Schrödinger's Legacy: Systems and Life

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1 Preamble: Biological Life and Physical Systems

Our command of the laws of physics and their use with computers to simulate how things work is highly advanced. It has reached a stage at which even the most detailed behaviour of complex machines and physical systems can be reproduced within a computer. For example, automotive engineers work with system models that enable them to (almost) completely specify and validate the vehicle within a computer before there is need to construct prototypes or cut metal in a factory. This lecture is about how science aims to do similar things with living organisms. I use the contributions of Erwin Schrödinger during his 16 years in Ireland as an initial point from which to describe how scientists are setting about this huge task. Starting with the scientific sense of inquiry that led Schrödinger to ask 'What is Life?', I sketch out the scientific developments that are beginning, at least in part, to provide an answer to this question. During this scientific tour, we will pause from time to time to consider the social, economic, and cultural implications of seeking a scientific basis for the mechanisms of life. As a finale, I describe a particular research project in which the components of life are mathematically modelled, simulated, and studied in a computer, in a manner that echoes the way in which computer-aided design is used to develop and analyse complex engineering systems.

2 Schrödinger in Ireland

2.1 Coming to Ireland

In addition to posts in his native Austria, Erwin Schrödinger held university positions in several countries during a long and fruitful career. The penultimate of these was at the Dublin Institute of Advanced Studies during his period in Ireland between 1939 and 1956. After the *Anschluss*, life in Austria became extremely difficult, even intolerable, for anyone who did not fit the National Socialist mold. Schrödinger chose exile and, with his wife, left his homeland shortly before the borders were closed. They travelled via Switzerland *en route* to Belgium and a position as visiting professor at the University of Ghent. After the invasion of Belgium in 1939 the Schrödingers escaped to England before travelling at the invitation of Eamon de Valera to Ireland. Schrödinger was to spend 16 years in Ireland and in his autobiographical notes [1] describes this phase of his life in affectionate terms, in particular the initial invitation and subsequent support of Eamon de Valera. With excellent working conditions provided at Trinity College Dublin, Schrödinger was able to build a strong theoretical physics research activity, organise international colloquia, and produce over 50 scientific papers.

Schrödinger experienced some personal disappointments in his work, notably in his search for a generalised gravitational theory, but there were also many successes. It is one of these successes that will concern us. Specifically, a component of this Irish period was a series of public lectures delivered in February 1943, given 'to an audience of about 400 that did not dwindle' and entitled *What is Life?* In retrospect these lectures, and the subsequent book [2], were among the most significant elements of his career in Ireland. The ideas that he laid out helped shape molecular biology, but they have also resonated down the years in other ways. *What is Life?* continues to influence scientific thought profoundly, not least in the new research area of **Systems Biology** that I describe in the course of this lecture.

2.2 The little book

From the notes for the public lectures, Schrödinger prepared a book, 'this little book' as he self-deprecatingly called it. The book bore the same title as the lecture series

- *What is Life?* He could not have imagined the impact that this book, with its informally presented ideas and (deliberately) imprecise scientific arguments, would have on the scientific world. With more than 100,000 copies sold, *What is Life?* is the most widely known and distributed of Schrödinger's works. What made the 'little book' a scientific best-seller? Certainly it is clearly written and is accessible to the lay-reader as well as to scientists from other disciplines. Beyond this however, it offered a novelty of thought that was timely, stimulating, and even controversial.[1]

The time was right for the little book because the nature of biological research was changing. Amongst other developments, the discovery of chromosomes in 1879, the rediscovery of Mendel's work on heredity in the early 20th century, and the linkage of chromosome activity to Mendel's ideas, had created the conditions for a molecular approach to biology. Stimulation also came from Schrödinger's own field of physics. There had been profound advances in physics during the latter half of the 19th and first half of the 20th Century. Through Planck, Einstein, Bohr, Heisenberg, Schrödinger himself, and innumerable others, the theoretical basis of modern physics developed rapidly. Profound discoveries were being made and there was a confidence that these would touch all fields of scientific endeavour. Planck had foreshadowed this in his 1920 Nobel Prize acceptance speech when he used the term *molecular physics* in a way that captured the contemporary focus on the (statistical) role of fundamental particles in physics.

The statistical basis of modern physics was particularly important to Schrödinger when pondering his Dublin lectures. Schrödinger started by noting that single molecules contribute to the behaviour of a physical object only as part of an average with very many other similar molecules. Whereas, in biological processes, each molecule could play a determining role. To quote the text directly:

> *...(biological processes) are controlled by a small number of atoms which represent only a small fraction of the total sum of every cell*

In resolving this, Schrödinger used the idea of *a pure mechanism* and *purely mechanical conduct* to describe biology at the molecular level. To quote directly again:

> *...the clue to the understanding of life is that it is based on a pure mechanism...*

and

> *The living organism seems to be a macroscopic system which in part of its behaviour approaches to that purely mechanical conduct to which all systems tend.*

This idea of an underlying deterministic 'knowable' and *purely mechanical conduct* is central to our theme. It implies that a biological process can be represented and analysed by sets of mathematical equations and understood as a system. This is the theme that provided impetus to the application of methods used to analyze machines and non-biological processes in biology. Schrödinger's concept of a *pure mechanism*, however, was not on its own enough, and other scientific developments were occurring that would also prove important. I describe these in Section 4.

3 Interlude: War and the Shaping of Science

Before continuing with the main theme of the lecture, it is useful to recall the social and political situation at the time that Schrödinger's book was published. The

[1] To understand the potential for controversy we need only recall that 19 years before *What is Life?* appeared the state of Tennessee had passed the Butler Act banning the teaching of evolution in state schools. The Butler Act was repealed in 1967.

wonderful community of outstanding scientists that had flourished in Europe prior to the Second World War had been broken up and dispersed. Those that remained were recruited to the military or to wartime research. On both sides, key scientific researchers and engineers worked on the atom bomb [3] or other wartime science and technology [4]. In neutral Ireland, Schrödinger was insulated from the main currents of world events and was thus able to let his research go freely wherever his curiosity led. This combination of scientific isolation and overwhelming world events is possibly why *What is Life?* attracted so little controversy at the time. Its publication as war in Europe was ending was a fortunate coincidence. *What is Life?* was met by a scientific audience that was in many respects disenchanted with physics research and its destructive consequences. The ideas in *What is Life?* presented an alternative to wartime science - the study of biological processes - and the promise of using familiar analytical tools of physics on the 'pure mechanisms' of life.

What is Life? was refreshingly different, and thus welcomed by a scientific audience receptive to change and the opportunity to creatively contribute to society. A further reason why the work was so well received can also be found in a remark attributed [5] to Paul Dirac in 1939:

> *In 1926 people who were not very good could do important work. Today people who are very good cannot find important problems to solve.*

It other words, it was getting harder to do high impact research in theoretical physics. For this additional reason talented researchers were casting around for other areas in which to make their name. Schrödinger pointed out an attractive opportunity.

4 The Rise of Systems Theory

While I have used Schrödinger as the starting point for this lecture, other apparently unrelated contributions should be mentioned as significant in the emergence of **Systems Biology**. These belong not in Schrödinger's field of physics[2], but in electrical engineering science. In the late nineteenth and early twentieth century, electrical engineering underwent radical changes. The abstract nature of electrical phenomena required special mathematical methods with which to analyse the complexity of electrical system behaviour. In turn, this led to the routine use of mathematical descriptions of signals and circuits, such that a 'systems approach' for design and analysis developed. In a general sense, the systems approach is the analysis of objects in terms of interconnected functional modules (or 'black boxes') with precise properties that can be described mathematically by sets of differential equations. Once the function of a module has been characterised (in terms of a mathematical model), then its contribution to an overall system performance is completely determined by the mathematical description. This embedding of function within modular sub-systems and the formation of larger sub-systems of interconnected modules is central to the systems approach. Moreover, as we will see in this section of the lecture, it offers a structured form within which to study the 'macroscopic systems' mentioned in the Schrödinger quotation which closed Section 2.

4.1 Systems, signals, and feedback

Schrödinger would have only been obliquely aware of the systems approach being adopted and perfected in electrical circuit and communications theory during the

[2] Actually a number of important contributors to systems theory, especially pioneers of feedback theory, came originally from a physics background.

late nineteenth and early twentieth century. Nonetheless, these developments were crucial to the progress towards a systems approach to biology. Based upon methods pioneered by Heaviside, electronic network designers in the early 20th Century were using modular 'black box' descriptions of electrical circuit modules and characterising them in terms of their actions on the forms of input signals experienced in practical applications. By using harmonic decompositions, signals were also described using standard modules with precise mathematical properties. Thus, signals and systems became part of an overall macroscopic description of a process and the behaviour of a complex system could be analyzed knowing that this description was not specific to one particular kind of input signal or stimulus.

Of particular relevance to the systems approach, and contemporaneous with Schrödinger's work in Dublin, was the invention of the negative feedback amplifier [6], and the development of the associated mathematical theory of feedback systems by, most notably, Nyquist [7] and Bode [8]. The foundations for feedback systems analysis had previously been laid by Maxwell, Routh, and their contemporaries. It was, however, through the study of how to make electrical amplifiers with consistent and robust performance in telecommunications that feedback theory took on a clearly identifiable form. Specifically, it was through amplifier design, and related military work, that a clear theoretical understanding emerged of the role of feedback in determining system performance. As I discuss later, the concept of feedback and its determining role in many biological functions is central to the systems approach to biology.

At the same time as feedback theory was developing, the mathematical characterisation of signals was also progressing through the need to recover information in the presence of noise and the need to predict future values of signals from current and past observations. Today this has relevance when systems biologists write and speak of 'predictive medicine' [9] and drug developers ask for computer-based models to guide their experiments. However, in the early 20th Century the objectives were to reduce noise in telegraphy and to improve gun target-tracking systems. The communications and gun aiming problems were essentially related. In target tracking the problem was to determine, in a statistical sense, an estimate of the future outcomes of random processes, while in communications the aim was signal recovery in the presence of noise.[3] Many scientists and mathematicians worked on these problems, but the theoretical contributions that are remembered are those of Lee and Wiener [11] and Kolmogorov.[4] These works, together with that of Shannon [13] on information content in signals and the ability to recover it, were the remaining key elements to a systems approach to forecasting future outputs of systems and future values of signals.[5]

Toward the end of this period Wiener began work with members of the Harvard Medical School. His resulting book, *Cybernetics* [16], published just 4 years after *What is Life?*, stimulated many researchers, in particular control engineers, to apply ideas of systems, signals, and feedback mechanisms to living organisms. Today *Cybernetics* is considered a seminal work amongst systems scientists and stands with Schrödinger's 'little book' as a primary source of inspiration for the theoretical elements of **Systems Biology**.

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[3]Of relevance to both these problems is Wiener's generalisation of Heaviside's harmonic analysis of signals and therein lies a link to W. R. Hamilton. Heaviside, with the great Yale scientist Willard Gibbs, was involved in the 'Quaternion Wars' debate [10].

[4]Kolmogorov's contribution is described in [12].

[5]This period in the development of signal and systems theory are described in [14, 15].

4.2 Analogues and models

The existence of a mathematical model is at the heart of systems and signals analysis, and a unified approach to such models is important. Thus, alongside the developments mentioned above, there was a great motivation to research the underlying unity of the dynamical behaviour of apparently different systems [17]. The practical trigger for this development was the use of *analogue systems*. The idea that the dynamical response of a complex machine could be studied through the response of an analogous electric circuit was being used to efficiently solve engineering problems [18]. For example, electric circuits that would fit on a bench top could reproduce the behaviour of complex mechanical structures in a matter of a few hours, thus greatly accelerating the pace of development and design.

A natural sequel to this was the emergence, through the methods of dynamic analogies, of a general theory of systems modelling that showed that for a particular mathematical model there would be a set of equivalent chemical, fluid, mechanical, electrical, and thermal processes which all displayed the dynamical behaviour of the model [19]. The distinguished MIT scholar, H. M. Paynter, made a highly important contribution to this unification through his bond graph method of mathematical modelling [20]. This technique, inspired (in a strange symmetry) by molecular bonding in chemistry, is important because it formalises ideas of interaction between elements of a system in a graphical form suited to current systems thinking and computer implementation, rather than the classical techniques of Hamilton and Lagrange [21]. The underlying unity of system behaviour and associated dynamical modelling is now standard to the systems approach in all fields and has inspired new generations of researchers to widen the scope of unified modelling to include biological processes.

4.3 Dynamical analysis of systems

The development of systems theory in the shape of feedback theory, dynamical analysis, and mathematical modelling, provided structured approaches for a systems approach to scientific problem solving. It furnished a disciplined mathematical and scientific structure with which to understand Schrödinger's 'pure mechanism'. In particular, *dynamical* analysis methods pointed a way whereby biological processes could be understood in terms of their complete time history.

Mathematical modelling provides the means for describing the dynamics of a process. The methods of systems analysis and feedback theory allow the model to be tested and underlying properties to be explored. It is the combination of systems analysis, mathematical modelling, and feedback theory that gives Systems Biology its distinctive theoretical character. What biologists want from this theory is the ability to guide their research and make it more systematic. A systems approach can do this by deriving valid dynamical models of biological processes and devising computer-based simulations based upon these models in a form that can help predict biological outcomes. Such 'predictive models' can then be used to test proposals for biological mechanisms and allow ideas to be refined before expensive laboratory programmes are initiated.[6]

4.4 An overall perspective

It would be disingenuous to suggest that systematic mathematical methods were not applied to biology prior to the emergence of Systems Biology. There is a long history of physicists and mathematicians playing seminal roles in biological sciences.

[6]The video clip of the *Ball and Beam System* under automatic control is an example of a system in which modelling, analysis, and feedback leads naturally to predictive action.

For example, in [22] Mackey and Santillán describe contributions from mathematics and physics from the 18^{th} Century onward. Starting with descriptions of the role of Galvani, Volta, and the great Helmholtz, they show how a systems approach was implicit in the interdisciplinary and analytical nature of many major discoveries in biology.

More recently and under the names of Mathematical Physiology and Biology [23, 24, 25], modelling and analysis of biological processes has been present for many decades. The value of this research has widely been recognised but has only recently been embraced and connected to the systems viewpoint. For example, the publications of Hodgkin and Huxley in 1952 gave a quantitative dynamical model of action potentials in nerve cell communication [26] and had important consequences that I refer to in Section 9, but it did not kindle mass interest from the systems perspective. Likewise, the writings of Ludwig von Bertalanffy [27] gave a clear case for a systems view of biology, and while respected, did not spark a mass scientific response. Mesarovic [28] is widely acknowledged for his role in specifically developing a systems theoretic approach to biology.

From the life sciences, it is in the last two decades that key thinkers have embraced the idea of a systems approach to biology.[7] Kordon in *The Language of the Cell* [31], describes the function and signalling within and between cells in a language that a chemical systems engineer would be familiar with, while Harold in the *The Way of the Cell* [32] clearly states the necessity for a dynamical systems approach to biological processes. From the systems science side the embrace has been enthusiastic, with significant numbers of applied mathematicians, control theorists, systems scientists and engineers turning toward biological and physiological problems. New journals from the Institute of Electrical Engineers and the Royal Society of London are dedicated to new results in Systems Biology, and there is a growing community of researchers serviced by a number of international conferences.

5 Interlude: The Drugs don't Work

Systems Biology is an idea who's time has come. But why now? Why not thirty, forty, or fifty years ago? Part of the reason is the combination of a maturity in systems science and the availability of computing tools with which to implement the science. Add to this a perception on the part of biologists that a systems approach is necessary if their subject is to advance. However, there are factors at play other than scientific curiosity, and we must turn to the pharmaceutical industries to fully understand the growing international interest in Systems Biology.

The pharmaceutical industries have been highly profitable and they traditionally invest a large proportion of their profits in the development of new drugs and treatments. Investment in drug development is an absolute necessity for a company's survival. The existence of a company depends upon the continuous development of new drugs which can replace those which are no longer profitable. In this intensely competitive environment every player is looking for the smallest advantage over their opponents. However, drug development is a time-consuming and expensive process which can be prone to failure. Even after a drug has been introduced to the market, unexpected side-effects may cause its withdrawal.

Investors are acutely aware of the role of development, and so pharmaceutical company reports include details of the numbers and status of the drugs that they are developing. The failure or withdrawal of a drug can severely damage a company's viability and value as an investment. For example, when Merck withdrew an important arthritis drug from the market, the company's market value almost

[7] See for example the articles by Lander [29] and Hartwell et al. [30].

halved [33]. Even the largest company is not immune and Pfizer has recalled drugs at the US Federal Drug Administration's request. These are not isolated examples. Similar withdrawals and failures have occurred in most pharmaceutical companies, with the smaller ones being particularly vulnerable. In Ireland, the withdrawal of the drug Tysabri by Elan had a particularly dramatic effect upon the company, not to mention dashing the hopes of the multiple sclerosis sufferers who might have benefited from the drug [34].

The problems of the drug companies have led one economics commentator, Jeremy Warner [35], in an article entitled *Drugs don't Work* to remark :

> *...science is reaching the limits of its inventiveness...The number of genuinely new compounds coming through are on a falling trend...the dementias, cancers and the other little understood illnesses of the mind and body remain out of reach....*

Warner is not a lone voice, there is a growing consensus in financial circles that the pharmaceutical industries need to reform [36]. What Warner does is to concisely state the underlying commercial and social imperatives for a systems approach to biology. Indirectly, he is arguing for the kind of analytical/systematic basis for development in the life science industries of the form that has been standard in other manufacturing industries for many years.

In order to realise this, we need to take the systems sciences, join them with mathematical biology/physiology in computer-based dynamical studies, and apply them in a concerted way to increase our understanding of complex diseases. Long term investment will be required and the process will not be easy, as other developments in instrumentation and biotechology[8] must be in place. Despite the time and cost, there are tangible commercial and scientific benefits that can follow from a systems understanding, including [37]:

Computer-based dynamical models that aid our understanding of disease mechanisms.

New instrumentation that can allow quantitative measurement of key biological parameters.

'Predictive models' that can guide the outcome of development and research programmes.

I suggest that these opportunities, together with the high-throughput methods and new measurement technologies mentioned in [9], constitute a compelling argument for research investment in a systems approach to the life sciences - in other words Systems Biology.

6 Systems and Biology: Cellular Signalling

> *...(biological processes) are controlled by a small number of atoms which represent only a small fraction of the total sum of every cell.*[9]

The previous parts of the lecture showed how the components necessary for a significant new approach to biological research have come about as research fields have matured and commercial/social imperatives have emerged. In this and the following section I attempt to give an insight into the research strands involved in a systems view of biology.

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[8] I touch on these issues in Section 8.

[9] Page 76 [1]

6.1 Cells: Nature's chemical factories

Systems approaches in biology were given an important boost by the realisation that the sequences of chemical reactions that control organisms could be thought of as signalling circuits similar to those used in electrical systems. Indeed, the similarity to electrical network methods is striking [38], and provides a bridge between biological signalling and other communications networks. In biological cell signalling, cells receive information from their surroundings via receptors in the cell's membrane. Signalling molecules attach to the receptor and information about the external signalling molecule is passed via receptors through the membrane and into the cell body. Once inside the cell, the information is passed on to other molecules in a sequence of chemical reactions that sets up a signalling pathway [39]. The signalling causes a response or change within the cell, which might be in the cell state, or a change in gene expression within the nucleus. By initiating in the nucleus the DNA $\rightarrow$ mRNA $\rightarrow$ protein synthesis sequence, the protein content of the cell is changed and with it the cell function. Thus the cell receives signals from its environment and responds to them, for example, by growing or dying. There are many receptor sites on a cell membrane and a bewilderingly large number of signalling pathways within the cell. Moreover, signalling pathways are often not known with certainty and may interact in unknown ways, thus giving an added level of complexity to the signalling mechanisms and their influence upon cell function.

In technological terms the cell is like a complex chemical factory, that receives inputs in the form of a range of raw materials and operating instructions, and in response produces products by processing the input materials according to the instructions. Thus we can in principle use the modelling and analysis methods of chemical process engineering [40] to understand the workings of signalling pathways within a cell. The difficulty in doing this is one of complexity and understanding. The human cell is hugely more complex than the most sophisticated chemical engineering factory. And although biologists have a good understanding of many signalling pathways, in most cases the precise structure of the pathway is not certain and there is no quantitative knowledge of the chemical concentrations.

Paradoxically, it is because of these unknowns that a systems approach can contribute to research in signalling pathways and their function. Using appropriate equations to describe the signalling reactions [24] to construct mathematical models of what biologists believe a signalling pathway to be, systems analysts are able to produce predictive models of the pathway dynamics [41]. Then, in close interaction with biologists, and based upon the observed behaviour of the true pathway, the model structure can be modified until it is biologically plausible. In this way beliefs concerning signalling structures can be rapidly tested, adjusted, and refined using computer-based simulations. The example that I use in this lecture of apoptosis (or programmed cell death) is from the work of my colleague Eric Bullinger [42], and shows the cell signalling steps that lead a cell to dismantle itself after receiving an external signal telling it that it is no longer required.

The role of feedback is a central issue in all structural investigations of cellular signalling. It has long been known that physiological processes depend crucially upon feedback control systems to ensure that our bodies are able to function in a wide range of circumstances. For example, Wiener relates [43] how it was the ubiquitous nature of feedback as an essential feature of living organisms that inspired him to develop his vision of Cybernetics.[10] Within cellular signalling however, the use of feedback is more subtle and less obvious. What is surprising is that many of these subtleties are familiar to systems researchers who recognise them

[10]Feedback truly is ubiquitous. In another seminal work, Lovelock's theory of Gaia [44] can be read as the story of feedback on a planetary scale.

from previous experiences with electrical and fluidic circuits such as oscillators and bimodal switches. Such parallels, guided by the underlying unity of dynamical models, are useful as they allow the known behaviour of the man-made system to be used to test the existence of similar mechanisms in cellular actions [45].

The question of complexity still remains, but here the systems theory idea of modularity has attracted the interest of biologists. I have already mentioned that the concept of considering collections of components as a 'black box' or functional module is fundamental to the systems approach to technological development. Biologists have noted that the same can be true in organisms [46]. Once the function of a biological network within a cell has been established in a form that is thought to be correct, then it can be considered as a module which in turn is part of a larger network and so on. It is this concept of nesting groups of modules within larger more complex modules that allows highly complex technological systems to be analyzed in a structured way. Likewise in cell signalling processes, results available from Olaf Wolkenhauer's laboratory[11] have illustrated how certain repeatedly used sequences of chemical reactions can be conveniently modularised in a way that enables complex sets of signalling processes to be modelled and *in-silico* (computer simulated) experiments to be performed. Even when the underlying models are approximations, the use of simulation in this way is a valuable adjunct to laboratory work.

We are now at a stage where systems engineers and biologists are jointly investigating cell signalling pathways in a combined process of laboratory experiment, mathematical modelling, and computer simulation. By correlating the model performance with observed experimental behaviour the model can be tuned and biological questions can be raised. The results are helping biologists refine their understanding of the probable structure of signalling pathways and investigate new biological mechanisms. Although mathematical biology has laid good foundations, the mathematical models are not perfect and the limitations are many. Nonetheless, the systematic act of modelling clarifies these limitations and advances our understanding of issues such as molecular crowding and channelling and other little-understood mechanisms within the cell. Despite the tentative nature of our understanding of signalling within the cell, some courageous research groups have plans to model and simulate all the intracellular mechanisms within a computer and thus produce a *virtual cell* or *silicon cell*.[12] These projects are huge in their ambition and may only partially succeed. However, they underscore a key point: if the cell is nature's chemical factory, then we should have a computer-based simulation of it - just as we do with man-made chemical factories.

6.2 Inter-cell signalling: Nature's communications system

If the cell is nature's chemical factory, then the signalling between cells is nature's communications system. Signalling molecules are the means of carrying information from one cell to another, thus forming a network of communicating cells. Receiving cells process the information and react in the ways outlined in the previous section. Intercellular signalling networks are central to coordinating the function of cellular organisms to survive, grow, and change. In the immune system for example, the inflammatory cascade is a sequence of inter-cell signalling initiated by activated macrophages. Another better known example is the signalling in the central nervous system, in which a chain of electrical and chemical signals combine to control and coordinate neural functions through networks of interconnected neurons [47].

[11] Web link www.sbi.uni-rostock.de

[12] For examples see: www.nrcam.uchc.edu and www.jjj.bio.vu.nl.

Although there is often a good knowledge of inter-cell signalling pathways, there is still a benefit from placing inter-cell communication in a systems framework. This is particularly true where the existing knowledge of a signalling network is not quantitative and/or does not capture the dynamical elements of the communication. Just as in intracellular signalling, a quantitative knowledge of the dynamics of intercellular signalling can be vitally important - particularly when feedback is involved. In particular, it is possible to have two topologically identical signalling networks that display completely different behaviour depending upon the dynamical and constitutive properties of the signalling network links. This principle is a long established part of network methods of modelling in the physical systems sciences [19] and there are a growing number of examples in the Systems Biology literature. The small example that I use in the lecture illustrates how the cross-fertilisation of ideas from one area can add understanding to another. In particular, it shows how a knowledge of network dynamics drawn from engineering systems is able to reveal that a particular feedback loop in the basal ganglia-thalmocortical motor circuit has a multiplicative adaptive form, rather than a previously suggested linear form [48]. While this is a rather simple example, it shows how insights imported from systems science can help explain a neural signalling mechanism that would be hard to measure directly.

At a more general level, communication between cells, groups of cells, and entire organisms can be shown to follow quite particular dynamical rules which are informative to the biologist and useful to the systems scientist. I give two examples which have been selected for their visual appeal. The first relates to the synchronisation of behaviour [49]. This has been widely observed in cellular signalling, for example glycolysis [50]. The example shown is of synchronisation in social groups of fireflies in the Malay jungle. At night, these insects emit regular flashes of light to attract partners. The video clip shows how each group synchronises their flashing over a short period of time and occasionally falls in to synchronisation with neighbouring groups [51].

A second visible example of apparently organised communication is that of swarming. Anyone who has seen the concerted flight of flocks of starlings over roosting and feeding sites will have been struck by the tight synchronisation of motion. This kind of swarm behaviour has been observed in a range of organisms and mathematical theories have been proposed to explain how orchestrated movement can occur in large groups.[13] In an interesting reversal of this point, the phenomenon of coordinated flight in birds and insects has attracted the attention of systems engineers who try to model the coordination skills seen in bird flocks as a possible way of controlling groups of unmanned aircraft or robots. This area, referred to as formation flying control, is one of topical interest, see for example [52].[14]

7 Interlude: Could a Biologist Repair a Radio?

As an engineer I greatly enjoy working with biologists - they are friendly, open, and deeply committed to their work. However, it is often like travelling in a country where one has only a tentative grasp of the language. There is that continuous striving for comprehension accompanied by the occasional *frisson* of satisfaction when communication is achieved. The language gap between life sciences and the physical sciences is significant and we work hard to bridge it. But the language

[13]The second ball and beam system video demonstration shows how sets of apparently independent objects - in this case steel balls - apparently synchronise their behaviour under of feedback.

[14]See also Biomimetics which is the use of biological mechanisms to inspire novel technological development.

difference is only an indicator of a deeper and more serious difference in scientific culture. In a letter entitled *Can a biologist fix a radio?*, Lazebnik [53] described the cultural difference from a biologist's viewpoint. In a satire of biological research he imagines applying the experimental techniques of a biologist to the repair of a radio - with disastrous results. In a wickedly funny manner, he criticizes the lack of consistent systematic methods in his fellow life scientists. In doing so, he argues strongly that biologists should adopt the same standard mathematical and system theoretic disciplines used in the physical sciences, (electronic engineering in his example). The fact that his letter was published in the prestigious journal *Cancer Cell* clearly indicates that it is considered worthy of discussion.

From the systems side of the argument we too have much to learn from the life sciences, and as a result I see any change that occurs in how biologists work as being part of an interdisciplinary cooperation. However, change *is* necessary if we are to move forward scientifically. The lesson of history is clear. It was only when disciplined mathematical methods became routinely applied in the physical sciences and were combined with traditional skills that the first Industrial Revolution took hold and yielded consistent economic and social development [54]. I believe that a similar pattern will be followed in the development of the life sciences.

8 Systems and Biology: Integrated Measurement and Analysis

> *It is no longer inconceivable that the miniature code (contained in the gene) should correspond with a highly complicated and specified plan of development and should somehow contain the means to put it into operation.*[15]

The human genome project [55] was an outstanding scientific achievement that, to use a culinary analogy, gave the ingredients list for the recipe of life, but not the recipe itself. Thus Schrödinger's *means to put it (e.g. the genetic information) into operation* remains unresolved by the genome project and provides a powerful further impetus for a systems approach to biology. Seen from the genomic perspective, the key to further progress is through high-throughput measurement technologies and analysis methods that will account for large (network) scale interaction between proteins. Results thus far indicate that this will be insufficient and the next move appears to be the integration of all relevant data within a (static) network model and additional high-throughput diagnostic devices that can measure protein concentrations with greater sensitivity. From the systems perspective, this is approaching the Systems Biology area but from the opposite direction to the systems analyst. Potentially the catalogues of data on biomolecules will eventually provide quantitative data that is currently lacking in the pure system theoretic approach. In this part of the lecture I briefly outline the background to high-throughput measurements and attempt to link them to trends in network analysis and the goal of better diagnostic medicine.

8.1 Measurement technologies

In order to sequence the human genome in a reasonable time, automatic methods were required to process the material. This brought an important innovation - namely, the introduction of industrial scale automated measurement procedures into biology. In the sequel to the Human Genome Project the impact of automation has

[15] Page 56 [1]

been to give a strong emphasis to yet further high-throughput measurement techniques in molecular biology. Micro-arrays in particular now allow the expression of thousands of genes to be simultaneously measured. However, a gene set alone is insufficient to explain the mechanisms of life, and beyond genomics lies the study of the molecular components associated with gene expression. The volume of molecular components that must be analysed is huge and automated high-throughput measurement is essential. At the heart of this is the development of new nanotechnology to accurately differentiate between biomolecular components. Hood and co-workers [9] have highlighted this requirement and expounded a methodology that links the rapid analysis of biomolecular material to the potential for early disease diagnosis through changes in protein expression in diseased cells. A key issue is that *dynamic* measurement of molecular concentrations and interactions are required - indicating a need for non-destructive real-time measurement technologies. Micro-arrays for gene analysis are based upon nanotechnology developed in the semiconductor industry, and it is to nanotechnology again that engineers and device researchers are turning to develop sensitive new bio-sensors, (e.g. [56]) and nanofluidic devices that can automate biomolecular measurement.

The above procedures are one aspect of Systems Biology measurement needs. In order to advance understanding of the cellular signalling area, a systems approach to experimentation is required so that practical experiments are performed in known conditions and are repeatable. In this context, specific types of process engineering equipment and instrumentation 'know-how' are required. These are known from the bio-technology industries and will need to find a place in the biologist's wet laboratory if the systems approach to experimentation is to be effective.

8.2 Interactions and networks

High-throughput measurements yield huge volumes of biomolecular data and dynamical systems analysis methods founded in current systems theory are not necessarily appropriate to this situation. The field of *Bio-informatics* is deployed in these situations to establish correlation between data sets. Correlation analysis does not explain the causal patterns at work in a system and dynamical modelling tools are needed to describe causal links and interactions between biomolecular components and their function within an organism. The issue of complexity also exists. There are simple single gene - single protein effects, but there are also highly complex functional inter-relationships between biomolecules. Thus, as noted in Section 6, the functional properties of an organism are dependent upon a network of *dynamically interacting* biomolecules, which may well contain high levels of complexity.

The search for meaning in biological network structures is complicated by the fact that the mechanisms of life are often highly redundant in their structure. Redundancy means that elements can be removed from a biological module without fatally altering the function of the module. As a result, living organisms are remarkably robust to change, a fact that is important in both evolution [57] and in ensuring insensitivity to changes in the environment. Robustness is basic to survival; however robustness makes it difficult to analyse the relevant interactions in a biomolecular network because of the nature of the interactions that occur in systems designed for redundancy. For example, if certain types of feedback loops exist in a biomolecular network then the influence of intermediate biomolecules can be obscured.

Recently, a considerable body of research has been devoted to identifying key structural properties that biological networks share with networks from other areas of science and technology. A major motivating factor behind this research has been the observation that traditional random and regular graph models are inadequate for the description of numerous real world networks, ranging from the World-Wide-

Web to the network of interacting proteins in organisms such as yeast [58]. In particular, it has been demonstrated that such protein-protein interaction networks and the metabolic networks of a wide variety of organisms are more accurately modelled by the class of so-called *scale-free networks* [59, 60, 58]. Similar observations have been made concerning the World Wide Web, networks of collaborating scientists, food webs of interacting species, sociological networks and other networks [61]. One of the more important consequences of the scale-free structure is the existence of significant numbers of highly connected nodes known as *hubs* , which play a key role in maintaining the connectivity of the overall network. Typically, scale-free networks are quite robust with respect to random failures at points or nodes within the network. This is because the vast majority of nodes in the network are not hubs, and hence their removal or failure typically has little impact on the overall structure. However, this same property renders the network highly vulnerable to a targeted attack as the removal of a hub can significantly affect the connectivity of the whole network [62]. This phenomenon has been investigated for biological networks in [59] where it has been shown that the removal of *hub* proteins appears to be far more likely to have lethal consequences for an organism than the removal of randomly selected nodes. This has led to the hypothesis that highly connected nodes in a biological network are more important biologically to an organism. It should be noted however, that some recent work indicates that the link between the connectedness of a node and its biological significance is somewhat more complicated than this might suggest [63]. Another related area of research interest in the life sciences is the impact of social network structure on disease propagation through a population. A number of authors have investigated this question recently for a variety of network topologies, including scale-free networks and small-world networks [64, 65, 66, 67]. This work is closely related to, and some of it follows from, earlier results in the field of epidemiology on disease spread in heterogeneous populations. In particular, the effect of variation in the connectivity of the nodes in a network on disease transmission has been investigated before [68].

8.3 Real-time health care and diagnostics

A systems approach can help increase our understanding of the mechanisms and prevention of disease. Together with the measurement methods in Section 8.1, it is conceivable that such an understanding can lead to biomolecular predictions of disease state or susceptibility. However, such predictions must be supplemented with ways of measuring a patient's biomolecular profile. In this connection, blood analysis provides an accessible window on the biomolecular profile. As a result real-time blood analysis is a target for instrumentation groups interested in Systems Biology measurements.

The example that I give in the lecture is from a collaboration in which we are working on a portable blood analysis instrument that uses novel systems theory to create a compact and portable device. The aim is a non-intrusive measurement device that can profile blood contents through the skin and present the analysis in real-time. *In-vitro* tests of the device [69] show that by applying appropriate signal processing theory we are able to measure relative concentrations of key blood components and provide a profile of the blood content based on the shape of its near infrared (NIR) spectrum. The *in-vitro* results have been encouraging and we intend to move on to *in-vivo* trials to further develop the device. Non-intrusive diagnostics of this kind are suitable for point-of-care screening, but need to be backed up with automated laboratory equipment with high sensitivity, good repeatability and good accuracy. These developments could well be based on high-throughput technologies of the kind described in [9, 56] in the nano-sensor field. Despite intensive development, measurement technologies for Systems Biology are, compared to the physical

sciences, in their infancy and much remains to be done.

9 Finale: The Physiome Project

In this final part of this lecture I outline a particular research project that I believe provides an outstanding example of what is possible through long term application and vision. Peter Hunter is Director of the University of Auckland Institute of Bioengineering.[16] Amongst many other activities, his Institute hosts the IUPS Physiome[17] Project. This is an international collaboration to develop a computational framework for understanding biological structure and function. The scope of the project is ambitious in that it aims to provide modelling tools for all biological processes from the protein level up to complete organisms [70, 71]. Although not explicitly declared to be a Systems Biology project, Hunter and his co-workers take, in my view, a systems approach to biology that captures the interdisciplinary dimension that Systems Biology should have. In particular, they consider the physiome to be a set of integrated systems, comprising sub-systems, which themselves contain sub-sub-systems, and so on. The huge range of physical size and time scales between the smallest sub-systems (biomolecules) and the largest system components (complete organisms) means that the researchers use a hierarchy of modelling and analysis procedures. At each system level different procedures are applied that are selected to be appropriate to the nature and time scales of the sub-system under consideration. This approach allows me to make an important clarifying point. I have emphasized the role of dynamical modelling in a systems approach to biology, and this might imply that only special forms of models (e.g. ordinary differential equations) should be considered. In point of fact however, the modelling procedure should be chosen to match the nature of the problem in hand. The complexity and range of challenges in the IUPS Physiome Project means that a wide range of modelling and analysis tools are used, but always within a systematic framework.

In addition to the IUPS Physiome Project, Hunter's Institute also [72] collaborates with Oxford University and others in the Wellcome Heart Physiome Project.[18] Originally motivated by the models of Hodgkin and Huxley that I mentioned earlier, Denis Noble of Oxford University has researched computer-based modelling of the heart since the early 1960's [73]. Separately and jointly, Hunter and Noble have made outstanding contributions to the mathematical modelling of biological systems [74, 72] and their collaboration is now embodied in the Heart Physiome Project. A realistic dynamical model of the human heart is a huge challenge. Despite the size of the challenge, the international team have created computer-based simulation models of the heart that display a range of known cardiac phenomena, in a manner that has attracted significant interest from medical and commercial sectors.

I mention the physiome projects for two reasons. First because they are the culmination of a commitment by dedicated scientists over a significant time period - thus underlining my point that Systems Biology requires a long term vision. Second, because it is an excellent illustration of the use of modelling as a unifying structure within an interdisciplinary and multi-layered project. Although the work has its roots with physiological modelling started forty years ago, research progress in the interim period means that their work now spans physiological modelling, cellular modelling, and molecular biology.

[16] Web link: www.bioeng.auckland.ac.nz

[17] Physiome = physio (life) + ome (as a whole)

[18] web link: www.bioeng.auckland.ac.nz/projects/heart/heart.php

It is not possible to give justice to the scope of the physiome projects within a short public lecture, but the slide sequence and video clip of this work provides a view of the range of activities in these enterprises. The concluding video sequence from Hunter's laboratory illustrates elements of what might be called the Systems Biology dream. Namely, a modular but comprehensive computer-based dynamical simulation of functional elements of the human body in which the basic building blocks are biologically accurate models of human cells.

10 Conclusion

Many countries in the developed world have identified Systems Biology as an economic, social, and scientific priority. As a result, it is developing rapidly and, as happens in any emergent area, there are many interpretations of and claims made for the field. There are two primary perspectives: one driven by systems analysts (Section 6) and one driven by high-throughput biomolecular measurement, (Section 8). In this lecture I have tried to fairly describe both of these, while holding to the view that Systems Biology is primarily about dynamics and interaction and their use in understanding biological functions.

In concluding this lecture I briefly lay out the research and development elements that can unify and advance the various perspectives on Systems Biology. They are:

Intracellular signalling. The mathematical modelling of the dynamical information signalling within cells.

Intercellular signalling. The mathematical modelling of dynamical communication of information between cells within tissue and between functional biological modules.

Biological networks. The complex networks that describe dynamical interactions within an organism at the biomolecular level.

Measurement and experimental technologies. The technologies needed for high-throughput biomolecular measurements, and the bioprocess engineering technologies which will ensure consistent repeatable experimental conditions.

Model integration. The integration of the intracellular, intercellular, and physiological model components, calibrated with data from laboratory measurement and experiment, into a dynamical computer-based simulation.

From a practical standpoint, the methodology that I propose for Systems Biology is the same that has led to our understanding and mastery of analysis in the physical world. As I noted at the beginning of this lecture, we can now model the behaviour of physical systems sufficiently well to (almost) completely design, develop, and evaluate the performance of complex systems without first building a prototype. An aspiration, albeit an optimistic and long term one, of Systems Biology is to repeat the process in the biological world. This statement needs to be accompanied by a strong caveat. It has taken over one hundred years of applied mathematical and engineering science research to bring us to the stage where we can design a motor car or an aircraft in a computer and simulate and predict its performance. The eukaryotic cell is indescribably more complex than the most elaborate of machines, and the interactions between proteins are so complex and numerous that an accurate analytical understanding of intra and inter cellular dynamics is a speculative and distant goal. However, we are aided by the fact that the models which we build do not have to be completely accurate. They need only be informative of the problem in hand.

A major stumbling block to further progress is the difficulty of measurement in biological processes and much effort needs to be focussed here. At the cellular level the real-time measurements of protein concentrations within the cytoplasm seems impossible - hence the concentration of inferential mathematical modelling mentioned in Section 6. In general, repeatable and accurate quantitative measurements of signalling also seem elusive unless advances in bioprocess technology become available. There is hope for real-time non-invasive measurement of blood content and this may assist, with high-throughput biomolecular assays and network analysis, in the development of predictive and preventative medicine.

I have also mentioned that there are strategic and commercial issues at play. Drug development is so costly and so lengthy, and the risks of failure so great, that the idea of predictive models that will allow drug companies to simulate and analyse cellular behaviour is very attractive. In this vein, governmental, non-governmental, and international health bodies have recognised that a systems approach to disease and therapies can offer public health benefits. Because of this, Systems Biology is currently the subject of intense commercial interest as a possible short cut for rapid drug development. In this context, I have tried to emphasise the dangers of expecting too much too soon. In the long term however it is conceivable that the use of scientific methods from the physical sciences in the study of Schrödinger's *pure mechanism* will lead to important scientific and health-care progress. The Physiome Project illustrates the directions that such progress might take.

If previous scientific and economic cycles are followed [75, 76], then we are on the brink of a revolution in how biological research and health care development are conducted. The long term winners in this process will be those who embrace a systems approach and automated bioprocess technologies. This will require changes which many will find disruptive and difficult [77]. However, the history of industrial and technological development shows us repeatedly that such change is unavoidable in our economic system [78], and that those who lead the change become the dominant contributors to scientific and economic development.

11 Final Remarks

In his autobiographical notes [1], Schrödinger described his 'Long Exile' in Ireland with warmth and expressed affection for 'this remote and beautiful island' and the people who offered him sanctuary. His work in Ireland on a general theory of gravitation was a disappointment to him, but the scientific impact of *What is Life?* endures. Ireland has seen many changes since Schrödinger's day. Ireland is no longer a remote island, but a dynamically evolving European country. It would provide a satisfying symmetry if the country where Schrödinger laid the basis for a systems approach to biology were to become an engine for its growth.

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