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Advancing Systems Biology for Medical Applications

Contents

Foreword

Systems biology is the systematic study of complex interactions in biological systems. It is a rapidly growing discipline that is playing an increasingly important role within the medical sciences. Among its anticipated benefits are contributions towards improving early diagnosis, designing patient-specific interventions, and accelerating the discovery of novel therapies for the benefit of European citizens. Several reports have recently provided science policy advice aimed at directing the advance of systems biology within Europe. Here, rather than revisiting the general recommendations given in such reports[1,2], we provide a more specific, practical guide towards achieving major breakthroughs in biomedical systems biology, thereby covering issues that had not previously been addressed in sufficient detail. In particular, we identify and outline the necessary steps to promote the creation of pivotal biomedical systems biology tools and facilitating their translation into crucial therapeutic advances.

SysBioMed is a Specific Support Action (SSA) funded through the EC Framework Programme 6. The core objective was to explore the potential of systems biology for medical research, therapy and drug development. To produce this Science Policy Briefing on systems biology, SysBioMed took a novel approach, bringing together recognised group leaders and young researchers to identify and prioritise suitable application areas for systems biology within the medical sciences. The challenges, hurdles and opportunities for systems biology in medical applications were discussed in 10 thematic workshops. This Science Policy Briefing selects and summarises some of the conclusions and recommendations generated during the workshops and discussions among the authors of this report.

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Introduction

Conventional modes of medical and biological explanation rely primarily on linear, verbal reasoning, with little or no mathematical description, and are only suited to address mechanisms that involve small numbers of components and short chains of causality. Most diseases that affect humankind, however, involve a large number and variety of components interacting through complex networks and, consequently, show highly nonlinear dynamics. New approaches are therefore required to develop further advances in modern medicine. Systems biology provides a particularly promising avenue to tackle complex systems through an interdisciplinary approach that combines experimental work with mathematical modelling. In the medical sciences, systems biology has the potential to make important contributions, amongst others, to facilitate early diagnosis (e.g. through the identification of biomarkers); to understand the aetiology, progression and symptomatology of various diseases; to refine treatment protocols; to identify new drugs and therapies; to design and test novel medical devices and to improve personalised prognosis and treatment, finally realising the promises of personalised medicine.

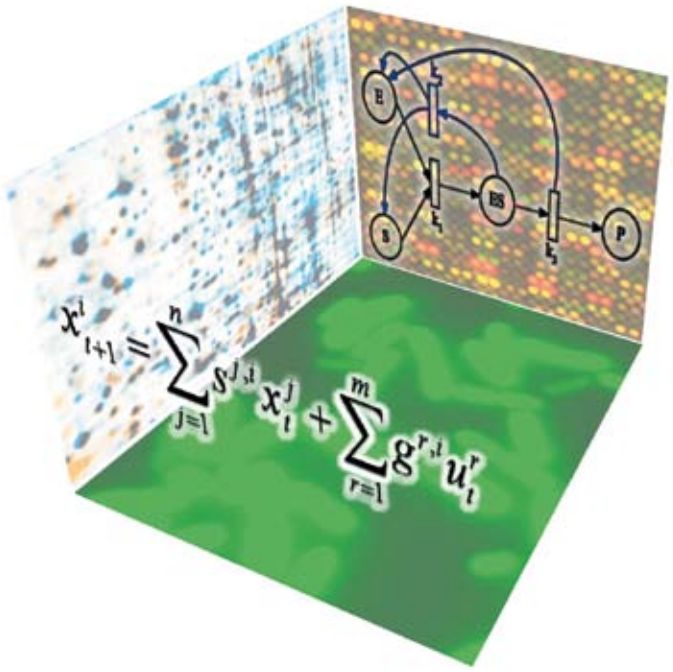

Figure 1. Systems Biology: integration of various data types leading to computational and mathematical modelling. Image courtesy of Professor Olaf Wolkenhauer.

Numerous reports and publications about advances within the rapidly growing field of systems biology have led to an abundance of alternative definitions for key concepts. In this report, the term *mathematical modelling* refers to the modelling and simulation of subcellular, cellular and macroscale phenomena, using primarily methods from dynamical systems theory. The aim of such models is to encode and test hypotheses about mechanisms underlying cell function. Typical examples are models for molecular networks, where the behaviour of cells is expressed in terms of quantitative changes in the levels of transcripts and gene products. Bioinformatics provides essential complementary tools, including procedures for pattern recognition, machine learning, statistical modelling (testing for differences, searching for associations and correlations), and secondary data extraction from databases.

Mathematical modelling enables the integration of biological and clinical data at various levels and, in doing so, has the potential to provide insight into complex diseases in the following ways:

- Modelling necessitates the statement of explicit hypotheses, a process which often improves our understanding of the biological system and can uncover critical points where understanding is still poor.
- Simulations can reveal hidden patterns and/or counter-intuitive mechanisms in complex systems.
- Theoretical thinking and mathematical modelling help generate new hypotheses that can be tested in the laboratory.

Dynamical systems theory is a mathematical tool to investigate complex biological systems demonstrating nonlinear spatio-temporal behaviour. However, the generation of experimental data suitable to parameterise, calibrate and validate such models is often time-consuming and expensive or not even possible with the technology available today.

In our report, we use the term *computational model* to refer to mathematical models that have been populated with information generated from bioinformatics resources. Hence, "the model" is then, in reality, an integrated collection of data and models from various (possibly heterogeneous) sources.

This Science Policy Briefing focuses on a selection of topics, which were identified as appropriate case studies for medical systems biology, and adopts a particular perspective that the authors consider important.

Application of Mathematical Modelling to Biomedical Problems

– First Success Stories for Systems Biology

The value and potential of systems biology is best illustrated by examples in which the formulation of a mathematical model was key for major scientific advances. A widely known and conceptually influential example is the work of Hodgkin and Huxley[3] on nerve impulses. Their groundbreaking findings, which led to the award of a Nobel Prize in 1963, would not have been possible without making computations based on a mathematical model. However, we do not need to look back 50 years. Recent success stories of the application of mathematical modelling include the following:

- The group led by Denis Noble constructed a virtual human heart model, connecting intracellular dynamics of electrical currents, receptors and channels with organ function as part of the Human Physiome Project. This model has been successfully used, for example, to predict side effects of drugs and to help design Ranolazine, an FDA-approved drug for treatment of chronic angina[4].
- Quantitative data was generated on the decay of the HIV virus load following combination therapy to treat AIDS. The corresponding mathematical models suggested a high turnover rate of the virus and made it possible to estimate the decay rates of free virus and infected cells. Such models can also be used to describe the HIV dynamics below detection levels and to predict the re-emergence of the virus following treatment[5,6].
- Similar models by Michor and colleagues succeeded in refining the targeted therapy of chronic myeloid leukaemia in the presence of Bcr-Abl fusion protein[7,8]. Likewise, hepatitis C viral dynamics were modelled to predict treatment responses[9,10].

The conclusions from these examples are:

- Success was achieved when quantitative data became available.
- Even simple mathematical models can be of practical use.
- The interdisciplinary process leading to the formulation of a model is in itself of intrinsic value.

The Value of Mathematical Modelling

In recent years, visionary whole-cell, whole-organ and whole-body modelling initiatives have emerged. Such models are built to analyse, simplify and reduce complex interactions, and to identify and quantify input–output relations as well as generic principles ("laws") that underpin the functioning of the corresponding systems. However, the value of models specifically tailored to answer particular research questions should not be overlooked. The use of cell-cycle models by the pharmaceutical industry, for instance, demonstrates that whole-cell models are not essential for evaluating the effect of phase-specific drugs.

Systems biology highlights the dynamic nature of the functioning or malfunctioning of cells in the development and progression of diseases. Although disease progression can be slow – sometimes a matter of years – it relies on cellular events, such as apoptosis, cell division, and differentiation that take place in a time scale of minutes or hours. In neurons, subcellular processes can occur in minutes or seconds. Hence, cells, organs and organisms rely on dynamic interactions between large numbers of components at and across different length- and time scales, the emergent behaviour being nonlinear in nature. The spatio-temporal dynamics of the system as a whole are of such complexity that their understanding challenges conventional approaches and makes mathematical modelling a necessity.

Mathematical modelling provides valuable *in silico* tools with which to carry out and iterate virtual experiments. One of the long-term goals of systems biology is to enable computational experiments that replace those that otherwise might be dismissed for being unethical, expensive, time consuming, or simply impossible. In an era in which computer requirements are no longer a serious limitation, the growing field of systems biology is expected to blossom even further, leading to fundamental breakthroughs in both biology and medicine. However, to overcome existing hurdles in medical systems biology and to form a new generation of scientific investigators and decision makers that can sustain these exciting developments, new targeted initiatives for research and training are required.

Promising Application Areas

A number of medical areas where systems biology applications look particularly promising were selected for more in-depth consideration in a series of workshops, organised as part of the Specific Support Action SysBioMed. The most important conclusions and recommendations arising from these workshops are highlighted below.

Cancer

Cancer is systemic by nature and reductionist approaches have failed to improve treatment and understanding substantially. Despite the variability in the nature of diseases related to cancer, it is expected that systems biology can make essential contributions to:

- The identification of early biomarkers for a non-invasive prognosis of tumour development.
- Personalised medicine by building computer models predicting different stages of the disease.
- Improving treatment of later stages by comparing biochemical networks and gene expression levels in primary tumours and metastases.

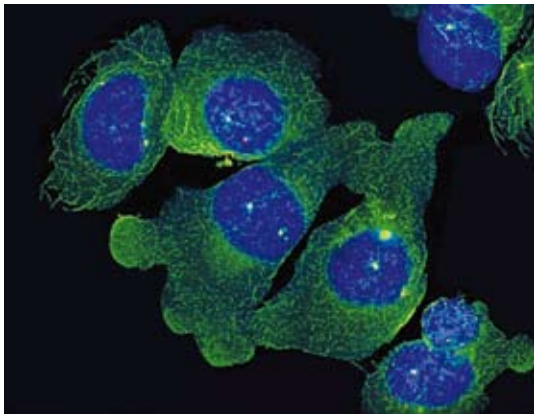

Figure 2. MCF-7 cells (human breast adenocarcinoma cell line) treated with the compound JJ58: tubulin (green), DNA (blue) and centrin (red). Image courtesy of Dr. Oliver Staples and Dr. Sonia Lain, Dept Surgery & Oncology, Ninewells Hospital, University of Dundee, UK. For further details, see reference 11.

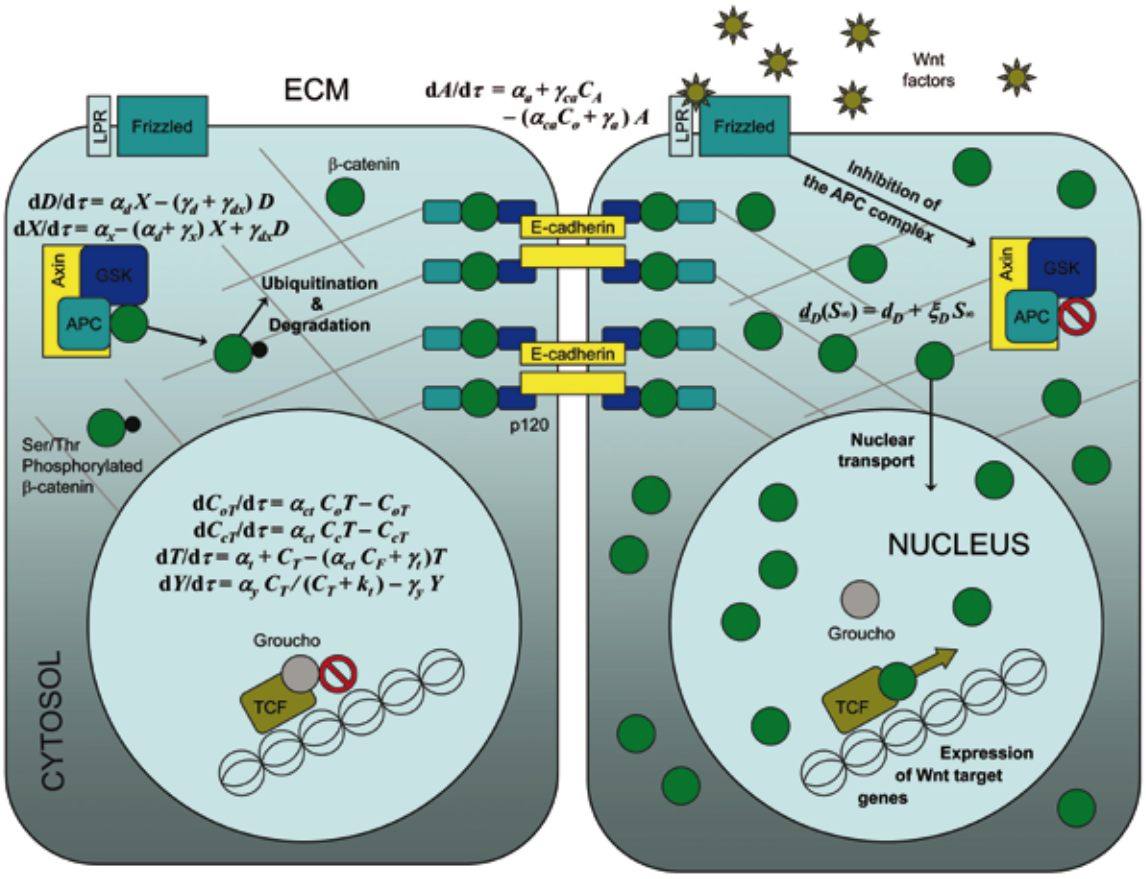

Figure 3. Simple schematic of the Wnt signalling pathway. The left and right cells illustrate the network in the absence and presence of extracellular Wnt factors, respectively. The figure and equations have been adapted from reference 12. Wnt signalling is involved in a wide range of physiological and pathological processes, including embryonic development, intestinal tissue renewal, Alzheimer's disease and various human cancers.

In cancer research, it is important to promote the use of mathematical and computational methods to integrate data on gene expression, phosphoproteomics, epigenetics and metabolomics. Linking such data to advanced models for fundamental processes (e.g. cell-cycle control, apoptosis and tumour growth) would also be beneficial. In addition, significant impact is expected from recent developments in proteomics and low-cost sequencing.

In the first instance, large-scale systems biology efforts should concentrate on specific cancer types that have high medical relevance, well-understood molecular pathology, high-quality experimental models and a variety of targeted therapies available. Systems biology is expected to provide new insights into the reason why certain therapies fail and thereby to help select the best anti-cancer drugs and their optimal treatment protocols.

We recommend to:

- Carry out studies on well-characterised, highly important cancer types such as colorectal cancer to better understand treatment responses by using models that encompass multiple spatio-temporal scales and data sets.
- Initiate systems biology projects focusing on tumour-induced angiogenesis using multi-scale mathematical modelling, incorporating biomechanical and fluid-dynamic effects.
- Invest further research effort in colorectal cancer modelling directed towards elucidating the interplay between the biochemical networks (e.g. Wnt, BMP, Notch, and Hedgehog pathways) involved in regulating normal intestinal tissue renewal and understanding how these networks become disregulated during the early stages of carcinogenesis.
- Fund projects that include comparisons of animal models, established cell lines and human samples. Such studies would require rethinking the existing funding schemes for large-scale projects at the EU level.

The Link between Cancer and Ageing

As the population of the EU gradually grows older, the social and economic strain posed by age-related diseases – such as cancer – is expected to become even greater. This prospect has created an urgent need for progress in the different areas of ageing research, with the ultimate goal of improving the quality of life of the elderly. Given that ageing is a complex multi-factorial process involving many biological and physiological phenomena, a multidisciplinary approach has become essential to integrate existing knowledge and, even more importantly, to generate new experimentally testable hypotheses. It is notable that, although cancer modelling and mathematical gerontology are both well-established areas of research, little theoretical effort has been specifically aimed at enhancing our understanding of the interrelations between ageing and cancer. A basic requirement, namely discriminating between time-dependent and ageing-dependent events, constitutes a major challenge.

We recommend to:

- Initiate interdisciplinary systems biology projects investigating the temporal, accumulative and integrative aspects of the ageing process that is caused by a gradual increase of molecular and cellular damage.
- Use mathematical modelling to elucidate the impact of cellular senescence on organismal ageing and malignant transformation, paying special attention to the role of stem-cell senescence and age-related changes in the stroma.
- Characterise quantitatively the behaviour of key molecular pathways that play a dual function in cancer and ageing, such as the p53/mdm2/sirtuin network and cell-cycle control.
- Exploit systems biology approaches to investigate the effect of caloric restriction on ageing, cancer onset and tumour growth.

Inflammatory Diseases

Inflammatory disorders encompass a large group of diseases, many of which are widespread, such as rheumatoid arthritis and asthma. A paradigm for the systemic nature of inflammation is its association with cancer. On the other hand, an inflammatory microenvironment may contribute to tumour progression, whereas an appropriate immune response is capable of suppressing or even eradicating tumours. Cytokine- and cell-based therapies for the treatment of chronic inflammation and anti-cancer immune therapies are being developed. Due to the complexity of the regulatory networks involved, the biological outcomes are not always predictable, sometimes leading to dramatic failures or considerable side effects. Systems biology approaches to inflammation research that create a bridge between the molecular and organism levels is feasible, as many tools for the necessary quantitative studies are available. These include advanced techniques to monitor molecular networks in primary immune cells, population dynamics of lymphocytes in animals and humans, and ready access to a great variety of mouse models. Moreover, multi-photon microscopy has recently been applied to image the dynamics of the immune system *in vivo*. Computational models are being developed for sub-modules at different levels, including signal transduction in lymphocytes and macrophages, lymphocyte differentiation and population dynamics.

We recommend to:

- Develop multi-scale computational models of the cytokine networks that control proliferation, homing, function, and survival of T lymphocytes and other inflammation-relevant cell types to predict the outcome of pharmacological intervention and cell-based therapy.
- Create tissue-specific *in vitro* and *in vivo* models to unravel the spatio-temporal dynamics of cell signalling and cellular organisation in inflammation and its interaction with cancer development.

Diabetes

Diabetes mellitus is rapidly becoming a global epidemic, especially type 2 diabetes and the associated metabolic syndrome(s), driven by the worldwide increase of obesity. The common varieties of both type 1 and type 2 diabetes are multifactorial polygenic diseases whose pathogenetic complexity has eluded conventional reductionist approaches. As a result, there are only a few efficacious drugs available apart from insulin, which is vital for people suffering from type 1 diabetes, and currently there is no cure or method of prevention. It is generally believed that the genetic basis of both type 1 and type 2 diabetes results from unfavourable combinations of multiple common gene alleles that determine beta cell function, susceptibility and survival, as well as metabolic homeostasis. Epigenetic factors probably also play a major role. Recent progress in genome-wide scans for association has started to reveal the genes that confer increased susceptibility to type 1 and 2 diabetes. The identity of these genes is often unexpected from a candidate gene viewpoint. A complete elucidation of these genes will make it possible to identify those nodes that have the most dramatic effect on the pathways essential for normal beta cell function and survival as well as insulin sensitivity and metabolic stability.

We recommend to:

- Build an integrated computational model of metabolic homeostasis that includes a quantitative description of the insulin signalling pathways and intercellular and tissue interactions. Such a model should account for the interplay between insulin sensitivity of target tissues and the beta cell secretory response and should integrate the “nodes” emerging from gene scans.
- Integrate data available on beta cell 3-D organisation, transcriptome, developmental paths, insulin secretion mechanisms, intracellular signalling by insulin, growth factors, GLP-1 and other regulators as well as apoptosis into an *in silico* virtual beta cell.
- Use the *in silico* 3-D beta cell to understand the particular vulnerability of the beta cell to processes that force it into a critical instability (e.g. cytokines and autoimmune processes in type 1 diabetes, and gluco- and lipo-toxicity in type 2 diabetes) and to investigate its response to drugs.

Chronobiology and Chronotherapy

Organisms have developed biological clocks that enable them to adapt to the 24 hour period of the solar day. The so-called circadian clocks are autonomous oscillators that regulate the temporal organisation of physiology, metabolism and behaviour. Hence, the dynamics of proliferation, metabolism, brain activity and immune response are strongly influenced by the circadian clock. The master clock located in the hypothalamus is driven by transcriptional–translational feedback loops. DNA arrays reveal that hormone secretion, sympathetic innervation, body temperature, feeding time and activity rhythms influence about 10% of all genes in peripheral tissues including cell-cycle regulators, cytokines, and genes involved in detoxification. A first generation of mathematical models is already available to simulate the hierarchical organisation of circadian rhythms.

The dynamics of cell proliferation, metabolism, brain activity and immune response are strongly influenced by circadian rhythmicity. Consequently, advanced mathematical models describing tissues in health or disease should account for daily variations of gene expression, metabolism and behaviour. Chronotherapy (i.e. an optimisation of dose–time medication schedules), has been successfully applied for decades. The response to chemotherapy exhibits a circadian rhythm since the proliferation of both normal and cancer cells is gated by the circadian clock, with cancer cells being less well synchronised. Moreover, the detoxification of cytostatic drugs depends on the time of their administration.

We recommend to:

- Focus on quantitative measurements of circadian rhythms in single cells, peripheral tissues and patients (“chronosensors”).
- Implement a systems biology approach by dynamic modelling of the circadian regulation of cellular metabolism and drug detoxification.
- Optimise the therapeutic index of a priority list of drugs by simulation of chronotherapeutic schedules.

Disorders of the Central Nervous System

Neuropathologies affecting basal ganglia, and in particular the dopaminergic system and its targets, form a major public health problem. The prevalence of neurodegenerative or neurodevelopmental diseases, such as Parkinson's disease, Huntington's chorea or schizophrenia, is increasing, in particular due to the ageing of western societies. Many behavioural disorders that share the same biological substrate, such as drug addiction, depression, obsessive compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), Tourette syndrome, are also increasing.

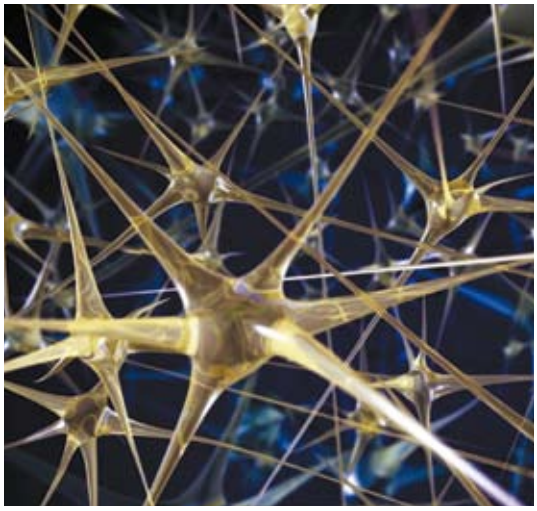

Figure 4. Symbolised neuronal networks (iStockphoto)

Many of these neuropathologies are in fact multifactorial diseases (e.g. Parkinson's disease or schizophrenia). However, the conjunction of genome wide analyses and cellular assays reveals that multiple causes can be linked through common signalling and metabolic pathways, for which a systems biology approach would be manifestly suited. Although both the pathogenesis and symptomatology of these disorders seem very different, the technological bottlenecks faced when developing an systems biology approach are similar. Furthermore, they will all benefit from quantitative descriptions of the same biological systems.

Based on the societal impact, the possibilities of the current technology, the availability of existing animal models, the access to patients and the existing and foreseeable modelling effort, it is recognised that a systems biology approach would be most useful if applied to studying Parkinson's disease, schizophrenia and drug addiction.

We recommend to:

- Initiate large-scale data gathering, centralised in a few experimental facilities, to obtain standardised information about the protein content of three major cell populations: mesencephalic dopamine neurons, striato-nigral ("D1") medium-spiny neurons and striato-palidal ("D2") medium-spiny neurons. This large-scale effort should determine at least: the proteome, the interactome, the concentration of the proteins and their subcellular locations within these cells.
- Apply a systematic approach to Parkinson's disease and drug addiction first as the understanding of schizophrenia is still in its infancy.

Integration of Experimental and Theoretical Approaches – Appropriate Data Generation for Advanced Modelling in Systems Biology

The limited availability of *high-quality quantitative data* still constitutes a major bottleneck for the application of mathematical modelling in biology and medicine. The generation of such data (e.g. quantitative proteomics) is more costly and time consuming than conventional experiments, making it nearly impossible for small research teams. Therefore, we recommend the creation of interdisciplinary centres of advanced technologies, including high-throughput DNA sequencing, metabolomics, proteomics and phosphoproteomics (SILAC, high-throughput mass spectrometry, capillary isoelectrofocusing), advanced antibody-based methods using array and FACS* technology, HT** microscopy/imaging, protein–protein interactions, combined RNAi, to promote efficient standardisation, access and sharing of data.

The *integration of data and models* is vital.

* FACS: fluorescence-activated cell sorting
** HT: high throughput

We recommend to:

- Generate comparative studies and foster integration of knowledge gained from different experimental model systems (cell lines, animal models, patient samples).
- Merge mathematical models of gene expression, regulation, signal transduction and metabolic networks (multilevel modelling).
- Combine different conceptual frameworks for mathematical modelling (e.g. deterministic/stochastic and discrete/continuum models).
- Couple information from bioinformatics resources, data mining and pattern recognition with dynamic models.
- Integrate models at different temporal and spatial scales (multiscale modelling). This involves the integration of functional models (e.g. signalling) and structural models (e.g. tumour growth).

Creating Dynamic Models of Biological Processes

A core component of medical systems biology is the ability to create dynamic models of biological processes. Several fundamental biological processes play a central role in more than one of the diseases discussed here. Among these processes are cell division, differentiation, programmed cell death (apoptosis) and signalling from the cell surface to the nucleus (signal transduction). The common interest in these phenomena makes understanding the networks responsible for their regulation a priority for systems biology research. Notably, although they involve molecular interactions taking place in a timescale ranging from nanoseconds to hours or days, these networks can affect disease processes that evolve over years or even decades. Formulating a multiscale model for a given disease thus implies the challenge of incorporating models describing molecular dynamics over short time intervals into long-term macroscale models. It is unfeasible to retain the fine level of detail at the subcellular level. Yet there are slow, macro-scale processes that can influence fast, subcellular events, and vice-versa.

Analogous issues arise when dealing with morphological and spatial features. In some scenarios, spatial effects are negligible, whereas in others they influence the behaviour of a system substantially. Cells can function differently depending on their location within an organ or tumour and signal transduction pathways can be switched on or off depending on the cell's shape and size. Again, this creates a need to divide the system into parts that can be modelled separately and then decide how to combine the results. In systems biology, assembling various parts is not only an issue for modellers. An intrinsic fragmentation needs also to be overcome on the experimental side. Different cellular processes, for example, tend to be studied in relative isolation by independent experimental groups, using different sets of techniques. Yet it is certain that these processes are inter-linked within the cell.

We recommend to:

- Foster and invest in systems biology approaches aimed at gaining insight into the regulation of fundamental phenomena (e.g. gene expression, cell cycle, apoptosis, and cellular metabolism).
- Prioritise endeavours focused on developing new strategies for coupling/embedding different models, formulated using different methodologies and describing phenomena occurring at very different time and length scales, into complex multiscale models.
- Establish model formulation standards to facilitate spatio-temporal integration.
- Encourage leading medical journals to support systems biology approaches.
- Promote cooperative interdisciplinary research, not only between modellers and experimentalists, but also between experimentalists working in different topic areas. The use of different methods and technologies results in operational divisions between research groups focusing on different cellular processes. This leads to discontinuities in the type, quality and extent of the information available to modellers. Integrated projects are the best way to overcome these problems.
- Fund the design of novel techniques for data-based system identification including theoretical concepts for the design of experiments, hypothesis testing and effective algorithms to solve problems of computational complexity and analysis.

Conclusions and Perspectives

The nascent field of systems biology has recently shown signs of moving from hype to hope for meaningful applications in biomedical sciences and drug discovery. While a number of fora have attempted to address the issue of practical medical applications of systems biology[13], the SysBioMed Specific Support Action has cast a wide net by gathering 110 key opinion leaders in specific biomedical areas and in mathematical modelling in 10 international workshops over one and a half years, to define the most promising early potential medical applications of systems biology, resulting in this Science Policy Briefing. We believe that if the recommendations contained in this document are successful in stimulating European institutions into supporting their implementation, this will propel Europe to the forefront of this fast developing field and help systems biology to fulfil its promise in making reality of personalized medicine, combinatorial therapy, shortened drug discovery and development, better targeted clinical trials, reduced and even alternatives to animal testing.

Acknowledgements

SIXTH FRAMEWORK PROGRAMME

SysBioMed is a EU FP6 funded Specific Support Action (SSA LSSG-CT-2006-037673), supported by the Directorate F: Health Research, Unit F.4: Genomics and Systems Biology. The project was initiated by Dr. Rosita Cottone (German Federal Ministry for Education and Research) and supervised by Dr. Frederick Marcus (European Commission). The co-applicants for the proposal were Professor Olaf Wolkenhauer (University of Rostock, scientific coordinator), Dr. Carole Moquin-Pattey (European Science Foundation – European Medical Research Councils), Dr. Astrid Lunkes (European Science Foundation – Life, Earth and Environmental Sciences) and Dr. Karsten Schürrle (Dechema e.V., project management). The core objective is to explore the potential of systems biology for medical research, therapy and drug development. More than 110 experts participated in 10 workshops. In addition, two summer schools were organised to reach out to young researchers.

More information on SysBioMed at:
www.sysbiomed.org

Contributors to Strategic and Thematic Workshops

The workshops are listed in a chronological order, not reflecting the order of those thematic areas that were highlighted in the text. The experts listed below contributed to the strategic and thematic workshops.

1st Strategic Workshop (February 2007)

Julio Banga (CSIC, Vigo, Spain), Nils Blüthgen, (University of Manchester, UK), Eric Bullinger (National University of Ireland), Marta Cascante (University of Barcelona, Spain), Rosita Cottone (BMBF, Germany), Pierre De Meyts (Hagedorn Research Institute Gentofte, Denmark), Diego di Bernado (TIGM, Italy), Maike Heidelberger (Projektträger Jülich, Germany), Hanspeter Herzel (Humbold University, Berlin, Germany), Thomas Höfer (DKFZ, Heidelberg, Germany), Robert Jaster (University of Rostock, Germany), Nicolas le Novère (EBI, Cambridge, UK), Astrid Lunkes (ESF, France), Ole Petter Ottersen (University of Oslo, Norway), Jochen Prehn (RCSI, Dublin, Ireland), Markus Rehm (RCSI, Dublin, Ireland), Karsten Schürrle (DECHEMA, Frankfurt, Germany), Veronika Simons (Projektträger Jülich, Germany), Jacky Snoep (Vrije University Amsterdam, The Netherlands), Jörg Stelling (ETH, Zürich, Switzerland), Jesper Tegner (Karolinska Institute, Sweden), Nestor Torres-Darias (La Laguna University, Spain), Mike White (University of Liverpool, UK), Olaf Wolkenhauer (University of Rostock, Germany).

Basal Ganglia Disorders (July 2007)

Nicolas le Novère (Chair, EBI, Cambridge, UK), Upinder Bhalla (NCBS, Bangalore, India), Jan G. Bjaalie (Karolinska Institute, Sweden), Thomas Bruhn (ESF, France), Rosita Cottone (BMBF, Germany), Jürgen Gallinat (Charité Berlin, Germany), Jean-Antoine Girault (INSERM, Paris, France), Jens Pahnke (University of Rostock, Germany), Kevin Guerney (University of Sheffield, UK), Jochen Prehn (RCSI, Dublin, Ireland), Serge Schiffmann (University of Brussels, Belgium), Karsten Schürrle (DECHEMA, Frankfurt, Germany), Guus Smith (Vrije University Amsterdam, The Netherlands), Olaf Wolkenhauer (University of Rostock, Germany).

Inflammatory Diseases (September 2007)

Thomas Höfer (Chair, DKFZ, Heidelberg, Germany), Philip Ashton-Rickards (Imperial College London, UK), Rosita Cottone (BMBF, Germany), Mathias Gstaiger (ETH, Zurich, Switzerland), Ursula Klingmüller (DKFZ, Heidelberg, Germany), Thomas Bruhn (ESF, France), Max Löhning (University Medicine Berlin, Germany), David Rand (University of Warwick, Coventry, UK), Karsten Schürrle (DECHEMA, Frankfurt, Germany), Edgar Serfling (Institute of Pathology, Würzburg, Germany), Maciej Swat (Biosystems Informatics Institute, Newcastle upon Tyne, UK), Mike White (University of Liverpool, UK), Olaf Wolkenhauer (University of Rostock, Germany).

Dynamic Principles of Cell Function (October 2007)

Frank Bruggemann (Chair, Vrije University, Amsterdam, The Netherlands), Nils Blüthgen, (University of Manchester, UK), David Fell (Oxford Brookes University, UK), Mark Girolami (University of Glasgow, UK), Astrid Lunkes (ESF, France), Elmar Nimmesgern (BMBF Berlin, Germany), Karsten Schürrle (DECHEMA, Frankfurt, Germany), Jacky Snoep (Vrije University Amsterdam, The Netherlands), Denis Thieffry (INSERM, Marseille, France), Ingeborg van Leeuwen (University of Nottingham, UK), Darren Wilkinson (Newcastle University, UK), Olaf Wolkenhauer (University of Rostock, Germany).

Cancer (November 2007)

Nils Blüthgen (Chair, University of Manchester, UK), Marta Cascante (University of Barcelona, Spain), Andrea Ciliberto (IFOM, Milan, Italy), Dirk Drasdo (INRIA, Paris, France), Jorrit Hornberg (NV Organon, The Netherlands), Robert Jaster (University of Rostock, Germany), Philippe Lenormand (CNRS, Nice, France), Carole Moquin-Pattey (ESF, France), Christine Sers (Charité Berlin, Germany), Karsten Schürrle (DECHEMA Frankfurt, Germany), Maciej Swat (Biosystems Informatics Institute, Newcastle upon Tyne, UK), Ingeborg van Leeuwen (University of Dundee, UK), Olaf Wolkenhauer (University of Rostock, Germany).

Diabetes (January 2008)

Pierre De Meyts (Chair, Hagedorn Research Institute, Gentofte, Denmark), Mikael Benson (Queen Silvia Children's Hospital, Gothenburg, Sweden), Thomas Bruhn (ESF, France), Marta Cascante (University of Barcelona, Spain), Rosita Cottone (BMBF, Germany), Bert Groen (Academic Medical Center Amsterdam, The Netherlands), Thomas Illig (National Research Center for Environment and Health, Germany), Kaspar Lage (Technical University of Denmark), Xiaohui Liu (Brunel University, UK), Jim McGuire (Steno Diabetes Center, Gentofte, Denmark), Jorn Nerup (Steno Diabetes Center, Gentofte, Denmark), Elmar Nimmesgern (BMBF Berlin, Germany), Flemming Pociot (Steno Diabetes Center, Gentofte, Denmark), Karsten Schürrle (DECHEMA Frankfurt, Germany), Markus Tiedge (University of Rostock, Germany), Roel van Driel (University of Amsterdam, The Netherlands), Olaf Wolkenhauer (University of Rostock, Germany).

The Cancer-Ageing Link (February 2008)

Ingeborg van Leeuwen (Chair, University of Dundee, UK), Julio Vera (Chair, University of Rostock, Germany), Rosita Cottone (BMBF, Germany), Alberto d'Onofrio (European Institute of Oncology, Milan, Italy), Stephen Downes (University of Ulster, UK), Georg Fuellen (Ernst Moritz Arndt University, Germany), Irmgard Irminger-Finger (University Hospitals Geneva, Switzerland), Bas Kooijman (Vrije University Amsterdam, The Netherlands), Sonia Lain (University of Dundee, UK), Astrid Lunkes (ESF, France), Carol Proctor (Newcastle University, UK), Karsten Schürrle (DECHEMA Frankfurt, Germany), Olaf Wolkenhauer (University of Rostock, Germany).

Chronobiology/Chronotherapy (February 2008)

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Colorectal Cancer (April 2008)

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2nd Strategic Workshop (September 2008)

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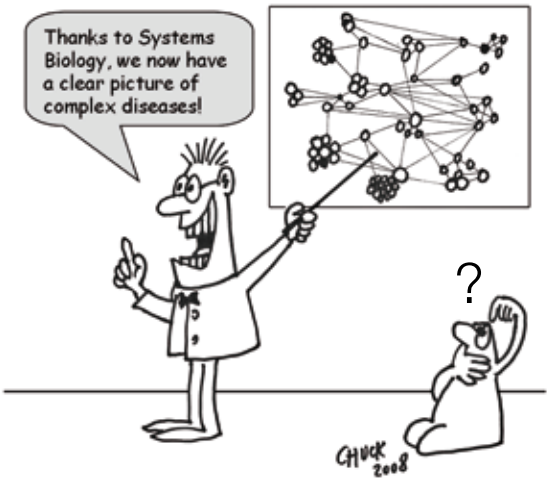

Figure 5. Original drawing made for SysBioMed by one of the members of the writing team (PdM)

References

1 ESF Forward Look report Systems Biology: a grand challenge for Europe, 2007 (download at: www.esf.org/publications/forward-looks.html)

2 ESF Taskforce report on Systems Biology, 2007 (download at: www.esf.org/publications.html)

3 http://nobelprize.org/nobel_prizes/medicine/laureates/1963/

4 Noble D. Computational models of the heart and their use in assessing the actions of drugs. *J Pharmacol Sci* **107**: 107–117, 2008

5 Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 Dynamics *in vivo*: Virion Clearance Rate, Infected Cell Life-Span, and Viral Generation Time. *Science* **271**: 1582–1586, 1996

6 Nowak MA, Anderson RM, Boerlijst MC, Bonhoeffer S, May RM, McMichael AJ. HIV-1 evolution and disease progression. *Science* **274**: 1008–1011, 1996

7 Michor F, Hughes TP, Iwasa Y, Branford S, Shah NP, Sawyers CL, Nowak MA. Dynamics of chronic myeloid leukaemia. *Nature* **435**: 1267–1270, 2005

8 Abbot, LH, Michor F: Mathematical models of targeted cancer therapy. *Br J Cancer* **95**:1136–1141, 2006

9 Neumann A.U, Lam N, Dahari H, Gretch DR, Layden TJ, Perelson AS. Hepatitis C viral dynamics *in vivo* and the anti-viral efficacy of interferon therapy. *Science* **282**: 103–107,1998

10 Layden TJ, Layden JE, Reddy KR, Levy-Drummer RS, Poulakos J, Neumann AU. First phase viral kinetic parameters as predictors of treatment response and their influence on the second phase viral decline. *J Viral Hepatitis* **9**: 340–345, 2002

11 Staples OD, Hollick JJ, Campbell J, Higgins M, McCarthy AR, Appleyard V, Murray KE, Baker L, Thompson A, Ronseaux S, Slawin AMZ, Lane DP, Westwood NJ, Lain S Characterization, chemical optimization and anti-tumour activity of a tubulin poison identified by a p53-based phenotypic screen, *Cell Cycle* **7**: 3417-3427, 2008.

12 IMM van Leeuwen, HM Byrne, OE Jensen, JR King Elucidating the interactions between the adhesive and transcriptional functions of beta-catenin in normal and cancerous cells, *J Theor Biol* **247**: 77-102, 2007

13 Henney A and Superti-Furga G. A network solution. *Nature*, **455**:730-731, 2008.

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