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THE DIFFUSION OF SCIENCE DRIVEN DRUG DISCOVERY: ORGANIZATIONAL CHANGE IN PHARMACEUTICAL RESEARCH

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ABSTRACT

Recent work linking the adoption of key organizational practices to productivity raises an important question: if adoption increases productivity so dramatically, why does adoption across an industry take so long? This paper explores this question in the context of one particularly interesting practice, the adoption of science driven drug discovery by the modern pharmaceutical industry. Over the past two decades, the established pharmaceutical industry has slowly shifted towards a more science-oriented drug discovery approach. Earlier studies have documented two key facts about the adoption of science-oriented drug discovery: (a) adopters experienced substantially higher rates of R&D after the late 1970s and (b) the rate of adoption across the industry was extremely slow. Motivated by the apparent contradiction between large boosts in performance and slow rates of adoption, this paper characterizes the sources of differences in rates of adoption between 1980 and 1993. The principal finding is that adoption of a science-oriented research approach was a function of initial conditions, or subject to "state dependence": some firms simply began the sample period at a much higher level of science orientation. Moreover, while these effects attenuated over time, our empirical results suggest that it took more than ten years before adoption was unrelated to initial conditions. In addition, consistent with theories developed in the context of technology adoption, we find that relative diffusion rates depend on the product market positioning of firms. More surprisingly, adoption rates are separately driven by the composition of sales within the firm. This latter finding suggests the potential importance of differences among firms in terms of the internal structure of power and attention, an area which has received only a small amount of theoretical attention.

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I. Introduction

There is considerable evidence that there are significant and persistent "fixed effects" across firms. In a host of productivity, investment and cost studies, for example, fixed effects are not only statistically significant, but often account for a substantial fraction of the overall variation of the dependent variable (Mundlak, 1961; Griliches, 1986). Recent work in the economics of organizations has highlighted variation in organizational practice as one source of these fixed effects (Ichniowski, Shaw and Prenusshi, 1997). But this interpretation immediately raises a critical question: if performance differences across firms are primarily due to differential adoption of organizational practices, then why are fixed effects so *persistent?* This paper explores this issue in the context of a particularly interesting organizational context -- the adoption of science-driven drug discovery in the global pharmaceutical industry.

Since the late 1970s, the established pharmaceutical industry has slowly shifted towards a more science-oriented approach to drug discovery research (also known as a shift towards “rational” drug design). Firms who adopted this approach shifted their research activities to rely increasingly on theories about the biological basis of disease. In order to access such findings, science-oriented firms began to allow (and even encourage) their researchers to interact more closely with the scientific community external to the firm, including publishing in the public scientific literature.

Earlier studies have demonstrated three key facts about the adoption of science-oriented drug discovery: (a) prior to the late 1970s, there is little reason to believe that such practices were substantially associated with important productivity gains for firms, (b) in part because of the explosion of knowledge in biology and biochemistry, adopters after the late 1970s experienced substantially higher rates of R&D productivity and © the rate of adoption across the industry was slow (Henderson and Cockburn, 1994; Gambardella, 1995). The apparent contradiction between large boosts to performance and slow rates of adoption raises several theoretical and empirical issues for industrial organization, strategy, and the economics of innovation.

First, economic theory provides little systematic guidance about how to investigate or explain the slow adoption of productive organizational practices in the context of a model of optimizing agents. While various theories for such behavior have been proposed (and are explored below), the evidence

presented here and elsewhere on slow and uneven diffusion of performance-enhancing organizational practices can coexist only uneasily with models of equilibrium adoption behavior. Absent economically significant differences across firms (along well-defined dimensions such as sunk costs or access to information), theory tells us that firms with similar technological and market opportunities should operate at the same point on the production possibilities frontier -- cost-minimization ought to drive all firms in an industry to adopt the same (or essentially similar) organizational practices. Consequently, the principal task of this paper is to identify and investigate potential sources of differences among firms which may have contributed to the observed divergence in adoption behavior.

However, setting out this task only raises a second and more troubling (though more practical) issue: what type of evidence should be drawn upon and what standard of proof should be used to identify the roots of firm heterogeneity? In some cases, a particular institutional setting (or careful research design) allows a single distinct theoretical possibility about the sources of hetereogeneity across firms to tested against data on variables which correspond closely to the theoretical constructs, In these cases, empirical work can provide an extremely precise characterization of how the evidence relates to the specific predictions of the theory in the context of a fully articulated model of optimizing behavior (e.g., Lazear, 1998; Athey and Stern, 1998). Unfortunately, many organizational practices which appear to generate productivity benefits present a more complex conundrum: while several theories can be plausibly tied to the phenomena in a general sense, no particular theory stands out as a unique candidate in the context of a fully specified equilibrium model. In such a case (which corresponds to our current application), it may be useful to engage in a somewhat more exploratory deck-clearing exercise. Specifically, by drawing in an informal manner on various economic theories to provide a more structured understanding of the phenomena, it may be possible to construct simple yet illuminating tests of several distinct hypotheses. While such tests are by no means dispositive, they can provide guidance about the relative empirical salience of different economic forces and provide a guide to further work which may involve more structural modeling.

Methodologically, this paper pursues this latter approach. We use qualitative research as a guide for the evaluation of the sources of differences among firms in terms of their incentives and costs of adopting science-based drug discovery. For example, various types of qualitative evidence suggest

that the benefits to science-oriented drug discovery were larger and more quickly established in key therapeutic areas, most notably cardiovascular therapies. Consequently, our empirical work focuses on this therapeutic category for evidence of the main economic hypotheses that we draw from the theoretical literature.

Our first hypothesis is that firms may have differed substantially in terms of the adjustment costs they faced in choosing to adopt science-oriented drug discovery once its productivity benefits became apparent. Specifically, we posit that some firms practiced some form of science-oriented drug discovery prior to the late 1970s for reasons which were unrelated to their productivity consequences in the 1980s, and that this head-start shaped the evolution of adoption throughout that decade. Corporate research culture, the specific histories of the management of different firms, and other largely exogenous factors may have led some firms to already be at a higher intensity of practice prior to the gradual assimilation of the biochemical revolution into the pharmaceutical industry. Once the returns to adoption shifted, these firms were in an especially favorable position to realize the concomitant productivity gains; diffusion to the remainder of the industry may have taken a long time because of the costs associated with adopting new organizational structures, hiring different types of researchers and scientists, and changing the behavior of current scientists in response to firms' attempts to adopt the new approach. If this view of the adoption process is correct, then differences among firms at a particular point in time is largely a function of the initial conditions -- put more formally, the adoption process is subject to *state-dependence*.

The second class of hypotheses that we consider draw on the idea that firms may have differed in terms of the benefits to adoption, at least from the perspective of the managers who have discretion over the adoption decision. In other words, the variation among firms is due to environmental *heterogeneity*. Specifically, we consider whether adoption is associated with differences in firms' technological orientation, product market positioning, or the pressures resulting from internal organizational forces. While science-oriented drug discovery seems *ex post* to be a valuable approach across most (if not all) therapeutic areas, the earliest, largest, and most visible returns to this research approach were in a small number of therapeutic categories. Thus, to the extent that a firm is active in product markets or in research areas which are associated with the science-driven approach, these

firms have higher incentives to adopt. More subtly, it is also possible that changes in the organization of research depend not so much on the absolute returns to adoption (such as would be predicted by focusing on technological or market positioning) but on the relative returns to adoption. It may be possible that those firms who were concentrated in the therapeutic areas with the highest returns (even if these firms were not the biggest "absolute" players in these markets) would be structured organizationally to be most sensitive to signals from these markets. As a result, adoption rates would be driven not by the absolute positions in these markets, but by the relative share of activity by these firms in those areas, reflecting, in part, the power and attention structure of the firm. Alternatively, if the firm's sales are dominated by sales in therapeutic areas where the returns to adoption are low, even if other factors (accumulated technological experience, for example) imply high returns elsewhere from adopting the practice, agency problems within the firm might lead it to make the "wrong" decision. In either case, these theories of heterogeneity among firms suggest that differences in adoption will be tied to observable differences in their technological, organizational, and market positioning.

Before turning to our application of these concepts in the context of science-driven drug discovery, it is useful to highlight an important consequence of these forces. Except in special cases, models involving state-dependence predict that, in the long run, the impact of state dependence will attenuate over time. Thus, in this context, in the long run, firms will *converge* to essentially similar organizational structures. On the other hand, the long run implications of heterogeneity is effectively an empirical issue, depending on whether those effects which provide initial incentives to adopt have an increasing or decreasing impact over time. With this in mind, we will be careful to distinguish the implications for convergence as we review our findings.

Our qualitative evidence is agnostic on this point. On the one hand, we find significant support for the likely importance of state dependence. Our interviews suggest that variation in geographical location, in the firm's "taste" for pure science and in the attitude and "vision" of the firm's leadership were important determinants of adoption. But on the other hand, our interviewees also stressed the importance of historical experience in particular technologies in driving adoption, and discussed the importance of the relative power of different therapeutic area "owners" within the firm in driving decisions.

With this evidence in mind, we turn to the quantitative perspective. Specifically, the paper examines the diffusion of a particular manifestation of science-oriented drug discovery: high rates of publication by the researchers who are ultimately responsible for the discovery of new drugs. We provide evidence for two main quantitative findings. First, there exists substantial state dependence which only slowly attenuates over time. The estimated rate of convergence conditional on controlling for state dependence suggests that the initial level of publication activity differentiates firms for more than ten years. In addition, consistent with theories developed in the context of technology adoption, we find that relative diffusion rates depend on the product market positioning of firms. More surprisingly, adoption rates are separately driven by the composition of sales within the firm. This latter finding may prompt additional investigation of the economic consequences of firms' internal structure of power and attention, an area which has received relatively little theoretical attention.

The paper proceeds as follows. The next two sections motivate our exploration of the adoption of science-based drug discovery. First, we review the accumulation of evidence on the performance effects of organizational design choices and their linkages to adoption behavior. We then document the changing nature of drug discovery over the past two decades, focusing on the increasing use of science-based techniques for conducting research, and the observable implications in terms of adoption of related organizational practices. In particular we explain why it was that using publications in the open scientific literature as a means of monitoring and motivating research workers increasingly became standard practice in the management of pharmaceutical research during the 1970s and 80s. We suggest that in the early part of this period there was some uncertainty as to whether this particular organizational practice would in fact increase research productivity, but that by the end of the period it was widely accepted as fundamental to "best practice" in pharmaceutical research. We then turn to the qualitative evidence regarding adoption in Section IV and use both historical accounts and interviews with industry participants to explore those factors that drove heterogeneity in the diffusion of the new practice across the industry. These insights are then incorporated into a simple empirical model. Section VI presents the data, and Section VII reviews our results. A final section concludes.

II The Sources and Persistence of Organizational Heterogeneity

As an empirical statement, it is uncontroversial that different firms, even in the same market or industry, are organized differently. At any given point in time, firms vary according to the technologies they employ, their mechanisms for coordinating action across workers and divisions, and in the incentives and training provided to employees.[1] What is controversial, however, is how economists should treat such differences. The question is whether firm differences *matter*:

(I) Does organizational heterogeneity affect performance?

(ii) If so, what factors drive the adoption of organizational practices?

(iii) And, do firm differences persist in the long run?

In part because of ambiguity surrounding the answer to (I), theoretical and empirical economic analysis in industrial organization has traditionally acknowledged but abstracted away from organizational heterogeneity. Two manifestations of this neglect are particularly important. First, from a theoretical perspective, both neoclassical and early game-theoretic models either assume or derive symmetric equilibrium. Faced with the same factor costs, technological opportunities, and industry demand curve, firms will, in equilibrium, operate with the same capital-labor ratio, and cost-minimization drives all firms to adopt the same (or essentially similar) organizational practices.[2] To the extent that theories accommodate asymmetry, the sources of those differences has historically been extremely narrow: the sunk cost gains from incumbency (Baumol, Panzar and Willig, 1981), learning-by-doing cost advantages (Spence, 1981), or stochastic shocks not under the firm's control (Jovanovic, 1979).

Given the lack of guidance from economic theory about the role that differences in organizational design might play, empirical research has generally followed the theoretical literature in acknowledging, but then abstracting from, such differences. For example, in studies of productivity used

[1]This is of course only a partial list of the way that firms have been found to differ, even those who face very similar labor, capital and product market environments.

[2] All organizational structures which correspond to a single cost and profit profile are essentially the same from the viewpoint of the economic model. However, some organizational theorists would suggest that organizational differences can still be important in such a case, in terms of the realized welfare or workers or in the level of public goods (spillovers) created by the firm.

to evaluate questions such as the gains from R&D or the division of factor payments, differences among firms are treated as a "fixed effect"; as a result, the empirical analysis simply differences out any underlying heterogeneity (see, the seminal paper of Mundlak (1961) or the survey by Griliches (1986)).[3] These studies therefore evaluate the *average* returns to inputs such as R&D, controlling for unobserved differences among firms.[4] In other words, until perhaps a decade ago, differences across firms were generally considered important to control for, but they were not in and of themselves of intrinsic interest.

In recent years, however, there has been an increasing amount of interest in the internal economics of organizations, both from a theoretical and empirical perspective. This renewal seems to be driven by two forces, one theoretical and one empirical. On the theoretical front, advances in theory suggest precise mechanisms by which equilibrium differences among firms might emerge. For example, when firms choose multiple organizational practices and the practices are complementary with each other, then even small differences in the firm's cost of adopting one practice can result in a discontinuous shift towards adopting all practices together (Milgrom and Roberts, 1990). More subtly, if decision making is decentralized (and information is limited) then complementarity may result in both (a) *inertia* for some firms, as pools of local information may not be aggregated in an efficient way to indicate the benefits of a coordinated change over multiple practices and (b) *momentum* for other firms, as adoption of one organizational practice by one decision maker (for whatever exogenous reasons) raises the marginal returns to adoption and investment by other decision makers within the firm (Milgrom, Roberts and Qian, 1991). In this sense, the mathematics of complementarity provides a formal statement of an intuition that has been critical to the work of evolutionary theorists, namely the idea that path dependencies and local learning in combination with differences in initial conditions

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[3]Of course, different researchers have used different statistical procedures to deal with the presence of fixed effects -- from fixed effects estimation, to first differences, to a variety of more sophisticated estimators (Hausman and Griliches, 1986).

[4] The use of fixed firm effects (or first-differencing) in the context of panel data has not, of course, been confined to productivity studies. Fixed effects are routinely used to "absorb" heterogeneity in many other applications.

engender firm effects (Nelson and Winter, 1982).[5,6]

While these theoretical advances have certainly contributed to wider appreciation of firm differences, perhaps the key factor driving the recent increase in attention is the accumulation of a persuasive body of econometric evidence that organizational heterogeneity matters for performance. Of course, research in business history and strategy has long documented such differences (Chandler, 1962; Enos, 1962; Abernathy, 1977; Rumelt, 1991; Clark and Fujimoto, 1991). However, by gathering more systematic data, by exploiting more powerful econometric techniques, and by accommodating (or at least controlling for) competitive and technological factors, a host of recent studies have highlighted the economic importance of organizational heterogeneity (Henderson, 1993; Henderson and Cockburn, 1994; Ichniowski, Shaw and Prenusshi, 1997; Helper, 1997; Brynjolffson and Hitt, 1997). For example, in their study of the productivity benefits from high-involvement work practices in steel finishing lines, Ichniowski, Shaw and Prenusshi (1997) (a) provide a detailed justification for their measure of performance, (b) isolate changes in organizational design from other factors such as shifts in labor quality or differences in technology, and © demonstrate the robustness of their results to various types of econometric specifications and estimation techniques. In doing so, this study provides a much more thorough foundation than earlier studies for the claim that human resource system matter for performance.[7]

Indeed, when reviewed together, the recent empirical evidence substantially raises our confidence that there does indeed exist a relationship between organizational heterogeneity and performance, at least in the short run. Given that the response, then, to the first question raised at the beginning of this section is in the affirmative, the two latter questions are immediately raised: (a) what

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[5]More formal work linking evolutionary theory and decision making under imperfect information is being pursued by several researchers within the strategy field, including Levinthal (1997) and Rivkin (1999).

[6]While our discussion here focuses on issues of complementarity, the potential for equilibrium organizational heterogeneity has also been derived in several other contexts, including contract theory (Hart and Moore, 1986) and games of market signaling (Hermalin, 1994).

[7]Indeed, there seems to be some degree of spillover from these studies to increases in the degree of sophistication employed in the strategy literature itself (McGahan and Porter, 1997; 1998).

factors shape differential adoption of organizational practices? and (b) does organizational heterogeneity persist in the long-term?

Both questions are extremely difficult to answer but of crucial importance. At first glance, many of the organizational practices identified as contributing to performance seem to be associated with relatively low costs of adoption. For example, Clark and Fujimoto (1991) document large productivity improvements in product development from the use of "heavyweight" project managers – a practice which presumably could (and, according to Clark and Fujimoto, *should*) be adopted by all firms within complicated manufacturing environments. But, the evidence on adoption suggests exactly the opposite: some firms were exploiting heavyweight project teams for over a decade before their more general adoption within the automotive industry.

This conjunction of large boosts to performance and slow adoption rates suggests that industry-level diffusion of productive organizational practices is of intrinsic economic interest. Slow adoption implies that differences in firm performance may be tied to firm sensitivity to emerging opportunities for practice adoption, thus shaping the distribution of industry profitability. From a policy perspective, slow adoption implies sub-optimal industry-level productivity growth, and provision of better information or incentives (such as subsidies) to encourage faster and wider adoption may be socially efficient if the productivity gains are sufficiently high.

The Drivers of the Diffusion of Organizational Practice

The literature on the diffusion of new products, innovation or ideas is enormous and we do not attempt to synthesize it here (Rodgers, 1983). Since Griliches' seminal study of hybrid corn, economists have generally assumed that variance in rates of diffusion reflects heterogeneity in costs and benefits across adopting entities, and have focused particularly on four sources of such variation: differences in product market position; differences in knowledge capital, differences in the structure of power across firms and lastly variance in the unobservable characteristics of the adopting entity that leads to heterogeneity in the costs and benefits of adopting an innovation or practice. This last form of unobserved heterogeneity can be thought of as the impact of "initial conditions."

Of these streams of explanations, the first has the longest tradition in the literature.

To the degree that the adoption of a particular organizational practice can be identified as the adoption of a productivity-enhancing "innovation," hypothesizing that adoption rates should be a function of relative product market position draws on a long tradition in industrial organization on incentives to innovate, and the degree to which a new “technology” will be adopted either by established firms or by firms who currently have no commercialized products in a given market (Gilbert and Newbury, 1980; Reinganum, 1981; Fudenberg and Tirole, 1985; and, e.g., Henderson, 1993; Karshenas and Stoneman, 1993; Hannan and McDowell, 1984.) It can be difficult to derive an unequivocal prediction from this literature, but nevertheless relative market power remains a plausible source of variance in adoption rates.

Perhaps the most likely source of heterogeneity among firms in the rate at which they adopt any particular organizational practice is the possibility that firms may differ in terms of the technology and input mix that they use at any one time. For example, a growing literature has developed on the skill bias of technological change, and, in particular, on the fact that those firms who employ more advanced technologies have higher incentives to screen their employees more thoroughly on quality and skill considerations (Berman, Bound, and Griliches, 1994.) To the degree that any single practice is more effective if used by a highly skilled workforce, for example, those firms that already employ more highly skilled people will have greater incentives to adopt it. Similarly if a given practice is likely to be particularly productive if used in the context of a given technology or market, then those firms that already possess such knowledge – those firms that have high levels of knowledge capital in the relevant areas – may have more powerful incentives to invest in it.

It is also possible that firm-level heterogeneity emerges because of differences in the structure of power and attention across firms, a less widely investigated hypothesis. These ideas have their roots in both the economics and organizational traditions. Within economics, research drawing on agency theory has argued that the asymmetry in goals between agents and principals may lead firms to adopt key organizational practices either too quickly or too slowly (Jensen, 1993; Van Nuys, 1993). Within organizational theory, a well established body of work has argued that organizations often fail to adopt new practices that would improve their performance, either because doing so would undermine their legitimacy (Hannan and Freeman, 1989) or because they develop organizational routines and cognitive

blinders that make it extraordinarily difficult to identify or act on new opportunities (Henderson, 1993; DiMaggio and Powell, 1983; Ocasio, 1995; March, 1991.) Thus to the degree that rates of adoption are affected by variables that reflect the distribution of power (in the sense of decision making authority) across the organization, rather than variables that are more obviously correlated with the costs and benefits of using the new practice, we argue that the diffusion of organizational practice, and hence at least some portion of "firm effects" may be shaped by strategic or organizational phenomena that should be of some significant interest to economists. These may include variables such as the current financial performance of the company, governance structure or the distribution of power across groups within the firm.

Lastly, a long tradition in the literature suggests that diffusion is driven by differences in *unobserved* returns across potential adopters (Griliches, 1957; Rodgers, 1983). To the extent that these unobservable factors are captured in the initial level to which the practice or innovation has been adopted, the adoption process will be subject to "state dependence" where state dependence is the sensitivity of the level of a given variable, y_t, to its initial value, y_0 . In most models, differences due to state-dependence will attenuate over time and all organizations will eventually converge to the same level of adoption (i.e., the same diffusion "ceiling"). As a result, in a model in which state-dependence with convergence is the dominant effect, the impact of organizational design on performance is essentially transitory in nature; important questions remain, however, about how long it takes to achieve the long run and whether policy can play a productive role in accelerating the convergence process.

In most discussions of the difference between state dependence and heterogeneity, the key issues turn on what is observable to the econometrician. Here, however, we draw on both qualitative and quantitative evidence to illuminate the distinction. While there are many factors which we may not be able to identify econometrically, our complementary qualitative research may shed light on the potential *sources* of state dependence itself. Or, conversely, by explicitly recognizing the potential importance of state dependence in a statistical sense, we more precisely identify the value of investigating the kinds of hard-to-measure factors suggested by our qualitative research.

To sum up, recent theoretical and empirical research has provided a much firmer foundation for the hypothesis that organizational differences among firms can be an important determinant of variation

in performance. We therefore shift attention to the sources of organizational differences across firms, and, in particular, to the heterogeneous rate of adoption of performance-improving practices across organizations. We highlight four potential sources of variance in rates of diffusion: state-dependence (or variation in initial conditions), and three more measurable sources of heterogeneity: differences in market positioning, differences in technological capabilities, and differences in the power and attention structure of the management of the firm. With these conceptual categories in mind, we now turn to a short description of the particular organizational practice we examine for the remainder of this paper, the adoption of science-oriented drug discovery.

III. The Benefits to Science-Oriented Drug Discovery

Science-driven, or "rational," drug discovery is both a technology for discovering new drugs, and a set of managerial practices for organizing and motivating research workers. Understanding the benefits of adopting these practices is valuable for at least three reasons.

First, this practice has been associated with substantial gains in R&D productivity (Henderson and Cockburn, 1994; Gambardella, 1995), and so, in line with our discussion from the previous section, its relatively slow adoption across the industry presents an interesting economic question. Second, the adoption of science-driven drug discovery entails making major changes to the organization of the R&D function of an organization. As we will discuss shortly, this approach requires new mechanisms for monitoring and for promotion, different ways of organizing researchers into teams, recruiting new types of human capital, and different types of interactions with researchers external to the firm. As such, adoption of the science-oriented approach presents a difficult and interesting managerial problem. Finally, the phenomena of science-oriented drug discovery is of substantial interest on its own terms. The nature of science-oriented drug discovery requires that firms become participants in Science, in a wider sense, rather than just users of scientific knowledge.[8] Firm's adoption of science-

[8] For example, the experiments which identify potentially valuable commercial drugs will also tend to be empirical tests of specific (and most likely previously unproven) biological or biochemical theories.

driven research methods therefore has immediate implications for science and technology policy (Nelson, 1962; Rosenberg, 1990; Dasgupta and David, 1994). With this in mind, we now review both the evolution of this research approach and the evidence for its productivity benefits in some detail before turning to the core of the paper, the evaluation of the differential rates of adoption across firms, using both qualitative and quantitative evidence.

The belief that biological theory could be an effective basis for drug discovery is an old one, with some impressive discoveries to its credit. For example in the first decade of the 20th century Paul Ehrlich drew on detailed research into bacteria biochemistry to assist him in his discovery of a cure for syphilis (Williams and Malick, 1987; Gambardella, 1995). Similarly, in the late 1950s university researchers discovered that insufficient levels of dopamine (a peptide neurotransmitter) in the mid-brain were a root biological cause of Parkinson's Disease. Building upon these discoveries researchers at Hoffman-La Roche focused on developing a therapeutic agent which would increase the level of dopamine in the brain. After several years of iteration and interaction between biologists, chemists, and clinicians, Hoffman-La Roche introduced L-Dopa, a dopamine precursor, as a therapy for Parkinson's disease in the mid-1960s (Beyer, 1976; Maxwell and Eckhardt, 1990). Sir James Black's celebrated discovery of cimetidine, an H_2 blocker, at SmithKline in the early seventies is another famous example of the potential power of this approach (Sapienza, 1989).

However prior to the late seventies the extensive use of leading edge biological theory in drug discovery remained an exception, rather than the rule. This was partly because the so called "random" method had proved to be extremely effective.[9] As Maxwell and Eckhardt note in their conclusions to their detailed study of 32 drug innovation histories, "screening...appears to be all but indispensable to

[9] "Random" drug discovery is the practice of the large scale screening of thousands of compounds in the hopes of discovering an effective agent. For example firms might inject hundreds of compounds into hypertensive rats in the hopes of finding something that will lower their blood pressure. Recent advances in combinatorial chemistry mean that large scale screening is now widely used, but prior to the late seventies the "mechanism of action" of most drugs discovered using this technique - the specific biochemical and molecular pathways that were responsible for their therapeutic effects - were not well understood. A more "science guided" or "rational" approach to drug discovery relies on knowledge of the biological basis of a disease to frame a research strategy. The request "find me something that makes the rat less depressed" is replaced with the request "find me something that inhibits the uptake of serotonin."

the discovery of innovative drugs, having been involved in the discovery of 25 of the 32 case histories covered by us." (Maxwell and Eckhardt, (1990, p. 409)). Indeed, during the early 1980s, many researchers expressed strong appreciation for screening methods in the absence of biological theory,

> *In some cases it is surprising how well medicinal chemistry can do without knowing the biological system involved. The narcotic analgesics may serve as an example. By means of rather simple screening methods an enormous number of potent and specific analgesics were being and could be developed.* (Carlsson, in Gross, (1983, p. 35))

Beginning in the late 1970s, however, an explosion of knowledge in the biological sciences -- the vast majority of it flowing from publicly funded research in the United States, appears to have dramatically increased the opportunity to profit from "rational" or "science driven" research. It became clear, for example, that many diseases (such as hypertension, ulcer, and depression) could probably be treated by moderating the level of production of specific proteins in specific areas of the body. For example controlling the level of renin in the body is one of the central challenges in treating hypertension. It was discovered that this control could be achieved through the exploitation of the "lock-and-key" action of cell surface neuropeptide receptors. The synthesis of captopril, the first of the tremendously successful ACE inhibitors, at Squibb in 1977 as the result of a research program framed around this discovery is often cited as the beginning of the "modern" drug discovery era.

Today, while "random" drug discovery remains an important technique in some circumstances, the belief that it is essential to invest in leading edge research and "science driven" drug discovery appears to be firmly entrenched in the industry. As early as 1987, Williams and Malick were writing:

> "*...the likelihood of serendipitous discovery of major drugs such as chlorpromazine and the benzodiazepines could not be guaranteed or expected to create a basis for capital investment. The success of...[the beta-blocker] propranolol, [the H_2 blocker] cimetidine and [the ACE inhibitor] captopril is evidence that a more rational, mechanistic approach to drug discovery can contribute to the development of therapeutic entities.*" (Williams and Malick, 1987, p4)

and

> "*The success associated with the mechanistic [rational] approach has, however, made pharmaceutical companies...aware of the fact that to be too far distant from the 'cutting edge' of science is to limit their chances of competing successfully in the marketplace*" (Williams and Malick, 1987, p4)

Empirical study of the diffusion of this approach is complicated by the fact that without detailed scientific data at the level of the individual scientist it is very difficult to construct a direct measure of the degree to which any single firm was conducting science-driven research. However, we can more easily observe measures of the degree to which a firm has adopted the concomitant organizational practices, and in the empirical analysis that follows we thus focus on the diffusion of a particular organizational practice – providing explicit incentives for researchers to publish scientific papers – as an indicator of the degree to which the firm has adopted the techniques of science driven drug discovery. This approach is consistent with prior work which has attempted to document the productivity consequences of science-based techniques of drug discovery (Henderson and Cockburn, 1994; Gambardella, 1995; Zucker and Darby, 1997; Cockburn and Henderson, 1998).

The adoption of "pro-publication" incentives is one of a number of organizational practices that in combination enabled pharmaceutical firms to conduct science-orientated research successfully. Merton (1973) established that publicly funded science relies on an incentive system that rewards participants on the basis of priority -- and hence on the basis of rapid publication. Using a scientist's standing in the public rank hierarchy as an important criterion in his or her promotion decision thus has the effect of forcing scientists who wish to be promoted to publish in the open scientific literature and to take part in the "race" that characterizes public science. This has a number of advantages for a firm wishing to move to a regime of science-based drug discovery. In the first place, it helps to ensure that the basic research conducted within the firm will be at the leading edge, since it will need to be capable of surviving peer review. Secondly, it probably improves the firm's ability to hire leading edge researchers. Permitting publication -- and committing to evaluate researchers on the basis of their standing in the disciplinary field -- is important in persuading high quality researchers that the firm will continue to be an environment in which they will enjoy working. Indeed, the salaries offered to scientists seem to reflect a compensating differential for the freedom to publish, suggesting the potential importance of adopting this practice in increasing realized R&D productivity through wage-saving gains (Stern, 1999). Endorsing standing in the scientific community as a method of evaluation may also have the effect of credibly committing the firm to investing in leading edge basic research, which may play an

equally important role in recruiting researchers. Finally, the use of this incentive mechanism ensures that the firm's scientists will be much more tightly connected to their publicly funded counterparts: as actively publishing researchers they are much more likely to be considered as colleagues by academic scientists, and to realize the benefits of being included in the "invisible college."

Though these practices may be costly to implement, they may have a significant impact on research productivity. As discussed by Rosenberg (1990) and Cohen and Levinthal (1990), private firms who would like to exploit novel scientific knowledge may have to purchase a "ticket of admission" which pays itself off in terms of higher R&D productivity and a higher rate of technological innovation.[10]

IV. The Adoption of Science-Oriented Drug Discovery: Qualitative Evidence

Previous research suggests that during the early 1980s, there was broad agreement within the pharmaceutical industry on the presence of large productivity gains from adopting science-oriented research techniques and pro-publication incentives. Nonetheless, there was very wide variation across firms in the speed and extent to which pro-publication practices was adopted. In an earlier study (Henderson and Cockburn, 1994), the intensity of provision of pro-publication incentives was measured by using an interview protocol to rate the degree to which firms used publication in the open literature as an explicit criterion in promotion decisions. Figure (1) shows the diffusion of "propublication incentives" across the small sample of firms in that study. While some firms were heavily invested in science in the beginning of the period, others switched only later and yet a third group were very slow to switch indeed. Given the seemingly spectacular returns associated with the use of the new approach and its widespread acceptance by the end of the sample period, the failure of some of the firms in that sample to adopt the practice more rapidly presents something of a puzzle.[11]

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[10] See also Cockburn and Henderson (1998) on the relationship between research productivity and "connectedness" as measured by coauthorship between private sector and public sector researchers.

[11] We abstract away from the question of whether the use of this incentive mechanism is complementary with other practices adopted by the firm. In Cockburn, Henderson, and Stern (1999), we explicitly explore this question by analyzing whether the intensity of incentives for applied research covary with basic research (or pro-publication) incentives; we interpret the evidence as suggesting the possibility of complementarity between these two incentive instruments.

As we suggested above, we believe that there are broadly two classes of explanation for this phenomenon: state dependence, or factors that are captured in the initial position of the firm and that are otherwise inherently difficult to model or observe; and heterogeneity, or factors that can be more straightforwardly observed and whose effects are captured by existing economic theory. Following our theoretical discussion, we divided these later factors into three classes: those reflecting differences in market position, those reflecting differences in technological expertise or knowledge capital and those reflecting differences in the structure of power within the organization.

Our discussion below reflects this structure. We begin with a discussion of the importance of initial position in driving adoption, and then turn to the importance of market position, technological capital and organizational pressures. Our qualitative evidence confirms the importance of all of these effects with one important exception: none of our respondents mentioned relative market position as a factor in the decision to adopt the techniques of science driven drug discovery. We suspect that this is because in the minds of many of them technological heterogeneity, or relative knowledge capital, proxied closely for market position. We return to this issue below.

The Qualitative data

Between September 1998 and April 1999 we conducted interviews at seven firms. Of the seven, all but one were based in the United States, and all but one are included in our sample. These interviews were loosely structured discussions that explored first, whether it was plausible that the adoption of science driven drug discovery in general and a propublication regime in particular might have had significant effects on research productivity and second, why it might have been the case that despite their plausible impact on productivity, many firms were slow to adopt them.

Differences in initial conditions: history, geography, leadership and "vision"

Many of our informants suggested that those firms that had historically had a deep and visible commitment to the pursuit of "pure" science may have found the costs of switching to the new approach significantly lower than those firms that had instead aggressively discouraged investments in basic research and publication. They suggested that since the adoption of "science driven" drug discovery

required systematic changes in a wide range of organizational practices, including changes in the incentive system and the ways in which new researchers were hired, those firms that already had some elements of this system in place, such as a respect for publication or the belief that it was a legitimate activity, may have had a significant advantage. They suggested that it was easier to hire more scientifically orientated researchers if the firm had a history of respecting scientific freedom, and of devoting resources to pure research, and that these firms found it easier to develop close relationships to universities since they had already had a body of experience in working with academic researchers.

Differences in geographical location were also often cited as important determinants of the decision to adopt the new research techniques since many managers believed that the benefits of adopting the new approach were significantly higher (and the costs significantly lower) for those firms whose research laboratories were located in reasonably close proximity to large communities of publicly funded researchers. Our interviewees suggested that such close proximity not only made it easier to attract the best quality researchers, but also made it much easier to maintain close connections to the public sector once they had joined the firm. This suggestion is consistent with a growing literature that suggests geographical proximity may play an important role in mediating the transfer of scientific information (Jaffe, 1986; Zucker, Darby, and Brewer, 1997).

Lastly, our informants often also suggested that differences in "leadership" or "vision" across firms may have had a very significant effect on the decision to adopt the new mode of research. One informant remembered:

> "*We spent most of the seventies going to T groups. It was fun, but we didn't get much science done... The managers of the firm were largely focused on using the cash generated by the pharmaceuticals group to look for diversification opportunities...*"

The decision to invest in the science driven approach was often identified with the hiring of key individuals:

> "*Oh, that's when we hired X. He built a completely new research facility and started to hire aggressively. He had a fundamental belief that if we did leading edge science we would find breakthrough drugs...*"

In this spirit, our informants also pointed to the importance of major changes in performance in

triggering change. The adoption of science driven drug discovery was often identified with major shocks to the firm, both positive and negative. Firms that had done unusually well from a particular drug sometimes invested the resulting income in moving towards a more science based approach. One scientist remembered:

> "*We were swimming in cash, and it was fashionable to invest in basic research, so we did.*."

Others remembered senior managers who believed quite strongly that the new techniques were not likely to prove effective, that publishing represented a distraction for researchers working within a firm and that basic research was best left up to the universities. According to Bristol Myers' Director of Research, G. Vita,

> *...new mechanisms of action are discovered by examining biological and biochemical processes in depth...but the basis is still the chemist's new chemical entity, on which we build...[because of side effects and the like]...the chemist's invention, clinical observation...will be the basis for drug discoveries for a long time.*
>
> (Vita, discussing Bartholinin, in Gross,1983, p. 145)

Differences in market position, technological experience, and the dynamics of organizational power.

In the light of the extensive literature describing the probable impact of market power and position on the decision to adopt innovation, it is perhaps surprising that none of our respondents mentioned relative market position as a factor in the decision to adopt the techniques of science driven drug discovery. We suspect that this is because in the minds of many of them, technological heterogeneity, or relative knowledge capital, was functionally equivalent to market position.

Nearly all the people with whom we spoke suggested that differences in the historical experience of the firm -- in their "knowledge capital" -- was critically important in shaping the adoption decision. They suggested that the new techniques were adopted most rapidly by those firms that were already heavily invested in those therapeutic areas in which the new techniques had initially the most promise. For example, the (university made) discovery that moderating the level of renin (a peptide protein) was the central challenge in the treatment of hypertension provided a strong signal that

university research (and a biological approach) might be useful in drug discovery in antihypertensives research, and many of our respondents suggested that this led those firms with extensive investments in cardiovascular science to adopt the new science driven techniques more aggressively. In contrast, the new techniques initially seemed likely to be of much less use in the search for new anti-infective therapies, and our interviewees speculated that this led those firms whose knowledge base was heavily orientated towards anti-infectives to be slower adopters of the new techniques.

The case of oncology, or cancer, provides an interesting intermediate case. While a tremendous amount of anti-cancer research was (and is) undertaken within the public sector, this research seems initially to have had less potential for guiding drug discovery efforts than in the case of anti-hypertensives. This may be partly because cancer is a much more complicated and heterogenous disease than hypertension. There are hundreds of varieties and, despite some optimism in the early 1980s, there is little hope that a single "magic bullet" will be developed which can serve as a treatment for a broad class of cancers. Towards the end of our sample period, despite intensive effort at the NIH (which at one point was investigating more than 10,000 compounds a year for action against cancer) and elsewhere, only one clinically relevant compound had been identified in the preceding ten years (The Economist, 1989; Kolata, 1986; Kaye, 1991). However more recent work on the underlying mechanisms that trigger uncontrolled cell proliferation have raised hope that more science driven approaches may prove helpful in discovering new cancer therapies, and several people suggested that anticipation of this development may have led to firms with expertise in oncology adopting the new techniques relatively quickly.

Finally, our qualitative evidence also suggests that the speed with which the new techniques were adopted was a function of the balance of power within the firm. Those firms that had obtained early success with the new techniques or that obtained a large fraction of their sales revenues from therapeutic classes in which the new techniques were likely to be particularly important appear to have become convinced that the new techniques were likely to be important much faster. In other firms, power was in the hands of managers who saw the firm's future quite differently: perhaps because of the fact that a significant majority of the firm's sales were in classes such as anti-infectives or cancer where the new techniques could be expected to initially have only minimal impact. In these firms, managers

appear to have initially dismissed the new techniques. As one of them said to us in an earlier round of interviews:

> "*Why should I let my people publish? It's just a waste of time that could be spent in the search for new drugs*."

Thus our qualitative work raises a number of important issues. In the first place, the views of industry informants provide support for the importance of both heterogeneity in technological position and variation in the relative power and position of different therapeutic areas within firms in driving the adoption of science driven drug discovery. They provide no explicit support for the importance of market position, but this may be well because market position is confounded in many of our interviewees' minds with technological experience. In the second place, they reinforce the probable impact of state dependence. Variation in geographical position, in the firm's historical attitude to "basic" research and in the vision of the firm's leaders all appear to have played an important role in shaping the adoption of science driven drug discovery.

V. Translating Qualitative Insights Into a Quantitative Framework: the Empirical Methodology

We build on these qualitative insights and develop a simple empirical model which provides more concrete evidence about the relative salience of different drivers of adoption of science-based drug discovery. As mentioned earlier, it is not our goal (at least in this paper) to develop or estimate a fully specified structural model of optimizing adoption behavior. Indeed, given the diverse set of plausible hypotheses about the drivers of adoption behavior, it is not clear that estimating such a model is currently feasible without preliminary empirical work which substantially narrows down the potential range of theories to be accommodated. Consequently, we confine ourselves here to identifying the principal covariates of adoption, recognizing that adoption is a dynamic process. This exploration allows us to begin distinguishing the empirical salience of competing hypotheses, and so provide an initial "guide" to evaluating different modeling choices in a more fully articulated structural model.

We focus on the intensity of adoption by individual firms, as measured by relative rates of participation in the public scientific community by scientists at the firm who are also contributing to

technological innovation. More precisely, and as further discussed in the next section, our core measure is the fraction of a firm's inventors who also publish in the scientific literature. This measure of the diffusion process ranges from zero to one, and serves as a proxy for the *intensity* of overall adoption at the firm level, aggregating over the population of scientists at the firm who are actively involved in the process of technological innovation.

The goal of the empirical work is to measure how diffusion intensity, y_t , relates to the initial level of adoption intensity, y_0 , as well various types of environmental heterogeneity (here we follow the conceptual framework emphasized by, among other, Heckman (1991)).. Following our earlier discussion, let Z_M , Z_O ,and Z_T represent measures of heterogeneity among firms in terms of their market positioning, organizational focus, and technological focus, respectively.

Our key hypotheses are about the relationship between y_t , y_0 , and **Z.** On the one hand, we are interested in measuring the sensitivity of y_t to y_0, that is, the degree of state dependence in the diffusion process. Within the context of state dependence, we are also interested in whether the impact of initial conditions attenuates over time (i.e., whether the coefficient on the interaction between y_0 and TIME is negative). On the other hand, we are interested in the specific ways in which **Z** impacts y_t : whether activity in certain therapeutic categories (such as cardiovasculars) significantly increases the intensity of adoption by firms and whether the sensitivity to therapeutic category participation changes over time (as captured by interactions between **Z** and TIME). Three issues arise in empirically evaluating these hypotheses.

First, as has been well-documented throughout the diffusion literature, the diffusion of most practices or technologies follows an S-shaped (or sigmoid) pattern through time. While there exist a variety of methods and functional specifications which accommodate this nonlinear patterns in the time dimension, the simplest transformation involves taking the log-odds ratio of the dependent variable measuring the intensity of diffusion (Griliches, 1957). As such, we assume that, for each firm, diffusion follows a logistic process and so use the log-odds version of that variable in our empirical work.[12]

[12]Our empirical results are surprisingly robust to changes in the functional form associated with diffusion process. Our robustness checks (not presented here, but available on request) included using the level of adoption intensity as well as the natural logarithm.

Second, in the absence of specific assumptions, the effect of state dependence will be confounded with measured sources of heterogeneity. Indeed, in the context of hazard models (for which the dependent process is discrete), it is well known that, unless y_o and $\mathbf{Z}$ are separable (or unless some other suitable parametric restriction is imposed), then one cannot separately identify the structural impact of state dependence from heterogeneity. Given our focus on estimating the simplest empirical model which allows the data to "speak for itself," in this paper we follow numerous prior studies and assume separability. However, in our interpretation of the empirical findings, we are sensitive to the strong nature of this assumption, and so discuss some qualifications which might result from relaxing it.

Finally, we examine time-varying heterogeneity (i.e., $\mathbf{Z_t}$ varies by period for each firm). While the claim for exogeneity of pre-existing environmental heterogeneity ($\mathbf{Z_0}$) is relatively strong, we found that we could not separately isolate the empirical effects of that degree of heterogeneity that was fixed for each firm at the beginning of the period. While there is no fundamental issue in using time-varying heterogeneity ($\mathbf{Z_t}$) to identify the importance of therapeutic category effects, this choice does raise some issues which will limit our interpretation of the results. In particular, as long as there is some structural relationship between the evolution of the firm's activities and its scientific orientation, then there may be some endogeneity associated with our empirical specification. While we believe that the very long lags between research decisions and their market consequences in this industry limits this possibility to some extent, we are accordingly cautious in our interpretation of our estimates.

Putting together all of the above, the empirical work will focus on the following simple model of adoption behavior by firms over time (suppressing the firm-specific subscript):

$$\ln\left(\frac{y_t}{1-y_t}\right) = \alpha_0 + \alpha_{y_0} y_0 + \alpha_{y_0,t} y_0 * \text{TIME} + \alpha_M Z_{M,t} + \alpha_{M*t} Z_{M,t} * \text{TIME} + \alpha_O Z_{O,t} + \alpha_{O*t} Z_{O,t} * \text{TIME} + \alpha_O Z_{O,t} + \alpha_{T*t} Z_{T,t} * \text{TIME} + \varepsilon_{j,t}$$

With this specification in mind, we now turn to a more detailed discussion of our quantitative data before presenting our empirical results.

VI. Data and Measurement

Sample Construction

The sample is composed of 16 large research-oriented pharmaceutical firms from throughout the world.[13] Nine of these firms have been used in our prior work (Henderson and Cockburn, 1994); the remainder were selected to incorporate the industry's leading R&D performers and to obtain world-wide geographical representation; overall the average firm in our sample is somewhat larger than the average publicly traded firm. While these firms do not constitute a random sample in a statistical sense, they are (a) reasonably representative of the pharmaceutical industry and (b) comprise a substantial portion of that industry (the firms in the sample account for approximately 50% of US pharmaceutical sales in 1993).

Data sources

The data set used in our econometric analysis draws on a variety of sources. Our main variables are derived from information on firms' patents, scientific papers, and product sales compiled at the level of therapeutic classes such as cardiovascular therapies, anti-infectives, or cancer drugs. Our source for patent data is Derwent Inc's *World Patent Index*. Scientific publications are taken from ISI's *Science Citation Index* and *Web of Science*. Sales data are from various publications of IMS America, a market research firm. Table (1) gives descriptive statistics for all of our variables (Cockburn and Henderson (1994; 1998) provide more detailed descriptions of each of these data sources).

The Measurement of "Pro-publication" Incentives

The dependent variable in our regressions is a measure of the intensity with which a firm provides "pro-publication" incentives to its research workers. Prior research on the effects of adoption of science-driven drug discovery have measured these pro-publication incentives in a number of ways, from author-defined measures based on detailed interview transcripts (as in our own work

[13]The firms are: Abbott, Bristol-Myers Squibb, Burroughs-Welcome, Ciba-Geigy, Glaxo, Fujisawa, Hoechst, Hoffman La-Roche, Lilly, Merck, Pfizer, Sandoz, Searle/Monsanto, SmithKline Beecham, Takeda, and Upjohn

(Henderson and Cockburn, 1994),[14] to "counts" of the number of papers produced by a firm (Gambardella, 1995) to the number of "stars" associated with a firm (Zucker, Darby, and Brewer, 1998).

In this paper, we introduce a new measure of this practice which we believe captures an important element of the practice which has not been fully incorporated into prior work. Specifically, we base our measure on the extent to which a firm's innovative researchers (i.e., those who patent) also actively publish in the scientific literature. This measure, PUBFRAC, is equal to the share of researchers who are listed on a firm's patents in a given year who publish in the scientific literature within two years of the patent application date. By explicitly tying publication and patenting together, this measure incorporates the degree to which a firm is encouraging those researchers who are directly involved in the firm's drug discovery process to participate in the public scientific literature. In addition, being measured as a share rather than an absolute number of papers or authors, this measure captures the *propensity* to publish, independent of the scale of the firm, either in terms of sales or number of employed scientists.

Several issues arise in regard to the construction and calculation of this variable. First, all of the data are drawn from public and widely available sources. For each firm in the sample, we first identified all papers (a) which were published between 1980 and 1994 in journals indexed by the *Science Citation Index* and (b) in which the name of the firm, or one of its subsidiaries appears in at least one of the authors' addresses. Of course, this allows us to use a measure of either the number of papers or distinct authors associated with a firm in a given year.[15] But while publication counts or

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[14] In Henderson and Cockburn (1994), we focused on whether a scientist's standing in the public rank hierarchy was used as a factor in promotion decisions. This variable was derived from detailed qualitative interviews conducted within ten major pharmaceutical firms. While this has the virtue of being a direct measure of a core aspect of the practice of interest, it suffers from two important limitations. First, being derived from qualitative interviews conducted by a single researcher, it is difficult to rebut questions about its reliability and replicability. Second, the variable's coverage is limited to a smaller number of firms and often over a shorter period of time and so limits limit its use relative to the broader and longer panel used here.

[15] As prior research has established, pharmaceutical companies publish heavily, with annual counts of papers comparable to, and sometimes exceeding, the output of similarly sized universities and research

authors are certainly correlated with the firm's commitment to science-driven drug discovery, they are also structurally related to the scale of the firm's research activities, and so may also be measuring (a) simple technological success (the discovery of interesting compounds allows for the generation of interesting papers) or (b) the activities of "star"scientists who may be associated with the firm in terms of, say, participation on their scientific board, but may not be directly involved in the firm's R&D organization. While both of these issues are interesting in their own right, we focus here on the coincidence of individual researcher participation in science-oriented publication and market-oriented patenting; our qualitative evidence suggests that this type of "multi-tasking" is central to the phenomena of science-oriented drug discovery. Simply put , the adoption of science-oriented drug discovery results in the *joint* appearance of researchers as *authors of papers* and *inventors of drugs*.[16]

Constructing PUBFRAC was, however, far from straightforward: we had to attempt to match the names of many thousands of individuals across two different datasets and consistently apply rules for ambiguous cases.[17] As a propensity measure, PUBFRAC ranges between zero and one, and its average is equal to 0.63 for the sample. At the beginning of the sample period it ranged between 0.23 and 0.76 across firms. By the end of the sample period the mean was substantially higher (see Figure 2) and the range across firms was much smaller.

Explanatory Variables

Our explanatory variables for the regressions in Tables (2) through (5) are: TIME, which is a

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institutes (Koenig, 1982; Hicks, 1995). Publication counts are clearly an important indicator of both research activity, and have been previously interpreted as capturing investments in "basic science" (Gambardella 1995).

[16]See Cockburn, Henderson, and Stern (1998) for a fuller discussion of the provision of "balanced," complementary incentives for both of these activities.

[17]Much of this matching was accomplished straightforwardly by standard database software, but a number of difficulties did induce some measurement error into the process. These included typographical errors in the source data, and differences across papers by the same author in the use of initials, surnames and given names; extensive hand-coding was necessary to complete the task. A consistent matching procedure was applied to all firms, and so we are reasonably confident that bias in the measurement of PUBFRAC is limited to differences across firms in the severity of these problems.

time trend set to zero in the year preceding the sample period; the initial value of the dependent variable in the year preceding the sample period; and contemporaneous values of the three sets of variables that intended to capture the observable sources of heterogeneity in adoption rates discussed above: technology, market position, and organizational design; plus interactions of all of these with TIME.

Technology base and knowledge capital

To capture differences in firms' technological capabilities (in the sense of accumulated knowledge capital in different therapeutic areas) we use measures constructed from data on their international patenting activity. These are derived from Derwent Inc's *World Patent Index,* a database which organizes information on patent filings in many countries into "patent families" made up of all the various national patents corresponding to a single invention. It also contains a unique proprietary set of "manual codes" applied to each patent family which can be used to assign patents to distinct therapeutic areas.[18]

As highlighted by a large body of prior work (see Lanjouw and Schankerman (1999) for a review), patents differ substantially in terms of their economic importance and so it is important to control for quality when attempting to construct a measure of the firm's knowledge stock. While various approaches are possible to address this issue (from weighting each patent according to their citation count to more subtle measures which include measures of the "scope" of a patent's importance in terms of its citations), we impose a simple but consistent criteria: we only count those patents which are granted in two out of the three major world markets: Japan, the US and Europe. After calculating an annual count of "important" patents by therapeutic area and priority date back to 1965, we then calculate a "knowledge stock" for each therapeutic class using the standard declining balance method, assuming a 20% depreciation rate.

We implement this procedure for all therapeutic areas and then calculate relative knowledge stock

[18] The US Patent Office, for example, classifies pharmaceutical patents largely on the basis of chemical structure: a classification that contains very little information about diseases or therapeutic classes. The Derwent manual codes are assigned by specialists in the field who classify each patent on the basis of its potential therapeutic action

shares for three therapeutic areas highlighted in the qualitative research: cardiovascular therapies, anti-infectives, and oncology.

There is substantial variation in these variables across therapeutic classes and across firms, reflecting very significant differences in firms' technology focus, and in the fecundity of research in different areas. The share of cardiovasculars in firms' stock of important patents ranges across firms from 3-18%, while anti-infectives vary from 7- 45%, and oncology ranges from 0-6%.

Product Market Position

We attempt to measure differences in market position by constructing measures of each firm's share of the US market for each therapeutic class. We construct the total size of the market by therapeutic class by summing sales data from 27 firms that between them comprise a very large proportion of the US market, since data difficulties prevented us from computing total US sales by therapeutic class. While this results in somewhat inflated values for market shares, we have no reason to believe that the size of the left out portion varies significantly over time. Significant differences among firms in their product market position in different therapeutic classes appear: total sales shares range from 0-24% in cardiovasculars, from 0-36% in anti-infectives and from 0-63% in oncology.

Organizational Effects

Our final set of explanatory variables are those intended to capture the effect of internal organization factors. We construct these from information on the distribution of sales across therapeutic classes within the firm. Our reasoning is that those firms whose sales portfolios are dominated by therapeutic classes that are least likely to gain from the new techniques will be relatively slow to adopt the new techniques, while those firms whose sales portfolio is dominated by products in "high return" therapeutic classes will be relatively faster. As before, there are quite marked differences among firms on these dimensions. The share of cardiovasculars in firm sales ranges from 0-72%, anti-infectives from 0-58% and oncology from 0-12%.

Note that both the "share of total sales" and "share of firm sales" variables are derived from US wholesale sales data obtained from publications of IMS America. The pharmaceutical market is a

global one, and while the US represents roughly 50% of the world market, nearly every firm in our sample has significant international sales. To the extent that the distribution of sales across therapeutic classes is not uniform across different countries, our market share measures will be somewhat distorted.

VII. Regression Results

We now turn to our evaluation of the estimating equation specified at the end of Section V, which provides essentially a reduced-form model of the "diffusion" of PUBFRAC. We begin by evaluating the degree of state dependence. Table (2) reports regression results which establish the dominant feature of these data: relatively slow diffusion of the organizational practice measured by PUBFRAC, with a powerful "convergence" effect. In columns (1) and (2) the only explanatory variable is TIME, whose positive and significant coefficient confirms that on average PUBFRAC increases over time for the firms in our sample. Recall that the functional form imposes the "standard" S-shaped diffusion curve, bounding PUBFRAC between one and zero, with the coefficient on TIME giving the rate parameter of the diffusion process. The coefficient of about 0.1 implies that it would take about 40 years for the average firm to move from the lowest level of PUBFRAC observed in the data to the highest. This parameter estimate is biased downwards since we fail to control for the substantial cross sectional variation in the initial level of PUBFRAC. Much faster within firm diffusion is apparent in the data, but controlling for firm effects in the intercept (the "origin" parameter of the classic diffusion model) in the fixed effects regression in column (2) affects the estimated rate parameter very little.

The principal source of inter-firm variability in diffusion rates lies elsewhere in these data, as can be seen in the results in column (3) we present our main baseline specification. Here, initial conditions in the form of the initial level of PUBFRAC (and its interaction with TIME) are added to the equation. In this regression we obtain an almost three times larger "rate" coefficient, much more accurately reflecting the within-firm diffusion curves which we see in the data. Furthermore, the very strong results on the initial conditions variables imply a powerful "state dependence plus convergence" effect. The positive and significant coefficient on $PUBFRAC_0$ combined with the negative and significant coefficient on $PUBFRAC_0$*TIME indicate that those firms which began the sample period with a high level of PUBFRAC stayed high, and moved relatively slowly towards the upper bound, while those that began with a low level of PUBFRAC moved more quickly to the upper bound. The magnitude of the coefficients implies that convergence takes more than 10 years, a rather large number. These parameter estimates are very stable (and quite precisely estimated) across all of the regressions which we present here. We find them quite compelling evidence for the presence of important state dependence in the

adoption of science-oriented techniques of drug discovery.

Moving to the question of the impact of environmental heterogeneity, Tables (3), (4), and (5) present results from estimating models in which our measures of technology, market position, and organization effects are included as additional regressors. Table (3) presents results where we focus our attention on cardiovascular therapies. We find a number of statistically significant coefficients, broadly consistent with our qualitative understanding of the adoption process. These findings suggest that some of inter-firm variability in diffusion rates is attributable to these observable aspects of firm heterogeneity, though there is only a very small increase in R^2 over the baseline state-dependence-plus-convergence model.

Taken at face value, the estimates imply the following. First, market position matters, in the sense that firms which had higher shares of the cardiovascular market began the sample period with a somewhat lower level of PUBFRAC than average, but caught up very rapidly. Second, power and attention within the firm matters, in the sense that firms in which cardiovascular products were a larger share fraction of sales had higher levels of PUBFRAC. Third, technological capabilities appear not to matter, in the sense that the fraction of cardiovasculars in firms' patent portfolios has no systematic effect on PUBFRAC. In general these results are obtained whether we look at the effects one-by-one or jointly, although note that technological competence becomes significant but with the "wrong" sign when all three effects are included in a single regression.[19]

In Tables (4) and (5) we extend the model by including information on more therapeutic classes. Table (4) includes these variables in levels and Table (5) includes levels plus their interactions with time. In both tables we obtain significant coefficients on a number of the variables, with the flavor

[19] As well, as we mentioned earlier, these data constructs are, statistically at least, rather uninformative about differences in initial conditions. Appendix A presents results where we use only the pre-sample initial values of the variables as regressors. Unlike the initial value of PUBFRAC, we get very imprecisely estimated coefficients everywhere except in the almost fully saturated model of A-4 where the regression begins to "blow up." Appendix B reports results from additional robustness testing, using fixed effects (thus absorbing all sources of initial conditions) and panel AR1 correction (thus controlling for correlations among firms over time above and beyond state dependence). Interestingly, the significance of the results increases, but given the small sample size we hesitate to make any more of these results than of those obtained by OLS.

of the cardiovascular results in Table (3) largely unchanged. However the only result which is consistently significant across all of our specifications is that for cardiovasculars' share of firm sales: this is always positively correlated with probability of adoption. For anti-infectives and oncology drugs not all of the estimates conform with our priors, and neither are they particularly stable across different specifications. While share of firm sales in oncology is positively associated with adoption, as some of our qualitative interviews suggested, share of patent stock in oncology is negatively associated with adoption in several regressions, which is puzzling. Similarly anti-infectives share -- whether of market, of firm sales or of patent shares -- is never negatively associated with adoption, as our qualitative work predicted, and is in several specifications positively associated with adoption. Much of this can be attributed to problems with multicollinearity, outliers, and dwindling degrees of freedom, but these weaker results may also reflect our lower degree of confidence in our qualitative analysis of the returns to Science in these areas. As in Table (3), perhaps the principal conclusion to be drawn is that observable aspects of firms' technological capabilities, market position, and internal organization do have some ability to account for variation in adoptions rates for PUBFRAC: in all of the regressions in Tables (4) and (5) we cannot reject a joint test for their significance. But as is clear from the detail of the estimates, these effects are much less statistically salient than the state-dependence-plus-convergence result; the only result of which we are reasonably confident is that share of firm sales in *cardiovasculars* -- the principal therapeutic category predicted to be important from our qualitative research -- was indeed positively associated with adoption.

VIII. Discussion and Conclusions

This paper was motivated by a simple empirical puzzle: if organizational practices (such as science-based drug discovery) are so productive, why are they not adopted in equal intensity by all firms at the same time? Our empirical investigation suggests a resolution: while some portion of the heterogeneity in adoption behavior can be linked to observable characteristics of firms and their environment, the lion's share of explained variation reflects the long-lasting influence of difficult to observe, firm-specific, historical commitments.

This perspective has several important implications. On the one hand, our findings do indeed

confirm that adoption seems to be associated with the internal and external environment of the firm. Specifically, there is (a) evidence for the importance of the distribution of power and attention *within* the organization, (b) intriguing but somewhat puzzling evidence about the role of markets in which the firm has a leading position and (c) little statistical evidence for the importance of the firm's knowledge capital stock. More precisely, our results suggest an association between the share of a firm's sales in cardiovasculars – the therapeutic category most closely associated with the benefits to science-oriented discovery – and the level of adoption. This rather straightforward result stands in contrast to the finding that firms with large shares of the cardiovascular market *increased* their adoption propensity over time; while this evidence can be construed as demonstrating a role for market-based incentive effects (in the spirit of Fudenberg and Tirole (1985)), such an interpretation would depend on extending the theory to explain why the adoption propensity started at a lower level than the average in the population and only increased to a positive level over time.

More surprisingly, perhaps, we find little evidence for the importance of technological experience in adopting science-driven drug discovery. While nearly every firm that we interviewed stressed the importance of "technological position" to the adoption decision, we can find no evidence for this effect in our data. Of course, it is possible that our respondents were putting a politically acceptable, "functionalist" face on a result that is much more robust -- namely that those firms in which a relatively large share of sales was in cardiovasculars adopted the new techniques more rapidly. Overall, these findings highlight the potential empirical importance of emerging theories about the consequences of power, attention, and decision-making authority within the firm (Ocasio, 1995; Rotemberg and Saloner, 1995).

While empirically evaluating different theories is important, it is also true that by far the largest source of systematic differences among firms is in initial conditions. Both the qualitative and quantitative approach suggest that early adoptors' motivations seem to have been only indirectly related to the large productivity gains eventually experienced by these firms. In this regard, interviewees strenuously highlighted, among other issues, geographical location, corporate culture, attitudes on the part of managers towards participation in science both for its societal benefits and as a recruiting device, and the vision of particularly powerful leaders within the organization. While some of these sources of state

dependence can usefully form the basis for empirical work in this area (Zucker, Darby and Brewer (1998)), our evaluation suggests that such an exercise should be careful not to focus on too narrow a set of potential alternatives. In our qualitative work, our respondents offered up a wealth of alternative explanations: without more specific guidance from theory, empirical work should consider the full range of these alternatives when attempting to uncover the sources of state dependence. In this spirit, future research might focus on the construction of a "horse race" among competing theories of initial conditions.

Evaluating the broader implications of this study for research on the impact of organizational heterogeneity on competitive dynamics depends, in part, on the "taste" of the researcher. To the extent that the goal of empirical work is to distinguish different formal theories from each other, then our results inform the current empirical debate about the relative importance of internal versus external drivers of organizational change. But, to the extent that the goal of quantitative work is to characterize the empirical distribution of the rate of adoption and the potential evolution of industry structure in response to the opportunities afforded by novel organizational practices, then our results inform a slightly older debate, about what *types* of theories are useful for modeling heterogeneity in firm behavior (Nelson and Winter, 1982).

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Table 1: Means and Standard Deviations

Variable	N	Mean	Standard Deviation
Dependent Variables			
$PubFrac_{i,t}$	153	0.647	0.143
$Ln(PubFrac_{i,t} / 1 ! PubFrac_{i,t})$	153	0.665	0.707
State Dependence			
$PubFrac_{i,0}$	16	0.561	0.135
Observed Heterogeneity: Independent Variables			
MARKETS: MARKET SHARE IN THERAPEUTIC CLASS			
$Cardiovascular_{i,t}$	153	0.053	0.087
$Anti\text{-}Infectives_{i,t}$	153	0.054	0.078
$Oncology_{i,t}$	153	0.033	0.100
ORGANIZATIONS: WITHIN-FIRM MARKET SHARE IN THERAPEUTIC CLASS			
$Cardiovascular_{i,t}$	153	0.185	0.199
$Anti\text{-}Infectives_{i,t}$	153	0.168	0.148
$Oncology_{i,t}$	153	0.014	0.045
TECHNOLOGY: WITHIN-FIRM PATENT SHARE IN THERAPEUTIC CLASS			
$Cardiovascular_{i,t}$	153	0.124	0.044
$Anti\text{-}Infectives_{i,t}$	153	0.157	0.073
$Oncology_{i,t}$	153	0.035	0.028

Table 2: Time and State Dependence

Dependent variable: $Ln(PubFrac_{i,t} / 1 ! PubFrac_{i,t})$	(4-1)	(4-2)	(4-3)
TIME	**0.106 (0.017)**	**0.117 (0.014)**	**0.271 (0.060)**
$PubFrac_{i,0}$			**3.659 (0.700)**
$PubFrac_{i,0}$ v TIME			**- 0.287 (0.108)**
CONSTANT	0.801 (0.105)	0.023 (0.088)	**- 1.982 (0.400)**
Fixed Effects	No	Yes	No
Adjusted R-squared	0.206	0.480	0.378
N	153	153	153

Notes to the Regression Tables:

Standard errors are in parentheses.
All regressions also include a constant.
Coefficients in **bold** are significant at better than the 10% level.

Table 3: Time, State Dependence, Contemporaneous Heterogeneity, along with Time Interaction Effects (cardiovascular drugs only)

Dependent variable: $\text{Ln}(\text{PubFrac}_{i,t} / 1 - \text{PubFrac}_{i,t})$	(4-1)	(4-2)	(4-3)	(4-4)
MARKETS: MARKET SHARE IN THERAPEUTIC CLASS				
$\text{Cardiovascular}_{i,t}$	**- 2.043 (1.206)**			**- 4.397 (1.410)**
$\text{Cardiovascular}_{i,t} \times \text{TIME}$	**0.412 (0.165)**			**0.539 (0.172)**
ORGANIZATIONS: WITHIN-FIRM MARKET SHARE IN THERAPEUTIC CLASS				
$\text{Cardiovascular}_{i,t}$		**0.603 (0.248)**		**1.041 (0.379)**
$\text{Cardiovascular}_{i,t} \times \text{TIME}$		- 0.008 (0.035)		0.014 (0.035)
TECHNOLOGY: WITHIN-FIRM PATENT SHARE IN THERAPEUTIC CLASS				
$\text{Cardiovascular}_{i,t}$			1.329 (1.168)	1.271 (1.296)
$\text{Cardiovascular}_{i,t} \times \text{TIME}$			- 0.238 (0.192)	**- 0.487 (0.198)**
TIME & BASELINE VARIABLES				
TIME	**0.298 (0.060)**	**0.270 (0.061)**	**0.284 (0.062)**	**0.297 (0.062)**
$\text{PubFrac}_{i,0}$	**4.002 (0.700)**	**3.952 (0.701)**	**3.562 (0.707)**	**4.467 (0.709)**
$\text{PubFrac}_{i,0} \times \text{TIME}$	**- 0.385 (0.112)**	**- 0.287 (0.107)**	**- 0.260 (0.110)**	**- 0.303 (0.112)**
CONSTANT	**- 2.044 (0.394)**	**- 2.241 (0.409)**	**- 2.107 (0.414)**	**- 2.530 (0.408)**
Adj. R-squared	0.399	0.393	0.377	0.436
# of Observations	153	153	153	153

Notes to the Regression Tables:

Standard errors are in parentheses.
All regressions also include a constant.
Coefficients in **bold** are significant at better than the 10% level.

Table 4: Time, State Dependence, and Contemporaneous Heterogeneity

Dependent variable: $\text{Ln}(\text{PubFrac}_{i,t} / 1 ! \text{PubFrac}_{i,t})$	(5-1)	(5-2)	(5-3)	(5-4)
MARKETS: MARKET SHARE IN THERAPEUTIC CLASS				
$\text{Cardiovascular}_{i,t}$	0.867 (0.559)			- 1.061 (0.898)
$\text{Anti-Infectives}_{i,t}$	**1.447** **(0.616)**			**2.635** **(0.837)**
$\text{Oncology}_{i,t}$	- 0.073 (0.489)			**- 2.082** **(1.073)**
ORGANIZATIONS: WITHIN-FIRM MARKET SHARE IN THERAPEUTIC CLASS				
$\text{Cardiovascular}_{i,t}$		**0.773** **(0.248)**		**1.175** **(0.394)**
$\text{Anti-Infectives}_{i,t}$		**0.689** **(0.332)**		- 0.260 (0.504)
$\text{Oncology}_{i,t}$		1.014 (1.026)		**8.118** **(2.590)**
TECHNOLOGY: WITHIN-FIRM PATENT SHARE IN THERAPEUTIC CLASS				
$\text{Cardiovascular}_{i,t}$			0.612 (1.201)	- 1.569 (1.290)
$\text{Anti-Infectives}_{i,t}$			0.373 (0.760)	- 0.152 (0.780)
$\text{Oncology}_{i,t}$			-1.041 (1.879)	**- 7.227** **(2.929)**
TIME & STATE DEPENDENCE				
TIME	**0.301** **(0.061)**	**0.270** **(0.059)**	**0.274** **(0.062)**	**0.264** **(0.061)**
$\text{PubFrac}_{i,0}$	**3.738** **(0.705)**	**3.733** **(0.698)**	**3.598** **(0.716)**	**4.166** **(0.743)**
$\text{PubFrac}_{i,0}$ x TIME	**- 0.349** **(0.110)**	**- 0.284** **(0.105)**	**- 0.283** **(0.110)**	**- 0.266** **(0.111)**
CONSTANT	**- 2.125** **(0.401)**	**- 2.300** **(0.405)**	**- 2.079** **(0.446)**	**- 2.121** **(0.448)**
Adj. R-squared	0.394	0.413	0.368	0.451
# of Observations	153	153	153	153

Notes to the Regression Tables:

Standard errors are in parentheses. All regressions also include a constant.

Coefficients in **bold** are significant at better than the 10% level.

Table 5: Time, State Dependence, Contemporaneous Heterogeneity, along with Time Interaction Effects

Dependent variable: $\text{Ln}(\text{PubFrac}_{i,t} / 1 - \text{PubFrac}_{i,t})$	(6-1)	(6-2)	(6-3)	(6-4)
MARKETS: MARKET SHARE IN THERAPEUTIC CLASS				
$\text{Cardiovascular}_{i,t}$	**- 2.317 (1.225)**			**- 4.921 (1.404)**
$\text{Anti-Infectives}_{i,t}$	- 1.023 (1.270)			0.623 (1.629)
$\text{Oncology}_{i,t}$	- 1.342 (0.867)			0.101 (1.447)
$\text{Cardiovascular}_{i,t}$ x TIME	**0.490 (0.166)**			**0.510 (0.172)**
$\text{Anti-Infectives}_{i,t}$ x TIME	**0.369 (0.199)**			**0.462 (0.257)**
$\text{Oncology}_{i,t}$ x TIME	**0.440 (0.252)**			0.009 (0.568)
ORGANIZATIONS: WITHIN-FIRM MARKET SHARE IN THERAPEUTIC CLASS				
$\text{Cardiovascular}_{i,t}$		**0.824 (0.256)**		1.267 (0.389)
$\text{Anti-Infectives}_{i,t}$		0.435 (0.414)		- 0.551 (0.599)
$\text{Oncology}_{i,t}$		- 1.999 (2.799)		- 8.030 (6.044)
$\text{Cardiovascular}_{i,t}$ x TIME		0.032 (0.043)		- 0.018 (0.045)
$\text{Anti-Infectives}_{i,t}$ x TIME		0.062 (0.069)		0.016 (0.085)
$\text{Oncology}_{i,t}$ x TIME		1.498 (1.297)		**5.484 (2.232)**
TECHNOLOGY: WITHIN-FIRM PATENT SHARE IN THERAPEUTIC CLASS				
$\text{Cardiovascular}_{i,t}$			0.718 (1.383)	- 0.036 (1.466)
$\text{Anti-Infectives}_{i,t}$			- 0.485 (0.829)	- 0.323 (0.857)
$\text{Oncology}_{i,t}$			1.143 (2.449)	0.520 (4.023)

Cardiovascular$_{i,t}$ x TIME			- 0.060 (0.270)	- 0.078 (0.280)
Anti-Infectives$_{i,t}$ x TIME			**0.238** **(0.086)**	0.141 (0.097)
Oncology$_{i,t}$ x TIME			- 0.580 (0.705)	**- 3.411** **(1.034)**

TIME & BASELINE VARIABLES				
TIME	**0.323** **(0.059)**	**0.262** **(0.062)**	**0.232** **(0.073)**	**0.337** **(0.081)**
PubFrac$_{i,0}$	**4.374** **(0.700)**	**3.924** **(0.706)**	**3.669** **(0.703)**	**5.105** **(0.732)**
PubFrac$_{i,0}$ x TIME	**- 0.497** **(0.113)**	**- 0.312** **(0.108)**	**- 0.287** **(0.109)**	**- 0.492** **(0.118)**
CONSTANT	**- 2.129** **(0.387)**	**- 2.344** **(0.407)**	**- 2.009** **(0.457)**	**- 2.556** **(0.482)**
Adj. R-squared	0.439	0.414	0.395	0.513
# of Observations	153	153	153	153

Notes to the Regression Tables:

Standard errors are in parentheses.
All regressions also include a constant.
Coefficients in **bold** are significant at better than the 10% level.

Appendix A: Time, State Dependence, Initial Heterogeneity, along with Time Interaction Effects

Dependent variable: $Ln(PubFrac_{i,t} / 1 ! PubFrac_{i,t})$	(A-1)	(A-2)	(A-3)	(A-4)
MARKETS: MARKET SHARE IN THERAPEUTIC CLASS				
$Cardiovascular_{i,0}$	0.416 (1.321)			0.904 (1.786)
$Anti\text{-}Infectives_{i,0}$	0.643 (1.225)			- 4.132 (5.547)
$Oncology_{i,0}$	- 1.081 (0.871)			-7.099 (10.813)
$Cardiovascular_{i,0} \times TIME$	0.148 (0.202)			0.061 (0.270)
$Anti\text{-}Infectives_{i,0} \times TIME$	- 0.004 (0.201)			1.089 (1.020)
$Oncology_{i,0} \times TIME$	0.354 (0.215)			1.732 (1.965)
ORGANIZATIONS: WITHIN-FIRM MARKET SHARE IN THERAPEUTIC CLASS				
$Cardiovascular_{i,0}$		0.676 (0.588)		1.155 (0.705)
$Anti\text{-}Infectives_{i,0}$		0.871 (0.669)		2.935 (1.835)
$Oncology_{i,0}$		- 5.041 (4.347)		15.157 (53.061)
$Cardiovascular_{i,0} \times TIME$		- 0.033 (0.088)		**- 0.256** **(0.108)**
$Anti\text{-}Infectives_{i,0} \times TIME$		- 0.057 (0.110)		**- 0.638** **(0.357)**
$Oncology_{i,0} \times TIME$		1.663 (1.067)		- 2.568 (9.590)
TECHNOLOGY: WITHIN-FIRM PATENT SHARE IN THERAPEUTIC CLASS				
$Cardiovascular_{i,0}$			- 0.237 (2.726)	- 1.489 (2.922)
$Anti\text{-}Infectives_{i,0}$			0.410 (1.047)	- 0.723 (1.134)
$Oncology_{i,0}$			- 0.065 (6.096)	**28.431** **(11.851)**
$Cardiovascular_{i,0} \times TIME$			0.028 (0.459)	0.267 (0.479)

Anti-Infectives$_{i,0}$ **v** TIME			0.166 (0.163)	**0.378** **(0.181)**
Oncology$_{i,0}$ **v** TIME			- 0.459 (1.041)	**- 8.032** **(1.827)**

TIME & BASELINE VARIABLES				
TIME	**0.268** **(0.063)**	**0.291** **(0.067)**	**0.248** **(0.086)**	**0.420** **(0.097)**
PubFrac$_{i,0}$	**3.786** **(0.708)**	**3.696** **(0.723)**	**3.715** **(0.725)**	**4.151** **(0.709)**
PubFrac$_{i,0}$ **v** TIME	**- 0.320** **(0.109)**	**- 0.309** **(0.111)**	**- 0.302** **(0.112)**	**- 0.431** **(0.110)**
CONSTANT	**- 2.072** **(0.421)**	**- 2.240** **(0.444)**	**- 2.066** **(0.538)**	**- 2.774** **(0.613)**
Adj. R-squared	0.395	0.382	0.392	0.507
# of Observations	153	153	153	153

Notes to the Regression Tables:

Standard errors are in parentheses.
All regressions also include a constant.
Coefficients in **bold** are significant at better than the 10% level.

Appendix B: Time, State Dependence, and Contemporaneous Heterogeneity

Dependent variable: $\text{Ln}(\text{PubFrac}_{i,t} / 1 - \text{PubFrac}_{i,t})$	(B-1) Fixed Effects	(B-2) AR(1)
MARKETS: MARKET SHARE IN THERAPEUTIC CLASS		
$\text{Cardiovascular}_{i,t}$	**- 10.501 (2.458)**	**- 5.190 (1.639)**
$\text{Anti-Infectives}_{i,t}$	- 10.808 (4.311)	0.908 (1.884)
$\text{Oncology}_{i,t}$	6.481 (4.540)	- 0.151 (1.479)
$\text{Cardiovascular}_{i,t} \times \text{TIME}$	**0.579 (0.204)**	**0.548 (0.201)**
$\text{Anti-Infectives}_{i,t} \times \text{TIME}$	**1.570 (0.478)**	0.356 (0.290)
$\text{Oncology}_{i,t} \times \text{TIME}$	**- 1.933 (1.308)**	- 0.009 (0.503)
ORGANIZATIONS: WITHIN-FIRM MARKET SHARE IN THERAPEUTIC CLASS		
$\text{Cardiovascular}_{i,t}$	1.083 (0.536)	**1.176 (0.450)**
$\text{Anti-Infectives}_{i,t}$	0.835 (0.751)	- 0.665 (0.668)
$\text{Oncology}_{i,t}$	9.341 (12.586)	- 7.405 (6.029)
$\text{Cardiovascular}_{i,t} \times \text{TIME}$	- 0.178 (0.087)	- 0.016 (0.055)
$\text{Anti-Infectives}_{i,t} \times \text{TIME}$	- 0.680 (0.219)	0.026 (0.101)
$\text{Oncology}_{i,t} \times \text{TIME}$	11.347 (3.995)	**5.400 (2.243)**
TECHNOLOGY: WITHIN-FIRM PATENT SHARE IN THERAPEUTIC CLASS		
$\text{Cardiovascular}_{i,t}$	- 3.242 (2.624)	0.163 (1.732)
$\text{Anti-Infectives}_{i,t}$	- 6.821 (2.276)	- 0.320 (1.028)
$\text{Oncology}_{i,t}$	- 5.014 (5.826)	1.323 (4.686)
$\text{Cardiovascular}_{i,t} \times \text{TIME}$	- 1.203 (0.536)	- 0.132 (0.337)

Anti-Infectives$_{i,t}$ **v** TIME	- 0.461 (0.307)	0.163 (0.118)
Oncology$_{i,t}$ **v** TIME	- 3.793 (1.442)	**- 3.407** **(1.197)**

TIME & BASELINE VARIABLES		
TIME	**0.363** **(0.090)**	**0.348** **(0.096)**
PubFrac$_{i,0}$		**5.141** **(0.883)**
PubFrac$_{i,0}$ **v** TIME		**- 0.499** **(0.140)**
CONSTANT	**2.311** **(0.610)**	**- 2.608** **(0.575)**
Adj. R-squared	0.607	
# of Observations	153	153

Notes to the Regression Tables:

Standard errors are in parentheses.
All regressions also include a constant.
Coefficients in **bold** are significant at better than the 10% level.

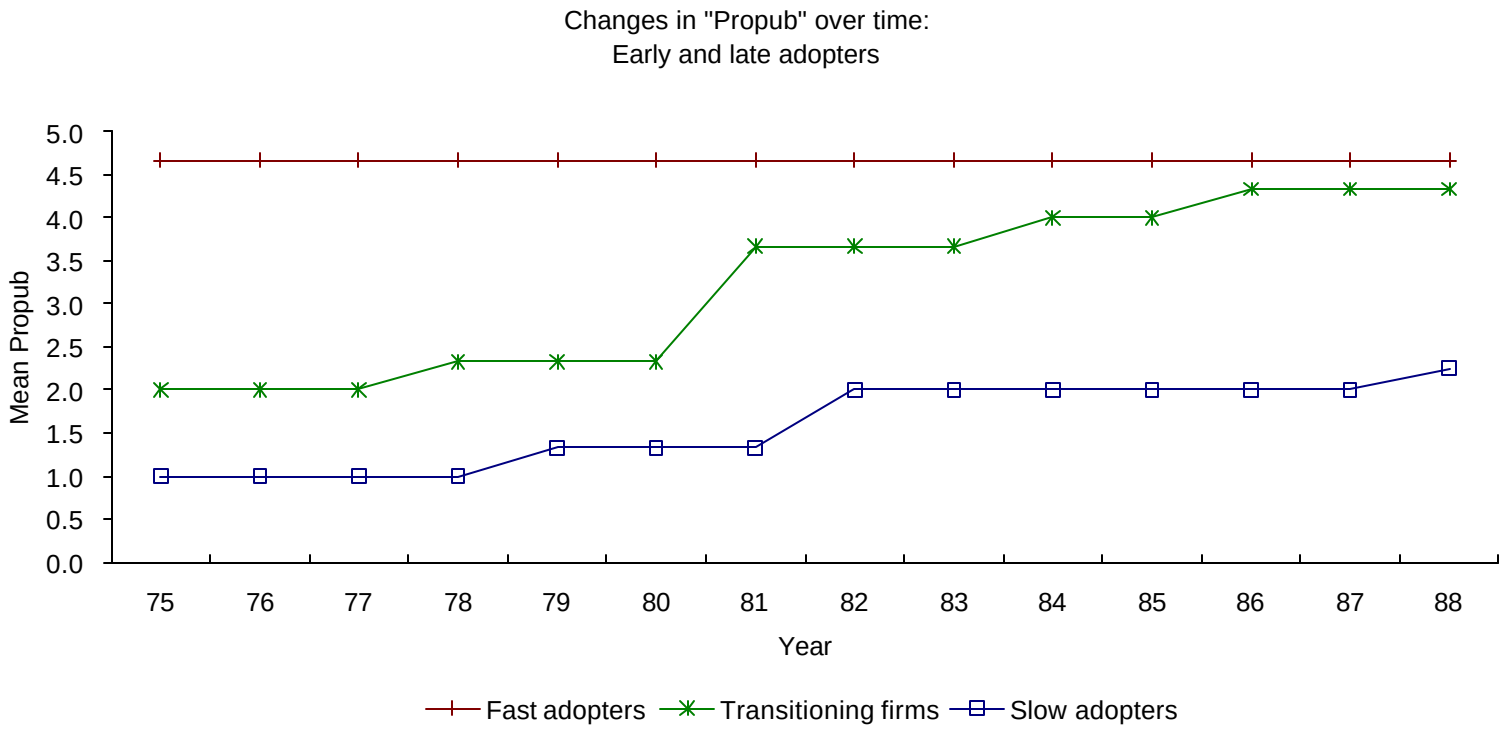
Changes in "Propub" over time:
Early and late adopters
Mean Propub
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
75
76
77
78
79
80
81
82
83
84
85
86
87
88
Year
Fast adopters
Transitioning firms
Slow adopters

FIGURE 2
PUBFRAC OVER TIME