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Complexity and Building Block Search: A Historical Account of Drug Discovery

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Abstract

The history of the pharmaceutical industry shows that innovators have searched for new drugs by building upon known, active substances, or what are called "chemical building blocks." The essence of this search is to test variations of the known chemical building blocks for some desired properties and to select the most effective variant from a collection of related variants. This collection is called a library, which guides and delimits future search. My study suggests that by managing libraries with proper design rules, innovators can sustain their R&D activities with modest risk. This sustainability is proposed as an important component of dynamic capabilities.

Keywords: Complexity, Evolution, Innovation, Modularity, Library

INTRODUCTION

The concept of dynamic capabilities has recently garnered attention in strategy research (Eisenhardt and Martin 2000; Helfat 1997; Lee, Lee, and Rho 2002; Teece, Pisano, and Shuen 1997; Zollo and Winter 2002). Dynamic capabilities are understood as a source of sustainable, competitive advantage in Schumpeterian regimes, where the existing base of competition is constantly chal-

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lenged. In particular, dynamic capabilities play a critical role in markets where firms constantly compete on the basis of developing new products or processes (Nelson and Winter 1977, 1978, 1982; Winter 1984). Firms need to constantly search for new sources of profits or carry out what Schumpeter (1934) called "new combinations," because, otherwise, their profits may be diminished over time with their rivals' innovative and imitative attacks. Yet, little is still known about how firms carry out new combinations or search for new sources of profits to sustain their long-term positions. Helfat (1997) called for further research on these dynamic capabilities. The objective of this paper is to shed light on these capabilities by tracing the history of the pharmaceutical industry.

An implicit assumption in the theoretical literature on Schumpeterian competition is that innovation is a stochastic process (Grabowski and Vernon 1987; Lee, Lee, and Lee 2003; Lee and Ryu 2002; Nelson and Winter 1978, 1982; Winter 1971, 1984). For example, even though firms may invest in R&D in search of new products or processes, the outcomes cannot be predicted in advance. Can firms sustain their competitive positions without prior knowledge of the outcome of their search for new sources of profits? Can luck alone sustain the positions of innovators? These questions are non-trivial, particularly when the search involves a high degree of risk and complexity. Consider, for example, the complex landscape for drug discovery. The space of possibilities for drug discovery is immense, virtually infinite, as the possible number of organic molecules is estimated to be 10^{264} (DePalma 2003). The challenge remains that innovative attempts, or new combinations of substances on this immense space, frequently result in useless outcomes. In dealing with this landscape, exhaustive search (testing all possible organic molecules for efficacy and toxicity) is practically impossible. Innovators have to sample the space. The literature on complexity has highlighted the difficulty of firm adaptation on such complex landscapes (e.g., Gavetti and Levinthal 2000; Kauffman 1993, 1995; Levinthal 1997; Rivkin 2000; Rivkin and Siggelkow 2003). An important implication of this body of research is that innovators cannot seek sustainable positions by simply relying on luck or randomly sampling the space.

Yet, innovators in the U.S. pharmaceutical industry have sustained R&D for more than a half century. Indeed, Nelson (1982) conjectured that R&D may not be a completely random process,

and that there might be capabilities that allow innovators to systematically improve the efficiency of a search process over time. Helfat (1997) identified one such capability in the U.S. petroleum industry. She showed that the firm's prior knowledge matters in carrying out R&D in a new direction.

My paper attempts to shed additional light on the relationship between prior knowledge and R&D by looking at the history of the pharmaceutical industry. Unlike most other high-tech industries, which began because of one or several innovations, the pharmaceutical industry has a long history during which innovation was rare. The U.S. pharmaceutical industry, for example, experienced R&D-based competition only after 1940 (Comanor 1963; Lee 1996, 2003; Temin 1980). By comparing the searches for new drugs prior to 1940 with those that occurred after 1940, I show how knowledge was used innovatively by firms to sustain their R&D.

My historical analysis shows that most innovators in this industry did not start searching for new drugs from some random point on the hopelessly immense space. Instead, they initiate their searches on known active substances, "chemical building blocks." The essence of this kind of building block search is to experiment with variants of known, active substances with some desired properties[1)] and to select the most effective variant from a collection of related ones. This collection is called a "library." In a nutshell, a search is delimited and guided by the library, which also contains knowledge of partial past successes. The use of this knowledge appears to make a difference in dealing with the complexity of the chemical landscape because it gives information about where to start and stop searching for new sources of profits on the hopelessly vast space. On the other hand, innovators using random sampling would not benefit from such knowledge, searching each point on the vast space with an equal chance — a slim chance of success for each trial, given their rivals' constant imitative and innovative attacks, may drive the innovators out eventually.

However, the building block approach may not always be effective for dealing with complexity. Its effectiveness depends on the

1) The building block search includes two types of variation, one-at-a-time modifications of a substance and the combinations of two or more substances (Plunkett and Ellman 1997). The former may be considered as equivalent to mutation or near-sighted (local) search, whereas the latter may run parallel with recombination or far-sighted search in biological evolution. I thank Dan Levinthal for bringing this issue to my attention.

management of libraries. History shows two boundary conditions associated with the management of libraries. First, the building block approach cannot produce beneficial new products when an innovator is unable to accurately retain previous discoveries in the library. Second, the power of the building block approach appears to reside in the proper design of libraries — e.g., libraries that include the correct initial building blocks. My paper examines the evolution of rules for designing libraries and how these rules may ensure the sustainability of some innovators in the R&D race. In other words, I suggest that the proper design and management of libraries allows innovators in the pharmaceutical industry to implement searches for new drugs with modest risk, which is an important component of dynamic capabilities.

In the second section of this paper, I introduce historical science methodology and explain why this methodology is needed for addressing how innovators search for new sources of profits. The third section traces the history of drug discovery and the rise of the R&D race in the U.S. pharmaceutical industry. The fourth section identifies the conditions under which the building block approach allows innovators to retain their competitive edge in the search for new drugs. In the final section, I discuss the implications of my analysis.

HISTORICAL SCIENCE METHODOLOGY

Since the key issue of this paper — how innovators search for new sources of profits — has been sparsely researched, the present paper adopts an exploratory approach, or what is called "historical science methodology," which has been essential in advancing knowledge in disciplines such as paleontology, geology, and astronomy. Researchers investigating current facts are likely to be trapped in what Dawkins (1987) called "the prison of a familiar timescale." Gaining critical insights is often possible only when one goes beyond this familiar timescale. For example, the early strand of evolutionary thinking in the eighteenth century stemmed from the examination of fossils that were morphologically peculiar (Eiseley 1961). The discovery of fossils of extinct species, which preserved life structures beyond the time domain of human observations, surprised researchers in Europe. Without such

observations, we might not have inferred that other species had existed prior to Homo sapiens. Furthermore, studies of evolution should incorporate the historical approach, as they deal with "those inordinately complex events that can occur but once in detailed glory" (Gould 1989: 1).

Nonetheless, this paper is not a historiography. The study of history is distinct from historical science in that the former entails gathering historical information and dealing with specific details to "prove the facts" (Van den Haag 1963: 214). Instead, my goal is to show what these facts can prove when they are recast in light of evolutionary theory and complexity theory.

CONSTANT SEARCH AND THE R&D RACE

The main objective of this paper is to examine how innovators constantly search for new sources of profits and sustain their long-term position. In this section, I trace the origins of the search for new drugs in the pharmaceutical industry. Through historical analysis, I look at how the development of screening methods for identifying, modifying, and testing many substances led to the R&D race.

Originally, invention and innovation were non-constant economic activities (Schmookler 1966). Search activities for new drugs were targeted mainly on plants, the world's oldest form of drugs. Mahoney (1959: 182) described plants as "the nature-grown botanicals, anything that blossoms or blooms, leaves, roots, herbs, barks, berries and gums, the most ancient allies of man in his war on sickness, pain and death." In this period, search activities were primarily in the form of expeditions. The archetypal story of a search that resulted in the discovery of a new therapeutic plant usually involved some mysterious American Indian (Young 1961). For example, Lilly discovered a venereal disease remedy when its information was available from an American Indian. Liebenau (1987) argued that science played no part in the formulation or promotion of such drugs. Their efficacy was dubious. Since science at the time did not provide ways to verify and measure the efficacy of these drugs, it is no surprise that quackeries mushroomed in the industry (Young 1961).

Furthermore, searches of this sort were sporadic or incidental

rather than constant. For example, Dr. Henry Hurd Rusby's 1884 expedition, which was sponsored by Parke-Davis, was hardly a routine part of Parke-Davis's business (Parke, Davis, and Company 1966; Rusby 1933). The expedition to South America was incidentally initiated by Davis' belief that the little-known drug coca had commercial potential. Not surprisingly, expeditions that were guided by wild conjectures or anecdotal tales of American Indian medicine men usually failed. Mahoney (1959) documented the failure of Upjohn and Penick, which cosponsored an expedition into African bush country to search for the source of the arrow poison described by Dr. Livingstone.

In sharp contrast to these infrequent, unsystematic searches in the early period, the daily screening activities that leading U.S. pharmaceutical firms began to use after World War II were extensive and constant. The emergence of these constant search activities changed the nature of competition.

The Origin of Constant Search

At the turn of the twentieth century, leading U.S. pharmaceutical firms attempted to exert more control over drug discovery by establishing industrial laboratories (Liebenau 1987; Swann 1985). In particular, the emergence of screening methods for identifying, modifying, and testing many substances catalyzed the industry's focus on a constant search for new drugs. These screening methods, or what Nelson and Winter (1982) called "search routine," seemed to be crucial to the development of R&D race because they guided innovators where and how to start search for new sources of profits.

One of the most important screening traditions was established by Paul Ehrilich, a German scientist, who had an ambition to bring chemical synthesis into the service of medicine (Earles 1970). Ehrlich thought that pharmaceutical firms could start searching for new drugs by synthesizing, modifying, and testing chemical compounds. His idea was captured in the following interview (Earles 1970: 401):

> "... in my study of immunity, it has occurred to me that by systematic and extensive chemical and biological experiments it should be possible to find artificial substances which are really

> and specifically curative for certain diseases ... we must take aim — *aim by chemical variation*! ..." (Italics added)

To achieve his goal, Ehrlich sought to identify a synthetic compound that would be effective against some target disease without damaging host body cells. After screening hundreds of synthesized compounds provided by Hoechst, Ehrlich and his team discovered Salvarsan, a cure for syphilis (Wainwright 1990). His screening method, as well as his insight into the relationship between diseases and drugs, provided a foundation for modern drug discovery.

By using Ehrlich's screening method, Derhard Domagk, who was in charge of a research laboratory at the Bayer Works in Germany, discovered Prontosil in 1935. This discovery is considered the beginning of the age of miracle drugs (Cooper 1969; Silverman and Lee 1974). In particular, sulfanilamide (i.e., sulfa), an active ingredient in Prontosil, attracted a great deal of attention. Subsequently, a dominant research theme in Europe and the United States was to search for new drugs by building upon what was known about the properties of sulfanilamide (Temin 1980). By looking for signs of desired activity in diverse variants of sulfanilamide, pharmaceutical firms developed many new products. This story exemplifies the importance of the "building block search." In the next section, I elaborate this concept and explain how this approach helped pharmaceutical firms maintain continuity in carrying out risky R&D.

The second important screening tradition that aided the constant search for new drugs was developed after Fleming's discovery of penicillin in 1929. Fleming, a microbiologist, discovered that *Penicillium notatum*, a kind of mold, could be used against bacterial infections. This finding suggested that microbes could be new sources of drugs. In 1940, by purifying and stabilizing Fleming's crude penicillin, Florey and Chain showed that penicillin can effectively fight against bacterial infections in laboratory animals and humans. This success triggered an unparalleled interest in all groups of microorganisms (Raper 1952). However, the research on penicillin offered no guidance about how to search for other sources of antibiotics, whereas the screening methods of Ehrlich and Domagk left clues for how to conduct the search for a new drug.

In 1944, Waksman filled this gap by developing a screening method to search for new sources of antibiotics. As a soil

microbiologist, he knew soil constituted a rich source of new antibiotics — some microbes in soil can kill pathogens. He came across an idea that one can search for new sources of antibiotics by screening soil samples from all over the world. Over time, Waksman developed a screening program as "[n]ew methods for testing freshly isolated cultures of microorganisms for their antimicrobial potency were gradually developed or adapted from older procedures" (Waksman 1954: 213).

The emergence of this screening procedure resulted in an increase in antibiotic research at the industrial laboratories and provided an impetus for the emergence of the R&D race in the U.S. pharmaceutical industry (Lee 1996, 2003; Temin 1980). Pharmaceutical companies that foresaw the potential of Waksman's screening program established "large-scale antibiotic screening operations" (Burlingham 1951: 89). Although screening microbes from soil samples has not been as popular as screening synthetic chemical compounds, terrestrial microbes have been major sources of new chemical structures (DePalma 2003).

Emergence of the R&D Race

After World War II, the U.S. pharmaceutical industry witnessed the emergence of the R&D race. Prior to the war, few really useful drugs were introduced into the market.[2)] As pharmaceutical firms invested in R&D by utilizing screening procedures, the rate of innovation increased sharply. Temin (1980) called a flurry of these activities "therapeutic revolution," and competition in the U.S. pharmaceutical industry changed dramatically, as a result. For leading pharmaceutical firms, competition was now based on innovation. Comanor (1963: 2) noted: "[R]ivalrous behavior has taken the form of competitive differentiation, and this has resulted in rapid rates of product introduction and obsolescence." Mahoney (1959: 17-18) estimated the rates of innovation for the prewar and postwar periods:

2) The range of drugs available for physicians had been limited prior to World War II. For example, Burlingham (1951: 16) noted: "as recently as World War I the really useful drugs in the average physician's bag were declared to be opium, mercury, quinine, digitalis, and iodine — exclusive of analgesics, anesthetics, and antitoxins." Similarly, the president of Merck described the range of drugs sold in the 1930s (cited in Temin 1980: 60): "You could count the basic medicines on the fingers of your two hands."

> Between 1905 and 1935 basic new drugs were added to the *U.S. pharmacopoeia* at an average rate of 6 per year. For the next twenty years the average was 37 per year and the frequency of publication was stepped up from 10- to 5-year intervals.

Industry commentators argued that large-scale R&D routines were "a prerequisite for staying in business" (Burlingham 1951: 15). By introducing new drugs, firms made many of their own products obsolete and, at the same time, challenged their competitors' products.[3] As mentioned earlier, R&D race pressed pharmaceutical firms to constantly search for new sources of profits. However, only a limited number of firms showed their commitment to innovation by increasing the number of scientists and engineers over time (Lee 1996, 2003). In this regime of competition, innovators had to do more than establish impediments to imitation in order to survive (Lee, Lee, and Rho 2002; Teece, Pisano and Shuen 1997). They also had to learn how to cope with the risk of constantly searching for new sources of profits.

BUILDING BLOCK SEARCH AND CONSTANT INNOVATION

How could innovators sustain their positions when their competitors constantly challenged and disturbed the existing base of competition? In this section, I address this question by focusing on the mechanism of innovation observed in the history of the pharmaceutical industry. My investigation is exploratory in nature, and I hope that the findings from this preliminary analysis will stimulate more systematic research in the future. But, first, I review the literature on economic evolution and highlight how an understanding of the mechanism of innovation advances our knowledge of dynamic capabilities.

Evolutionary Economics and the Limitations of Selection

A theoretical literature that is most relevant to the concepts of

3) For example, Burlingham (1951: 15) noted: "In fact, it has reached a point where the research departments of most pharmaceutical companies spend a major part of their time trying to obsolesce their own products — knowing the competition has the same object."

the R&D race and dynamical capabilities is evolutionary economics. This stream of research began by Alchian (1950), who argued that sensible economic analysis can be done even without assuming profit maximization. As an alternative to standard economic analysis, this new approach is based on evolutionary mechanisms. Among them, selection has long attracted the most attention. Winter (1971) first formalized selection as a dynamic rule that allows high-performing firms to grow faster while forcing low-performing firms to contract. Building upon Winter (1971), Nelson and Winter (1978, 1982) developed numerical models (hereafter, the N-W model) of the R&D race by identifying two forces that spur competition over time. The first force is innovative search, the firm's effort to challenge the existing ways of operating. The second force is imitative search, the firm's effort to imitate the best industry practices. The N-W model assumes that each firm in the market seeks to improve its performance by allocating its resources to innovative and imitative searches. The firm's performance is evaluated by the combined results of innovative and imitative searches relative to those of its competitors. Given this structure as well as the simplified assumption on the demand side, the essence of selection is that successful firms drive out lagging rivals over time.

In the N-W model, innovative search is the mechanism of variation because it allows new products or processes to flow into the market. However, the N-W model assumes that innovation is random. As a result, it sidesteps the question of how innovation happens. The N-W model states that a firm is successful if it develops a new, superior product or process. Otherwise, the firm retains its previous product or process. A larger firm that allocates more resources to R&D is assumed to have a better chance of success (Grabowski and Vernon 1987; Lee, Lee, and Lee 2003; Lee and Ryu 2002; Nelson and Winter 1978, 1982; Winter 1971, 1984). This simplification, based on the size-dependent stochastic process, allowed us to focus on the complexity of the selection process, without being burdened by any additional complication inherent in innovation. Thus far, this line of research has greatly contributed to our understanding of the R&D race.

However, it has been argued that selection gives only a limited understanding of how complex systems evolve (Kauffman 1993, 1995). Nelson (1982) and Helfat (1997) called for research on how knowledge affects the efficiency of innovation. By shifting our focus

to the mechanism of innovation, we can advance our understanding of industry evolution. In particular, we can better understand why innovators who are exposed to the risk of R&D are not often driven out by imitators. The focus of this paper is on the mechanism that allows innovators to carry out R&D more efficiently, thereby reducing risk in R&D and increasing the innovator's staying power in the R&D race.

Building Block Search and the Efficiency of R&D

My paper proposes that the building block search provides an efficient mechanism for the development of new products. A key element of the building block search is to develop new products by building upon partial solutions that were discovered in the past. If some of these were previously useful in a diverse range of problems, they should be reusable for innovation in the future. The building block search reduces the time and cost of R&D by reusing these proven, partial solutions as starting points. This search process is quite distinct from the random experiments. I argue that the efficiency gain from the building block search could act as a staying power in R&D race.

To illustrate how the building block search works, one only has to consider the development of new software. If every programmer had to create each line of code from scratch whenever she develops new software, it would not be very efficient. In reality, there are libraries of numerous well-defined and carefully tested modules. In many cases, the programmer's job is to choose some proven or adapted modules in the library as building blocks to create new programs. The more diverse modules there are in a library, the easier it is for the programmer to create a new reliable program.

Indeed, a key idea behind "object-oriented programming" (OOP) — a new paradigm in software engineering — is to facilitate software reusability and improve productivity in software development by harnessing the power of the building block approach. In particular, the object-oriented programming exploits modular product architecture, which has attracted a great deal of attention in the management literature (e.g., Baldwin and Clark 2000; Sanchez and Mahoney 1996). An object is a module that interacts with other objects in specific ways. For example, one can think of the pie chart as an object that is made up of smaller objects, with each

individual slice representing a color, a legend, or a title (Cadenhead 2001). In the OOP approach, a programmer does not create all the details of the pie chart from scratch — the implementation of this alone in a graphical user interface would requires many thousand lines of code. Instead, she develops the pie chart with a few lines of code by building upon the existing modules in a library.

One may wonder whether the building block approach differs from innovation based on modularity. The difference can be illustrated with drug discovery which deals with non-modular building blocks. In the case of OOP, new product development is characterized as mixing and matching of compatible components — this is possible since a platform leader such as Sun Microsystems sets a standard, making all components compatible with one another. Such compatibility greatly facilitates new product development. On the other hand, drug discovery, to some extent, still relies on random variations of building blocks due to the lack of knowledge about molecular interactions,[4] whereas such randomness is more or less absent in software development because modular product architecture requires more complete information about how components interact with one another (Sanchez and Mahoney 1996). The question is: would the "building block" approach still increase the efficiency of drug discovery?

In the history of drug discovery, it is rather easy to find examples of innovation based on the building blocks of known, active substances. As discussed earlier, when Ehrlich was looking for a cure for syphilis, his search was initially directed toward the countless arsenic compounds that were synthesized by Hoechst (Wainwright 1990). After many trials and failures, Salvarsan was discovered. Ehrlich called it "606" because it was discovered after the 606th combination was tried (Ackerknecht 1982). This could be characterized as the completely blind search that most evolutionary models assume.

Later, it was found that the original Salvarsan was toxic and difficult to administer, which stimulated the need for a new drug. Where should one search for an alternative drug? Should he or she start again from some random point on the space of immense

4) Recently, rational drug design emerged as an alternative to the traditional screening method for drug discovery thanks to the improved understanding of the molecular interactions that underlie diseases (Bugg, Carson, and Montgomery 1993; Henderson 1994). Despite its initial hype, however, this approach has shown limited success.

possibilities (i.e., countless arsenic compounds)? This sort of completely blind search may waste lots of resources for a long time. That is not how Neosalvarsan — a water-soluble and less toxic combination that replaced the original in therapy — was discovered. The search for Neosalvarsan started right from Salvarsan, a known partial solution. A researcher could modify some part of the molecule and see if the variant improved on the original. If it did not, he could discard it and try again. Of course, each trial would be a blind process, but locating where to start searching extensively would make a big difference. Is this an unusual example? Medicinal chemists knew that the modification and improvement of existing active molecules was a popular way to search for a new drug. For example, Wermuth (2003: 70) noted: "[T]he chemical transformation of known active molecules constitutes the most widespread practice in pharmaceutical research." Wermuth (2003) observed how each generation of compounds had been instrumental in the creation of new compounds, as was the case with sulfamides, penicillins, steroids, prostaglandins and tricyclic phychotropics families. It is evident that pharmaceutical firms develop new drugs by building upon existing substances that have shown potential efficacy in the past.

Furthermore, history has shown that libraries of chemical compounds were critical to the development of new drugs. An innovator's chemical library typically consists of a large number of chemical compounds. A chemical library is often considered as a search space for screening activities. Search possibilities for the innovator were constrained by the molecular diversity of its library (Thomke and Keummerle 2002). Not surprisingly, chemical libraries have been regarded as important assets for drug discovery, and have been carefully guarded (Carr 1998; Fagan and Hayes 1998). In sum, the building block approach increases the efficiency of a search for a new product by using the past solutions as the staring points.

Replicability and Building Block Search

Although the building block approach has been the most popular way to search for new drugs in the pharmaceutical industry, it has some boundary conditions for its effectiveness. History shows that the effectiveness of the building block approach depends, at least,

on two conditions: (1) whether innovators are able to replicate or preserve past solutions and (2) whether the libraries are properly designed. In this section, I discuss the first boundary condition.

The building block search may not produce useful new products if the firm is unable to exactly replicate or preserve past solutions. Apparently, this issue is related to whether past discoveries or partial solutions in a library can be retained rigidly. Extending the programming analogy illustrates this point. Suppose a programmer writes a complex program by building upon existing modules. If some lines of code in the existing modules are randomly altered due to the instability of the environment,[5] the program may not behave in an expected fashion. The more of these errors there are, the more likely it is that the program will malfunction. This example suggests that the rigid replication of past discoveries is a prerequisite for harnessing the power of the building block search.

The history of the pharmaceutical industry also illustrates the negative consequences of errors in replication. For example, biologicals are perishable and easily contaminated. Some slippage in the replication of a once-discovered therapeutic agent could mean a loss of its therapeutic effect or even a catastrophe. Indeed, an outbreak of tetanus in Camden, New Jersey in 1901 was allegedly connected to contaminated smallpox vaccine (Liebenau 1987). Fueled by this incident, the Biologicals Control Act, one of the first modern drug regulations in the United States, was passed in 1902 to regulate the production and sale of biologicals. Drug companies were not allowed to sell some biologicals (Liebenau 1987) unless they employed scientists who could control the potential contamination of biologicals.

Replicability also matters in R&D. Its importance can be illustrated in the evolution of mold therapy. History indicates that the ancient Chinese and Indians used a crude form of mold to cure some infections (Ackerknecht 1982), and that the Mayans used a fungus to treat ulcers and intestinal infections (Florey 1949). Also, fossil evidence of traces for tetracycline was found in the remains of a tribe who lived in Sudanese Nubia around 350 AD (Wainwright

5) In software engineering, this sort of instability is well known. It is likely to occur when many programmers write code together and inadvertently change the values of the global variables others created. This could cause problems that are often not easy to debug. One of the motives behind object-oriented programming is to remove this type of instability by encapsulating these variables within one module, which minimally interact with other modules.

1990). In the pre-antibiotic era, however, these crude therapies, were linked neither to the understanding of complex, bacterial infections nor to the development of antibiotics.

Scientific progress on antibiotic research took a long time. Mosses was perhaps the first to suggest the therapeutic value of a microbe in a letter to *Lancet* in 1852 (Florey 1949). Mosses' conjecture was not corroborated, however, until Fleming's discovery of penicillin and its bactericidal effect in 1928 (Cooper 1969). Even Fleming's work did not directly result in the development of an efficacious cure since the crude penicillin he found was neither pure nor stable (Wainwright 1990). Nonetheless, because Fleming's crude version of penicillin was preserved, Florey and his colleagues did not have to reinvent the wheel when they decided to develop a stable and pure form of penicillin (Cooper 1969).

This story suggests that although complex therapeutic agents such as penicillin can be built through a long series of chance events, serendipity alone is insufficient for the building block approach to work. When ready-made discoveries cannot be reproduced or preserved over time, chance events may be of little use.

Thus far, I have provided only anecdotal evidence from history. More systematic, numerical evidence for the importance of replicability is shown in the literature on genetic algorithms (GAs). GAs have been known as robust optimization algorithms (Holland 1975). Studies have shown that GAs fail to find optimal solutions when the replication of the adapted partial solutions in the past is not possible (Goldberg 1989; Mitchell 1997). In this literature, random errors in copying the past solutions are associated with mutation operator. Although making such random errors is an important source of generating diversity, it tends to degrade GAs' performance (Holland 1992). This quality, which limits the power of natural selection, is well known in evolutionary biology (Eigen and Schuster 1979; Kauffman 1995). The literature on GAs highlights the importance of replication or preservation of past discoveries in developing something new. In sum, the building block approach may not be effective if the firm is unable to replicate or preserve past solutions.

Complexity of New Combinations and Management by Design

This section identifies the second condition under which the

building block approach may not work effectively. In particular, the focus of discussion is on how the complexity associated with the design of R&D libraries weakens the power of the building block approach and how innovators in the pharmaceutical industry have managed this kind of complexity by identifying proper design rules for R&D libraries.

Schumpeter (1934) once recognized that the fundamental nature of innovation lies in new combinations of (either existing or new) inputs. Carrying out new combinations, however, may not be always useful when new combinations involve a great degree of complexity. They may procreate a vast number of useless outcomes, dramatically raising R&D costs. Let us first examine the complexity of new combinations, which often poses difficulties for new product development. Suppose that there are two therapeutic components A and B. Assume that component A is effective against target disease A' and that component B is against target disease B'. In a linear world, where there is no interaction between the two components, a combination of A and B will maintain therapeutic effects on target disease A' as well as target disease B'. By combining many different components, drug companies can develop "blockbuster" drugs with a wide range of benefits. In the presence of component interactions, however, a combination of the two could also produce an unexpected, disastrous reaction to the body or nullify the potency of a compound (Graedon and Graedon 1999). In other words, new combinations in a nonlinear world trigger complexity by possibly generating useless or even harmful drugs. This type of complexity is negligible in a well-designed, modular product architecture, which minimizes such unexpected interactions among components.

The history of the pharmaceutical industry shows how the complexity of combining chemical compounds undermined new product development. In the United States, combination drugs proliferated prior to the Kefauver-Harris Amendments in 1962 (a major drug regulation). Pharmaceutical firms introduced what were called "fixed-ratio" combination products. For example, Silverman and Lee (1974: 109) noted: "A combination of penicillin, aspirin, phenacetin, codeine, and various antihistamines was heavily pushed for treatment of the common cold." By the mid-1960s, fixed–ratio combination products accounted for 40% of popular prescription drugs. In particular, leading pharmaceutical

firms profited from selling antibiotic combinations — for example, Squibb's Mysteclin-F contained tetracycline and amphotericin; Upjohn's Panalba combined tetracycline and novobiocin. These combinations were claimed as valuable because "one component may be effective against one invading microbe while the other may combat a different organism" (Silverman and Lee 1974: 128). They even claimed that the antibiotic combinations ushered in the new era of antibiotic therapy. All these claims, which relied on a linear-world view, were unsubstantiated. In fact, the American Medical Association held that most of these combination drugs were not efficacious, and that they even posed needless risk to patients. The efficacy of combination drugs became a heated controversy in the midst of the major regulatory change around 1962. Eventually the FDA required pharmaceutical firms to show substantial evidence on the efficacy of their combination drugs. Without such evidence, most of them had to be withdrawn from the market. This shows how unexpected interactions among components can create complexity in developing new products.

Regarding this kind of complexity, Kauffman (1993, 1995) developed a simple theoretical model called the NK model, which stimulated subsequent research in the management field (e.g., Levinthal 1997; Rivkin 2000; Rivkin and Siggelkow 2003). The primary objectives for developing this model were to understand the power and limitations of natural selection and to examine what kinds of complex systems can be assembled by an evolutionary process. In the model, there are two aspects of complexity, which are controlled by parameters, N and K. N represents the number of components for a system (e.g., the number of genes in the gene pool or the number of components for developing a new product), and K represents the degree of unexpected interactions among components. In reality, N is very large. For example, there are a couple of thousands of genes even for a simple microorganism. Also there are millions of chemical compounds for drug discovery. The search space, or what is called a landscape, is spanned by all possible combinations of N components. For example, one can conceive of the landscape for drug discovery by envisioning all possible combinations of chemicals, which are estimated to be 10^{264} (DePalma 2003). Researchers can evaluate each combination by testing whether it has desirable properties (e.g., efficacy and safety) in the context of a particular target disease.

Given large N, the value of K determines the difficulty of adaptation or of innovation. When $K = 0$, the NK model shows that the search space or "landscape" for adaptation becomes "smooth" with one best solution; this would be equivalent to the linear world where a combination drug would have the ability to fight against several diseases. Adaptation on this linear landscape is relatively easy because the linearity makes the burden of search manageable and because partial success in the past provides cues for where to take a next step on the search space. Furthermore, a minor change in a system always brings about only a minor consequence. In the context of new product development, a small modification of a useful product will not make it useless all of a sudden. As a result, it is rather easy to develop a useful, new product by building on existing components in the library.

On the other hand, when K is as big as $N - 1$, the landscape becomes completely random or "rugged." We are dealing with the nonlinear problems where combinations of components in a system generate completely unknown consequences. In this case, it is difficult for species or agents to adapt by searching for a new, useful solution. It is primarily because the search space sharply expands and because experience and past successes offer little guidance for the next search (Kauffman 1993, 1995; Levinthal 1997; Rivkin 2000). A small misstep may result in an unexpectedly large change. Furthermore, recombination, the nature's sophisticated search mechanism, will not work. For example, the mating of male and female organisms tends to produce deleterious offspring on a random landscape. Kauffman (1993, 1995) argues that on random landscapes, selection is debilitated in guiding evolution, and Rivkin (2000) argued that the complexity of random landscapes undermines learning.

This literature suggests that innovation is very hard on a random landscape. A high degree of randomness in the landscape, for example, means that the knowledge of one good compound gives no clue about whether some of other structurally related compounds would be also efficacious. New combinations that build upon past partial solutions could generate a host of useless compounds. The received view is that no search rule can surpass a random search (Haupt and Haupt 1998). That is, new product development depends purely on luck. Given that the possibilities of research are immense, with small probability of promoting a new and successful

pharmaceutical product, innovation-seeking firms are more likely to be driven out by those that produce known products.

Kauffman conjectured that real landscapes may lie between these two ideal types — i.e., they may be characterized by modest values of *K*. That is, a landscape may look rugged, but they are "correlated." An interesting implication of this correlated landscape is that a special region exists in such a landscape where the good solutions cluster. For instance, if one finds a useful drug by chance, she is likely to find another beneficial drug or a better one by modifying the original one. Kauffman (1995: 177) argued: "It is useful to an adaptive process to locate this special region in the space of possibilities." With respect to the R&D race, innovators can locate this kind of special region by collecting the right building blocks for the library. By restricting their search process in this way, innovators can potentially increase the probability of discovering useful drugs in a timely manner.

Is this numerical finding merely the outcome of an idealized model? Can it correspond to reality? Many clues indicate that the real landscape for drug discovery is not completely random. History is full of examples that efficacious drugs are clustered around some region rather than scattered randomly over the entire landscape. As discussed earlier, for example, sulfanilamide (i.e., sulfa), an active ingredient in Prontosil, trigged a dominant theme in drug discovery in the 1930s and 1940s. Drug discovery was carried out through molecular modification by using sulfa compounds as building blocks (Cooper 1969). By modifying the sulfa compounds, over 10,000 drugs were developed by 1960. Also, Wainwright (1990: 184) noted: "[O]f the vast number of antibiotics that are now available, only some 70 are used by doctors, five of which originate from fungi, while the remainder are of actinomycete origin." Actinomycetes are a species of soil microorganism that Waksman used for developing streptomycin. The molecular structure of this particular species had been extensively exploited for developing many other antibiotics. These examples suggest that good solutions are clustered around some region in the search space. That is, the landscapes for drug discovery did not seem to be completely random.

Medicinal chemists also appear to take advantage of the correlations in the landscape. For example, the search strategy based on molecular modifications exploits the correlated aspect of the search space, as Wermuth (2003: 70) noted:

> It is indeed extremely rare, and practically improbable, that a given biological activity is unique to a single molecule. Molecular modifications allow the preparation of additional products for which one can expect, if the investigation has been sufficiently prolonged, a comparable activity to that of the copied model, perhaps even a better one.

Given that the landscape is somewhat correlated, how can an innovator manage the complexity of innovation? Can the innovator locate a special region where beneficial solutions cluster through the proper design of a library? In the past, innovators relied solely on chemical libraries set up by their own researchers (Gwynne 2003). There was little flexibility in the design of libraries because it took substantial time to synthesize new chemicals. Consequently, the search possibilities for new product development were largely limited by what the firms had explored in the past. Due to the difficulties of building large chemical libraries, the search for new drugs was limited, for the most part, to large pharmaceutical firms.

Recently, however, the development of a new technology called "combinatorial chemistry" has allowed drug firms to design large chemical libraries of structurally related compounds (Plunkett and Ellman 1997). Using this technology, some startup companies have specialized in constructing and selling libraries to pharmaceutical companies. As a result, innovators can redesign and diversify libraries with in-house or outsourced components.[6)]

An innovator can assemble a wide variety of molecular diversity by starting with an assortment of small, reactive molecules, which are called chemical building blocks (Gordon 1998). The combinatorial process "proceeds by the systematic interconnection of a set, or sets, of chemical building blocks" (Gordon 1998: 17). Plunkett and Ellman (1997: 69) illustrated how molecular diversity

6) Pharmaceutical companies embraced this new technology in different ways. MacCoss and Baillie (2004: 1812) noted: "For instance, some invested heavily in the mid-1990s in combinatorial chemistry and made this technology a key driver of their efforts to discover new leads and to expand their existing sample collections, particularly when traditional sources of compounds failed to deliver new leads. Others have used these technologies in appropriate projects and have forged alliances with smaller companies that specialize in such efforts, thus freeing up their internal operations to use their historical institutional knowledge of medicinal chemistry, but now guided by more information... This approach has led to more outsourcing of research medicinal chemistry than was common practice a few years ago.

could be generated in a library:

> As a simplified example, consider four molecules: A1, A2, B1 and B2. The molecules A1 and A2 are structurally related and are thus said to belong to the same class of compounds; B1 and B2 belong to a second class. Suppose that these two classes of compounds can react to form molecules, some variant of which we suspect could produce a potent drug. The techniques of combinatorial chemistry allow us to construct easily all the possible combinations: A1-B1, A1-B2, A2-B1 and A2-B2 … Then, under appropriate conditions, we would mix and match every amine with every carboxylic acids to form new molecules called amides (-CONH-). The reaction of each of the 30 amines with each of the 30 carboxylic acids gives a total of 30×30, or 900, different combinations. If we were to add a third set of 30 building blocks, the total number of final structures would be 27,000 (30×30×30). And if we used more than 30 molecules in each set, the number of final combinations would rise rapidly.

In the 1990s, combinatorial chemistry focused on simple tried-and-true synthetic sequences by scaling up the sheer size of libraries (Borman 2002). Drug companies quickly learned that the construction of a large chemical library alone often increases search costs dramatically without increasing hit rates (Service 2004). For example, Abbott experienced that the hit rate with a library of a couple of million compounds was much lower than with compounds from other sources (DePalma 2003).

Drug companies also learned that their clinical costs can be reduced by weeding out compounds that are likely to fail in clinical trials (Service 2004). Plunkett and Ellman (1997) argued that the selection of the initial building blocks is significant for designing a useful library. In other words, the starting materials should be molecules that indicate desired pharmaceutical properties. As a consequence, the initial emphasis on creating a large library has gone out of fashion, and smaller, more focused libraries have attracted attention in the industry (Borman 2003).

Innovators can reduce substantial search costs simply by excluding compounds that are not drug-like. The industry became interested in identifying criteria for determining which compounds are drug-like and which ones are not. For example, Lipinski et al.

(1997) presented what is known as the "rule of five" for predicting drug-like properties. This has been regarded as "an excellent working hypothesis for predicting good drug-like properties in new compounds" (MacCoss and Baillie 2004: 1811). An example that utilizes drug-like properties is the Prestwick Chemical Library.[7] Over 85% of its compounds are marketed drugs, and consequently, most compounds in this library are bioavailable and safe for human consumption. When an innovator develops a new compound utilizing this library, it may be rapidly tested in patients (Wermuth 2003). The chances for developing good candidate drugs are claimed to be higher in this way than if the initial compound is toxic. Another approach that has growing appeal for pharmaceutical firms is targeted libraries (Gwynne 2003). With this design concept, an innovator designs its library with specific target diseases in mind. Obviously, the diversity of a chemical library will be limited in this way, but the hit rate would be higher. Richard Thomas, the director of medicinal chemistry research at Pharmacia noted: "Without a target in mind you can screen forever without coming up with a hit" (Gwynne 2003: 46).

Recently, there has been extensive research regarding the design of better chemical libraries. With refined design rules, industry players are more likely to locate what Kauffman (1993, 1995) called a special region in which good solutions cluster. With better design rules in place, innovators can avoid wasting resources and time on the development of useless compounds. This, in turn, may help innovators gain additional staying power in the R&D race.[8]

In summary, the key characteristic of well-designed libraries is whether they point to regions where good pharmaceutical solutions are clustered. New combinations of library components can generate useless products when the products unexpectedly interact with one another. The building block approach, which relies on new combinations of components, will be ineffective if the library is not properly designed. The identification of appropriate design rules for libraries — e.g., identifying drug-like properties, or more specifically, the rule of five in Lipinski et al. (1997) — is an impor-

7) This library is developed by Prestwick Chemical Inc.: www.prestwickcehmical.com.

8) For the moment, the promise of new technologies has not been fully realized, and innovators have encountered declining R&D productivity. However, a majority of experts expect new technologies to fuel innovation and deliver new medicines (Service 2004).

tant factor in the management of complexity.

CONCLUSION

By examining the history of pharmaceutical innovation, this study sheds light on how the industry has harnessed the mechanism of innovation and continued to generate new products despite the complexity of drug discovery. This paper extends the insights of evolutionary economics, which, in the past, has focused mainly on selection, while treating innovation as stochastic in its analysis of the R&D race. In particular, the examination of the building block search, the preeminent way of developing new products in the pharmaceutical industry, reveals that innovators did not leave innovation purely to chance. Molecular modifications based on known, active chemical building blocks have helped innovators reduce the risk of R&D in the face of rivals' constant imitative and innovative attacks. Thus, the building block approach can provide innovators with staying power in their constant search for new sources of profits. This staying power is proposed as an important dimension of dynamic capabilities. However, the building block approach is not always effective. A firm's staying power may be weakened if past discoveries or knowledge cannot be preserved or replicated. Furthermore, if a firm's library is improperly designed, the firm may waste time and resources by screening useless compounds. In short, history suggests that dynamic capabilities lie in retaining and evolving libraries with proper design rules.

This paper also builds upon recent research about complexity. Since Kauffman (1993, 1995) introduced the concept of the random landscape in his discussion of complexity, management scholars have paid special attention to the difficulties of managing complexity (e.g., Gavetti and Levinthal 2000; Levinthal 1997; Rivkin 2000; Rivkin and Siggelkow 2003). In particular, Rivkin (2000: 843) indicated his concern that this approach might potentially mislead laymen to hold a "fatalistic view of management." If complexity would always undermine learning and if a small misstep can frequently lead to a catastrophe, complexity theory can offer few useful implications for managers. Although this extreme scenario is theoretically possible, it seems unlikely to

happen in the real world (Kauffman 1993, 1995).

This paper highlights a bright side of complexity theory. Although the landscape for drug discovery appears to be very complex, leading pharmaceutical firms have sustained their R&D for more than a half century. They have been able to manage the complexity inherent in drug discovery by harnessing the power of a variation mechanism: They have developed new drugs by trying variations of known molecules with some desired properties and by selecting the most effective compounds from a collection of related ones. This mechanism is closely akin to how the immune system solves its own complex problems (Plunkett and Ellman 1997). My study suggests that retaining and evolving libraries with proper design rules are the key to the management of complexity in innovation. When a library contains improper initial building blocks, innovators may waste time and effort generating many useless compounds. In contrast, a well-designed library points to a special region in the search space where potentially good solutions cluster. For example, identifying drug-like properties — the rule of five in Lipinski et al. (1997) — is an important early step in building a well-designed library for drug discovery.

In addition, the notion of libraries may add new insights into the literature on resources (e.g., Barney 1991), knowledge (e.g., Grant 1996; Helfat 1994, 1997; Winter 1987), and dynamic capabilities (Eisenhardt and Martin 2000; Helfat 1997; Lee, Lee, and Rho 2002; Teece, Pisano, and Shuen 1997; Zollo and Winter 2002). This literature has attracted substantial attention, as strategy researchers have recognized the limitations of viewing competitive advantage from the perspective of safeguarding the privileged market position. For this stream of research, the present work opens up a number of promising agendas for future studies. As mentioned earlier, drug firms add more molecules to their libraries in the process of discovering new drugs. Accordingly, a drug firm's chemical library is a collection of its past research outputs as well as a starting point (i.e., resources) for future drug research. Within the pharmaceutical industry, firm heterogeneity can be traced by identifying the molecular diversity of the chemical library each firm has built up (Thomke and Kuemmerle 2002). Furthermore, unlike physical resources, the use of these libraries does not reduce in value monotonically. Due to the reusability of active substances, a firm can increase the value of its library, to some extent, by using

it frequently and adding more substances to it. Henderson and Cockburn (1996) found evidence for the presence of the economies of scope in pharmaceutical R&D. One explanation for their finding may be that molecules developed in one research program were reused in other programs. More systematic empirical research, however, is needed to confirm this possibility.

Interestingly, the importance of a library for the development of new products in pharmaceutical industries appears to be relevant in other industries as well. In the semiconductor, consulting, and software industries, libraries appear to be as crucial as those in the pharmaceutical industry. However, there appear to be at least two major differences, which offer promising opportunities for the direction of future research. First, drug discovery still relies on blind variations of non-modular building blocks. On the other hand, this mode of research is more or less absent in industries where modular product architecture is popular (e.g., semiconductors and software). This difference is related to the complexity of unexpected interactions. In drug discovery, innovators may waste time and effort generating many ineffective compounds when initial building blocks are improperly chosen in a library. The absence of this problem is an important benefit of having a modular product architecture, where design rules have evolved to reduce unexpected interactions among components. For example, in software engineering, Object Oriented Programming emerged to curtail unexpected interactions between components in a library. Innovation in this design paradigm is, to a large extent, considered as the reassembly of ready-made components and sub-components from a library. Comparative studies of libraries for modular and non-modular building blocks seem to offer deep insights into the question of how modularity affects new product development.

Another interesting difference is that while pharmaceutical firms have carefully guarded their chemical libraries, software companies often deliberately open some elements of their libraries to other firms including competitors. For example, Sun Microsystems permits any software engineers to obtain access to the library of Java. Opening such libraries can facilitate development of many software applications, which, in turn, spurs the rapid growth of the mass market. In particular, this is an important source of network effects for programming languages. When the library for some

language is highly valued by users, this popularity may serve as a barrier for the market to move to an alternative language.

Promising opportunities for research on libraries appear to lie ahead. Future research into the issues above could deepen our understanding of the role of resources, knowledge, modularity, and dynamic capabilities. Although most of the points I have made in this paper are anecdotal or speculative, I hope they will stimulate fruitful research in the future.

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