation in the new set of co-ordinates is equivalent to establishing a relation among the g_k and thus among the m_k.

In order to simplify the system we note that if we divide both members of E.3.7 by Q and substitute $P = \ln Q$ we have the linear differential equation in P

$$\frac{\partial P}{\partial t} = h(z) + \alpha \frac{\partial P}{\partial z}(z = 1) - \{(\alpha + \mu) z - \mu\} \frac{\partial P}{\partial z}, \qquad \text{E.3.9}$$

thanks to the equality $P_z(z = 1) = Q_z(z = 1)/Q(z = 1) = Q_z(z = 1)$, where P_z and Q_z denote the partial derivative with respect to z of P and Q respectively. The function P is called the factorial cumulant generating function.

Thus the fact that $Q(z = 1) = 1$ is extremely important. In fact, we shall now use the variables $\rho_k(t) = D^k P(t, z = 1)$, where D is the derivative with respect to z. We note that any g_k is expressible as a polynomial of degree k of the variables $\rho_1, \rho_2, \ldots, \rho_k$, and this is due to $Q(z = 1) = 1$. The variables ρ_k are called **factorial cumulants**.

By deriving both members of equation E.3.9 with respect to z k times, and then putting $z = 1$ we obtain the very simple linear differential equation in ρ_k

$$\dot{\rho}_k = h_k - \alpha \rho_{k+1} - (\alpha + \mu) k \rho_k. \qquad \text{E.3.10}$$

Notice that although this method of linearisation might probably be a known procedure, we have been unable to find a reference to it.

3.2.2 The factorial cumulants

Before proceeding to the next section, we give the details of the relation between the factorial cumulants ρ_k, the factorial moments and the moments. This is a digression from the central theme of this chapter, which can be skipped completely. For references look at [48-STA-2001] and [15-ITO-1993].

As any textbook in Statistics or Probability will say (see references in the bibliography), the factorial moments g_k and the moments m_k are given by

$$
\begin{aligned}
g_k &= \left\lfloor \frac{\partial^k Q(t)}{\partial t^n} \right\rfloor_1 \\
m_k &= \left\lfloor \frac{\partial^k M(t)}{\partial t^n} \right\rfloor_0
\end{aligned}
$$

where $Q(t)$ is the probability generating function, that is the expectation of t, $Q(t) = E(t^X)$, and $M(t)$ is the moment generating function, that is the expectation of e^t, $M(t) = E(e^{tX}) = Q(e^t)$.

By definition, the factorial cumulants ρ_k are given by

$$
\rho_k = \left\lfloor \frac{\partial^k P(t)}{\partial t^n} \right\rfloor_1 .
$$

Remembering that $P(t) = \ln Q(t)$ and that $Q(1) = 1$, one can write

$$
\begin{aligned}
\rho_1 &= \left\lfloor \frac{\partial P(t)}{\partial t} \right\rfloor_1 = \left\lfloor \frac{1}{Q(t)} \frac{\partial Q(t)}{\partial t} \right\rfloor_1 = g_1 \\
\rho_2 &= \left\lfloor \frac{\partial^2 P(t)}{\partial t^2} \right\rfloor_1 = \left\lfloor -\frac{1}{(Q(t))^2} \left(\frac{\partial Q(t)}{\partial t} \right)^2 + \frac{1}{Q(t)} \frac{\partial^2 Q(t)}{\partial t^2} \right\rfloor_1 = -g_1^2 + g_2 \\
\rho_3 &= \left\lfloor \frac{\partial^3 P(t)}{\partial t^3} \right\rfloor_1 \\
&= \left\lfloor \frac{2}{(Q(t))^3} \left(\frac{\partial Q(t)}{\partial t} \right)^3 - \frac{2}{(Q(t))^2} \frac{\partial Q(t)}{\partial t} \frac{\partial^2 Q(t)}{\partial t^2} \right. \\
&\qquad \left. - \frac{1}{(Q(t))^2} \frac{\partial Q(t)}{\partial t} \frac{\partial^2 Q(t)}{\partial t^2} + \frac{1}{Q(t)} \frac{\partial^3 Q(t)}{\partial t^3} \right\rfloor_1 \\
&= 2g_1^3 - 3g_1 g_2 + g_3
\end{aligned}
$$

and

$$
\begin{aligned}
m_1 &= \left\lfloor \frac{\partial M(t)}{\partial t} \right\rfloor_0 = \left\lfloor \frac{\partial Q(e^t)}{\partial t} e^t \right\rfloor_0 = g_1 \\
m_2 &= \left\lfloor \frac{\partial^2 M(t)}{\partial t^2} \right\rfloor_0 = \left\lfloor \frac{\partial^2 Q(e^t)}{\partial t^2} e^{2t} + \frac{\partial Q(e^t)}{\partial t} e^t \right\rfloor_0 = g_2 + g_1 \\
m_3 &= \left\lfloor \frac{\partial^3 M(t)}{\partial t^3} \right\rfloor_0 \\
&= \left\lfloor \frac{\partial^3 Q(e^t)}{\partial t^3} e^{3t} + 2\frac{\partial^2 Q(e^t)}{\partial t^2} e^{2t} + \frac{\partial^2 Q(e^t)}{\partial t^2} e^{2t} + \frac{\partial Q(e^t)}{\partial t} e^t \right\rfloor_0 \\
&= g_3 + 3g_2 + g_1.
\end{aligned}
$$

We can finally relate the first three factorial moments to the first three factorial cumulants.

$$m_1 = g_1 = \rho_1$$

$$g_2 = \rho_2 + g_1^2 = \rho_2 + \rho_1^2$$

$$m_2 = g_2 + g_1 = \rho_2 + \rho_1^2 + \rho_1$$

$$\sigma^2 = m_2 - m_1^2 = \rho_1 + \rho_2 + \rho_1^2 - \rho_1^2 = \rho_1 + \rho_2$$

$$g_3 = \rho_3 - 2\rho_1^3 + 3\rho_1(\rho_2 + \rho_1^2) = \rho_3 + \rho_1^3 + 3\rho_1\rho_2$$

$$m_3 = g_3 + 3g_2 + g_1 = \rho_3 + \rho_1^3 + 3\rho_1\rho_2 + 3\rho_1^2 + 3\rho_2 + \rho_1.$$

3.2.3 The functional spaces

We shall now give the function space settings for this equation. Let R be the sequence (ρ_k), let L stand for the space of all R such that $\|R\|^2 = \sum \rho_k^2 < \infty$, and let V be the subspace of L of all R such that $\sum k^2 \rho_k^2 < \infty$. These two spaces can be seen as the two Sobolev spaces L^2 and H^1 defined on a discrete measure space, that is the space of all square-summable functions and the space of all these functions whose distributional derivative is square-summable. The ρ_k are then, using this similarity, the "Fourier coefficients" of those functions. However we shall not carry forward this similitude. We now prove that these two spaces are Hilbert spaces.

LEMMA L.3.1 *The spaces L and V are Hilbert spaces, on the scalar field $\mathbb{R}$, when* *endowed with the following scalar products:*

$$\langle R_1, R_2 \rangle_L = \sum_k a_k b_k,$$

$$\langle R_1, R_2 \rangle_V = \sum_k k^2 a_k b_k,$$

where $R_1 = (a_k)$ *and* $R_2 = (b_k)$.

Proof It is evident that they are scalar products:

- the conjugate property is satisfied: $\langle R_1, R_2 \rangle_L = \sum_k a_k b_k = \sum_k b_k a_k = \langle R_2, R_1 \rangle_L$, and similarly for $\langle R_1, R_2 \rangle_V$;
- the linearity property is satisfied:

$$\begin{aligned}\langle \alpha R_1 + \beta R_2, R_3 \rangle_L =& \sum_k (\alpha a_k + \beta b_k) c_k \\ =& \alpha \sum_k a_k c_k + \beta \sum_k b_k c_k \\ =& \alpha \langle R_1, R_3 \rangle_L + \beta \langle R_2, R_3 \rangle_L,\end{aligned}$$

  and similarly for $\langle \alpha R_1 + \beta R_2, R_3 \rangle_V$;
- the non-negativity property is satisfied: $\langle R_1, R_1 \rangle_L = \sum_k (a_k)^2 \geq 0$, and similarly for $\langle R_1, R_1 \rangle_V$;
- the non-degeneracy property is satisfied: suppose R_1 is such that $\langle R_1, R_1 \rangle_L = 0$, then clearly every component $a_k = 0$, thus $R_1 = \mathbb{0}$, and similarly for $\langle R_1, R_1 \rangle_V$.

The only thing that remains to be proved is that L and V are complete; we will prove it only for V, as the proof for L is similar and is usually given as an exercise in any functional analysis book. Take R_n a Cauchy sequence in V, we have to prove that it converges to a point in V. Take thus $\epsilon > 0$ and the corresponding N such that $\forall n, m > N \quad \|R_n - R_m\|_V \leq \epsilon$; let a_{nk} be the components of R_n and a_{mk} those of R_m:

$$\|R_n - R_m\|_V^2 = \langle R_n - R_m, R_n - R_m \rangle_V = \sum_{k=1}^{\infty} k^2 \left(a_{nk} - a_{mk}\right)^2 < \epsilon^2;$$

In particular it is true that $\forall k$ we also have that $k\,|a_{nk} - a_{mk}| < \epsilon$; thus we have formally that

$$\forall \epsilon > 0 \quad \exists N(\epsilon) > 0 \quad \text{such that} \quad \forall n, m > N \quad \forall k \quad k\,|a_{nk} - a_{mk}| < \epsilon;$$

and thanks to the fact that k does not depend on N nor on ϵ, the above expression is equivalent to

$$\forall k \quad \forall \epsilon > 0 \quad \exists N(\epsilon) > 0 \quad \text{such that} \quad \forall n, m > N \quad k\, |a_{nk} - a_{mk}| < \epsilon. \qquad \text{E.3.11}$$

If we now fix k and set $\epsilon = \varepsilon k$, E.3.11 makes the sequence a_{nk} a Cauchy sequence in $\mathbb{R}$, so a convergent one. We now define the point-wise limit

$$R = \left\{ a_k = \lim_{n \to \infty} a_{nk} \right\},$$

and prove that it belongs to V, and that $R_n \to R$ in V.

From the fact that $\{R_n\}$ is a Cauchy sequence in V, it follows that for any $\epsilon > 0$ there exists N such that for all $n, m > N$, $\|R_n - R_m\| < \epsilon^2$; in particular we can take any $j \in \mathbb{N}$ and write

$$\sum_{k=1}^{j} k^2 \, |a_{nk} - a_{mk}|^2 \leq \|R_n - R_m\|_V^2 < \epsilon^2.$$

Having fixed $j \in \mathbb{N}$ the above is a finite sum, thus we can let $m \to \infty$ and obtain

$$\sum_{k=1}^{j} k^2 \, |a_{nk} - a_k|^2 < \epsilon^2. \qquad \text{E.3.12}$$

Use now the triangular inequality $|a| - |b| \leq |a - b|$ we can rewrite E.3.12 as

$$\sqrt{\sum_{k=1}^{j} k^2 \, |a_k|^2} \leq \epsilon + \sqrt{\sum_{k=1}^{j} k^2 \, |a_{nk}|^2} \leq \epsilon + \|R_n\|_V < \infty. \qquad \text{E.3.13}$$

Notice that E.3.13 is valid for all $j \in \mathbb{N}$ and thus letting $j \to \infty$ in E.3.13 will show that $R \in V$. Letting $j \to \infty$ in E.3.12 will show that $R_n \to R$ in the V-norm.

//////

Now let $T : L \to L$, be the operator defined by $TR = (\rho_2, \rho_3, \ldots)$, and let $\Delta : V \to L$ be the operator defined by $\Delta R = (k\rho_k)$. Define now $A : L \to L$ as $AR = \alpha TR + (\alpha + \mu)\Delta R$. A is a linear operator, whose domain in L is V.

We can now rewrite equation E.3.10 (page 147) as

$$\dot{R} = -\alpha TR - (\alpha + \mu)\Delta R + H = -AR + H, \qquad \text{E.3.14}$$

where we remember that H is the vector with component $h_k = D_z^k h(z)|_{z=1}$, and R has components ρ_k.

We now follow chapter 3 of [39-TEM-1998] to prove existence and uniqueness of solutions of E.3.14. To do this we have to establish that A is coercive, that is, there exists a positive constant C such that for every $R \in V$

$$\langle AR, R\rangle_L \geq C \, \|R\|_L^2 \, .$$

First of all, we have that

$$\|TR\|^2 = \sum_j \left|\rho_{j+1}\right| \leq \sum_j \left|\rho_j\right| = \|R\|^2 :$$

Now, thanks to the Cauchy-Schwarz relation valid in all Hilbert spaces $|\langle u, v\rangle| \leq \|u\| \, \|v\|$ we have that

$$|\langle \alpha TR, R\rangle_L| \leq \alpha \, \|TR\| \, \|R\| \leq \alpha \, \|R\|_L^2 \, . \qquad \text{E.3.15}$$

On the other hand, as the norm $\|.\|$ is a summation on all $k \geq 1$, we also have

$$\langle (\alpha+\mu)\Delta R, R\rangle_L = (\alpha+\mu) \sum k\rho_k^2 \geq (\alpha+\mu) \sum \rho_k^2 = (\alpha+\mu) \, \|R\|_L^2 \, . \qquad \text{E.3.16}$$

We finally have

$$\begin{aligned} \langle AR, R\rangle_L =& \langle \alpha TR, R\rangle_L + \langle (\alpha+\mu)\Delta R, R\rangle_L \\ \geq& -\alpha \, \|R\|_L^2 + (\alpha+\mu) \, \|R\|_L^2 \\ =& \mu \, \|R\|_L^2 \, . \end{aligned} \qquad \text{E.3.17}$$

This has very important consequences for us. First of all, theorem 3.1 in chapter 3 of [39-TEM-1998] asserts that under these conditions the differential equation E.3.14 admits one and only one solution. Secondly, theorem 2.1 in chapter 2 of [39-TEM-1998] shows that the operator A is an isomorphism from V to L. This means that, for any given $H \in L$, the following equation

$$\mathbb{0} = -AR + H \qquad \text{E.3.18}$$

admits one and only one solution $\overline{R} \in V$. Such $\overline{R}$ is the only fixed point for our dynamical system. We shall prove in the next section that this fixed point is globally and exponentially attracting.

3.3 Almost an Inertial Manifold

In this section we present all our results regarding the normal approximation and its similarity to Inertial Manifolds.

3.3.1 The fixed point and Inertial Manifolds

In this section and the next two sections, apart from proving that system E.3.14 admits one and only one exponentially attracting fixed point $\overline{R}$, we wish to analyse what happens when we introduce either the deterministic or normal approximation. As we shall see, these two approximations allow us to find approximated dynamical systems, which also admit fixed points $(\tilde{\rho}_1)$ and $(\hat{\rho}_1, \hat{\rho}_2)$. We shall prove that, under admissible parameter values, these fixed points are close. This is the first part of the explanation of why these two types of Moment Closure work well in this example: if we fix our attention on the steady states, then they are very close. As we saw in the introduction, this is not a global dynamical explanation; we treat this point of view in the following sections.
Let us now begin this section by proving the following lemma.

THEOREM T.3.2 ***The fixed point $\overline{R}$ of E.3.14 is exponentially attracting.***

Proof Take any point $R_0 \in V$ and take R as the unique solution of E.3.14 (page 152) with R_0 as initial condition. Both R and $\overline{R}$ satisfy E.3.14:

$$\dot{R} = H - AR,$$

$$\dot{\overline{R}} = H - A\overline{R}.$$

Take now the difference between the two, take the scalar product on both sides by $R - \overline{R}$, write $u(t) = R(t) - \overline{R}(t)$ and obtain:

$$\langle \dot{u}, u \rangle_L = \langle -Au, u \rangle_L \leq -C \, \|u\|_L^2 \, .$$

The left hand side is equal to

$$\langle \dot{u}, u \rangle_L = \frac{1}{2} \frac{\partial \, \|u\|_L^2}{\partial t},$$

thus we have, by a trivial integration,

$$\|u(t)\|_L^2 \leq \|u(0)\|_L^2 \, e^{-2Ct},$$

which proves that the fixed point $\overline{R}$ is globally and exponentially attracting in L.

//////

The fact that the system E.3.14 admits an exponentially attracting fixed point, clearly defines an Inertial Manifold: the fixed point $\overline{R}$ itself. In fact, $\overline{R}$ is finite dimensional, invariant and exponentially attracting. Using this point, we can actually define more Inertial Manifolds.

On the one hand, the closure of any trajectory defines an Inertial Manifold. In fact, the closure of any trajectory will be composed of the trajectory itself plus the fixed point. By definition such set is finite dimensional, invariant and exponentially attracting.

We shall find useful to prove that other manifolds too are Inertial Manifolds. In fact, we can show that the hyperplane of dimension n obtained by fixing all the coordinates, with the exception of the first n ones, equal to the fixed point coordinates, is an Inertial Manifold for the original system:

$$\begin{aligned}\mathcal{M}_n =& \left\{\rho_1, \ldots, \rho_n, \Phi_n(\rho_1, \ldots, \rho_n)\right\} \\ =& \left\{\rho_1, \ldots, \rho_n, \bar{\rho}_{n+1}, \bar{\rho}_{n+2}, \ldots\right\}.\end{aligned}$$

We will use these hyperplanes $\mathcal{M}_n$ to show that the normal and deterministic approximation are actually defining a good approximation not only for the first and second moment, but for all moments. We will do this in sections **3.3.4** and **3.3.5**, where we will obtain via the moment closure functions new systems which will admit the moment closure functions as Inertial Manifolds and which will be close to $\mathcal{M}_n$ for $t \to \infty$ and $\epsilon = \alpha/\mu \to 0$.

LEMMA L.3.3 *For every $n \in \mathbb{N}$ the function Φ_n defined by*

$$\Phi_n : \mathbb{R}^n \to L - \mathbb{R}^n$$

$$\Phi_n : (\rho_1, \ldots, \rho_n) \mapsto (\bar{\rho}_{n+1}, \bar{\rho}_{n+2}, \ldots),$$

where $\bar{\rho}_i$ are the coordinates of the fixed point of E.3.10, is an Inertial Manifold for the dynamical system E.3.10.

Proof The manifold $\mathcal{M}_n$ is given by $\{(x, \Phi_n(x)); \;\; x \in \mathbb{R}^n\}$. Explicitly:

$$\mathcal{M}_n = \left\{x, \Phi_n(x)\right\} = \left\{\rho_1, \ldots, \rho_n, \bar{\rho}_{n+1}, \bar{\rho}_{n+2}, \ldots\right\}$$

Clearly $\mathcal{M}_n$ is Lipschitz and finite dimensional, being an hyperplane. Furthermore, as the fixed point $\bar{R}$ belongs to $\mathcal{M}_n$, it is also globally exponentially attracting.

Regarding invariance, we show that $(x, \Phi_n(x))$ satisfies equation E.3.10 (page 147) for all k. First of all, note that by definition of Φ_n, that is being composed of the coordinates of the fixed point, it is immediate that equation E.3.10 is satisfied for all $k > n$:

$$\dot{\rho}_k = h_k - \alpha\bar{\rho}_{k+1} - (\alpha+\mu)k\bar{\rho}_k = 0. \tag{E.3.19}$$

Regarding the first n coordinates, note that this is the same as solving the corresponding inertial form for $k \le n$

$$\dot{\rho}_k = h_k - \alpha\rho_{k+1} - (\alpha+\mu)k\rho_k$$

$$\dot{\rho}_n = h_n - \alpha\bar{\rho}_{n+1} - (\alpha+\mu)n\rho_n$$

Setting $x = (\rho_1, \ldots, \rho_n)$ the above can be written as the following finite dimensional system:

$$\dot{x} = H_n - Ax \tag{E.3.20}$$

where $H_n = (h_1, h_2, \ldots, h_n - \alpha\bar{\rho}_{n+1})$ and A is the upper diagonal matrix

$$A = \begin{pmatrix} -(\alpha+\mu) & -\alpha & 0 & 0 & \ldots & 0 \\ 0 & -2(\alpha+\mu) & -\alpha & 0 & \ldots & 0 \\ \ldots & & & & & \\ 0 & 0 & \ldots & 0 & -(n-1)(\alpha+\mu) & -\alpha \\ 0 & 0 & \ldots & 0 & 0 & -n(\alpha+\mu) \end{pmatrix}.$$

Clearly, A is invertible and thus for any initial condition x_0 E.3.20 admits the unique solution

$$x(t) = H_n A^{-1} + (x_0 - H_n A^{-1})e^{-At}.$$

//////

In the next section we study the rate of attraction to each $\mathcal{M}_n$.

3.3.2 The best Inertial Manifold

We now proceed to study the rate of attraction of any trajectory of E.3.10 to the various Inertial Manifolds $\mathcal{M}_n$. Clearly they all attract the trajectory in an exponential fashion, this meaning that taking a trajectory $R(t)$ of E.3.10 corresponding to an initial solution R_0, as we did in the proof of **T.3.2** (page 154), the distance between $R(t)$ and the Inertial Manifold satisfies

$$\operatorname{dist}\big(R(t), \mathcal{M}_n\big) \leq e^{-\lambda(n)t}.$$

Investigating the dependency of $\lambda(n)$ on n, we shall be able to find the *best* Inertial Manifold, that is the Inertial Manifold $\mathcal{M}_n$ with the largest $\lambda(n)$.

To perform this task, we could just quote any theorem of [39-TEM-1998], giving definitions of $\lambda(n)$ in terms of the eigenvalues of A and Lipschitz constants: remember that the Lipschitz constant of H is zero, all the eigenvalues of the dynamical system E.3.10 are negative, the k^{th} eigenvalue being $-(\alpha + \mu)k$, and that the gap between one eigenvalue and the next increases with k.

However we prefer to detail the not so difficult calculations needed in this simple case; this is because these calculations will give us a very good hindsight on what is happening and a better understanding of the relation between the Moment Closure technique and the Inertial Manifold method. At the end of the day, this chapter of the thesis is dedicated to understanding this relationship (if any) and not to develop any difficult mathematical theory.

So, as we did in the proof of **T.3.2**, let us take the fixed point $\bar{R}$ and $R(t)$. Instead of calculating the difference $\bar{R} - R(t)$, as we did in **T.3.2**, we just calculate the difference between the projection of $\bar{R}$ and $R(t)$ on $Q = V - \mathbb{R}^n$. Write $u_n(t) = Q\bar{R} - QR(t)$, and evaluate

$$\langle \dot{u}_n, u_n \rangle = \langle -QAu_n, u_n \rangle. \qquad \text{E.3.21}$$

Instead of using the generic constant C used in **T.3.2**, we calculate it more accurately; we follow the same calculations as for E.3.15 (page 153), E.3.16 and E.3.17.

First of all, remembering that $n > 1$, we can write the projected form of E.3.15:

$$|\langle \alpha QTR, QR \rangle_L| \leq \alpha \, \|QR\|_L^2 \leq \alpha n \, \|QR\|_L^2 \, .$$

Now write the correspondent equation for E.3.16:

$$\langle (\alpha + \mu) Q\Delta R, QR \rangle_L = (\alpha + \mu) \sum_{k>n} k\rho_k^2 \geq (\alpha + \mu) n \, \|QR\|_L^2 \, .$$

Finally:

$$\langle QAR, QR\rangle_L \geq n\mu \, \|QR\|_L^2 \, .$$

Going now back to E.3.21, one can write

$$\langle \dot{u}_n, u_n \rangle \leq -n\mu \, \|u_n\|_L^2 \, ,$$

which gives

$$\|u_n(t)\|_L^2 \leq \|u_n(0)\|_L^2 \, e^{-2n\mu t}.$$

It is now clear that the bigger the n, the faster the rate of attraction. This is why the normal approximation gives better results than the deterministic one. This also implies that we could find an even better approximation by considering the first three moments, and then the first four. In fact $\mathcal{M}_n \supset \mathcal{M}_{n+1}$ and $\lambda(n) < \lambda(n+1)$. Remembering definition **D.1.6** (page 20), we have proved that the manifold $\mathcal{M}_{n+1}$ is slower than the manifold $\mathcal{M}_n$ because the rate of attraction along the fast coordinates is faster.

It might initially appear that this results is self-evident; in fact we are saying that taking into account one more moment will give better approximations. Nevertheless we have to stress that we are considering a dynamical process, and the best slow manifold will be given by the Inertial Manifold with the bigger rate of attraction. The rate of attraction to the n^{th} coordinate is given by the n^{th} eigenvalue.

In this example it happens that the order of the coordinates is the same as the order of the eigenvalues but in general it might not be true that $\lambda(n) < \lambda(n+1)$. In such a case, in order to apply the theory of Inertial Manifold, one would have to rearrange the coordinates so that the associated eigenvalues are then ordered. For example, it might happen that the second moment appears before the first moment and that in between there might be many other moments. In general, it might happen that for some n and m such that $n > m$, $\lambda(n) < \lambda(m)$ and so the moment of order n appears before the moment of order m. This implies that the above result is not self-evident and that one has to do the analysis contained in this chapter.

3.3.3 Comparison of the steady states for the full and approximated models

In this section, we analyse how the fixed point is related to the deterministic and normal approximations studied in [72-ISH-1995]. In this paper the author finds that using either of the two relations among the moments

$$\sigma^2 = 0 \qquad \text{E.3.22}$$

or

$$m_3 = 3m_1\sigma^2 + m_1^3 \qquad \text{E.3.23}$$

does indeed result in a very good approximation. Using the algebra in section 3.2.2, we translate these two relations for the moments in the equivalent for our coordinates ρ_k:

$$m_1 = \rho_1,$$

$$\sigma^2 = \rho_1 + \rho_2,$$

$$m_3 = \rho_3 + \rho_1^3 + 3\rho_1\rho_2 + 3\rho_1^2 + 3\rho_2 + \rho_1.$$

Using the above relations, equation E.3.22 reads as

$$\rho_1 + \rho_2 = 0 \qquad \text{E.3.24}$$

and E.3.23 as

$$\rho_3 + 3\rho_2 + \rho_1 = 0. \qquad \text{E.3.25}$$

Using the first relation $\sigma^2 = 0$ or E.3.24, i.e. the deterministic approximation, we can solve the approximated equation for ρ_1; E.3.10 becomes

$$\dot{\rho}_1 = h_1 - \mu\rho_1. \qquad \text{E.3.26}$$

Let us note that the solution of this equation converges exponentially towards a fixed point $\tilde{\rho}_1 = h_1/\mu$. If the situation was that $\tilde{\rho}_1$ was equal to the first co-ordinate of $\overline{R}$, then it would be immediately clear why the approximation is a good one. However, we shall presently see that this is not the case.

We have the same situation when we use the relation E.3.25, the normal approximation. This time we have the approximated equations for the first two co-ordinates:

$$\dot{\rho}_1 = h_1 - \alpha\rho_2 - (\alpha + \mu)\rho_1$$

$$\dot{\rho}_2 = h_2 + (\alpha - 2\mu)\rho_2 + \alpha\rho_1 \qquad \text{E.3.27}$$

Again the solutions to this equation tend towards a fixed point $(\hat{\rho}_1, \hat{\rho}_2)$, which are different from the first two co-ordinates of $\bar{R}$. However, let us note that the eigenvalues of the stability matrix for E.3.27

$$\begin{pmatrix} -(\alpha+\mu) & -\alpha \\ \alpha & (\alpha-2\mu) \end{pmatrix}$$

have negative real parts, and are real and negative for $\mu > 4\alpha$ which is true for the particular values assumed in the biology of [72-ISH-1995]: $\mu = 10$ and $\alpha = 0.02$.

We shall now proceed to prove that the approximations used in [72-ISH-1995] are good because the parameters are such that the fixed points of E.3.26, E.3.27 and E.3.14 are very close when $\alpha \ll \mu$, that is when the parasite-induced mortality is smaller than the parasites death rate.

In order to accomplish this task, let us first find a formula for $\bar{R}$. The co-ordinates of the fixed point $\bar{R}$ satisfy the following equations

$$\bar{\rho}_{k+1} = \frac{h_k}{\alpha} - \frac{\alpha+\mu}{\alpha} k \bar{\rho}_k \qquad (k = 1, 2 \ldots). \qquad \text{E.3.28}$$

Using E.3.28 recursively, we obtain

$$\begin{aligned}
\bar{\rho}_{k+1} =& \frac{h_k}{\alpha} - \frac{\alpha+\mu}{\alpha} k \left[\frac{h_{k-1}}{\alpha} - \frac{\alpha+\mu}{\alpha}(k-1)\rho_{k-1} \right] \\
=& \frac{h_k}{\alpha} - \frac{(\alpha+\mu)}{\alpha^2} k h_{k-1} + \frac{(\alpha+\mu)^2}{\alpha^2} k(k-1)\rho_{k-1} \\
=& \frac{h_k}{\alpha} - \frac{(\alpha+\mu)}{\alpha^2} k h_{k-1} + \frac{(\alpha+\mu)^2}{\alpha^2} k(k-1) \left[\frac{h_{k-2}}{\alpha} - \frac{\alpha+\mu}{\alpha}(k-2)\rho_{k-2} \right] \\
=& \frac{h_k}{\alpha} - \frac{(\alpha+\mu)}{\alpha^2} k h_{k-1} + \frac{(\alpha+\mu)^2}{\alpha^3} k(k-1) h_{k-2} \\
& - \frac{(\alpha+\mu)^3}{\alpha^3} k(k-1)(k-2)\rho_{k-2} \\
=& \ldots \\
=& (-1)^k \left(\frac{\alpha+\mu}{\alpha} \right)^k k! \left[\bar{\rho}_1 + \frac{1}{\alpha} \sum_{j=1}^{k} \left((-1)^j h_j \frac{1}{j!} \left(\frac{\alpha}{\alpha+\mu} \right)^j \right) \right].
\end{aligned}$$

So all the co-ordinates of $\bar{R}$ are expressible just in terms of $\bar{\rho}_1$. Imposing that $\bar{R} \in V$ means that $\sum_k k^2 \bar{\rho}_k^2 < \infty$. This can be obtained only if $\bar{\rho}_k \to 0$, i.e. only if

$$\bar{\rho}_1 = -\frac{1}{\alpha} \sum_{k=1}^{\infty} (-1)^k h_k \frac{1}{k!} \left(\frac{\alpha}{\alpha+\mu} \right)^k . \qquad \text{E.3.29}$$

As H belongs to V the h_k are bounded, let's say by $\mathcal{H}$, and thus $\bar{\rho}_1$ is finite because it is dominated by the exponential series

$$\frac{\mathcal{H}}{\alpha}\sum\frac{1}{k!}\left(\frac{\alpha}{\alpha+\mu}\right)^k=\frac{\mathcal{H}}{\alpha}\exp\left\{\frac{\alpha}{\alpha+\mu}\right\}.$$

Note also that we could have used this sort of algebraic argument to prove the existence and uniqueness of the fixed point, the above proving uniqueness.

We write explicitly the expansion of $\bar{\rho}_1$ up to the first two terms:

$$\bar{\rho}_1=\frac{h_1}{\alpha+\mu}-\frac{\alpha h_2}{2(\alpha+\mu)^2}+\text{tail},$$

and the expression for $\bar{\sigma}^2$, the variance of the fixed point:

$$\begin{aligned}\bar{\sigma}^2 =&\bar{\rho}_1+\bar{\rho}_2\\ &\text{using E.3.28}\\ =&\frac{h_1}{\alpha}-\frac{\mu}{\alpha}\bar{\rho}_1\\ &\text{using E.3.29 (page 160)}\\ =&\frac{h_1}{\alpha+\mu}+\frac{\mu h_2}{2(\alpha+\mu)^2}+\text{tail}.\end{aligned}$$

Now the fixed point for the deterministic approximation has, as first co-ordinate,

$$\tilde{\rho}_1=\frac{h_1}{\mu}.$$

At this point we are interested in the parameters values. In [72-ISH-1995] the value of α is much smaller than the value of μ; in a typical case $\alpha=0.02$ and $\mu=10$. Thus we assume that the ratio α/μ tends to 0.

Let $\epsilon=\alpha/\mu$, so that $\alpha=\epsilon\mu$, and let $\epsilon\to 0$. With this relation we have

$$\bar{\rho}_1\approx\frac{h_1}{(1+\epsilon)\mu},$$

which converges to $\tilde{\rho}_1$ as $\epsilon\to 0$; this explains the good approximation. Also note that as in [72-ISH-1995] $\tilde{\rho}_1\geq\bar{\rho}_1$ and that the deterministic assumption is equivalent to the assumption $\epsilon=0$.

We now give the expressions for the first co-ordinate (the mean) of the fixed point given by the normal approximation, which agree with the limiting form of the exact mean of the normal approximation given in [72-ISH-1995]. This is obtained by setting $\dot{\rho}_1 = \dot{\rho}_2 = 0$ in E.3.27.

$$\hat{\rho}_1 = \frac{2\mu - \alpha}{\mu(\alpha + 2\mu)} h_1 - \frac{\alpha}{\mu(\alpha + 2\mu)} h_2.$$

Again we substitute $\alpha = \epsilon\mu$ and obtain

$$\hat{\rho}_1 = \frac{2 - \epsilon}{(2 + \epsilon)\mu} h_1 - \frac{\epsilon}{(2 + \epsilon)\mu} h_2$$
$$\bar{\rho}_1 \approx \frac{1}{(1 + \epsilon)\mu} h_1 - \frac{\epsilon}{2(1 + \epsilon)^2\mu} h_2.$$

Note again that as $\epsilon \to 0$, the distance between $\bar{\rho}_1$ and $\hat{\rho}_1$ tends to 0. In [72-ISH-1995] the author also notes that the approximated mean is always smaller than the true mean. In fact it is easy to verify that for $\epsilon \geq 0$ we have

$$\frac{2 - \epsilon}{(2 + \epsilon)} \leq \frac{1}{(1 + \epsilon)}$$
$$\frac{\epsilon}{(2 + \epsilon)} \geq \frac{\epsilon}{2(1 + \epsilon)^2}.$$

Finally we prove that the variance given by the normal approximation

$$\begin{aligned}\hat{\sigma}^2 =& \hat{\rho}_1 + \hat{\rho}_2 \\ =& \frac{2}{\alpha + 2\mu} h_1 + \frac{1}{\alpha + 2\mu} h_2 = \frac{2}{(2 + \epsilon)\mu} h_1 + \frac{1}{(2 + \epsilon)\mu} h_2.\end{aligned}$$

and the variance of the real fixed point, obtained using E.3.28 and E.3.29 (page 160),

$$\bar{\sigma}^2 \approx \frac{1}{(1 + \epsilon)\mu} h_1 + \frac{1}{2(1 + \epsilon)^2\mu} h_2,$$

again converge towards the same limit. Furthermore it is straightforward algebra to prove that, as noted in [72-ISH-1995], $\hat{\sigma}^2 \geq \bar{\sigma}^2$. Also note that the expression $\hat{\sigma}^2$ agrees with the limiting form of the exact variance of the normal approximation given in [72-ISH-1995].

Note that these results do not depend on the form of H. It is enough to suppose that $H \in L$. We shall see the biological significance of this in section **3.5**.

Finally, it is important to stress the fact that the arguments above are concerned only with the first two coordinates in the case of the normal approximation and the first coordinate in the case of the deterministic approximation. Nothing is said about the behaviour of the higher coordinates. We try to overcome this limitation in the following sections.

3.3.4 Perturbations of the Inertial Manifold

In the previous section we studied the modified equations obtained by using the deterministic and normal assumptions. The modified systems and the original one admit globally attracting fixed points, and we noted that, when α is a small parameter, the first coordinates of the fixed points are close.

In this section we give a more dynamical account of what is happening. We show that both the deterministic and normal approximations are Inertial Manifolds for dynamical systems related to the original one, and that these Inertial Manifolds are very close to the Inertial Manifold of E.3.10, for the actual parameter values α and μ and for $t \to \infty$. We go a step further and we give a general algorithm that can be applied to show that a Moment Closure approximation is an Inertial Manifold for a dynamical system related to E.3.10 (page 147). Notice that the last step is the only one depending on the values of the parameters α and μ.

We are trying to overcome the limitation of the previous section where the only thing we said is that the first coordinates of the fixed points are close. See the explanation at page 38 in section 1.4.2 for more details on this limitation.

In the case these Moment Closure functions were Inertial Manifolds, then all higher coordinates would be expressed as functions of the first one (deterministic approximation) or the first two (normal approximation). Here we prove that this is the case for a *perturbation* of E.3.10, but only for the second coordinate (deterministic approximation) and for the third coordinate (normal approximation).

Our aim is thus to use the moment closure function to define a dynamical system, which will be a perturbation of the original one, though in a peculiar sense, so that the moment closure is an Inertial Manifold for this system. It is important to stress that the new system is defined for all the coordinates ρ_k, and not just for the first n coordinates defining the moment closure being used. This is how we can overcome the limitation of the previous section, and actually study the relation between the higher coordinates of the approximated system and those of the original one.

Therefore, in this section we define $\mathcal{M}_n$ as the Inertial Manifold of E.3.10, and for a Moment Closure approximation, given as a function of the first n coordinates, we define $\widetilde{\mathcal{M}}_n$ which is equal to $\mathcal{M}_n$ except for the $(n+1)^{\text{th}}$ coordinate. We then prove that this $(n+1)^{\text{th}}$ coordinate is close to the $(n+1)^{\text{th}}$ coordinate of $\mathcal{M}_n$, at least for $\epsilon \to 0$ and $t \to \infty$.

Here goes the algorithm:

- First of all, we have shown in lemma **L.3.3** (page 155) that the hyperplane of dimension n obtained by fixing all the coordinates, with the exception of the first n ones, equal to the fixed point coordinates, is an Inertial Manifold for the original system:

$$\begin{aligned}\mathcal{M}_n =&\{\rho_1, \ldots, \rho_n, \Phi_n(\rho_1, \ldots, \rho_n)\} \\ =&\{\rho_1, \ldots, \rho_n, \bar{\rho}_{n+1}, \bar{\rho}_{n+2}, \ldots\}.\end{aligned}$$

- Then we introduce a Moment Closure approximation of order n, defined by a function $\widetilde{\Phi}_n(\rho_1, \ldots, \rho_n)$ such that the Moment Closure can be expressed as $\rho_{n+1} + \widetilde{\Phi}_n(\rho_1, \ldots, \rho_n) = 0$. The deterministic approximation is then defined by the function

$$\widetilde{\Phi}_1(\rho_1) = \rho_1$$

and the normal approximation by the function

$$\widetilde{\Phi}_2(\rho_1, \rho_2) = 3\rho_2 + \rho_1.$$

- Introduce now the change of variables

$$\begin{aligned}\widetilde{\rho}_{n+1} =&\rho_{n+1} + \widetilde{\Phi}_n(\rho_1, \ldots, \rho_n) - \Phi_{n,n+1}(\rho_1, \ldots, \rho_n) \\ =&\rho_{n+1} + \widetilde{\Phi}_n(\rho_1, \ldots, \rho_n) - \bar{\rho}_{n+1}\end{aligned} \qquad \text{E.3.30}$$

where $\Phi_{n,j}(\rho_1, \ldots, \rho_n)$ is the j^{th} coordinate of the function Φ_n defining $\mathcal{M}_n$. With this notation, for the deterministic approximation we have

$$\widetilde{\rho}_2 = \rho_2 + \rho_1 - \bar{\rho}_2,$$

and for the normal approximation

$$\widetilde{\rho}_3 = \rho_3 + 3\rho_2 + \rho_1 - \bar{\rho}_3.$$

– To simplify the notation, we now write $\widetilde{\Phi}_n$ for $\widetilde{\Phi}_n(\rho_1,\ldots,\rho_n)$ and $\Phi_{n,j}$ for $\Phi_{n,j}(\rho_1,\ldots,\rho_n)$. Finally we show that, if $\widetilde{\Phi}_n$ is Lipschitz, the manifold

$$\widetilde{\mathcal{M}}_n = \left\{\rho_1,\ldots,\rho_n,\tilde{\Phi}_n,\Phi_{n,n+2},\Phi_{n,n+3},\ldots\right\} \qquad \text{E.3.31}$$

is an Inertial Manifold for the dynamical system

$$\begin{aligned}
\dot{\rho}_k &= h_k - \alpha\rho_{k+1} - (\alpha+\mu)k\rho_k && \text{for } k \le n,\\
\dot{\tilde{\rho}}_{n+1} &= \frac{\mathrm{d}\widetilde{\Phi}_n(\rho_1,\ldots,\rho_n)}{\mathrm{d}t}, \\
\dot{\rho}_k &= h_k - \alpha\rho_{k+1} - (\alpha+\mu)k\rho_k && \text{for } k \ge n+2,
\end{aligned} \qquad \text{E.3.32}$$

which is obtained by substituting $\dot{\rho}_k$ with $\dot{\tilde{\rho}}_{n+1} = \frac{\mathrm{d}\widetilde{\Phi}_n(\rho_1,\ldots,\rho_n)}{\mathrm{d}t}$ into the system E.3.10.

– In the L norm, the distance between $\mathcal{M}_n$ and $\widetilde{\mathcal{M}}_n$ is given by the square sum of the difference of all coordinates. Being the two manifolds equal for all coordinates, except the $(n+1)^{\text{th}}$ coordinate, we have that

$$\operatorname{dist}\left(\mathcal{M}_n,\widetilde{\mathcal{M}}_n\right) = \left|\bar{\rho}_{n+1} - \widetilde{\Phi}_n\right|^2 .$$

We show that this difference goes to zero at infinity for the normal and deterministic approximation for the values of the parameters α and μ used in the biological example of [72-ISH-1995]; that is

$$\widetilde{\mathcal{M}}_n \xrightarrow[\substack{t\to\infty\\ \epsilon\to 0}]{} \mathcal{M}_n$$

We now continue with formal proofs of the steps of the above algorithm. The first point was already proved in lemma **L.3.3** (page 155). The other steps of the procedure defined at the beginning of this section are quite automatic. The most interesting bit is the last step, that is the proof that $(\bar{\rho}_{n+1} - \widetilde{\Phi}_n)$ is small. Clearly this cannot be done in general; that is depending on the values of the parameters α and μ and on the Moment Closure function, the algorithm will be valid or not.

We prove in the following lemmas two results that we shall need later to prove that the procedure can be applied to the deterministic and the normal approximations.

LEMMA L.3.4 *The difference $(\bar{\rho}_2 - \bar{\rho}_1)$, expressed as a quantity depending on α and $\mu = \alpha/\epsilon$, goes to zero as $\epsilon \to 0$.*

Proof Using E.3.28 (page 160) and E.3.29, we have

$$\begin{aligned}
\bar{\rho}_2 =& \frac{h_1}{\alpha} - \frac{\alpha+\mu}{\alpha}\bar{\rho}_1 \\
=& \frac{h_1}{\alpha} - \frac{\alpha+\mu}{\alpha}\left(-\frac{1}{\alpha}\sum_{k=1}^{\infty}(-1)^k h_k \frac{1}{k!}\left(\frac{\alpha}{\alpha+\mu}\right)^k\right) \\
=& \frac{h_1}{\alpha} - \frac{\alpha+\mu}{\alpha}\left(\frac{1}{\alpha}h_1\frac{\alpha}{\alpha+\mu}\right) - \frac{\alpha+\mu}{\alpha}\left(-\frac{1}{\alpha}\sum_{k=2}^{\infty}(-1)^k h_k \frac{1}{k!}\left(\frac{\alpha}{\alpha+\mu}\right)^k\right) \\
=& +\frac{1}{\alpha}\sum_{k=2}^{\infty} h_k \frac{(-1)^k}{k!}\left(\frac{\alpha}{\alpha+\mu}\right)^{k-1}. \qquad \text{E.3.33}
\end{aligned}$$

Now we can write

$$\begin{aligned}
|\bar{\rho}_1 - \bar{\rho}_2| =& \Bigg| \frac{h_1}{\alpha+\mu} \\
& - \frac{1}{\alpha}\sum_{k=2}^{\infty}(-1)^k h_k \frac{1}{k!}\left(\frac{\alpha}{\alpha+\mu}\right)^k \\
& - \frac{1}{\alpha}\sum_{k=2}^{\infty} h_k \frac{(-1)^k}{k!}\left(\frac{\alpha}{\alpha+\mu}\right)^{k-1} \Bigg| \qquad \text{E.3.34} \\
=& \left| \frac{h_1}{\alpha+\mu} - \frac{1}{\alpha}\sum_{k=2}^{\infty}(-1)^k h_k \frac{1}{k!}\left(\frac{\alpha^k + \alpha^{k-1}(\alpha+\mu)}{(\alpha+\mu)^k}\right) \right| \\
\leq& \frac{\mathcal{H}}{\alpha+\mu} + \frac{\mathcal{H}}{\alpha}\sum_{k=2}^{\infty}\frac{\alpha^{k-1}\mu + 2\alpha^k}{k!(\alpha+\mu)^k},
\end{aligned}$$

where $\mathcal{H}$ is a constant dominating the sequence $\{h_k\}$, for example its norm. With the assumption $\mu = \alpha/\epsilon$, it is true that the above difference is bounded by a term tending to zero for $\epsilon \to 0$. We can see this in the following calculation:

$$\begin{aligned}
|\bar{\rho}_1 - \bar{\rho}_2| \leq& \frac{\mathcal{H}\epsilon}{\epsilon\alpha+\alpha} + \frac{\mathcal{H}}{\alpha}\sum_{k=2}^{\infty}\frac{\epsilon^k(\alpha^{k-1}\alpha + 2\epsilon\alpha^k)}{\epsilon k!(\epsilon\alpha+\alpha)^k}, \\
=& \frac{\mathcal{H}\epsilon}{\epsilon\alpha+\alpha} + \frac{\mathcal{H}}{\alpha}\sum_{k=2}^{\infty}\frac{\epsilon^k(1+2\epsilon)}{\epsilon k!(\epsilon+1)^k} \\
=& \frac{\mathcal{H}\epsilon}{\epsilon\alpha+\alpha} + \frac{\mathcal{H}}{\alpha}\frac{(1+2\epsilon)}{\epsilon}\sum_{k=2}^{\infty}\frac{\epsilon^k}{k!(\epsilon+1)^k} \\
=& \frac{\mathcal{H}\epsilon}{\epsilon\alpha+\alpha} + \frac{\mathcal{H}}{\alpha}\frac{(1+2\epsilon)}{\epsilon}\left[e^{\epsilon/(\epsilon+1)} - 1 - \frac{\epsilon}{\epsilon+1}\right] \\
=& \frac{\mathcal{H}\epsilon}{\epsilon\alpha+\alpha} + \frac{\mathcal{H}}{\alpha}\frac{(1+2\epsilon)}{\epsilon}\left[e^{\epsilon/(\epsilon+1)} - \frac{1+2\epsilon}{\epsilon+1}\right],
\end{aligned}$$

which goes to zero as $\epsilon \to 0$, as an easy application of l'Hôpital's rule will show.

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LEMMA L.3.5 *The difference $(\bar{\rho}_3 - 3\bar{\rho}_2 - \bar{\rho}_1)$, expressed as a quantity depending on α and $\mu = \alpha/\epsilon$, goes to zero as $\epsilon \to 0$.*

Proof First of all, using E.3.33, we find the expression for $\bar{\rho}_3$:

$$\begin{aligned}\bar{\rho}_3 &= \frac{h_2}{\alpha} - 2\frac{\alpha+\mu}{\alpha}\bar{\rho}_2 \\ &= \frac{h_2}{\alpha} - 2\frac{\alpha+\mu}{\alpha}\frac{1}{\alpha}\sum_{k=2}^{\infty} h_k \frac{(-1)^k}{k!}\left(\frac{\alpha}{\alpha+\mu}\right)^{k-1} \\ &= \frac{h_2}{\alpha} - 2\frac{\alpha+\mu}{\alpha^2}\frac{h_2(-1)^2}{2!}\frac{\alpha}{\alpha+\mu} - 2\frac{\alpha+\mu}{\alpha^2}\sum_{k=3}^{\infty} h_k \frac{(-1)^k}{k!}\left(\frac{\alpha}{\alpha+\mu}\right)^{k-1} \\ &= -\frac{2}{\alpha}\sum_{k=3}^{\infty} h_k \frac{(-1)^k}{k!}\left(\frac{\alpha}{\alpha+\mu}\right)^{k-2}.\end{aligned}$$

Again we note that $\widetilde{\Phi}(\rho_1, \rho_2) \to 3\bar{\rho}_2 + \bar{\rho}_1$. Take the difference between this number and $\bar{\rho}_3$:

$$\begin{aligned}|\bar{\rho}_3 - 3\bar{\rho}_2 - \bar{\rho}_1| =& \Bigg| -\frac{2}{\alpha}\sum_{k=3}^{\infty} h_k \frac{(-1)^k}{k!}\left(\frac{\alpha}{\alpha+\mu}\right)^{k-2} \\ & - \frac{3}{\alpha}\sum_{k=2}^{\infty} h_k \frac{(-1)^k}{k!}\left(\frac{\alpha}{\alpha+\mu}\right)^{k-1} \\ & + \frac{1}{\alpha}\sum_{k=1}^{\infty} h_k \frac{(-1)^k}{k!}\left(\frac{\alpha}{\alpha+\mu}\right)^{k} \Bigg| \\ =& \frac{1}{\alpha}\Bigg| -\frac{3}{2}\frac{h_2\alpha}{\alpha+\mu} - \frac{h_1\alpha}{\alpha+\mu} + \frac{h_2}{2}\left(\frac{\alpha}{\alpha+\mu}\right)^2 \\ & + \sum_{k=3}^{\infty} h_k \frac{(-1)^k}{k!}\left[-2\left(\frac{\alpha}{\alpha+\mu}\right)^{k-2} - 3\left(\frac{\alpha}{\alpha+\mu}\right)^{k-1} + \left(\frac{\alpha}{\alpha+\mu}\right)^{k}\right]\Bigg|,\end{aligned}$$

which again, with the assumption $\mu = \alpha/\epsilon$, is bounded by a term tending to zero for $\epsilon \to 0$. We can see it in the following calculation:

$$\begin{aligned}|\bar{\rho}_3 - 3\bar{\rho}_2 - \bar{\rho}_1| \leq& \frac{1}{\alpha}\Bigg\{ \frac{3}{2}\frac{\mathscr{H}\epsilon\alpha}{\epsilon\alpha+\alpha} + \frac{\mathscr{H}\epsilon\alpha}{\epsilon\alpha+\alpha} + \frac{\mathscr{H}}{2}\left(\frac{\epsilon\alpha}{\epsilon\alpha+\alpha}\right)^2 \\ & + \mathscr{H}\sum_{k=3}^{\infty}\frac{1}{k!}\left[2\left(\frac{\epsilon\alpha}{\epsilon\alpha+\alpha}\right)^{k-2} + 3\left(\frac{\epsilon\alpha}{\epsilon\alpha+\alpha}\right)^{k-1} + \left(\frac{\epsilon\alpha}{\epsilon\alpha+\alpha}\right)^{k}\right]\Bigg\} \\ =& \frac{1}{\alpha}\Bigg\{ \mathscr{H}\frac{\epsilon}{\epsilon+1}\frac{6\epsilon+5}{2(\epsilon+1)} + \mathscr{H}\frac{6\epsilon^2+7\epsilon+2}{(\epsilon+1)^2}\sum_{k=3}^{\infty}\frac{1}{k!}\left(\frac{\epsilon}{\epsilon+1}\right)^{k-2}\Bigg\}.\end{aligned}$$

The first term of the right hand side clearly goes to 0 as $\epsilon \to 0$, whilst the second term behaves like $2\mathcal{H}$ multiplied by the following exponential series:

$$\sum_{k=3}^{\infty} \frac{1}{k!} \left(\frac{\epsilon}{\epsilon+1}\right)^{k-2} = \left(\frac{\epsilon+1}{\epsilon}\right)^2 \sum_{k=3}^{\infty} \frac{1}{k!} \left(\frac{\epsilon}{\epsilon+1}\right)^{k}$$
$$= \left(\frac{\epsilon+1}{\epsilon}\right)^2 \left[e^{e/\epsilon+1} - 1 - \frac{\epsilon}{\epsilon+1} - \frac{\epsilon}{2\epsilon+2}\right],$$

which again is a series whose limit for $\epsilon \to 0$ is 0 thanks to l'Hôpital's rule.

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We finally prove a lemma regarding the dynamical system E.3.10, valid for any value of α and μ.

LEMMA L.3.6 $\widetilde{\mathcal{M}}_n$ *defined in E.3.31 is an Inertial Manifold for E.3.32.*

Proof To simplify the notation, in the following $\widetilde{\Phi}_n$ stands for $\widetilde{\Phi}_n(\rho_1, \ldots, \rho_n)$ and $\widetilde{\Phi}_n(t)$ for $\widetilde{\Phi}_n(\rho_1(t), \ldots, \rho_n(t))$.

First we prove invariance. Take a point $R = \{r_k\}$ lying on the manifold $\widetilde{\mathcal{M}}_n$, i.e satisfying the equations

$$r_{n+1} = \widetilde{\Phi}_n = \widetilde{\Phi}_n(r_1, \ldots, r_n),$$

$$r_k = \bar{\rho}_k \qquad \text{for } k \geq n+2.$$

Take this point as an initial condition and show that the solution of E.3.32 associated to this fixed points lies on the manifold.

By definition E.3.31 of $\widetilde{\mathcal{M}}_n$ we have

$$\widetilde{\rho}_{n+1}(0) = r_{n+1} = \widetilde{\Phi}_n(0)$$

and by definition E.3.30 of $\widetilde{\rho}_{n+1}$ we have

$$\widetilde{\rho}_{n+1}(0) = \rho_{n+1}(0) + \widetilde{\Phi}_n(0) - \bar{\rho}_{n+1}.$$

The two above equations put together give

$$\widetilde{\Phi}_n(0) = \widetilde{\rho}_{n+1}(0) = \rho_{n+1}(0) + \widetilde{\Phi}_n(0) - \bar{\rho}_{n+1}$$

which clearly implies

$$\rho_{n+1}(0) = \bar{\rho}_{n+1}.$$

Now, we have to remember that equation E.3.32 is the same as E.3.10, with a change of variables. This means that for $i \geq 1$, r_{n+i} has the coordinates of the fixed point $\overline{R}$ of E.3.10, and, as in this equation for the j^{th} coordinate depends only on the j^{th} and $(j+1)^{\text{th}}$ coordinates, we can conclude that

$$\rho_{n+i}(t) = \bar{\rho}_{n+i}$$

for all $i \geq 1$ and for all $t \geq 0$.

In particular, $\rho_{n+1}(t) = \bar{\rho}_{n+1}$ and thus

$$\widetilde{\rho}_{n+1}(t) = \rho_{n+1}(t) + \widetilde{\Phi}_n(t) - \bar{\rho}_{n+1} = \widetilde{\Phi}_n(t).$$

This shows invariance: if we start on $\widetilde{\mathcal{M}}_n$, that is if $\widetilde{\rho}_{n+1}(0) = r_{n+1} = \widetilde{\Phi}_n(0)$, then the trajectory will always stay on $\widetilde{\mathcal{M}}_n$, that is $\widetilde{\rho}_{n+1}(t) = \widetilde{\Phi}_n(t)$.

The fact that the manifold is exponentially attracting is trivial, as every trajectory is exponentially attracted to the point

$$\widetilde{R} = \left\{\bar{\rho}_1, \ldots, \bar{\rho}_n, \widetilde{\Phi}_n(\bar{\rho}_1, \ldots, \bar{\rho}_n), \bar{\rho}_{n+2}, \ldots\right\}$$

which lies on the manifold. In fact, we know that $\forall i \geq 1$ $\rho_i(t) \to \bar{\rho}_i$ exponentially. This means that

$$\begin{aligned}\widetilde{\rho}_{n+1}(t) &= \rho_{n+1}(t) + \widetilde{\Phi}_n(t) - \bar{\rho}_{n+1} \\ &\to \bar{\rho}_{n+1} + \widetilde{\Phi}_n(\bar{\rho}_1, \ldots, \bar{\rho}_n) - \bar{\rho}_{n+1} \\ &= \widetilde{\Phi}_n(\bar{\rho}_1, \ldots, \bar{\rho}_n).\end{aligned}$$

Finally the manifold $\widetilde{\mathcal{M}}_n$ is finite dimensional, and it is Lipschitz if so is $\widetilde{\Phi}_n$.

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We are now ready to prove that the deterministic and normal approximation are very close to the original Inertial Manifold.

THEOREM T.3.7 ***Given $\widetilde{\mathcal{M}}_1$ and $\widetilde{\mathcal{M}}_2$ the manifolds respectively given by the Moment Closure approximations $\widetilde{\Phi}_1(\rho_1) = \rho_1$ and $\widetilde{\Phi}_2(\rho_1, \rho_2) = 3\rho_2 + \rho_1$, then the distance between $\mathcal{M}_1$ and $\widetilde{\mathcal{M}}_1$ and the distance $\mathcal{M}_2$ and $\widetilde{\mathcal{M}}_2$ can be expressed as a term $\delta(\epsilon, t)$ which goes to zero as $\epsilon \to 0$ and $t \to \infty$.***

Proof In lemmas **L.3.4** and **L.3.5** we have seen that for the deterministic and normal approximation

$$\lim_{\epsilon \to 0} \widetilde{\Phi}_n(\bar{\rho}_1, \ldots, \bar{\rho}_n) = \bar{\rho}_{n+1}.$$

In the last paragraph of the above proof, we have used the fact that $\forall \epsilon > 0$

$$\lim_{t \to \infty} \widetilde{\Phi}_n(\rho_1(t), \ldots, \rho_n(t)) = \widetilde{\Phi}_n(\bar{\rho}_1, \ldots, \bar{\rho}_n).$$

If in the above limits we express $\widetilde{\Phi}_n$ as a function of ϵ and time t, by making formally explicit the dependency on α and $\mu = \alpha/\epsilon$ and on time through $\rho_1(t), \ldots, \rho_n(t)$, then it is clear that $\widetilde{\rho}_{n+1}$ would be equal to ρ_{n+1} plus a small term $\delta(\epsilon, t) = \widetilde{\Phi}_n(t) - \bar{\rho}_{n+1}$. The above limits show that $\delta(\epsilon, t) \to 0$ as $\epsilon \to 0$ and $t \to \infty$.

//////

It is important to remark the limitations of what we have shown. In fact, we have proved that in the limit of **both** $\epsilon \to 0$ and $t \to \infty$ the two inertial manifolds are close. So it is not possible for us to speak properly of a *"perturbation"*; in fact the manifold $\widetilde{\mathcal{M}}_n$ is a linear, first degree approximation of another linear manifold $\mathcal{M}_n$. Clearly, two hyperplanes cannot be an approximation of each other for all times.

3.3.5 Higher factorial cumulants for the normal approximation

In this section we wish to give some insight on the behaviour of the higher factorial cumulants for the normal approximation. In fact, if the normal approximation were really an Inertial Manifold, then it would be describing all higher factorial cumulants as functions of the first two, as explained in section 1.4.2. In section 3.3.3 we have seen that the $\hat{\rho}_1$ is close to $\bar{\rho}_1$ and $\hat{\rho}_2$ is close to $\bar{\rho}_2$. In section 3.3.4 we have further seen that the normal approximation expresses, at least for $\epsilon \to 0$ and $t \to \infty$ the third component ρ_3 as a function of ρ_1 and ρ_2. Here we investigate whether all the other higher components of the manifold given as the graph of the function defining the normal approximation are close to the corresponding higher components of the Inertial Manifold of the original dynamical system E.3.10 (page 147).

First of all, setting $f(t) = \ln(E(t^X))$ and $g(t) = e^t$, the cumulants are given by the formula

$$\kappa_n = \left\lfloor \frac{\partial^n f(g(t))}{\partial t^n} \right\rfloor_0 .$$

Now, use Faà di Bruno's formula (see glossary)

$$\frac{\partial^n f(g(t))}{\partial t^n} = \sum_{\pi \in \Upsilon_n} \frac{\partial^{|\pi|} f(g(t))}{\partial t^{|\pi|}} \prod_{B \in \pi} \frac{\partial^{|B|} g(t)}{\partial t^{|B|}},$$

where Υ_n are all the partitions of the set $\{1, \ldots, n\}$, π is such a partition, $B \in \pi$ means the variable B runs through the list of all of the blocks of the partition π, and $|A|$ denotes the cardinality of the set A.

Remembering that the factorial cumulant is defined as

$$\rho_n = \left\lfloor \frac{\partial^n f(t)}{\partial t^n} \right\rfloor_1$$

and that $g(0) = 1$ and $g'(t) = g(t)$, we have easily that

$$\forall \pi \qquad \left\lfloor \prod_{B \in \pi} \frac{\partial^{|B|} g(t)}{\partial t^{|B|}} \right\rfloor_0 = 1,$$

so that

$$\kappa_n = \left\lfloor \frac{\partial^n f(g(t))}{\partial t^n} \right\rfloor_0 = \left\lfloor \sum_{\pi \in \Upsilon_n} \frac{\partial^{|\pi|} f(g(t))}{\partial t^{|\pi|}} \right\rfloor_0 = \sum_{\pi \in \Pi_n} \rho_\pi . \qquad \text{E.3.35}$$

Now, we use the normal approximation, that is the fact that all cumulants $\kappa_n = 0$ for $n \geq 3$, to find a formula for the ρ_n. Remember that there is only one partition π_1 of the first n numbers $\{1, 2, \ldots, n\}$ with cardinality n, which is $\pi_1 = \{\{1\}, \ldots, \{n\}\}$. Thus the normal approximation can be expressed, for $n \geq 3$, in terms of the factorial cumulants as

$$\rho_n = - \sum_{\pi \in \widetilde{\Upsilon}_n} \rho_\pi \qquad \text{E.3.36}$$

where $\widetilde{\Upsilon}_n$ are all the partitions of the set of the first n numbers minus the one partition with cardinality n.

Take now a closer look at E.3.36, for example for $n = 3$. There are 3 partitions π_i such that $|\pi_i| = 2$, that is with cardinality 2; these are the partitions with two sets, one of size 1 and the other of size 2, namely $\pi_2 = \{\{1,2\};\{3\}\}$, $\pi_3 = \{\{1,3\};\{2\}\}$ and $\pi_4 = \{\{2,3\};\{1\}\}$. Also, there is only one way of partitioning this set such that $|\pi_5| = 1$, that is $\pi_5 = \{\{1,2,3\}\}$. Thus E.3.36 reads as follows, for $n = 3$:

$$\rho_3 = -\widetilde{\Phi}_2(\rho_1, \rho_2) = -3\rho_2 - \rho_1,$$

which is exactly the negative of the function defining the normal approximation in the ρ coordinates. Remember that we used this relation in lemma **L.3.5** (page 167), where we proved that the difference $\widetilde{\Phi}_2(\bar{\rho}_1, \bar{\rho}_2) - \bar{\rho}_3$ tends to zero. We used this fact to prove that the change of variable in the system E.3.32 (page 165)

$$\widetilde{\rho}_3 = \rho_3 + \widetilde{\Phi}_2(\rho_1, \rho_2) - \bar{\rho}_3.$$

would give us an approximated Inertial Manifold, close to the original one for $\epsilon \to 0$ and $t \to \infty$.

Now, we would like to extend this result to the higher coordinates $\bar{\rho}_n$ of the fixed point $\bar{R}$ for $n \geq 4$. In order to do this, we first notice that E.3.36 is actually saying that we can recursively solve the ρ_n and express them as a polynomial function of ρ_1 and ρ_2. Let us denote such a function by Ψ_n. This is the same of the normal approximation function, but expressed in the factorial cumulants coordinates.

LEMMA L.3.8 *For all $n \geq 3$, $\bar{\rho}_n$ is close to $\Psi_n(\bar{\rho}_1, \bar{\rho}_2)$, as $\epsilon \to \infty$.*

Proof The proof is not difficult as it consists just of some algebraic manipulations of the above formulas. First we find a formula for $\bar{\rho}_n$ as a function of h_k, α, μ. Then we show that this function is such that $\bar{\rho}_n - \Psi_n(\bar{\rho}_1, \bar{\rho}_2)$ tends to zero as $\epsilon \to 0$.

We show that each $\bar{\rho}_n$ satisfies the formula

$$\bar{\rho}_n = (-1)^n \frac{(n-1)!}{\alpha} \sum_{k=n}^{\infty} h_k \frac{(-1)^k}{k!} \left(\frac{\alpha}{\alpha + \mu} \right)^{k-n+1}. \qquad \text{E.3.37}$$

We have shown in lemma **L.3.4** (page 166) that the above is true for $n = 2$ and in lemma **L.3.5** (page 167) that it is true for $n = 3$. We now use induction to prove it for all n. Suppose it is true for n and use formula E.3.28 (page 160) for $\bar{\rho}_{n+1}$:

$$\begin{aligned}
\bar{\rho}_{n+1} =& \frac{h_n}{\alpha} - \frac{\alpha+\mu}{\alpha} n \bar{\rho}_n \\
& \text{using E.3.37 for } \rho_n \\
=& \frac{h_n}{\alpha} - \frac{\alpha+\mu}{\alpha} n \left\{ (-1)^n \frac{(n-1)!}{\alpha} \sum_{k=n}^{\infty} h_k \frac{(-1)^k}{k!} \left(\frac{\alpha}{\alpha+\mu} \right)^{k-n+1} \right\} \\
=& \frac{h_n}{\alpha} - \frac{\alpha+\mu}{\alpha} n (-1)^n \frac{(n-1)!}{\alpha} h_n \frac{(-1)^n}{n!} \left(\frac{\alpha}{\alpha+\mu} \right)^{n-n+1} \\
& - \frac{\alpha+\mu}{\alpha} n (-1)^n \frac{(n-1)!}{\alpha} \sum_{k=n+1}^{\infty} h_k \frac{(-1)^k}{k!} \left(\frac{\alpha}{\alpha+\mu} \right)^{k-n+1} \\
=& \frac{h_n}{\alpha} - \frac{h_n}{\alpha} + (-1)^{n+1} \frac{n!}{\alpha} \sum_{k=n+1}^{\infty} h_k \frac{(-1)^k}{k!} \left(\frac{\alpha}{\alpha+\mu} \right)^{k-(n+1)+1}
\end{aligned}$$

which is exactly formula E.3.37.

Let us turn now our attention to E.3.36. Introduce the Stirling numbers of second kind (see glossary) $\mathcal{S}_{n,k}$ which are defined for $k = 1, \ldots, n$ as the number of partitions of the set $\{1, \ldots, n\}$ with cardinality k. Now, formula E.3.36 can be written as

$$\rho_n = -\sum_{k=1}^{n-1} \mathcal{S}_{n,k} \rho_k. \qquad \text{E.3.38}$$

This means that, if the normal approximation holds, the ρ_n are a linear combination of the previous factorial cumulants. Apply now recursively the above formula to ρ_{n-1}:

$$\begin{aligned}
\rho_n =& -\sum_{k=1}^{n-1} \mathcal{S}_{n,k} \rho_k \\
=& -\mathcal{S}_{n,n-1} \rho_{n-1} - \sum_{k=1}^{n-2} \mathcal{S}_{n,k} \rho_k \\
& \text{applying E.3.38 again} \\
=& \mathcal{S}_{n,n-1} \sum_{k=1}^{n-2} \mathcal{S}_{n-1,\,k} \rho_k - \sum_{k=1}^{n-2} \mathcal{S}_{n,k} \rho_k \\
=& \sum_{k=1}^{n-2} \left(\mathcal{S}_{n,n-1} \mathcal{S}_{n-1,\,k} - \mathcal{S}_{n,k} \right) \rho_k.
\end{aligned} \qquad \text{E.3.39}$$

It is clear now that ρ_n can be expressed as a very special polynomial of ρ_1 and ρ_2:

$$\rho_n = \Psi_n(\rho_1, \rho_2) = \omega_{n,1}\, \rho_1 + \omega_{n,2}\, \rho_2, \qquad \text{E.3.40}$$

where $\omega_{n,1}$ and $\omega_{n,2}$ are two numbers given by the recursive formula E.3.39.

We are now ready to show that no matter the actual form of $\omega_{n,1}$ and $\omega_{n,2}$, the fact that the formula E.3.40 is linear in ρ_1 and ρ_2 guarantees that $\bar{\rho}_n - \Psi_n(\bar{\rho}_1, \bar{\rho}_2)$ is close to zero.To do this, use the formulas E.3.37 (page 172), E.3.33 (page 166) and E.3.29 (page 160):

$$\begin{aligned}\left|\bar{\rho}_n - \Psi_n(\bar{\rho}_1, \bar{\rho}_2)\right| = \Bigg| & (-1)^n \frac{(n-1)!}{\alpha} \sum_{k=n}^{\infty} h_k \frac{(-1)^k}{k!} \left(\frac{\alpha}{\alpha+\mu}\right)^{k-n+1} \\ & + \omega_{n,1} \frac{1}{\alpha} \sum_{k=1}^{\infty} (-1)^k h_k \frac{1}{k!} \left(\frac{\alpha}{\alpha+\mu}\right)^{k} \\ & - \omega_{n,2} \frac{1}{\alpha} \sum_{k=2}^{\infty} h_k \frac{(-1)^k}{k!} \left(\frac{\alpha}{\alpha+\mu}\right)^{k-1} \Bigg|\end{aligned}$$

so that

$$\begin{aligned}&\left|\bar{\rho}_n - \Psi_n(\bar{\rho}_1, \bar{\rho}_2)\right| \\ &\leq \frac{\mathcal{H}}{\alpha} \Bigg\{ (n-1)! \sum_{k=n}^{\infty} \frac{1}{k!} \left(\frac{\alpha}{\alpha+\mu}\right)^{k-n+1} \\ &\quad + \omega_{n,1} \sum_{k=1}^{\infty} \frac{1}{k!} \left(\frac{\alpha}{\alpha+\mu}\right)^{k} + \omega_{n,2} \sum_{k=2}^{\infty} \frac{1}{k!} \left(\frac{\alpha}{\alpha+\mu}\right)^{k-1} \Bigg\} \\ &= \frac{\mathcal{H}}{\alpha} \Bigg\{ \omega_{n,1} \frac{\alpha}{\alpha+\mu} + \sum_{k=2}^{n-1} \left[\frac{1}{k!} \left(\frac{\alpha}{\alpha+\mu}\right)^{k-1} \frac{(\omega_{n,1}+\omega_{n,2})\,\alpha + \omega_{n,2}\mu}{\alpha+\mu} \right] \\ &\quad + \left[(n-1)! + \omega_{n,1} \left(\frac{\alpha}{\alpha+\mu}\right)^{n-1} + \omega_{n,1} \left(\frac{\alpha}{\alpha+\mu}\right)^{n-2} \right] \sum_{k=n}^{\infty} \frac{1}{k!} \left(\frac{\alpha}{\alpha+\mu}\right)^{k-n+1} \Bigg\}.\end{aligned}$$

Substitute now $\mu = \alpha/\epsilon$ in the above, as we did in lemmas **L.3.4** (page 166) and **L.3.5** (page 167).

$$\begin{aligned}&\left|\bar{\rho}_n - \Psi_n(\bar{\rho}_1, \bar{\rho}_2)\right| \\ &\leq \frac{\mathcal{H}}{\alpha} \Bigg\{ \omega_{n,1} \frac{\epsilon}{1+\epsilon} + \sum_{k=2}^{n-1} \left[\frac{1}{k!} \left(\frac{\epsilon}{1+\epsilon}\right)^{k-1} \frac{(\omega_{n,1}+\omega_{n,2})\,\epsilon + \omega_{n,2}}{1+\epsilon} \right] \\ &\quad + \left[(n-1)! + \omega_{n,1} \left(\frac{\epsilon}{1+\epsilon}\right)^{n-1} + \omega_{n,1} \left(\frac{\epsilon}{1+\epsilon}\right)^{n-2} \right] \sum_{k=n}^{\infty} \frac{1}{k!} \left(\frac{\epsilon}{1+\epsilon}\right)^{k-n+1} \Bigg\}.\end{aligned}$$

Obviously

$$\frac{\epsilon}{1+\epsilon} \xrightarrow[\epsilon \to 0]{} 0.$$

The following finite sum also tends to 0 for $\epsilon \to 0$:

$$\sum_{k=2}^{n-1} \left[\frac{1}{k!} \left(\frac{\epsilon}{1+\epsilon} \right)^{k-1} \frac{(\omega_{n,1} + \omega_{n,2})\,\epsilon + \omega_{n,2}}{1+\epsilon} \right] \xrightarrow[\epsilon \to 0]{} 0.$$

The following term tends to $(n-1)!$:

$$(n-1)! + \omega_{n,1} \Big(\frac{\epsilon}{1+\epsilon} \Big)^{n-1} + \omega_{n,1} \Big(\frac{\epsilon}{1+\epsilon} \Big)^{n-2} \xrightarrow[\epsilon \to 0]{} (n-1)!,$$

which is finite for any n. We need only showing that the following infinite series tends to 0 as $\epsilon \to 0$:

$$\begin{aligned} \sum_{k=n}^{\infty} \frac{1}{k!} \Big(\frac{\epsilon}{1+\epsilon} \Big)^{k-n+1} &= \Big(\frac{1+\epsilon}{\epsilon} \Big)^{n-1} \sum_{k=n}^{\infty} \frac{1}{k!} \Big(\frac{\epsilon}{1+\epsilon} \Big)^{k} \\ &= \Big(\frac{1+\epsilon}{\epsilon} \Big)^{n-1} \left[e^{\epsilon/(1+\epsilon)} - \sum_{k=0}^{n-1} \frac{1}{k!} \Big(\frac{\epsilon}{1+\epsilon} \Big)^{k} \right]. \end{aligned}$$

Once again an application of l'Hôpital's rule guarantees that the above tends to 0 as $\epsilon \to 0$.

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In this section we have proven that the coordinates of the fixed point, for the particular choice of the parameter values, are such that they are indeed close to the normal approximation for all $n \geq 3$ and that they can be expressed by a function Ψ_n of just $\bar{\rho}_1$ and $\bar{\rho}_2$. Again, though this looks as an Inertial Manifold, we have to remark that this is not the case. In fact, if this were the case, then for any initial condition, $\rho_n(t) \to \Psi_n(\rho_1, \rho_2)$ for $t \to \infty$. This is not what we have shown. We have shown that $\bar{\rho}_n \to \Psi_n(\bar{\rho}_1, \bar{\rho}_2)$ for $\epsilon \to 0$. Furthermore, we have not proven one essential bit: this manifold is not invariant for E.3.10 (page 147). Thus it cannot be an Inertial Manifold.

However, the following is true:

$$\rho_n(t) - \Psi_n(\rho_1(t), \rho_2(t)) \xrightarrow[t \to \infty]{} \bar{\rho}_n(t) - \Psi_n(\bar{\rho}_1(t), \bar{\rho}_2(t)) \xrightarrow[\epsilon \to 0]{} 0,$$

so that in a sense the normal approximation holds for all ρ_k but for small values of ϵ and for big times t, similarly with what happens with third coordinate of the approximated Inertial Manifold of the previous section.

In fact, if we go back to the algorithm of section 3.3.4, then we can see that in the case of the normal approximation one might substitute the manifold $\widetilde{\mathcal{M}}_2$ with the following

$$\bar{\mathcal{M}} = \big\{ \rho_1, \rho_2, \Psi_3(\rho_1, \rho_2), \Psi_4(\rho_1, \rho_2), \ldots, \Psi_n(\rho_1, \rho_2), \ldots \big\}. \qquad \text{E.3.41}$$

In the above lemma **L.3.8** we have shown that each coordinate is such that

$$\Psi_n(\rho_1, \rho_2) \xrightarrow[\substack{t\to\infty \\ \epsilon\to 0}]{} \bar{\rho}_n.$$

However, it is important to stress that if $\mathcal{M}$ and $\bar{\mathcal{M}}$ were close in the L norm, that is if

$$\bar{\mathcal{M}} \xrightarrow[\substack{t\to\infty \\ \epsilon\to 0}]{} \mathcal{M},$$

then we should have that

$$\operatorname{dist}\left(\mathcal{M}, \bar{\mathcal{M}}\right)_L = \sum_n |\rho_n - \Psi_n(\rho_1, \rho_2)|^2 \xrightarrow[\substack{t\to\infty \\ \epsilon\to 0}]{} 0.$$

The above is not true, as this infinite series contains a term that grows as $n!(e^\epsilon - 1)$, and thus it does not go to zero as both $n \to \infty$ and $\epsilon \to 0$.

Therefore, while on the one hand we have shown that all coordinates of $\bar{\mathcal{M}}$ are close to the corresponding coordinate of $\mathcal{M}$, and thus we have improved on the definition of $\tilde{\mathcal{M}}_2$, on the other hand this time we cannot say that that $\bar{\mathcal{M}}$ is a *"perturbation"* of $\mathcal{M}$ for small ϵ and big t.

Nevertheless, we can easily adapt the proof of lemma **L.3.6** (page 168) to obtain a *"perturbation"* of E.3.10, which admits $\bar{\mathcal{M}}$ as an Inertial Manifold.

THEOREM T.3.9 ***The manifold $\bar{\mathcal{M}}$ defined in E.3.41 is an Inertial Manifold for the dynamical system obtained by the change of variables***

$$\boldsymbol{\tilde{\rho}_n = \Phi_n(\rho_n, \rho_1, \rho_2) = \rho_n + \Psi_n(\rho_1, \rho_2) - \bar{\rho}_n \qquad \forall n \geq 3.}$$

Proof The proof is exactly the same as that of **L.3.6**, so we omit some of the minor details. The dynamical system is

$$\begin{aligned} \dot{\rho}_1 &= h_1 - \alpha\rho_2 - (\alpha + \mu)\rho_1 \\ \dot{\rho}_2 &= h_2 - \alpha\rho_3 - 2(\alpha + \mu)\rho_2 \\ \dot{\tilde{\rho}}_n &= \frac{\mathrm{d}\Phi_n(\rho_n, \rho_1, \rho_2)}{\mathrm{d}t} \qquad \forall n \geq 3 \end{aligned} \qquad \text{E.3.42}$$

We first prove invariance. Take a point $R = \{r_1, r_2, \Psi_3(r_1, r_2), \ldots\} \in \bar{\mathcal{M}}$ and $\widetilde{\rho}_n(t)$ as the solution of E.3.42. By definition of $\tilde{\rho}_n$ and by definition of $\bar{\mathcal{M}}$ we have:

$$\Psi_n(r_1, r_2) = \tilde{\rho}_n(0) = \rho_n(0) + \Psi_n(r_1, r_2) - \bar{\rho}_n.$$

Thus $\rho_n(0) = \bar{\rho}_n$, that is $\{\rho_n(0)\} \in \mathcal{M}$, so that $\rho_n(t) \in \mathcal{M}$ for all times. This means that

$$\tilde{\rho}_n(t) = \rho_n(t) + \Psi_n(\rho_1(t), \rho_2(t)) - \bar{\rho}_n = \Psi_n(\rho_1(t), \rho_2(t)),$$

which proves invariance.

Remember that for E.3.10 $\rho_n(t) \to \bar{\rho}_n$ exponentially, when $\rho_n(t)$ is a solution starting at any initial point. Thus

$$\tilde{\rho}_n(t) = \rho_n(t) + \Psi_n(\rho_1(t), \rho_2(t)) - \bar{\rho}_n \longrightarrow \bar{\rho}_n + \Psi_n(\bar{\rho}_1, \bar{\rho}_2) - \bar{\rho}_n = \Psi_n(\bar{\rho}_1, \bar{\rho}_2),$$

and again the exponential attraction is proved.

The manifold $\bar{\mathcal{M}}$ is clearly finite dimensional and Lipschitz.

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Again we wish to stress the fact that $\bar{\mathcal{M}}$ is a good coordinate-wise approximation of $\mathcal{M}$ only for $t \to \infty$ and $\epsilon \to 0$. In fact, once more, $\bar{\mathcal{M}}$ is a linear function of ρ_1 and ρ_2, that is a two-dimensional hyperplane and which cannot be a global good approximation to another hyperplane.

3.4 Our choice of coordinates

We would like to spend some time explaining our choice of coordinates. In fact, considering that the change of coordinates from the cumulants to the factorial cumulants is linear, it would seem so much better to work in a set of coordinates with which the scientific community is more familiar. Apart from the simple fact that we initially developed the theory using the factorial cumulants, there are a number of reasons why we discarded the idea of rewriting the whole section of this thesis using the cumulants as the main coordinate system.

Let us take a look closely at equation E.3.35 (page 171), which describes the linear relation between the cumulants κ_n and the factorial cumulants ρ_n:

$$\kappa_n = \sum_{\pi \in \Pi_n} \rho_\pi .$$

Clearly the cumulant of order n depends on the factorial cumulants $\rho_1, \ldots, \rho_n$ via a linear, invertible relation.

Thus when we considered whether we would be getting any additional or slightly different result, we found out that the answer was bounded to be “no”. The change of coordinates from the cumulants to the factorial cumulants is linear, so that we would be getting again one globally, exponentially attracting fixed point, the moment closure functions would be defining “perturbations” of the original system with the same limitations we expressed in the previous sections, these systems would have an Inertial Manifold that approximate the original one as both $t \to \infty$ and $\epsilon \to 0$, the rate of attraction would be exactly the same and finally the the manifold $\bar{\mathcal{M}}$ would be a coordinate-wise, good exponential approximation of $\mathcal{M}$, but not a global approximation.

On the other hand, when we pondered whether obtaining such results would be easier, we found out that it would be indeed much more complicated.

In fact, consider now equation E.3.10 (page 147). This equation expresses the derivative of ρ_n via a function of ρ_n and ρ_{n+1}. Additionally the dependency on the $(n+1)^{\text{th}}$ coordinate is given through a small parameter α.

These facts put together mean that if we were to write down the differential equation for the cumulant κ_n, it would depend on all the cumulants $\kappa_1, \ldots, \kappa_n, \kappa_{n+1}$, and the dependency on κ_{n+1} will be given again through the same small parameter α:

$$\begin{pmatrix} \dot{\kappa}_1 \\ \dot{\kappa}_2 \\ \vdots \\ \dot{\kappa}_n \\ \vdots \end{pmatrix} = \begin{pmatrix} z_{11} & \alpha z_{21} & 0 & 0 & \dots & 0 & \dots \\ z_{21} & z_{22} & \alpha z_{23} & 0 & \dots & 0 & \dots \\ \vdots & & & \ddots & & & \\ z_{n1} & z_{n2} & \dots & z_{nn} & \alpha z_{n,n+1} & 0 & \dots \\ \vdots & & & & & & \end{pmatrix} \begin{pmatrix} \kappa_1 \\ \kappa_2 \\ \vdots \\ \kappa_n \\ \vdots \end{pmatrix}. \qquad \text{E.3.43}$$

It is immediate now that the algebra involved in solving the following issues would be much more complicated and convoluted:

- The formula for the fixed point would be almost impossible to handle; this is a mayor factor, considering how heavily we rely on such formula when evaluating the distance between $\widetilde{\Phi}_n(\bar{\rho}_1, \dots, \bar{\rho}_n)$ and $\bar{\rho}_{n+1}$.
- The rate of attraction could not be given exactly as we do in section 3.3.2; in fact one cannot calculate explicitly the eigenvalues of equation E.3.43, and we should be relying on some perturbation theorem, such as that in [6-ROS-1955]. This theorem states that if we have a linear operator T and a bounded linear operator U and a small parameter ϵ then the i$^{\text{th}}$ eigenvalue of $T + \epsilon U$ can be expressed as a continuous function of ϵU, that is $\lambda_i = \lambda_i(\epsilon U)$, which is invertible in a neighbourhood of $U = \mathbb{0}$ and such that $\lambda_i(\mathbb{0}) = \mathbb{0}$ is the i$^{\text{th}}$ eigenvalue of T. This theorem is an infinite dimensional version of the implicit function theorem and it is saying that the eigenvalues of the perturbed operator $T + \epsilon U$ are similar to those of T. However verifying the conditions for such theorem to hold is not really straightforward, as it involves calculating the norms of these operators in dual Banach spaces, as well the norm of the Fréchet derivative of a Banach space function defined through these operators.
- For the same reasons above, the proof that the differential equation for the cumulants is defined via a coercive operator given in section 3.2.3, and the proof of theorem **T.3.2** (page 154), will have to be completely revised, as we use the eigenvalues of the matrix A appearing in the differential equation for the factorial cumulants.
- Thus the proof itself of the fact that $\mathcal{M}$ is an Inertial Manifold would be more complicated.

Our conclusions are thus that using the cumulants as a basis would have the only advantage of working with a set of coordinates more commonly used in Mathematics. The disadvantage would be to have a much messier algebra, a more complicated functional analysis settings and norms which would be more difficult to evaluate; at the end of the day, a more error prone proof of exactly the same results. No additional results would be proven, and those that we could prove would have the same limitations. We concluded that such little gain was not worth the extra, additional effort.

3.5 Interpreting the results

The aim of this section is to explain how our results of the previous sections are helpful in clarifying the behaviour of the biological model described in [72-ISH-1995].

In section 3.3.4 we have proved that the normal approximation defines an Inertial Manifold $\widetilde{\mathcal{M}}_2$ which converges to the true Inertial Manifold for $\epsilon \to 0$ and $t \to \infty$, the convergence in time being exponential. In simple words, this means that when the parameter $\epsilon = \alpha/\mu$ is small, that is when α is small, then we can expect that a good approximation of the true steady state is reached very quickly. The numerical calculations used by Isham confirm this result, in fact *"the approximations do well even at small ages"*. In Isham's paper host age is measured in years, and we can appreciate from the graphics included in the paper that the approximation is good fairly quickly, within a few months; that is, one does not have to wait a long transient before the approximated results are good. The remark is important from a statistical point of view, as Isham states that in this model a normal distribution cannot be justified for small ages.

Going back to the random variable $M(a)$, that is the number of parasites present in a host of age a, we can say that all the moments of $M(a)$ are very close to those of a normally distributed random variable. Notice that we say "all the moments" and not that the random variable itself is normally distributed. Isham is quite insistent on this, and reiterates a few times that the fact that the moments she evaluates (mean and variance) are close to those provided by the normal approximation does not mean that $M(a)$ is approximately normally distributed. Using her words, *"it is possible for the approximate moments to be good even in cases where the normal distribution is a wholly inappropriate approximation to the true distribution"*.

The above fact is fully reflected in section 3.3.5; here we prove that through the normal approximation we can defined a new manifold $\bar{\mathcal{M}}$, whose higher coordinates are all expressed in terms of the moment closure function. This is in contrast with the manifold $\widetilde{\mathcal{M}}_2$ of the previous section, where the normal approximation is used only to define the third coordinate of $\widetilde{\mathcal{M}}_2$. One thus expects the manifold $\bar{\mathcal{M}}$ to represent more closely the nature of the normal approximation. In fact, while one can prove that the manifold $\widetilde{\mathcal{M}}_2$ converges in norm to the true Inertial Manifold $\mathcal{M}$, one can prove only a partial results for $\bar{\mathcal{M}}$: the convergence is coordinate-wise.

To this regard, our results confirm those in [72-ISH-1995] and improve on them in the sense that we consider all the higher moments, that is we have generalised and formalised the arguments given in the quoted paper to all higher moments. From an Inertial Manifold point of view, this is quite important: Inertial Manifolds are a way of approximating higher coordinates as function of a finite set of lower coordinates. This is the motivation of sections 3.3.4 and 3.3.5. We understand from this that the fact that the first two coordinates are well approximated is not the central point of having an Inertial Manifold; however, when there is an asymptotically complete Inertial Manifold, one does expect this result to hold. The fact that our original Inertial Manifold is such is quite trivial, as the Inertial Manifold is just a fixed point, so that **all** coordinates are exponentially approximated by the fixed point coordinates.

One more comment that the author of [72-ISH-1995] writes is that the normal approximation is *"surprisingly good even close to the boundary, when $M(a)$ is zero or very small"*. In a sense, the normal approximation is not generally expected to give good results for all initial values. Nevertheless, in this particular model, the normal approximation is related to the existence of an Inertial Manifold, and these manifolds are **globally**, exponentially attracting manifolds. This means, that the approximation will be good for all initial values, even for those initial values which are not biologically meaningful.

Finally, there is one more remark that we wish to make. In Isham's paper, results and comparisons are made for a number of different probability distribution functions C of a host acquiring parasites at age a. The numerical calculations given in this paper prove that the above results are valid for the distribution functions used, that is the approximation gives good results fairly quickly for any of these functions. As we have already noted in section 3.3.3, our results are valid for all $H \in L$, and H represents the probability distribution C in our model. It means that we have proved formally that the actual way in which the host acquires parasites is not important, and regardless of the form of C, always the normal approximation will give good results after a short transient.

3.6 Applying the results to other models

In this section we wish to give a few hints on how one could apply the theory developed in this chapter to other statistical models where a moment closure function is used to reduce the dimensions of the system. Remember that the underlying question we would like to answer is whether or not the moment closure function captures the complete behaviour of the system. As we have seen, a manifold which does attract the whole dynamics, and so describes the whole behaviour of the system, is an Inertial Manifold.

It is important to notice two things. Firstly, the example we have studied is quite a simple one, and thus all calculations can be carried out in a straight forward manner. This has the advantage that one can concentrate on the ideas rather than on the technical details; but it has the drawback that, in other models, this might not be the case, and more complicated formulas can arise. Secondly, we do not give any parametric method to obtain the Inertial Manifold, nor we give any formula whose result could tell us if a moment closure function is close or not to the Inertial Manifold. We are not aware of any formula as such, so the proof of the answers to these questions will be part of the process in each case.

1) The first step is to define the differential equations for all the moments, cumulants or factorial moments or any other coordinate one prefers; it is important to stress this point as sometimes authors in statistics just explicitly give the first few equations, as they might be extremely complicated. However, if this step is not done, one cannot apply any of the results in this chapter. One then will have defined an equation like

$$\dot{u} = -Au + F(u)$$

or

$$\dot{u} = -A(u)u + F(u)$$

where u is the variable of all the moments $u = \{m_k\}$ or all the cumulants or factorial moments.

2) The next step will have to be that of defining the appropriate functional space settings; this is important as the properties of the operator A in the above dynamical system might depend on the space being used. For example, the easiest way

of identifying the existence of an Inertial Manifold is through the classical gap condition, which is more easily verified if A is a self-adjoint operator.

3) One will study if the classical gap condition or a generalisation of it, as the one used in chapter **2**, is satisfied or not. The objective here is to find an Inertial Manifold, hopefully as a function of a finite set of N coordinates to all the others. Notice again that the finite set of N coordinates might not be given by the first N moments, and one will have usually to rearrange the moments so that the first coordinates correspond to the finite subspace of the N slow moments.

4) Having obtained an Inertial Manifold in such a way, we notice that this manifold represents a relation amongst the moments, and so defines the limiting distribution for the whole system. This distribution is nice because it is defined by a finite set of N moments, though not necessarily the first N ones. This will generally mean that this might not be a known distribution, so that the study of its statistical properties is necessary.

5) The final step will be to study whether the given moment closure function is close or not to the Inertial Manifold. One can do this by using techniques similar to those of sections 3.3.4 and 3.3.5. In fact, a moment closure function defines a manifold and we wish to identify if the manifold given by the moment closure function is close or not to the Inertial Manifold, at least coordinate-wise. One then might complete this step by identifying if the two manifolds converge in norm or not.

Chapter 4

Glossary

4 Glossary

We present here the definitions of all those concepts used throughout the thesis, organised into two sections, the first one dedicated to Functional Analysis and Dynamical Systems, and the second one to Probability and Statistics. Within each section, they are presented in strict alphabetical order.

4.1 Functional Analysis and Dynamical Systems

• **Adjoint Operator** *Given an operator $A : H \to H$, where H is a Hilbert space, the linear operator A^* is defined as the adjoint of A if*

$$\langle Ax, y \rangle = \langle x, A^* y \rangle$$

for every $x, y \in H$.

An operator $A : H \to H$, is self-adjoint if $A^* = A$. As noted in [8-RUD-1987], page 349, the difference between a self-adjoint operator and a symmetric one, resides in the domain of the equality. For a symmetric operator the requirement is that $A^*(x) = A(x)$ only for those elements x in the domain of A. For a self-adjoint operator the requirement is that $A^*(x) = A(x)$ for all $x \in H$.

• **Asymptotic Completeness** *An Inertial Manifold $\mathcal{M}$ is said to be asymptotic complete if for any point $m \notin \mathcal{M}$ there exists a point $n \in \mathcal{M}$ such that the distance between the flow starting at m and the flow starting at n decreases exponentially:*

$$\text{dist}\,(S(t)m, S(t)n) \le e^{-\alpha t}.$$

• **Banach Fixed Point Theorem** *Let X be a closed subset of a Banach Space Y with norm $\|\cdot\|_Y$, and let $h : X \to X$ a function satisfying*

$$\|h(x) - h(y)\|_Y \le d\, \|x - y\|_Y$$

for all $x, y \in X$ for a constant $d < 1$. Then we say that h is a contraction and h has a unique fixed point.

This is a very standard theorem and its proof can be found in section 2.1.1 of [37-ROB-2001].

• **Banach Space** *It is a vector space endowed with a norm, and that is complete under the metric induced by the norm.*

• **Bounded Linear Operator** *A linear operator A from $X \to Y$, where X and Y are two normed spaces, is said to be bounded if there exists a number $c < \infty$ such that*

$$\|Ax\|_Y \leq c \, \|x\|_X$$

for all $x \in X$.

The number c depends on A. If one defines $\|A\| = \inf\{c; \|Ax\|_Y \leq c \, \|x\|_X\}$, then this is a norm on the collection $\mathcal{B}(X, Y)$ of such operators; if Y is Banach, so is $\mathcal{B}(X, Y)$.
The norm of an operator can be also defined by the following equivalent definitions:

$$\begin{aligned}
\|A\| &= \inf\left\{c; \|Ax\|_Y \leq c \, \|x\|_X \; \forall x \in X\right\} \\
&= \sup\left\{ \|Ax\|_Y \, ; x \in X, \|x\|_X \leq 1\right\} \\
&= \sup\left\{ \|Ax\|_Y \, ; x \in X, \|x\|_X = 1\right\} \\
&= \sup\left\{ \|Ax\|_Y \, / \, \|x\|_X \, ; x \in X, x \neq 0\right\}.
\end{aligned}$$

See, for example, [8-RUD-1987] for a complete treatment of these operators.

• **Cone Condition** *Also called the "Cone Invariance Property". Given a dynamical system $\dot{u} = F(u)$, with u split into two orthogonal set of coordinates $u = (p, q)$, and two solutions $u_1(t) = (p_1(t), q_1(t))$ and $u_2(t) = (p_2(t), q_2(t))$, the Cone Condition holds if*

$$|q_1(0) - q_2(0)| \leq \gamma \, |p_1(0) - p_2(0)|$$

implies that for all $t \geq 0$

$$|q_1(t) - q_2(t)| \leq \gamma \, |p_1(t) - p_2(t)| \, .$$

This property says that the cone of radius γ centred at $(0, 0)$ is invariant under the flow; that is if $u_2(0)$ is within the cone centred at $u_1(0)$, then $u_2(t)$ will always remain inside the cone centred at $u_1(t)$ for all times. Note that u_1 and u_2 are interchangeable.
Note that it does not say anything about the behaviour of the solutions outside the cone.

• **$C^r(\Omega)$** *It is the space of functions whose derivatives up to r are continuous.*

$C^r \supset C^{r+1}$.

$C^0(\bar{\Omega})$ is complete with the sup norm.

The closure of C^0 with the L^p norm ($p < \infty$) is L^p.

C^∞ if the set of all those functions which are in C^r for every r.

• **Dual Space** *Given a Banach space X, its dual space X^* is the space of linear functionals from X to X.*

If H is a Hilbert space, then H^* is isometric to H.

$(L^p)^*$ is isometric to L^q for $1 < p < \infty$, where $\frac{1}{p} + \frac{1}{q} = 1$.

$L^1 \subset (L^\infty)^*$.

If $f \in L^p$ and $g \in L^q$ with $\frac{1}{p} + \frac{1}{q} = 1$, then $fg \in L^1$.

• **Dynamical System** *A dynamical system is defined by a triplet $(\mathcal{U}, \mathcal{T}, \mathcal{S})$ where $\mathcal{U}$ is a state space, $\mathcal{T}$ a set of times, and $\mathcal{S}$ a rule for evolution, $\mathcal{S} : \mathcal{U} \times \mathcal{T} \to \mathcal{U}$, that gives the consequent(s) to a state $u \in \mathcal{U}$.*

A dynamical system is a model describing the temporal evolution of a system: given a $u \in \mathcal{U}$, the rule $\mathcal{S}$ tells us where u will be after a time $t \in \mathcal{T}$.

In our case the time $\mathcal{T}$ is the continuous time $\mathbb{R}$ and the phase space is always a Hilbert or Banach space. Our rule will be the semigroup $S(t)$ associated to a differential equation: $\mathcal{S}(u,t) = S(t)u$. This is often called the trajectory and when u is the solution of a differential equation it is also indicated as $u(t)$; if one wants to make explicit the dependency on the initial condition u_0, then it may be indicated as $S(t)u_0$ or as $u_{u_0}(t)$.

This definition is taken from [35-MEI-2007].

• **Evolution Operator** *A two parameter family $U(t,s)$, $0 \leq s \leq t \leq T$ of bounded* *linear operators on a space X is called an evolution operator if*

$$U(s,s) = \mathbb{I},$$

$$U(t,r)U(r,s) = U(t,s) \quad \text{for } 0 \leq s \leq r \leq t \leq T,$$

$$(t,s) \to U(t,s) \quad \text{is continuous for } 0 \leq s \leq t \leq T.$$

$\mathbb{I}$ is the identity operator from X to X. In [20-PAZ-1983] it is called an evolution systems. This is the generalisation of a semigroup and we treat it in more detail in section **2.3**.

• **Exponential Tracking Property** *This is the same as asymptotic completeness.*

• **Faà di Bruno's formula** *Given two smooth real valued functions $f(t)$ and $g(t)$ the n^{th} derivative of the composite function $f(g(t))$ is given by*

$$\frac{\partial^n f(g(t))}{\partial t^n} = \sum_{\pi \in \Upsilon_n} \frac{\partial^{|\pi|} f(g(t))}{\partial t^{|\pi|}} \prod_{B \in \pi} \frac{\partial^{|B|} g(t)}{\partial t^{|B|}},$$

where Υ_n are all the partitions of the set $\{1,\dots,n\}$, π is such a partition, $B \in \pi$ means the variable B runs through the list of all of the "blocks" of the partition π, and $|A|$ denotes the cardinality of the set A.

A partition of a set $X = \{1,2,\dots,n\}$ is the a set of nonempty subsets of X such that every element $x \in X$ is in exactly one of these subsets. The union of all these subsets is equal to X and the intersection of any two of these subsets is empty. These subsets are sometimes called "blocks". The cardinality of a partition is the number of blocks of that partition.

References and explanation of the formula can be found in [5-JON-2002].

• **Fréchet derivative** *Let V and W be two Banach spaces, and let f be a function from $U \subseteq V$ to W. f is said to be Fréchet differentiable at the point $x \in U$ if there exists a bounded linear operator $A: V \to W$ such that*

$$\lim_{h \to 0} \frac{\|f(x+h) - f(x) - Ah\|_W}{\|h\|_V} = 0.$$

• **Gap Condition** *Given a dynamical system like* $\dot{u} = -Au + V(u)$, *where* A *is a positive operator, a gap condition is said to hold if the difference between two consecutive eigenvalues is big enough compared to the Lipschitz constant of* V.

In the literature there are a number of formulations of the gap condition. A review is contained in [58-ROB-1993].

The condition of our main theorem **T.2.3** (page 75) is similar to a Gap Condition, but not the same, as explained in section 2.4.5.

The Gap Condition implies the Strong Squeezing Property.

• **Gerschgorin Theorem** *All eigenvalues of a matrix* $A = (a_{ij})$ *must lie in the union of circles* $\bigcup_{i=1}^{M} W_i$ *where*

$$W_i = \left\{ z \in \mathbb{C} : |z - a_{ii}| \le \sum_{j \ne i} \left| a_{ij} \right| \right\}.$$

• **Gronwall's Inequality** *Let* I *denote an interval of the real line of the form* $[x, \infty)$. *Let* a *and* b *be real-valued continuous, integrable functions defined on* I *and let* c *be a constant. Then if*

$$a(t) \le c + \int_x^t b(s)a(s)ds,$$

then

$$a(t) \le c \exp\left(\int_x^t b(s)ds \right).$$

This is also sometimes called Gronwall's lemma.

Refer to [37-ROB-2001] for a proof of this Lemma.

• **Global Attractor** *Given a semigroup* $S(t)$, *a global attractor* $\mathcal{A}$ *is the maximal compact invariant set*

$$S(t)\mathcal{A} = \mathcal{A} \qquad \forall t \ge 0$$

and the minimal set that attracts all bounded sets:

$$\mathrm{dist}(S(t)X, \mathcal{A}) \to 0 \qquad \text{as} \qquad t \to \infty$$

for all bounded sets $X \in U$.

In proposition 10.14 at page 276 of [37-ROB-2001], the author proves that given a trajectory $u(t) = S(t)u_0$, $\epsilon > 0$ and $T > 0$, then there exists a time $\tau = \tau(\epsilon, T)$ and a point $v_0 \in \mathcal{A}$ such that

$$|u(\tau + t) - S(t)v_0| \leq \epsilon \qquad \forall \quad 0 \leq t \leq T. \qquad \text{E.4.1}$$

In this sense, one can think of the attractor as describing the whole dynamics: though a trajectory may never actually be in the attractor itself, there is always a point close to it in the sense of E.4.1.

• **Hilbert Space** *It is a vector space endowed with a scalar product, and that is complete under the metric induced by the scalar product.*

All Hilbert spaces are Banach Spaces.

• **Inertial Form** *Given a Hilbert or Banach space V, $u \in V$ and a dynamical system $\dot{u} = F(u)$, which admits an Inertial Manifold expressed as a graph of a function $h : \mathbb{R}^n \to V - \mathbb{R}^n$, and denoting by P the projection from V to $\mathbb{R}^n$ and by p an element of $\mathbb{R}^n$, the inertial form is*

$$\dot{p} = PF(p + h(p)).$$

The above equation is actually an ODE, and, h being an Inertial Manifold it describes with an exponentially small error the dynamics of the whole, potentially infinite dimensional, system.

• **Inertial Manifold** *In a Dynamical System $(\mathcal{U}, \mathcal{T}, \mathcal{S})$ an Inertial Manifold is a finite dimensional, Lipschitz manifold that is also invariant and exponentially globally attracting for the dynamics of $\mathcal{S}$.*

Notice that there is no requirement for an Inertial Manifold to be the graph of a function.

• **Infinitesimal Generator of a Semigroup** *Given $T(t)$ a semigroup on the space X, the linear operator A defined by*

$$\text{Domain}\,(A) = \left\{ x \in X : \quad \lim_{t \to 0^+} \frac{T(t)x - x}{t} \quad \text{exists} \right\}$$

and

$$Ax = \lim_{t \to 0^+} \frac{T(t)x - x}{t}$$

is called the infinitesimal generator of the semigroup $T(t)$.

• **L'Hôpital's Rule** *Given two continuous C^1 functions f and g from $\mathbb{R} \to \mathbb{R}$, when determining the limit of a quotient $f(x)/g(x)$ when both f and g approach 0 as $x \to c$, l'Hôpital's rule states that if $f'(x)/g'(x)$ converges, then $f(x)/g(x)$ converges, and to the same limit.*

$$\lim_{x \to c} \frac{f(x)}{g(x)} = \lim_{x \to c} \frac{f'(x)}{g'(x)}.$$

References can be found in [10-SPI-1994].

• $\mathcal{L}ip$ *It is the space of Lipschitz functions with the norm*

$$\|f\|_{\mathcal{L}ip} = \|f\|_\infty + \sup_{x,y \in \Omega} \frac{|f(x) - f(y)|}{|x - y|}$$

It is a complete space.

• **L^p for $1 \geq p < \infty$** *Given a space X and a measure μ, L^p is the space of functions such that*

$$\int_X |f(x)|^p \, d\mu < \infty$$

Note that if we associate the measure that counts the points to the space N, then the integral is equal to $\sum_{n \in N} |f(n)|^p$. These spaces are called l^p. One can think of l^2 as $\mathbb{R}^\infty$.

L^p is a Banach space, L^2 is a Hilbert space.

Two functions will be identified when they are equal a.e. This means that L^p is a space of classes of functions.

• **L^∞** *It is the space of functions which are bounded a.e.*

This is also called the sup norm.

• **Phase Space** *A phase space $\mathcal{U}$ is a space of possible values that a variable u can assume in time.*

This means that for every time t, $u(t) \in \mathcal{U}$.

• **Picard-Lindelöf Theorem** *Given a function $f(x,t) : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n$, Lipschitz in a neighbourhood of $(x_0, t_0) \in \Omega \subseteq \mathbb{R}^n \times \mathbb{R}$, then the initial value problem*

$$\dot{x} = f(x,t)$$

$$x(t_0) = x_0$$

has a unique solution $x(t)$ in an interval of t_0.

Notice that a function f that is globally Lipschitz and bounded on the whole of $\mathbb{R}^n \times \mathbb{R}$ implies a global existence for all times.
Refer to [37-ROB-2001] for a proof of this Lemma.

• **Positive Definite Operator** *A bounded linear operator $A \in \mathcal{B}(H)$ defined in a Hilbert space H is said to be positive if*

$$\langle Ax, x \rangle \geq x$$

for all $x \in H$.

We use positive definite operator, or just positive operator.
According to theorem 12.32 at page 330 of [8-RUD-1987], a bounded operator is positive if and only if it is self-adjoint and all its eigenvalues are positive.

• **Resolvent** *The resolvent set of a linear operator A on a space X is the set of all complex numbers λ for which $\lambda\mathbb{I} - A$ is invertible, where $\mathbb{I}$ is the identity operator from*

X to X, that is for which $(\lambda\mathbb{I} - A)^{-1}$ is a bounded linear operator. The family of operators $R(\lambda) = (\lambda\mathbb{I} - A)^{-1}$ is called the resolvent of A.

The resolvent of A satisfies for all $x \in X$

$$R(\lambda)x = \int_0^\infty e^{-\lambda t} T(t),$$

where $T(t)$ is the semigroup associated to A.

The complement of the resolvent set is the spectrum.

- **Semigroup** *A one parameter family $T(t)$, $0 \leq t \leq \infty$ of bounded linear operator from X to X is a semigroup if*

$$T(0) = \mathbb{I}$$

$$T(t+s) = T(t)T(s) \qquad \forall t, s \geq 0$$

where $\mathbb{I}$ is the identity operator on X.

See [20-PAZ-1983] or [18-AHM-1991] for good references on semigroups.

- **Squeezing Property** *Give a dynamical system $\dot{u} = F(u)$, with u split into two orthogonal set of coordinates $u = (p, q)$, and two solutions $u_1(t) = (p_1(t), q_1(t))$ and $u_2(t) = (p_2(t), q_2(t))$, the squeezing property holds if, whenever*

$$|q_1(0) - q_2(0)| \geq \gamma\, |p_1(0) - p_2(0)|$$

then for all $t > 0$ either $q_2(t)$ belongs to the cone centred at $q_1(t)$ for all $t \geq t_0$ or

$$|q_1(t) - q_2(t)| \leq |q_1(0) - q_2(0)|\, e^{-kt}$$

for some $k \geq 0$.

The property says that if $q_2(t)$ is at some time outside the cone centred at $q_1(t)$ and radius γ, then the $q_2(t)$ is drawn exponentially close to the boundary of the cone.

Note that this property does not state anything about the behaviour inside the cone.

• **Stirling Numbers of Second Kind** *The Stirling number of second kind* $\mathcal{S}_{n,k}$ *is defined for* $k = 1, \ldots, n$ *as the number of ways of partitioning the set* $\{1, \ldots, n\}$ *into* k *disjoint non-empty subsets.*

Notice that a partition of the set $\{1, \ldots, n\}$ with cardinality k has exactly k disjoint non-empty subsets, and thus the Stirling number is the number of partitions of the set $\{1, \ldots, n\}$ with cardinality k.

References can be found in [16-LOV-2007].

• **Strong Squeezing Property** *The strong squeezing property is said to hold for a dynamical system if both the cone condition and the squeezing property are verified for such dynamical system.*

It is when the two properties come together that one can prove the existence of an Inertial Manifold.

• **Strongly Continuous Semigroup** *A semigroup* $T(t)$ *on the Banach space* X *is strongly continuous if*

$$\lim_{t \to 0^+} T(t)x = x, \qquad \forall x \in X.$$

• **Symmetric Operator** *An operator* $A : H \to H$*, where* H *is a Hilbert space, is symmetric if*

$$\langle Ax, y \rangle = \langle x, Ay \rangle$$

for all x, y *in the domain of* A*.*

• **Uniformly Continuous Semigroup** *A semigroup on* X *is uniformly continuous if*

$$\lim_{t \to 0^+} \| T(t) - \mathbb{I} \| = 0.$$

$\mathbb{I}$ is the identity operator from X to X. A uniformly continuous semigroup is always a strongly continuous semigroup.

An operator A is the infinitesimal generator of a uniformly continuous semigroup $T(t)$ if and only if it is a bounded linear operator. Furthermore $T(t) = e^{At}$.

4.2 Probability and Statistics

• **Central Moment** *The central moment of order k is the k^{th} moment around the mean, and is given by $\mu_k = E((X-\mu)^k)$.*

The first central moment is always 0. the second central moment is called the variance and is equal to $\mu_2 = \sigma^2 = E(X^2) - (EX)^2 = E((X-m_1)^2) = EX^2 - 2m_1 EX + m_1^2 E1 = m_2 - m_1^2$, where m_1 is the first moment, that is the mean, and m_2 the second moment.

• **Cumulant** *Given the function $g(t) = \ln(E(e^{tX}))$, the cumulant of order n is the n^{th} derivative of $g(t)$ evaluated at zero:*

$$\kappa_n = \left\lfloor \frac{d^n g(t)}{dt^n} \right\rfloor_{t=0}$$

$E(e^{tX})$ is the expectation of the function e^{tX}.

The cumulants are related to the moments m_n by the polynomial function

$$\kappa_n = m_n - \sum_{k=1}^{n-1} \binom{n-1}{k-1} \kappa_k m_{n-k}.$$

The first three cumulants κ_1, κ_2 and κ_3 of a distribution are equal to the expected value, the variance, and the centred third moment, respectively.

• **Cumulant Generating Function** *It is the logarithm of the moment generating function: $g(t) = \ln M(t) = \ln E(e^{tX})$.*

The cumulant generating function can be expressed as

$$g(t) = \sum_{j=0}^{+\infty} \kappa_j \frac{t^j}{j!}$$

where κ_j is called the κ^{th} cumulant and

$$\kappa_j = \left. \frac{\mathrm{d}^j g(t)}{\mathrm{d}t^j} \right|_{t=0} .$$

• **Density Function** *$f(s)$ is a function that denotes the probability or mass function at a point x.*

• **Deterministic approximation** *The deterministic approximation is a Moment Closure method obtained by setting the variance equal to 0.*

It can be expressed as $\sigma^2 = 0$; in terms of moments as $m_2 - m_1^2 = 0$; in terms of cumulants as $\kappa_2 = 0$ and in terms of factorial cumulants as $\rho_1 + \rho_2 = 0$.

• **Distribution Function** *$F(x)$ denotes the probability of the random variable X being less than or equal to x:*

$$F(x) = P(X \leq x).$$

The distribution function is non-decreasing, continuous on the right, $F(-\infty) = 0$, $F(+\infty) = 1$, $P(X \in [a, b]) = F(b) - F(a)$ and in terms of the density function:

$$F(x) = \int_{-\infty}^{0} f(x)dx.$$

• **Expectation** *The expectation of a function $g(X)$ gives us an idea of the average value of the function, and it is given by*

$$E(g(X)) = \int_{-\infty}^{+\infty} g(X)dF = \int_{-\infty}^{+\infty} g(X)f(X)dx.$$

The expectation is linear, that is $E(\lambda X + Y) = \lambda E(X) + E(Y)$, and non-decreasing, that is if $X \geq Y$, then $E(X) \geq E(Y)$.

• **Factorial Cumulant** *The factorial cumulant ρ_n of order n is the n^{th} derivative of the function $g(t) = \ln(E(t^X))$ evaluated at $t = 1$.*

• **Factorial Cumulant Generating Function** *The factorial cumulant generating function is given by* $g(t) = \log(E(t^X))$.

It is the natural logarithm of the probability generating function.

• **Factorial Moment** *The factorial moment of order* k *is given by* $\nu_k = E(X(X-1)\dots(X-k+1))$.

• **Factorial Moment Generating Function** *The factorial moment generating function is defined as* $M(t) = E(t^X)$.

The factorial moment of order n is then the n^{th} derivative of $M(t)$ evaluated at 1.

• **Moment** *The moment of order* k *is given by* $m_k = E(X^k)$.

The moment m_1 is also known as the mean or simply as the expected value.

• **Moment Closure** *A moment closure is a function that expresses the moment of order* $n+1$ *as a function of the moments of order* $1, \dots, n$.

It is used to reduce the study of an infinite set of differential equations, one for each moment, to the study of the first n equations.

• **Moment Generating Function** *The moment generating function is the expected value of the function* $\exp(tX)$*:*

$$M(t) = E(e^{tX}) = \sum_{k=0}^{+\infty} m_k \frac{t^k}{k!}.$$

By differentiating k times with respect to t and evaluating at $t = 0$ (if the derivative exists), we have that

$$m_k = E(X^k) = \left.\frac{\mathrm{d}^k M(t)}{\mathrm{d}t^k}\right|_{t=0}.$$

• **Normal approximation** *The normal approximation is a Moment Closure method obtained by setting the third cumulant equal to 0.*

It can be expressed as $\kappa_3^2 = 0$; in terms of moments as $m_3 - 3m_2m_1 + 2m_1^3 = 0$; in terms of factorial cumulants as $\rho_3 + 3\rho_2 + \rho_1 = 0$.

• **Probability Function** *Let Ω be a space of outcomes, $\mathcal{A}$ be the σ-field of events associated with an experiment, then P a real valued function such that*

$$P(A) \geq 0 \qquad \forall A \in \mathcal{A},$$

$$P(\Omega) = 1,$$

$$\text{if } A = \sum_{i=1}^{\infty} A_i \Rightarrow P(A) = \sum_{i=1}^{\infty} P(A_i),$$

is called a probability function.

• **Probability Generating Function** *It is the same of the factorial moment generating function, that is$M(t) = E(t^X)$.*

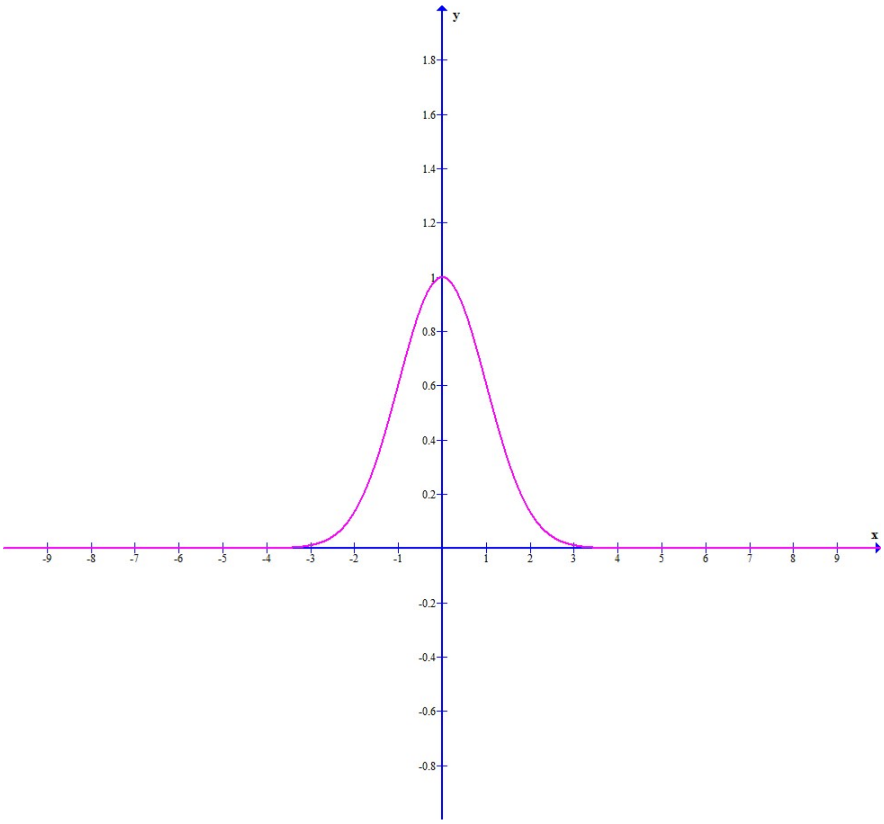
• **Random Variable** *A random variable on a probability space $(\Omega, \mathcal{F}, P)$ is a Borel measurable function from $\Omega \to \mathbb{R}$. $\mathcal{F}$ is the σ-field, and P is the probability measure.*

• **σ-field** *Given a space Ω, a σ-field $\mathcal{A}$ is collection of subsets of Ω which is closed under complementation and under countable union (intersection) of its members.*

• **Standard Normal Distribution** *It is the distribution with density function*

$$f(x) = \frac{1}{\sqrt{2\pi}} e^{-x^2/2}.$$

By the central limit theorem, it is the distribution that best approximate a set of independent identically distributed random variables such that their sum has a finite variance.



The mean of the standard normal distribution is 0.

$$
\begin{aligned}
m_1 &= \int_{-\infty}^{+\infty} x \frac{1}{\sqrt{2\pi}} e^{-x^2/2} dx = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{+\infty} \frac{\mathrm{d}}{\mathrm{d}x}(-e^{-x^2/2}) \mathrm{d}x \\
&= \frac{1}{\sqrt{2\pi}} \left[-e^{-x^2/2} \right]_{-\infty}^{+\infty} = 0.
\end{aligned}
$$

The variance of the standard normal distribution is 1.

$$
\begin{aligned}
\sigma^2 &= \int_{-\infty}^{+\infty} x^2 \frac{1}{\sqrt{2\pi}} e^{-x^2/2} dx \\
&= \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{+\infty} \frac{\mathrm{d}}{\mathrm{d}x}(-xe^{-x^2/2}) \mathrm{d}x + \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{+\infty} e^{-x^2/2} \mathrm{d}x \\
&= 0 + 1,
\end{aligned}
$$

where we have used the Gaussian Integral $\int_{-\infty}^{+\infty} e^{-x^2} = \sqrt{\pi}$.

The moment generating function of the standard distribution is $M(t) = e^{t^2/2}$.

The first cumulant of the normal distribution is equal to its mean, thus for the standard normal distribution $\kappa_1 = 0$. The second cumulant $\kappa_2 = \sigma^2$. For all other cumulants, $\kappa_i = 0 \ \forall i \geq 3$.

Chapter 5

Bibliography

5 Bibliography

An important feature of this thesis is that it draws from different fields of science and mathematics to explore the concept of reduction of a system to one of lower dimensions. Therefore it appeared to us an interesting idea to reflect this in the bibliography as well. Rather than following a strict, arid alphabetical order, we decided to present the bibliography in different sections according to the particular field the article or book belongs to.

The references are presented according to the subdivision that follows. One can easily recognise a pattern, that is somehow the pattern we followed to reach the final result: from the biological problem we went on to study the equations in their formal setting, then recognise their properties as a dynamical system and finally discover the existence of an Inertial Manifold.

- **Biology**: in this section we refer to the works of this Natural Science that originated the Mathematical investigation;
- **Functional Analysis**: here we give an account of the basic text books that we used to build a background in Functional Analysis, and that have been the basis to create a correct setting where our equations make sense;

- **Probability**: in this section we present those reference text books that present the theory of Probability; as in this thesis we present the definition of probability based on the definition of the Lebesgue measure, this section follows the one on Functional Analysis;
- **Semigroups**: we present those basic references that present the theory of semigroups applied to evolution equations;
- **Non-linear dynamics**: here we give an account of those texts that deal with nonlinear evolution equations; the difference from the previous section is the emphasis: while on the previous one the main focus of attention was semigroups, here it is the understanding of evolution equations, and when semigroups are used they are seen as a tool;
- **Inertial manifolds**: this is a bibliography of all those works within the real of non-linear dynamics that are directly related to the study of Inertial Manifold;
- **Moment closure**: here we present those papers and books that deal with various examples on the use of Moment Closure techniques in statistics.

5.1 Biology

The object of this thesis being to present original mathematical results, we do not attempt to reproduce a complete reference for the biological problems we studied; rather we present just the initial source of the mathematical problems and we refer to their bibliography for further biological references.

[1-BAI-1997] S. BAIGENT, J. STARK, A. WARNER; *Modelling the effect of the gap junction nonlinearities in systems of coupled cells*; J. Theor. Biol.; 186; pag. 223-239; 1997.

[2-HAR-2001] K. HARDY, S. SPANOS, D. BECKER, P. IANNELLI, R.M.L. WINSTON, J. STARK; *From cell death to embryo arrest: Mathematical models of human preimplantation embryo development*; Proceedings of the National Academy of Sciences (PNAS); 98 no. 4; pag. 1655-1660; 2001.

[3-SLA-1975] C. SLACK, A.E. WARNER; *Properties of surface and junctional membrane of embryonic cells isolated from blastula stages of Xenopus Laevis*; J. Physiol.; 248; pag. 97-120; 1975.

5.2 Functional settings

Books on the fundamentals.

5.2.1 Functional analysis

Apart from the very specific paper by Rosenbloom, these are very well know text books in Functional Analysis and do not need any presentation.

[4-BRE-2005] HAÏM BREZIS; *Analyse fonctionnelle (French edition)*; Dunod; 2005.

[5-JON-2002] W. JONHSON; *The Curious History of Faa di Bruno's Formula*; The American Mathematical Monthly; 109; pag. 217-234; 2002.

[6-ROS-1955] P. ROSENBLOOM; *Perturbation of linear operators in Banach spaces*; Arch. Math.; 6; pag. 89-101; 1955.

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[8-RUD-1987] W. RUDIN; *Real and complex analysis*; McGraw-Hill Higher Education; 1987.

[9-SHO-1994] R.E. SHOWALTER; *Hilbert Spaces Methods for Partial Differential Equations*; Electron. J. Diff. Eqns., Monograph 01; 1994.

[10-SPI-1994] M. SPIVAK; *Calculus*; Publish or Perish; 1994.

5.2.2 Probability

The books by Bailey and Parzen are classical. Those by Ash and Bath are more modern and present the theory of provability within the framework of Lebesgue measure theory. Bath's book is more detailed in the proofs, while I find Ash's book more readable.

[11-ASH-2000] R. ASH; *Probability & measure theory*; Elsevier; 2000.

[12-BEA-1997] N.G. BEAN, L. BRIGHT, G. LATOUCHE, C. E. M. PEARCE, P. K. POLLETT AND P. G. TAYLOR; *The quasi-stationary behavior of quasi-birth-and-death processes*; Ann. Appl. Probab.; 7; pag. 134-155; 1997.

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[16-LOV-2007] L. LOVÁSZ; *Combinatorial problems and exercises* ; AMS Chelsea Publishing; 2007.

[17-PAR-1960] E. PARZEN; *Modern Probability Theory and Its Applications*; John Wiley & Sons, Inc; 1960.

5.3 Evolution Equations

Papers and books on evolution equations, Nonlinear Dynamics, invariant manifolds, finally Inertial Manifolds and finally Moment Closure.

5.3.1 Semigroups

These are all classical references on the theory of semigroups, both on the theory itself and on the application to the study of evolution differential equations.

[18-AHM-1991] N.V. AHMED; *Semigroup theory with applications to systems and control*; Longman Scientific & Technical (Pitman Research Notes in Mathematics Series); 1991.

[19-HIL-1957] E. HILLE, R. PHILLIPS; *Functional analysis and semi-groups*; American Mathematical Society; 1957.

[20-PAZ-1983] A. PAZY; *Semigroups of linear operators and applications to partial differential equations*; Springer Verlag; 1983.

5.3.2 Dynamical Systems

Here we give an account on those books and papers that are directly concerned with the study of evolution equations, nonlinear dynamical systems. Some focus generally on perturbation theory; others are centred around centre or invariant manifolds, like the classical book by Carr. Finally Robinson's and Temam's books are very general and at the same time very complete introductions to Nonlinear Dynamics; both include large chapters on Inertial Manifolds. I especially like Robinson's book, which is written with the usual, unique style that characterises this author: at the same time pedagogical and rigourous, it is one of the very few books in Mathematics that one reads as a novel.

[21-BER-2001] N. BERGLUND; *Geometrical Theory of Dynamical Systems*; Lecture Notes, Department of Mathematics, ETH Zurich; 2001.

[22-BER-2001] N. BERGLUND; *Perturbation Theory of Dynamical Systems*; Lecture Notes, Department of Mathematics, ETH Zurich; 2001.

[23-CAR-1981] J. CARR; *Applications of Centre Manifold Theory*; Springer Verlag, Applied Mathematical Sciences; 1981.

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[28-FEN-1979] N. FENICHEL; *Geometric singular perturbation theory for ordinary differential equations*; J. Diff. Eq.; 31; pag. 53-89; 1979.

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5.3.3 Inertial Manifolds

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5.3.4 Moment closure

These are the papers that present the examples from population biology modelled with statistical methods, and especially using Moment Closure techniques. Most of them are focused on interpreting the results and studying how well they fit the observed data. Most papers refer back to the 1957 classical paper by Whittle for an explanation of why this technique works, whilst Lloyd and Isham, in her paper in honour of Sir David Cox, refer also to our paper published in 2001.

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