PROFESSOR JASMINKA GODOVAC-ZIMMERMANN

A call for change in systems biology

The Molecular Cell Dynamics Group at University College London School of Life & Medical Sciences, are leading pioneering research that addresses fundamental questions in systems biology and proteomics; work which could represent a paradigm shift from the methods currently employed

THESE ARE EXCITING times for biology, as new tools and methods are paving the way for scientists to engage with some of the most important questions to humanity, such as: 'what is life?' In the 1970s this question had a definitive working answer and scientists working on unmanned exploration missions to Mars and other planets knew what to look for. But now, with advances in gene sequencing, the creation of the first 'artificial' life, the discovery of the 'arsenic bug' and a more mature understanding of cellular and genetic biology, the question is being examined in new ways.

WHAT IS 'LIFE'?

Proteomics – the large-scale study of the functions of proteins, and systems biology – holistic research on complex interactions in biological systems, are two interrelated fields that may offer insight into this question and others of critical importance to health, biotechnology and other fields. A leading scientist in systems biology and proteomics, Jasminka Godovac-Zimmermann is Professor of Protein Biochemistry at University College, London. She believes that there are a number of difficult questions that these fields need to answer, such as: "What can we learn about the fundamental nature of life by in-depth, large scale efforts to characterise the networks and network fluxes that exist in living cells?"

One of the limitations in answering the question 'what is life?' is that proteomics has been conditioned by the approaches taken in genomics, as Godovac-Zimmermann explains: "Proteomics scientists have mainly tended to measure the amount of gene-products in a cell. But, at the level of 'what constitutes life', we already know that quantity, form, location, fluxes and time are probably all equally important". A better approach, according to Godovac-Zimmermann, is to take a more considered stance: "Where proteomics has major conceptual advantages and can make vital, unique contributions is in measuring the form and location characteristics that are not accessible with genomics". However, unique contributions present unique challenges, she points out: "The major future challenge for proteomics, biology and medicine is no longer in cataloguing components of cells or organisms, but in elucidating how these components interact to constitute living systems".

IMPORTANT ADVANCES

Another area in which proteomics and systems biology are offering valuable insight is in the search for cures to some of

Biological science in a changing world

Professor Jasminka Godovac-Zimmermann is a leading light in proteomics and systems biology. In this interview she gives her opinion on where discoveries in these fields are leading and the future of scientific research in general

Can you begin by outlining your primary research interests and what inspired you to become an active participant in this field?

From the very beginning my interests have focused on the question, 'what is life?' Over the years I have reinvented my specific research interests several times as new tools became available, moving from protein chemistry to cellular signalling systems to proteomics and now increasingly to systems biology. For me, proteomics represented a natural progression to an area that could ask important questions that came after the human genome project.

There is still a tendency to expect proteomics to find 'magic-bullet' genes or proteins as targets for the treatment of cancer. Is this a realistic expectation?

For a long time now it has been apparent that living systems are enormously interconnected networks of very large numbers of molecular actors. My own opinion is that we should be focusing on understanding these networks and that, when we do, much more efficacious 'applications' will become possible. I am sceptical that 'network manipulation' will be based on single molecule 'magic bullets'.

If you could select one achievable goal for the next decade, what would it be?

The current chaotic, unorganised inputs of information seem unlikely to lead to deeper understanding. I believe we would make much better progress by organising some strong, collaborative teams to investigate questions like: what is it that makes this particular cell system a living object?

This would require some technical developments in several fields. However, the biggest challenges may well be in developing appropriate conceptual interpretations, which will only become apparent when enormous, integrated data sets have been obtained on a common, controlled cell system. We should note that scientists like Stuart Kauffman have pointed out that there are indications that living systems may challenge basic ideas, like the concept of what entropy really is, and begin thoroughly exploring these new ideas.

The field has experienced exponential growth in the last decade? Do you see the pace of discovery relenting in the near future?

I believe proteomics needs to grow much more and that new technology is still needed. Bottom-up proteomics has been essential to

the most devastating diseases. Godovac-Zimmermann and co-workers are looking into the possibility of selective killing of cancer cells by manipulation of the crucial DNA replication licensing process of the mitotic cell cycle. A number of cell and molecular biology groups have suggested, through specific point observations, that inhibition of several particular steps might selectively kill cancer cells. Godovac-Zimmermann explains her group's initial contribution: "We investigated how these point observations were connected to wider aspects of cellular homeostasis". She continues: "Unsurprisingly, we discovered that the point observations were parts of very complex, interacting functional networks that include processes distributed throughout the cell". Now, her group are collaborating with cell and molecular biology groups to characterise these various networks.

Her team are also investigating factors which contribute to susceptibility to herpes simplex virus encephalitis: one of the most devastating infections of the central nervous system and particularly problematic for young children. In a similar way to the cancer investigation, this study began by taking point observations from other groups, in this case medicine, cell biology and genomic screening. They have already identified a number of new, unexpected proteins and pathways that provide new perspectives for further characterisation of the cause of the disease.

COLLABORATION FOR PROGRESS

Although there are new research tools which allow thousands of cellular components to be investigated, current systems biology tools tend to only provide fragments of understanding from the observed information. Godovac-Zimmermann explains a central problem: "At present, we seem to lack crucial basic concepts about the functioning of living systems that could greatly potentiate applications".

By taking tools from a wide variety of disciplines – from biology to chemistry, physics, applied mathematics, computer science and beyond – proteomics aims to plug gaps in our knowledge and provide a deeper understanding than any single approach. Interdisciplinary research requires extensive collaboration, but Godovac-Zimmerman believes this has been unduly limited: "It has been a mistake to treat proteomics groups as appendices to conventional biology groups". If research is to advance, proteomics needs to be treated as a field in and of itself, where researchers from other disciplines can meet to solve some of the biggest questions.

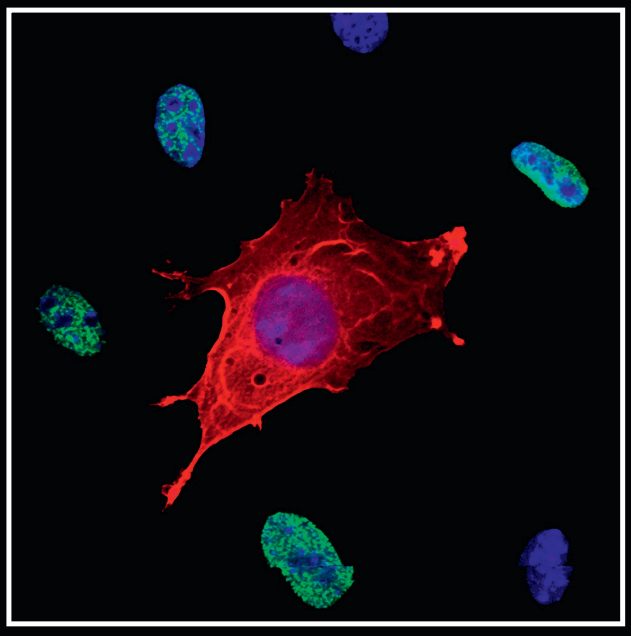

FIGURE 1. LOOKING FOR SPACE, TIME, QUANTITY, FORM AND DYNAMIC FLUXES IN HUMAN CELLS

DATA HARVESTING TO INTERPRETATION

Vast quantities of data have been produced which may provide answers to some of these questions. But the volume of data is becoming an increasing problem. Consequently, meta-analysis is increasingly seen as a vital tool for generating new concepts. However, the increasing volume of uncoordinated data may be a problem, as Godovac-Zimmermann elaborates: "So far we have not given sufficient attention to ensuring that the input data is coherent and that the resulting databases are reliable and relevant, both of which are essential for large-scale '-omics' science".

In fact, the incorporation of all this fragmented information into current systems biology tools could even be making the situation worse. Current 'data harvesting' tends to simply throw

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demonstrating the utility of high-throughput proteomics, but it tends to mirror the genomics quantity approach and discard crucial information on form and location of cellular proteins. Although, in the near future, current proteomic methods will generate enormous amounts of data, we also need to keep alive a plethora of research groups working on developing new technologies that will be essential to exploiting the areas where proteomics can supply unique information.

In the past you have stated that you believe there is a lack of high-quality education for young scientists. Is this situation changing?

If students are not provided with a broad education that includes fundamental elements of many fields, they are crippled as future scientists in terms of often not even knowing which concepts and tools are available. An individual cannot be an expert in everything, but he needs to know the basic concepts of many fields and to know which questions to ask of the experts. It is a big mistake to narrow education too much to specific, current, vocational needs of corporations or governments, and produce 'cogs' that may well be obsolete within 10 – 20 years. In the UK, I see this situation getting worse, not better.

Increasingly, research institutions are feeling the pinch, being asked to streamline their research and infrastructure, as well as avoiding duplication. Can you tell us your thoughts on the effect that the global economic downturn is having on research?

To start with, many of the recent cases of scientific fraud remind us that duplication of studies is a cornerstone of scientific advancement. No reproducibility, or no parallels in similar systems, equals no credibility. To that we might add that scientific progress often seems like ecology: plentiful diversity and lots of interactions are needed for systems to evolve. So 'streamlining', especially if designed by politicians or political committees, seems likely to be highly counterproductive.

In your opinion, how might the effects of cuts be lessened?

If we have to tighten our belts, two guiding principles might be useful. First, reverse

the profligacy of recent years – cut the 'centralised state planning organisations' that impose massive bureaucracy on universities and cut at least one central administrative position for every academic position lost. Second, perhaps we should take note of the fact that in some of the world's most successful universities the academics hire and fire the administrators.

PROTEOMICS IN SYSTEMS BIOLOGY – DOES FORM, QUANTITY, LOCATION OR FLUX OF PROTEINS DOMINATE CELLULAR FUNCTION?

OBJECTIVES

Exploitation of the human genome in systems biology has tended to concentrate on the amounts of gene expression, although it is well known that over 50 per cent of eukaryotic genes generate multiple transcriptional variants and the majority of proteins are subject to various kinds of functionally important post-translational modifications. We have established high throughput proteomics methods that can address at least some of the complexity in protein spatio-temporal distribution/flux in cells.

KEY COLLABORATORS

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The major future challenge for proteomics, biology and medicine is in elucidating how components interact in living systems

together snippets of information from all possible sources. This technique usually ignores the fact that there are many cases where the function of a protein in one cell type may not be the same as in another. As Godovac-Zimmermann elucidates: "In viral encephalitis we see strong cell variability between different patients at the individual protein level, but this is usually completely ignored and we do not yet have good ways of characterising the degree to which different patients have commonalities at a higher level of network responses. This might mean that enormous quantities of over-aggregated data in systems biology databanks actually obscure crucial information".

STIFLING INNOVATION

Not only is the quantity of information a problem, there are also problems with quality and interpretation. Commercial attempts to provide meta-analysis tools suffer from lack of transparency with regard to input data and methods, from instability of the output databases and from severe constraints on how the data can be manipulated by users. Godovac-Zimmermann suggests it would be simpler if all of this information were held in the same place. "Unfortunately no institution has been given the responsibility of providing a public, well-organised, central repository of molecular information!"

Even if data is plentiful and high quality, bias can creep into their interpretation, according to Godovac-Zimmermann: "New data tends to be 'interpreted' in terms of previously popular research areas. For example, we have seen indications in our project of the selective killing of cancer cells that overly facile assignment of observations to previously known functional networks may obscure the existence of parallel networks that may be complementary to, or competitors of, the better known networks".

There is a more fundamental problem facing systems biology researchers, and scientists in general: a change in the way that funding is allocated. The danger, particularly in publicly funded research, is that immediate commercial interests stifle creativity and fundamental innovation. The pressure for short-term results of limited scope, defined in detail in advance, has become more and more of a prerequisite for scientific project proposals. However, Godovac-Zimmermann believes that 'good' science will always find a way to get through: "Truly creative scientists may ignore the stated goals and do what really interests them once they have the funding," she concludes.

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