The Academy of Medical Sciences

The Royal Academy of Engineering

Systems Biology: a vision for engineering and medicine

A report from the Academy of Medical Sciences
and The Royal Academy of Engineering

February 2007

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Acknowledgements

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This report is published by the Academy of Medical Sciences and The Royal Academy of Engineering and has been endorsed by their Officers and Council. Contributions by the working group and respondents to the call for evidence are made purely in an advisory capacity. The review group added a further 'peer-review' stage of quality control to the process of report production. The members of the working group, the review group and the consultation respondents participated in this report in an individual capacity and not as representatives of, or on behalf of, their affiliated hospitals, universities, organisations or associations (where indicated in the appendices). Their participation should not be taken as endorsement by these bodies.

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Foreword

Sir Colin Dollery

Professor Richard Kitney

Understanding the function of complex biological systems is one of the greatest challenges facing science. The rewards of success will range from better medicines to new engineering materials. The sequencing of the human genome, although of fundamental importance, does not even provide a complete parts list of the protein molecules that exist in a biological organism because of complexities of downstream processing and complex folding required to make a functioning receptor or enzyme from a long chain of amino acids. Furthermore, protein molecules do not function alone but exist in complex assemblies and pathways that form the building blocks of organelles, cells, organs and organisms, including man. The functioning of brain or muscle, liver or kidney, let alone a whole man, is much greater than the sum of its parts.

To tackle this problem requires an iterative application of biomedical knowledge and experiment with mathematical, computational and engineering techniques to build and test complex mathematical models. Systems and control engineering concepts, a modular approach and vastly increased computing capacity are of critical importance. The models, once developed and validated, can be used to study a vastly greater range of situations and interventions than would be possible by applying classical reductionist experimental methods that usually involve changes in a small number of variables. This new approach is now termed "Systems Biology".

In addition to the impact that Systems Biology is likely to have in biomedical sciences, significant potential exists in relation to its wider application in engineering and the physical sciences both directly and via the associated field of Synthetic Biology. Such is the importance of Systems Biology to the economy and to the future of both biomedical science and engineering that the Academy of Medical Sciences and The Royal Academy of Engineering established a working party under our joint chairmanship to enquire into the present situation in the United Kingdom and to make recommendations for the future. The working party noted with approval the groundwork of the BBSRC and EPSRC in the application of Systems Biology to molecules and cells and identified great opportunities for developing Systems Biology applications to whole organs, complete organisms and particularly to man. The report outlines those opportunities, recommends substantially increased investment and considers the financial, organisational, manpower and educational developments that will be needed. It is primarily aimed at policy and decision makers in a range of fields. This constituency comprises government, industry, Research Councils, other grant giving bodies (eg. Wellcome Trust), the Fellowships of the two Academies, the medical Royal Colleges and universities. It is also anticipated that the report will be of considerable interest to international bodies such as the European Commission and the World Health Organisation.

In an world increasingly dependent upon R&D and knowledge, Systems Biology is an area in which the United Kingdom must compete if it is to secure economic progress.

Sir Colin Dollery

Professor Richard Kitney

Summary

Systems Biology is a groundbreaking scientific approach that seeks to understand how all the individual components of a biological system interact in time and space to determine the functioning of the system. It allows insight into the large amount of data from molecular biology and genomic research, integrated with an understanding of physiology, to model the complex function of cells, organs and whole organisms, bringing with it the potential to improve our knowledge of health and disease.

Systems Biology has become a viable approach as a result of recent developments in the biological sciences, systems engineering, imaging, mathematics and computing. It uses an iterative cycle of computational modelling and laboratory experiment to understand how the components work together in a system, a characteristic feature of Systems Biology. This method offers a wealth of opportunities across medicine, engineering and other fields. One of its most immediate impacts will be in the pharmaceutical sector where, by means of a more effective drug development process, Systems Biology will bring innovative drugs to patients more quickly and cheaply. It will be a vital tool in elucidating the many interacting factors that contribute to the causes of common medical conditions, in the near-term yielding important information on cardiovascular disease and liver function and, in the longer term, increasing our understanding of cancer and dementia. Systems Biology will provide a platform for the development of Synthetic Biology: the design and re-design of biological parts, devices and systems with applications ranging from materials with enhanced properties to biofuels.

The US currently leads the world in many aspects of systems biology research. Growth is also rapid in Japan and several other EU countries. Against this background, UK systems biology research is patchy. The recent and welcome Biotechnology and Biological Sciences Research Council (BBSRC)/Engineering and Physical Sciences Research Council (EPSRC) investment in Systems Biology of molecules and cells has not been matched by a corresponding investment in organ systems and whole organisms. Growth in Systems Biology is threatened by the serious decline in UK capacity in its underpinning disciplines, including many of the physiological, pharmacological, engineering, mathematical and physical sciences. The interdisciplinary nature of Systems Biology also presents a challenge to the traditional structure of UK academic research and training, as well as to current arrangements for research funding and assessment. Interdisciplinarity is an increasingly important feature of most scientific research, but there is an urgent need to catalyse activity at these new interfaces and so avoid important aspects of this work falling into gaps between university departments and research funders.

Recent initiatives by the BBSRC and the EPSRC have undoubtedly energised UK systems biology research at the level of cells and proteins. Nevertheless, there are vast unexploited opportunities at the levels of tissues, organs and whole organisms, particularly in medicine and the pharmaceutical/biotechnology industries, as well as in the emerging field of Synthetic Biology. Failure to build the systems and synthetic biology research base will have important consequences for UK science and ultimately for public health and economic prosperity. Without sufficient UK capability, top researchers will be attracted abroad. Industry could also look to the US, South Asia and the Far East for research and development opportunities.

The potential of Systems Biology will only be realised if the UK Government takes determined and prompt action. There is a pressing need for a major and sustained initiative to build capacity in terms of human capital, research infrastructure and additional resources. Future generations of systems biologists will require formal training in biological, engineering and mathematical sciences, with undergraduates exposed to interdisciplinary problems while being trained in a core discipline. New and extended postgraduate courses in Systems Biology should be created, along with an expansion in postdoctoral opportunities. New centres of excellence should be established to build capacity and pursue research in areas that are not being explored by existing or planned initiatives. In bidding for these new centres, universities should specify their plans to address the structural, organisational and human resource issues known to hinder interdisciplinary research.

Ensuring that the UK secures an internationally competitive position in Systems Biology requires substantial new investment by government and industry, together with a change in attitudes and working practices in the universities. Central to success will be the coordination of activities across academia, industry, research funders, the NHS and government. Systems Biology will inevitably become an approach that pervades scientific research, in much the same way that molecular biology has come to underpin the biological sciences. It will transform the vast quantities of biological information currently available into applications for engineering and medicine. The recommendations in this report represent essential steps towards the realisation of this potential.

Recommendations

Systems Biology: its role in advancing knowledge and building the nation's wealth
Systems Biology, the iterative application of mathematical modelling and engineering systems analysis to biological and medical systems, promises to transform our understanding of physiology and medicine and yield wide-ranging applications in engineering, biotechnology, pharmaceutical development, clinical medicine and public health. It is of critical importance in building the nation's wealth. Such is its relevance that the two Academies recommend a major additional investment, in addition to that already being made by the BBSRC and the EPSRC.

1. Establish a number of new major systems biology centres in the UK
The new centres should be located within leading universities that have internationally competitive research in biology, medicine, engineering and physical sciences. They must be a focus of activity effectively networked to smaller centres in other universities, including those currently being established by the BBSRC and the EPSRC, and linked to international initiatives. It is essential that centres seek collaborations with industry and the NHS to ensure that projects of high national economic importance receive priority. Systems Biology is destined to become a pervasive scientific approach and advancing this objective should form part of the mission statement of the centres. Centres must be outward looking and avoid becoming scientific ghettos. Their remit should focus on world-class research, ranging from basic science to clinical practice and industrial products, and should include formal training and education (i.e. Masters and PhD programmes) in Systems Biology (including Synthetic Biology, which involves the design and re-design of biological parts, devices and systems - with applications ranging from materials with enhanced properties to biofuels). The programme for each individual centre should reflect the strengths of the university (or universities) taking part, but each centre will need to have a mixture of biology and medicine on the one hand and engineering, physical sciences and mathematics on the other.

Funding should be allocated on the basis of competitive bids to Research Councils UK and centres should be chosen to tackle a wide range of challenging research topics. Examples of topics that might form part of the work of centres include: the toxicity and safety of medicines; the function of neuronal synapses; the growth of human cancers; ageing; and the spread of infections in hospitals. However, this list is neither comprehensive nor exhaustive and is not intended to limit applicants. The example of the BBSRC and the EPSRC might be followed with a first phase succeeded by one or more additional phases. Engineering research, particularly in the field of Synthetic Biology, is set to grow rapidly and must form a significant part of the work of some of the centres proposed in this initiative.

2. Additional investment
An investment of approximately £325m is required over a period of 10 years to establish three to five new centres. This consists of approximately £75m for initial capital costs to be spent over the first three years, and £24m per annum as recurrent expenditure. The size of each centre may vary. It is estimated that, at current prices, a centre capable of housing between 30 and 35 scientists and support staff, as well as up to 30 doctoral students, would have a core recurrent budget of £5m a year, including consumables. Additional costs would be incurred for equipment, constructing new buildings or adapting existing facilities. A capital budget of about £15m per centre would be necessary to meet this expenditure, although, as far as possible, existing resources should be re-deployed by the host university. Centres of

this size would provide sufficient capacity to work on one major project and one or two subsidiary projects. After 10 years, successful centres should be progressively integrated into their host university.

The new initiative would be more costly than the present BBSRC/EPSRC programme because of the inclusion of projects involving a substantial engineering and medical component. Hence, additional government support is needed to realise this important opportunity for the UK. Partnerships should also be sought to offset part of these costs through strategic collaborations with industry, medical charities, the MRC, NHS R&D and the DTI.

3. Interdisciplinary research environment

Universities bidding for one of the new centres should be required to specify their plans for addressing the structural, organisational and human resource issues that are known to hinder interdisciplinary research. Implementation of these plans would be a condition of a successful grant application.

The interdisciplinarity of Systems Biology poses a challenge to the traditional structure of university departments and the current arrangements of research grants committees in the public, private and charity sectors. Academic organisation, funding streams and research assessment mechanisms must evolve to encourage growth of interdisciplinary research activities such as Systems Biology. This needs to be reflected in approaches to leadership, career development, peer review and publication criteria. Universities must break down barriers between disciplines and consider new methods of organisation that promote the development of novel scientific approaches. A substantial change in culture is required, in which biology and medicine become more quantitative. The Research Assessment Exercise, as currently structured, continues to be a barrier to interdisciplinary research.

4. Interdisciplinary skills

Given the urgent need to develop the skills required to undertake Systems Biology, new postgraduate courses and the expansion of postdoctoral opportunities should be created. For instance, undergraduates, including medical students, should be offered options in the core disciplines that support Systems Biology, as well as increased exposure to interdisciplinary problems and modules.

Further urgent action is needed to revive subjects important to the development of Systems Biology such as physiology, pharmacology, engineering and mathematics. Such initiatives in education and training should be closely coordinated with programmes in the BBSRC/EPSRC centres.

Systems Biology is not simply an exercise in mathematical modelling: it requires a deep knowledge of the complexities of the biomedical problem being addressed, together with a thorough understanding of the power and limitations of the engineering and mathematical concepts being used. Courses in biology and medicine for engineers, mathematicians and physical scientists are crucial, but they must be combined with an expansion of mathematical training for biological and medical scientists to develop multi-skilled, interdisciplinary teams. Initially, in view of the shortage of trained personnel in the UK, there may be a need to create schemes that establish a new cadre of young systems biologists, involving overseas recruitment where necessary.

1. Introduction

'…we need to overcome the idea, so prevalent in both academic and bureaucratic circles, that the only work worth taking seriously is highly detailed research in a speciality. We need to celebrate the equally vital contribution of those who dare to take what I call "a crude look at the whole".'

Murray Gell-Mann, Nobel Laureate in Physics, 1994

1.1 Background

Groundbreaking developments in the biological sciences over the past 50 years have dramatically improved our understanding of human health and disease, an important example being the publication of the initial sequence of the human genome. This remarkable progress in biology has been accompanied by equally important developments in imaging technologies, systems engineering, signal processing, mathematical biology, computation and in our ability to model, design and realise ever more complex systems.

The genetic code (specifying the proteins that form the main building blocks of all life) has been likened to a parts list for an engineering project. The reality is, however, that only very limited information about function can be deduced directly from the genome. Knowledge derived from the genome has already had an enormous impact on biology and medicine but, whereas the individual function of some proteins may be well known, the interactions between the many proteins that constitute a system and how they function together are poorly understood. This is attributable to a distinctive feature of biological systems, that of 'emergent behaviour', whereby the whole is more than the sum of its parts.

Scientists are now facing the challenge of turning the vast quantities of descriptive information from the revolution in molecular biology into useful knowledge that can aid the understanding of the overall function and behaviour of systems. Hence, we are now entering a new era of biology and medicine where the mechanisms that underpin health and disease at the levels of genes, proteins, cells, organs, physiological systems and whole organisms are being progressively uncovered. The complexity and interrelationships of these systems challenge standard ways of scientific description and understanding and require a new paradigm – Systems Biology – an approach underpinned by the life, physical and engineering sciences.

Systems Biology assimilates the advances in these fields to create an innovative and powerful scientific approach. It will become pervasive and influential throughout biology, medicine and engineering, in a manner similar to the way in which molecular biology underpins much of biomedicine today.

1.2 Defining Systems Biology

Systems Biology is an emerging methodology that has yet to be defined. Nevertheless, what most people would describe as 'Systems Biology' is being applied in many different contexts. A MedLine search for 'Systems Biology' in 2000 revealed fewer than 10 papers[1]. In early 2006, a similar search produced nearly 700 papers. Rather than providing a rigid definition that might quickly be overtaken by scientific advances, this report offers instead a working definition so that its future impact and opportunities can be considered.

For the purposes of this report, **Systems Biology** is defined as the quantitative analysis of the dynamic interactions between several components of a biological system and aims to

1 Levesque & Benfey, 2004

understand the behaviour of the system as a whole, as opposed to the behaviour of its individual constituents. It applies the concepts of systems engineering to the study of complex biological systems through iteration between computational and/or mathematical modelling and experimentation.

Thus, unlike much of traditional reductionist biomedical sciences, Systems Biology investigates the functioning of a biological system as a whole, rather than studying individual components in isolation. It is underpinned by many disciplines including engineering, medicine, biology, physiology, pharmacology and chemistry, computing, mathematics and physics. In addition, it draws upon and often contributes to bioinformatics, mathematical biology and the 'omic' sciences.

1.3 The promise of Systems Biology

Systems Biology will affect many areas of the biomedical sciences, healthcare and engineering. The recent Government strategy on 'Best Research for Best Health' emphasises the importance of translating world-class research into clinical practice, to which Systems Biology can contribute considerably[2]. In the near future, positive outcomes are likely to be first observed in the pharmaceutical sector where Systems Biology can advance the research and development of new and specific drug targets, thus contributing to the move towards personalised medicine.

Systems Biology bridges the gap between biology and engineering, utilising fundamental principles such as systems analysis, control and signal theory from the latter. In return, Systems Biology provides the foundation for the development of **Synthetic Biology**: the design and construction of new biological parts, devices and systems, and the re-design of existing, natural biological systems for useful purposes[3]. In the long-term, advances in this field will provide innovative engineering solutions (e.g. stronger and lighter materials) that have the potential to drive wealth creation in several industry sectors.

The UK Government's Science and Innovation Investment Framework 2004-2014 identifies Systems Biology as an exemplar of multidisciplinary research and an area where the UK has current world-class strength and could develop a lead. Although figures demonstrating the benefits of Systems Biology are not given, the following are identified as some of the key outcomes[4]:

- A skills base that is fit for the future - a critical mass of highly skilled researchers able to function to a high standard in a multidisciplinary research environment.
- More effective therapeutics that tackle the underlying causes of disease rather than treating the symptoms - pharmaceuticals with fewer side effects.
- Providing bio-industry with the ability to model and manipulate biological processes better so as to provide novel compounds for the chemical, pharmaceutical and food sectors, thereby improving the competitive edge of these industries.
- A better understanding of healthy ageing and how to maintain a population that remains healthy and productive for longer.
- The development of predictive (*in silico*) toxicology models of cells and organs leading to improved drug screens and reduced need for animal testing.

Clearly, Systems Biology is of national importance and transcends the work of several Research Councils. Given the health and economic opportunities that it presents, as well as the substantial international and industrial interest, a major national initiative is needed to build upon the current efforts of the BBSRC, the EPSRC and others.

2 Department of Health, 2006
3 http://syntheticbiology.org
4 HM Treasury, 2004

1.4 Scope of the report

In 2005, the Academy of Medical Sciences and The Royal Academy of Engineering identified Systems Biology as an area of scientific and economic priority and established a joint working group to undertake a review of developments and opportunities in the UK. Members and reviewers are identified in Appendix I.

The working group adopted the following terms of reference:

- To provide a high-quality review of the existing activity and capacity within the UK, highlighting positive and negative differences in Systems Biology research capability through comparison with other countries.
- To consider the role of biomedical science and engineering in the context of Systems Biology and how the interface between the two disciplines, and others, should be developed to maximise opportunities.
- To consider potential developments in Systems Biology and their likely impact.
- To identify key policy issues relating to Systems Biology and its potential contributions to the health and wealth of the nation.
- To produce an authoritative report, accessible to both the specialist and lay reader.
- To advise government, industry, academia and other stakeholders of the findings of the report and, where appropriate, recommend action.
- To determine the characteristics that Systems Biology research exhibits for providing a working definition of the term.

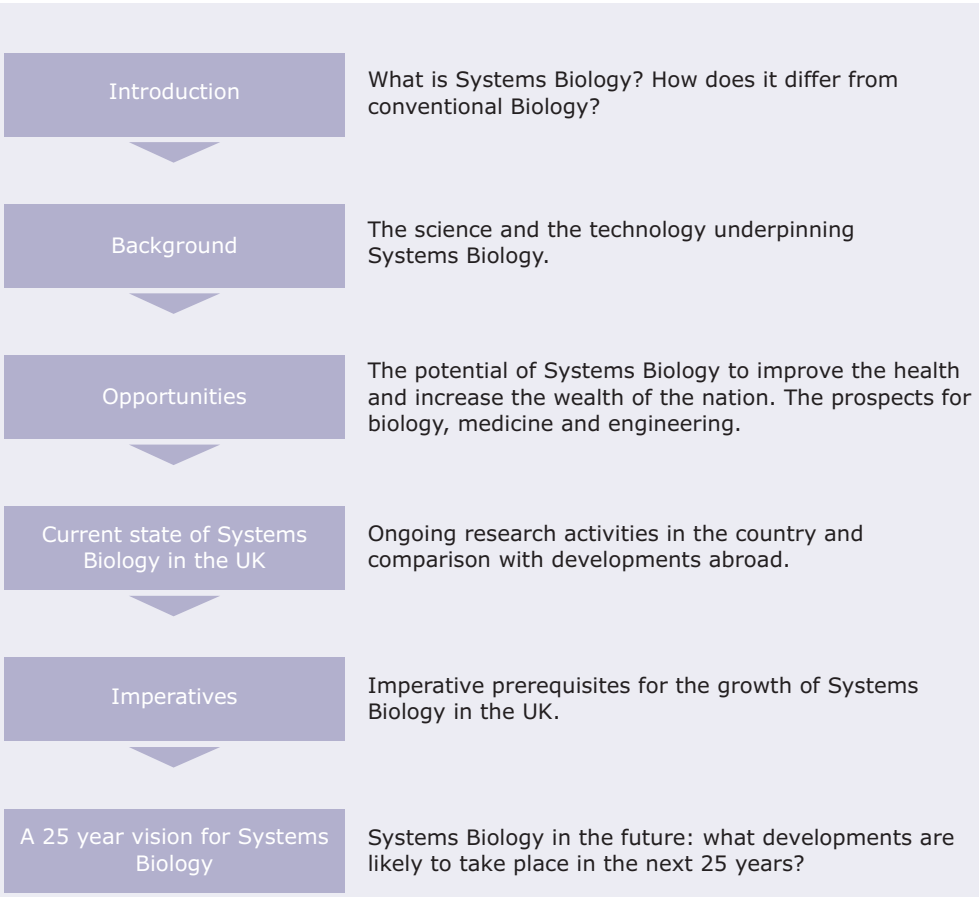
Systems Biology is likely to have a significant impact on many areas of science and technology including plant science, food microbiology, energy and environmental science. Although the importance of these and other topics was acknowledged, the two Academies decided upon a sharper focus that was closely aligned with the interests of their constituencies. It was agreed that the project should focus on the **biomedical and engineering** applications of Systems Biology. The report therefore addresses research ranging from macromolecules to the whole organism in both academia and industry. It also addresses issues of education in this novel and evolving field.

In 2005 the two Academies issued a series of calls for evidence to UK universities, research funders, medical research charities, Scientific Societies, medical Royal Colleges, government, industry and others. The information gathered was considered and assimilated in the production of this report, along with the evidence that emerged from meetings with key stakeholders and extensive published material. Names of respondents to the consultation are given in Appendix III.

This report has been prepared to inform policy-makers, government, research funders, universities, academics and industry, as well as other interested parties.

The five chapters that follow expand upon this introductory section and examine respectively:

- The scientific and technological developments that are now making a systems approach viable.
- The potential and opportunities of Systems Biology for groundbreaking progress in biology, medicine and engineering.
- The evidence gathered over the course of the inquiry.
- The issues that must be addressed without delay to enable Systems Biology to develop to a degree that makes the UK a leading country in its development and exploitation.
- The advances that are likely to characterise the field in the next 25 years.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Current state of Systems Biology in the UK
Ongoing research activities in the country and comparison with developments abroad.
Imperatives
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A 25 year vision for Systems Biology
Systems Biology in the future: what developments are likely to take place in the next 25 years?

2. Background

'Considering the inconceivable complexity of processes even in a simple cell, it is little short of a miracle that the simplest possible model - namely, a linear equation between two variables - actually applies in quite a general number of cases.'

Ludwig von Bertalanffy, biologist, 1968

2.1 The challenge of biological complexity

Biological systems exhibit complexity at multiple spatial levels. The human genome may only have about 25,000 genes, but these are used to make over 100,000 proteins, many of which serve more than one function. The number of conceivable interactions between all the human genes and their protein products is so immense (around $2e^{166713}$) that evolution can have explored only a minute fraction of these interactions during the four billion years of life on Earth[5]. Even if we consider only pairwise interactions between the proteins, five thousand million combinations are possible. However, some interactions are more likely than others because evolution is a very efficient process: it does not try out combinations randomly, but operates along pre-existing sets of connections.

Tissues and organs are the next level of biological complexity. Even apparently homogeneous organs, such as the liver, function in a systematic coordinated manner far different from the isolated behaviour of the cells that constitute them. Cells are also acutely sensitive to the surrounding environment and their interactions with adjacent cells: for instance, isolated liver cells in a nutrient solution may remain alive but quickly lose many of their specialised functions.

More complex still is the whole organism that is, again, much more than the sum of its organ and cellular parts. Although not the main focus of this report, a further level of biological complexity comes at the level of populations of organisms, where topics as diverse as the spread of infectious disease, ecosystems and economies have been researched.

Biological complexity cuts across time as well as space. At the molecular level timescales of 10^{-9} seconds, characteristic of Brownian motion, are important, whereas at the level of the whole organism the systems might be considered over 10^{9} seconds, of the order of a human lifetime[6]. Figure 1 illustrates the wide range of spatial and temporal levels that need to be taken into account when trying to understand biological systems. Systems Biology can help to unravel this biological complexity, and provide knowledge of the function of biological systems.

2.2 The application of engineering principles to biological research

2.2.1 Systems theory

The publication of Norbert Wiener's book, '*Cybernetics*', established the basis for studying systems within the human body using systems theory[7]. Signal processing is another very important area of engineering that, together with systems theory, has applications in a wide range of fields, including physiology. Within Systems Biology, systems theory and signal processing can be used to understand how the body works at different spatial and temporal levels.

Systems theory has been used in the design, construction and study of aircraft control systems, information and telecommunication networks and economies. Control systems in different organisms tend to have very similar

5 'There wouldn't be enough material in the whole universe nature to have tried out all the possible interactions even over the long period of billions of years of the evolutionary process'. Noble, 2006.

6 Hunter *et al*., 2002

7 Wiener, 1948

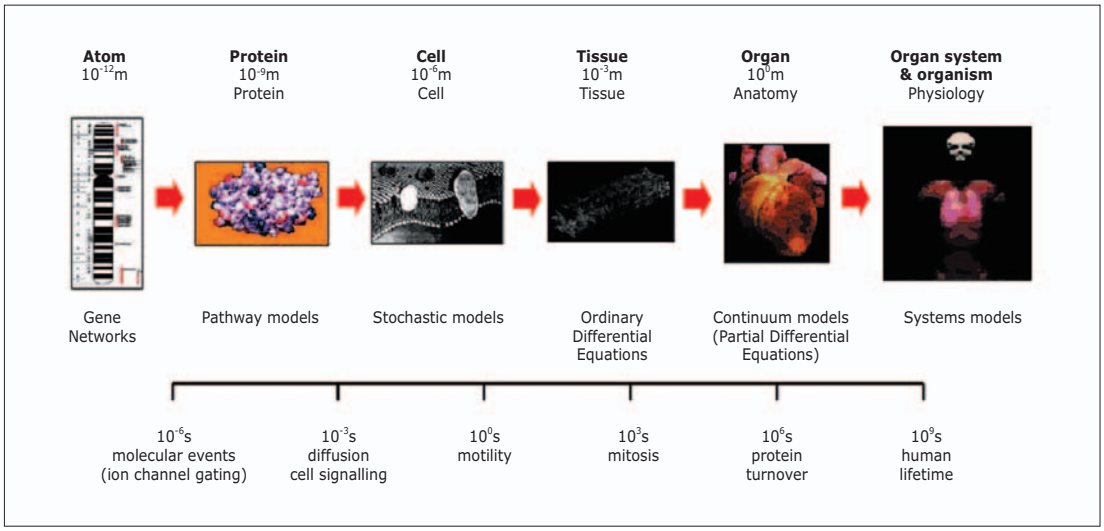

Figure 1: Spatial and temporal levels encompassed by biological systems[8].

building blocks and commonalties can be exploited for scientific investigation. Key elements of systems theory are the concepts of feedforward and feedback loops and modularity. A feedforward loop refers to that part of a system where information flows in order to produce some form of action. A simple example is that of a driver turning the steering wheel of a car thus leading the vehicle to follow a bend in the road. Here, both the driver and the steering mechanism are part of the overall system for steering the car. In contrast, a feedback loop refers to that part of a system that is used to monitor a situation: here information is fed back to a central point that monitors the performance of the system. In the context of the previous example, this would involve the driver looking at the bend in the road and the visual information being fed back to the visual cortices in the brain. The system then compares the position of the car in relation to the bend and, if necessary, prompts further action.

2.2.2 Modularity

Modularity refers to the ability within systems theory and engineering design to consider systems as a set of constituent parts. In the example given above, the components of the feedforward loop consist of the driver's brain and the musculoskeletal system (one module) and the steering mechanism of the car (the second module). In the feedback loop the modules comprise the driver's eyes and his brain. In both engineering and biology, systems often include multiple feedforward and feedback loops with multiple modules, as well as loops that operate at different spatial and temporal scales. However, such systems often consist of a set of standard modules which, when put together, produce a particular emergent function.

Modularity is a key principle of the analysis of engineering systems. One of the fundamental questions for system biologists is whether modularity is a universal principle in nature or just a property of certain classes of biological systems. The realisation that gene duplication and subsequent modification by mutation and natural selection is a fundamental process in the evolution of organisms gives strong support to a modular approach. In fact, life forms constantly re-use systems that already exist rather than taking time to evolve new gene products.

2.2.3 Systems analysis

Systems analysis is not simply computational. In many ways it is reminiscent of physics in that it seeks 'laws' or general principles of

8 Hunter *et al*., 2002. With kind permission of Springer Science and Business Media.

systems operations exemplified by the laws of metabolic and hierarchical control analysis. It is also mathematical, in that it questions the logic of the system, including the constraints it operates under, the degree of modularity of functions in organisms, their robustness (fail-safe mechanisms) and the rules for development. Ultimately it must align with quantitative theories of evolution. These are vast wide-ranging questions and there is considerable disagreement on the extent to which such logic of systems operates, compared with the serendipitous process of historical evolution.

2.2.4 Biological systems

Biological organisms are much more complicated than any machine designed by man. However, there are similarities between the way in which organs and whole organisms are assembled from molecules and cells and the design methods used by engineers in the construction of complex systems. The application of such methods to biology will, however, require novel engineering tools to be developed since biological systems possess key features that artificial ones do not. Specifically, biological systems have an exceptional capacity for self-organisation and assembly, using rules and mechanisms that have been shaped by natural selection. Biological systems also have significant capacity for continuing self-maintenance through turnover and renewal of component parts. Perhaps the property that distinguishes biological systems most is their ability to auto-adapt their organisation to changing circumstances through altered gene expression, or more directly, through signal transduction and modification of proteins. This adaptation culminates at higher levels of organisation as evidenced by phenomena such as the development of resistance to antibiotic therapy or tolerance to recreational drugs.

The mechanisms by which component parts interact are often highly stochastic in nature; that is, susceptible to the play of chance, which becomes particularly important when only a few components are being considered. Nevertheless, biological systems are robust.

2.3 Trends and drivers

The application of a systems biology approach to a biomedical question depends upon the quality and quantity of the data available about the system under study. Systems thinking is not new to biology, having been historically applied in the physiological sciences and elsewhere. However, it had to be abandoned because of the lack of necessary data and tools[9]. To date, persisting difficulties in informing models with sufficient and adequate experimental data are driving a convergence of several disciplines as diverse as molecular biology, computing and mathematics to enable the progress of Systems Biology. Key drivers are outlined below. The list that is far from comprehensive as other authors have already provided more detailed discussion about the roots of Systems Biology[10, 11].

2.3.1 Molecular biology

The revolution in molecular biology, manifest in the Human Genome Project, has driven and has been driven by technological advances that have simplified the simultaneous measurement of a large number of biological parameters. Examples include microchip arrays that employ antibody fragments for detection and measurement of thousands of gene products (mRNA) in a single assay and the development of similar chips for use with protein molecules. More established techniques, such as mass spectrometry, have made comparable progress and are now capable of measuring molecules of higher mass with greater throughput. These advances are helping the provision of ever more quantitative information about biological systems at different spatial and temporal levels and can be employed to make more useful and predictive models.

9 Westerhoff & Palsson, 2004
10 Westerhoff & Palsson, 2004
11 World Technology Evaluation Centre, 2005

2.3.2 Bioinformatics

Advanced informatics and bioinformatics play a major role in the handling and interpretation of the vast amount of data generated by the developments characterising molecular biology in the last 50 years. About 50 terabytes of descriptive data relating to the human genome have already been acquired but its use rests upon its conversion into operational information, which remains a fundamental challenge. Success in this enterprise will be critically dependent on the ability to extract data from the many sources (databases and literature) and bring it together in a mutually intelligible format that describes the structure and function of complex biological systems.

2.3.3 Imaging

Biological systems operate in four dimensions and their spatial and temporal organisations are critical to function. Advances in imaging methods have been, and will be, critical to biology and medicine, and to Systems Biology. For instance, imaging is increasingly being used to understand the action of pharmaceuticals *in vivo* and will deliver the direct application of systems approaches to clinical medicine. Significant parallels exist between advanced imaging and Systems Biology in that both require a combination of mathematical, statistical and biological training. Neuroscience, for instance, is an area where close relations between biologists and imaging scientists will be essential and where Systems Biology will play a significant role in translational/experimental medicine.

It is essential that imaging scientists and systems biologists develop and maintain a dialogue. Imaging is progressing rapidly and opportunities exist to influence some of its developments for the provision of appropriate tools for Systems Biology. Currently, the gathering of adequate data for the development of models that test the behaviour of biological systems over time is extremely difficult. A key tool will be high resolution and dynamic functional imaging, from which, for example, dynamic time series data can be automatically extracted at a single cell level in living cells.

2.3.4 Computer power and information and communication technologies

Since 1994 the power of computers has continued to expand rapidly. As Gordon Moore predicted in 1965, the number of transistors on a silicon chip has doubled every 18 months and looks set to continue to do so[12]. Increased computing power supports Systems Biology by helping researchers to build and use ever more complex models.

As systems biology data mining becomes increasingly intensive, the computational power that will be required for more sophisticated applications in the future is likely to exceed the capabilities of local computers. Furthermore, the demand for computational operations involving data sources that may be distributed across many sites, where they are maintained and updated on a regular basis, is increasing along with the interactions between researchers working in different and often distant locations. In circumstances such as these, telecommunications and distributed computing are key to the exchange of information. For reasons relating to cost and because they are already in place, commercial telecommunication systems, ranging from relatively slow standard telephone lines to much faster ATM networks, are often used. For instance, downloading a set of 10,000 images from a distributed database via a standard (i.e. domestic) broadband connection would take 2.7 minutes per image and therefore a total of 18 days. However, much faster networks are available for academic purposes. For example, the California Research and Education Network (CALREN) allows the downloading of images at a rate of 80ms each; it therefore takes only 10 minutes to download the whole set. Hence, major infrastructures such as distributed processing, federated databases and grid computing are likely to be required for the progress of Systems Biology. In the area of

12 Moore, 1965

distributed computing significant progress has been made already by the UK e-science initiative, supported by the relevant Research Councils and embodied in the national and regional e-science centres. This has placed UK e-science in a strong international position and illustrates the importance of maintaining and expanding the infrastructure for the support of future systems biology developments.

2.3.5 Modelling

The meaning of the word 'model' is highly dependent on the context of use. Within this report the term 'modelling' refers to predictive modelling of the underlying process that generates the experimental data, rather than modelling the data itself. Modelling is already well developed within engineering, mathematics and physics and is beginning to be more widely used within the life sciences. Mathematical and computational modelling of living systems is a key feature of Systems Biology and is used to make predictions about complex biological structures and functions.

A model is a simplified and abstract reproduction that allows insight into the essence of a system and helps to identify gaps in biological knowledge. It is instrumental in the management of the complexity of biological systems where all the variables that might be of interest need to be monitored simultaneously, and simulates and yields results that approximate to the emergent behaviour of the biological system under scrutiny[13]. Its output may indicate a limited range of experiments whose results may, in turn, be used to test and refine the model by a cycle of iteration between simulation and experimentation (Figure 2). Within Systems Biology, modelling therefore complements observation and experimentation, helping to deepen our understanding of the dynamics within the system being studied[14].

Biological systems encompass a wide range of spatial and temporal scales, each of which requires a particular kind of quantitative analysis. However, substantial incompatibilities still exist between the mathematical formulations at each of these different scales, and this constitutes one of the key challenges that currently face systems biologists.

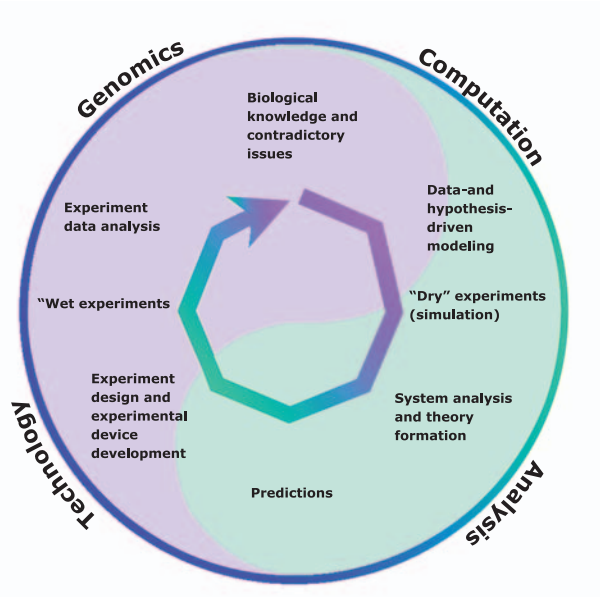

Figure 2: Hypothesis driven research in Systems Biology[15].

2.3.6 Statistical inference

Statistical inference plays an important role in Systems Biology. Many systems involve large numbers of components whose interactions are each governed by rate factors that must be estimated from experimental data. Moreover, the networks underpinning such systems may not be known in detail, in which case both the structure of the network and its constituents must be inferred. To make matters yet more challenging, the constraints of biological experimentation are often very different from those that characterise engineering and the physical sciences, requiring that engineers, mathematicians, statisticians and biomedical scientists interact closely to develop the most effective solutions to entirely novel classes of problems. Inference is at the cutting-edge of statistical research and its further growth will be a key component to progress in Systems Biology.

13 Finkelstein *et al*., 2004

14 BBSRC, 2003

15 Kitano, 2002.

2.3.7 Engineering design

Advances in engineering design and techniques carry a significant potential in driving the progress of Systems Biology. Interventions to biological systems intended to improve health, whether environmental, pharmacological or clinical, need to be carefully thought through and carried out to maximise benefit and reduce harm. The refinement of techniques and tools enables devices and systems to achieve a defined performance within precise tolerance limits, potentially allowing better interventions to complex biological systems. They will be increasingly necessary to permit more reliable system-wide predictions of the effects of biomedical advances and to achieve desired clinical results to a predefined tolerance, or at least to have a quantitative bound on the biological uncertainty.

2.4 Approaches to building a system

2.4.1 Molecular to cellular systems

A systems approach to molecular biology seeks to enable the prediction of the functioning of a cell given a sequenced genome and, ultimately, the behaviour of networks of cells. At present, this is not feasible and even predicting the interactions of a functional group of proteins on a signalling pathway is extremely challenging. The progress of Systems Biology depends strongly on the development of models of complex systems. In turn, this requires sufficient and accurate experimental data about the behaviour of the system under study (top-down) and about the structure and function of the component molecules (bottom-up). In practice, a judicious combination of the two, sometimes referred to as the 'middle-out' approach, may be the most practical solution. If this can be done, experimental biology and medicine will gain vast benefits from the simulation of complex systems and development of models with predictive capabilities. Examples of current research foci include modelling sensory networks, initially of bacteria, with the possibility that this may be extended to multicellular organisms, including plants and animals.

To date, efforts in the field of Systems Biology have focused on the use of models to represent the interaction between proteins. However, it is not yet clear how to incorporate the structural and biophysical properties of the constituent molecules. Even simple cellular networks can display highly complex behaviour if either long-range connections or the spatial heterogeneity of the *in vivo* intra-cellular environment, or simply the nonlinearity of the kinetics, are included as the system's parameters. It is therefore challenging to scale-up models to higher levels. Arguably, stochastic models, those that contain 'random' elements, may be able to provide the bridge between molecular level and higher-level descriptions. These models have had some success in describing the behaviour of small numbers of molecular components evolving in time, but it is still not clear how to set parameters that may have an effect both on the molecular level and the higher level descriptions.

2.4.2 Whole-organ modelling

An exhaustive bottom-up reconstruction of a complex organ such as the heart would be very difficult. Therefore, when modelling higher-level physiological systems, activity at lower spatial levels is represented with simplified equations. The engineering principle of modularity discussed earlier in this chapter can be exploited so that sub-systems within a larger model are represented by 'black boxes', interconnected with feedback and feedforward loops, where the input and output, but not the intervening steps, are considered. Ultimately, advances in Systems Biology will also allow the detailed understanding of the function of these black box modules. Such modularity permits the adoption of a middle-out, rather than bottom-up or top-down, approach. When choosing the middle-out option, analysis starts at the level for which there are large amounts of usable data and then reaches out in either direction (this is the 'out' part of the metaphor) to consider the next linked modular sub-system. All three approaches are needed, although the general view is that top-down and

middle-out approaches are likely to be more fruitful in addressing future therapeutic needs, at least for the near-term future. Modularity also enables the identification of relevant features of the lower-level mechanisms. Importantly, this allows the complexity of the overall model to be kept within bounds; for example, sodium or calcium transport can be described by a few simple equations. It is important to note that incomplete or approximate models can have significant value and application, and it is not necessary to wait for all the details of a system to be defined before a model can be used. Indeed, the outcome of a model can be used in combination with experimental data for further refinement of the model itself through the cycle of iteration between modelling and experimentation described earlier.

The results of modelling complex systems are frequently counterintuitive. Beyond a certain degree of complexity, qualitative thinking is not only inadequate, it can even be misleading. A good example of this is provided by the mechanism of mechano-electric feedback, in which the contraction of the heart influences its electrical properties. Some of the results, particularly on the actions of changes in cell volume (characteristics of many disease states), are unexpected and have been responsible for determining the next stage in experimental work. The unravelling of such complex physiological processes can only occur as a result of the iterative exchange between experiment and simulation.

2.5 Success stories

Systems Biology is increasingly contributing to the understanding of medical conditions and the way these react to treatments. For instance, the US company Entelos Inc. has developed functional computer models of diabetes, obesity, rheumatoid arthritis and asthma that are being used in the design of clinical trials[16].

As part of the Physiome Project, a model of the heart has also been developed to assess the risk of '*torsade de pointes*' (a potentially fatal cardiac arrhythmia that can be provoked by rare inherited conditions affecting an ion channel in the heart) and test some therapeutic drugs that prolong the repolarisation of the heart muscle by inhibiting the function of this channel (see section on cardiac toxicity in Chapter 3). The model has already been used successfully in the assessment of drug safety by regulatory bodies in the US and Europe.

Another successful model has been developed to assess the determinants of the response to COX inhibitors, an analgesic class of drugs. There is a relatively poor correlation between the blood plasma concentration of this class of drug and the analgaesic or adverse effects in chronic inflammatory conditions. Consequently, it is difficult to predict the appropriate dose regimes for the treatment of chronic inflammatory pain. The modelling of changes in endogenous mediators of inflammation has helped to elucidate the relation between exposure to the drug and the therapeutic response[17].

16 www.entelos.com
17 Huntjens *et al*., 2005

3. Opportunities

'Although the road ahead is long and winding, it leads to a future where biology and medicine are transformed into precision engineering.'

Hiroaki Kitano, systems biologist, 2002

3.1 Introduction

As well as advancing fundamental scientific understanding, Systems Biology promises practical benefits in medicine, engineering and elsewhere. Although its potential applications are as diverse as they are plentiful, this chapter describes only some of them to illustrate how a systems approach can assist in addressing problems of great scientific and economic importance. Such examples are intended neither to be prescriptive nor to constrain the range of research areas that may form the expansion of Systems Biology in the UK.

3.2 The UK pharmaceutical sector

The UK's pharmaceutical industry is a success story and is second only to that of the US. It is a significant employer of highly qualified cost-effective R&D manpower and a consistent major net exporter: around one in five of the world's top hundred medicines were discovered and developed in the UK. Two UK companies, GlaxoSmithKline and AstraZeneca, were second and fifth in the 2004 world league, having 9% and 5% of total market share respectively[18]. In addition, other global companies such as Pfizer have a major R&D presence in the UK. However, over the past two decades there has been a persistent and worrying shift of pharmaceutical R&D from Europe, including the UK, to the US. Moreover, although an active source and developer of new drugs, the UK's biopharmaceutical industry is dwarfed by its American rival.

The pharmaceutical sector has increasingly become reliant upon biotechnology services and products. Over the last decade, a number of private biotech companies, mainly based in the US, have focused on the development of computer models of human disease for use in drug discovery and clinical trials. Large US pharmaceutical companies are benefiting from these applications by adopting a policy aimed at buying and incorporating biotech firms into their main business, and exploiting their intellectual property (IP) rights: a practice that in Europe is still uncommon.

3.3 Drug research and development

The pharmaceutical and biopharmaceutical sectors are those likely to benefit most from Systems Biology in the immediate future. Over the last decade the cost of developing new drugs has increased dramatically (Figure 3).

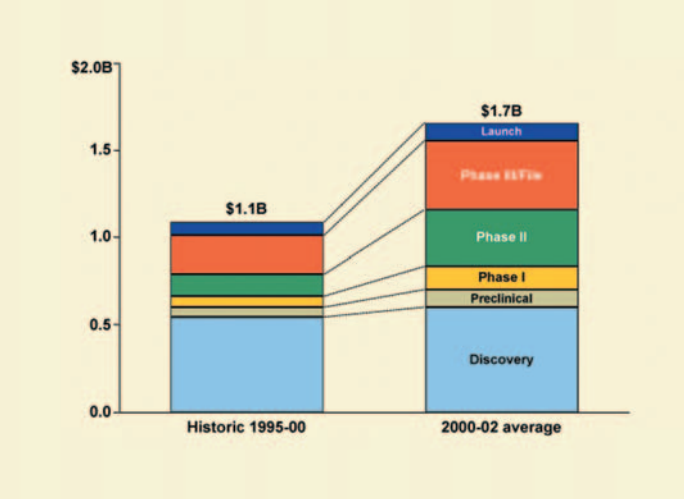

Figure 3: Change in average cost to develop successful drugs over time[19].

This has been accompanied by an increase in the average total development time for drugs from just over 8 years in the 1960s to just over 14 years in the 1980s and 1990s. In addition, current estimates indicate that only 5% to 8%

18 www.abpi.org.uk
19 Windhover's *in Vivo*, 2003

of Phase I projects developing new molecules produce a marketable output, by which time anything up to $1bn will have been spent[20]. Unsurprisingly, the pharmaceutical sector is seeking innovative tools that could make drug discovery and development more effective.

Systems Biology could lead to significant economic benefit by providing applications that anticipate project failure earlier and reduce development times. One example of the application of cell-based Systems Biology estimated that it could reduce drug discovery costs by $390m (£225m) and shorten development times by three years for each drug that reaches the market[21].

Over the past few decades, pharmaceutical R&D has focused on creating potent drugs directed at single targets. This approach was very successful in the past when biomedical knowledge as well as cures and treatments for most common conditions were limited. Nowadays, the medical conditions that affect a significant proportion of the population in industrialised countries are more complex, not least because of their multifactorial nature. The sequencing of the human genome has led to a considerable increase in the number of potential targets that can be considered in drug discovery and promises to shed light on the aetiology of such conditions. Yet, the knowledge of the physiological properties and the role that these targets play in disease development is still limited.

In terms of drug targets, there is a case that much of 'the low hanging fruit' was picked in the period between the late 1940s and the mid 1980s. The decline in output of new molecular entities and medicines (Figure 4) recorded over the last 10 years, despite the steadily growing R&D expenditure and significant increase in sales, bears testimony to the fact that advances with new targets are more difficult and that R&D projects have become much more prone to failure[22]. Some fear that the pharmaceutical industry may not be able to continue in its present mode of operation if it is to remain profitable; nonetheless, it is faced with the challenge of identifying targets that will result in the delivery of effective new medicines. New tools are required to support the development of novel and more specific drugs and Systems Biology can assist in their selection.

A basic problem is that the many factors that predispose to, and cause, complex diseases are poorly understood let alone the way in which they interact. The very fact that there are multiple drivers for these conditions suggests that a reductionist approach focusing on individual entities in isolation is no longer appropriate and may even be misleading. It is therefore necessary to consider 'novel' drugs designed to act upon multiple targets in the context of the functional networks that underlie the development of complex diseases.

Many of the new developments are likely to turn into effective medicines when combinations of drugs are used to exert a moderate effect at each of several points in a biological control system. Indeed, many common diseases such as hypertension and diabetes are already treated with a combination of two or three medicines hitting different targets in the control network that underlies the condition.

Investigating the possible combinations by trial and error in man is onerous but feasible with two components. However, it quickly becomes extremely complicated with three components and well nigh impossible with four or more. It is circumstances like this that will require a systems approach and the use of sophisticated and progressively refined models. Systems Biology, therefore, promises to assist in the development of more specific compounds and in the identification of optimal drug targets on the basis of their importance as key 'nodes' within an overall network, rather than on the basis of their properties as isolated components.

20 Glover, 2002
21 Butcher, 2005
22 Centre for Medicine Research, 2004

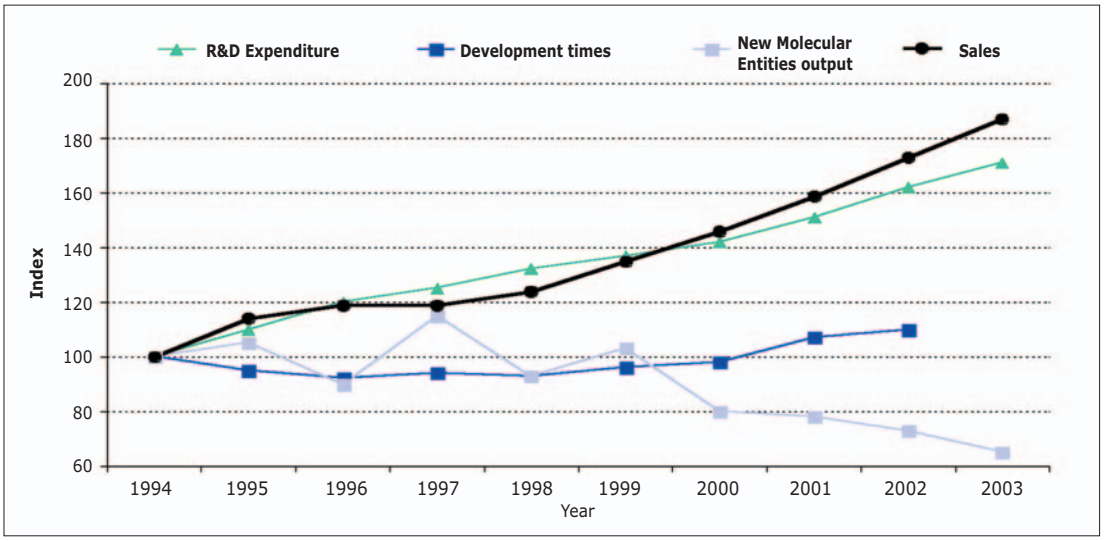

Figure 4: Trends in key indicators for the pharmaceutical industry 1994-2003[23].

Time- and cost-effective drug development

Increased levels of lipids, a type of fat, in the blood are an important risk factor for cardiovascular disease. Certain drugs, like statins, can help to reduce blood lipids. But a more significant lipid reduction can be achieved by combining statins with other drugs (e.g. ezetimibe) that work in different ways.

Recently, Pfizer, a major US pharmaceutical company, sought to investigate the lipid lowering effects of a new experimental drug called gemcabene. Early studies indicated that gemcabene did not lower lipids as much as statins, so would have to be used in combination with them to be commercially viable[24]. As part of the drug's development, Pfizer decided to undertake a model-based analysis to compare the lipid lowering effects of gemcabene versus ezetimibe in combination with a statin[25].

The results of the modelling indicated that gemcabene did not offer superior lipid-lowering benefits to ezetimibe when used in combination with a statin. This result contributed significantly to the rapid decision to stop development of the drug.

It has been estimated that the use of modelling data helped Pfizer save £0.8m to £1.6m in costs and four to six months delay[26].

Increasingly powerful drugs will be aimed at a decreasing percentage of people and eventually at single individuals. Modelling can be used to integrate *in vivo* information across species. Coupled with *in vitro* and *in silico* data, it can predict pharmacokinetic and pharmacodynamic behaviour in humans and potentially link chemical structure and physico-chemical properties of the compound with drug behaviour *in vivo*.

Large-scale integrated models of disease, such as diabetes and obesity, are being developed for the simulation of the clinical effects resulting from manipulations of one or more drug targets[27]. These models will facilitate the selection of the most appropriate targets and help in planning clinical trials. Coupling this approach with pertinent genomic information holds the promise of identifying patients likely to benefit most from, or to be harmed by, a particular therapy as well as helping in the stratification of patients in clinical trials.

To use an often quoted analogy from electronics, if the genome map has provided a detailed parts list, physiology, aided by Systems Biology, can provide the wiring diagram of the functional networks that combine to translate a molecular stimulus into a physiological response.

23 Centre for Medicine Research, 2004
24 Madema *et al*., 2005
25 Madema *et al*., 2005
26 BioIT World, 2006
27 www.entelos.com

3.4 Drug safety

Attrition of new compounds during drug development is predominantly due to toxicity. Combined with lack of clinical efficacy and safety issues arising during clinical development, it accounts for the failure of up to 60% of drug development projects[28].

3.4.1 Hepatotoxicity

Drug toxicity usually involves a complex mix of defence, injury and repair, each invoking its own control system. At present, there is no substitute for the study of intact animals and man to assess the safety of medicines. One of the greatest problems of drug safety arises when, in response to the drug, a tiny minority of patients suffer a very serious form of toxicity such as severe damage to liver function, whereas most patients tolerate it well. In many cases, this is due to genetic variations in drug metabolising enzymes or the immune system that influence liver function of the individual and the response to injury. The number of known functional variations continues to expand rapidly and a systems approach will be instrumental in managing the biological complexity.

Liver toxicity is one of the most common factors underlying failure of drug development. In many cases, warning signals can be identified at the preclinical stage and steps can be taken to avoid problems in development. However, the liver is a complex and sensitive organ with many critical functions, some of which work differently in the animal models used for drug testing. These differences mean that, although much can be done to screen for liver or other forms of toxicity at the preclinical stage, the predictive power of animal models is limited by the obvious differences that distinguish them from human biological and physiological systems. For instance, it has been observed that animal models and screens failed to predict over 30% of all cases of late-stage clinical liver toxicity[29].

Safety remains a concern even when drugs have reached the market, after substantial investment has already been made: for instance, 95 medicines were withdrawn from the US market between 1960 and 1999 because of serious drug safety concerns[30]. In financial terms, late-stage compound attrition due to liver toxicity can be significant: the recent difficulties with Exanta® contributed to a 30% drop in AstraZeneca share price in 2004[31].

Hepatotoxicity presents an opportunity for companies to establish pre-competitive efforts aimed at the development of models simulating liver physiology. An initiative to understand some aspects of hepatocyte function is already underway in Germany (HepatoSys Network) and in the Netherlands and may form part of the future European Framework initiative[32]. In addition, Innovative Medicines for Europe, a multilateral project under the sixth European Framework programme involving a consortium of companies, seeks, as one of its objectives, to predict human hepatic toxicity of compounds using *in vitro* data and genomic information. If successful, the outcome would facilitate better preclinical screening.

3.4.2 Cardiac toxicity

Over the last few years it has been recognised that a number of drugs can interfere with the electrical function of the heart causing *torsade de pointes*, a potential life threatening cardiac arrhythmia. These drugs come from diverse pharmacological groups, ranging from terfenadine, an antihistamine, to grepafloxacin, an antibacterial. Because of concern about the potential seriousness of this effect, regulatory authorities recommend that almost all new medicines be tested on special types of isolated cell (*in vitro*), in intact animals and in human volunteers (*in vivo*) to see if they prolong the electrical repolarisation phase of the heart (QT interval).

It is well established that genetic variation in ion channels, particularly the potassium

28 Schuster *et al*., 2005
29 Sigman, 2003
30 Academy of Medical Sciences, 2005
31 Financial Times, 2005
32 www.systembiologie.de/en/index.html

channel, causes predisposition to *torsade* although this affects different people to different degrees. The practical importance of this problem, and the rapidly advancing state of knowledge about the physiology of the heart, makes this an ideal subject for a concerted approach through Systems Biology. This could bring together knowledge of the clinical factors that predispose to the 'long QT' associated with *torsade*, the electrophysiology of the heart, information about molecular configuration of the channels and genetic variants, medicinal chemistry expertise about the interaction of drugs with the channels and, finally, a range of mathematical and engineering analytical and modelling skills. The heart model developed within the context of the Human Physiome Project is leading the way and its adoption by US and European regulatory bodies in the assessment of new compounds reflects the importance of the problem as well as the efficacy of the technology and the approach employed to develop it.

3.5 Animal testing

As mentioned previously, the main uses of animal testing in industry are to model human diseases and to investigate drug safety. Systems Biology requires large amounts of experimental data to make problems tractable and modelling feasible, and it would be misleading to imply that Systems Biology will significantly reduce the use of animals in the short-term. However, if increasingly accurate predictions can be made about disease responses and drug safety by means of *in silico* experiments, fewer animal experiments may be needed to verify them.

3.6 Personalised healthcare

Traditionally patients are diagnosed and treated as if they belong to homogenous groups within disease catergories. With the development of multiple sources of detailed clinical information about the disease phenotype and the increasing importance of genomic, proteomic and metabolic profiling, it is likely that future developments will place ever greater emphasis on individual risk assessment and treatment selection. Figure 5 shows that synthesis and sequencing productivity are increasing at least as fast as Moore's law[33]. Some commentators suggest that by 2050 it will be possible to sequence an individual's entire genome for around £100, about the same cost as a CT or MRI scan today[34].

Systems Biology will undoubtedly be key in the move towards more individualised medicine by helping to translate some of the descriptive biomedical information into functional knowledge. For instance, it might facilitate analysis of the vast quantities of biological data gathered during late stage clinical trials in order to explain the unusual responsiveness of some patients to a drug. However, it must be acknowledged that the challenges facing personalised medical care are formidable both in terms of cost and organisation. For practical reasons most clinical trials of therapeutic interventions of all kinds, not just new medicines, deal with patient populations that have been carefully selected as being free of other diseases or active treatments that might complicate interpretation of the results. Away from these trials the reality is very different. Most patients requiring therapeutic interventions are older than those selected for trials and multiple simultaneous treatments are the rule rather than the exception. A male, aged 65, taking medication for raised blood pressure, raised cholesterol and prostate problems, is commonplace. His female equivalent might substitute a treatment for osteoporosis for that for prostate problems but be on the same medicines for blood pressure and blood lipids. If either has arthritic pain, a non-steroidal anti-inflammatory will be added as a fourth component. If one or the other has asthma, chronic bronchitis or diabetes – all common diseases – a fifth medicine will be included in the cocktail. In addition, non-medical treatment may also involve dietary change, weight reduction, increased physical exercise, reduced tobacco and alcohol use. The

33 Carlson, 2003
34 Dawkins, 2003

number of permutations and combinations rapidly becomes very large and confusing for both patient and doctor, and it is about to become even more complex as identified genetic factors predisposing to disease, or affecting the choice of treatment, increase in significance. Even the best doctors find this complexity difficult to handle well and elderly patients readily become confused with the multiplicity of medical interventions and advice received: their adherence to treatment is poor, the full benefits are not delivered and the financial resources are used sub-optimally.

Given the wealth of knowledge and the vast number of variations possible within the human genome and the environment, only a limited number of options exist to deal with all the information available. One possibility is the creation and use of a vast array of stored information in the form '*It is risky to give drug Y to a patient with polymorphism X or intercurrent disease Z*'. However, this approach is almost useless for making predictions about complex conditions, which are often unique to the patient under examination, and is likely to overwhelm practitioners and researchers with numerous and redundant low relevance warnings. Alternatively, Systems Biology could be used to help understand the mechanisms that underpin human biological function so that treatment can be matched to the individual circumstances and genetic make up of the patient.

However, the promise of personalised medicines is still a widely debated issue and a large divide exists between those who are enthusiastic about it and the sceptics who believe that it is still a remote possibility. For instance, a recent Royal Society report concluded that it was unlikely that

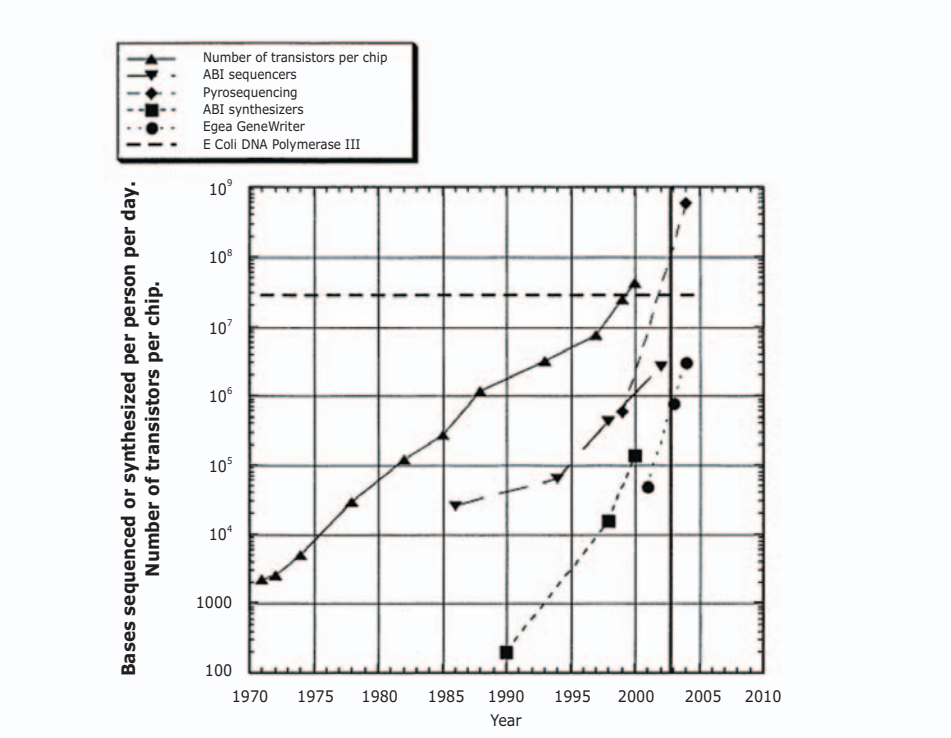

Figure 5: On this semi-log plot, DNA synthesis and sequencing productivity are both increasing at least as fast as Moore's law (upwards triangles). Each of the remaining points is the amount of DNA that can be processed by one person running multiple machines for one eight hour day, defined by the time required for pre-processing and sample handling on each instrument. Not included in these estimates is the time required for sequence analysis. For comparison, the approximate rate at which a single molecule of *Escherichia coli* DNA Polymerase III replicates DNA is shown (dashed horizontal line), referenced to an eight hour day[35].

35 Carlson, 2003

pharmacogenetics, one aspect of personalised medicines, would have an immediate impact on clinical practice, with its true potential not becoming apparent for another 15-20 years[36].

3.6.1 Biomarkers and imaging

Biomarkers are biological indicators that are used to assess the biological state of an organism, the progression of a disease or the effect of treatments. Blood pressure and heart rate, for instance, are simple indicators of cardiovascular function. New and more complex biomarkers include biological molecules such as the tumour specific carcino-embryonic antigen that can be used to track progression of colon cancer. In some cases, multiple biomarkers are used in risk assessment. For example blood pressure, LDL cholesterol, blood sugar predict the risk of a myocardial infarction. There is currently great interest in the potential of new indicators that have been discovered using methods such as gene expression and proteomics. However, the interpretation of their significance will have to take account of physiological and pathophysiological variability and the extent to which they are linked to disease mechanism. In many cases, patterns of changes in a number of biomarkers, rather than the biomarkers themselves, whose function may remain unknown, are used as biological indicators. In order to use biomarkers to their greatest effect, a correct definition of their reading and their appropriate qualification will be essential and Systems Biology has the potential to provide the right tools to do so.

Imaging techniques, similar to biological indicators, are instrumental in allowing insight into healthy as well as diseased biological systems and will enable advances in the pursuit of personalised medicine. Such technology allows medical imaging of molecular and pharmacological processes directly in patients: this is already practicable with positron emission tomography (PET) but rapid development of molecular imaging using magnetic resonance, ultrasound and optical imaging techniques is also taking place.

3.7 Complex diseases and scientific problems

Systems Biology is arguably the only research approach that has the potential to disentangle the multiple factors that contribute to the pathogenesis of many common diseases. For example hypertension, diabetes, obesity and rheumatoid arthritis are known to be polygenetic in origin although individual genes may not have been identified. Ultimately, the prevention of these conditions rests upon a comprehensive approach that engages with each of the more important predisposing factors, genetic and environmental, that operate upon individuals. A systems approach is already proving valuable in the study of complex scientific subjects and the research aimed at the prevention and management of medical conditions. Illustrative examples explored in the following sections are: neuroscience, cancer, ageing and infectious diseases.

3.7.1 Neuroscience

The ultimate objective of neuroscience is to gain insight into higher cognitive functions and human behaviour. While Systems Biology has a generic role to play in revealing basic cellular properties ranging from the genome to organelles and sub-cellular structures, in the context of neuroscience it is at the intercellular (synaptic), cell population and network levels that it becomes most useful.

In the medium-term, it is probably at the level of synapses that Systems Biology will have its greatest impact in neuroscience. Although the molecular biology of synaptic transmission has been well described, the study of the mechanisms underlying plasticity, and hence memory and learning, is proving thornier than expected. In part, the difficulties arise from the copious number of proteins involved. The investigation of the way they arrange themselves in the synapse and the gene expression that is responsible for their synthesis requires firstly an understanding of

36 Royal Society, 2005

the function of the proteins and, subsequently, modelling of the way in which they interact to cause plastic changes. Modelling the mechanisms underlying synaptic plasticity will be key to unveiling how these changes occur. However it is one of the greatest challenges facing neuroscientists.

Systems Biology will also be crucial for gaining insight into the system at the level of networks of neural cells. Here, much is still unknown about the coordinated functioning of cell populations, the way in which these, as systems, process signals and how they, in turn, are translated into normal behaviours as well as the pathological ones that characterise complex diseases such as dementia, depression, schizophrenia and autism.

3.7.2 Cancer

Cancer is a molecular disease that involves mutations (usually more than one) in genes that control cellular division or death. Molecular biology is having spectacular success in defining the exact mutations that may, for example, cause uncontrolled cellular division and growth. Hence, the treatment of cancer is evolving away from the traditional method of using highly toxic drugs in maximum tolerated doses towards an approach that is highly targeted to specific defects. A timely example is provided by the use of the antibody Herceptin® to treat breast cancer characterised by the over-expression of the HER2 protein.

Tumours can be effective at eluding interventions aimed at destroying them. For instance, some cancers express factors that eject drugs from the tumour cells, thus preventing their action. However, cancer cells need a blood supply to divide and grow and this need is being exploited by specific drugs that inhibit the growth of blood vessels into tumours. Treatment of cancers must be monitored and imaging technologies are key in assessing the response of tumours to treatment. In particular, methods that measure blood flow or metabolism are giving much earlier assessment of tumour response than the standard way of measuring tumour size. The tracking and the modelling of factors that influence drug delivery and penetration, and tumour response are critical to the understanding of cancer mechanisms and their treatment: Systems Biology is the approach most likely to succeed in this endeavour.

3.7.3 Ageing

Developed countries around the world are observing a significant increase in life expectancy. Longevity, however, is not always accompanied by a corresponding increase in quality of life, a mismatch that is stretching the resources of national health services. For example, age-related loss of mobility is often associated with musculoskeletal problems including the gradual loss of muscle mass (sarcopenia), bone thinning (osteoporosis) and degeneration of joints (osteoarthritis). These conditions cannot currently be prevented but some can be delayed, and to some extent reversed, by treatment. This requires a sound understanding of the processes underlying ageing but their intrinsic complexity, involving multiple mechanisms with effects at multiple physiological levels, is presenting researchers with considerable problems.

Research is helping to develop a hypothesis concerning the genetic basis of ageing and the mechanisms involved. One theory suggests that ageing is due to gradual accumulation of cellular damage leading eventually to functional impairment of older tissues and organs[37]. Genetic effects on the rate of ageing are mediated primarily through genes that influence somatic maintenance and repair and which may respond to environmental cues, particularly the level and quality of nutrients. The concept of ageing as an accumulation of damage at multiple points, each injury making only a modest contribution to the whole, suggests that reductionist studies will fail to capture the essence of what drives the ageing process and thus illustrates the need for a systems approach.

37 Arking, 1998

3.7.4 Infectious diseases

The spread of infections and the ability of pathogens to deploy strategies that minimise or defeat host defences against them are issues that demand a systems approach. Knowledge of the means by which organisms exploit weaknesses in host defence systems is increasing rapidly. Some viruses (e.g. influenza, HIV) take advantage of rapid mutation to evade immune surveillance or drug action. The Epstein Barr virus (infectious mononucleosis and Burkitt's lymphoma), tuberculosis bacterium, malaria parasite and even some strains of streptococci are all examples of common pathogens that have developed strategies to evade or neutralise host defence. The difficulty of dealing with these infections is testimony to the gravity of the clinical problem that pathogens create.

Studies of infections require a combination of knowledge of the pathogen, the host, the environment and the available treatments. It will only be possible to manage such a wealth of information using a systems approach. Problems of hospital-acquired infections such as MRSA or *Clostridium difficile*, for example, are suitable subjects for a systems-based enquiry.

Epidemiology makes extensive use of predictive modelling. Indeed, one important application of Systems Biology in the public health arena is through complex stochastic models that have been developed to support planning for the control of a novel influenza A, the agent responsible for flu pandemics. Such models use 'individuals-based' simulation approaches for the 60 million UK inhabitants, while taking account of detailed studies of population movement and mixing in the country. Computational problems such as this are very complex and require novel interdisciplinary approaches to blending biological, clinical, epidemiological, demographic and behavioural data. They can therefore benefit from the tools that Systems Biology can provide.

3.8 Prevention versus treatment

Notwithstanding the hugely important role that Systems Biology plays in understanding disease and designing drugs that treat them, the greatest opportunities may lie in health maintenance and disease prevention. The second Wanless report and subsequent Department of Health White Paper on 'Choosing Health' identified prevention as a key component of future public health strategy[38, 39]. Even modest measures that could retard the effect of ageing on brain, heart, bones, joints and skin would have a large impact on the quality of life and future healthcare demands of older people and consequently on the provision of health services. Young people are vulnerable too. Multifactorial diseases such as diabetes and obesity are becoming prevalent in younger people and unless effective measures are taken to prevent an early and significant decline in their health, healthcare demand will increase exponentially.

It is apparent that multiple and diverse factors interact in determining health, quality of life and ageing. These include genetic make up, diet, physical activity, stress, smoke and alcohol, therapeutic and social drugs, housing, pollution, education, and only a systems approach will permit the understanding of how best to prevent and delay health decline.

3.9 Synthetic Biology

Synthetic Biology is an emerging area of research that aims to design and manufacture biologically based devices and systems that are not naturally available, including the re-design and fabrication of existing biological systems. The foundations of Synthetic Biology lie in the increasing availability of complete genetic information for many organisms, including humans, and the ability to manipulate such information using genetic engineering to produce novel outcomes. More specifically, engineering principles, including systems and signal theory, are employed to define biological

38 Wanless, 2004
39 Department of Health, 2004

systems in terms of functional modules through the construction of an inventory of 'bioparts'[40]. These can then be reassembled into novel devices, acting as components for new systems in future applications.

Whereas Systems Biology focuses on the comprehensive study of natural biological systems, often within a biomedical context, Synthetic Biology seeks to build novel and artificial biological systems and it is, therefore, described as the engineering application of the biological sciences rather than an extension of bioscience research.

The relationship between Synthetic Biology and Systems Biology can, perhaps, best be represented by a hierarchical structure (Figure 6) showing how Synthetic Biology builds upon Systems Biology. The basis of quantitative Systems Biology lies in the application of engineering systems and signal theory to the analysis of biological systems (Level 1). This allows the *definition* of systems in terms of mathematical equations, often as individual functional blocks known as transfer functions. Defined systems can then be *reduced* (Level 2) to bioparts and such a process constitutes a core feature of Synthetic Biology. The function of each biopart is expressed in terms of accurate input/output characteristics: these are described on a standard specification sheet, which system designers can use as reference. Bioparts are listed in inventories and can be combined into devices and finally into systems (Levels 3).

As standard engineering devices, such as oscillators, can be built for use in fluidics, pneumatics and electronics, biologically based oscillators can equally now be realised in terms of protein concentrations. Tolerances are built into the design of any engineering part, device or system to compensate for imperfections in the manufacturing. Bioparts tend to have wider tolerances than standard engineering parts and biologically based devices are designed to accommodate such features.

The sections that follow describe examples of possible developments that may characterise the field of Synthetic Biology over the next decade and beyond. However, it is important to emphasise that although Systems Biology is

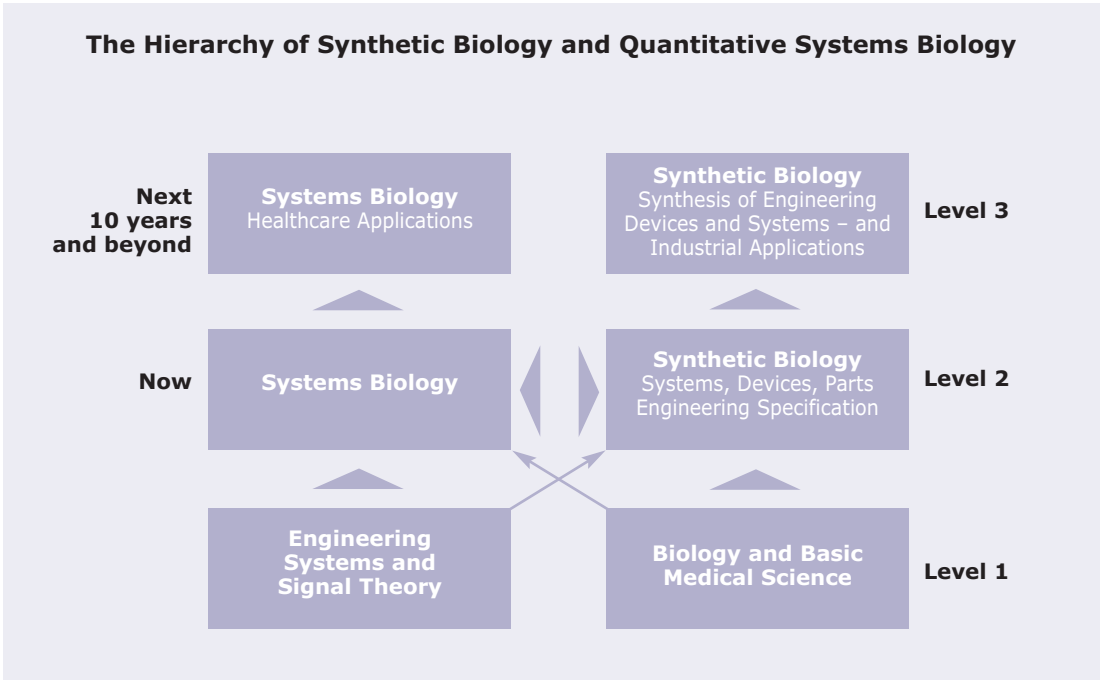

Figure 6: How Systems and Synthetic Biology build upon foundations provided by engineering systems theory, signal theory and basic biomedical sciences.

40 A biopart can be described as the minimum amount of DNA required to fulfil a function. The DNA can either be naturally available or artificially assembled in sequences that do not occur in nature. Devices or composite parts are described (in a registry of parts) as comprising multiple bioparts. Devices can be combined to form systems.

likely to yield prolific biopharmaceutical and biotechnological developments in the immediate future, the application of Synthetic Biology to more general areas of industry is, at present, more speculative. Nevertheless, it is envisaged that the field will develop and the areas of application become more clearly defined. If these developments take place, they will be likely to attract significant amounts of commercial investment.

3.9.1 Chemical engineering

In the 19th century, chemists learned how to synthesise compounds that had hitherto only existed in nature. This was extended in the 20th century to the development of plastics and other materials, which now find extensive use in most industrial sectors. Today's chemical industry, which relies on oil for the manufacturing of a considerable fraction of its products, is likely to gain significant benefit from Synthetic Biology. As oil reserves diminish and both demand and price increase, scientists are looking at more sustainable energy sources. For example, the possibility of creating fuel by using cell-based processes that rely on glucose as their energy source. The least complicated method to produce bioethanol (a type of biofuel), for example, involves the use of biomasses containing monomeric sugars, which can be fermented directly to ethanol. Sugar cane and sugar beet are biomasses that contain substantial amounts of monomeric sugars and were extensively used in the first half of the 20th century for the production of industrial grade ethanol via the fermentation of molasses.

Synthetic Biology techniques have the potential for optimising glucose dependent cell-based processes. While acknowledging that the quantity of fuel so produced will never be able to meet the global energy demand, it will undoubtedly be sufficient to contribute towards filling a significant portion of the market.

3.9.2 Materials

An important application of Synthetic Biology involves the harnessing of biological processes (on an industrial scale) to produce new materials. In many industry sectors there is a pressing need to use very strong but extremely light materials. In aircraft design, for example, a significant lessening of the weight of aeroplanes would immediately result in a reduction of fuel consumption. Thus, knowledge and manipulation of the biological processes that control the production of such materials, via a combination of Systems Biology and Synthetic Biology, could result in the synthesis of a whole range of novel materials that could see significant innovation in several industry sectors such as civil engineering, aeronautical engineering and the automotive industry.

Many of the desired properties described above characterise some of the natural materials. However, these are available in quantities that are too limited to be considered for industrial purposes. Engineers have tried to replicate naturally occurring designs, in many cases successfully. One example can be found in the area of synthetic structural composites where a considerable amount of work has been done on mollusc shells, which are particularly tough[41]. Here, the architectural configuration and material characteristics of the shell have been copied to build synthetic structural composites. Another example is the Golden Orb spider, which makes the largest and strongest web. Indigenous populations in the South Pacific have long used the silk of the web to make fishing nets and traps, and at least one company is now using biotechnology techniques for the production of strong silk identical to that of spiders[42]. Thus, if cellular activity could be exploited, the synthesis of new materials by means of Synthetic Biology applications would become feasible and could be made accurate and efficient.

3.9.3 Biologically based electronics and computing

As discussed in the introductory part of this section, the core of Synthetic Biology rests in the construction of biologically based parts,

41 Mayer, 2005
42 ScienceNewsOnline, 1996

devices and systems which, in many cases, conform conceptually to their engineering equivalents. Electronics and computing are no exception to the applications of Synthetic Biology. However, it must be pointed out that the operating speeds, time constants and power consumption of biologically synthesised 'electronic' parts and devices are likely to be very different from silicon based electronic devices and computers. For example, biologically synthesised devices may be operationally much slower than their electronic equivalents. However, this may be an advantage if such devices are to be used to monitor biological processes as, for example, the time constants of the devices would match those of the environment in which they would operate. In addition, they may be driven by power supplies that derive their energy from the surrounding environment. Biologically synthesised devices may also be capable of operating in environments that would be inhospitable to their electronic counterparts.

3.9.4 The US lead

Whereas Europe is just beginning to foresee the potential of Synthetic Biology, most of the important activity to date has occurred in leading US universities and research institutions. These, for example the Caltech Center for Biological Circuit Design, are investing directly in Synthetic Biology research and education. Similarly, UC Berkeley, UC San Francisco and the Lawrence Berkeley National Laboratory have together started a Department of Synthetic Biology. MIT hosts a Synthetic Biology working group, runs Synthetic Biology modules as part of its new undergraduate biological engineering course and has produced a registry of standard bioparts. Harvard's undergraduate course on molecular and cellular biology offers a one year Synthetic Biology track.

US Federal Research Agencies are also now providing significant financial support in the field. The National Science Foundation (NSF) will announce a Synthetic Biology Research Centre, worth about $40m, in the near future; the US Department of Energy will shortly launch a programme valued at $700 million for research in renewable energy sources involving Synthetic Biology applications. Both the NSF and National Institute of Health (NIH) are providing awards for young investigators to pursue research in the field. Significant investments have also come from corporate and private sources: Microsoft has donated approximately $700,000 to partly fund the International Genetically Engineered Machine Competition; Codon Devices Inc. have raised $14m to develop the next generation of DNA synthesis technology, and Synthetic Genomics Inc. has made available approximately $30m for research in the area.

4. The current state of Systems Biology in the UK

'*Life is a relationship among molecules and not a property of any molecule*'

Linus Pauling, Nobel Laureate in Chemistry, 1962

4.1 Introduction

With the aim of sketching a national vision for the future of Systems Biology, the Academies surveyed the current state of developments in the field within the UK and in some overseas countries. Evidence was sought from Research Councils, universities, medical research charities, government, medical Royal Colleges, Scientific Societies and industry. Although the Academies' investigations were not exhaustive and may have missed individual initiatives, in aggregate the evidence collected provides a useful indication of the state of Systems Biology in the UK and abroad.

4.2 Centres

The most substantial systems biology initiative in the UK is the BBSRC/EPSRC Centres for Integrative Systems Biology (CISBs)[43]. Two funding rounds in 2005/6 saw a total of nearly £47m divided between the six centres at UK universities judged to have the vision, depth of knowledge, breadth of intellectual leadership and research resources to integrate traditionally separate subjects in top class interdisciplinary research programmes. Although most funding was provided by the BBSRC, about a sixth of the total was granted from the EPSRC to facilitate the integration of engineering, mathematics and physical sciences with the life sciences. After the first five years, the costs of supporting the centres are expected to be met by the host universities, although they are committed to providing some direct and indirect support from the outset. In the future, the Academies hope to see much greater involvement by other biomedical research funding bodies (e.g. MRC, NHS R&D, Wellcome Trust, Cancer Research UK and others) as part of the national initiative recommended in this report (see Chapter 5).

The research focus of the CISBs reflects the remits of the BBSRC and the EPSRC, concentrating on biology at the molecular and cellular level in plants, micro-organisms and animals as well as humans. The principal research directions of the centres announced after the first round of CISB funding focused on host-pathogen interactions of micro-organisms (Imperial College), basic cell function in yeast (University of Manchester) and ageing/nutrition (Newcastle University)[44]. The Oxford Centre for Integrative Systems Biology that focuses on cellular signalling provides an example of a CISB supported by the second round of funding. Further information about selected existing and planned centres in the UK can be found in Table 1.

A number of UK universities have established systems biology research centres outside the BBSRC/EPSRC initiative. Like the CISBs, many are relatively new and focus on basic science and low spatial levels: the main research theme of the nascent Cambridge Systems Biology Centre (CSBC) investigates signalling pathways in the model metazoan *Drosophila melanogaster*, while the new Cardiff Centre for Systems Biology describes biodiversity, predictive cytomics and transcriptomics as its principal research themes[45].

Although many systems biology centres focus on research at the molecular and cellular level, some apply systems approaches to tissues, organs and organisms. The Universities of Nottingham and Leeds have, or are planning, two centres apiece, each focusing on different aspects of Systems Biology[46]. The Nottingham Centre for Integrative and Systems Biology in

43 www.bbsrc.ac.uk
44 www3.imperial.ac.uk/cisbic, www.mcisb.org/, www.ncl.ac.uk/cisban/
45 www.camsysbiol.org/, www.uwcm.ac.uk/cisb/
46 www.nottingham.ac.uk/, www.leeds.ac.uk/

Table 1: Select Systems Biology centres in the UK

Name	Institution	Director	Status at Dec. 2005	Research focus	Further details
Cambridge Systems Biology Centre	University of Cambridge	Dr Steven Russell	Being established	Systems approaches to signalling pathways in the model metazoan *Drosophila melanogaster*	http://www.camsysbiol.org/index.php
Cardiff Centre for Integrated Systems Biology	University of Cardiff	Professor Paul Smith coordinates activity	Proposed/ Being established	Biodiversity, cytomics and transcriptomics	http://www.uwcm.ac.uk/cisb/index.htm
Centre for Excitable Systems Biology	University of Leeds	Professor Arun Holden	Proposed		
Centre for Integrative Systems Biology and Medicine	University of Nottingham	Professor Paul Greenhaff	Established	Employ systems and network-based approaches to address questions of clinical relevance, including arterial hypertension, sepsis, muscle atrophy, growth and metabolism, and nutritional genomics	http://www.nottingham.ac.uk/cisbm/
Centre for Integrative Systems	Imperial College London	Professor Douglas Young	Newly established BBSRC/EPSRC Centre 1st round	Host-pathogen interactions of micro-organisms	http://www.doc.ic.ac.uk/bioinformatics/CISB/
Centre for Plant Integrative Biology	University of Nottingham	Professor Charlie Hodgman	Newly funded BBSRC/EPSRC Centre 2nd round	Develop a 'virtual root' which will serve as an exemplar for using integrated Systems Biology to model multi-cellular systems	
Centre for Systems Biology at Edinburgh	University of Edinburgh	Professor Andrew Millar and Professor Igor Goryanin	Newly funded BBSRC/EPSRC Centre 2nd round	Methods to model dynamic biological systems, focusing on RNA metabolism, the interferon pathway and circadian clocks	http://csbe.bio.ed.ac.uk/management.html
Centre for the Integrated Systems Biology of Ageing and Nutrition (CISBAN)	Newcastle University	Professor Tom Kirkwood	Newly established BBSRC/EPSRC Centre 1st round	Ageing and nutrition	http://www.ncl.ac.uk/cisban/
Centre for Mathematics and Physics in the Life Sciences and Experimental Biology (CoMPLEX)	University College London	Professor Andrew Pomiankowski	Established Beacon Project DTC	Various but includes modelling the human liver at multiple spatial levels from the cell upward	http://www.ucl.ac.uk/CoMPLEX/About/index.htm
Institute of Membrane and Systems Biology	University of Leeds	Professor David Beech	Established	Various at multiple spatial levels	http://www.fbs.leeds.ac.uk/institutes/imsb.htm
Manchester Centre for Integrative Systems Biology	University of Manchester	Professor Douglas Kell	Newly established BBSRC/EPSRC Centre 1st round Associated DTC	Basic cell function in yeast	http://www.mcisb.org/
Doctoral Training Centre in Life Science Interface	University of Oxford	Professor David Gavaghan	Established EPSRC funded	Bionanotechnology, bioinformatics, medical images and signal, integrative biology	http://www.lsi.ox.ac.uk/
Doctoral Training Centre in Systems Biology	University of Oxford		Associated DTC	Complex language that single cell organisms use to control their behaviour	
Oxford Centre for Integrative Systems Biology	University of Oxford	Professor Judy Armitage	Being established	Complex language that single cell organisms use to control their behaviour	http://www.admin.ox.ac.uk/po/news/200506/apr/twentyfive.shtml
Sheffield Centre for Integrative Microbial Pathogenicity	University of Sheffield	No overarching control	Proposed	Microbial pathogenicity	
Warwick Systems Biology Centre	University of Warwick	Professor David Rand and Professor Liz Wellington	Established Associated DTC	Various, many at the cellular and molecular level	http://www2.warwick.ac.uk/fac/sci/systemsbiology/

Medicine (NCISBM), for example, employs systems and network based approaches to address questions of clinical relevance, including arterial hypertension, sepsis, muscle atrophy, growth and metabolism, and nutritional genomics[47]. Although not exclusively dedicated to systems biology research, the Centre for Mathematics and Physics in the Life Sciences and Experimental Biology (CoMPLEX) at University College London hosts a DTI Beacon Project (see section 4.6), a collaborative study in computational biology that seeks to build a model of the human liver by composing models of biological entities down to the level of cells[48]. Both NCISBM and CoMPLEX were established prior to the CISB initiative.

Dedicated academic centres rarely encompass all of the systems biology activities being carried out within the host university. Many have outreach programmes aimed at facilitating interactions with other researchers within the institution. These schemes include seminars and research days such as those organised for the opening of the CISBs. Other methods include 'hotel style' research facilities such as those offered at CSBC. A novel idea pioneered by Newcastle University consists of a dedicated Systems Biology Resource Centre to help develop Systems Biology in other areas of life sciences research, alongside the BBSRC/EPRSC Centre for Integrated Systems Biology of Ageing and Nutrition (CISBAN)[49]. At some institutions the dedicated centre is explicitly tasked with co-ordinating systems biology activity across the university. But in other cases, like Manchester, centres are also part of, or closely associated with, broader interdisciplinary life science research initiatives[50].

Not all universities are taking the centres route. An interesting initiative is planned at the University of Liverpool. This has established a virtual Centre for Biocomplexity that links four of the six faculties potentially incorporating around 70% of academic staff who, between them, have collected £27m total grant income since 2000. Interactions across the university will be facilitated through a comprehensive programme that includes workshops, newsletters, a website, videoconferencing, seminars and conferences.

The Academies were heartened to discover the substantial amount of work being carried out in the field of Systems Biology within the UK, although activities are fragmented and in need of resources and coordination.

4.3 Capacity building

The EPSRC Life Sciences Interface Programme has established nine doctoral training centres (DTCs) to prepare scientists with the skills to apply engineering, mathematics and physics to the challenges of modern medicine and biology[51]. The scheme has been set up in collaboration with other Research Councils (BBSRC, MRC and NERC) and although it covers the interface between the life sciences, engineering and the physical sciences, most centres, however, have a substantial systems biology component with applications at different spatial levels. Each centre has been awarded £1m-£1.5m to support up to five annual cohorts of a maximum of 10 students. In their responses to the Academies' call for evidence many of the systems biology centres discussed above expressed an interest in bidding for DTC status.

A second initiative that could support the education and training of systems biologists involves the Integrative Mammalian Biology Capacity Building Awards. Integrative biology is the study of how gene products integrate into the function of whole tissues in intact organisms. Understanding gene function in humans and other mammals ultimately requires mammalian models. The information that these can provide is central to the development of new therapeutic approaches to tackle human and animal

47 www.nottingham.ac.uk/cisbm/index.php
48 www.ucl.ac.uk/CoMPLEX/, www.beaconprojects.org.uk/
49 http://bioinf.ncl.ac.uk/sbrc/
50 http://193.60.152.78/
51 www.epsrc.ac.uk

diseases and to help deliver safe and effective medicines. The awards are jointly funded by the BBSRC, BPS Integrative Pharmacology Fund (AstraZeneca, GlaxoSmithKline, Pfizer), HEFCE, MRC and SHEFC[52]. To reverse declining UK capacity in this very important field a total of £12m has been made available for four awards.

The joint MRC, BBSRC and EPSRC Discipline Hopping Awards represent another cross-council initiative that can support systems biology capacity building[53]. The objective of these awards is to provide short-term support to facilitate new collaborations between engineers, physical scientists and life scientists, with the aim of fostering long-term interaction. The scheme allows life scientists to apply for funding to investigate and develop ideas, skills and collaboration in the physical sciences and vice versa. As a result of a recent DTI Foresight project[54], these awards have focused on cognitive systems, the study of which requires a systems approach. In addition, the MRC in collaboration with the EPSRC, offers smaller Institutional Bridging Awards[55] to develop collaborative research programmes between the physical and life sciences as well as a joint training scheme with the US National Institute of General Medical Sciences in computational biology[56]. Systems biologists can apply for these three types of award but they are not aimed exclusively at them.

4.4 Other funding

Of all UK research funders, the BBSRC has invested the most resources directly into Systems Biology. As of spring 2006 its Oasis database indicates that it has invested at least £7.6m in grants for Systems Biology, excluding the initiatives discussed above and those at its research centres. Research described as 'theoretical biology' and 'integrative biology' represents approximately £6m of additional grants. The BBSRC has also supported around £170m of research underpinning Systems Biology, most significantly through the genome sequencing projects, as well as at least £38m for post-genomic science. Moreover, a sum of £30m has been committed to further establish systems biology research in universities and institutes.

In addition to the DTCs initiative described above, as of spring 2006 the EPSRC grant list indicated that it provided £6.3m of grants described as 'Systems Biology', principally through academic fellowships. Grants labelled as 'integrative biology' as well as relevant grants defined as 'modelling' total about an additional £4.2m. Elements of the EPSRC's Complexity Science work stream, worth just over £1m, also overlap with Systems Biology. The Academies are also aware that the EPSRC and the BBSRC have been considering supporting the development of technical applications for research in Systems Biology.

In addition to its involvement in some of the initiatives mentioned above, the MRC supports the Oxford Heart Physiome project and some independent systems biology research. The MRC's particular interest in Systems Biology lies between the levels of the cell and organism. Evidence submitted to the Academies highlighted work in neuroscience, biostatistics, enabling technologies, post-genomics and elsewhere. The Wellcome Trust supports some systems biology research, including projects such as the Heart Physiome Project and the Integrative Animal and Human Physiology Initiative[57]. Evidence from medical research charities such as the Arthritis Research Campaign, British Heart Foundation and Cancer Research UK indicates that Systems Biology is becoming an increasingly important component of their research programmes. The Department of Health reported a nil return on systems biology research conducted by its R&D Policy Research Programme and by NHS R&D programmes.

52 www.mrc.ac.uk
53 www.mrc.ac.uk
54 www.foresight.gov.uk
55 www.mrc.ac.uk
56 www.mrc.ac.uk
57 www.wellcome.ac.uk

4.5 Industry

Systems Biology is being applied in many industrial sectors including pharmaceuticals, biopharmaceuticals, biotechnology, food and personal care, some of which are outside the scope of this report. Based on the evidence received by the Academies, companies that have adopted Systems Biology in their activities can be divided into two broad categories: those that employ Systems Biology to make end products and those that create systems biology tools, which are sold to, and used by, the companies in the first group. Many Small and Medium sized Enterprises (SMEs) in the biotech sector for example, belong to the latter category and, mainly in the US, seek to license their tools to larger pharmaceutical firms.

Some confusion exists about the understanding of 'Systems Biology', as it is often interpreted as a purely informatics solution to the question of biological complexity. Currently, only a few companies are putting the core concept of Systems Biology properly into practice by informing their research through the iterative cycle between experimentation and modelling. For instance, a substantial number of companies principally focus on informatics tools and undertake little experimental activity. Also, in sectors that rely on external partnership, such as biotechnology, multidisciplinary teams are uncommon. In contrast, the exchange between biological experimentation and computational modelling occurs routinely in large pharmaceutical companies. Here, multidisciplinary teams, where life scientists, engineers and physical scientists work together, are the norm.

The majority of the universities that provided evidence expressed a desire to collaborate with industry. Many academic-industrial collaborations are in the pipeline although only a minority have been finalised. Researchers from the six BBSRC/EPSRC centres are being invited to participate in a second initiative, worth a total of £5m, which aims to help UK bio-industries exploit the cutting edge expertise and facilities in the centres. Academia-industry collaboration has been promoted through industry funded academic posts, such as the AstraZeneca Chair of Systems Biology at the University of Manchester, or industrial 'clubs', such as that established at Imperial College. A few universities also identified systems biology related spin-out companies or industrial secondments, placements and training. The majority of the university responses mentioned IP policies, although none were specific to Systems Biology. Universities tend to retain ownership of the IP created by their staff but provide incentives for inventors and researchers to generate IP. Most institutions mentioned some kind of commercialisation unit or subsidiary company with the task of dealing with IP issues, amongst other matters.

4.6 DTI Beacon Projects

In 2002 the DTI BioScience Unit launched an initiative aimed at promoting collaborations between industry and academia to create a critical mass in the field of Systems Biology in the UK[58]. The initiative is supported by a budget of £8m and involves several companies, including Microsoft, Unilever and Pfizer. The projects are ambitious and combine world-class, cutting-edge science with the potential to deliver wide-ranging benefits to industry including:

- Imaging changes in disease.
- Computer models to predict drug action.
- New rapid approaches to detecting diseases.
- Computer models to detect toxicity.
- Biochemistry *in silico*.
- Seeing genes in action.

As Systems Biology falls within the remit of the DTI's Technology Programme, it could be identified as a focus for future collaborative R&D support or a Knowledge Transfer Network.

58 www.beaconprojects.org.uk/

4.7 Medical Royal Colleges and Scientific Societies

Our survey of medical Royal Colleges indicated that they are not involved in this activity perhaps reflecting their preoccupation with specialist training and the quality of specialised clinical services. Scientific Societies, on the other hand, expressed greater interest. The activities being undertaken are principally organised in the form of scientific meetings, such as the Royal Society of Edinburgh's one-day conference on mathematical biology in 2005, or new journals, such as the Institution of Engineering and Technology's (formerly the Institution of Electrical Engineers) '*Proceedings in Systems Biology*' of the Royal Society of Chemistry's 'Molecular Biosystems'. An interesting recent development is the €250K (~£170K) Royal Society and Academies des Sciences Microsoft European Award for work at the intersection between biological sciences and computing[59].

4.8 The international picture

Currently the US leads the world in the application of Systems Biology to high throughput genome wide datasets. The Institute for Systems Biology in Seattle is probably the most advanced systems biology centre in the world. It was co-founded by Leroy Hood in 2000 and has now expanded to 11 groups and more than 170 staff members with an annual budget of more than $25m[60]. Other US initiatives, such as QB3 at the University of California, Stanford BioX and those at the Whitehead Institute, have dedicated similar capacity and resources to Systems Biology[61]. A recent report from the World Technology Evaluation Centre (WTEC) highlights that the current US lead is largely due to investment by funding organisations and research institutions made over the last five to seven years[62].

Whereas the US has the most significant targeted investment in Systems Biology, several other countries have been following a similar trend in the last few years[63]. In January 2004, the German Federal Ministry for Education and Research funded an interdisciplinary systems biology research initiative, the German hepatocyte programme HepatoSys Network, with the aim of achieving a holistic understanding of human liver cells biology[64]. The Swiss initiative in Systems Biology, Systems X, involves the Swiss Federal Institute of Technology in Zurich and the Universities of Basel and Zurich, and aims to enhance and expand transdisciplinary research and education at the highest level in the field[65]. Japan boasts a number of important research initiatives, often supported through traditional government programmes, including the Kitano Symbiotic Systems Project, and work at Riken, Kyoto, Keio and Tokyo Universities[66]. Significant research is also being undertaken in Australia, Belgium, Canada, the Netherlands, New Zealand, Singapore and South Korea.

The European Union funds several projects concerned with Systems Biology within the Sixth Framework Programme, for example EUSYSBIO, DIAMONDS, COSBICS and the BioSim Network[67]. Importantly for the future, the proposal for the Seventh Framework Programme 2007-2013 includes significant references to Systems Biology under the themes of health and biotechnology. Moreover, the European Science Foundation has identified Systems Biology as 'a Grand Challenge for Europe' that requires pan-European efforts to meet it[68]. The Federation of the European Biochemical Societies (FEBS) disseminates

59 www.royalsoc.ac.uk/
60 www.systemsbiology.org/
61 www.qb3.org/, http://biox.stanford.edu/, www.wi.mit.edu/
62 World Technology Evaluation Centre, 2005
63 World Technology Evaluation Centre, 2005
64 www.systembiologie.de/en/index.html
65 www.systemsx.ch/index.html
66 World Technology Evaluation Centre, 2005
67 Jehenson & Marcus (eds.), 2004
68 European Science Foundation, 2005

Systems Biology advances through its main publication '*The FEBS Journal*'[69].

4.8.1 International collaboration

Researchers in different countries and institutions have produced a plethora of models to simulate various biological phenomena. Yet, only a small proportion of these models are accessible to those outside the groups that developed them or have been documented in a form other than in the scientific papers where they were originally published[70]. Much of the promise of Systems Biology will be realised from insights that emerge from the combination of multiple experimental approaches and analytical techniques. For this to be achieved, it is essential that data are generated in a form that is suitable for sharing between different investigators and centres. International collaboration will therefore be central to the development of the field. Global consortia have already been established to address specific aspects of Systems Biology. For instance, the Physiome Project seeks to accomplish a quantitative description of the whole human organism, while the Receptor Tyrosine Kinase (RTK) Consortium strives to facilitate and coordinate international efforts for the understanding of RTK signalling pathways and their relationship to human pathologies[71].

International links with UK universities have been established, often in response to pressure from the grass roots rather than the centres. The search for research excellence and new academic colleagues transcends national borders. For instance, during the preparation of a systems biology programme targeting micro-organisms, the German Ministry for Education and Research accepted suggestions from scientists that bidding should be opened up internationally. Organisations from the UK, the Netherlands, Austria, Spain and Norway joined the German government in the creation of a 'transnational funding programme'. Its first deadline in January 2006 was met with a large number of high quality applications. The programme will be subsumed in the EraSysBio collaboration which may serve as a stepping-stone towards a substantial transnational systems biology programme in biomedicine.

It takes more than modelling software to connect models: the terminology used for system components, as well as their operational function, should be congruent. Separate models are required to test the diverse behaviors exhibited by a system but also to investigate systems at different spatial and temporal levels. Many discrete models cannot yet be combined to effect the modelling of larger systems. Universal standards and protocols are yet to be set and it is likely that these will originate from the international systems biology consortia. It is in this context where groups outside the US lead. For the last five years, the Silicon Cell Initiative has been running a website that collects models published in associated journals and makes them publicly available[72]. The European Bioinformatics Institute has recently started a repository for models that aims to establish more extensive linkage to databases[73]. All these initiatives adhere to the world-wide standard of systems biology Mark-Up Language, making models exchangeable in a uniform format. Nevertheless, establishing international standards can be time consuming and requires collaboration between multiple key stakeholders.

69 www.febsjournal.org/
70 Finkelstein *et al*., 2004
71 www.physiome.org, www.rtkconsort.org
72 www.siliconcell.net
73 www.ebi.ac.uk/services/

5. Imperatives

'*The problem of biology is not to stand aghast at the complexity but to conquer it.*'

Sidney Brenner, Nobel Laureate in Physiology or Medicine, 2004

5.1 Working across cultures

Research in the field of Systems Biology requires close interactions and collaborations between many disciplines that have traditionally operated separately such as medicine, biology, engineering, computer science, chemistry, physics and mathematics. Although research methods may be specific to an individual discipline, research objectives can be shared. There has long been recognition of the value of interdisciplinary collaboration, however the successful realisation of a common research agenda has been the exception rather than the rule.

Limited training in disciplines other than one's own may lead to misconceptions and misunderstandings with regard to what scientists from different backgrounds actually do, how they do it and what could potentially be achieved. Life scientists often fail to appreciate the distinctions between the sub-disciplines within engineering, mathematics and the physical sciences whereas physical scientists often react with surprise and frustration to the fuzziness of biological concepts and data, and the fact that biology keeps evolving. This reflects the dichotomy between the two types of disciplines that is principally due to the differing nature of the problems they try to address. The physical scientist, for instance, expends great effort to reduce experimental variability, while the life scientist may seek patients that show extremes of disease susceptibility or drug response as clues to new understanding through genetic variations.

Important differences also exist in the understanding of common concepts such as 'model', 'elegance' or 'theory', the meaning attributed by the two classes of researchers to such terms and the contexts in which they are used. A simple example of a cultural barrier is the tendency for life scientists to use a Microsoft word processor whereas many computer scientists use LaTex. In isolation this would be a trivial challenge, but it is symptomatic of deeper divisions. Hence, there is a need to ease communication and to breach the gap between the practices in the life sciences and those in engineering, mathematics and physical sciences. The evidence submitted to the working group revealed a host of different methods for bringing researchers from different disciplines together including workshops, training, seminars and conferences. However, they need to be applied more extensively and routinely.

Research in traditional disciplines is conducted by reducing a problem to its elementary components and studying each of them separately. Reductionistic research tends to be monothematic and therefore conducted by scientists who are highly specialised in closely related subjects, if not sub-specialties of the same one. In contrast, Systems Biology demands a focus on the problem as a whole and therefore a combination of skills, knowledge and expertise that embraces multiple disciplines. However, at present, assorted teams are unusual in academic environments but they have to become a common feature if Systems Biology is to advance. A good model that could inspire the organisation of university laboratories is provided by the research practices of pharmaceutical companies. Here, researchers are arranged in interdisciplinary teams and operate in a problem-focused mode whereby individual contributions are aimed at advancing the progress of the team towards the solution, rather than that of the individual scientist.

Adapting academic research practices to interdisciplinary trends will therefore require the reorganisation of traditional universities, research groups and laboratory space. Teaching arrangements will also have to be adjusted in order to ensure appropriate training of future systems biologists. But more general issues such as the Research Assessment Exercise (RAE) and peer-review system also need to be addressed. Finally, research will have to be supported by appropriate infrastructures and organised in a manner that facilitates exchange of knowledge and expertise between disciplines.

5.2 Infrastructure: centres or distributed networks?

One of the major issues, fervently debated among the experts and within the joint Academies working group, is whether researchers from different disciplines should be brought together within a single physical environment (centre) or team up as a distributed network. Within a centre, the opportunities for researchers to spend time together and to interact on multiple levels are significantly facilitated. Moreover, a shared infrastructure that can accommodate multidisciplinary teams may be the optimal arrangement to provide all the tools necessary for research in a rapidly evolving field such as Systems Biology.

In the short-term, the advantages of a centre are very appealing but, with suitable planning and effort, strong integration can equally be achieved in a distributed network. In addition, in the medium to long-term, there is the danger that centres may lose the vibrancy that characterised them initially. However, as Systems Biology is likely to become a pervasive approach throughout science, the expertise built in the centres will have to become an integral part of the hosting institution, similar to the plans drawn for the CISB centres. Nonetheless, there is a legitimate concern that centres may become isolated silos and not disseminate their expertise into the wider academic research environment.

Dynamic and visionary leaders can gather sufficient resources and create effective research infrastructures both in the form of actual research centres and distributed networks of collaborators. However, when considering the most efficient and rapid way to increase the UK's systems biology capacity in the immediate term, there are arguments in favour of co-location of researchers within single large academic centres. Distributed collaborations would still need a core to focus their efforts. While developments in information and communication technologies have allowed progress in high-speed networking of data, and facilities such as tele-conferencing have made international exchanges much easier, close physical proximity with informal regular interactions is most likely to build effective teams and result in timely research outcomes. The conclusions of the WTEC report, discussed in chapter 4, and the success of the BBSRC/EPSRC's Interdisciplinary Research Centres lends weight to centres as a favoured, but not exclusive, model for building up systems biology research rapidly.

Centres are likely to be an effective model for facilitating cross-discipline familiarisation. Although this can be aided by formal training programmes, much of the required understanding develops through 'osmosis', whereby time spent together opens up opportunities for discussion and other interactions necessary for joint research, and provides for the understanding of the differing research ethos, priorities, working practices and uncertainties in each contributing discipline.

Physical co-location of researchers has merits beyond those of facilitating cross-disciplinary interaction. Currently, many aspects of systems biology research require access to physically large and expensive pieces of equipment. It would be more efficient to centralise these in a

few high quality facilities rather than spread them too thinly. In contrast, some components of Systems Biology, such as computational modelling, are less capital-intensive and therefore could be more distributed.

Evidence submitted to this inquiry indicated that there was great enthusiasm for collaborations in both industry and academia, notwithstanding the numerous hindering factors. Centres provide a more convenient 'one stop shop' for industry-academia relations than distributed networks and might be better able to offer the security and longer term collaborations that industry in the UK needs.

5.3 New systems biology centres of excellence in the UK

As discussed in the previous chapters, the UK already boasts a number of centres, many of which are supported or driven by recent BBSRC/ESPRC initiatives and focus on systems at the molecular and cellular level. However, additional systems biology centres are needed to address medical or engineering problems that do not fall easily within the remit of existing initiatives and/or expand on fragmented projects that have been developed outside the BBSRC/EPSRC programmes.

Systems Biology aims to gain insight into the functioning of organs, physiological systems and ultimately the whole organism. The existing initiatives are not sufficient to create the critical mass and the knowledge base needed to achieve this objective. Thus, the Academies recommend the **establishment of new centres located within leading universities that have internationally competitive research in biology, medicine, engineering and physical sciences. They must be a focus of activity with effective networking to smaller centres in other universities, including those currently being established by the BBSRC and EPSRC, and linked to international initiatives. It is essential that the centres should seek collaborations with industry and the NHS to ensure that projects of high national economic importance receive priority. Systems Biology is destined to become a pervasive scientific approach and advancing this objective should form part of the mission statement of the centres. These must be outward looking and avoid becoming scientific ghettos. Their remit should focus on world-class research, ranging from basic science to clinical practice to industrial products and include formal training and education (i.e. Masters and PhD programmes) in Systems Biology (including Synthetic Biology, which involves the design and re-design of biological parts, devices and systems - with applications ranging from materials with enhanced properties to biofuels). The programme for each individual centre should reflect the strengths of the university (or universities) taking part but each centre will need to have a mixture of biology and medicine on the one hand and engineering, physical sciences and mathematics on the other.**

Funding should be allocated on the basis of competitive bids to Research Councils UK and centres should be chosen to tackle a wide range of challenging research topics. Examples of topics which might form part of the work of centres include: the toxicity and safety of medicines; the function of neuronal synapses; the growth of human cancers; ageing and the spread of infections in hospitals; however, this list is neither comprehensive nor exhaustive and is not intended to limit applicants. The example of the BBSRC and the EPSRC might be followed with a first phase followed by one or more additional phases. Engineering research, particularly in the field of Synthetic Biology, is set to grow rapidly and must form a significant part of the work of some of the centres proposed in this initiative.

The new centres should network widely, develop and spread expertise, drive the

creation of new methodologies, allow researchers around the country access to these developments and encourage knowledge sharing. Much of the work in the field is focused on complex problems where the goals are 'public' so outcomes must be made freely accessible. But some goals, such as the development of new drugs, will be inevitably 'private'. However, research at pre-competitive levels is not commercially sensitive and, therefore, can be shared.

The centres should be linked by the SuperJanet5 network, hold regular electronic conferences and one annual meeting with the BBSRC/EPSRC centres. There is considerable potential for sharing systems modules within the UK network with other European centres and world wide. The establishment of an overarching research body (either national or European) should be considered to assist coordination of tasks and ensure competitive progress. It is essential that the new centres should seek collaborations with MRC, NHS R&D and industry to ensure that feasible projects of high national biomedical importance receive appropriate priority. Pharmaceutical firms are highly focused on specific objectives and it is likely that, rather than working towards the general development of a systems biology knowledge base, they will work with both academic centres of excellence and small boutique firms to address particular issues as well as develop knowledge management systems to facilitate decision-making.

5.4 Additional investment

Systems Biology promises to improve the health and the wealth of the nation and raise its competitiveness to international levels. If these opportunities are not to be missed, significant resources must be invested in addition to the funds that are already being spent in the field. The Academies therefore recommend that **an investment of approximately £325m is made over a period of 10 years to establish three to five new centres. This consists of approximately £75m for initial capital costs to be spent over the first three years, and £24m per annum as recurrent expenditure. The size of each centre may vary. It is estimated that, at current prices, a centre capable of housing between 30 and 35 scientists and support staff, as well as up to 30 doctoral students, would have a core recurrent budget of £5m a year, including consumables. Additional costs would be incurred for equipment, constructing new buildings or adapting existing facilities. A capital budget of about £15m per centre would be necessary to meet this expenditure, although, as far as possible, existing resources should be re-deployed by the host university. Centres of this size would provide sufficient capacity to work on one major project and one or two subsidiary projects. After 10 years successful centres should be progressively integrated into their host university.**

The new initiative would be more costly than the present BBSRC/EPSRC programme because of the inclusion of projects involving a substantial engineering and medical component. Hence, additional government support is needed to realise this important opportunity for the UK. Partnerships should also be sought to offset part of these costs through strategic collaborations with industry, medical charities, the MRC, NHS R&D and the DTI.

The Academies foresee that, within the next 10 years, Systems Biology will evolve into an essential and pervasive component of scientific inquiry. It will provide innovative tools for the management of complex scientific issues and consequently reflect the quality of the work carried out in major research institutions. Provided that the centres pass periodic peer review, the Academies consider that a life of about 10 years should be sufficient to embed them within the university research framework. There may need to be a transitional period

during which universities incorporate the centres into their existing organisation, research funding agencies ensure that their grants committees are appropriately organised and HEFCs adapt their research assessment mechanisms for a better and fairer recognition of research excellence in interdisciplinary areas.

5.5 Leadership

Lack of overarching direction often hinders interdisciplinary research work, hence senior academics with a strong vision will be vital to drive Systems Biology forward. Worryingly, the replies from the universities to the Academies' call for evidence did not always appear to recognise the need for strong central leadership to overcome these problems. Only a few of them gave specific information about the responsibility that their directors would have in setting the direction of systems biology programmes, control of budgets, appointments and promotions.

The success of leaders in the field of Systems Biology will depend strongly on the extent to which they accomplish the creation of the environment that researchers need to develop an understanding of different working cultures, and manage also to implement strategies that integrate these cultures into shared working practices. Senior academics may have the initial vision for a project in Systems Biology but it will inevitably be the junior researchers, and their networking with peers, who develop the collaborative relations that eventually deliver the results. The infrastructure and working environment for the project must therefore be one that generates and fuels interaction at all levels. Junior researchers need to be encouraged and supported to commit time to such relations, and the familiarity and knowledge that they gain in the other discipline needs to be recognised. Leaders will therefore be expected to manage proactively the process of cross-discipline assimilation, clarifying research goals and preventing fragmentation.

Successful leaders often come with the most challenging, but potentially rewarding, visions and the ability to create excitement in a new area. The UK has many successful academics, but relatively few who can claim excellence in a second discipline. In the near future, it may be difficult to find a sufficient number of senior group leaders able to develop interdisciplinary teams and provide appropriate training and career development. This issue could be addressed by, for example, creating early and mid-career research development opportunities for highly imaginative and dynamic scientists that would enable them to branch out into a new subject area. Expansion and updating of existing discipline hopping schemes would be very helpful although the creation of 'new blood' posts and some overseas recruitment may be necessary.

5.6 Assessment and career progression

The HEFCs rightly strive to maintain the strength of individual and well-established disciplines but interdisciplinary research areas, which need to be nurtured so that they can become established and grow, can encounter difficulties when assessed by the RAE. Unlike much traditional research, interdisciplinary grant proposals may fall within the remit of two, three or even more main panels, making it much more difficult to assess them to a common standard, and the more disciplines involved the bigger the problem tends to be. Assessment criteria may differ, sometimes profoundly, between the life sciences and engineering, mathematics and the physical sciences. For example, in the assessment of mathematics less emphasis is placed on research grant income because much of the research is done by the individual academic without the need for a research team, a laboratory and specialised equipment. Conversely, in the life sciences research requires larger teams, a varied equipment base and experimental animals; it is therefore more expensive and thus leads to grant income

being used as a major index of success. There is a consensus among many senior academics that, despite some recent changes, it is simply not possible to adapt the RAE in a manner that will result in robust and fair assessment of interdisciplinary activities[74, 75]. The Academies hope that the newly proposed metric-based assessment procedures will be better designed for the appraisal of new research trends.

In most institutions assessment procedures determine promotions, which therefore also tend to be subject-specific. Consequently, researchers who engage in interdisciplinary research may be penalised. None of the universities responding to the call for evidence mentioned promotion procedures specifically designed for interdisciplinary research, although a few, such as Newcastle, mentioned measures for interdisciplinary staff in general. It is therefore desirable that institutions undertaking systems biology research consider new mechanisms of assessment and promotion to ensure that career progression is not hindered by the unsuitability of assessment procedures.

Young scientists who decide to explore a second discipline as part of their interdisciplinary training take disproportionate risks with their careers. The time required to establish themselves as interdisciplinary researchers is prolonged by the need to master their adopted new discipline and to develop their thinking to the point where major publications and funding proposals are possible. This can lead to slower development of the indicators that they require to demonstrate their scientific ability: a significant issue for both the individual and the hosting institution in the context of the RAE.

A further barrier is that research papers in different disciplines are subject to different peer-review practices. Within the mathematical and statistical sciences, for example, refereeing a manuscript takes, on average, longer than in the life sciences: this has a direct effect on the pace and urgency of research. There are also very different practices with regard to the number of authors and the order of their names on publications. Traditionally, in the life sciences, the order of authorship indicates the extent of an individual's contribution to the paper. This has repercussions on career progression and assessment as the more frequently a researcher is listed amongst the first few authors the more successful he/she is judged to be. Systems Biology often requires equally important contributions from many different researchers with different specialities and the order in which the authors are listed cannot, therefore, be reflective of the importance of their work. In the particle physics community, for example, papers frequently have tens of authors whose contribution is perceived as equally valuable and little significance is attached to the order of their names. Similar practices may be adopted to overcome the problem posed by Systems Biology.

Such factors and others constitute impediments to the development of interdisciplinary research and deter talented scientists. Individuals may consequently decide to pursue their career elsewhere, outside the UK or, alternatively, choose not to explore hybrid research fields and compromise their work within the boundaries imposed by the traditional classification of subjects and research areas. Circumstances such as these are undesirable and measures should be taken to ensure that universities provide appropriate environments for innovative research trends and for those scientists who wish to embark on such developments.

The Academies therefore recommend that **universities bidding for one of the new centres should be required to specify their plans for addressing the structural, organisational and human resource issues that are known to hinder interdisciplinary research; implementation of these plans would be a condition of a successful grant application.**

74 Academy of Medical Sciences, 2004
75 Royal Society, 2003

The interdisciplinarity of Systems Biology poses a challenge to the traditional structure of university departments and the current arrangements of research grants committees in the public, private and charity sectors. Academic organisation, funding streams and research assessment mechanisms must be evolved to encourage growth of interdisciplinary research activities such as Systems Biology. This needs to be reflected in approaches to leadership, career development, peer review and publication criteria. Universities must break down barriers between disciplines and consider new methods of organisation that promote the development of novel scientific approaches. A substantial change in culture is required, in which biology and medicine become more quantitative. The Research Assessment Exercise, as currently structured, continues to be a barrier to interdisciplinary research.

5.7 Education and training

If the UK is to remain competitive in the biomedical sciences as well as engineering, mathematics and the physical sciences in the 21st century, the challenges of training a cadre of researchers to deliver effectively the necessary capability in Systems Biology need to be addressed. Major initiatives in Systems Biology will require a very broad base of disciplines and associated skills but the exact mix of talents needed will change with time. Although the academic foundations of future systems biology researchers are almost certainly laid in schools, a detailed analysis of secondary education is beyond the remit of this report. Nevertheless, the importance of revitalising STEM subjects in schools to ensure the provision of sufficient numbers of high-calibre researchers in the future is recognised. Demonstration of the contribution that physics and chemistry can make to biology may lead to increased student interest in these subjects. A similar benefit is likely to result from showing the significant role that engineering also plays in biomedical research.

Currently, biological and the more numerical sciences are often taught separately. But interdisciplinary research requires engineers, mathematicians and physical scientists to have a thorough understanding of biology. They need both the expertise and the environment necessary to think about fundamental biological problems. Simply adding a little biological knowledge to their background will not be sufficient. Complementary issues arise when considering the training of biomedical scientists. For instance, life science undergraduates, including medical students, may receive some training in statistics, occasional exposure to bioinformatics and minimal introduction to mathematical modelling. This is not adequate to provide them with the skills required to engage fully in systems biology research.

It is paramount that students who embark on systems biology courses undergo rigorous training. For this reason teaching, at any level, should be delivered by the most research active staff, among whom today's systems biologists are to be found. However, given the conflict between the demands posed by teaching and the intense pressure to produce and publish high-quality research, universities must find ways to ensure that research active staff who choose to teach are rewarded appropriately.

A key question to consider is the amount of expertise that future systems biologists will require in a core discipline before moving into interdisciplinary research. Most academics need to feel 'rooted' within a parent discipline because from it they derive their primary peer support and recognition. At a recent BBSRC meeting that considered strategies to develop Systems Biology in the UK, many academics and industrialists indicated a preference for systems biologists to be trained in a core discipline before undertaking interdisciplinary work[76]. Discipline-hopping awards can help researchers to begin exploring a new subject. But, in their present form, these schemes are aimed more at familiarising the awardees with

76 BBSRC, 2006

the working culture of the other discipline than allowing the researcher to acquire new skills.

It can therefore be argued that future systems biology researchers should initially be trained in a 'parent' discipline at an undergraduate level before undertaking postgraduate systems biology training. Nonetheless, their undergraduate courses should also include exposure to problems and interaction with peers from other disciplines. For instance, final-year undergraduate programmes, or masters degrees, in one of the life sciences could include discipline-hopping modules in engineering, mathematics or the physical sciences and vice versa.

Currently, the education and training of systems biology researchers in the UK begins at postgraduate level. Many of the universities that provided evidence have, or will be, introducing masters or PhDs in systems biology. Interestingly, none of the universities that responded offer whole undergraduate degrees in the field, although a few, such as Glasgow, are planning to offer undergraduate modules. The tendency to establish postgraduate, rather than undergraduate, Systems Biology courses reflects the importance of mastering a parent discipline before moving on to a more wide-ranging training. Alternatively, universities may simply be piloting Systems Biology at postgraduate level before a wider roll out across higher education.

Inevitably, training in Systems Biology will be lengthy and expensive. It is a new area of research and therefore it is difficult to single out any one model of education and training as superior at this early stage. Nonetheless, rooting in a parent discipline allows the acquisition of a thorough understanding of the scientific method as well as providing a safe return path. The importance of this should not be underestimated, especially in light of the currently uncertain career opportunities in cross-discipline research. Indeed, systems biologists should be given opportunities to maintain their expertise in their parent discipline, for example by provision of protected time to pursue monodisciplinary research.

The UK is only now developing provision for training in Systems Biology. The substantial investment in DTCs that the EPSRC and the BBSRC are leading include four-year PhD courses. Some of these centres have taken explicit measures to provide students with a more interdisciplinary training. These include 'buddy systems' (two students, one of theoretical and one of experimental background running parallel PhD projects) and visits to other collaborating systems biology laboratories to carry out diverse work on a single project.

Nevertheless, current doctoral training programmes will need adjustment. The training of researchers with sufficient theoretical background to apply and develop modelling techniques and, at the same time, with an adequate knowledge of experimental biology to engage with the functionality of the data, will require cross-discipline work and the extension of PhD programmes to four or five years. Students may benefit from having supervisors in two of the disciplines that underpin Systems Biology, for example a biologist and an engineer, as is already the case at some of the institutions that submitted evidence to this inquiry[77]. As for the extended PhD programmes, financial incentives will have to be made available to attract high quality candidates and compensate for the delays that the extra time required to assimilate a new discipline can cause to early career progression.

Some respondents to the call for evidence highlighted the lack of postdoctoral training opportunities in Systems Biology rather than postgraduate programmes that are currently being addressed by the EPSRC and the BBSRC. However, others argued that postgraduate training would meet the need provided that sufficient research funds were available to allow for the longer training and the time to prepare publications.

77 A good model designed to address interdisciplinary education and training is provided by the Forum Scientium in Sweden (www.ifm.liu.se/scientium).

5.8 The foundations of systems biology training

The postgraduate model of systems biology training relies upon an appropriate supply of undergraduates taught in the core disciplines that underpin Systems Biology. Unfortunately these are currently in short supply. Figures from the Higher Education Statistics Agency indicate that, between 1994 and 2004 the number of graduates in engineering and technology, and physical sciences fell by 10% and 11% respectively[78]. Similarly, in recent years the UK's traditional strengths in pure and applied research in physiology and pharmacology have declined. Both the MRC and Wellcome Trust have expressed concern about the decline of the physiological sciences in the UK, particularly in terms of capacity. A substantial number of highly skilled *in vivo* physiologists will be lost to retirement in the next five years as, among other factors, the focus of research support has shifted towards an increasingly reductionist analysis of molecular pathways and their foundation in genomics. Systems Biology offers an exciting opportunity to revive physiology and pharmacology before the shortage of manpower in these disciplines begins to affect the UK science base and industry seriously. In its discussions with the Academies, the MRC showed a clear awareness of the importance of Systems Biology in rebuilding the physiological sciences and the Academies look forward to proposals in this area.

A recent report from the Association of the British Pharmaceutical Industry indicated that many science graduates lack sufficient skills in disciplines such as mathematics, physiological science and computer analysis, which are important to both Systems Biology and the pharmaceutical industry[79]. One important finding was the growing demand for computational scientists for the analysis of increasingly large biological and chemical data sets using a variety of modelling techniques.

Modelling is ever more being recognised as an integral tool within the pharmaceutical sector. However, whereas on the one hand modellers are more in demand, on the other, the number of experimentalists will always have to be higher since the collection of suitable biological data, needed to test models, is more resource intensive. It is the lack of proper data that creates most bottlenecks in systems biology research.

The growth of Systems Biology will further focus the importance of modelling in drug R&D and this is likely to require a shift in the way research funds are spent in order to develop the skills needed. Nevertheless, the anticipation of needs and the resources and career paths that can become available can be difficult. Government is taking steps aimed at making the UK science base more responsive to the needs of the economy. But while it is acknowledged that the pull from industry should play an important role in education and training, it should be considered along with other important variables when assessing strategic educational requirements for the country.

5.9 Education and training model

The Bologna model provides a framework for training systems biologists. If systems biology training is based on the Bologna model, this would comprise:

- BSc/BEng - three years, e.g. a first degree in engineering or physics.
- MSc - two years, a masters in biology or basic medical science.
- PhD - three years (minimum), a doctorate in Systems Biology.

This model is not intended to be prescriptive but provides a practical guide to systems biology training. Whichever model is eventually implemented, it must incorporate a significant component of flexibility to accommodate several special circumstances. For example, issues may arise with regard to professional

78 www.hesa.ac.uk/holisdocs/pubinfo/stud.htm
79 Association of the British Pharmaceutical Industry, 2005

accreditation in subjects such as engineering, where a four year MEng degree is required to fulfil the academic requirements for chartered status. This may be addressed by a specifically designed five year funding scheme. Not all of those submitting evidence agreed that the proposed model was the best available and some felt that it was too long. However, MSc/PhD programmes can sometimes be completed in five years, particularly if the MSc component involves a project that can count towards the first phase of the PhD. These schemes can be very useful in that they allow continuity of research during passage to postgraduate level and consequently avoid delays. The demands posed by systems biology training should not be underestimated and to compress the time required would inevitably compromise the rigour and quality of the training.

Medical degrees present another special case. The training required to pursue a clinical research career is extensive (11-12 years minimum) and many feel that it is already excessively long. In addition, most budding clinical academics also undertake a three year PhD in a laboratory discipline. Yet, for many of the foreseen systems biology applications close involvement of physicians is essential. Experience shows that, despite initial fears of mathematics, medical students can quickly assimilate the subject to a surprisingly high level of proficiency. Hence, one favoured solution is to ensure the availability of courses in engineering, mathematics and the physical sciences during the first phases of medical training. At the undergraduate level, optional modules in mathematics, modelling and simulation would help attract a more diverse range of recruits, who would therefore provide a more assorted set of skills and talents. At the graduate level, one year intensive additional courses should be made available to interested medical graduates and supported by appropriate training grants. The courses should include a thorough module in mathematics, followed by courses in systems theory, signal processing, computer programming, modelling, etc. Many medical schools are already embracing interdisciplinary trends and developing and implementing graduate entry courses that provide an opportunity to attract mathematically trained students into biomedicine.

The Academies recommend that, **given the urgent need to develop the skills required to undertake Systems Biology, new postgraduate courses and the expansion of postdoctoral opportunities should be created. For instance, undergraduates, including medical students, should be offered options in the core disciplines that support Systems Biology, as well as increased exposure to interdisciplinary problems and modules.**

Further urgent action is needed to revive subjects important to the development of Systems Biology such as physiology, pharmacology, engineering and mathematics. Such initiatives in education and training should be closely coordinated with programmes in the BBSRC/EPSRC centres.

Systems Biology is not simply an exercise in mathematical modelling: it requires a deep knowledge of the complexities of the biomedical problem being addressed, together with a thorough understanding of the power and limitations of the engineering and mathematical concepts being used. Courses in biology and medicine for engineers, mathematicians and physical scientists are crucial, but they must be combined with an expansion of mathematical training for biological and medical scientists to develop multi-skilled, interdisciplinary teams. Initially, in view of the shortage of trained personnel in the UK, there may be a need to create schemes that establish a new cadre of young systems biologists, involving overseas recruitment where necessary.

6. A 25 year vision for Systems Biology

'*Prediction is difficult, especially if it concerns the future.'*

Mark Twain, humorist and writer, 1835-1910

Presenting a realistic vision for Systems Biology projecting more than two decades into the future is difficult, not least because much of its potential will depend on technological advances, and it is hard to predict how far and how fast these will occur. It is also a challenge to formulate such a perspective without assuming advances that, at the moment, may appear to lie in the realms of science fiction. Nevertheless, considering the advances that have characterised the last 25 years, sceptics would probably have made similar assertions in relation to predicting our ability to achieve many of the high-throughput, highly detailed molecular technologies that are now almost routine. At that time it was not anticipated that the human genome would have been mapped by 2005 and that stem cell and molecular cloning technologies would have create cloned animals. Neither was it envisaged quite how great the impact of computers and network technologies would have been in acquiring and sharing data across the world. Coincidentally, the personal computer, an invention that unquestionably changed the world, has just celebrated its 25th birthday. To quote the American clergyman Harry Emerson Fosdick: '*The world is moving so fast these days that the one who says it can't be done is generally interrupted by someone doing it'.*

Perhaps one way to formulate a vision is by considering how Systems Biology is expected to develop by 2030, what tools it may produce, the resources likely to be required to achieve the objectives and, finally, by mapping out milestones for the assessment of progress towards these goals.

If the pace of technological development proceeds as anticipated by the analysis conducted in the 2029 Project, the impact of Systems Biology on healthcare will be substantial[80]. By that time, it is likely that modelling of human disease will be the accepted norm rather than the exception. This will lead to a routine understanding of the physiological mechanisms that are disrupted in the pathogenesis of complex diseases and the development of therapies whose effects are understood in the context of the whole organism rather than in isolated assays. Synthetic Biology will have developed sufficiently for its areas of application to have become clearly defined and for business to invest confidently in the field. Areas such as chemical engineering, biomaterials, electronics and computing will be undergoing significant transformation. Multidisciplinary science will be routine, with biologists, engineers and mathematicians all able to communicate 'in the same language'. During this time, there will have been a clear move from team working by scientists trained in single disciplines to teams of scientists from both biological and physical disciplines working together on specific projects.

In order to address the challenges of human health through the delivery of novel therapies, academia and industry will have evolved mechanisms of working together to develop and apply new science more effectively. By this time, it is likely that Systems Biology will have become another tool to be applied experimentally, much as molecular biology is today, and will not demand the existence of large, complex organisational infrastructures. It is also probable that clinical support systems that use systems biology equipment will have become a routine part of improving care of patients affected by multiple conditions who require treatment with a wide array of possible diagnostic and therapeutic alternatives.

80 Institute for Alternative Futures, 2005

However, before this vision can become reality, there is a need to build confidence in the ability of Systems Biology to deliver tangible results and value. In order to influence a change in attitudes and working practices, and also to break down conventional disciplinary barriers, programmes of work will need to be designed specifically to produce evidence aimed at increasing confidence in, and understanding of, the potential impact of Systems Biology.

The recommendations made in this report represent suggestions that are essential steps in this direction. The detailed programmes of work that eventually underpin these recommendations will need to be structured to deliver tangible and measurable near, medium and long-term objectives aimed ultimately at achieving the 25 year vision. Central to the success in achieving this is the urgent need to establish effective and robust mechanisms for industry and academia to cooperate in this task.

In a recent publication, the European Science Foundation described Systems Biology as 'a Grand Challenge for Europe', based on the assertion that the initiative to establish and realise the full potential of Systems Biology is too great for any one nation to undertake alone[81]. Delivering a concerted UK systems biology initiative, as proposed in this report, will offer a strong foundation to, and will also help to steer, this emerging grand challenge towards achieving the 25 year vision.

81 European Science Foundation, 2005

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Appendix I Working and review group members

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Appendix II Acronyms and abbreviations

ATM	Automated Teller Machine
BBSRC	Biotechnology and Biological Sciences Research Council
BPS	British Pharmacological Society
CISBs	Centres for Integrative Systems Biology
CoMPLEX	Centre for Mathematics and Physics in the Life Sciences and Experimental Biology
COX	Cyclooxygenase
CSBC	Cambridge Systems Biology Centre
CT	Computerised Tomography
DNA	Deoxyribonucleic Acid
DTC	Doctoral Training Centre
DTI	Department of Trade and Industry
EPSRC	Engineering and Physical Sciences Research Council
EU	European Unicn
FEBS	Federation of the European Biochemical Societies
HEFCE	Higher Education Funding Council for England
HER2	Human Epidermal Growth Factor Receptor 2
IP	Intellectual Property
LDL	Low-Density Lipoprotein
MIT	Massachusetts Institute of Technology
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MRSA	Methicillin-Resistant *Staphylococcus aureus*
NCISBM	Nottingham Centre for Integrative and Systems Biology in Medicine
NERC	Natural Environment Research Council
NHS	National Health Service
NIH	National Institute of Health
NSF	National Science Foundation
RAE	Research Assessment Exercise
R&D	Research and Development
RTK	Receptor Tyrosine Kinase
SHEFC	Scottish Higher Education Funding Council
SMEs	Small and Medium-Sized Enterprises
STEM	Science, Technology, Engineering and Mathematics
UC	University of California
UK	United Kingdom
US	United States of America
WTEC	World Technology Evaluation Centre

Appendix III Consultation and call for evidence

Evidence was obtained using the following methods:

- Letters from the Chairmen of the working group were sent to the Vice-Chancellors of Russell Group universities and Chief Executives of major UK biomedical and engineering research funders requesting an overview of systems biology activity at their organisations. Russell Group universities that declared substantive work in the field were then sent a second letter containing a more detailed set of questions.
- Letters were sent to the Presidents of the medical Royal Colleges and selected Scientific Societies to inquire about systems biology activity being undertaken by their organisations.
- Letters were sent to the Chief Executives of companies with known UK based R&D and possible interest in Systems Biology inquiring about their activity in this area.
- Meetings were held between the Chairmen and representatives from the BBSRC, DTI, EPSRC, MRC and Wellcome Trust.
- A wider call for evidence was placed on the websites of both Academies, which was also drawn to the attention of individuals known to have an interest in the area.

Responses were received from the following organisations:

Government

- Department of Trade and Industry
- European Commission
- Office of Science and Innovation (formerly Office of Science and Technology)
- National Health Service R&D

Industry

- AstraZeneca
- GlaxoSmithKline
- Hewlett-Packard
- IBM
- Johnson & Johnson
- Novo Nordisk
- Pfizer
- Renovo
- Siemens
- Unilever

Medical Research Charities

- Arthritis Research Campaign
- Association of Medical Research Charities
- British Heart Foundation
- Cancer Research UK
- Wellcome Trust

Medical Royal Colleges

- Faculty of Dental Surgery
- Royal College of Anaesthetists
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Obstetricians and Gynaecologists
- Royal College of Ophthalmologists
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Physicians
- Royal College of Physicians of Edinburgh
- Royal College of Physicians and Surgeons of Glasgow
- Royal College of Surgeons
- Royal College of Surgeons of Edinburgh

Research and Funding Councils

- Biotechnology and Biological Sciences Research Council
- Economic and Social Research Council
- Engineering and Physical Sciences Research Council
- Higher Education Funding Council for England
- Higher Education Funding Council for Wales
- Medical Research Council
- Research Councils UK
- Scottish Higher Education Funding Council

Scientific Societies

- Association of Clinical Biochemists
- Biochemical Society
- British Computer Society
- British Nutrition Society
- British Pharmacological Society
- British Society for Cell Biology
- British Society for Proteome Research
- Institute of Biology
- Institute of Biomedical Sciences
- Institute of Physics
- Institute of Physics and Engineering in Medicine
- Institution of Chemical Engineers
- Institution of Engineering and Technology (formerly Institution of Electrical Engineers)
- London Mathematical Society
- Physiological Society

- Royal Pharmaceutical Society
- Royal Society
- Royal Society of Chemistry
- Royal Society of Edinburgh
- Royal Statistical Society
- Society for Experimental Biology

Universities

- Imperial College London
- King's College London
- London School of Economics
- Newcastle University
- University College London
- University of Birmingham
- University of Bristol
- University of Cambridge
- University of Cardiff
- University of Edinburgh
- University of Glasgow
- University of Leeds
- University of Liverpool
- University of Manchester
- University of Nottingham
- University of Oxford
- University of Sheffield
- University of Southampton
- University of Surrey
- University of Warwick

Other

- GARnet
- Genome Arabidopsis Research Network
- Professor Erol Gelenbe
- Professor John Mathers
- Professor P M Williams

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