
Economies of Scale in Experimentation: Knowledge and Technology in Pharmaceutical R&D

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This paper explores how changes in genetics, database, high-throughput screening and bioinformatics technologies have allowed pharmaceutical firms to exploit economies of scale in experimentation. Traditional craft-based, sequential experimentation in chemistry and biology has been complemented by firstly, the automated, mass-production analysis of populations and secondly, by 'in silico' experimentation using simulations and databases. The changes are analysed within a Chandlerian framework that highlights how increases in the 'throughput' of R&D are dependent on organizational and managerial responses to systemic uncertainty.

1. *Purpose*

This paper aims to show how pharmaceutical companies have attempted to exploit economies of scale in both chemical and biological experimentation in order to improve the throughput of their R&D processes. In doing so, it aims to extend the Chandlerian framework into R&D and explores the organizational and managerial implications of a shift towards the automated analysis of large populations of samples.

2. *Introduction*

Do economies of scale exist in pharmaceuticals experimentation? And if so, do they provide a competitive advantage for large firms and therefore favour a particular organizational form, in a way that is consistent with Chandler's framework? At first glance, one might be sceptical. Economies of scale are traditionally found in production systems where the physical nature of the

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technology allows dramatic increases in the size of the production processes. The outputs of these processes are tangible goods rather than the intangible knowledge produced by R&D.

Similarly, Chandler's theory of the modern business enterprise focuses on how large manufacturing firms supplanted the 'invisible hand' of the market to coordinate the production of goods (Chandler, 1990). His internalist explanation stresses how substantial economies of speed, scale and scope were achieved by large firms that combined investments in high fixed-cost capital goods with the managerial hierarchies required to coordinate the throughput of materials through high volume production systems. These high cost investments in technology and organization then paved the way for lower unit-cost production.

The modern pharmaceutical industry does not fit this pattern. It is R&D intensive rather than production intensive (Pavitt, 1984) and consequently has not made major changes to its capital:labour ratios as the costs of production are dwarfed by the costs of development and marketing (OTA, 1993; Scherer, 1993; but see Pisano, 1998). Pharmaceutical firms' R&D processes tend to produce only two or three new drugs a year, which are sold to health-care organizations under heavily regulated conditions rather than to mass markets. Moreover, an internalist perspective fails to account for the way that pharmaceutical firms are embedded in scientific, technical and regulatory networks (see e.g. Gambardella, 1992; Stankiewicz, 1993; Gabrowski and Vernon, 1994; McKelvey, 1994; Thomas, 1994; Galambos and Sewell, 1995; Zucker and Darby, 1997; Galambos and Sturchio, 1998; Henderson *et al.*, 1998; Martin, 1998). Lastly, the industry relies on patents rather than volume production to secure its profits (Pavitt, 1984; Levin *et al.*, 1987).

Having highlighted the substantial differences, it is important to note that economies of scale *do* exist within pharmaceutical experimentation. Jansen (1996), for example, reports how one pharmaceutical firm increased its screening capacity 100-fold over 4 years. This paper will argue that these changes can be explained using a Chandlerian framework that has been modified in two ways. First, since the output of R&D is knowledge and documentation for regulators, rather than tangible products, the framework needs to explore the impact of technology on the generation of intangible capital, in particular distributed, technology-specific knowledge. Secondly, since economic rents in the pharmaceutical industry come from obtaining patent protection after solving the complex technical problems involved in drug development, the framework needs to recognize the economic importance of increasing the throughput and capacity of the R&D process. This throughput is dependent on avoiding failures and experimental 'dead ends,' and so

depends on the capacity to solve problems, rather than the physical characteristics of production processes.

These two modifications have been made by exploring the interaction between the technologies and cognitive processes involved in innovation; in particular, by examining the interaction between the economic incentives to improve the throughput of R&D and the organizational, cognitive and technical constraints on technical change. Rosenberg, in a series of important articles on the technologies involved in innovation, has pointed out that, unlike production, the capital goods of R&D are not high fixed cost machinery but the instrumentation that has the potential to reduce the costs and increase the productivity of research. He suggests that advances in scientific knowledge (including methods and instrumentation) do not produce technology directly, but instead gradually reduce the cost of solving complex technical problems (Rosenberg, 1974, 1992, p. 389; cf. Mowery and Rosenberg, 1979, 1989, pp. 214–217).¹

If Rosenberg's insights into instrumentation and improved scientific knowledge are correct, and the paper will argue that they are, then there seems no reason why pharmaceutical firms should not invest in technology if they can ensure that the costs are covered by an increased throughput of drugs *à la* Chandler. Since the tacit knowledge required to solve technical problems is embodied in people and embedded in organizations, it is, to use a Chandlerian term, 'highly inter-dependent'. As a consequence, economic advantages can be obtained by organizing the division of labour to ensure that high cost activities are exploited to the full (Chandler, 1990, Lazonick, 1991, Babbage 1836, cf. Rosenberg, 1994:24–46). This in turn requires the coordination of flows between interdependent activity cells.

Moreover, as Rosenberg (1974) notes, investments in research and instrumentation open up new markets that had previously been inaccessible because of the complexity of the technical problems involved. In the pharmaceutical industry solving technical problems first is important because it generates the patent protection required to exclude competitors from markets (Levin *et al.*, 1987; OTA, 1993). This increases the value of R&D and improves profitability.

This paper will show that large pharmaceutical firms have invested in new experimental technologies and organizational changes to reduce the cost of finding new drugs (and to find new drugs that were previously too technically complex to develop), and moreover they have done this by exploiting

¹ This view is increasingly received wisdom in innovation studies (Vincenti, 1990; Pavitt, 1996). A number of authors have highlighted the importance of person-embodied tacit problem solving skills coming from basic research (Rosenberg, 1990; Pavitt, 1991; Salter and Martin, 2000).

experimental economies of scale within the R&D process. The question then remains ‘how is this possible?’ The empirical evidence will show that both chemistry and biology have shifted from craft-based, sequential processes of experimentation on single compounds to automated mass-production processes of parallel experimentation on populations complemented by computer simulations, or what are referred to in this paper as *in silico* experiments [cf. Rothwell’s (1992) fifth-generation innovation process].

This change has been highlighted in the technical literature. Gelbert and Gregg (1997, p. 669) note that

the process of drug discovery has been rapidly evolving over the last two to three decades. Prior to that time it focused primarily on empiricism . . . this has radically changed with the rapid introduction of cutting edge scientific technologies . . . The changes in the drug discovery process, which have allowed orders of magnitude improvements in the efficiencies in some steps of the process, have been due to the complex interplay between a number of rapidly evolving new technologies . . .

which Andrade and Sander highlight as the ‘. . . “high-throughput”, “massively parallel”, robotised and miniaturised methods of biological experimentation’ (1997, p. 675).

The paper will argue that, unlike scale economies in production that generally increase the scale of production processes, these economies of scale in experimentation have dramatically reduced the size of the experimental unit. As part of this change, traditional, craft-based scientific approaches have been complemented by automated processes whereby:

- The nature of scientific understanding becomes more fundamental.
- Experimentation shifts from a single unit to the population.
- Experimentation shifts from a craft process to an automated mass-production process.
- The scale of experimentation undergoes fundamental changes.
- The cycles of ‘trial and error’ experimentation are complemented by computer simulations.
- Complementary screening is performed *in silico* by computer simulations.

This process has happened in both chemistry and biology, and has required the introduction of information and visualization technologies that could control and collect the vast quantities of data generated by these processes

and present it in such a way that scientists could tacitly understand its implications.

The paper is structured as follows. The following section positions the paper within the literature and explores how knowledge is used in pharmaceutical firms. Sections 4 and 5 illustrate the theory by showing how the small-molecule pharmaceutical innovation process has changed over time to illustrate economies of scale in both chemical and biological experimentation. The last section discusses the empirical evidence in light of the theory and draws conclusions about future directions of research.

2.1 Limitations of the Methodology

The paper uses a case study methodology to illustrate the changing nature of experimental technology. Case study research is limited in its generalizability and creates dangers of producing results that are time-, sector-, country- and technology-specific. The changes in experimentation have been abstracted from empirical work in seven large US and European firms, and a number of weaknesses are present in the data. Firstly, it overemphasizes technical change in one particular drug discovery methodology without placing it in the context of organizational, cultural and regulatory change or any alternative methodologies. Secondly, it overemphasizes discovery at the expense of marketing. Thirdly, it necessarily oversimplifies the nature of technical implementation, and care must be taken not to extrapolate from the very clean, rational stylized process to the nitty-gritty of the real world. Fourthly, it downplays the inherent uncertainty involved in technical change and many of the innovations highlighted here, in particular computer aided molecular discovery and high throughput screening (HTS), have not yet lived up to their initial expectations. Lastly, it cannot be emphasized enough that the changes described here are complements to traditional 'wet' chemistry and biology, both of which continue to play the key role in drug discovery.

The paper alleviates these weaknesses by linking the empirical evidence to an established Chandlerian framework in an attempt to produce a more holistic understanding of the complexities of large pharmaceutical firms by analysing one of their subsystems—R&D. The empirical evidence should be interpreted as supporting Rosenberg's and Chandler's insights, and demonstrating the existence of economies of scale in intangible capital. The next section will explore the nature of innovation before exploring the specifics of pharmaceutical experimentation.

3. *Knowledge and Pharmaceutical Experimentation*

The role of knowledge in technical change has been the subject of an increasing amount of attention in the 1990s. However, the exact role of knowledge in the mechanisms that produce technology is poorly understood and often the established theoretical explanations are directly contradicted by empirical evidence (Pavitt, 1987, 1996, 1997). There have been two major traditions of work in the economics literature on the nature of knowledge. The first neoclassical tradition adopts a logical structure developed from nineteenth century applications of energy models to allocation problems (Mirowski, 1989). In doing so, its primary concern is with appropriability, and following Arrow (1962), it tends to treat knowledge in terms of the allocation of information while assuming that the utilization of that information is unproblematic (Mowery and Rosenberg, 1989, pp. 4–7).

The second Schumpeterian tradition, while recognizing the importance of appropriability, has tended to stress other factors. In particular, the sector-specific variations in knowledge use (Pavitt, 1984), its tacit and inherently uncertain nature (Freeman, 1982; Nelson and Winter, 1982; Freeman and Soete, 1998), its cumulative features (Dosi, 1982) and the considerable difficulty of utilizing it (Mowery and Rosenberg, 1989; Pavitt, 1997). In this second tradition knowledge is treated as a capacity that is embedded in the organizational routines of firms (Nelson and Winter, 1982; Dosi *et al.*, 1999). Learning and experimentation within firms allow them to solve complex technical problems and comprehend external sources of information (Cohen and Levinthal, 1990; Pavitt, 1990). Once cognitive problems are solved, firms must overcome their ‘core-rigidities’ and reconfigure their internal and external organization to turn technologies into products (Leonard-Barton, 1995; Granstrand *et al.*, 1997; Pavitt, 1997). In pharmaceuticals this process is complicated by the intellectual property issues (not analysed in this paper) associated with different techniques (Heller and Eisenberg, 1998). Rosenberg has argued that the ability to solve technical problems is dependent on a range of tangible technologies, in particular advanced instrumentation, which can reduce the costs of problem solving (Rosenberg, 1974, 1992).

What impact new technologies have on innovation has been the subject of recent debate. Some, such as Dasgupta and David (1994), have argued that information technology will lead to a codification of tacit knowledge, while I have argued that tacit knowledge is an intrinsic feature of technical change (Nightingale, 1998), and therefore is unlikely to be codified in the way argued by Dasgupta and David. While this paper is not about the ‘conversion’ problems associated with moving from one category (knowledge as a capacity)

into another (information as a state), it does explore how the technologies used in innovation generate information and how this information is understood. To do this, the paper follows in the second Schumpeterian tradition and explores the relationship between cognitive issues and the changing technologies of pharmaceutical experimentation by treating knowledge as an embodied cognitive capacity, quite distinct from organizational forms, technologies and information. The impact of changes in the technologies of experimentation on tacit knowledge requirements will be discussed in the conclusion.

Previous work (Nightingale, 1998), building on the work of Turro (1986), Barrow (1988), Vincenti (1990) and Searle (1995), produced a theory of innovation based on a 'direction argument'. In the theory science is understood as a problem-centred, social practice of exploring and mapping patterns in nature, where 'patterns' refers to the constant relationships and symmetries that may or may not be written down as laws of nature. These patterns exist in the behaviour of the real world, in the scientist's tacit knowledge and as abstract mathematical structures that map out the changing relationships being investigated (Oppenheimer, 1956; Barrow, 1988).² Once these patterns are understood, they can be extrapolated from 'known starting conditions' to approximate 'unknown end results'. However, this extrapolation of patterns for prediction is often uncertain, even if the starting conditions are well specified, as firstly, the symmetry between the behaviour of the real world and the patterns codified by scientists is not always conserved, and secondly, because various errors can grow in nonlinear ways.³

Innovation processes, on the other hand, often start with 'known end results' and attempt to find the initially 'unknown starting conditions' that will produce the desired behaviour. Symmetry breaking means that these 'unknown starting conditions' cannot be found directly using scientific knowledge, which can only be used to go in the opposite direction—from known starting conditions to unknown end results. In effect, science is a one way

² Tacit knowledge is defined as a category of neurophysiological causation that provides context to actions (Nightingale, 1998).

³ Nonlinear error growth occurs when small differences in starting conditions produce large differences in end results. Symmetry breaking occurs when the symmetry between an abstract law of nature and its real world outcome is unstable. For example, a perfect cone balanced on its tip will always fall, as any deviations, even down to quantum fluctuations, will create an increasing downwards force upon it. The direction in which the cone falls breaks the unstable symmetry between the laws of nature and its physical outcome, and creates extra information not contained in the original law of nature—creating extra complexity (Barrow, 1988). For simple systems the mathematical laws of physics are often all that is required to describe the system, while for systems with large amounts of symmetry breaking additional empirical information is required. This is why physicists can explore patterns mathematically, while chemists and biologists who deal with more complex (i.e. more symmetry breaking) phenomena must rely more on experiments.

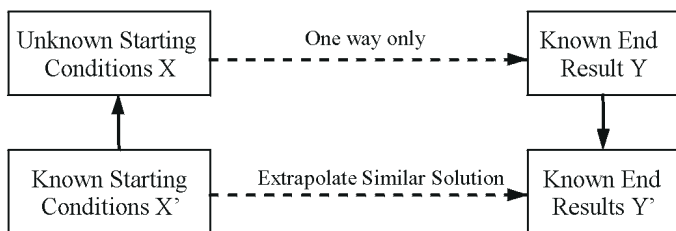


FIGURE 1. Innovation moves from known end result Y to unknown starting conditions X , via Y' and X' .

TABLE 1. Technological Traditions for the Modification Methodology

Desired end result	Q: What causes similar end result?	Extrapolate functional solution
Cure disease	→ modified natural product	→ modify natural product

TABLE 2. Technological Traditions for Structure-based Drug Discovery

Desired end result	Q: What causes similar end result?	Extrapolate functional solution
Cure disease	→ a biochemical mechanism	→ prevent the mechanism
Prevent mechanism	→ preventing protein catalysis	→ prevent protein catalysis
Incapacitate protein	→ block active site or cleft	→ block active site
Block active site	→ bind a molecule to active site	→ find molecule that binds
Molecule that binds	→ specific 3-D chemistry	→ find molecule to match it

street and technical change is going in the opposite direction. Consequently, engineers rely on the assumption that similar problems will have similar solutions. They then use their tacit knowledge to ‘see’ how the problem they face relates to similar problems they have faced in the past (Fergusson, 1977, 1992; Vincenti, 1990; Nightingale, 1998). If this similar problem has a known solution, the technologist can extrapolate an uncertain, similar solution, making the problem more specific (Vincenti, 1990; see Figure 1).

This knowledge about which solutions are appropriate for which problems is technology-specific and generates ways of solving problems called ‘technological traditions’. Two different traditions of drug discovery are illustrated in Tables 1 and 2. Table 1 shows the technological tradition based around modifying a natural product with a known effect, e.g. the development of aspirin from willow bark. Table 2 illustrates the technological

traditions associated with an alternative methodology, structure-based drug discovery, developed in the mid-1970s. This methodology is based around a 'lock and key' philosophy of finding a molecule that will bind to a protein and turn it off.⁴ This prevents the protein catalysing a disease-causing biochemical mechanism and hopefully stops the disease. While there are a number of other methodologies involved in modern drug discovery, this paper will concentrate on structure-based drug discovery and the impact of various experimental technologies on it. Its technological traditions form a downwards spiralling hierarchy that turns the initial vague problem of 'curing a disease' to a series of more specific problems involving finding a molecule to block a three-dimensional (3-D) site within a disease-causing protein.

Once the technological traditions define how a problem will be solved and research has generated the problem's performance criteria, technologists use previous design experience to suggest a likely 'first cut' solution. This 'first cut' solution is the set of starting conditions that the technologists think is likely to approximate the required end result. Since innovation is inherently uncertain, tests are normally required to fine-tune these initial design choices (Petroski, 1986). The testing process serves two purposes: first, it shows if the product will perform as required, and secondly, it helps generate understanding about the relationship between changes in the parameters of the proposed solution (i.e. starting conditions) and the end result (Vincenti, 1990). This new knowledge is then used to modify the solutions for the next round of testing, as shown in Figure 2.

During this cycle of understanding, modifying and testing uncertain solutions, scientific knowledge is used to understand and predict patterns of behaviour, screen out unlikely alternatives and understand how things function. While scientific understanding may be inaccurate, it does provide a route to test assumptions about behaviour (Vincenti, 1990; Gray, 1995) and provides understanding that can be used to modify the design and reduce the number of experimental dead ends that are explored (Deutsch, 1997).

Figure 2 shows that testing can be done in three ways that correspond to the three 'levels' of pattern—the real world, the scientists' mind's eye and the abstract mathematical level. Thus testing can be done by real world experiments, by tacit pattern extrapolation and by extrapolation of mathematical patterns. The extrapolation of mathematical patterns has recently increased in importance because firstly, increased computing power has improved how well discrete computer-based calculations approximate continuous math-

⁴ In the body some biochemical reactions are catalysed by proteins (enzymes) that stabilize a transition state during reactions. This lowers the amount of energy needed for the reaction to proceed and speeds it up.

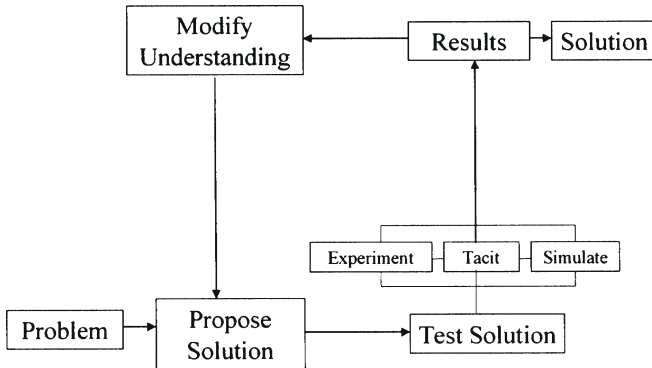


FIGURE 2. The design cycle.

emational functions, and secondly, because innovations in visualization technologies have allowed engineers and scientists to better understand the results of experiments conducted on mathematical representations in computers. The reliability of these *in silico* experiments depends on the extent of symmetry breaking and nonlinear error growth, which is very high in many areas of medicinal chemistry and biology, making uncertain and often inaccurate *in silico* experiments complements rather than alternatives to real world ‘wet’ experiments (see footnote 3).

3.1 Technical Traditions to Innovation Process

Because technological traditions define how problems are resolved into more specific subproblems, the initial choices define the performance criteria of later choices. As such, they generate a hierarchy of solutions and subproblems, with initial choices constraining the possible alternatives at lower levels (Vincenti, 1990). For example, the technological traditions for structure-based drug discovery listed in Table 2 generate an ordered sequence of tasks, because some problems can only be attempted after other solutions have been found.

Following down the right hand column on Table 2 produces a sequence of tasks outlined in Figure 3: (i) perform basic biological research to find the disease causing mechanism; (ii) perform research to find an active protein in the disease causing mechanism; (iii) find its 3-D structure; (iv) characterize its active site; (v) select and test molecules to find a lead compound; and (vi) optimize the lead compound and pass onto clinical trials. This in turn forms the basis, and only the basis, for the innovation process outlined in Figure 4.

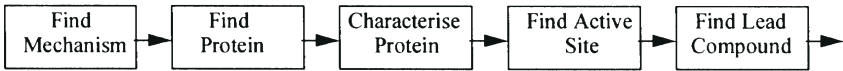


FIGURE 3. The sequence of tasks generated by the technological traditions in Table 2.

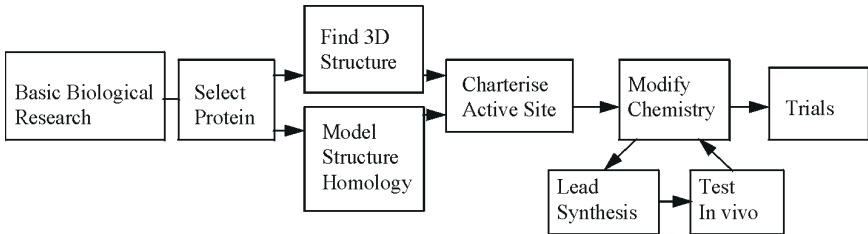


FIGURE 4. The sequence of tasks in Figure 3 forms the basis of a stylized innovation process.

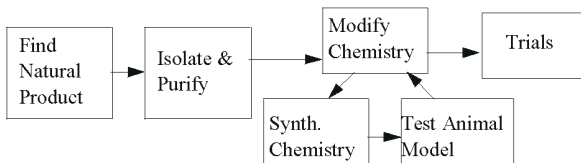


FIGURE 5. The stylized innovation process generated from Table 1.

A similar procedure using the technological traditions in Table 1 has been used to produce Figure 5.

However, the *exact* nature of the innovation process is influenced by technological, economic, institutional and organizational features, which for the pharmaceutical sector include being embedded in heavily regulated clinical trials and regulatory reviews. The next subsection explores the impact of some of the economic constraints within the firm.

3.2 Economic Constraints on Innovation Processes

Firms generally innovate to improve development and production or to produce products that command higher prices in the market. As a result, their innovation processes are constrained by economic and organizational considerations. Within the pharmaceutical industry the cost structure of the innovation process is dominated by the high fixed cost of R&D (~\$500m) and the long time scales (typically 10–12 years) involved before revenue is generated (OTA, 1993; Scherer, 1993; Henderson *et al.*, 1998). These high fixed costs have to be spread over a drug development programme that is

effective and efficient, producing large numbers of highly profitable drugs (Drews, 1995). The profit distribution is also highly skewed, with only approximately one-third of drugs covering their development costs, while the throughput of drugs is heavily constrained by very high failure rates, as shown in Table 3 (DiMasi *et al.*, 1991; DiMasi, 1995; Sykes, 1997).

In the late 1990s, of 100 molecules that enter development, typically only about 10 [Parket (1998) puts the figure as low as six] will achieve registration. Since the cumulative costs of each stage rises sharply this creates emphasis on reducing failures and in particular late failures. Pharmaceutical firms must therefore ensure that their R&D pipeline produces enough drugs to cover their development costs, with the actual number of drugs developed dependent on the number of development projects and their failure rates. As a consequence the capacity of the R&D pipeline increases with the number of development projects and decreases with increasing failure rates.

This paper will argue in Chandlerian terms that firms invest in R&D to increase the 'throughput' of profitable drugs in order to reduce the corresponding variable cost. If these investments produce a high level of product throughput then pharmaceutical firms can have impressive cost advantages over firms with lower throughput. As Table 3 shows, the major determinant of the capacity of the R&D process is the very high failure rates and it follows that reducing failures, especially costly late failures, is the key to improved profitability. If a company could increase its success rate in Phase II clinical trials from one-in-three to two-in-three, this would have a substantial impact on variable costs and profitability. There are therefore 'throughput' arguments for a minimum efficient size of the type highlighted by Babbage (1836).

Economies of scale are not, however, the only factors influencing minimum efficient size. The pharmaceutical R&D process is characterized by low numbers of new drug introductions—typically between one and three major new medicines a year, per firm. Since the risks of failure are so high, and the cost and time of development so large, a volatile throughput of new products can have a substantial impact on profitability. This volatility affects the cost of capital, and large pharmaceutical firms have developed 'pipelines' of new drugs across a number of therapeutic areas in order to ensure a regular stream of new products. For example, to ensure a throughput of two new drugs a year given a success rate of 20% in the development process, 10 candidates must enter the process each year. Should any one of these projects fail, the implications, while substantial, are not disastrous. The same cannot be said for a small biotechnology start-up with only two potential products. As a consequence, the cost of capital for biotechnology start-ups is substantially higher than for established firms. In Chandlerian terms, a firm specializing on

TABLE 3. Typical Survival Rates of Drugs Entering Trials

	Preclinical	Phase I ^a	Phase IIb	Phase III ^c	Registra- tion	Market
Survival rate per 1000	1000	480	220	71	61	60
Percentage to market	6	12.5	27	85	97.5	100
Percentage to next phase	48	46	32	87	97.5	

Adapted from Parket (1998).

^a50–100 healthy volunteers.

^b200–400 patients.

^c3000+ patients.

TABLE 4

Dynamic economies of scale and scope in knowledge	Static economies of scale and scope in production
Reduce number of failures	increase capacity
Reduce volatility of throughput	increase scope of production
Reduce time of development	economies of speed
Improve quality	increase value of output
Increase number of products in pipeline	economies of scale

one product line may have the same ‘scale’ R&D process as other firms and yet still be below the minimum efficient scale because it cannot manage the risks inherent in the process and the resultant volatility in the profit stream in the same way as firms with 10 or so drug candidates entering development each year.⁵

There are other means of improving the economics of R&D that can be directly related to Chandlerian economies of scale and scope (see Table 4). For example, reducing the time of development produces economies of speed as it increases the intensity of (particularly financial) capacity utilization, increasing the number of drugs produced in any given time period. As Scherer has shown, reductions in the time taken for regulatory reviews and clinical trials can also have a considerable impact on cost structures (OTA, 1993; Scherer, 1993). Similarly, economies of scale exist for firms placing drugs through FDA approval processes.

Similarly, economies of scale can be found by increasing the number of products in development. This method is limited because many stages, such as clinical trials, do not offer opportunities for economies of scale. Improving the quality of products can be used to increase the value of the R&D

⁵ I am grateful to Ed Steinmueller for highlighting the importance of the relationship between economies of scope, uncertainty of ‘arrival times’ and minimum efficient scale.

process. Quality is determined by *potency* (how tightly a compound binds to a substrate) and *specificity*. High potency allows the dosage to be reduced, reducing the likelihood of side effects. Similarly, a highly specific compound is less likely to interfere with other biological mechanisms. Increasing the quality of products has the potential to increase revenue.

3.3 Increasing Capacity by Reducing Failures: Cost and Quality of Experiments

The previous section argued that ensuring a high throughput of profitable drugs spreads fixed costs further and can increase profitability. Capacity is increased by reducing failures, and failure generally occurs for three reasons: the drug does not affect the target; the drug does affect the target but the target does not affect the disease; and the drug affects the disease target which affects the disease but fails in the market place (Sykes, 1997). The first two reasons are dependent on solving complex technical problems. As Rosenberg (1974, 1990, 1992) has argued, investments in research, training and instrumentation have the potential to allow firms to solve complex problems before their competitors. Pharmaceutical firms therefore invest in research and recoup their investments from an increase in the ‘capacity’ of their product pipeline.

The economic value of experiments involves a trade-off between their objective cost and the subjective quality of the understanding they produce, as a good understanding of the relationship between chemical structure and biological activity is more likely to produce drugs that will pass clinical trials and go on to be profitable products.⁶ The model of problem solving outlined above and described in Figure 2 shows that the subjective quality of the understanding will depend on:

- The starting point of the experiment in terms of the difference between the knowledge the scientist has of the phenomenon and its reality. Thus, complex phenomena are harder to understand, and smarter scientists are better than inexperienced scientists at understanding experimental results.
- The amount of extra understanding that is generated by each cycle, which is a function of the accuracy of the experiment and the ‘cognitive

⁶ Judgements of potential value are based on a tacit understanding of an intrinsically uncertain future. The term ‘subjective quality’ implies that the ability to judge the ‘objective’ basis depends on experience. Thus a non-scientist and a scientist would have very different understandings of the potential value of a molecule. But the scientist’s training would ensure that his/her perception is closer to the ‘truth’.

distance' between the results and the scientists' previous beliefs. An experiment that is testing an irrelevant phenomenon will not generate understanding and a large number of experiments may have to be done to find the correct 'context of similarity'.

- The accuracy of the experiments, which depends on the quality of instrumentation, the presentation of the data and the difficulty of the problem being faced.
- The number of experiments in terms of both the amounts of data generated and the number of experimental cycles that take place.

The objective cost of the experiments on the other hand will be a function of the number of experiments, their fixed cost and their variable cost. As Chandler has shown for mass-production industries, changes in 'scale' can fundamentally affect the relationship between fixed and variable costs. If a scientist does two experiments in parallel using the same equipment, then the variable cost doubles while the fixed cost remains the same. Thus for parallel experiments the cost structure is a function of the fixed cost plus the number of experiments multiplied by the variable cost.

Since the knowledge gained from experiments of a fixed quality is a function of the number that are performed, and the cost structure changes with a shift from serial to parallel experimentation, there is a considerable economic drive towards parallel experimentation if the variable cost can be reduced and the quality maintained. This variable cost will depend on the costs of the reagents, sample and assay, the cost of disposal (potentially very high), the cost of storage and the cost of maintaining a safe environment—all of which are functions of size (i.e. the volume and amounts of reagents). So while Chandlerian production processes got bigger to take advantage of economies of scale, experiments get smaller. An example of this relationship can be seen in Table 5, which highlights the reductions in the volumes of reagent and the increases in the number of experimental samples per test plate.

3.4 Increasing the Value of Experiments

The previous section has argued that there is an economic incentive towards reducing failure in the drug development process as this increases 'capacity'—Chandler's point.⁷ Reductions in failures come from improvements in

⁷ Jansen (1996) highlights the importance of the managerial aspects of change and notes that, of the 100-fold increase in screening capacity over 4 years, the automation provided a 4-fold increase but process improvements provided a 25-fold increase.

TABLE 5. Summary of Available Microplate Formats Within the 96-well Footprint

Plate density	96	384	864	1536
Array format	8 × 12	16 × 36	24 × 36	32 × 48
Increase over 96-well plate	—	4-fold	9-fold	16-fold
Centre-to-centre spacing (pitch) (mm)	9	4.5	3	2.25
Well diameter (mm)	7	4	2	1.5
Assay volume (range) (µl)	50–300	20–100	5–20	0.5–10
Potential reagent saving	—	4-fold	20-fold	at least 40-fold

Reproduced from Houston and Banks (1997, p. 737).

experimentation which improve the ability of scientists to correctly select therapeutic targets and modify lead compounds—Rosenberg’s point. The ability to do this in turn depends on having the tacit knowledge to recognize the ‘context of similarity’ between changes in starting conditions and changes in end results. In chemistry this is the ability to recognize the relationship between chemical structure and biological activity based on a form of tacit knowledge that medicinal chemists call ‘chemical intuition,’ and in biology it is the ability to understand biochemical mechanisms and recognize potential sites for therapeutic intervention. There are therefore a number of economic strategies for improving this tacit knowledge and the potential success of experimentation. These are as follows.

Running Experiments in Parallel and Reducing Size The quality and quantity of experiments can be increased by running them in parallel and increasing the number of experimental units so that the results of large numbers of experiments are understood together in relation to one another. This can involve running a population of samples against the same tests or running multiple tests together. For example, in the 1980s molecules were tested sequentially for toxicity, absorption, metabolism and carcinogenicity in a process that might take many years. In the late 1990s the process has moved towards a parallel approach where ‘potency, selectivity, metabolism, tissue penetration and carcinogenicity [are] . . . determined simultaneously’ (Sykes, 1997, p. 17). Thus, instead of six animals being dosed with a single compound and tested over a week, now a single animal is tested with up to 100 compounds and improved mass-spectroscopy is used to generate equivalent data in a single day (Sykes, 1997).

Improve Quality of Experiments Improvements in instrumentation produce a more accurate understanding of the relationship between cause and effect. Similarly, concentrating on ‘more fundamental’ features allows

experimental scientists to improve their 'context of similarity'. For example, in chemistry this can involve exploring 3-D structure and Quantum Mechanical electrostatic potentials rather than simply 2-D molecules. In biology it can involve a shift from animal models to *in vivo* model systems in tissues, cell lines and individual enzyme substrates. This improved understanding can reduce the number of trial-and-error experiments, improving the cost and time performance.

Perform Experiments in Silico and Use Simulations to Screen Molecules

Experiments in the real world are constrained by cost, the amount of waste they produce, the amount of space that they take up, the amount of time that they take to do, the accuracy with which the results can be detected and interpreted, the physical ability to 'see' results at the microscopic scale, the ability to analyse important phenomena that are disrupted by instrumentation and the extremely fast speeds at which biochemical reactions take place. Since experiments are extrapolating patterns between starting conditions to discover unknown end results, and these patterns can be codified mathematically (in theory), it is theoretically possible to perform simulations instead of experiments. While computer simulations are not accurate enough to replace 'wet' experiments, they are useful as complements. The obvious next step from using simulations to explore biophysical behaviour is to use them to screen samples in order to remove samples that fail to match a given criterion and reduce the number of real world experiments.

The next section will show how pharmaceutical firms adopted these strategies.

4. The Dynamics of Chemical Experimentation

This section explores how the technology of experimentation in the pharmaceutical industry has changed over the 1990s. It argues that both biology and chemistry have moved towards the parallel analysis of populations complemented by increased use of *in silico* experimentation on databases.

Within drug discovery, medicinal chemistry experiments are performed to allow scientists to understand the relationship between chemical structure and biological activity. This knowledge is then used to bias where the chemists look in 'chemical space' for compounds to test. Initially experiments were based on sequential analysis of single compounds using animal models, but over the late 1980s and 1990s it has shifted towards the analysis of populations supported by *in silico* computer-aided molecular discovery. Towards the middle of the 1990s, innovation in high throughput screening (HTS)

technologies in chemistry and genetics technologies in biology have allowed scientists to run experiments in parallel and exploit economies of scale.

4.1. Computer-aided Molecular Discovery

One of the main bottlenecks in structure-based drug discovery is finding and modifying the lead compounds that will act as a 'key' and fit into the active site on the protein (the lock) and turn it off. Lead compounds are generally found by screening large numbers of compounds until one is found which binds to the active site on the protein.⁸ Medicinal chemists then use their knowledge about the relationship between chemical structure and biological activity to suggest modifications that will improve the performance of the compound. This knowledge is generated by an experimental cycle of proposing and testing potential solutions and then using the results to modify the chemists' understanding of the relationship between chemical structure and biological activity (cf. Figure 2). As Blundell *et al* (1989, p. 448) note, experimental cycles 'can be seen not only as a series of steps leading to an improved . . . product, but also as steps designed to test or falsify the hypothesis generated earlier in the cycle'. The experiments themselves involve moving from the known starting conditions of the proposed solution to the unknown end results of the test. Since this is an extrapolation of patterns of behaviour that can be expressed in mathematical terms, in principle it can be performed by a simulation if sufficient computing power is available (cf. Figure 2). The simulations allow medicinal chemists to model chemical bonds and 3-D structures, and explore how different chemical compounds interact with the protein (Blundell *et al.*, 1988; Gambardella, 1995).

The ability of molecules to fit into the active cleft in disease-causing proteins depends on their 3-D conformation and their electron distribution. The 3-D conformation determines if the molecule will fit, while the electron distribution determines if it will stick. The energy of the molecule can be calculated using the quantum mechanical wave-function Ψ of the molecule and is used to 'quantify interactions inside and outside molecules that reflect molecular properties' (Hann, 1994, p. 132). For example, 3-D structure is determined by minimizing energy calculations, while bonding properties are based on the electron distributions. While algorithms for both types of simulations have been around since the 1960s and supercomputers since the

⁸ A similar process works with the other main drug targets apart from enzymes: nuclear (hormone receptors), ion channel and seven-transmembrane-domain (7TM) receptors. There are many other methodologies for finding drugs and other ways in which they act. The 'lock and key' methodology is an illustrative rather than representative example.

1970s, simulations were not widely used until high resolution visualization technology was developed in the 1980s that allowed medicinal chemists to understand what the simulations 'showed'. This technology initially came from Evans and Sutherland in 1978, but was quickly followed by Silicon Graphics' faster RASTER system and a range of other products.

Visualization technology is important because it allowed medicinal chemists to explore the biophysics of chemical interactions in 3-D. Beforehand, chemists based their understanding on 2-D pictures of complex molecules. However, because chemistry takes place in a 3-D world, the translation from 3-D chemistry to a 2-D picture and then back to 3-D in the chemist's mind introduces a series of distortions. By having the representation in 3-D, these distortions are removed.⁹

While simulations are very useful, the quantum mechanical nature of the calculations requires large amounts of computing power to produce accurate approximations and simulations are therefore used as complements rather than alternatives to 'wet' chemistry. They do, however, have two very important uses. Firstly, they allow chemists to explore their implicit theories of why certain behaviours take place, and in doing so act as a 'virtual microscope' (Gray, 1995), exploring behaviour that would be impossible to see with instrumentation. Secondly, if the simulations are accurate enough they can be used to screen databases of compounds to select compounds that are likely to be drugs for further empirical testing. While nowhere near as accurate as experiments, this process can be significantly cheaper and faster since 'Ligands can be examined at a rate of 10–100 per minute enabling the examination of a database of 100,000 compounds in less than a week' (Whittle and Blundell, 1994, p. 356). Moreover, the data generated can be compared with experimental data to highlight anomalies. Visualization technology allows this analysis to proceed at a more fundamental level, as it allows medicinal chemists to literally 'see' theoretical features that cannot be picked up by instrumentation—such as different electron densities—in terms of different colours. As such, it allows chemistry to be understood in terms of more abstract and mathematical patterns. For example, molecules can be understood as electron distributions on a 3-D 'backbone' structure or 'pharmacophore' rather than as atoms and bonds (P. Murray Rust, personal communication). This in turn has the potential to improve the selection of compounds.

While computer simulations were originally introduced to replace experiments, their lack of accuracy and higher than expected costs has limited their

⁹ As Turro (1986, p. 888) notes 'to many organic chemists, models are the 'pictures' on which the imagination may be exercised and which enhance an intuitive understanding of the object or concept under consideration' (cf. Ugi *et al.*, 1970; Hann, 1994, p. 198).

use and, compared with early expectations, their performance has been disappointing. Moreover, in the early 1990s it became clear that companies following 'rational drug discovery' strategies were in danger of developing very similar drugs with similar performance which automatically restricted their potential market. As a response many pharmaceutical firms have moved away from 'overly rational' approaches and have tried to introduce some 'randomness' into development to distinguish their products from competitors. One of the key technologies in this shift away from rational drug discovery was the development of HTS technologies.

4.2 High-throughput Screening and Population Chemistry

These new plate formats have arisen as a potential answer to the problematic question being asked at most major pharmaceutical companies: 'How can we screen more targets and more samples cheaply?' (Houston and Banks, 1997, p. 737)

HTS represents a shift from a craft-based experimental cycle whereby scientists test single compounds in series at a human scale to a mass-production process whereby very large numbers of compounds are tested in parallel at the microscale by automated robots. As a result, the yearly throughput of a typical lead discovery group increased from about 75 000 samples tested on about 20 targets to over a million samples tested on over 100 targets (Houston and Banks, 1997, pp. 734–735).¹⁰

The shift from serial testing to the automated testing of large populations required coordinated changes in all three aspects of the 'chemical' design cycle on the right hand side of Figure 4: i.e. changes in testing, changes in the production of chemicals for testing (proposing and producing uncertain solutions) and changes in how the results of experiments are understood (modifying understanding). These changes are highlighted below.

4.3 High-throughput Screening

HTS is the biological technology that allows large numbers of chemicals to be automatically tested for biological activity. In the 1990s it has 'become the major tool for lead identification, where novel assay formats, assay

¹⁰ HTS requires firms to trade off quality, speed and quantity. The automated systems can in principle screen millions of samples a year, but maintaining experimental quality in large mixtures becomes increasingly problematic. However, lead compounds can sometimes be found in months rather than the previous 2 years, improving throughput.

miniaturisation and automation have been utilised to enable cost effective, rapid and successful drug discovery' (Houston and Banks, 1997, p. 734). It comprises a system for data handling, an array of compounds to be tested, a robot to perform the testing and a biological test configured for automation. The test itself is a biological system that has been engineered so that it will produce a detectable signal when it is activated by a compound. This can involve linking it to a fluorescent or radioactive source or the use of biosensors.¹¹ Originally developed as an instrumentation technology, biological assays have gradually decreased in size and improved in sensitivity. As they have become more robust they have been increasingly used for parallel screening.

4.4 Combinatorial Chemistry

The introduction of new high-throughput testing created a bottleneck in the discovery process as the production of compounds did not expand at the same rate. With a shift from being able to test hundreds of compounds to being able to test tens-of-thousands of compounds in the early 1990s, it quickly became obvious that pharmaceutical firms could test all their compounds very quickly. From the perspective of Hughes (1983), the interconnected nature of the innovation process meant that improvements in screening technologies increased demand for compounds and created a 'reverse salient' in synthetic chemistry. This acted as a Rosenbergian 'focusing device,' or Hughesian 'critical problem,' and concentrated innovative activity. Combinatorial chemistry was developed to fill the vacuum—a technology whereby large numbers of compounds are made by the 'systemic and repetitive covalent connection of a set of different "building blocks" of varying structures to each other to yield a large array of diverse molecular entities' (Gordon *et al.*, 1994, p. 1733). Instead of the old 'Woodwardian' serial method of hand-crafting specific compounds, combinatorial chemistry is a mass-production technology that synthesizes large numbers of compounds in parallel, as mixtures using computer-controlled robots [for a review of other methods see Gallop *et al.* (1994), Gordon *et al.* (1994), and references therein].

¹¹ *In vivo* testing involves trade-offs between the depth and breath of experimental knowledge. As testing has shifted from animal models to the tissue, cell and then biomolecular substrate, the scientist has been able to understand biological phenomena in great depth. But, while *in vitro* tests provide very detailed information about specific substrates, unlike animal tests, they are silent on other biological effects. HTS does not evaluate the drug's absorption, breakdown, toxicity or selectivity. Although some drugs have come directly from HTS, the narrow nature of biological information they provide had generally seen them used in conjunction with traditional medicinal chemistry.

TABLE 6. The Different Domains of Chemical Experimentation

	Real world	<i>In silico</i>
Single molecule	serial synthesis and testing	computer-aided molecular discovery—simulations used as ‘virtual microscopes’
Populations of molecules	combinatorial chemistry and HTS	QSARs—simulated screens

4.5 Database Innovation

The shift from serial to population experimentation has produced huge amounts of data, requiring changes in how it is understood. Improvements have been seen in data management software, statistical analysis software and the visualization technologies required to represent the large amounts of complex data from experiments on large populations. When experiments were done in a serial fashion experimentation followed the pattern described in Figure 2. With populations, however, it is possible to compare and explore patterns within the population. Thus, a population of compounds that are active against a specific screen can be analysed to see if they contain common features. While this has been a traditional part of medicinal chemistry, in the form of quantitative structure–activity relationships (QSARs), large populations and modern computerized statistical analysis have increased its prominence.

Populations of compounds can also be tested against counterscreens to use statistical techniques to understand why a molecule is selective for a particular substrate. This is part of a shift towards *in silico* analysis of populations whereby data is stored and used to help reanalyse new data. In doing so, anomalies in the patterns between structure and activity in one context can be used to explore old data. This allows a change in the ‘sense of similarity,’ producing a more detailed understanding of the structure–activity relationship. Since false positives have costly effects, it is important to complement this *in silico* analysis with experimental results (see Table 6).

4.6 Designing Populations *in Silico*

If medicinal chemistry is like fishing for a compound, structural-based drug discovery is ‘fishing with a hook’ and involves using tacit knowledge to narrow down the volume of the pond where the catch is likely to be found. HTS, however, allows the pond to be divided into small areas that are

searched in parallel and is like ‘fishing with a net,’ where as much of the pond as possible is trawled (M. Hann, personal communication). Once a trawl has found a ‘hit,’ established medicinal chemistry techniques based on statistics, intuition and single compound testing are used.

However, the problem of where to trawl is still present. Simply increasing the number of experiments may produce no benefits if they are irrelevant to the problem being solved. The general methodology is to ‘trawl’ through as diverse a volume of chemical space as possible. However, this raises the question of how to define ‘chemical space’ and ‘chemical diversity’ as the structure–activity relationship is context dependent, i.e. a group of compounds that are similar in one context may be very different in another (Gordon, 1995).

Choosing the correct way to describe the compounds before the experiment is difficult because there are a large number of possible ‘contexts of similarity,’ and the ‘correct’ one is only known after the experimental results are collected. This is Bradshaw’s (1995) paradox: ‘We need to know the biological results before we can decide on the appropriate space to represent our compounds’. If it were possible to test all the possible drugs this problem would not exist, but as there are $\sim 10^{180}$ possible drugs and $\sim 10^{18}$ potential drugs, testing all of them is neither logistically or economically practical. Instead, intelligence and tacit knowledge must be used to bias the test sample towards likely successes and away from irrelevant or repeated compounds.

This rational biasing of the samples proceeds by defining the ‘chemical space’ where the drug is likely to be found. Various features, like size and toxicology, can be used to remove volumes of the chemical space that are unlikely to produce drugs. The chemical space is then defined by ‘descriptors’ that correspond to various physical properties that are known to make compounds ‘drug like’. The compounds are then ‘clustered’ together and a representative sample is selected and used to search as much of the chemical space as possible within realistic economic boundaries.¹²

Different firms use different descriptors to analyse chemical space, reflecting an economic trade-off between the quality of the descriptors and the computational cost. Descriptors can also be tested and compared to see how well they pick out known active compounds from previous experimental data. Unsurprisingly, the effectiveness of different descriptors varies in different biological contexts and this knowledge can bias the selection of appropriate descriptors.

For example, 3-D shape is an obvious criterion for ‘fitting’ into a protein,

¹² Clustering several million compounds is often computationally impractical. Compounds are therefore excluded from the statistical analysis based on ‘intuition’ and knowledge of chemical properties.

but the computational cost of measuring, calculating and clustering around the 3-D shape makes it inappropriate for large databases. Work at Chiron (California, USA) in the mid-1990s on 3-D descriptors found very little difference from clusters done on far simpler 2-D 'fingerprints' (Spellmeyer, 1995). In general, diminishing returns to the number and quality of descriptors very quickly set in.¹³

There is also a historical path dependence implicit in the biasing of populations as '[a]ll drug company compound files are biased by the historical programs of that institution, since a disproportionate share of compounds of particular types will have been deposited' (Gordon *et al.*, 1994, 1399). For example, a company may have historical competencies in antiviral drugs and therefore has compounds and experience of making molecules that are biased towards antiviral-'like' drugs.

This bias can be recognized and used to intentionally create libraries. So a medicinal chemist searching for a cure for AIDS could read a technical paper describing how a certain class of molecules bind to an HIV protein (e.g. Rich *et al.*, 1990) and then use this knowledge to bias the library with similar compounds. Libraries are therefore constructed based on knowledge of the relationship between chemical structure and biological activity. As Gordon *et al.* (1994, p. 1399) put it: '*The notion of intentionally biasing a chemical library is a form of drug design, but not applied to individuals but rather to groups or populations of molecules. [Thus] . . . all libraries are biased in some ways.*'

Once the first round of testing has been done, the statistical results can be used to bias a second 'trawl,' as data are now available on the appropriate context for similarity. This rearticulation of understanding can then bias the next round of empirical testing towards more appropriate populations. This involves reusing *in silico* data to design *in vivo* experiments. At Pfizer this computational approach is used to pick up some of the compounds that HTS misses. When applied to a database of compounds, computational searches based on 3-D flexibility found compounds known to be active against HIV-protease that were missed by HTS. The screening of 500 000 precalculated compounds took 1–3 h (Finn, 1995). Thus the simulated *in silico* testing of populations of compounds can be used to complement the real testing of populations of compounds.

¹³ Interestingly, the chemical diversity of the top 50 and 100 drugs on the market is greater (by various measures) than the chemical diversity of almost all the compound libraries that can be made or bought (in 1995), which has pushed synthesis towards non-standard chemistry (Spellmeyer, 1995). An explanation advanced in the industry is that, because traditional organic chemistry has historically been concerned with copying natural compounds and reactions, it is easier to synthesize compounds that are 'similar' to naturally occurring ones. Pathogens have evolved to be immune to these types of compounds but have no defences against the new non-natural compounds. As K. Pavitt (personal communication) points out, this is an example of a localized search in a complex environment leading to path dependency.

TABLE 7. The Changing Features of Chemical Experimentation

Changes	Feature		
	Propose solution—(synthesize compounds)	Test solution	Modify understanding
From craft to mass production technologies	From craft-based serial synthesis to combinatorial chemistry.	From testing single compounds in animal models to <i>in vitro</i> analysis at biomolecular level using automated, parallel HTS.	From a tacit sense of similarity to using 3-D visualization technologies and statistical analysis to understand populations.
Scale—size	From beaker to micro- and submicro-level; from single to mixtures of compounds.	From 96 to 384, 864, 1536 and 3456 compounds per shelf; increases in speed so that 190 000 compounds can be tested in a few weeks rather than 2 years.	Shift from understanding experiments on single molecule to statistically analysing data on millions of experiments.
Automation	Introduction of robotics to automate and standardize synthesis; automated quality control.	Robots used 24 h a day to produce an approximately 30-fold increase in throughput.	Increased use of visualization and simulations to understand biophysics, and increasing statistical analysis of populations and simulated populations.

As this section has shown through the 1990s, chemical experimentation in the pharmaceutical industry has shifted from single compounds to populations. In doing so, experiments have reduced in size and have become increasingly automated, with computer simulations being used to complement physical experiments. The Chandlerian point about control being the handmaiden of economies of scale is supported by the increased use of computerized databases in the design and interpretation of experiments. Table 7 summaries the evidence and shows how the three stages of the experimental design cycle—(i) proposing solutions, (ii) testing and (iii) modifying understanding in the light of new evidence—have changed. The first row shows how each stage has moved from being craft-based to being part of a mass-production process. The second row shows how increases in the number of tests and decreases in their scale have affected each stage. The last row

shows the increased use of technology to perform tasks that were once done by hand.

5. *The Rise of in Silico Population Biology*

The previous section outlined changes in the chemistry of drug discovery; this section outlines similar changes in biology. In doing so it necessarily simplifies an enormously complex and research-intensive process as biological experiments shifted from analysing individual proteins to analysing populations of genes.¹⁴ The shift from the protein level to the gene level creates added complications, but the basic process that was seen in chemistry is repeated: experiments that were originally hand-crafted have increasingly become automated processes performed in parallel on populations with complementary analysis of stored and simulated data.¹⁵ The huge amounts of data involved in genetics (a single laboratory can produce more than 100 gigabytes of data per day) has required complementary innovations in information technologies and changes in the way experiments are understood and designed.

These changes have been part of an attempt to increase the throughput of R&D which is limited by the ability to find effective targets for therapeutic intervention. With the 'lock and key' methodology of structure-based drug discovery, starting out with a protein target that plays no role in the disease will doom the project from the start. As a consequence improving understanding of what proteins are involved in which biological mechanisms can reduce failures and improve R&D capacity. However, the biology of disease is hugely complex and a lot of costly, slow and laborious research is needed to unravel it.

Fortunately the possible biological processes involved in diseases are limited by chemical possibilities and evolutionary redundancy (whereby evolution adapts pre-existing features to new functions). Evolutionary redundancy constrains biology because of strict symmetry conditions that govern the relationship between genes and the peptides that make up proteins (i.e. the genetic code). These strict symmetry conditions create strongly conserved patterns within biology that allow knowledge from one biological domain to be extrapolated to another by evolutionary analogy. For example, humans

¹⁴ Biological research involves more sophisticated scientific research and experimental cycles that gather data than chemistry, as the mechanisms involved in disease are often unknown.

¹⁵ While genetics has always analysed populations, the 1990s have seen a shift towards the analysis of populations of gene populations, e.g. analysing the differences between the populations of genes of diseased and non-diseased groups, or the analysis of the expression of a given population of genes over time.

have many metabolic pathways that go back to our early biological ancestors. Since these are shared by creatures with the same ancestors, knowing how they work in a mouse, for example, can be used to understand how they work in humans. Similarly, knowing how one mechanism works in one area of the body can provide understanding about how another similar mechanism works elsewhere. As a consequence, there are relationships between the sequences of similar genes and the function of the corresponding proteins that can be learnt and used to understand the biology of disease and produce targets for therapeutic intervention.

The ability to use this genetic knowledge has developed significantly over the last half century and dramatically through the 1990s. The next subsections will show how initial research on single gene mutation diseases helped develop reusable genetic data and a more fundamental understanding of biology. These data in turn, and the technologies that were developed to use them, allowed biologists to explore the genetics of more complex diseases. Over time, the amount of data has increased, and more and more experiments can be conducted by searching databases and analysing populations of genes *in silico*. These searches have complemented wet biological experimentation, improved the ability of biologists to understand the mechanisms of diseases and hopefully improved the capacity of R&D. As the size and number of databases have increased, more and more research is conducted *in silico* and medicinal biology has become a more theoretical science (Gilbert, 1991; Murray Rust, 1994; Lander, 1996; Gelbert and Gregg, 1997; Weinstein *et al.*, 1997).

This shift has gone through a number of overlapping stages. Firstly, biology was a craft-based 'wet' science, and pharmaceutical research relied on brute empiricism with limited biological understanding. In the 1970s and 1980s, research on genetic mutations generated new technologies and maps of the genome. As sequencing technologies and genetic databases improved, genes could be found within already sequenced data. However, using this information to produce drugs requires understanding the gene's functions. HTS technologies were developed to analyse genetic functions in a number of model organisms and databases were developed that link functional information on genes. The next stage occurred when improved databases and sequencing technologies allowed biologists to analyse populations of genes and build up understanding of mechanisms and models of disease action in order to suggest sites of therapeutic intervention. Diseases are now understood in terms of the differential expression of genes, which in turn cause the production of proteins that catalyse disease-causing biochemical pathways. Since these pathways involve

multiple proteins and genes, diseases are understood as polygenetic and multifactorial.

5.1 Science Becomes More Fundamental: the Shift from Classical to Molecular Genetics

Modern genetics has its roots in Gregor Mendel and Weismann's work on inheritance. In the 1940s understanding of the role of genes in biology started to improve after experiments showed that moulds and bacteria with mutated alleles were unable to synthesize essential proteins (enzymes). By the 1950s the connection between genes and proteins was recognized, but it was Watson and Crick's discovery of the structure of DNA that suggested a mechanism to relate genetic material to the rest of biology by explaining how nucleotides relate to peptide sequences. Within a decade the genetic code was broken.¹⁶

Medical research in the 1970s and 1980s concentrated on finding the single gene mutations that caused inherited genetic disorders such as cystic fibrosis and Huntington's disease, where analysis of the family tree should reveal if the disease is dominant or recessive. Early work on these genetic diseases in the 1950s relied on elucidation of biochemical mechanisms to generate a protein involved in the disease, and from the protein the researchers would work back to find the gene using very slow gel separation of protein fragments. This method involved laborious analysis, whereby biochemical knowledge was needed to suggest a gene 'candidate,' where it is likely to be found and what it is likely to do.

5.2 *In Silico* Experimentation and the Shift Towards Reverse Genetics

The shift towards *in silico* experimentation, where genes are found using computers, happened when research moved from the 'candidate method' towards 'reverse genetics' in the mid-1980s. With 'reverse genetics' the researcher relies on a dense marker map of the genome and good clinical characterization (which is typical of single gene defect diseases) to statistically analyse the correlation between genetic markers and disease states. The

¹⁶ Each triplet (codon) of bases on the gene codes for a particular amino acid and additional stop codons code for termination of transcription. There are four possibilities (A, C, G, T) at each base in the triplet, creating 64 codons that code for the 20 amino acids that make up proteins. Within the cell, the DNA in the genome is activated by special enzymes that switch on (express) specific genes and then complementary proteins within the cell use the unzipped gene as a template to produce mRNA, which is then passed to a different part of the cell where it is translated into the amino acid chains that make up proteins. These amino acid chains then fold up into very complex 3-D patterns and the resulting proteins typically have active sites that will catalyse various biochemical reactions.

higher the correlation between having the disease and having the genome marker, the closer together the marker and the mutated gene are on the genome. Once the gene location is approximated, the next stage is to focus down on that region and pepper it with markers in an attempt to find the exact location of the gene, then find its sequence and produce diagnostics.

These techniques became increasingly possible following the development of automated ways of amplifying and sequencing DNA.¹⁷ Of particular importance were the development of the 'Southern blot,' the polymerase chain reaction (PCR) that allowed DNA to be copied, Saiki's development of thermostable enzymes that allowed the PCR reaction to be automated, automated methods of creating 'primers' that cut the genome at specific points and the discovery of various markers which allowed more detailed genome maps to be developed. Since the data on the location and sequence of genes and markers generated by these technologies could be reused, the scientific community developed a number of publicly available databases.

The development of genome databases followed the sequencing of small (~5000 base pairs) DNA viruses, such as 'Simian virus 40' and 'phage ϕ X174' in 1977. As the technology of sequencing improved, larger viruses with important healthcare effects began to be sequenced. Potentially useful biological information coming from the early research groups focused attention on mapping the entire human genome, and in the late 1980s federal funding and money from the Wellcome Foundation was used to set up an international genome sequencing operation. As these databases increased in quantity and quality it became increasingly possible to search for genes within the sequenced data and biology slowly shifted from a predominantly 'wet' experimental science to an increasingly theoretical *in silico* science (Gilbert, 1991).

5.3 Functional Genetics and *in Silico* Screening

While improved sequencing methods and databases have made finding genes and producing diagnostics easier, they have not produced many cures. Finding the gene does not tell you its function, nor does it suggest how that function relates to the mechanism of disease causation, or how that mechanism can be

¹⁷ Restriction enzymes were developed in 1966 that allowed DNA to be cut and pasted into bacteria, which could then be used to clone DNA. The development of improved sequencing methods by Sanger in 1975 and Gilber and Maxim in 1977, and the development of automated DNA sequencing by Carruthers and Hood in 1983 made finding the molecular structure of genes easier. These involved making the DNA reproduce various copies of itself of varying lengths using dideoxy bases. If the experiment is run using different radioactively tagged As, Cs, Gs and Ts, and these are then run through a gel, each gel line will separate the DNA out into different lengths. If all four are compared against each other, the resulting separation should show the 'letter' associated with each base in turn.

modified. Since ‘genetic’ diseases account for less than 2% of the disease load, genetic research has not yet had a revolutionary effect on medicine. It has, however, had a profound effect on two areas of medicinal research: firstly, on the development of new technologies associated with rapid gene sequencing, gene engineering and database management, and secondly, it has allowed diseases to be understood at a more fundamental level. Previously, as Table 2 showed, disease biochemistry was typically understood in terms of proteins catalysing biochemical mechanisms. The development of modern medicinal genetics technologies has shifted this thinking, so that rather than starting with the protein, the problem solving process goes back one stage further and asks what causes the production of the proteins that catalyse the biochemical mechanism. The answer provided by the new genetics research is that proteins are caused by the differential expression of genes. Since the linkages between proteins and genes are strongly constrained by the genetic code, this allows medicinal biologists to explore proteins by exploring populations of genes.

With this new methodology, the shift from knowing what genes are involved in disease to finding a cure requires medical biologists to understand how the genes function. Early functional genomics research focused on fruitflies, yeast and nematode worms that had long histories as model organisms as their short life cycles enabled the role of specific genes to be quickly analysed. This information on gene function could be extrapolated to ‘similar’ genes using evolutionary redundancy (whereby evolution builds on what has gone before and reuses the same materials) within and between species to extend knowledge from one domain to another. Thus genes of medicinal interest in humans can be investigated by analysing ‘similar’ genes in organisms like yeast, mice, zebra fish and nematode worms. This allows genetic information to link:

- biology to chemistry
- evolution to developmental biology, structural biology, ecology, and medicine
- biological mechanisms between species
- biological mechanisms within the same species
- patterns that contrast diseased and non-diseased states (thus, for genetic diseases differences in the phenotype can be traced to differences in the genome)

As a consequence, the very complex biological investigation of genes’ functions has been increasingly complemented by database searches for ‘similar’ genes with known functions. As with the generation of chemical descriptors,

the correct ‘sense of similarity’ is only known after the answer has been found, and considerable tacit knowledge and research experience is needed to find the most useful context (Bork and Bairoch, 1996).

Information from these computational studies is then used to help provide context for the ‘wet’ biology involved in determining genetic function. This involves ensuring that the gene differentiates between diseased and non-diseased states, finding the mutation and showing its effects. The gene is removed, cloned and inserted into a model organism to examine how it functions. This commonly involves generating transgenic animals where random recombination between the artificial vector and the animal’s genome is used to generate either knock-out animals, where the gene is removed, or ‘transgenic’ animals, where the diseased gene is inserted into the animal’s genome. The animals are then analysed to look at the effects on various tissues. This ability to use transgenic animals, to explore the consequences of knocking out genes, and the ability to exploit evolutionary redundancy and use similar sequences to fill in gaps in sequences has enabled medicinal biologists to build up better models of how diseases occur and potentially how they can be cured.

While genetically engineered mouse models have very similar biology to humans, they suffer from high cost and low throughput. As a consequence, high-throughput biological systems have been developed to characterize genes based on yeast, nematode worm or fruitfly systems that have been adapted for robot manipulation and growth in 96-well dishes (Gelbert and Gregg, 1997, p. 670).

5.4 Single Populations to Populations of Populations

As the amount of biological data has increased and the tools for analysing genetic profiles have improved, research has started to explore biology beyond the single gene to populations of genes. New technologies based on expressed sequence tag libraries, ‘gene chip’ technologies and single nucleotide polymorphisms can now analyse large populations of genes. This allows the exact coding sequence of genes to be found and directly related to proteins, allowing very fast ‘shotgun’ sequencing. The increase in the speed of sequencing has allowed more genes to be analysed so that scientists can explore different expression levels of thousands of genes in diseased and non-diseased tissues—hopefully showing the genes and proteins involved in disease.¹⁸

The use of these technologies has shown that large numbers of genes are

¹⁸ This has not yet produced increases in R&D throughput as the biological problems are considerably more complex than was initially thought.

involved in many diseases that were traditionally thought not to have a genetic basis (Gelbart, 1998; cf. King *et al.*, 1992). As a consequence, the role of genes in disease has shifted from the concern with single gene mutations that produced diseases in all cases to polygenetic, multifactorial diseases where the genetic variations may dispose a patient towards certain diseases given certain external environmental factors. This shift towards a polygenetic, multifactorial understanding of the role of populations of genes in disease has required innovations in the databases and statistical techniques for analysing genetic data (since many of the established statistical techniques do not work for polygenetic diseases).

The development of these new technologies has in turn required very complex computer systems to control the 'tidal wave of data' coming from these new technologies (Deloukas, 1998). The development of these IT systems has been termed bioinformatics

a science . . . that uses biological data and knowledge stored in computer databases, complemented by computational methods, to derive new biological knowledge. It is a theoretical biology firmly grounded in comprehensive and detailed experimental facts. Currently, bioinformatics is making a key contribution to the organisation and analysis of the massive amount of biological data from genome sequencing projects and increasingly from other areas of 'high-throughput,' 'massively parallel,' robotised and miniaturised methods of biological experimentation. (Andrade and Sander, 1997, p. 675)

These computer systems are interconnected and constantly updated as new genetic information is released. Programs within the systems automatically explore the new data and inform the relevant research groups that data they are interested in has been made public. These programs also automatically look for new genes within the sequence databases and again automatically inform the relevant parties. This automated analysis of genes and sequence data is done within the databases on 'virtual genes' based on their genetic sequences. While it is a long way from replacing 'wet' biology, it does represent the ultimate in scale reductions as the genes exist only as electronic pulses and their analysis is limited only by the (often substantial) costs of calculation.

As biology has increasingly moved *in silico* the ability to coordinate and control the data to ensure the correct throughput of information into the research programmes has become more important. Large pharmaceutical firms have invested heavily in gaining access to this information, by develop-

ing their own systems and by linking to biotech firms (Hopkins, 1998; Martin, 1998; Crowther, 1999; Jones, 1999). From a Hughesian (1983) perspective, the bioinformatics systems and the databases of chemical information form part of the 'control systems' of the overall innovation process, and improvements in R&D throughput are dependent on how the information they contain is used—what Davies (1996) has termed 'economies of system' in his study of telecommunications networks.

As finding the 'drug target' has been the main bottleneck in drug discovery, the development of effective ways of finding 'disease' proteins from their genes has improved the prospects of drug discovery. The development of these new genetics technologies has produced an about turn, so that in the early 1990s the main problem for pharmaceutical R&D was finding targets, while at the end of the 1990s the main problem was deciding which of hundreds of potential targets would be most profitable. The biochemistry of these new targets is better understood and failures are less likely, further increasing the potential capacity of the drug discovery programme. Since the analysis is based on a more fundamental understanding of diseases and their mechanisms, it has the potential (unfulfilled at present) to attack the causes of disease, rather than, as with most modern drugs, the symptoms.

As Table 8 shows, the changes in biology are consistent with the changes in chemistry and with the framework developed earlier.

The next section discusses the implications of these changes and points towards areas where further research is needed.

6. *Discussion and Conclusion*

The empirical evidence has illustrated how pharmaceutical firms have exploited economies of scale in the creation of intangible capital in an attempt to increase the throughput of their R&D processes. The evidence supported Rosenberg's insights that new experimental technologies and research methods can reduce the cost of solving complex technical problems. However, these cost savings are related to the 'throughput' of the R&D process and would not be realized by firms producing small numbers of drugs. Firms require large numbers of drugs in their R&D 'pipeline' to first spread the high fixed costs of these new technologies and secondly to manage the uncertainty and volatility of product success. Pharmaceutical firms have therefore exploited economies of scale and scope across therapeutic areas, suggesting that the organizational and technological features of modern drug discovery may favour a particular organizational form—a large firm with a large R&D department—in a way that is consistent with Chandler's framework.

TABLE 8

Changes	Experimental design and proposing solutions	Testing	Modify understanding
From craft to mass production	From a craft-based wet biology of finding proteins and then genes to an automated high-throughput process of finding genes and their function complemented by <i>in silico</i> analysis.	From the use of microscopes and physical instrumentation to the automated generation of data on populations of genes.	Biology has shifted from an empirical science to an increasingly theoretical one based on the computerized statistical analysis of large amounts of empirical and <i>in silico</i> information and its representation by advanced visualization technologies.
Changes in scale and size	The experimental unit has shifted from the human body to animal models (1950s), then on to tissues (1960s), the biochemistry of cells and protein mechanism (1970s and 1980s), and onto hundreds of thousands of genes (1990s).	Sequencing has shifted from single genes to populations of thousands of genes. Functional genetics has shifted from single transgenic animals to high-throughput screening systems.	The amount of data produced by genetics laboratories has increased from dealing with 200 or so markers in the early 1990s to 100 gigabytes in 1996 and terabytes of data in 1998.
Automation	Biology has shifted from experiments on laboratory animals to increasingly automated systems where genes and their functions are found and analysed on databases.	Genetic sequencing is increasingly automated, with high-throughput model systems engineered for functional genetics.	Simulations of biological mechanisms based on linkages to databases.

The empirical evidence highlighted the shift from a sequential process of hand-crafted experiments to a parallel process involving the increasingly automated analysis of large populations. Since the costs of experiments are related to the volume of sample, economies of scale in experimentation have produced decreases in size (of the experimental unit)—in contrast to the increases in the size of production technologies. The shift towards performing complementary analysis *in silico* extends this emphasis towards reducing the

scale of experiments further by making them ‘virtual’—whereby costs are constrained by computing power.

The case study evidence, while exploring only a sample of technologies and simplifying a very complex process, has shown that both chemistry and biology have gone through several overlapping and interacting changes:

- Firstly, a shift towards more fundamental science. This involved a shift in chemistry from conceptualizing molecules as static atoms and bonds to seeing them in terms of electron distributions and 3-D dynamic structures. In biology it involved linking biochemical mechanisms to the expression of genes.
- Secondly, a shift towards *complementing* experiments with computer simulations. In chemistry this involved using computers to visualize how the drug molecule bonds to the protein. In biology this involved using databases to analyse genes and their functions.
- Thirdly, a shift towards performing experiments and analysis on populations. In chemistry this involved using HTS and combinatorial chemistry. In biology this involved using various high throughput biological systems to understand biological mechanisms, using genetic information on diseased and non-diseased populations (to find the position of genes), exploring the similarity between families of genes across species (to find similar functions), and exploring populations of genes within an individual (to find how different expression levels relate to different biological features).
- Fourthly, experiments on populations created unprecedented amounts of data that required the introduction of database technologies. In chemistry this involved using statistical analysis to explore similarities between compounds, and databases to cluster various ‘descriptors’ in the design of experiments. In biology it involved the generation of bio-informatics technologies.
- Lastly, databases were used to conduct complementary *in silico* experiments on old and new data. In chemistry this can be seen in the use of databases to screen populations of compounds for testing and to statistically contrast different screens. In biology the shift has involved searching for genes on databases, and exploring their functions by relating them to ‘similar’ genes in other environments.

The introduction of these new technologies raises a number of issues about the relationship between scientific knowledge and innovation. The evidence supports the generally accepted view that scientific knowledge does not

produce technology directly. This was explained in terms of the direction argument. An alternative conception of innovation based on the notion of 'technological traditions' was presented where the application of 'similar' solutions to 'similar' problems generated a sequence of tasks that formed the basis for the innovation process.

Since scientific knowledge cannot directly generate a desired outcome, technologists perform a large amount of research to understand the phenomenon they are trying to modify and then rely on their tacit knowledge to suggest an uncertain 'first cut' solution. This is tested and the results of the tests are used to modify how technologists understand the relationship between changing starting conditions and end results, and consequently to 'tune' the technology towards its desired behaviour. The testing process can be done in increasingly accurate ways by relying on tacit understanding, by mathematical pattern extrapolation using simulations and by empirical testing. While high-throughput processes are used at the start of research tasks, the final stages of biological analysis and chemical synthesis are still very craft-based.

The ability of simulations to accurately predict behaviour is limited firstly, by computational cost, secondly, by nonlinear error growth and thirdly, by breakdowns in the symmetry between the laws of nature and their real world outcomes (which generate extra information not contained in the original laws of nature—see footnote 3). Simulations are therefore used differently in chemistry and biology.

Because chemical simulations are often quantum mechanical, the computational cost is very high for large numbers of atoms and more accurate approximations. This limits their accuracy and application, and while simulations are very useful for testing hypotheses, they have not replaced experiments, as was initially hoped. In biology the additional problems of large amounts of symmetry breaking and nonlinear error growth has made the simulation of biochemical reactions very inaccurate and their use is extremely limited. However, evolutionary redundancy and the strict symmetry conditions between genes and proteins create strongly constrained patterns that biologists can exploit.

Biologists use computers to interrelate proteins and their gene sequences, and to explore databases for similar sequences with known functions. The substantial differences within and between chemistry and biology in the use of simulations suggests that thinking of scientific knowledge as an all-encompassing category may be too simplistic for practical applications, as its role in technical change is very problem-specific (and therefore sector-specific).

While this paper has not been specifically about the 'conversion of tacit knowledge,' it does raise issues about its role in technical change. Information technologies have allowed medicinal chemistry and biology to become more fundamental and, while some skills have been replaced—more by the introduction of 'off the shelf' kits than by information technology (see Gilbert, 1991)—the general skill requirements have increased. This is especially true of the additional computational skills required to perform the new techniques. Moreover, since visualization technologies are needed to understand and analyse large populations of data, the notion that tacit knowledge has been converted into 'codified knowledge' seems problematic. Whatever the impact on tacit knowledge, the empirical evidence clearly shows a substantial increase in the amount of electronic information generated during drug discovery, and if 'codification' is taken to mean this, then it is supported by the account described here.

Questions remain about a number of issues. While the effects of these technical changes will be uncertain for a number of years, initial evidence does not suggest radical improvement. While many pharmaceutical companies are stressing that their programmes are of higher quality, there is little evidence that this is translating into improved performance. Care must be taken here as most of the major pharmaceutical firms are concentrating on considerably more complex illnesses than have been attempted before. It may be the case that investment in these new technologies is an 'ante' to remain in a more competitive game. More research needs to be done to see if their attempts to increase efficiency actually improve performance.

This initial failure of 'subcomponent' technologies to contribute towards overall 'systems' performance is partly related to problems of coordination and control of information and knowledge within the innovation process. There are two aspects of this. Firstly, the complexity of the innovation process means that it is very hard to understand the relationship between micro-changes and macro-effects. This problem is not specific to the pharmaceutical industry. The introduction of mass production in manufacturing at the start of the last century required long periods of incremental learning and organizational change before performance improved. As a consequence, the pharmaceutical industry would be expected to take some time to optimize its processes. As Nelson (1991) notes, firms differ substantially in how they adapt their internal organization to new technologies and environments.

Secondly, and more importantly, because the quality of experiments depends on how well they modify technologists' tacit understanding, even if the effects could be calculated they cannot be directly measured. For example, while it is easy to count changes in the number of experiments, the corres-

ponding improvements in understanding are far harder to measure. Since testing the wrong type of compounds is a waste of time, simple quantity measures are ineffective on their own, and the correct trade-offs between experimental quality and quantity (highlighted in footnotes 10 and 11) are extremely uncertain.¹⁹ Furthermore, what effect any changes in one part of the innovation process have on the rest of the system is even more uncertain because the correct tacit 'sense of similarity' is only known for sure after the drug has been found and shown to be a medical and commercial success. For example, improvements to the trade-off between quantity and quality might lead to a compound that binds very tightly to a protein; however, it will fail as a drug if the protein has no effect on the disease. Thus uncertainties in the system are pervasive, and the key to systems' performance involves controlling and managing these uncertainties.

This inherent systemic uncertainty about the subjective quality of experiments explains why nearly a century separates the introduction of mass production in manufacturing and R&D. The pharmaceutical industry is not technologically unsophisticated compared with late-nineteenth-century small-arms manufacturers; rather, it is attempting a far more complex project. What is different about the pharmaceutical innovation processes as a technical system is that it lacks a 'load factor' (Hughes, 1983, pp. 218–221) that can be used to objectively measure the contribution of each part to the overall process performance. Production engineers in manufacturing have well-defined parameters and distributions which they can use to calculate and optimize throughput, while the complexities of drug discovery mean that decision making is decentralized to experts, whose choices are often based on tacit knowledge rather than well-defined parameters. This is because Bradshaw's paradox applies to the whole innovation process: one cannot be sure that researchers are looking in the right place until they find what they are looking for. As a consequence, unlike a physical production system, it is very hard to relate performance measures of the whole system—i.e. drugs produced per million dollars of R&D—to performance measures of the component parts.

However, as with Bradshaw's paradox, there are a number of ways of reducing uncertainty, even if certainty cannot be fully established. The

¹⁹ This uncertainty can be seen in the lack of consensus about the correct strategy. Some firms have moved towards the 'big hammer' approach and are analysing huge numbers of compounds, while others are concentrating on much smaller populations. There is no consensus at present as to which approach will pay off. The difference in strategies in HTS is related to an interesting philosophical issue: given that there are about 10^{180} possible compounds of the right molecular weight to be drugs (there are approximately 10^{78} particles in the universe), moving from testing 10^4 to testing 10^7 compounds can either be seen as a 1000-fold increase or as an inconsequential waste of time as both 10^4 and 10^7 approximate to zero when compared with 10^{180} .

empirical evidence showed how pharmaceutical firms use cycles of experiments to test the implicit hypotheses behind their choices, how they exploit path-dependent biases in the samples they use for testing, how they avoid duplicating drugs produced in other firms by 'randomizing' the search process, how they use more fundamental biology to ensure that the drugs they are developing will produce the biological effects they desire, how they develop sophisticated information technology systems to collect and coordinate the 'tidal waves' of information coming from experiments, and how they rely on well-trained chemists and biologists to interpret experimental data. Additionally, pharmaceutical firms engage in scientific and research networks to ensure that their research is world class, internally peer-review technical choices, attempt to systematize research, achieve economies of scope by concentrating on specific targets and therapeutic areas, and reorganize the processes of research based around multi-disciplinary teams and project-based organizational structures. While these changes cannot remove the inherent uncertainty associated with drug discovery, they do create economically important differences in performance. This paper has only touched on these issues and a more systematic investigation of the organizational features that turn potential economies into actual economies of scale is needed.

The relationship between these organizational issues and technological uncertainty has been the subject of recent research (Clark and Wheelwright, 1992; Brooks, 1995; Pinto and Kharbanda, 1995; Hobday, 1998). While there is consensus that the traditional functional bureaucracy is efficient at dealing with well-defined, standardized tasks and more decentralized 'project-based' forms are better at dealing with high levels of uncertainty, the exact relationship between organizational architecture and system performance is badly understood, despite the work of Woodward (1958), Burns and Stalker (1961), Brooks (1995) and Teece (1996). This is highlighted as an area of future research.

The effectiveness of different organizational and managerial responses to systemic uncertainty will have an important effect on firm performance. If large pharmaceutical firms can 'optimize' the interconnections within the innovation system and improve overall throughput, then they will increase their advantages over smaller firms. If, however, the problems are intractable, then the Chandlerian 'inter-dependencies' between tasks will be reduced and smaller firms will be in a position to compete on parts of the process. At present a number of 'platform' biotechnology firms are offering a range of subcontracted research services, and as many of these new technologies have

reduced the fixed costs of research, the short-term dominance of large firms cannot be assured.²⁰

In the medium term the ability of pharmaceutical firms to use genetic information to customize products to specific genetic populations promises to fundamentally influence the throughput of drug discovery, and therefore the boundary between drug discovery and healthcare provision. In general, policy thinking in this area has been guided by rather naïve conceptions of industrial and corporate change, and this is highlighted as an area of future research.

In the short term, however, the ability of large pharmaceutical firms to turn potential economies of scale into actual economies of scale will depend on their ability to organize and manage the flows of information between tasks. Already there is anecdotal evidence that some firms are using bioinformatics systems to successfully link research tasks (Hopkins, 1998; Jones, 1999). However, the literature on innovation in complex systemic technologies would suggest that moving towards large-scale improvements, while possible, will be extremely difficult (Hughes, 1983; Davies, 1996; Hobday, 1998; Nightingale and Poll 2000). As with choosing the appropriate organizational architecture, the use of information technology to link research tasks is too complex to rigidly plan. Instead, firms will have to rely on organizational flexibility, diversity in technical options and a ‘muddling through’ approach, when faced with technological uncertainty (Stirling, 1998).

That a neo-Chandlerian framework required only a change of emphasis rather than a change of substance to explore the production of intangible capital within pharmaceutical R&D is encouraging. The changes involved incorporating Rosenberg’s insights into the role of ‘instrumentation as experimental capital-goods,’ seeing that economies of scale in experimentation produce reductions in size and recognizing that the systemic uncertainties involved preclude a bureaucratic functional organization. While a narrow technological focus, to the exclusion of issues such as marketing, prevents a holistic analysis of the role of technology and organization in determining the efficiency of particular organizational forms, the changes in the technology of experimentation and the management of intangible capital analysed in this paper suggests that their efficiency is related to increased throughput. While organizational issues require further investigation, as they will affect the minimum efficient size of pharmaceutical firms, the ability to cost effectively exploit the new technologies of experimentation and generate sufficient new drugs to reduce the volatility of product launches means that a particular organizational form—the large firm—may be more efficient

²⁰ I am grateful to an anonymous referee for highlighting this important point.

than its smaller rivals. If large pharmaceutical firms can overcome the organizational problems associated with high levels of uncertainty, then they should continue to dominate drug development. Considering that Chandler's framework had a deliberately narrow focus (Chandler, 1977, p. 6, 1990, pp. 12–13) and was not intended to explain changes in pharmaceutical technology in the 1990s, the moral of this paper is perhaps that his insights are surprisingly robust.

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