The Role of Computer Aided Process Engineering in Physiology and Clinical Medicine[1]

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Abstract

This paper discusses the potential role for Computer Aided Process Engineering (CAPE) in developing engineering analysis and design approaches to biological systems across multiple levels – cell signalling networks, gene, protein and metabolic networks, cellular systems, through to physiological systems. The 21st Century challenge in the Life Sciences is to bring together widely dispersed models and knowledge in order to enable a system-wide understanding of these complex systems. This systems level understanding should have broad clinical benefits. Computer Aided Process Engineering can bring systems approaches to i) improving understanding of these complex chemical and physical (particularly molecular transport in complex flow regimes) interactions at multiple scales in living systems, ii) analysis of these models to help to identify critical missing information and to explore the consequences on major output variables resulting from disturbances to the system, and iii) to 'design' potential interventions in *in vivo* systems which can have significant beneficial, or potentially harmful,

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effects which need to be understood. This paper develops these three themes drawing on recent projects at UCL. The first project has modeled the effects of blood flow on endothelial cells lining arteries, taking into account cell shape change resulting in changes in the cell skeleton which cause consequent chemical changes. A second is a project which is building an *in-silico* model of the human liver, tieing together models from the molecular level to the liver. The composite model models glucose regulation in the liver and associated organs. Both projects involve molecular transport, chemical reactions, and complex multiscale systems, tackled by approaches from CAPE.

Chemical Engineers solve multiple scale problems in manufacturing processes – from molecular scale through unit operations scale to plant-wide and enterprise wide systems – so have an appropriate skill set for tackling problems in physiology and clinical medicine, in collaboration with life and clinical scientists.

Keywords

Computer Aided Process Engineering, Process Systems Engineering, Systems Biology, Systems Medicine, modeling, engineering design

1. Introduction

This paper explores the role that experts in Computer Aided Process Engineering can contribute to the significant recent developments in Biology and to the way Life Scientists go about their business, and potentially help the way clinicians diagnose and make operational decisions. In this paper the terms Computer Aided Process Engineering (CAPE) and Process Systems Engineering (PSE) are used interchangeably, as the field where models of process systems are analysed and used to solve process problems computationally (Kraslawski, Klatt and

Marquardt). The aim of this paper is to show how the term ‘process’ can be extended beyond the definition commonly accepted by Chemical Engineers.

At the 7th World Congress of Chemical Engineering in Glasgow Denis Noble spoke in his plenary lecture about the computational model of the heart that he and his research group have developed over the past twenty or more years (Noble, 2002). Their project reflects true systems thinking in physiology. The model is used for part of the drug approval process for the Food and Drug Administration and is the first such model to be used in this way. The model has three levels, mostly involving electrical signals, but he was insistent on the need to involve more chemistry and that it must align with engineering principles. He is convinced that Engineers, and Chemical Engineers in particular, have a very important role to play in computational physiology.

Physiologists have long considered whole systems, well before the growth of quantitative modelling approaches. However Life Scientists have used reductionist techniques to advance their understanding, driven by the revolution in molecular biology and the growth of genetic analysis. Individual phenomena are isolated and studied in detail with only qualitative reference to interacting phenomena. Systems Biology has emerged as the area where biology is analysed as complex interacting systems, and done so using quantitative modelling techniques and system wide analysis (Kitano, 2002). This has arisen from the huge expansion of data, from the enormous improvements in computational and numerical techniques, and in the recognition of the importance of system wide effects. Recently there is a strong move to develop systems approaches to medical problems which is being called Systems Medicine (Auffray et al.).

The need for systems thinkers in the Life Sciences, in the research community and in the pharmaceutical industry and clinical services, is now widely acknowledged (Kitano, 2002). The US National Academy of Engineering and National Science Foundation Report 'Beyond the Molecular Frontier' identified a strong role for Chemical Engineers to play in the interface with Biology and Medicine. This interaction could have significant potential to benefit research efforts worldwide in the next ten years. The systems approach is instilled in Chemical Engineers and specialists in Computer Aided Process Engineering should be able to help train a new type of engineering biologist who can work at the molecular and system wide levels applying systems engineering approaches to physiological and clinical problems. This is already occurring for cellular systems.

Section 2 introduces some of the work done to address biological problems using systems approaches. It is not a comprehensive review but seeks to identify some of the areas where the contribution from the Chemical Engineering community is clear. Section three explains how the use of CAPE approaches can help to explore the understanding of life science systems, demonstrating this with the modelling of endothelial cells lining artery walls. Section four discusses how analysis tools can be used in this domain and shows similarities between physiological systems and chemical manufacturing process systems. The glucose homeostasis system in humans is used to demonstrate the similarity. It is not the objective to show full results for these systems but rather to demonstrate how the skills of the CAPE community can be used to address these types of problems. Section five postulates how the approach to process design can make valuable contributions in physiology and medicine. Greater fidelity of the models will be required before clinical advice can be safely used. Finally the paper discusses the ways the education of Chemical Engineers can prepare graduates to get involved and to contribute to this exciting field.

2. Computer Aided Process Engineering in Systems Biology

Systems Biology has been emerging as a key approach for using quantitative analysis to understanding biological systems. It arose from the need to deal with very large amounts of data from the development of the analysis of the genome (Westerhoff and Palsson, 2004). Recently the idea of considering clinical problems from a quantitative systems perspective has been proposed and is giving rise to significant new lines of research, spawning the new subject of Systems Medicine (Auffray et al., 2009; Ahn et al., 2006). Clinicians have always attempted to consider holistic approaches to medical diagnosis and treatment but the change being brought about is the huge increase in quantitative understanding of biological systems and the use of personalised data from patients. Foteinou et al. (2008) discussed the use of systems-based models to better understand and modulate inflammatory responses in particular.

Chemical Engineers have long been involved in the quantitative analysis of biological and biomedical problems. Peppas and Langer (2004) have written a historical perspective of the involvement of Chemical Engineers in Biomedical Engineering with 'implications which would not be felt until the mid 1970's but which had started in chemical engineering in the early 60's.'

Bailey and his co-workers (see for example Bailey, 2001a&b, and a summary of much of his work on eukaryotic systems in Fussenegger and Betenbaugh, 2002) developed approaches to metabolic control analysis particularly for biological manufacturing but also for broader biological problems. Recently Stephanopoulos et al. (2005) wrote of the challenges in nanoscale process systems engineering, focusing particularly on the systems engineering of cells as complex nanoscale factories. Eissing et al. (2009) recently wrote of the use of models for the analysis of the network that controls cell death. Doyle and Stelling (2006) reviewed progress using

engineering approaches to the analysis of metabolic networks, considering robustness aspects in particular.

Recently there have been a number of articles outlining quantitative challenges for Chemical Engineers in medical system. Vekilov (2008) highlighted the role we can play as problem solvers in clinical medicine, concentrating on exploring polymerisation phenomena in disease. The immune system is a complex system for which chemical engineers, and process systems engineers in particular, are very well suited to 'exploring the interplay between the dynamics of the immune system and the viral diversity.' Deem (2004, 2005) has developed quantitative models and investigated how the immune system responds to disease and vaccination. Chakraborty (2003) discusses how cells in the immune system communicate and make decisions to mount an immune response and comments that 'the chemical engineer's rare ability to think about phenomena that occur over a wide range of length and time scales is useful for studying complex problems in cellular and molecular immunology.' Yin (2007) proposes that viruses be considered as products whose behaviour of how they grow, spread and persist needs to be considered within populations considering temporal and spatial effects. He also states that Chemical Engineers are needed 'especially in the defining and advancing of quantitative and integrative methods and models.' Joly and Pinto reviewed the advances of mathematical modelling of HIV-1 pathogenesis presenting a general framework for optimizing drug therapy benefits. This approach will also lead to advances in drug design (see for example Petitti et al. (2008) for an example of modelling controlled release of a drug encapsulated as a solid core) and formulation design (Zucca et al.) where in the future a model of the physical attributes of the drug formulation can be used with a model of the physiology where it will be delivered to develop an optimal design.

Some years ago an academic project, the Physiome Project (www.physiome.org.nz), was launched seeking to provide a computational framework for understanding human and other eukaryotic physiology through computational tools and models. A recent European Funded Network of Excellence entitled the Virtual Physiological Human aims to help support and progress European research in biomedical modelling and simulation of the human body (Gavaghan et al., 2009, http://www.vph-noe.eu/).

There have been a number of papers exploring how to be able to ensure that models from disparate sources can be compared and published in a transparent fashion. Nickerson and Buist (2009) describe a standard for biological models, particularly designed to facilitate comparability to assist the peer review process. The physiome standard has so far concentrated on mathematical models of cellular electrophysiology using the CellML standard (Beard et al. 2009, www.cellml.org), a standard for models of biophysical mechanisms which has applications to all models of cellular processes where spatial gradients are ignored. Spatial information is handled by a complementary standard called field modelling language, FieldML, Christie *et al*. (2009) www.fieldml.org). A second standard is SBML, the Systems Biology Markup Language (sbml.org), which is a computer-readable format for representing models of biological processes applicable particularly to simulations of metabolism and cell-signaling.

Model repositories have been developed to store biological models for public access. Two examples are the JWS Online Cellular Modelling System (jjj.mib.ac.uk) and the European Bioinformatics Institute Biomodels Database (www.ebi.ac.uk/biomodels), used together to explore complex biological and physiological systems. These repositories encourage the use of the standards described above.

Another approach has been to develop a system that allows heterogeneous models to be integrated using computational wrappers to enable communication between models within a model management system (Hetherington et al., 2007). This is not unlike the CAPE-OPEN approach well known in the CAPE community (www.colan.org).

There is increasing commercial interest for the use of integrated systems of biological models. Entelos (Stokes, 2000) have large scale biological system models that span multiple scales focussed on specific targets for drug discovery.

The use of models to obtain proposed actions on the basis of models is rarer. There have been a number of contributions developing model based control approaches to drug delivery both as general systematic approaches (Dua and Pistikopoulos, Somayaji et al., Morari and Gentilini, Parker and Doyle, Linninger et al.) but also a number of contributions specifically developed for cancer therapies (Dua et al. (2008), Bandara et al, Harrold and Parker) and for ophthalmic therapy (Pettiti et al. (2009)). Csete and Doyle (2002) have proposed a reverse engineering approach focusing on the analysis of complex dynamics of biological feedback systems. Tyson et al. (2003) review some of the common design principles in biological regulatory signalling modules.

Chemical Engineers have been contributing to the quantification in Biology and there is a strong appetite for greater involvement. The potential is exciting not just for the technical challenges but also for the opportunity to make a major social contribution. The approach by clinicians as problem solvers on the basis of the analysis of observed phenomena is similar to the traditional role of engineers in solving industrial problems. In the rest of the paper we will consider three roles that Process Systems Engineers can contribute. The first challenge is enhancing understanding through modelling. The second challenge is for detailed analysis of the models.

The third challenge is to use the models to develop proposed actions, which could be chemical (drug activated), dietary, environmental, or clinical. This in engineering terms is a design problem. The paper will discuss each of these three in turn with examples.

3. Enhancing Understanding

Hangos and Cameron (2001) make great emphasis on the need to be clear about the purpose of a modelling task. A key role for modelling is recognised as helping to clarify understanding. This is particularly true for complex systems where it is often not possible to design experiments that focus on one specific phenomenon either because it is unmeasurable or because several phenomena are intractably interconnected. These problems are very evident in the Life Sciences where in spite of major advances in the measurement of genetic and metabolic species, many measurements are physically unattainable and vary dynamically at levels for which in vivo accuracy is still far from adequate.

To clarify which phenomena are driving a particular system a number of hypotheses can be tested using a mathematical model. This is common in Chemical Engineering particularly where there are multiple phases and local measurement is difficult, for example in reaction engineering systems and processes involving particulates. These are examples of multiscale systems involving molecular, bulk transport, and sometimes process level driving phenomena. Since measurement of key species in the systems is often difficult or impossible, the use of models to predict gross behaviour which can be matched unambiguously to data is essential. Systems engineering techniques facilitate the ability to make conclusions about specific phenomena in complex systems which are not directly measurable.

An example of this from work at UCL has been the modelling of the behaviour of endothelial cells lining the walls of arteries responding to changes in blood flow. There is evidence that the force due to fluid flow stimulates chemical signalling and causes the cells to elongate (Wojciak-Stothard and Ridley, 2003). Under some conditions macrophages accumulate in the arterial wall, ultimately leading to atherosclerosis. The location of atherosclerotic plaques is correlated to regions where the flow is non-laminar (for example where arteries bifurcate) – suggesting that the endothelial cell interpretation of blood flow is critical in the pathogenesis of atherosclerosis. The work sought to explain a number of questions: Which cell component interprets physical force? How does this component initiate signalling? How is the signalling network shut off?

Figure 1 shows how force act on the system and causes consequent effects. To explore this behaviour we developed a three level model (details of the models can be found in Allen (2009) and Allen et al. (2009)). A model has been developed of the forces exerted by the fluid flow (blood) on the surface of the cell, assuming laminar flow over an endothelial cell (initially) represented as a spherical cap. This model is a boundary integral representation of the Stokes Equation for flow over a cell with the cell surface discretised into small triangles, of varying area (~ 0.4 μm^2). A second model (a mechanical model) was developed of the effect of force on the cell wall on the behaviour of the cytoskeleton, a structure of tensile elements working as cables (actin filaments) and compressible elements as struts (microtubules) which keep the shape of the cell. The force normal to the cell surface is taken to act on a viscous spring model known as a Kelvin body, with a dashpot of fixed viscosity and two parallel springs. The Kelvin body represents a cellular component that transduces mechanical force into a biochemical signal which causes activation of an enzyme, Src (a tyrosine kinase), which is hypothesised to regulate the Rho GTPase enzymes (Rac and Rho). Rho GTPases control cellular structure and morphology. In particular, localised Rac activity initiates growth of extensions called lamellipodia. The chemical pathway (simplified) for this is shown in figure 2 and is assumed to

have much faster dynamics than the structural changes. Together these models allow us to model the effect of changes in the fluid flow on the signalling and consequent elongation of the cells (fig 1).

The model clarified a number of issues. For example the best hypothesis is that integrin complexes, which transduce signals from outside into the cell, interpret the physical force and cause changes to Src activation levels (the first question above). They are known to become activated in response to tension and the composite model supports this. The exact mechanism is unclear but the Kelvin body model produces a suitable response.

However the model also suggested a number of other questions that need answers, such as how to deal with modelling sheets of cells effectively given that there is inter-cellular communication and restricted mechanical effects as a result of boundaries with other cells.

This model has chemical and mechanical effects and involves cellular and metabolic scales. It is not a traditional 'process system' but does involve many of the characteristics that the process systems community is used to dealing with. This problem involves two scales and requires the consideration of a system of three models to connect the effects and to generate simulated results for comparison with data. The models here are both chemical and mechanical, embracing the scales which are familiar to Chemical Engineers. Using the systems view of Computer Aided Process Engineering has facilitated the development of an integrated model leading to the ability to test and verify hypotheses about the way the system works in spite of the measurement difficulties.

4. CAPE analysis

One of the CAPE community's key strengths is the ability to analyse models efficiently to explore their properties in the physical context of the system. Hangos and Cameron (2001) define two types of model analysis: those where there is a yes/no answer, and those which involve a 'Find' or 'Compute' component, for example, determining outputs resulting from stimuli, observability and controllability properties (see for example Russel et al.), or obtaining sensitivity information.

Of relevance to the Life Sciences is the analysis of the robustness of systems with multiple feedbacks. Living systems are known to be very robust. Some recent work of ours showed it is possible to use network properties and an optimisation problem determining the size of a network determined as the minimum of the distances between any two nodes to explore the behaviour of a network under attack from viruses (Dartnell et al.). It was shown how the most virulent tumour inducing viruses, adenovirus, HPV 16/18 and SV40, attack the most connected nodes of the p53 network (which controls cell death), the p53 and pRb cellular proteins, acting like 'viral hackers'.

A second important task is the identification of areas of weakness in a model, where the model may be insufficiently accurate to be able to make predictions of the desired accuracy. Of course this means defining the accuracy of data which are already within the model as well as the level of accuracy required for the purpose for which the model is being developed. This becomes very important in complex models where internal parameters cannot be measured and outputs may not obviously be related to inputs. Such problems are acute when dealing with complex physiological problems involving a number of organs.

Figure 3 shows a simple process flowsheet. A feed stream containing a component, A, needed for an important process, together with some waste is fed to a plug flow reactor. In this reactor

some of the feed is reacted to form a byproduct, B, which is stored for future use. It is important that the product stream from this process contains a bounded amount of component A. A is converted to B by a reaction catalysed by catalyst, C, and converted back to A in the reverse reaction catalysed by component D. The CSTR produces an amount of C or D depending on the level of A fed to it. If the level is too high it will produce C catalysing the forward reaction producing more B in the membrane reactor where it is stored. If the level is too low it produces an amount of D catalysing the reverse reaction. The membrane reactor at the same time acts as a sophisticated filter removing the waste.

This simple flowsheet is in fact a simplified version of the system which regulates the level of glucose in the bloodstream (figure 4). Glucose enters the bloodstream from the gut and is used in all the other organs of the body, especially the brain. It is important that the level of glucose is maintained within certain levels to ensure good response of the various human (or animal) functions; this regulation is known as glucose homeostasis. If glucose levels are high the pancreas produces insulin, the hormone that instructs the liver (and other tissue, especially muscle) to convert glucose into glycogen which is stored for later use. If the level of glucose in the blood is low the pancreas produces glucagon which stimulates the conversion of glycogen back into glucose which can be released into the blood stream. The liver cells, or hepatocytes, also convert waste products in the blood into bile which is filtered through the bile duct for excretion.

This is a complex system involving a number of organs and to explore the behaviour of the system requires a number of interconnected models with feedback between them. Seven models of parts of the glucose homeostasis system (written in different modelling languages as indicated) were developed by the large team listed in the Acknowledgements:

Glucagon receptor model (Mathematica™) – models the activation of a receptor on the surface of hepatocytes by the hormone glucagon which causes subsequent internal signaling resulting in the production of IP3, a secondary messenger molecule. The model contains five differential equations describing the various states of the receptor (free, sequestered, ligand-bound and phophorylated ligand bound), the activation of G-proteins and the production of IP3.

Calcium model (XPPAUT™) – models the calcium signaling pathway activated by IP3 and contains two differential equations for the cytoplasmic and endoplasmic reticulum calcium concentrations. The net flows of calcium are assumed to have Hill function dynamics i.e. of the form $x^n/(c^n + x^n)$.

cAMP model (Mathematica™) – models the activation of a receptor and the consequent production of cyclic AMP. The model involves five differential equations for concentrations of cyclic AMP and S-Adenosyl methionine (SAM), the proportion of unmodified receptors, and the proportions of inactive and nuclear localized protein kinase A (PKA). Responses are assumed to follow Hill function dynamics.

Insulin model (XPPAUT™) – models the response of the liver to insulin. Consists of one differential equation describing the activation of glycogen synthase kinase (GSK), the key responding protein.

Blood model (XPPAUT™) – models the transport of glucose between the blood, the liver and the pancreas and contains one differential equation for the concentration of glucose in the blood

Glycogenolysis model (XPPAUT™) – models four factors that control glycogen breakdown and synthesis: direct control by glucose and glucose-6-phosphate, control by calcium ions, control by cyclic AMP, and control by insulin. This model contains a fuzzy logic model describing response of the activity level of glycogen synthase (Sta) which controls the rate

of glycogen synthesis, and glycogen phosphorylase (Pho) which controls the rate of glycogen breakdown. These are used within a four differential equation model for Pho, Sta, glycogen, and intracellular glucose.

Pancreas model (Mathematica™) – models the release of glucagon or insulin using time delayed threshold responses. The model consists of two differential equations for blood concentration of glucagon and insulin. Each release is assumed to follow Hill function dynamics.

Saffrey et al. (2007) describe a model management system for the development of models of physiological systems, and this system in particular (see also Hetherington et al. (2007)). The system stores models, data, and analysis results in a searchable system. The system enables models to be linked together as a composite model and run to generate results. Biological models are developed by laboratories using a wide variety of different modelling languages so the system has been developed to enable such models to communicate and to run simulations. Models are 'wrapped' to provide a common interface for communication in a way similar to the CAPE-OPEN standard (www.colan.org).

The seven models were linked together in the model management system to simulate the behaviour of the integrated system. A detailed description of the model with comprehensive results can be found in Hetherington et al. (2009). The model was able to reproduce ultradian oscillations which are observed in glucose behaviour of healthy systems. These oscillations, which occur with a period of approximately an hour, result from feedback between liver and pancreas (Simon and Brandenburger, 2001). Fig 5 shows the model matched to commercial data for ultradian oscillations following an oral glucose tolerance test.

This is an example of a multiscale physiological process system which has a number of characteristics which make the contribution of Process Systems Engineers of value. The approach to the modelling task itself is one that we are familiar with albeit in a different domain. The application of conservation and constitutive equations for these systems is valid but we need to work closely with life scientists in the modelling task for clarifying the purpose of the model, generating the modelling equations, and obtaining the data. Where we add value is in our quantitative approach, utilising the approach of breaking complex systems into unit operations or functional modules, and the ability to determine which potential components of the model will be important and which can be ignored on the basis of quantitative exploration of the components.

5. Design

A major strength from Engineering is in design: the prediction of appropriate values for a system to achieve particular outcomes. Model based engineering design techniques are used to determine what actions should be taken to achieve a desired outcome. This is a well-explored approach in Engineering: in safety engineering, process design and operations, and supply chain analysis for example, where gross consequences for a system of external stimuli are simulated and evidence produced for design decisions. Objectives in traditional process design include achieving particular product amounts and qualities while maximising financial return, and keeping the environmental cost to a minimum.

The equivalent in the case of physiological systems is in designing interventions in living (*in vivo)* systems which can have significant beneficial, or potentially harmful, effects. Such interventions can be environmental, through the introduction of chemical or physical agents, pharmacological, through clinical interventions, or genetic. The challenge for the future will be

to use system models to design actions for physiological systems where the level of uncertainty is high but the need for bounded accuracy critical if clinical decisions are to be made. This will make the fitness for purpose (Hangos and Cameron) a very important aspect of model development, model curation, and data generation. Here we will show how this type of problem appears in the glucose homeostasis example above in order to exemplify the way engineering design approaches could be used more widely in physiology and clinical medicine in the future.

With composite models within a computational system described in section 4 it will be possible to use a wide range of the techniques used by the Computer Aided Process Engineering community to obtain useful actions. Three examples of such techniques are: to use optimisation techniques to identify optimal solutions such as optimal insulin doses for diabetics; to use stochastic techniques to identify probabilistic solutions to identify where model sensitivities are important, such as determining which of the many rate constants need to be most accurately measured; and to use interval methods (Hansen and Walster) to identify worst case tolerances for actions given desired clinical or environmental outcomes.

It is this last area where we are currently addressing our attentions. Defining desired outputs in quantitative terms, such as minimum levels of glucose to avoid the onset of type 2 diabetes with possible consequences of non-alcoholic fatty liver disease (NAFLD) which occurs more frequently in those with diabetes, it will be possible using the integrated model to devise clinical actions that should be taken to avoid major problems. Simple integrated models also will allow us to use interval techniques to provide quantified levels of accuracy required for experimental data that will provide the desired uncertainty bounds in the outputs. This requires construction of models which calculate intervals for output variables given intervals for the input variables (Byrne and Bogle**).**

The objective will be to obtain a methodology which aims to minimise a biologically defined quality objective J (clinical or dietary for example) which will be an interval (a range in allowable blood glucose measurement for example) subject to an integrated model and intervals for measured state variables (such as glucose concentration) X and non-interval state variables x, u are manipulated variables (a chemical stimulus for example), d disturbance variables coming from unmodelled parts of the system or outside the body, and θ the 'design' variables which characterise the system (such as chemical kinetics of glycogen-glucose chemistry). This problem can be solved for point objectives using traditional optimisation techniques but also to obtain interval bounds as a conservative range using interval methods. Interval methods are very conservative which is valuable given the approximations involved and the criticality of the outcomes.

The techniques used in Computer Aided Process Engineering, such as optimisation, stochastic analysis, and interval methods, will be increasingly needed for biological and medical advances to be able to make reliable system-wide quantitative predictions of their effects. The solutions will provide guidance as to the sort of clinical or environmental actions that should be taken to design a robust system which will not fail given certain ranges of disturbances to key variables. If these variables are measurable then we would design a solution which indicated what the range of measurements would be permissible before serious extra action need be taken to avoid a failure of the system.

6. Process Engineering Education

The involvement in medical areas provides a new potential research area and employment area for Process Systems Engineers. Process Systems Engineering training already gives graduates the ability to apply computational problem solving techniques to a wide range of

problem domains: in the process industries, natural sciences research, financial services and now increasingly in Systems Biology and in Systems Medicine.

To make students more aware requires principally the use of examples and the practice at using the techniques that have been taught in the context of process analysis. These examples are difficult to develop without appropriate domain knowledge. It is therefore important that those wishing to work in this area make appropriate collaborations. For example at UCL there is a mechanism for promoting collaboration through short and long projects in the Centre for Mathematics and Physics in the Life Sciences and Experimental Biology (CoMPLEX). The first year of a doctorate involves a series of short six week projects and a four month project prior to the start of the PhD project. All projects must have two supervisors, one life scientist and one modeller. By developing research collaboration mechanisms Process Systems Engineers can become involved in understanding and solving Systems Biology problems and to contribute to the formation of young engineers keen to get involved.

7. Conclusions

In this paper we have sought to show how some of the problems in Physiology and Clinical Medicine can be addressed by the approaches used in Computer Aided Process Engineering. The problems involve chemical and physical change in the chemical factories in the body and often involve complex multiscale systems. These are the type of problems with which the Computer Aided Process Engineering community has much experience.

The paper has focussed on how the community can make contributions using familiar techniques in three ways. While there is great knowledge of physiological systems there is still much to learn through using system models where key measurements are not available. Only

through the use of integrated system models can some of the complexities be unravelled and linked to measurable quantities, aiding better understanding. Model analysis tools can be deployed to explore the behaviour and sensitivities of the systems. Finally it will be possible to use design methodologies to recommend actions for physiological systems, either to improve normal behaviour or to find ways to alleviate diseased states.

The greatest challenge is in obtaining models that can predict the behaviour of physiological systems to a sufficiently accurate degree. Models that will be used in any clinical way will require much greater accuracy that those that are used for understanding and analysis where gross trends can help clarify phenomena which drive a system. Clinical usage is still a long way off. But the involvement of the Computer Aided Process Engineering community can help the development of suitable methodologies and aid the model development and data generation process to significantly speed up the development of practical outcomes using the new approaches of Systems Biology and Systems Medicine.

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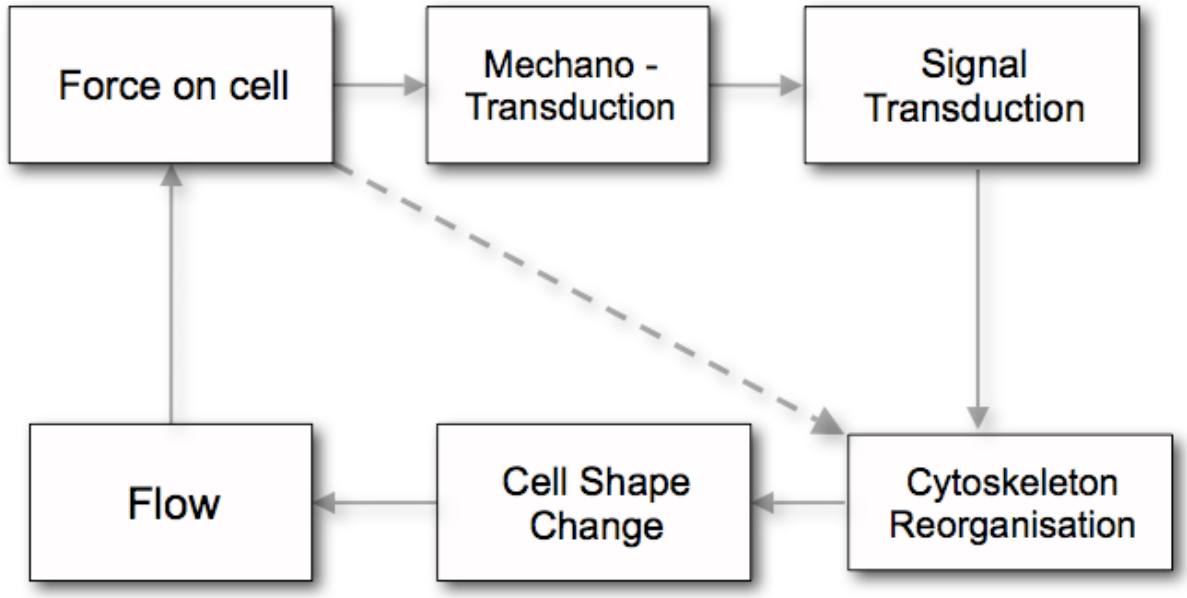
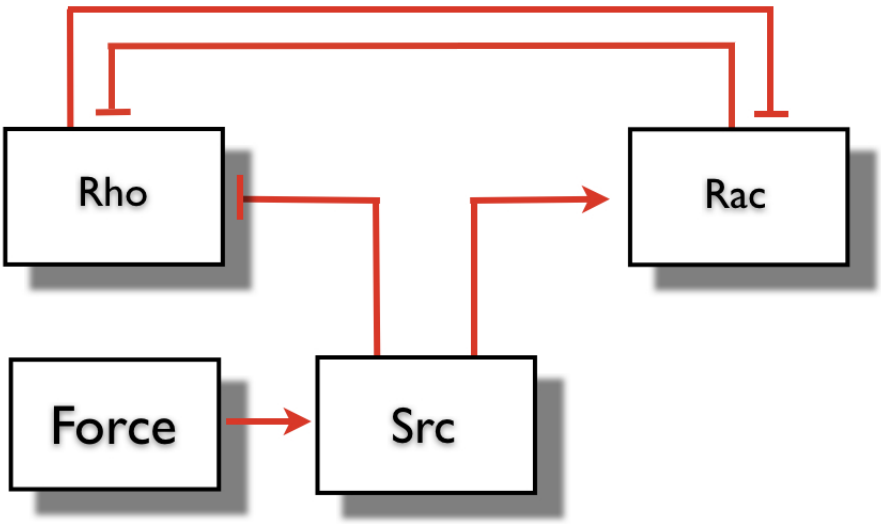
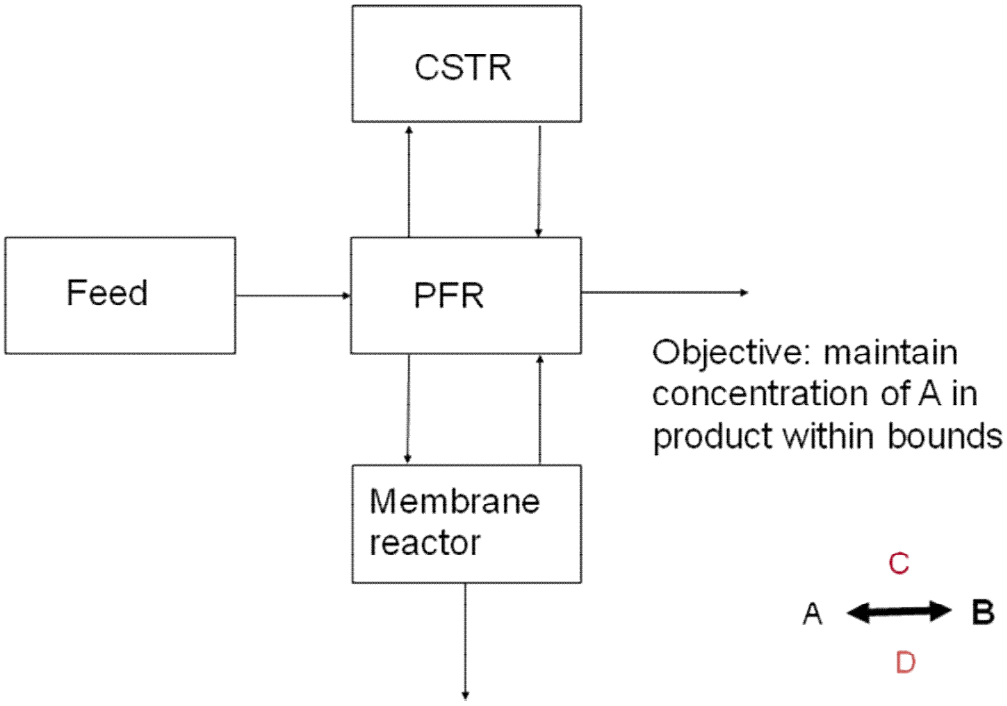


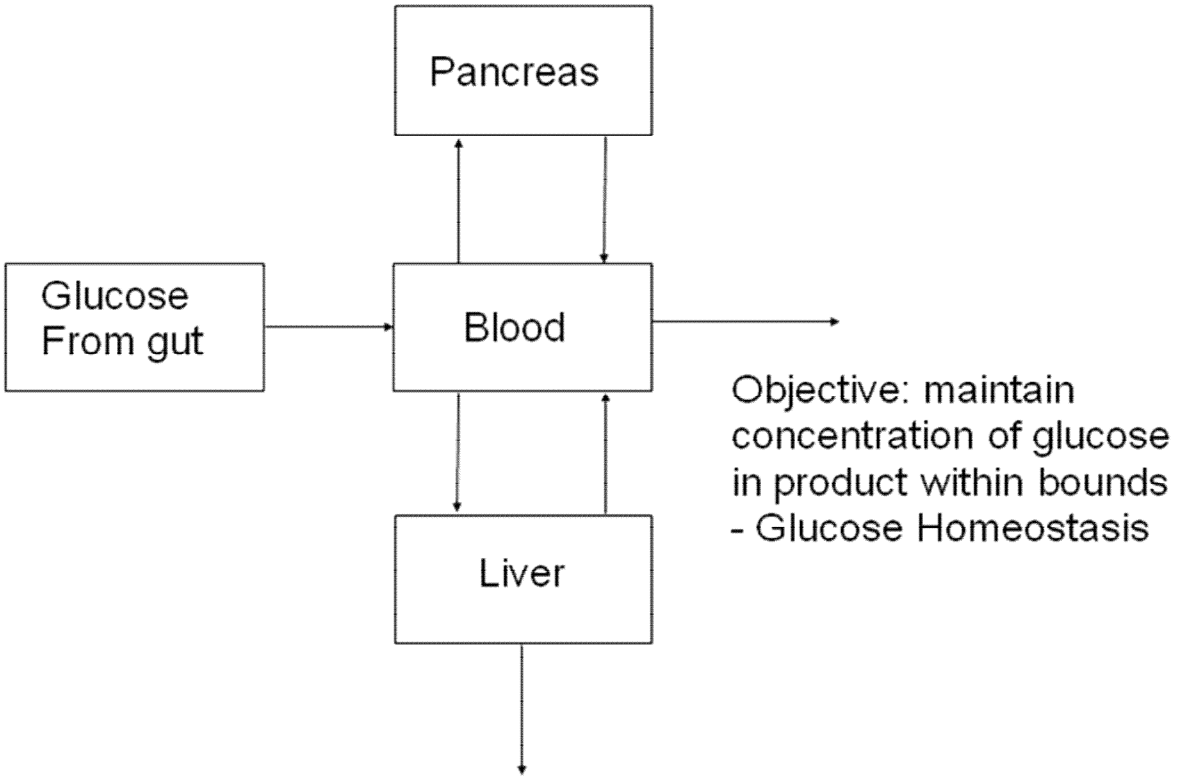
Structure for the composite model for the response of endothelial cells to changes in blood flow
Fig 1



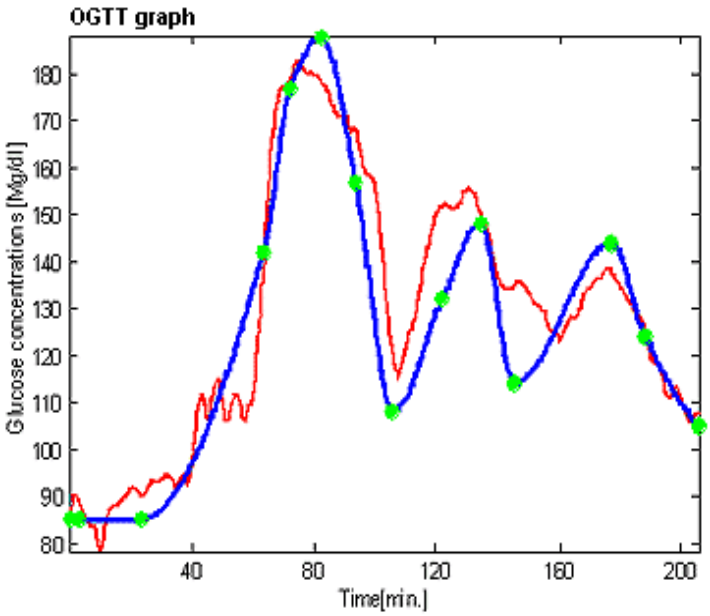
Chemical signalling network for response to force on the cell from blood flow
Fig 2



Generic flowsheet for glucose regulation system as a Chemical Engineering system
Fig 3



Flowsheet for glucose regulation system in the body
Fig 4



Model prediction matched against commercial data of the consequences of the standard oral glucose tolerance test resulting in ultradian oscillations in the liver
Fig 5