Systems Biology and the Spirit of Tustin

The 2008 Tustin Lecture

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Prologue

Arnold Tustin is best known for his contributions to control theory and its application to electrical machines. However, his interests were much wider than electrical engineering, for he was a polymath who brought a systems approach to each of the areas that he investigated. In modern jargon he thought 'outside the box' and in doing so championed the use of control systems theory beyond its traditional engineering limits. His impact was such that, in addition to his engineering contributions, he is also well known for his systems treatments of economics and to a lesser extent, the subject of this talk, biology.

Erwin Schrödinger was the first to suggest a systems approach to biology. In 1943 he wrote: *the clue to the understanding of life is that it is based on a pure mechanism* and made numerous similar allusions to the living cell as a system [1]. In the subsequent decades other distinguished scientists built upon Schrödinger's ideas and a mathematical/systems view of biology gradually began to grow. In recent years this growth has accelerated, with urgency added by concerns for the future of health–care systems and our inability to understand and cure important diseases. This extra social and economic pressure has led to a new multi-disciplinary movement within science – a movement that we call systems biology. The term movement is used because systems biology should be more than merely a new area of research. It marks a radical change of focus from the systematic and mathematical analysis of *physical* systems to the corresponding analysis of *living* systems.

From an historical perspective, we are at a stage in science comparable to the post–Newtonian developments of physics, engineering and technology – with the key difference that now we are trying to create a solid quantitative mathematical basis for biology, physiology and the study of disease. The enormous complexity of living systems means that understanding their behaviour in a quantitative mathematical way is very difficult. However, much of the difficulty is associated with the complexity of the dynamical properties of biological systems. This means that the tools of control, feedback theory and dynamical systems analysis should be central to a systems approach to biology. It is of inestimable importance that today's generation of control systems engineers recognise this and respond, in the Spirit of Tustin, to the opportunities that it presents.

Contents

1 Introduction

1.1 The Spirit of Tustin

As is appropriate in a lecture dedicated to the memory of Arnold Tustin, I will say some introductory words about the man, the work that earned this dedication and its connection to the theme of this talk. There is however a small problem; while the scientific literature is rich in references to North American contributions to control systems engineering, this is not generally true of other countries. This is no criticism of the USA – it is simply that America enthusiastically celebrates the achievements of its citizens in a way that other nations do not. This is especially so in engineering, and far too often we depend upon the dedication of individual historians for a record of achievements. In the case of Arnold Tustin, it is the scholarship of Christopher Bissell and Stuart Bennett that helps us. In an interview [2] and an obituary [3], Bissell captured the essential features of Arnold Tustin's character and contributions, while Bennett's invaluable book [4] describes Tustin's contributions in their historical context. I draw upon these sources for the following paragraphs.

Tustin's wartime contributions to control were documented in confidential reports [4] which were not publicly available for a number of years after they were written. In fact, it was not until 1947 and the appearance of four papers in the Journal of the Institute of Electrical Engineers that the true level of Arnold Tustin's contribution to 20th century 'classical' control was fully revealed. He first distinguished himself in the practical development of electrical machine control [5]. Related to this, his work with Daniell on nonlinearity in feedback control was important to the development of the describing function method [6] and he invented a signal flow graph representation that predated the similar method developed by Mason.

Elsewhere, he pioneered methods for modelling and analysis of human operators in feedback systems [7] and his ideas still influence 'operator in the loop' research. In control systems analysis he is best remembered for his time series methods for sampled data control [8]. His approach rapidly superseded alternative pulse control ideas and created the basis for modern sampled data methods for control systems analysis. The times series contributions won him lasting recognition with the association of his name with the bilinear 'Tustin' transformation.

In addition to his undoubted energy and professionalism, the essence of Arnold Tustin was his use of a systems approach to diverse problems. He did this by combining a natural curiosity with a broad practical experience, contextual insight and appropriate mathematical tools. With this unique combination, arguably the essentials for a systems approach, he was able to abstract the essence of a particular problem and thus resolve specific technical difficulties in a manner that had wider implications. The question naturally arises – how did he develop this systems approach? I suggest that the answer lies in his formative experiences; first as a boy experimenting with basic hand tools, then as an apprentice seeing the great range of endeavour required in a large

industrial concern and later, following higher education, as a professional electrical engineer. With this broad preparation it was almost inevitable that his interests would be attracted, via contact with such talents as Pestarini [9] and Daniell [4], to the philosophical processes and mathematical methods of control systems theory. From this it was only a short step to the analysis of systems of a more general kind, most notably economic systems [10]. Thus we have the Spirit of Tustin – a broad practical experience, leading to a systems approach to specific problems, combined with an ability to form the solution into a generally applicable setting.

Tustin used his knowledge of mathematics and dynamical systems to bring the power of a systems approach to the important problems of his times. The wartime work was vital for military needs, while his subsequent economic systems research was a natural response to the post–war economic situation. Tustin also recognised the need for a control theoretic basis for biology. He wrote about the area as early as 1952 [11] and continued his interest into his final years[1]. This leads me to speculate that, were he working today, he would be at the forefront of efforts to apply control ideas in biology, and in doing so addressing one of the most significant scientific requirements of modern times – the need to understand the mechanisms that control living systems and regulate disease.

1.2 Organisation of the Talk

I have tried to steer between the extremes of generality and detail by selecting a set of key themes that I believe are central to realigning control systems theory from physical sciences to life sciences. These are: *mathematical modelling*, *analysis of dynamics* and *underlying control principles*. In addition, I will draw upon three previous talks, each one addressing a different facet of systems biology [2]. Thus the account in Section 2 of the background to systems biology uses material from the quasi–historical talk *Schrödinger's Legacy*. This was given at the beginning of my time in Ireland and was part of a campaign to introduce systems biology to the Irish science community.

Section 3 reviews the uses of control methods in biology. It is based upon *The Rôle of Control and Systems Theory in Systems Biology* [12], a lecture specifically written for control specialists. An exhaustive catalogue of control methods in biology would be inappropriate here, so I only review the content of [12] and instead present some illustrative and hopefully motivational, examples. These are a mix of the work of colleagues in other laboratories and some results from the systems biology group at the Hamilton Institute.

The fundamental reason for a systems approach to biology is not only to find out *how* living systems work, but also *why* they go wrong. For this reason in Section 4 we look at systems biology as motivated by a systems approach to disease. This is based upon our attempts to place the physiological and

[1] In his interview [2], Christopher Bissell found Arnold Tustin, then blind and in his nineties, working on biology with the aid of a young amanuensis.

[2] These lectures are available from the reports section of `www.systemsbiology.ie`.

cellular processes that contribute to a particular disease (Parkinson's Disease) in a systems framework.

Section 5 is a coda on the need for changes in control systems research to embrace living, as well as technological, systems. The arguments are drawn from a lecture (*On the Industrialisation of Biology*) that was originally prepared for an audience of research strategists and science policy planners. However, the theme is also appropriate in a lecture dedicated to Arnold Tustin, since I feel sure that were he alive today, he would be making similar representations to the science community and government.

2 Systems Biology: A Historical Perspective

2.1 Schrödinger and What is Life?

A diligent historian can trace the development of a systems approach to biology back through many centuries, from the Ancients to the work of Linnaeus, Mendel and Darwin, and thus to modern times. For our purposes, the story begins in the first quarter of the 20th Century when, as the major results of modern physics became established, scientists who had achieved great things in quantum physics and relativity theory began to explore other areas. Max Delbrück was an important figure in this process, but its most significant impetus was given by Erwin Schrödinger in his 1944 book *What is Life?* [1]. Significantly, the German language version of the book came with the subtitle *The living cell observed through the eyes of a physicist.* This is important because, if we replace physicist with control systems analyst, then we come close to the interpretation of system biology that Tustin would have intended.

Schrödinger's little book was a publishing sensation – it captured the imagination of both scientists and the scientifically literate public alike, with many physical scientists and mathematicians drawing inspiration from its pages. Even now *What is Life?* remains in print and is the most widely known and distributed of Schrödinger's many works.

A theme of *What is Life?* was that specific functions could be attributed to individual molecules in determining biological outcomes. This laid the foundations for what we now call molecular biology and provided specific clues for Crick and Watson's search for an asymmetric crystal and code script at the heart of the chromosome [13]. In addition to the molecular theme, Schrödinger also repeatedly and forcefully described the need to consider living objects as machines with systematically determinable functions. This was a clear plea for quantitative systems analysis and is thus the first recognisable waymark to a systems approach in biology.

2.2 Huxley, Hodgkin and Mathematical Biology

Crick and Watson were not alone in taking inspiration from Schrödinger. Others were also inspired to apply mathematical analysis and the methods of physical

sciences to biology, the best known being Huxley and Hodgkin. In a series of papers in the early 1950's, Huxley and Hodgkin described practical measurements of the ionic processes in the giant axon of the squid. More importantly they described a mathematical model that explained their practical observations [14]. The combination of a mathematical model with biological measurement was central to their work, since it graphically demonstrated that a mathematical model could be used to predict the behaviour of cells. It was an outstanding scientific achievement [15] and stimulated other mathematical modelling work in biology, leading eventually to the areas we now know as mathematical biology/physiology.

It was the ability to make quantitative measurements that laid the foundations for Huxley and Hodgkin's success. However, in other areas of biology such rich and easily accessible sources of accurate biological measurement were not available. As a result the valuable modelling work done in this period had to wait for developments in instrumentation. Nonetheless, the work continued and the idea of a systems approach to biology owes a debt to the pioneers of mathematical biology and their works [16]. Indeed, the influence of Huxley and Hodgkin can be seen clearly through early work of one of today's leading figures, Denis Noble [17], and subsequently in work with scientists such as Peter Hunter on the virtual heart [18] and the Physiome Project [19].

2.3 Wiener and Cybernetics

In addition to his contributions to technological control and communications, Norbert Wiener also studied the principles of communication and feedback control in living entities. Wiener was not the first to think of feedback in living systems – Cannon had discussed it in the 1930's [20] in connection with the self regulation of metabolic processes. The important feature of Wiener's work was his explicit use of feedback theory as a mathematical tool with which to analyze biological phenomena. Wiener's other contribution was to give the idea a name – cybernetics [21]. Just as the hero of The Crucible [22] valued his name above all else, so Wiener realised that the way to create a following for a research area was to name it well. The name cybernetics, combined with Wiener's reputation and the popular appeal of his books, meant that many control engineers began to seek applications in the life sciences. But the new area failed to find the compelling economic and social motivation required to establish it properly; more time was needed.

2.4 Mesarović, Bertalanffy - Complex Systems and Systems Biology

A technical difficulty experienced by early cybernetics was the huge complexity of biological processes. Apart from certain generalisations and a handful of special results, the complexity of living systems was beyond the scope of 1950's control theory. However, a number of theorists began to see complexity as an important systems property *in itself* and continued to look at biology from a

more abstract viewpoint. Key figures in this movement were Ludwig von Bertalanffy and Mihajlo Mesarović. Bertalanffy was insistent that systems should be viewed as a whole, rather than by the reductionist approach that characterises much biological research [23]. Mesarović's interest in complexity in systems inspired similar ideas and it was he who first coined the term systems biology [24]. As with cybernetics, the existence of a name was crucial, and although systems biology has since been interpreted in a number of ways, Mesarović's perspective was vital to the later developments explained below.

In the years that followed the 1960's it becomes less relevant to name individual scientists, as growing numbers of researchers contributed to the development of theoretical and analytical methods. However, the area was to a degree quiescent – waiting for developments in experimental and measurement technology to mature. This area was given special impetus by the large scale automation of biological instrumentation needed in the Human Genome Project [25].

2.5 Automation of Biological Measurement

> *...more important than human genius is the development of technology...*

This remark was made in an historical account of scientific discovery [26], but it is also relevant to recent developments in a systems approach to biology. Indeed the difficulties in making rapid, accurate and repeatable biological measurements are so great that it is unlikely that systems biology would have found roots were it not for new developments in biological measurement. Measurement technology for biology had been improving continuously throughout the 20th Century (see Chapter 4 of [27]), but the need for better, faster, measurement methods came dramatically into focus with the publicity that surrounded the Human Genome Project in the 1990's. The success of the Project became dependent upon automated analysis of biological samples and this greatly accelerated and systematised gene sequence measurement.

The needs of the Human Genome Project gave an important impetus to technology development and the use of automatic sequencing machines, each capable of generating huge supplies of data, became routine. This in its turn stimulated developments of other measurement technologies and automated instrumentation grew in other areas of biological measurement such as imaging and cytometry. With quantitative data from reliable instrumentation, the stage was set for the emergence of a systems approach to biology.

2.6 The Growth of Systems Biology

The availability of large volumes of reliable data, combined with systems analysts motivated to study it, triggered rapid growth in systems biology. Growth brought with it diversity, and a number of interpretations of systems biology began to flower. This process was led by such charismatic figures as Leroy Hood and Hiroaki Kitano, each of whom has founded Institutes of Systems Biology

with their own distinct approaches. Hood is a pioneer of biological measurement technology and his Institute leans naturally in this direction. Kitano, originally an engineer in the Japanese electronics industry, is an enthusiast who attributes a more catholic meaning to a systems approach. His arguments evolve with time, but lean toward a bio-informatic interpretation of a systems approach.

Bio-informatics (meaning data processing of large *static* data sets from automated bio–measurements) has become confused with a systems approach to biology in which *causality* and the *dynamics* of the living process are central. This has given systems biology something of an identity crisis with the term frequently used sloppily, or as a fashionable slogan. Happily, as the thoughtful essay by Cornish-Bowden [28] shows, this is not universally true and there is a growing appreciation of systems biology's wider meaning.

As we will see later, it is currently mathematical modelling of cellular dynamics that is the main attraction of systems biology to biologists (see for example the recent essay [29]). Stemming directly from this popularity and the corresponding simulation of model dynamics, there is a gathering realisation among biologists of the importance of dynamics in living systems. This is slowly maturing into an acceptance that the analysis of dynamical behaviour and the methods of control and systems theory will be central to an understanding of biological function. In this context, the publication by the journal *Cell* of a paper with control experts as authors was a landmark event [30].

As important as the scientific motivations for a systems approach to life science is the pressing need to understand the mechanisms of diseases that have so far defeated conventional life science. As I will discuss later, the 'simpler' diseases have been conquered and those that remain seem intractable in their complexity. A hope is that mathematical and engineering methods, originally developed to understand physical systems, can help understand and systematise complexity in living systems. In this spirit, systems biology can be interpreted as a scientific response to a fundamental change in the requirements that society places on science and engineering. The pioneering work in mathematical biology and computational physiology provides a vital basis for the process of scientific realignment that this requires. In the next stage of scientific realignment it will be control, feedback and dynamical systems theory that are the core tools.

2.7 The Rôle of Control Systems Analysis

Their training in the physical and mathematical sciences does not adequately prepare control systems engineers for the life sciences. So a plan is needed to help give structure to how control and systems theory might contribute to various fields within the life sciences. Figure 1 outlines such a structure. In the left hand column the relevant areas of generic study and application domains are listed. The right hand column lists some of the control and systems approaches that have been found useful or are potentially useful. The first three items are obvious generic aspects of control systems, the lower three are specific topics that I have selected as being of particular potential. A more detailed classification and description of control topics in the life sciences is given in [12], here I will

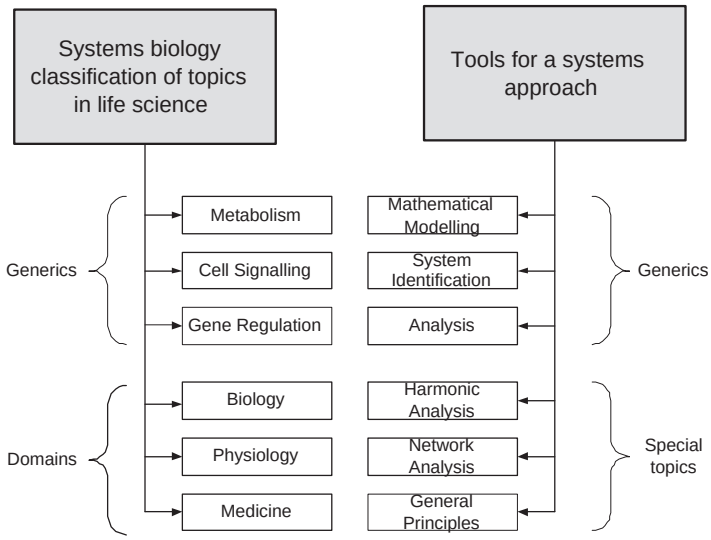

Figure 1: A systems biology classification of life science topics(left hand side) and relevant tools for a (control) systems approach (right hand side).

cover them only briefly before considering some motivational examples.

The left hand side of Figure 1 begins with a classification of generic areas in systems biology: (i) the dynamical behaviour of the metabolism, (ii) the signalling processes within a cell and (iii) the process of gene regulation. Each of these contains huge complexities and variation and the aim of a systems approach is to seek out general features, impose some standard form to the diversity, investigate the basic operational principles to which they might conform and then quantify their particular performance. The subsequent task is then to apply the ideas in the application domains: biology, physiology and medicine.

The right hand column lists the control and systems methods that we have found relevant in a systems approach to life. Some are obvious generic tools, but which have special nuances in life science systems. The relevance of the special topics, like network analysis and harmonic analysis, maybe less clear. Network analysis is important because of the complex interaction of the functional building blocks of biology – the proteins. Maps of protein interaction have been determined for a number of organisms, however further research is required to determine how these interactions relate to biological functions. The methods of network mathematics will be highly relevant to these issues [31].

The mechanisms of life at all scales, from the molecular to population dynamics, depend upon regular oscillatory patterns. Thus harmonic analysis will be crucial to understanding the function of biological processes. This points up a difficulty in the use of protein–protein interaction maps. Specifically, currently available maps are based on steady state information, whereas the time depen-

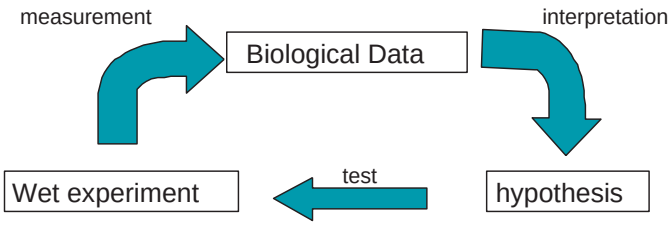

Figure 2: Depicting the traditional sequence for biological investigation.

dant protein interactions will be important for explaining biological dynamics. More will be said of this later.

3 Control Systems Themes in Life Science

In this section, we consider the implications of the generic tools and two of the special topics listed in the right hand side of Figure 1; starting with the generic tools.

3.1 Identification, Mathematical Modelling and Analysis

Mathematical modelling and computer simulation have become a popular adjunct to biological experimentation. Simulation in particular is used as an 'what if' tool with which to investigate hypotheses – much as a control engineer might do when examining the behaviour of a complex machine. Modelling has become more important as the biological implications of dynamical and spatial effects in cell signalling come to light [32]. In some cases, the modelling of cell signalling pathways has improved or corrected our knowledge of the chemical steps involved in certain signalling pathways [33].

The popularity of mathematical modelling stems from the difficulties in conducting biological and physiological laboratory work. The traditional sequence of an investigation is shown in Figure 2, in which a hypothesis is tested in the laboratory, the results are interpreted by the investigator leading to the modification of the hypothesis and its re–testing. Such experiments can be time consuming, labour–intensive, expensive and difficult to reproduce. Moreover they too often depend upon the subjective judgements of individuals, with judgements made some time after the experiment has been conducted.

Figure 3 show the model–based alternative. In this methodology, the mathematical model becomes the embodiment of the investigator's hypothesis. So that, with a candidate mathematical model of the biological process in hand, there is an objective quantitative criterion against which to assess the results of a practical experiment. On the basis of the practical observations the model can be changed, or other experiments performed to refine it. But there are

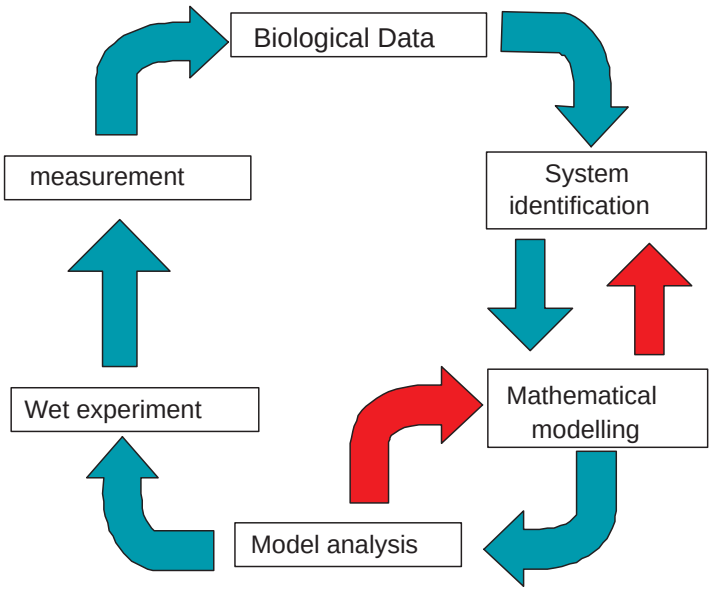

Figure 3: Depicting the model–based sequence for biological investigation.

other important features of Figure 3. These are (i) the use of system identification/parameter estimation to replace the qualitative interpretation of experimental data and (ii) the analysis of the model dynamic and static performance.

System identification and analysis of model dynamics are crucial phases in the systems approach. In particular, the interplay between identification and the mathematical modelling process allows more relevant information to be extracted from data. Likewise, feedback from analysis can indicate areas where the model might be improved. To emphasis the importance of these two feedback processes, the arrows associated with them are shown in red.

The issues of model–based judgement and estimation of model parameters, combined with measurement problems, have made modelling and computer simulation an attractive adjunct to laboratory experimentation. There is even a name for it – *in–silico* experimentation – to sit alongside existing terms *in–vitro* and *in–vivo* experimentation. With due regard for the dangers of over reliance on mathematical modelling and model based analysis, one proposition is to use *in–silico* experiments to efficiently design actual laboratory experiments [34]. Such use of models to inform how a real process *might* behave was a point emphasised by Tustin when writing on economics [35] in the 1950's. It is of equal importance today as biologists struggle to understand the frequently non–intuitive patterns of causality and dynamics observed *in–vivo*. The following examples illustrate this.

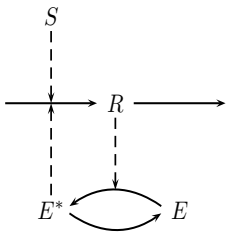

Figure 4: A simple biochemical reaction network illustrating mutual activation.

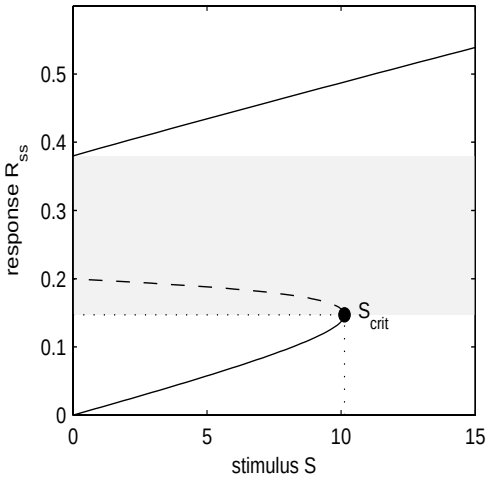

Figure 5: Showing the bistability induced by positive feedback. For stimuli between 0 and S_{crit} the response may take values on either branch of the continuous line.

3.1.1 Feedback and biochemical dynamics

> *FEEDBACK: It is the fundamental principle that underlies all self-regulating systems, not only machines but also the processes of life...*
> Arnold Tustin, Scientific American, Sept, 1953 [11].

In addition to the potential efficiencies of *in–silico* experimentation, mathematical modelling of cell signalling has analytical benefits. In the context of this lecture, the most important is how modelling reveals the part played by the interconnecting structures of feedback and feedforward in specific functions. Using an example drawn from [36], we consider a generic example of how feedback induced bi-stability can make one biological process behave in different ways during practical experimentation [37].

Figure 4 shows a positive feedback biochemical cycle in which a response R activates a protein E, which in its activated form E^*, activates R. The nonlinear nature of the activations results in a dynamical system with two stable points (figure 5) which, dependent upon the stimulation S and initial conditions $R(0)$, produce characteristically different responses. For example, Figure 6 and 7, show the responses for different stimulation amplitudes and reaction starting points. In a laboratory experiment, and without the model, these would be interpreted as different biological phenomena, rather than nonlinear manifestations of the same dynamical system. Such clarification of nonlinear dynamics in a biological circuit can be of enormous benefit in unifying apparently unrelated experimental observations and thereby generalising experimental results. As reported in the source article for this example [37]:

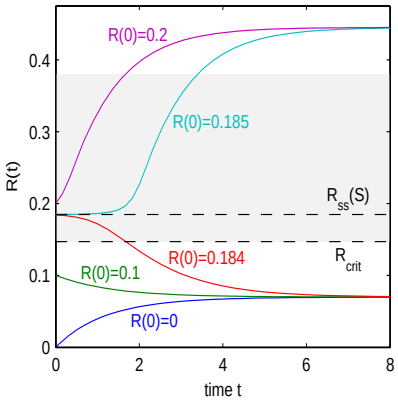

Figure 6: Illustrating the different forms of response obtained for different initial conditions on the response $R(0)$.

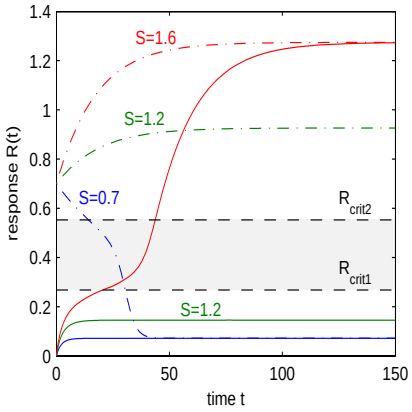

Figure 7: Illustrating the different forms of response obtained for different patterns of the stimulation signal S.

> *It would take an experimental biologist many time consuming and expensive experiments to obtain comparable results under each operating condition. And then there would be no way of determining that all the results were generated by the same biological mechanism.*

As a codicil to this example, we note that despite the complexity of its responses, the reaction network considered (Figure 4) would still only be a very small part of a complete bio-chemical pathway.

3.1.2 Stochastic models in biology

Simulations based upon deterministic ordinary differential equation models can provide valuable insights in many cases. However, randomness is intrinsic to the mechanisms of life and probabilistic modelling will be an essential tool as we become more sophisticated in our modelling of biological systems. Thus, although deterministic models (in their various forms [38]) of bio-chemical signalling cascades can be biologically informative, stochastic models are as important. Specifically, as the biochemical concentrations become lower, the variability of the molecular population in each stage of a signaling pathway increases and with it comes random variations in the reaction processes. The interpretation of what constitutes a 'low' number of molecules is a subject of debate. However, it has been suggested [27] that when the number of molecules participating in a reaction are of the order of dozens or hundreds, then the random element becomes significant and a probabilistic approach is needed [39],

Intrinsic randomness induced by small molecular populations in cell signalling extends upward to the variability in the behaviour of populations and species. As an illustration of this we briefly mention modelling of the adaptive

immune response. The dynamic evolution of a community of stimulated lymphocytes depends upon the interplay between the time taken for a cell to die T_{die} and the time to divide T_{div}. When on average T_{die} is less than T_{div}, then a population diminishes; when it is greater the population grows.

When viewed experimentally the divisions and deaths appear to occur at random with no deterministic structure able to explain how a population of cells might grow or decline. However, by using a probabilistic approach in which T_{die} and T_{div} are determined by independent distributions, Hodgkin's laboratory has developed a model – the cyton model [40] – that explains practical observations.

This probabilistic population model relates to the deterministic modelling of biochemical pathways in a way that illustrates the well–known maxim that a model should use the level of complexity appropriate to the problem, but no more. Thus for the lymphocyte population machinery a representation in terms of a population distribution is appropriate [41] and gives a predictive model, albeit of a probabilistic nature. The cyton model suggests that uncertainty in cell signalling dynamics may determine the probabilistic behaviour of lymphocyte populations. How and why such uncertainty arranges itself in a way that determines cell fates in different circumstances is, however, unknown.

3.2 Underlying Principles

Mathematical modelling provides an important way in which a systems approach can contribute to our understanding of living systems. However, from the control theorist's perspective the greater challenge is the discovery of underlying systems principles that might offer generally applicable rules for the mechanisms of life. Much of the current research in this direction concerns system properties such as adaptation [42], robustness [30, 43] and complexity [44]. However, optimality principles also have an important place in explaining the high degree of specialization and effectiveness exhibited during evolution.

In general terms it has been argued that species can be thought of as evolving in the manner of an iterative optimization process [45]. While evolution as a general optimisation process is interesting in the abstract, it is not clear how we might quantify specific cost functions and constraints that describe general evolutionary phenomena. However, by taking advantage of our knowledge of engineering systems, it *is* possible to place some forms of biological and physiological systems within quite precise optimisation frameworks. As an example, consider the following example of optimisation within cellular metabolism.

Organisms modulate biosynthetic activity by controlling gene expression in such a way that cellular functions are insensitive to variable external conditions. Since energy is limited, some pathways are deactivated and the expression of genes that code for the corresponding biomolecules is interrupted, when a certain pathway is not required. This phenomenon was illustrated in an elegant experiment [46] that showed how the activation of amino-acid biosynthetic pathways in *E. coli* takes a well-defined sequential temporal pattern in a manner controlled by gene expression. Such patterns had been previously suggested in a simplified version [47] and consist of a gene expression program in which each

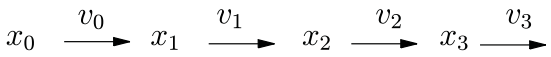

Figure 8: An unbranched metabolic pathway in which x_0 is the concentration of the substrate feeding the pathway, x_i is the concentration of the metabolite at the ith stage and v_i is the chemical rate of the ith reaction.

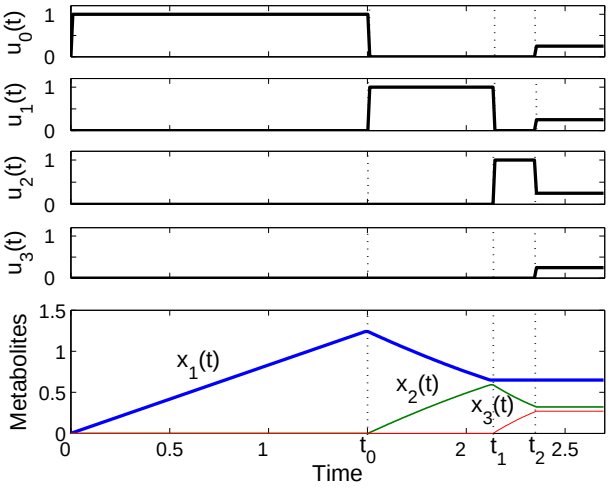

Figure 9: The enzyme and metabolite concentration profiles showing the time optimal characteristics of the dynamics. In the figure, $u_i(t)$ is the concentration of the enzyme catalyzing the ith reaction. Note the bang-bang control profile exhibited by the concentrations of the enzymes during pathway activation up to time t_2. After this point, the steady state production of x_3 is maintained by a combination of enzyme levels which is compatible with the total enzyme abundance.

reaction in the network reaches its maximum activity in the same sequence as the reaction appears in the pathway topology.

Such practically observed phenomena are reminiscent of strategies in optimal control programmes. This connection was made in a recent paper [48] in which the sequential behaviour for an unbranched biochemical pathway (as shown in Fig. 8) was posed as a control problem optimising a weighted sum of time and cellular resources. Specifically, it was shown that for a minimal time pathway activation a bang-bang control of the catalytic enzymes (Fig. 9) of the pathway is required, and in a sequence such as described in [47]. Moreover, the analysis reveals that the activation sequence is due to both pathway topology and structure of the chemical dynamics. This discovery is important because it shows how a familiar optimal principle, used in *design* of control systems, seems to have a *naturally occurring analogue* in metabolic dynamics.

3.3 Harmonic Systems

We use frequency domain methods to analyze and explain the physical world in terms of signal propagation, and harmonic analysis is an essential tool in communications and control systems technology. Given the universal nature of harmonic behaviour in physical systems, it is therefore natural that we ask whether living systems employ frequency modulation for communication and control. The answer is an unequivocal 'yes'. For example, oscillatory behaviour is important for communication in neurological systems [49]. In particular, the frequency selectivity represented by the distinct alpha, beta, delta and gamma-bands is apparently used to achieve distinct signalling and communications objectives. Additionally, because neural connections are formed by dense groups of connections, the issue of synchronisation (or the lack of it) within a neuronal/axonal group is important. Thus both frequency and phase–timing of oscillations appear to be used to encode neural information.

The brain is only one example of a biological sub–system in which frequency sensitivity and selectivity is important. In fact oscillatory behaviour is important in all stages of living systems with determining rôles in physiological behaviour [50], the signalling pathways in cells and gene expression [51], [52]. This raises a parallel with technological systems in which frequency modulation and/or phase shift keying is used to encode information. The pursuit of this idea from a systems viewpoint has radical implications for how we probe the biological function of proteins and genes. Specifically, areas of genomics and proteomics are currently based on averaged 'steady state' data. If gene expression genuinely *is* sensitive to oscillations in the cytoplasm, then we are currently only looking at the origin on the frequency spectrum of protein/gene function, and hence only one point on the total map of protein function.

Let us take this point further; frequency dependence is a fundamental expression of the dynamical nature of physical systems, thus the observation that the responses of biological systems may also be frequency dependent is a potentially useful analogue between technical and biological components. More specifically, for control systems analysts versed in systems dynamics, there is the exciting possibility of translating frequency domain methods from engineering to biology.

The analysis of oscillatory processes in living organisms is already rich, e.g. Winfree [53] and Goldbeter [54], [55] and control systems theorists are beginning to be seen [56]. There remain however many stimulating opportunities for generalised harmonic analysis of biological phenomena. Here again we hear the voice of Tustin [10] as he echoed Schlumpeter's advocacy of harmonic analysis in economic theory [57].

4 Toward a Systems Approach to Disease

The topics described previously are those that have been either helpful to biologists, (*in–silico* modelling), intellectually challenging to control theorists (control principles of life) or both (analysis of biological system behaviour). In this

section we ask how systems biology might help in a very practical way, by improving our understanding of diseases whose complexity has so far defeated us. I will discuss a systems approach to a particular neurodegenerative condition – Parkinson's Disease (PD). I should stress that there is no new science what will be discussed here, rather it is a consideration of disease from a systems perspective and the use of engineering systems tools and methodologies that is different. First some background.

4.1 Why a Systems Approach to Neurodegenerative Diseases?

Here, where men sit and hear each other groan;
Where palsy shakes a few, sad, last grey hairs,
Where youth grows pale, and spectre–thin, and dies;
(Ode to a Nightingale, John Keats, 1819)

Except that today we do not die so soon; good health care, diet and lifestyle ensure that our bodies last much longer than before. As a result, while remaining physically able into old age, our brains fall increasingly prey to neurodegenerative conditions that we do not understand and cannot yet adequately treat. It is particularly important that we pay attention to these conditions, yet they remain 'Cinderella diseases' which remain hidden within families and ultimately in nursing homes for the elderly, while more dramatic diseases stand centre stage. All diseases should receive the best research resources we can deploy, however there are compelling arguments for focussed research into the causes of neurodegeneration. The human cost of neurodegeneration is already huge, with care largely left in the hands of families and treatment rationed on economic grounds. The financial burden on society is large and growing; if demographic trends continue, then the costs of caring for the victims of neurodegenerative diseases will overwhelm the developed world within the foreseeable future[3].

4.2 Parkinson's Disease

In 'Ode to a Nightingale', Keats was almost certainly alluding to a pamphlet written two years earlier by a London doctor – James Parkinson. The pamphlet, 'An Essay on the Shaking Palsy' [58], became famous as the first account of a previously unclassified condition – the shaking palsy. Some 60 years later the famous French scientist and founder of modern neurology, Jean Martin Charcot, coined the term Parkinson's Disease (PD) and linked Parkinson's observations of physical shaking of the limbs to neurology [59]. Charcot's connection was crucial, but it was not until the late 19th Century and Sherrington's clarification of how the nervous system worked [60] that PD was related to specific changes

[3]As an aside, I cannot help but speculate how different the situation would be if an equivalent technological problem existed that had similarly disastrous implications for industry and commerce. Funds and scientific resources would be marshalled and deployed in a manner found only in times of conflict.

in certain areas of the brain. In turn, this led to malfunction within the motor circuits of the brain being associated with Parkinsonian tremors.

The next significant development was in the 1960's [61] and the discovery that a lack of dopamine in the substantia nigra was implicated in PD. This was a major event since it gave a biochemical basis for the physiological symptoms and led to the first effective treatment. The treatment was Levadopa, a drug that could pass through the blood-brain barrier and be metabolised into dopamine, thus supplementing the depleted supply. Levadopa was followed by drugs that attempt to make best use of existing dopamine in the brain by sensitising the dopamine receptors in brain cells, and drugs which inhibit the breakdown of dopamine in the brain.

A suggestion that environmental toxins may be partially responsible gained special importance in the 1970's when contaminated recreational drugs were found to cause cell death in the regions most affected by Parkinson's Disease. Further studies have linked pesticides with Parkinson–like symptoms.

Only a small fraction of Parkinson's Disease cases are inherited. However, a study of the genetic basis for familial PD can help identify genetic mutations that might also contribute to the normal non-familial form of the disease (termed idiopathic or sporadic PD). In this context, results in the 1990's from genetic studies of families with a history of inherited Parkinson's Disease [62] discovered mutations in a number of genes, including alpha synuclein. Subsequently, the protein alpha synuclein was found to be a main component of protein agglomerations, called Lewy Bodies, in the brains of victims of the sporadic/idiopathic form of Parkinson's Disease. On the basis of alpha synuclein deposits found in Parkinson's sufferers, Braak and his colleagues [63] have proposed a staging theory in which the disease starts in the enteric system, moves up to the brain stem, enters the brain, eventually reaching the substantia nigra and finally the cerebral cortex. More controversially, Braak has also hypothesized that a pathogen entering the enteric system through the gut may initiate the disease trajectory.

Separately from pharmacological and biological studies, neuroscientists have found that external electrical stimulation could be used to identify the function of different brain areas. This led to speculation on the use of electrical stimulation as a treatment for brain disorders and in the 1990's experiments were described [64] for a stimulation system for the treatment of tremors. Spectacular results were shown in which the electrical stimulation of the subthalamic nucleus dramatically reduced Parkinsonian tremors and restored normal motor function.

This is how in the space of 190 years, our understanding of Parkinson's Disease has developed from that of a physical disability – the shaking palsy – to a complex picture of a multi-facetted biochemical systems failure in which a number of biological, physiological and environmental issues coincide. In the next section we will consider how such a multiplicity of factors can be considered within a systems context.

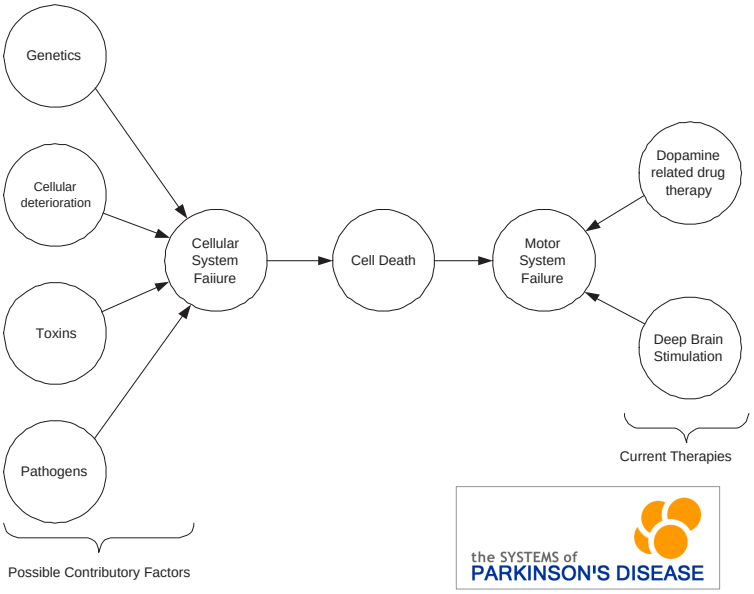

Figure 10: Showing the factors potentially implicated in Parkinson's Disease (left hand side) and the current therapies (right hand side).

4.3 The Systems Characterising Parkinson's Disease

The systems approach to Parkinson's Disease outlined here is based on the methodology that might be used to investigate a complex technological system. In this context, Figure 10 is a schematic representation of factors potentially implicated in Parkinson's Disease and the current treatments. Referring to the left hand column in the figure the implicated factors are:

Genetic factors. These are implicated through mutations in certain genes (although the instances of familial Parkinson's Disease are unusual).

Cellular deterioration. In its usual form Parkinson's Disease is associated with the elderly hence mechanisms of cellular deterioration are important factors.

Toxins. Experiences with pesticides and contaminated drugs indicate that toxins may be contributory factors.

Staging and Pathogens. The staging theory is associated with the hypothesis that a pathogen entering the enteric system may be responsible.

An unknown combination of these factors is implicated in causing cellular failures. As suggested by the centre section of Figure 10, these failures eventually trigger a programmed sequence of cell death in specific areas (especially the

substantia nigra) of the brain. It is this which causes motor circuit failures in the brain and the movement disorders that are the visible characteristic of the disease.

There is no cure and the treatments that exist (see the right hand side of Figure 10) alleviate behavioural symptoms. Drug therapies are the well established treatment and compensate for deficiencies in dopamine production in the substantia nigra. Their effectiveness is not uniform across patients and diminishes with time. Research into the reasons for this and the search for alternatives are high priorities in the drugs industry. Deep brain stimulation is a relatively new, but apparently highly effective electrical therapy. How and why it works remains an unknown.

4.4 A Systems Approach

Building on the background sketched in the preceding paragraphs, I will explain how our systems approach to this disease is progressing.

Step 1. Implicated factors. First, we have tried, in general terms, to determine from the literature which are the internal and external factors which might cause systems failure. These are indicated diagrammatically on the left hand side of Figure 10 and described in the previous paragraph.

Step 2. System components. Next we examine each implicated factor from step 1 in more detail and identify it's component sub–systems. For the moment we have concentrated on the cellular deterioration factor from stage 1 and the following sub-elements: (1) the cellular energy metabolism, (2) age related cell damage and (3) damage due to oxidative compounds.

Step 3. Sub–system modelling. In the next stage we will construct, or capture from the literature, mathematical models of the implicated systems components. For example, we are currently considering the cellular energy supply shown in Figure 11.

Step 4. Understand actions of treatments. In addition to the system modelling we also try to understand the actions of therapies upon the mechanisms of disease.

Step 5. Model assembly and analysis. When sufficient sub-element models exist, they are be assembled and analysed for their potential contribution to system failure.

In the technological world, the resources to study, model and analyse a complex system (such as an automobile or aircraft) are usually brought together by industry and motivated through the mechanisms of the market economy. The lack of a commercial incentive, and the huge complexity of the problems, means that this will not happen in the analysis of disease. Instead we will build upon the established procedures of biological information sharing and the precedent

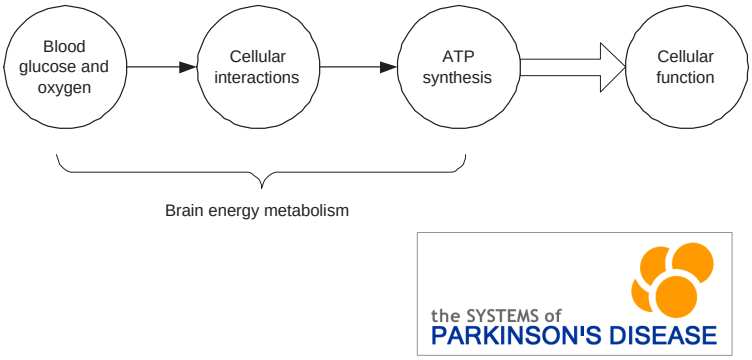

Figure 11: Showing the sequence of activities in the brain energy system as it supplies resources, via the ATP energy molecule, for cellular activity.

provided by the Physiome Project [65, 66] and the various data bases that exist for biological models [67].

We implement our models using the open source Systems Biology Toolbox [68] and make them available in the common model interchange format of the Systems Biology Markup Language [69] for sharing with other research teams. In this way we can create a model data base, but with the explicit focus upon a particular disease and in a way that facilitates international collaboration. Likewise, we conduct our analysis using standard engineering tools such as Matlab or freeware equivalents. The next sections will give a flavour of our approach using the model of the brain energy metabolism as an example.

4.5 Sub-System Modelling

A basic assumption is that the efficiency with which neurons can acquire energy from the bloodstream decreases with age. Moreover, we believe that this will cause corresponding reductions in cellular functions, potentially leading to Parkinsonian pathologies. An important element of this potential factor in neurodegeneration is the brain energy metabolism (Figure 11). There is however, some controversy over how the brain metabolism works [70], with opinions divided over the contributions of lactate and asytrocytic cells. This is precisely the kind of problem where mathematical models are of value. They provide a quantitative basis for discussion of rival biological hypotheses as well as forming a basis for an investigation of disease mechanisms.

For example, using a mathematical model originally developed by Aubert and Costalet [71], we are able to investigate the dynamics and structure of the brain energy metabolism. By varying the inputs and the astrocyte–neuron interactions it is possible to quantitatively estimate the corresponding metabolic and cellular responses. Figure 12 shows a simplified outline of the model, with inputs (brain stimulation, energy supply from the blood flow) and compart-

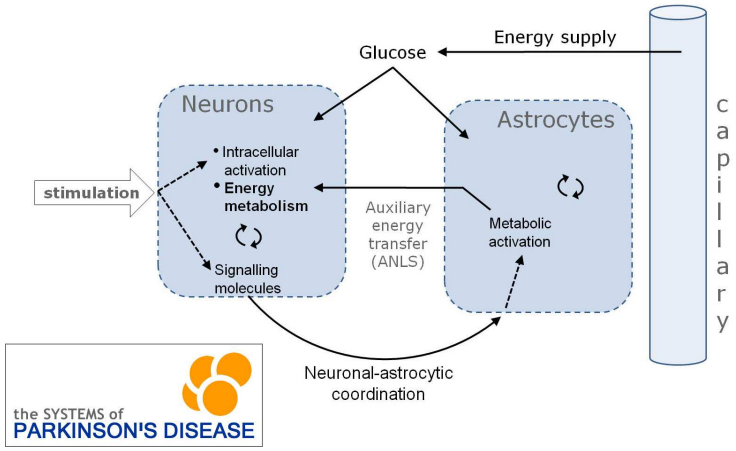

Figure 12: Schematic view of the brain metabolism model with two inputs (brain stimulation, glucose from the blood flow) and three compartments (brain blood capillary, neurons, astrocytes).

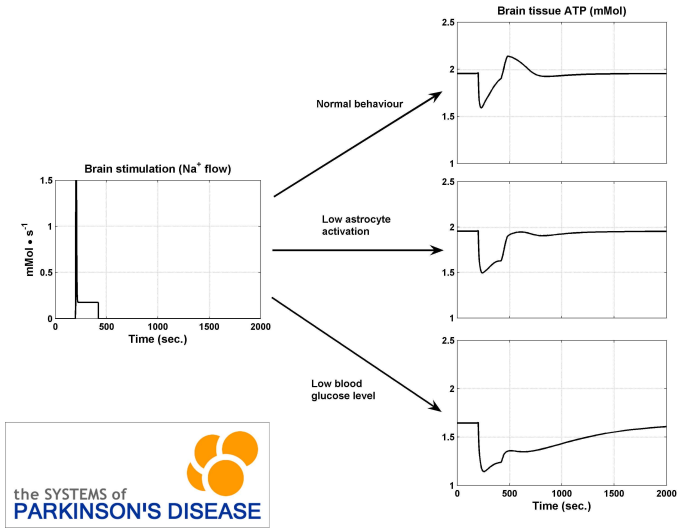

Figure 13: Illustrating the energetic behaviour of brain tissue (characterised by the concentration of the 'energy molecule' ATP) during stimulation and for the physiological conditions (i) normal physiology, (ii) low astrocyte activation and (iii) low blood glucose levels. Brain stimulation is represented by an increase in the sodium flow.

ments (capillary, neurons, astrocytes). Typical simulation results for the energy metabolism during a stimulation are shown in Figure 13. This figure shows how the ATP (the cellular 'energy currency') in the brain tissue will evolve under different physiological conditions.

Using the model as a starting point we are developing an approach that will consider the major phenomena involved in brain energy metabolism, namely: brain stimulation, nutrient exchanges with the blood flow, intracellular and inter-cellular activation of metabolism etc. The systems approach here is thus applied on a very broad scale, with the individual cells (neurons or astrocytes) considered as sub–systems within the macroscopic biological entity that is the brain energy system. As observed by Aubert and Costalat [71], this approach will yield valuable insights into the brain energy metabolism and its structure (e.g. astrocyte–neuron interactions). The size (the brain energy metabolism model has approximately 40 states), nonlinearity and the difficulty in calibration of biological models create limitations on their use. Nonetheless, they provide a quantitative and objective repository of our knowledge and as such they will play an important role in the systems investigation of Parkinson's Disease.

4.6 Control Principles and Disease

I believe that modelling the various elements that might contribute to a particular ailment will form the bedrock of a systems approach to disease. However, the potential of control oriented analysis from a more abstract standpoint should not be discarded. For example, Kitano [43] (a champion of robustness ideas in biology) has interpreted the diseased state of an organism as if it were a point of sensitivity in a dynamic system. Viewed in this light, therapies become mechanisms for restoring the system to a robust operational state.

Control principles discussed at this level of abstraction are of general interest. Control principles can however be usefully invoked to help understand aspects of specific therapies. In the case of the Systems of Parkinson's Disease, we believe that harmonic analysis ideas (Section 3.3), may contribute to an understanding of how deep brain stimulation works. A full discussion of this is outside the scope of this talk, but as the demonstrations in the lecture will show, the general principle of harmonic synchronisation is relevant to this and other electro-chemical therapies.

5 The Spirit of Tustin Revisited

During the preparation of this lecture I have tried to understand the development of Tustin's professional philosophy. I formed an impression of a man who, although trained as an engineer, was motivated more by the importance of a problem rather than a particular discipline. In wartime the problems were crystalised for him in the difficulties of electrical machine control. In post-war reconstruction it was the modelling and stability of economic systems. Later his

interest turned to his third and last great adventure – applying systems ideas in biology, a topic that he had mentioned as early as 1952 [11].

Seen through the prism of time, what I have called the *Spirit of Tustin* is revealed as a deep belief in the explanatory power of control and systems theory, combined with the will to apply it to the important social issues of the day. Were Arnold Tustin to be active now, I feel sure he would immediately recognise the strategic importance of a systems approach to the life sciences. He would note that we are at a time of change in the development of science and technology. He would likewise see that the trends and cyclical indicators point toward a mathematical/quantitative approach to life sciences as the next frontier; an *industrialisation of biology* as I have described it elsewhere.

In the 1950's Tustin added his voice to those of other great engineers by suggesting that control systems analysis would be needed to understand the systems of life. Today, a combination of economic forces and social needs are driving such a systems approach in a dramatic way. In addition to the need to understand and cure disease, there is a corresponding need to replace technological industries that have moved to other countries. These dual forces impose a social responsibility on us all to develop alternative sources of knowhow that can support replacement industries based in the life sciences. This process of change is inevitable and it is crucial that the current leaders of control systems research grasp the opportunity for renewal that it presents. If this is done correctly, then a new energy can be injected into control systems studies. An energy that will stimulate new theories and important new problems that are relevant to our common futures.

However, there are many dangers. Institutional conservatism must be overcome and territorial boundaries between life and engineering sciences removed. This will not be easy and too much public and private money has already been spent on institutes of systems biology that contain little more than conventional biology window dressed with bioinformatics. If these institutes fail to deliver then the funding backlash will be catastrophic for progress. It is therefore essential that the control systems community show leadership and – in the Spirit of Tustin – develop and implement an agenda for change.

An agenda that dramatically emphasises the importance of dynamics, causality and systems theory. An agenda that embodies a radical combination of systems skills with biological knowhow. And most especially, an agenda that offers a progressive vision for control and systems science that addresses the many unknown features that characterise the mechanisms of life.

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Any errors or omissions remain my responsibility.

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