On the Industrialisation of Biology

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1 Introduction

These are challenging times for those charged with the well-being of our peoples. Health care systems face ever–increasing demands to improve standards and performance, while life science researchers struggle to understand the complexities of currently incurable diseases. For pharmaceutical companies particularly, the time needed to develop new treatments continues to increase and there are costly failures among the drugs that do emerge from the development process. One reason for this situation is the complexity of the underlying biological mechanisms that we need to understand in order to make medical progress. This, combined with the traditional background of biological research methods, has stimulated the argument for what can be called a *systems approach* to the life sciences.

The case can be summarised as follows: the time to research and develop complex physical products (cars, aircraft, etc) has been starkly reduced by the systematic use of mathematical modelling, performance analysis and computer simulation. As a consequence, modern products are not only developed more quickly, but have greatly improved quality and predictability of performance when compared to those manufactured by traditional methods. The question then arises: If modern industrial engineering methods can make the development of physical systems and products more effective then can the same be done for the living systems of biological and medical science? Unfortunately, the systems approach to life science has mechanistic overtones of industrialisation and automation. As a result there is an undercurrent of conservatism and skepticism working against it. Such reactions can be healthy and often rotate around the suspicion that the systems approach (or systems biology as it is known) may be a short-lived affair that will briefly flourish and then fade amid unfulfilled promises.

The case developed in this article is that systems biology is not a passing fad, but part of a fundamental change that will occur as skills and technology from outside the traditional boundaries of biology are recruited to the life sciences. It will further be argued that contact with life science problems will enable an equally important change in systems theory and the technological sciences. More generally, a case is made that, combined with technological developments and commercial pressures, systems biology is an integral part of a change in how we approach biology, medicine and health-care. Finally, it is maintained that this change is historically inevitable, and has a predictable course that can be traced through a knowledge of the mechanisms of scientific and industrial development. To establish these arguments, the implications of a systems approach to Biology are considered from a historical perspective. Using lessons from the past it is argued that we are living through a period of rapid change in life sciences that has strong parallels with the Industrial Revolution. Changes that will lead to, in effect, the Industrialisation of Biology.

2 The Elements of Change

2.1 Fashion or Permanence?

Let us first consider the skeptic's concerns by distinguishing between transient fashions and a concerted process of innovation leading to permanent change. The main features that enable us to distinguish between passing fashion and permanence are continuity and consistency. A fashion often emerges without precedent or obvious need, whereas the elements of a revolution have a clear connectivity to their historical context and are consistent with contemporary requirements. For example, in the context of Medieval industrial history, Gimpel [1] gives examples of issues which drive technical progress, the most important of which are:

1. The change should yield fundamental advantage over existing technologies.
2. There should be a clear imperative for change.
3. Access to the means of scientific change and new ways in which to realise them.
4. There should be an absence of constraints on change and its commercial exploitation.

A few moments of thought are sufficient to confirm that a systems approach to biology has many of these ingredients. Specifically, and with respect to item 1, it is obvious that an organisation that could systematically predict the outcome of medical treatment based on computer-based mathematical models would be at a very significant advantage. This is because, despite advances in medical science and the contributions of computer science, the design of medication and drugs is still prone to failure. Even after exhaustive experimental trials drugs can fail [2] and with profound long term implications for companies [3].

Such failures are a function of our ignorance of the general biological mechanisms that make living organisms work. In particular, we lack analytical methods with which to describe the dynamical and structural complexity of biological processes in succinct yet generalisable forms. Taken together with the commercial consequences, this creates an imperative for change, e.g. item 2. Moreover, and with respect to item 3, there is a growing source of readily available technologies with which to innovate. For example, useful mathematical models of biological processes can be developed using known mathematical techniques, low cost computers and software. Likewise, new technologies are becoming available that can measure biologically important variables and thus verify and calibrate the mathematical models.

Seen from this perspective, the systems approach to biology is clearly not a passing fashion. It is part of an sustained process of change from classical biology to a culture in which life sciences have access to a wider set of tools and expertise drawn from the world of physics and engineering. In this framework the biologist will become a member of an interdisciplinary team of experts that includes engineers, applied mathematicians, dynamical systems analysts, instrumentation engineers, chemists, physicists, and computer specialists.

2.2 Evolution or Revolution?

It has been argued that the life sciences are not experiencing a revolution (in the sense of the Industrial Revolution), but rather a completely natural evolution in how mathematics and technology are applied to biology. In questioning this position one can refer to many precedents, the most important of which (The Industrial Revolution) is pursued in section 3. For the moment we use innovations research, and in particular the idea of *disruptive innovation* as developed by Clayton Christensen, [4, 5, 6]. In his highly influential book, *The Innovators Dilemma*, Christensen describes the surprising sequence by which developers of products and processes are under continuous competitive pressure to improve. He makes the particular point that innovative competition usually comes from outside the immediate group of competitors and exploits a new approach that radically disrupts an established market. One of his examples is the development of the mass storage market for computers – a market that is currently again experiencing disruption as low cost high density flash memories compete with hard disk technology.

There is a surprisingly close similarity between the *disruptive innovation* of Christensen and what is happening in biology. The systems scientists and engineers who have begun work on problems in biological research represent a potential *disruptive mechanism* for traditional biology. Specifically, by developing analytical measurement techniques, together with mathematical methods that use the measurements, they have the potential to increase the speed and effectiveness of biological research [7]. In this sense, the use of computer based simulations of biological processes, (the *in silico* approach) is a disruptive innovation that can unlock the door to new discoveries, enterprises and products. As in Christensen's examples, these new approaches will leave behind those who are too conservative or who are unable to respond to new realities. In this spirit, systems biology brings innovations in a way that is part of a wider undercurrent of change in the life sciences.

Disruptive events in the life sciences are being matched by significant changes in the physical sciences and engineering in particular. The advanced nature of our manufacturing and automation systems means there is a paucity of tractable new technical problems in traditional engineering areas. Likewise manufacturing facilities are moving from the developed nations to low cost economies in the Far East. As this happens the infrastructure that supports technological advancement diminishes in the developed world. In order to survive, those associated with research or development of technological systems must find work in challenging new areas such as the life sciences.

2.3 The Wave Theory

There is a theory which says that economic, social and scientific progress operates in periodic cycles. This approach was originated by Kondratieff [8] who developed the idea that economic and social change occurs in successive waves. Kondratieff's wave theory was adopted by Schlumpeter [9] who further developed it in connection with radical change in industry and science, and proposed the Industrial Revolution as the first wave. While the validity of wave theory has been questioned, it can nonetheless be associated rather accurately with important historical events. In the following paragraphs we outline some of these and test whether systems biology meets the relevant criteria.

The chronological sequence of events in the wave theory of progress, are linked to developments in society as a whole. The first stage is the growth of some social or economic imperative after some *cul-de-sac* has been entered, or some stifling *impasse* reached which prevents the resolution of a pressing need. This is then linked to some basic motivation to resolve the situation, followed by the appearance of a sub-set of society able and willing to solve the associated problems. In turn, this is followed by a sequence of inventions and new processes to meet the demands exerted by radical change. Historically, and because of the necessity for close communication to establish scientific and technological momentum, the response to all of these factors was often concentrated in a specific geographical location; e.g the Midlands of England, or Silicon Valley. After the sequence has exhausted itself, there is a time period during which the implications and benefits of change are absorbed and before conditions for a further wave of change are re-established.

Clearly many aspects of wave theory are re-expressions of the points made in Section 2.1 – but seen from a socioeconomic perspective rather than a technological one. With reference to systems biology, a scientific motivation could be the complexity of living organisms and the concomitant *impasse* reached in the development of medicines. In the economic framework of wave theory, we can associate the shortcomings of health-care with the inability of medical science to create valid and reliable treatments for important diseases. One of the consequences of this failure being a growing burden on health-care services and society.

The structural issues (Section 2.1), technological sequence (Section 2.2) and wave theory cycle are inextricably linked, but are described separately here for the purpose of emphasis. However, other viewpoints exist. Most significantly, there is a close association between the foregoing arguments and those expressed in Kuhn's *The Structure of Scientific Revolution* [10] – an association which is pursued in the following section.

2.4 The Need for New Structures

Radical change in industry, as explained by the disruptive innovation theories of Christensen, usually comes from outside the normal framework of research and development – in the same way that revolutionary political change comes from outside the political establishment. Similarly in science, it is often the groups or individuals outside the mainstream of convention that show new ways forward. The parallels between political and industrial conservatism, and the impact of disruptive innovation on science are strong but incomplete in one respect. Specifically, the manner in which the scientific establishment is financed means that they are not bound by the normal laws of commerce. As a result organised science tends to resist change rather than embracing it. Established organisations resist change to existing structures in many ways: by marginalising proponents of new ideas, or smothering emergent behaviour, to give two examples. A key point here is that major new scientific approaches do not fit easily into such organisational structures. This has echoes of the 'paradigm shift' model of scientific development [10] and the strains that it places on prevailing scientific forms. Such strains often grow out of organisational lethargy, but also because their makers intentionally surround them with protective mechanisms to prevent them being pointlessly deflected from their purpose. Thus fundamental change is almost required to take place outside of existing environments.

In industrial circles the issues underlying this are well understood and the best policy makers actively plan for it by creating new structures which are free from the baggage that constrain existing enterprises. It remains to be seen whether universities and other elements of the scientific establishment can engineer the multi-disciplinary research platforms that are required for systems biology.

3 Lessons from the Industrial Revolution

3.1 From Craft to Process

This section provides an illustration of how things proceed in a time of innovative change. It does this by taking examples from the Industrial Revolution that flourished in eighteenth and nineteenth-century England, and projects them forward to our times. The roots of change in mechanical manufacture in the eighteenth and nineteenth century were as complex as those now confronting biology in the twenty-first century. In the face of such complexity, cause becomes intertwined with effect, but despite this interweaving there are certain themes which prevail. Most important is that the changes that took place during the Industrial Revolution, and those that are taking place now in biology, are all characterised by the transition from essentially individual craft skills to automated processes, with the corresponding increases of scale, speed, and precision. The central step in the automation of mechanical manufacture was the automation of previously manual procedures and the use of technology to greatly increase the speed and precision with which they could be performed. One can argue that the sequencing machines that automated key features of the Human Genome Project [11] did just this and thus marked a watershed in biological sciences as surely as the Spinning Jenny transformed the weaving trade [12].

3.2 Organisation and Concentration

One of the remarkable things about manufacturing before the eighteenth-century was its geographically distributed nature. Thus, one of the important innovations of the Industrial Revolution was the concentration in one place of all the required manufacturing arts. This was pioneered by Boulton and Watt in their Soho Foundry (built in 1795 in Birmingham) and their rival Murray in his Round Foundry (built in 1797 in Leeds). In these factories were integrated the skills of engine manufacture and assembly that had previously been located separately at sites convenient to the final installation of a great machine, rather than its manufacture. This concentration of effort by millwrights and engineers achieved a number of economic advantages, but it also advanced the underlying science of manufacture. By gathering the technical abilities involved in machine building in one location the development of machines and technology was greatly accelerated.

3.3 Precision, Measurement and Standards

The early machines of the Industrial Revolution did not require high standards of precision. For example, the original Newcomen atmospheric engine operated at low pressures and speeds and thus functioned adaquately with inaccurately bored cylinders. With his developments to the steam engine, Watt made requirements of precision that placed new demands for increased accuracy upon the machine makers. In response to these demands the manufacture of machines began the move to levels of precision and repeatability that could only themselves be achieved by yet more machines and a further mechanisation of hand crafts. Improvements in accuracy of measurement and actuation were central to the Industrial Revolution – they provided the basis for repeatability of functions, interchangeability of parts, and laid the basis for automation. While the original steps in this process were taken in engine making, they reached a pinnacle in the designs and development of the great engineer Joseph Whitworth. His central contribution was a systematic synthesis of techniques and designs to produce superlatively precise means of making and measuring objects. Although he is popularly known for introducing the Whitworth screw standard, this was actually a development of one of Maudsley's master strokes – the standardisation of screw threads. This point reveals Whitworth's genius as a perfectionist who brought together the best innovations he could find, improved on them and incorporated them into his own standard designs. The practicality and flexibility of his factory's products further accelerated progress by making excellent precision machine tools universally accessible to all.

3.4 Proliferation

As an employee of Joseph Bramah, the young Henry Maudsley [13] began the process of improving the methods and machines used in manufacture in an entirely systematic manner. When he established his own workshop in 1797, Maudsley took this process of systematisation to new levels of refinement in a way that caused him to be a source of inspiration for his peers and students. The principles of construction for most basic machines were already well known – Maudsley's contribution was one of systematic development, integration, and innovation in a way that set standards which soon spread and became universally adopted. His designs were definitive to the point that, like Whitworth, the roots of all modern machine tools could be recognised in the products of his workshop.

In the same spirit, Maudsley's technologies also spread through the people whose lives he touched. In this manner, his innovations in mechanical engineering practice proliferated throughout all aspects of manufacture through his clients (such as Marc Brunel [14]) and his former employees (such as Whitworth and Nasmyth [15]). This human multiplier effect, whereby talented people train yet more talented people, is an important function of scientific revolution - more will be said on this later.

3.5 Interdisciplinarity

As previously noted, cause and effect are inextricably linked in the Industrial Revolution. However, one feature which recurs continually is interdisciplinarity whereby the combination of different talents led to new solutions and directions – thus providing a further multiplier effect on progress. To draw an example from the previous paragraph, the great engineer Marc Brunel [14] commissioned Maudsley to design machines which automated block making for the British Navy [13], and in turn improved the effectiveness of the fleet. Clements, a student of Maudsley, manufactured and assisted in the design of Babbage's Calculating Engines [16], and consulted with Lady Lovelace[1]. In a further interdisciplinary twist, Babbage wrote passionately on the social and economic role of automation [17] in a manifesto for change that resonates still with the intensity of his beliefs.

These are specific examples of interdisciplinarity, but the trend was in fact general. The Soho and Round Foundries referred to earlier led to a general concentration of manufacturing skills, and in so doing provided a crucible within which new forms of interdisciplinary creativity were forged. In her excellent description of the Lunar Societies, Jenny Uglow [18] gives a further dimension to the interdisciplinarity associated with the Industrial Revolution. She describes particular examples whereby scientists such as Priestley, Darwin (Charles's grandfather), and industrialists like Wedgewood would meet and discuss their problems and results. Through meetings of this kind, many manufacturing problems were solved hand-in-hand with the development of new scientific discoveries. It was in this way that crucial technical problems were solved that simultaneously advanced commerce and science. A crucial point here is that this was done without the gap in time and culture that often exists between scientific discovery and its advantageous use in society.

3.6 Parallels in Biology: Technology

The central argument of this article is that we are living through a revolution in biology, and that the systems approach, as embodied by systems biology, is a crucial component of this revolution. It will be a long affair – maybe longer than the nominal 100 year span of the Industrial Revolution. Thus the process is in no way near completion. We are however sufficiently well underway that parallels can be established between the Industrial Revolution and current changes in the automation of the biological arts. Consider for example the development of flow cytometry [19]. Cytometry is a vital enabling technology for biological investigation and its development through the twentieth century bears striking similarities to the automation of handcrafts which fuelled the Industrial Revolution.

Specifically, the pressure to automate came from a wish to increase the speed with which cellular measurements could be made. Using the properties of laminar flow, an instrument was developed in the 1930's [20] that was capable of detecting single cells in a fluid suspension flowing through a tube in which laminar flow existed.

[1] Ada Lovelace, a close friend and co-worker of Babbage, devised the programmes for his calculating engines and is held by many to have been the first computer programmer[16].

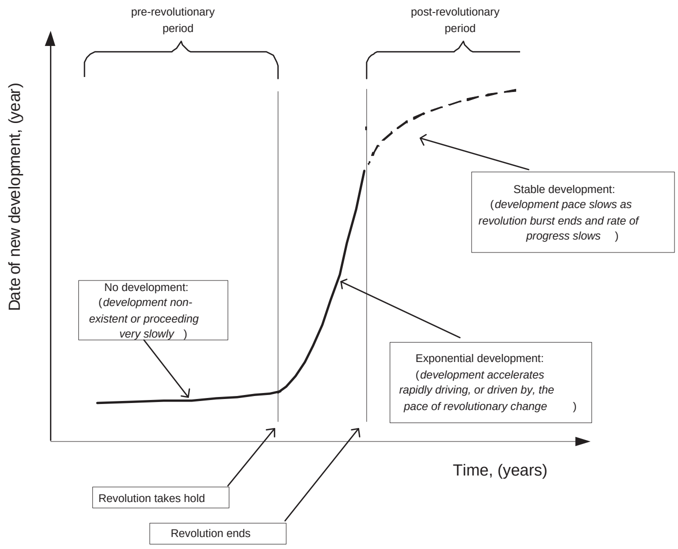

Figure 1: The progress curve of development for enabling technologies associated with revolutionary change shows three distinct stages: pre-revolutionary, revolutionary and post-revolutionary

In the 1960's instruments based on this idea were combined with image processing methods for rapid, semi-automated cell sorting and analysis [21]. Subsequently, and in an elegant example of lateral technology transfer, methods from ink-jet printing were used to increase the speed and selectivity of automatic cell sorting. This and other innovations stimulated a cycle of technological development that has led to current techniques for high–throughput quantitative flow cytometry [22].

Cytometry is important because it is an enabling technology for the rapid changes taking place in biology. Graphic evidence of the parallel between current developments in biology and the Industrial Revolution can be gained by comparing the rate of developments in cytometry with the corresponding pace of a technology that was enabling for the Industrial Revolution. Specifically, we can expect that during revolutionary change in any area the rate of progress in the enabling technologies will follow the *progress curve* illustrated in Figure 1. The shape of the progress curve is explained as follows: in the pre-revolution phase, development is slow or static, accelerating during the revolutionary phase to approach exponential growth. Post-revolution, the development rate reduces or even flattens completely as suggested by the final dotted part of Figure 1. For our discussion, the important parts of the progress curve are the pre-revolutionary and revolutionary phases, since these give us approximate start times for a period of sustained revolutionary change.

We consider rotary cutting machines (lathes and boring devices) as an example of an enabling technology for the Industrial Revolution and select landmark events with which to plot the progress curve. In this context, Table 1 and Figure 2 record some of the events in the development of rotary cutting machines as drawn from the literature [23]. Note the way in which the Figure shows the anticipated progress curve associated with periods of revolutionary change. There is a long period of low activity from the first record of the pole lathe (item A) until improvements in the (hand) drive mechanism appear, and then a further hundred years delay before water power is used in cannon boring and cutting becomes more sophisticated. A further 150 years passes before Wilkinson developes a machine suitable for boring

A	850: First documented appearance of the pole lathe.
B	1450: The unidirectional hand-powered flywheel assisted lathe drive.
C	1540: The water powered boring cannon machine.
D	1578: Lathes with ornamental cutting templates.
E	1725: Use of a boring machine for boring atmospheric engine cylinders.
F	1755: Wilkinson's patented boring machine for steam engine cylinders.
G	1760: Smeaton's rack feed boring machine – winch traverse.
H	1762: Screwing making machines.
I	1778: Ramsden's cross feed for screw cutting.
J	1795: Rigby's screw feed.
K	1827: Clement's facing lathe – constant speed cross feed.
L	1835: Whitworth's automatic longitudinal and cross feed.
M	1845: Whitworth's integrated standard lathe design.

Table 1: Key dates in the development of rotary cutting machinery. The innovations/events listed the Table provide the data for the progress curve shown in Figure 2

the cylinder of a steam engine. From this point (1755) onward the underlying forces for mechanisation increase in intensity, and key innovations in rotary cutting appear in rapid succession. The Figure stops at the date which marks the appearance of Whitworth's standard metal cutting lathe – a machine that incorporates all the essential features of the modern metal cutting lathe, and Fitch's turret lathe – an innovation that characterises the dawn of mass automated production.

We now turn to biology, and track the pace of innovation using the times of important developments in cytometry. Figure 3, shows some of the main events in the measurements of cell properties, with the corresponding innovative events listed in Table 2. A comparison of Figures 2 and 3 shows a marked similarity in the underlying trends in both examples. While the data used in this comparison was not selected scientifically, it is nonetheless characteristic of the times, and the remarkable family resemblance with the standard progress curve (Figure 1) supports the key assertion that a revolution is underway in biology.

The selection of the two examples used here (rotary cutting and cytometry) was done with some care. More than anything else the advances in the speed, accuracy and automation of rotary cutting are characteristic of the revolutionary transition from the mechanical arts in the 1700's to the mass production that characterises modern manufacturing. In a corresponding spirit, the transition of cell measurement from manual qualitative observation to automatic high-throughput quantitative measurement captures in a compelling manner a parallel process in biology. Namely, the systematisation, automation and eventual industrialisation of biological investigation. Finally, a comparision of the progress curves shown in Figures 2 and 3 can be used to suggest a starting point for change in the life sciences. The common wisdom is that the Industrial Revolution started in earnest in the 1750's around the point at which the progress curve in Figure 2 begins to rise sharply. The corresponding point of rapid change in Figure 3 is around 1950, and so it is reasonable to suggest that the revolution in the life sciences began at around that time.

3.7 Parallels in Biology: Mathematics

New scientific theories emerge from needs to explain data from new measurement devices. Thus the historical sequence is that innovative equipment is first developed, which is then used to perform new tasks or make new observations, to be

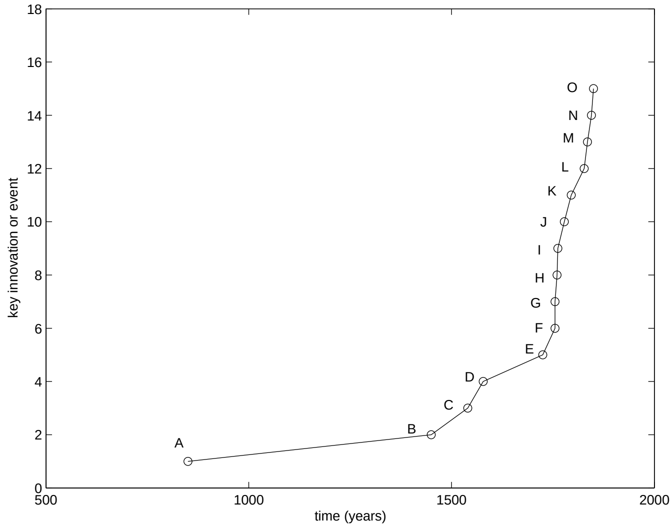

Figure 2: The first two phases of the progress curve covering development of rotary cutting machinery starting with the pole lathe (item A) and ending with Whitworth's standard metal cutting lathe (item M). The innovations/events indicated on the curve are listed in Table 1

A	1665: Hooke's Micrographia .
B	1838: Schleiden and Schwann.
C	1934: Moldovan.
D	1937: Chatton distinguishes between eukaryotic and prokaryotic cells.
E	1947: Gucker.
F	1953: Crossland Taylor.
G	1955: Coulter cell.
H	1965: Kamentsky.
I	1965: Fulwyler.
J	1970: application to mammalian cells.
K	1977: application to micro–organism cells.
L	1979: Hutter and Eissel.

Table 2: The significant events in the development of cytometry from Robert Hooke [24] to Hutter and Eissel. The innovations/events indicated in the table are plotted in the progress curve shown in Figure 3

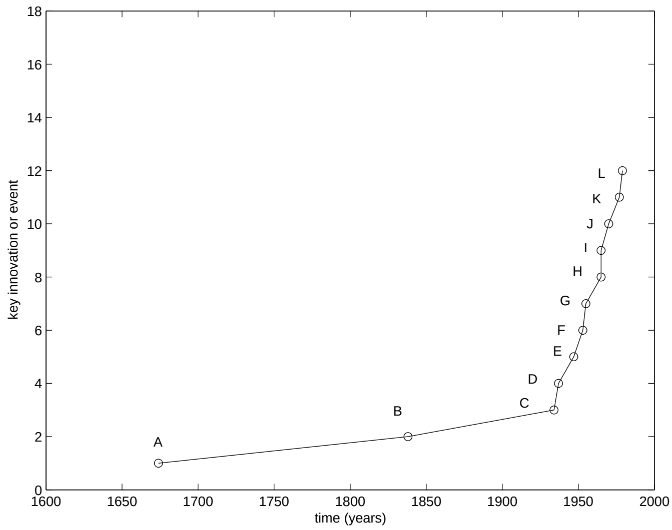

Figure 3: The first part and beginnings of the second part of the progress curve covering the development of cytometry, starting with van Leeuwenhoek (item A) and ending with Hutter and Eissel (item L). The innovations/events indicated on the curve are listed in Table 2

followed by the corresponding theoretical analysis [25]. In the case of the Industrial Revolution practical innovations in machines accelerated from 1750 onward, while the mathematical analysis with which to understand and refine their performance followed years (often many years) later. For example, Watt's Governor for steam engines was a development crucial to the Industrial Revolution. However, it had been in widespread practical use for decades before a mathematical analysis appeared that allowed its behaviour to be understood and improved [26].

A similar sequence is occurring in biology, with the mathematics and systems theory required to understand and interpret the data produced by new technologies appearing an appropriate time lag after the corresponding measurement technology. There are two striking things about this process. First, many of the tools with which to understand the temporal changes in living organisms are emerging from the same branch of mathematics (feedback theory and dynamical systems) that led to the analytical characterisation of Watt's Governor. The second remarkable point is that the use of feedback theory in biology is in part driven by the economic changes described in 2.2. Specifically, for most of the previous century the mathematics of feedback and control was a buoyant area for research, because there were many novel technological applications in which control was vitally important. Those days are now drawing to an end, with the number of tractable and commercially important problems in technological control theory being starkly reduced. The area has become introspective such that what results emerge often have only a limited impact upon society and industry.

The contrast between decreasing technological opportunities and the importance of regulatory and feedback mechanisms in biological systems is stark and has had the historically inevitable result. Thus, many of the most talented control systems analysts are now turning their intellects toward the mathematics of systems, dynamics and feedback in the life sciences [27].

4 The Lessons for a Systems Approach to Biology

Transferring historical precedent to modern situations should be done with great care – cases alter and new factors emerge. However, general themes speak through the ages and it would be unwise to ignore their message. In this spirit, we first assert that, as in the century-long Industrial Revolution, biology has for some time been moving from a craft to a systematic process. This change is occurring even though many of the biologist's talents are highly personal, being associated with experimental techniques acquired over many years of specialisation. Not only is this change happening, it has accelerated in recent years – just as it did with the mechanical crafts during the early stages of the Industrial Revolution. The urgency of these changes demand that we deal with the general themes that emerge from historical precedents. This is the purpose of this penultimate section.

4.1 Strategy for Change

In his Pride and Fall Sequence, Corelli Barnett described the concept of *total strategy* [28]. Barnett's objective was to underline the lack of an integrated plan as a central weakness of modern political and industrial life. There was no overall plan in the Industrial Revolution – the process developed from a series of accidents of history. Fuelled by the creativity and energy of great people, it grew organically out of the demands of commerce and industry. When one looks more closely however, the signs of systematic planning are clearly present in the activities of the key contributors to the process, albeit tempered by strongly responsive personalities which allowed new opportunities to be seized as they occurred.

In contrast to the eighteenth-century, the area of industrial and technological strategy is now well understood and systematic procedures have been developed to guide change. Some of this was referred to in Section 2 at a general level, however there is a wealth of more specific guidance available on known methodologies for implementing change and innovation. These range from methodologies for constructing interdisciplinary teams [29], structuring innovation environments [30], [31], to structured implementation, [32]. These and other similar sources give tried-and-tested guidance on implementing change. Despite the relative modernity of these methods, is it interesting to note that they all incorporate the themes of organisation, concentration of resources, interdisciplinary teams, and the importance of standards and planning that were key to the Industrial Revolution.

4.2 The Role of Mathematical Modelling

To fully understand current developments in biological research it is essential to balance our increased understanding of the mechanisms of scientific change against the important advances that have been made in scientific and technological knowledge. Of particular importance to systems biology is the increased application of mathematics in all of science since the Industrial Revolution. This is due in part to the increased level and sophistication of our mathematical knowledge. Equally important however, is our ability to implement mathematical algorithms efficiently using low cost computers and mathematical programming tools. This allows anyone with a personal computer and the corresponding skills to investigate mathematical models of how we perceive reality and to do so in a way that is accessible and user-friendly. In this respect, we are at a great advantage compared to our forebears for whom mathematical modelling was an arduous time-consuming task, and computer simulation an impossibility.

Of course, the use of applied mathematics to investigate practical problems and suggest improvements is not new, and there are many examples of how mathematical models have achieved what thousands of hours of practical experiment could not. The example of Stanley Hooker and the Merlin engine supercharger is a dramatic example in which mathematical analysis greatly improved the performance of a system at a crucial time [33]. More generally, and in a contemporary setting, the performance of almost all complex products is first proven using computer simulations of mathematical models before any prototypes are built – the Airbus A300 series is a stunning example of this trend. In the future, similar things will be said about life science systems, with mathematical modelling describing at a variety of levels the functions of living organisms and their components. For an indicator of developments in this direction see the Physiome Project Roadmap [34, 35] and one of the virtual cell consortia, such as www.e-cell.org.

4.3 The Role of Measurement

Quantitative information concerning biological processes is essential to the beneficial use of the mathematical models mentioned in the foregoing subsection. Without data obtained by analytical measurement it is not possible to determine model parameters. Thus quantitative information is essential to the beneficial use of mathematical models. The apparent huge complexity and diversity observed in biological phenomena implies a need for large amounts of data with which to characterise them. This has driven technological development in the direction of automatic high volume data gathering to the point at which high–throughput measurement is itself a vibrant research area [36] and, as noted earlier, resembles the automation of handcrafts in the Industrial Revolution.

The progress toward high speed automatic biological measurement was accelerated most dramatically by the demands of the Human Genome Project [11] for high volume rapid measurement of genetic [37], molecular [38], and cellular [22] states. The 'omic' measurement technologies which emerged – vital though they be – provide *static* information on biological state. Beyond this, the important challenge in measurement is the measurement of time courses of biological events in sufficient numbers and with sufficiently fast sampling rates to capture *dynamic* phenomena within organisms. Specifically, a bottle-neck to the analytical understanding of biological interactions is the difficulty in measuring these interactions over closely spaced intervals of time and with a density that will allow random elements to be systematically removed.

New understanding can be made with existing measurement technology by paying close attention to measurement requirements for subsequent analysis, and by using structural features of mathematical models of the dynamics of cell behaviour [39, 40]. Beyond this, if techniques from technological systems theory can be adapted [41, 42, 43] such that models can be accurately calibrated from appropriately sampled time course data, then the power of modelling to aid our understanding of the control mechanisms behind biological function would be greatly enhanced. As a specific example of this, the work of Hodgkin and co-workers [44] on a cellular calculus for T cell signal integration was enabled by automated high-throughput measurements from flow cytometry instrumentation of the type discussed earlier.

Better quantitative knowledge of control mechanisms in biology may also produce efficiencies in data gathering requirements. Specifically, the dynamics of cellular processes are non-linear and it is known that nonlinear systems produce apparently very different phenomena under different operating conditions [45]. An implication here is that measurements which allow the determination of these nonlinearities may lead to models of biological mechanisms which are much simpler than experiments currently suggest.

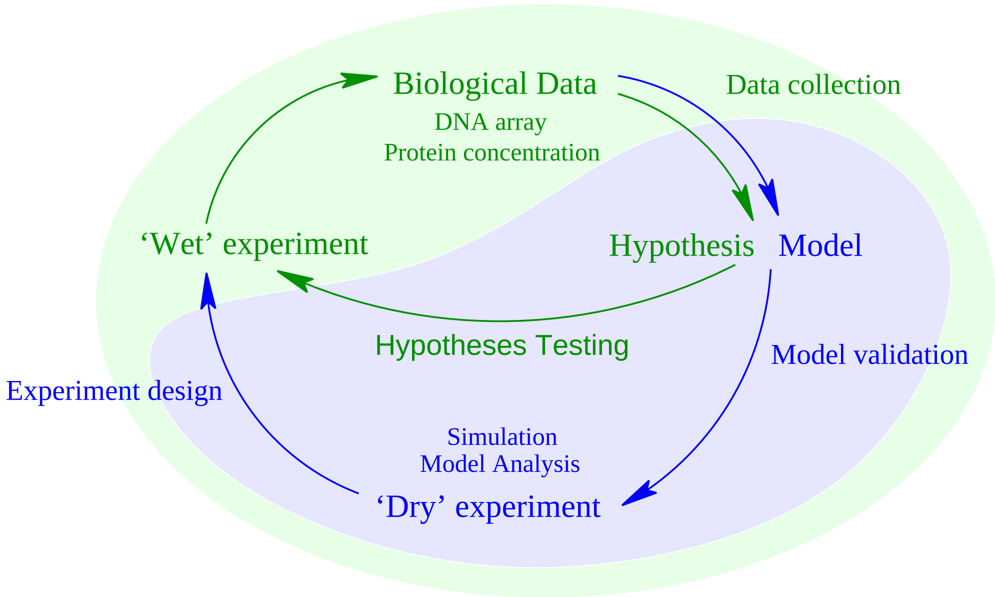

Figure 4: The hypothesis driven and systems analysis driven loops for biological experimentation.

4.4 The Role of a Systems Approach

Lastly we ask: how can a systems approach contribute to a revolution in biology? To answer this question we return again to the scientific lessons contained in the Industrial Revolution. This period is remembered primarily for the machines that were invented and the social changes that they wrought. However, underlying these visible manifestations was the true motive force of the times – namely, a systematic analysis of practical tasks by highly intelligent people who wished to solve scientific problems and improve the manufacturing arts. In the eighteenth and nineteenth centuries this systematic approach to manufacturing marked a change from a slow evolution of skills based on individual experiences, to the use of all available scientific and technical knowledge in a detailed analysis of the task in hand. Within the modern context of biology, the systems approach that characterises systems biology is closely analogous to this and can be visualised in terms of the feedback loops shown in Figure 4.

The sketch shows two feedback loops. The inner loop is the traditional discovery process whereby individual investigators use insights to generate hypotheses from the outcome of a biological experiment and on the basis of these insights perform new biological experiments. The second is a *systems analysis* process, whereby the data from 'wet' experiments are combined with mathematical models which are in turn simulated in 'dry' experiments. An analysis of outputs from dry simulation and wet reality are then used to motivate and design further wet experiments. By cycling through this systems analysis loop, knowledge is accumulated and systematically embedded in the model.

The operational form of the systems analysis procedure sketched in Figure 4 is similar to that used in modern computer-aided product design. Likewise, its philosophical basis in the repeated testing of model against reality would have been completely natural to members of the Lunar Societies [18] in the late 1700's. In a related historical vein, the application of mathematical systems theory and modelling in biology is not novel (e.g. see [46, 47]). What is new is the drive, motivated by urgent needs in society [48], to apply systems methods to biology on an industrial scale and in a way that guides basic discovery and accelerates the development of therapeutic strategies. As Peter Hunter's roadmap indicates [35] this process is hugely complex since the systematic description of organisms in a computer model is orders of magnitude more complex than the design of the most sophisticated of technological products. However, as hinted earlier the purpose and benefit of a mathematical model is to embody general principles in a way that reduces the apparent complexity associated with individual experimental observations. Thus a successful systems approach *reduces* complexity by embedding it within a general mathematical description.

5 Two Cultures: Pure and Applied Science

The ideas presented here are an engineer's perspective on how the life sciences will develop based on those principles of systematisation and industrialisation that advanced society after the Industrial Revolution. The process is well under way in the life sciences, and biologists working in industry will recognise the clear parallels between the progress of automation in the Industrial Revolution and changes in their work patterns. On the other hand, some life scientists may object to the ideas presented here on the basis that they devalue their research. This is understandable, since the ideas and themes of this article come from a field of history that few life scientists will know, and as pointed out in *An Instance of the Fingerpost*, [49], the various participants in a drama will interpret things differently depending on their experiences and beliefs.

Objections to the ideas of systematisation and industrialisation of life sciences are rooted in the cultural division between 'pure' and 'applied' science. This difference is similar to C.P. Snow's 'two cultures'– the arts and the sciences, and can be equally divisive. The essential objection to the concept of systematisation and industrialisation is a view that discovery in the life sciences is a pure science born out of individual intellectual curiosity. The argument is that something that is done for reasons of intellectual curiosity can not be subjected to the rules and values of technology and industry.

A weakness in this viewpoint is that it relies upon a strict division between the 'pure' and the 'applied', whereas there is no such strict separation in science. Scientific inquiry of any kind occupies a spectrum of activities from the pure to applied, with pure skills permeating into applied work. This can be explained in terms of both the evolution of skills over time and the hierarchy of scientific inquiry. These points are dealt with separately, since although they are simple, they are central to what happened in the Industrial Revolution and what is happening now in biology.

5.1 Temporal Evolution of Skills

The distinction has been made between posing and solving scientific problems (which is associated with pure research) and technical development (which is associated with applied work). These two issues may seem distinct, but are in fact linked - being at the opposite ends of a continuum of issues that dominate at different times in periods of scientific development. Figure 5 shows this in simplified form. From this it can be argued that the industrialisation of the manufacturing arts has been running for so long that we are predominantly at the far right of the Figure, with applied science being a dominant requirement. For biology however, our knowledge is so scant that we are, for the majority of questions, at the far left of Figure 5.

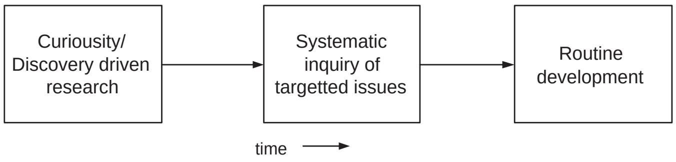

Figure 5: The temporal evolution of scientific inquiry from 'pure' (left) to 'applied' (right)

For these reasons, it is important to recognise when comparing biology with manufacturing after the Industrial Revolution that we are at different ends of the spectrum shown in Figure 5. Thus objectors to the systematisation and industrialisation of biology are not comparing like with like. Unless of course they cast their minds back and compare biology today with the state of the mechanical arts in the early 1700's.

5.2 The Hierarchy Of Scientific Inquiry

Figure 5 is a simplification of a richer process in which there is a hierarchy of scientific inquiry. At the top sits the most abstract form of scientific thought. Here ideas and theories concerning unknown phenomena are formed and tested in debate. Next comes scientific investigation of the phenomena in which theories are tested by experiment, and so on down through levels of decreasing uncertainty and increasing applied content, toward developmental science and technological application. However, scientific thought is not static, and as shown in Figure 6, as it matures the good science percolates down through the layers until in the limit it becomes routine technology. Thus, just as in the 1700's there were debates about the nature of matter that had fundamental implications for the future manufacturing arts, so the current debates about the nature of biological processes will in time resolve and move through the hierarchy with corresponding implications on future, and as yet unknown, applications.

6 Concluding Points

6.1 Conservatism

At the beginning of this article mention was made of a conservatism toward a systems approach to the life sciences. The conservative reaction that leads organisations to resist change has been discussed in Section 2.4. However the conservatism also has personal and professional facets which show themselves differently in the life and physical sciences. For example, in the life sciences the idea of a systems approach and the concomitant industrialisation of aspects of the life sciences has unpleasant overtones of anonymous group activity and de-skilling. This is a valid concern, but need not be the case for biology. Of course, activities that once demanded high individual skills will be automated as researchers move on to greater challenges – gene sequencing for example was once at the leading edge of research and is now automated. As indicated in Section 2 this is part of a natural process of innovation and development, and we now know enough about the industrialisation process to ensure that there is place for individual creative contribution [50]. Indeed the disruptive innovations described earlier [6] often depend upon small groups of radical outsiders, and organisations are increasingly designed to accommodate such groups. For this reason, as well as the stubborn perseverance that only comes from

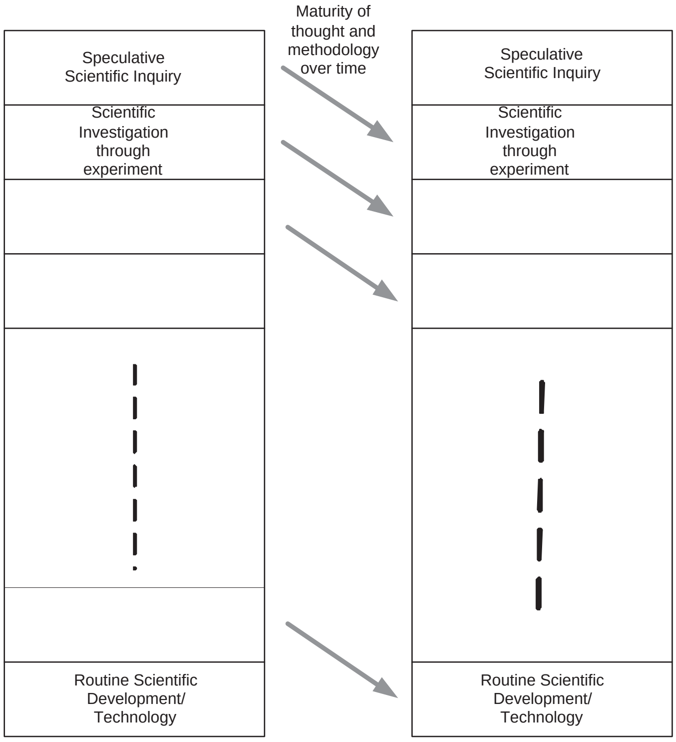

Figure 6: The hierarchy of scientific inquiry and its evolution over time

the passionate lone researcher, the future of individual creativity is safe. However it should be noted that in the model for biological research that has been sketched out here, it is through interdisciplinary collaboration that individuals will have the best opportunities for creative contribution. This has territorial implications for the pure biologist, since there may be times within a collaboration when it is another discipline, maybe even engineering, that makes the breakthrough.

From the engineering and applied sciences perspective, conservatism also exists and is strongly correlated with the current need for scientists to show continuous research productivity. It is an unintended consequence of the modern tendency to micro-manage research and development, that corporate and individual research productivity is too regularly and too crudely assessed. This creates a reluctance among scientists to risk changing to an unfamiliar, but potentially more promising, area where there is much to be learnt before new research ideas emerge. This propagates to research managers who are correspondingly reluctant to support topics where there are uncertainties and unknowns.

As peripheral illumination to this, it is interesting to note that it was the Industrial Revolution that created organised research and development in the applied physical sciences. It is ironic therefore that these same organisations that owe their existence to a revolution in the manufacturing arts can act as a brake on a corresponding revolution in the biological arts.

6.2 Scepticism

I alluded earlier to a scepticism that systems biology might be a passing fad. Such scepticism is a healthy counterweight to unreasoned investment, and here again we can find salutary lessons in the past as, for example, in the Dutch tulip mania [51], the South Seas Bubble [52], and the canal and railway manias [53]. Many other examples can be found in successive waves of social, scientific and industrial change, in which excessive enthusiasm created climates in which investment is distorted and perverted [54]. We would do well to mind this as investment in systems biology continues to grow.

6.3 Purpose

Just as the economic and commercial driving forces of the Industrial Revolution were underpinned by social purpose, so it should be for the current systematisation of biology. There is a burning social need to join our life science and systems science skills to better study the many diseases which we neither fully understand nor can adequately treat. Such needs remind us of the words of the great civil engineer Thomas Telford, [55] writing during the Industrial Revolution:

> *I admire commercial enterprise; it is the vigourous outgrowth of our industrial life: I admire everything that gives it free scope, as wherever it goes, activity energy, intelligence - all that we call civilisation – accompany it; but I hold that the aim and end of all ought not to be a mere bag of money, but something far higher and far better.*

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