Competition and Innovation: A Structural Model using the Pharmaceutical Market.

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Abstract

How do pharmaceutical companies react to their competitors' R&D decisions? How do firms' experiences and their characteristics affect their profitability from innovations? Answering these questions can have important policy implications for antitrust or for designing incentives to promote pharmaceutical innovations. I built a structural model for pharmaceutical innovation and used a data set of clinical trials to estimate this model. I show that the net effect of a firm's innovation on their rivals' decision to innovate in the same therapeutic area is negative. I also show that firms' past experiences in innovating in a therapeutic area have important and positive effects on their profits, while other observable characteristics do not have a significant effect.

1 Introduction

Understanding the determinants of innovation is one of the most important, enduring problems in economics. The "perennial gale of Creative Destruction" idealized by Schumpeter (1976) was driven by new consumer goods and new technologies: but what are the conditions that lead to such innovation? For Schumpeter, the opportunity to capture monopoly profits, joined with large firms' financial capacity to invest in research, were the keys. Arrow (1962) argued, in contrast, that it is competition that generates stronger incentives to innovate, because competitive firms need not be concerned about cannibalizing current profits. Arrow (1962) pioneered theoretical models that analyzed product and price competition when there is R&D collaboration between firms. These early models, which were later elaborated by Spence (1986), provide the key insight that incentives to invest in R&D are reduced by the presence of technology spillovers. But strategic interaction among firms within an industry includes both a technology spillover effect and a product rivalry effect. While technology (or knowledge) spillovers can increase the productivity of other firms that operate in similar technology areas, innovation by product market rivals has a negative effect on a firm's value due to the incentive effect of greater competition in the product market. If the former dominates the latter effect, then the net effect of innovation on other firms will be positive (Jaffe, 1986). This selective tour through the economic history of innovation highlights several key questions addressed by this paper. What is the net effect of product market competition on innovation? Can we say whether the technology spillover effect dominates the

product rivalry effect in specific circumstances? How important are firms' characteristics for their profitability from innovation? This paper attempts to answer these questions in the context of the pharmaceutical industry.

The pharmaceutical industry offers a particularly attractive observatory for examining the economics of innovation for several reasons. First, this industry is a perennial high spender on research and development: R&D spending averages 17% of revenues (Investopedia, 2019). Second, within the industry there are many markets that are segmented, and large firms compete in varying subsets of those markets. Third, clinical trials represent a particularly meaningful measure of innovation. Clinical trials represent the majority of total R&D expenditures for pharmaceutical companies, and are an unavoidable part of getting a product approved and onto the market (DiMasi et al., 2016). Moreover, trials are disease-specific and corporate sponsorship is public. Thus, not only is innovation in the pharmaceutical industry of great intrinsic interest, but it also offers a set of features that makes it possible to characterize some of the interactions between innovative firms.

In this industry, most innovative products are protected by patents, but a patent does not create a monopoly. Competition between patented products arguably has a larger impact on firm's profitability that competition from generic manufacturers once patents are out of the way (Lichtenberg and Philipson, 2002). Thus, the product rivalry impact of competition in innovation is extremely important. On the other hand, there is a great deal of learning across firms. There are several mechanisms: first, there is a revolving door in scientists and executives across companies (LaMattina, 2017); sec-

ond, the companies themselves often learn from shared sources (Bignami and Mattsson, 2019); and third, the process of patenting reveals key information which can be used by rivals (Magazzini et al., 2009).

The main purpose of this paper is to estimate the *net* effect of product-market competition and knowledge spillovers on innovation in the pharmaceutical industry. However, assessing the net effect can be quite challenging: firms simultaneously decide how much to innovate, but their decisions affect each other. This is a concern for the identification of any model of innovation. The simultaneity problem can be resolved by different econometric methods. I chose to estimate a structural model which also allows the measurement of deep parameters. Therefore, the analytical approach of this paper can be extended to allow counterfactual experiments.

The results from this kind of structural model, which allows one to determine the net effect of a firm's innovation on other players in the market, can have important policy implications. For example, an estimate of the net effect of one firms' investment in innovation on others could help assess whether there is over-investment or under-investment in R&D. For such an assessment, we need to compare social and private rates of return to R&D. The conventional wisdom is that if product market rivalry effects dominate technology spillovers, then there is under-investment in R&D from a welfare perspective (Bloom et al., 2013). The estimated structural model in this paper can be used in future works to predict how mergers between firms will affect innovation; how changes in the cost of trials will affect innovation; and how changes in prices would affect investment in innovation.

I use a two-step method for identification and estimation of the model

in this paper. First, I estimate the conditional choice probability for the choices of each firm directly from the data. Second, I use the estimated choice probabilities to calculate expected marginal payoffs. and the actual marginal payoffs is identified and estimated by using exogenous variation in player-specific observable regressors that are excluded from competitors payoffs. I use the firms' history of innovation in each market as a variable that satisfies this exclusion restriction. In the model presented in this paper each player decides how many clinical trials to conduct for each disease. Their choice is a function of their experiences in a therapeutic area and the number of innovations by their rival firms. I limit this analysis to the top pharmaceutical companies in terms of the number of innovations.

The results from estimation of this model show that the negative competition effect dominates the positive spillover effect. This indicates that the net effect of a firm's innovation is negative on other firms' decision to innovate in the same market. I also show that firms' experiences in innovating for a disease is very important in determining profitability from future innovation. Additionally, the result indicates that other firms' characteristics have little effect on their payoffs from innovation. Furthermore, I perform several robustness checks and show the main results are true in a variety of settings.

The rest of the paper is organized as follows: Section 2 gives a brief description of the pharmaceutical industry and the process for drug development. It also details the data used for estimation of the model. Section 3 introduces a discrete choice model of incomplete information, which I will use to explain firms' decisions on innovation. Section 4 presents the identi-

fication argument for estimating this model. In Section 5, I show how this model can be estimated from suitable data. Section 6 presents the result of the estimation and several robustness checks using alternative specifications.

2 The Pharmaceutical Industry and the data

The innovative pharmaceutical industry is not only important to the economy, but intimately touches the lives of almost everyone in the world. The industry is complex and sophisticated, and operates in a highly regulated environment. The large pharmaceutical firms that are the subject of this paper engage in several core activities: they develop, manufacture and market new drugs. These activities combine both fierce competition and the exercise of monopoly power. The companies compete aggressively to advance new drugs to the market, but once approved, price competition is typically quite limited. The price sensitivity of patients is mitigated by the presence of insurance; and the physicians who prescribe drugs are obliged to prescribe the best drug for their patient's health, which does not normally involved too close a consideration of price. The key competitive advantage of a firm is therefore in having patented drugs that treat some patients better than any other therapy. This means that innovation is in many ways the main area of competition in the pharmaceutical industry.

Innovation, of course, is itself tremendously complex: launching a new drug into the market is both lengthy and very expensive. The process of

bringing a new drug to market typically involves multiple steps. Generally, basic science often done in universities elucidates interesting targets, for example a protein to be blocked. This prompts a search for possible molecules that may address the target. Once the bench science identifies feasible molecules, they may be tested in the lab and are eventually trialed in animals. These initial steps, often performed by a university spin-off or a small biotech, are not very expensive but are almost always unsuccessful. If the animal trials are successful, additional funding will be sought for further chemical work and to refine the drug. Then, following regulatory approval, Phase 1 tests for safety in healthy humans are performed. Phase 1 trials cost an average of about $25M per drug, and about 40% of drugs fail at this stage. All numbers on clinical trial costs are taken from (DiMasi et al., 2016).

If successful in Phase 1, the drug may be advanced to Phase 2, to see if it has the desired effects in patients with the disease or condition it is supposed to treat. Phase 2 is also an opportunity to refine the dosing of the medication. Phase 2 clinical trials are typically considerably more costly because it is necessary to find the right patients and to control carefully how the drug is used over a longer period of time. In many cases, there are multiple Phase 2 trials for a single drug. Phase 2 trials cost an average of about $57M per drug, and about 65% of drugs entering Phase 2 fail at this stage.

Successful drugs then may advance to Phase 3 trials, which tend to be longer and have a larger number of patients, to identify less common adverse effects. Usually the Phase 3 trials provide the main evidence required by regulators to permit the drug to be sold on the market. The price tag increases

again, averaging about $255M per drug, and about 39% of drugs entering Phase 3 fail at this stage.

Finally, the innovator submits the drug for regulatory approval. In the US, about 10% of drugs submitted are not approved, which means that there is only about an 11% rate of success for drugs starting Phase 1 to advance to regulatory approval. The timelines are quite long, with the average successful drug taking about 10 years to go from the start of Phase 1 to approval, and the overall costs very substantial. One widely used estimate places the cost per new drug at around $2.6B, after accounting for the costs of failures and the cost of capital (DiMasi et al., 2016). Most of this cost is attributable to the clinical trials.

Because Phase 2 and 3 clinical trials are so costly, small biotechs cannot usually obtain the financing to advance the drug to the point of approval, and instead aim to sell the compound or the entire company to a "big pharma" firm that has the deep pockets and expertise in capital allocation. Once a firm has an approved drug, that drug will effectively compete only in the market for a given disease. Not surprisingly, we see that firms often specialize to some extent in their fields of operation. For example, Roche has a focus on oncology, and Takeda focuses on four therapeutic areas: Oncology, Gastroenterology, Rare Diseases and Neuroscience.

During this long process of drug discovery, clinical trials, and regulatory approval, the activities of firms are substantially known by all industry participants. The initial science showing the target, if publicly funded, is known to all players, who may choose to follow up if they see it as sufficiently interesting. The importance of specializing in certain areas is obvious here, since

it is impossible for any firm to follow all the science across all therapeutic areas with enough depth to distinguish which findings offer the most prospective value. There is a stage that can be seen as private, when the firms do in vitro testing and analysis and then testing in animal models. However, much of this analysis is done by small biotechs, which need capital to pursue their work. Their strategic tool for obtaining capital is to patent aggressively (Industry Canada, 2013). Patenting, of course, reveals their research to potential investors, which includes the "big pharma" firms that may eventually acquire them. Patents fully disclose how to do an invention, as well as its proposed utility, although when granted they prevent other firms from copying the invention for 20 years. When a project advances into clinical trials, this is known too, since all clinical trials must be registered, in advance, in the public register "clinicaltrials.gov". The outcomes of the trial must also be made public. Thus, as a product advances into Phase 3 clinical trials, all the firms with an interest in the therapeutic area have likely been watching its progress from the basis science, through a series of patents, and into clinical trials with their published results.

The result of the openness of the progress towards approval of a new drug is that firms are relatively well informed about potential competitors as they advance their own products. We could reasonably expect that, when making decisions about whether to invest hundreds of millions into a Phase 3 clinical trial program, firms take into account the progress of competitive therapies. The importance of understanding the competitive landscape is highlighted by DiMasi and Paquette (2004), who show that, by the 1990s, "first-in-class" drugs in the US enjoyed less than two years of market exclusivity

before a "me-too" drug entered employing a similar mechanism of action to address the same therapeutic target. In many cases, multiple competing patented drugs enter within a few years of each other. For example, while Gilead's sofosbuvir (Sovaldi) obtained a lead in treating patients for hepatitis C when it was introduced in late 2013, it was followed within two years by simeprevir, daclastavir, dasabuvir, ombitasvir-paritaprevir-ditonavir (a combination drug), and ledipasvir. (Berdud et al., 2018) These drugs were all in clinical trials at the same time as each other, with sofosbuvir having a slight lead. Competition within a therapeutic category is important because competing drugs not only capture market share but also often result in price discounting as buyers seek the best deal. Famously, in the United States Express Scripts, a large pharmacy benefit manager, refused to include Sovaldi in its formulary (or list of insured drugs) because it was negotiating for better pricing, ending up with an exclusive deal for AbbVie's combination drug.(Pollack, 2014) Thus, firms have every reason to be keenly interested in the therapies being advanced by their competitors.

2.1 Data

Since I am trying to investigate the decisions of big pharmaceutical regarding health innovation, I chose the number of Phase 3 clinical trials as a proxy for innovation. Given that these trials are so expensive, only the big firms are able to conduct them, and those firms would only invest if they highly value the inventions embodied in those drugs. Therefore, we can see them as a key stage in innovation competition between big pharmaceutical companies.

Also, the number of clinical trials is a better measure of innovation than the number of drugs approved, since the former are fully controlled by investors and the latter are not.

I used IMS R&D Focus as my primary source for information on drug development. This data set is widely used by the pharmaceutical industry to help understand the competitive environment. The records in this data set are drug projects. Each drug can target multiple indications and several pharmaceutical firms could be involved in their development. This data set includes all the known drug projects from the mid-1980s to the present, regardless of their success or failure in clinical trials or pre-clinical studies. Since it takes, on average, a decade to bring a new drug to the market, I focused on the number of Phase 3 clinical trials between 2008 and 2017 as the measure of innovation. As mentioned before, some drugs have multiple clinical trials at each stage. Therefore, some projects in this data set have multiple recorded Phase 3 clinical trials with different starting times. In those cases, I counted them only if the first recorded Phase 3 trial for the drug happened between 2008 and 2017.

The next step is to define the market for these drugs. All projects in the IMS database have at least one Anatomical Therapeutic Classification (ATC). I chose each 3-digit ATC code as a separate market, meaning if a drug was reported in more detailed categories, I only count it in its parent group. For example, the code "J1G" covers fluoroquinolones, a class of antibiotics including norfloxacin, fleroxacin, gatifloxacin, grepafloxacin, ofloxacin, pefloxacin and sparfloxacin. These all have a similar mechanism of action (Bryskier, 1993). There is a more detailed 4-digit categorization which distin-

guished between oral ("J1G1"), injectable ("J1G2"), and inhaled ("J1G9") forms of fluoroquinolones. I aggregated the 4-digits codes up to the 3-digit level, which results in 195 different 3-digit markets in my data. I also define category as the first letter of the ATC code. For example, codes "J2A" (agents for fungal infections) and "J1G" (fluoroquinolones) are both in category "J", which covers general anti-infectives. Using this definition, markets are divided into 13 categories. The motivation for defining these categories is to identify all the potential entrants in each market.

The challenge for the observer is knowing who is a potential entrant in each market. Realistically, not every firm is actually a potential entrant. As discussed above, firms cannot cover every therapeutic area, and they tend to specialize in just a few areas. Novo Nordisk, which specializes in diabetes, is not realistically a likely entrant into drugs for malaria. Thus, my assumption is that firms are more likely to enter therapeutic markets that are related to markets in which they are already doing clinical trials.

I considered each of the top 10 firms who conducted, at least, three Phase 3 clinical trials in each *category* as one of the main players. If there was a tie for tenth player, then I included all tied firms, e.g. if the tenth player, for example, has four clinical trials, all the other firms in the category with four clinical trials will be considered as top players as well. Thus there are more than 10 players in some categories. The reason for requiring at least three clinical trials is that some categories are small, and we can end up with many small companies with only one or two clinical trials in those categories. These are, generally, non-industry players such as universities or smaller firms who collaborate with a bigger firms on clinical trials. The categories and the main

players of each category are listed in Table 7 of Appendix (A). As I mentioned before, some firms focus their research into certain therapeutic areas. For example, "Pfizer" primarily focuses on 6 therapeutic areas: Internal Medicine, Vaccines, Oncology, Inflammation & Immunology, Rare Disease and Consumer Healthcare Pfizer (2019). So, counting each top firm as a potential entrant of every market in all categories would be unrealistic. Therefore, I only considered each of the main players of a category as a potential entrant of every market in that category. For example, "Merck & Co" is one of the main players in Category "J". So, I consider this firm as one of the potential entrants in all the markets of that category, although it does not have any clinical trials for some markets such as "J1A".

I identified 2314 drug projects in the IMS data with Phase 3 clinical trials between 2008 and 2017. Some of these drugs were developed for multiple diseases, so they are connected to multiple markets. The defined top pharmaceutical companies were involved in 855 (%37) of the considered clinical trials. The frequency of observing different numbers of Phase 3 clinical trials by each firm in different markets is listed in Table 1. For example, this table shows that the frequency of observing 12 clinical trials is 2, which means twice in our data we observed that a firm had 12 clinical trials in a single market. We can define the number of Phase 3 clinical trials by each firm as their choices for innovation in a market. But as we can see in Table 1, by doing that we will have many choices and the frequency of some of these choices will be very small. That will be problematic for estimating any model.

As we can see in this table, the frequency of observing a higher number of clinical trials (CT) decreases exponentially. So, a natural way of decreasing

Number of Clinical Trials	Frequency
0.0	1531
1.0	253
2.0	113
3.0	50
4.0	19
5.0	13
6.0	8
7.0	3
8.0	2
9.0	2
10.0	0
11.0	1
12.0	2

Table 1: The frequency of observing different numbers of phase 3 clinical trials by each firm in different markets.

the number of choices would be a logarithmic transformation. Additionally, this transformation will help us to estimate the elasticity of changing each input variable. Therefore, to have a discrete set of choices, I rounded $1+CT$ to the nearest integer and defined it as the choice of each firm in a market. I show each firm's choice with y, which is the endogenous variable in this paper. Only 2 out of 1997 of these choices had a value bigger than 2. So, I changed their values into 2 to eliminate the need to try to estimate this infrequent outcome. The exact definition of those choices and their frequency in the data is summarized in Table 2. Also, the last 3 columns of Table 8 in Appendix (A) lists the frequency of each top firms choices. For example, $Y_1 = 18$ for Roche means this firm made the choice $y = 1$ in 37 of the studied markets.

Choices (y)	Number of Clinical Trials (CT)	Frequency
0	$CT = 0$	1531
1	$1 \leq CT < 4$	416
2	$4 \leq CT < 12$	50

Table 2: Definition and frequency of choices.

It is common to use firms' incumbency status as the player-specific variable that satisfies the exclusion restriction needed for identification of a structural model. In a similar spirit, I use each companies' number of Phase 3 clinical trials in each market in the past as such a variable. More precisely, if we denote the number of Phase 3 clinical trials between 1998 and 2007 by $\bar{CT}$, the exclusion variable is defined as: $z = \ln(1 + \bar{CT})$.

I also need to control for market-specific features. Markets themselves have differing levels of innovation, with some markets attracting many competitive entrants and some few. So we can imagine some market specific characteristic that affects the choices of all firms in a market. A technological breakthrough or potential market size can be examples of these kinds of characteristics. The sequential nature of drug development can help us to control for some of the unobservables, although it might not be able to perfectly capture all reasons for the attractiveness of a market. I use the *total* number of Phase 2 clinical trials in each market between 2008 and 2017 for this purpose. It is clear that those factors that make a market more attractive to all the players (such as potential market size or relevant scientific

advances), would also encourage Phase 2 clinical trials in that market as well. I denote this explanatory variable by μ in the following sections. To be consistent with our definition of y and z, I defined the logarithmic transformation of the number of Phase 2 clinical trials between 2008 and 2017 as the variable μ. We can thus summarize the exogenous variables from the data as: $x = \{\mu, z\}$.

3 Model

In this section, I introduce a static game with ordered actions to model firms' decisions on health innovation. In this game each player chooses one action from a finite and discrete set. I use $i \in \mathbb{I} = \{1, ..., I\}$ to index players. Each player simultaneously chooses an action y_i from the set $\mathbb{Y} = \{0, .., J\}$ in each market. A player's payoff depends on the state variables and its competitors' choices. I use $-i$ to denote player i's competitors and y_{-i} to denote their own actions in each market.

A firm's profit in each market is a function of two types of state variables: First, a vector of state variables $x \in X$. These are common knowledge to all players and the econometrician. Some of these variables are market-specific and some of them are both market-specific and firm-specific. Second, players' private information, denoted by ε_i. This private information can, for example, include the firm's cost of operations in each market, or its marketing and distribution capacity. Although this private information is not known to competitors, they can form beliefs about its realization. I assume that all players and the econometrician know the cumulative distribution function of

the private information. Additionally, I assume players' private information sets are independent. Assumption 1 summarizes the restrictions assumed on the state variables:

Assumption 1. *(State variables)*

I The state variable x is observed by all players, but the private information variable ε_i is observed only by player i.

II The vector of state variables x is independent of the vector of private information ε_i, and each ε_i is independent of the private information of its rivals ε_{-i}.

III The distribution of ε_i is continuous, and the form of this distribution is common knowledge among the players and the econometrician.

Given these state variables, we can show player i's payoff from choosing y_i as $\pi_i(y_i, y_{-i}, x, \varepsilon_i)$. In this model, each firm makes a decision about its level of innovation in each market in which it is a player. So, these actions are naturally ordered and an ordered-response model will be an appropriate option for defining players' payoffs (Bresnahan and Reiss, 1991; Aradillas-López and Gandhi, 2016; Marcoux, 2019). Some restrictions are needed on the payoff function to ensure the model can be identified and estimated. Assumption 2 states my restrictions on the payoff function:

Assumption 2. *(Payoff function)*

- *Functional forms of payoff functions are common knowledge among the players.*

- *Private information enters the payoff function additively. More specifically, I assume the payoff function has the following form:*

$$\pi_i(y_i, y_{-i}, x, \varepsilon_i) = y_i[\zeta_i(y_{-i}, x) + \varepsilon_i] - \bar{c}(y_i). \tag{1}$$

We can interpret $\bar{c_i}(y_i)$ as part of the cost that is choice-specific and not visible to the econometrician. This variable might be visible to the other players. The term $y_i[\zeta_i(y_{-i}, x) + \varepsilon_i]$ in Equation 1 captures both the expected revenue and the remainder of the cost (*i.e.* the portion of the cost that is observable to the econometrician). Note that this term is a function of state variables and rivals' decisions, which means it incorporates strategic interactions between firms.

I show the conditional choice probability (CCP) of player i choosing y_i at a given realization of the common-knowledge state variables x by $P_i(y_i|x)$. Note that the CCP of a firm is a function of the state variables of rival firms via their choices. So here $x = \{x_1, ..., x_I\}$ is a vector of all the players' state variables. I show the CCP of a firm's competitors as $P_{-i}(y_{-i}|x)$, and define the expected value of the index function $\zeta_i(y_{-i}, x)$ as:

$$\zeta_i^p(x) \equiv \sum_{y_{-i}} P_{-i}(y_{-i}|x)\zeta_i(y_{-i}, x).$$

Thus, we can write the expected profit of firm i as:

$$\pi_i^p(y_i, x, \varepsilon_i) = y_i[\zeta_i^p(x) + \varepsilon_i] - \bar{c}(y_i). \tag{2}$$

I define the marginal value of the choice specific unobservable as $c_j \equiv \bar{c}(j+1) - \bar{c}(j)$. Given this variable and Equation 2, we can conclude player i makes choices as follows:

$$\begin{cases} y_i = 0 & \text{if } \zeta_i^p(x) + \varepsilon_i \leq c_1 \\ y_i = j \ (0 < j < J) & \text{if } c_j < \zeta_i^p(x) + \varepsilon_i \leq c_{j+1} \\ y_i = J & \text{if } c_J < \zeta_i^p(x) + \varepsilon_i \end{cases}$$

I denote the cumulative distribution of the variable for the private information by $\Lambda(e)$. I also assume that this variable follows a logistic distribution, so we can write $\Lambda(e) = \frac{\exp(e)}{1+\exp(e)}$. As we can see, the vector of values $c = \{c_1, ..., c_J\}$ acts as a set of thresholds in this model. We treat them as parameters to be estimated. Given the distribution of ε_i, the CCPs should have the following form:

$$P_i(j|x) = \begin{cases} \Lambda(c_1 - \zeta_i^p(x)) & \text{if } j = 0 \\ \Lambda(c_{j+1} - \zeta_i^p(x)) - \Lambda(c_j - \zeta_i^p(x)) & \text{if } 0 < j < J \\ 1 - \Lambda(c_J - \zeta_i^p(x)) & \text{if } j = J \end{cases} \tag{3}$$

If we show the right-hand side of Equation 3 by $\varphi_i(j, x, P_{-i}; c)$, the pure strategy Bayesian Nash Equilibrium (BNE) of this game will be a vector of CCPs which satisfy the following equations:

$$P_i(j|x) = \varphi_i(j, x, P_{-i}; c),$$

for any $y_i \in \mathbb{Y}$ and $i \in \mathbb{I}$. Therefore a BNE of this game is a fixed point

of the best response mapping, such that each player's beliefs are consistent with their competitors'.

I emphasize that the empirical game presented here may have multiple equilibria, which can make the estimation of the parameters more complicated. To avoid this problem, I assume that each player in the game uses the same equilibrium strategy when multiple equilibria exist. This is a common assumption in the literature (Aguirregabiria and Mira, 2007; Bajari et al., 2010; Aradillas-Lopez, 2012).

4 Identification

In this section I present the identification argument for estimating the model introduced in Section 3. This argument is based on identification of similar problems in the literature. (Bajari et al., 2010; Aradillas-López and Gandhi, 2016; Marcoux, 2019). The model presented in this paper is particularly similar to the model in Marcoux (2019). However, they estimate the model without having a variable satisfying the exclusion restriction. Their strategy is to use a predetermined outcome, which is realized before the start of the game, to estimate a firm-specific unobservable. Then the estimated unobservable is used as a variable satisfying the exclusion restriction and making identification possible. As I mentioned in Section 2.1, I can directly observe a player-specific variable that satisfies the execution restriction. Therefore, the identification argument and the estimation of the model in this paper is comparatively straightforward.

Hotz and Miller (1993) shows that if Assumptions 1 and 2 are satisfied, there exists a one-to-one mapping between players' expected normalized payoffs and their corresponding best-response conditional choice probabilities, and that this mapping is invertible. So, if CCPs can be estimated directly from the data, then the Hotz-Miller inversion can be used to uniquely recover equilibrium expected normalized payoffs. After that, these expected normalized payoffs can be treated as known, and they can be used to recover the normalized payoffs. For the model in this paper, I want to estimate what I will call pseudo-marginal payoffs $\bar{\pi}_i(y_{-i}, x) = \zeta_i(y_{-i}, x) - c_j$. Since ε_i is absent from the definition of $\bar{\pi}_i(y_{-i}, x)$, it is not exactly the marginal payoff. However, for convenience, I refer to this function as a pseudo-marginal payoff in the rest of this paper. The expected value of these pseudo-marginal payoffs can be calculated from Equation 3 as:

$$\bar{\pi}_i^p(x) = \frac{1 - \sum_{j=1}^{y-1} P_i(j|x)}{\sum_{j=1}^{y-1} P_i(j|x)}. \tag{4}$$

Thus, we can estimate $P_i(j|x)$ directly from the data and we can use Equation 4 to recover $\bar{\pi}_i^p(x)$. The next step is to calculate $\bar{\pi}_i(y_{-i}, x)$, but the Assumptions 1 and 2 are not sufficient for identification of these pseudo-marginal payoffs. Identification of similar models in the literature requires a variable which can provide an extra source of exogenous variation to identify the normalized payoffs from the expected normalized payoffs. As I mentioned in Section 2.1, I use firms' previous experience in innovation in each market (variable z_i) for this purpose. More precisely, I assume the following restriction for this variable:

Assumption 3. *(Exclusion restriction)*

The state variable $z_i \subseteq x$ enters the payoff function of player i, but it is excluded from the payoff function of all other players. I assume this state variable is drawn from a finite set as: $z_i \in \{0, ..., Z\}$.

Given this variable and the expected pseudo-marginal payoffs, $\bar{\pi}_i(y_{-i}, x)$ can be identified from the data. The relationship between a pseudo-marginal payoff and its expected value is as follows:

$$\bar{\pi}_i^p(x) = \sum_{y_{-i}} P_{-i}(y_{-i}|x)\bar{\pi}_i(y_{-i}, x). \tag{5}$$

As discussed above, in Equation 5, $\bar{\pi}_i^p(x)$ and $P_{-i}(y_{-i}|x)$ are identified, but $\bar{\pi}_i(y_{-i}, x)$ is unknown. For each player we have $(J+1)^{N-1}$ index functions and J threshold. Therefore, we have $(J+1)^{N-1} + J$ unknowns and J linear equations, so the model is under-identified. To overcome this problem, we use the exclusion restriction assumed for variable z_i. This variable can change for a firm's competitors and shift their choice probabilities, without changing the firm's pseudo-marginal payoff. This increases the number of equations, without increasing the number of unknowns, thus resolving the under-identification problem. Proposition 1 states the required condition for identification of the model in this paper:

Proposition 1. *If Assumptions 1, 2 and 3 are satisfied, and if there is sufficient variation in conditional choice probabilities, the pseudo-marginal payoff of each player is identifiable from the data.*

Proof. The conditional choice probability ($P_{-i}(y_{-i}|x)$) on the right hand side

of Equation 5 can be estimated directly from the data. Then, the expected pseudo-marginal payoffs ($\bar{\pi}_i^p(x)$) on the left hand side of this equation can be recovered, using Hotz-Miller inversion. But the pseudo-marginal payoffs ($\bar{\pi}_i(y_{-i}, x)$) on the right hand side of Equation 5 would still not be identified. Having variable $z_i \in \{0, ..., Z\}$ satisfy the exclusion restriction, we can construct JZ^{N-1} linear equation for each player. The number of unknowns is $(J+1)^{N-1} + J$. To be able to identify the pseudo-marginal payoff, the number of equations should be larger than the number of unknowns, meaning $JZ^{N-1} \geqslant (J+1)^{N-1} + J$. Therefore, to identify the model, we require: $Z^{N-1} \geqslant \frac{(J+1)^{N-1}}{J} + 1$. In our data Z is more than twice as large as $J+1$, so this condition is satisfied. Also, for the system of the equation to satisfy the rank condition, we need sufficient variation in conditional choice probability. ■

5 Estimation

In the previous two sections I introduced a static game to explain firms' decisions about investing in Phase 3 clinical trials. In my data, I can observe independent repetitions of this game in different markets. I index each market by m and show the total number of markets as M. So, the data available for estimating the model can be summarized as: $y_{im}, x_m : m = 1, ..., M$. While in the previous section, I presented the identification argument for a semi-parametric model, I assume a functional form for the index function in this section. Several reasons motivate me to assume a parametric specification for the index function: first, it helps me to avoid the prob-

lems caused by having a relatively small sample size, and trying to estimate $\zeta_i(y_{-i}, x_m)$ non-parametrically. Second, it makes the interpretation of the results more straightforward. Third, it makes counterfactual experiments feasible. Although I do not perform counterfactual experiment in this paper, the estimated result can be used for this purpose in future works. We should also note that, since assuming a functional form for the index function does not increase the number of unknowns in Equation 5, the identification argument presented in the previous section remains valid. I use the following parametric specification for the index function:

$$\zeta_i(y_{-i}, x_m; \theta) = x_m'\beta + \delta \sum_{n \neq i} y_{nm}, \tag{6}$$

where $\theta = [\beta', \delta]'$. As in Section 3, we can show the expected value of these index functions as $\zeta_i^P(x_m; \theta)$, and write the conditional choice probability of player i choosing option j in market m as:

$$P_i(j|x_m; \theta) = \begin{cases} \Lambda(c_1 - \zeta_i^P(x_m; \theta)) & \text{if } j = 0 \\ \Lambda(c_{j+1} - \zeta_i^P(x_m; \theta)) - \Lambda(c_j - \zeta_i^P(x_m; \theta)) & \text{if } 0 < j < J \\ 1 - \Lambda(c_J - \zeta_i^P(x_m; \theta)) & \text{if } j = J \end{cases} \tag{7}$$

Then, if we show the right hand side of Equation 7 as $\varphi(j, x_m, P_{-i}; \theta, c)$, we can write the maximum likelihood function as:

$$L(y|x) = \prod_{m=1}^{M} \prod_{i=1}^{I} \prod_{j=0}^{J} \varphi(j, x_m, P_{-i}; \theta, c)^{1\{y_{im}=j\}}.$$

We can maximize this likelihood function to estimate θ and c. But this method is computationally cumbersome, since it requires calculating the equilibrium solution in each step of the maximization. This makes the estimation process resource-intensive and time-consuming.

However, as discussed above, we can estimate CCPs directly from the data. I use a flexible semi-parametric estimation method to recover CCPs. The details about this estimation method are presented in Appendix B. I show the estimated CCP values by $\hat{P}_i(j|x_m)$. We can avoid calculating the BNE solution in every step of the optimization by substituting these estimated CCPs into the right hand side of Equation 7. Then, we use the pseudo maximum likelihood method to estimate θ and c.

Given the estimated $\hat{P}_i(y_i|x_m)$, we can calculate the expected values of the index function as follows:

$$\zeta_i^{\hat{P}}(x_m;\theta) = x_m'\beta + \delta \sum_{n\neq i} \sum_{j=0}^{J} \hat{P}_n(j|x_m) j. \tag{8}$$

Therefore the conditional choice probability of player i choosing option j in market m is given by:

$$P_i(j|x_m;\theta) = \begin{cases} \Lambda(c(1) - \zeta_i^{\hat{p}}(x_m;\theta)), & \text{if } j = 0 \\ \Lambda(c(j) - \zeta_i^{\hat{p}}(x_m;\theta)) - \Lambda(c(j-1) - \zeta_i^{\hat{p}}(x_m;\theta)), & \text{if } 0 < j < J \\ 1 - \Lambda(c(J-1) - \zeta_i^{\hat{p}}(x_m;\theta)), & \text{if } j = J \end{cases}$$

If we show the right hand side of this equation as $\varphi(j, x_m, \hat{P}_{-i}; \theta, c)$, we can

write the Pseudo maximum likelihood of the observations in the data as:

$$L(y|x) = \prod_{m=1}^{M} \prod_{i=1}^{I} \prod_{j=0}^{J} \varphi(j, x_m, \hat{P}_{-i}; \theta, c)^{1\{y_{im}=j\}}.$$

Then, we can maximize this likelihood function to estimate $\hat{\theta}$ and $\hat{c}$.

6 Results

The estimated coefficients of this model are presented in Table 3. We are mostly interested in the interaction variable δ. As mentioned above, these firms compete with each other through drug sales, but they also learn from each other's failures and successes in innovating for different diseases. The estimated value for the interaction variable, shown in Table 3, is negative and significant. This indicates that, on average, the negative effect from rivalry dominates the positive effect from knowledge spillover. It is important to keep in mind that we are estimating the coefficients for the index function. So, to be precise, the negative δ means that, if there is more innovation by a firm's rivals in a market, the marginal profit of that firm from increasing y will decrease.

As we can see in Table 3, the most important factor for the marginal profit of the firms is their past experiences (z). The coefficient for this variable is 4.39. Considering the logarithmic transformation of these variables, the profit of the firms substantially increases if they already have experience in the market. Since those experiences can decrease the cost of R&D and distribution of the drugs, estimating a positive coefficient for z is not surpris-

variable	Coefficients	[0.025	0.975]
μ	1.00	0.80	1.21
z	4.39	3.85	4.94
δ	-0.16	-0.24	-0.09
c_0	4.00	3.56	4.45
c_1	9.52	8.62	10.42

Table 3: The estimated parameters of the model.

ing. This can explain why firms have a tendency to focus on the few markets that they are familiar with.

The estimated coefficient for the variable μ is reassuringly close to 1. Considering that Phase 2 clinical trials are a necessary precursor to Phase 3 trials, a coefficient near 1 is expected, and any deviation from it would be concerning.

We can see the estimated value of marginal costs, c_0 and c_1, are clearly distinguished with no overlap of confidence intervals. Again, reassuringly, we note that c_1 is bigger than c_0. We know that the marginal profit should be bigger than the marginal cost for a firm to make a choice with higher value. Therefore, having a higher $c_1 - c_0$ compared to c_0 indicates that going from $y = 1$ to $y = 2$ is more "difficult" for firms than going from $y = 0$ to $y = 1$. The interpretation of this is that there is some threshold for expected profitability to get a firm to invest in one clinical trial in a therapeutic area. To get them to invest in multiple trials requires a higher profitability.

6.1 Sensitivity Analysis

In this section I investigate how including other potentially important variables can affect the estimated result. As discussed above, we can see in the data that firms focus their efforts into innovating in a few markets and specialize in certain therapeutic areas. Our main result showed that profit is positively related to a firm's past experiences in a market, which can partly explain why they specialize. But concentrating in fewer markets can potentially give firms competitive advantages over their rivals, which can also explain why those firms specialize in certain therapeutic areas. Here I want to check if this concentration has any direct effect on a firm's profit from innovation. I calculate the Herfindahl index (H) of each firm across disease areas, which is a measure of concentration by the firms into particular therapeutic focus. More specifically, if $s_{im} = \frac{y_{im}}{\sum_m y_{im}}$ shows the proportion of firm i's clinical trials in market m, H for each firm is defined as: $H_i = \sum_m s_{im}^2$. The third column of Table 8 in Appendix (A) shows the value of this variable for the firms considered in this study. To measure the effect of H on firms' ability to compete, I assume that the interaction term for each firm is a function of its H. The intuition is that a firm with high H is relatively undiversified, which can make it more vulnerable to competition in its chosen markets. Therefore, I assume the following functional form for δ:

$$\delta = \delta_0 + \delta_H \times H.$$

As long as there is independent variation across H and P_{-i}, all coefficients for the variables can be estimated. Table 4 shows the result of estimating

variable	Coefficients	[0.025	0.975]
μ	1.00	0.80	1.21
z	4.40	3.85	4.94
δ_0	-0.16	-0.24	-0.08
δ_H	0.00	-0.38	0.38
c_0	4.00	3.56	4.45
c_1	9.52	8.62	10.42

Table 4: Adding the Herfindahl index (H) does not change the estimation.

this version of the model. As we can see, δ_1 is insignificant. This suggests that firms who concentrate their resources into innovating in fewer markets are not less well-equipped to deal with competition. So, the main reason for specialization is how their past experiences in innovating for certain diseases affect their profitability from further innovation. It is also noteworthy that adding H did not change the estimated coefficient for any other variable.

The next variable variable I consider is firm size. The second column of Table 8 in Appendix (A) shows the 2017 global revenues of the firms included in this study, abstracted from each firm's annual financial report. I define the variable $r = \log(Revenue)$ and include it as one of the input variables, thus redefining x as $x = \{\mu, z, r\}$. This requires me to re-estimate the CCPs, considering the new variables. After recovering CCPs from the data, I estimate a model which includes firm size. The estimated coefficients from this new model are reported in Table 5. The estimated value for the coefficient of r is insignificant, meaning that firm size does not have a significant effect on their marginal profit from choosing higher levels of innovation. Again, I note that including this variable does not change the estimated coefficients

variable	Coefficients	[0.025	0.975]
μ	1.00	0.80	1.20
z	4.40	3.86	4.95
r	-0.02	-0.10	0.06
δ	-0.16	-0.24	-0.08
c_0	3.94	3.44	4.45
c_1	9.46	8.53	10.39

Table 5: Adding the size of firms (R) does not change the estimation.

for the other variables reported in Table 3.

Next, I check the sensitivity of the estimated result to the definition of y. Rather than doing the pseudo-logarithmic transformation of the number of trials, I now assume the firm's choices are the actual number of Phase 3 clinical trials. the frequency of Phase 3 clinical trials is shown in Table 1 above. We lack data for a robust statistic for choices bigger than 4, so I assume $y = 4$ if $4 \leq CT$. I also assume z and μ are the number of Phase 3 trials by each firm in the past and the total number of phase 2 clinical trials in a market respectively, and not their logarithmic transformation. So, for this section, I have minimal manipulation of the input variables and the endogenous variable.

The estimated value of coefficients for different variables with minimal manipulation of the data is presented in Table 6. As expected, the absolute value of the estimated coefficient changes when we do not have logarithmic transformation. But the sign of the estimated values and the interpretation of the results stay the same. We can still see that that the sign for interaction term δ is negative, meaning that rivals' innovation overall has a negative

variable	Coefficients	[0.025	0.975]
μ	0.02	0.02	0.03
z	1.35	1.17	1.53
δ	-0.12	-0.18	-0.06
c_0	1.66	1.50	1.82
c_1	3.08	2.85	3.30
c_2	4.37	4.04	4.70
c_3	5.60	5.14	6.07

Table 6: Estimated value of coefficient for variables with minimal data manipulation.

effect on a firm's innovation investment decision. We can also see that the estimated coefficients for z and μ are positive, and the absolute value of the coefficient z is bigger than the absolute value of the estimated coefficient for other variables. This confirms that the firm's experience in a therapeutic area is the critical factor for their marginal profit from innovating more in a market. I also estimated the model with some manipulation of the data, for example defining choices the same as in previous estimation but without logarithmic transformation of the input variable. None of those different forms of data manipulation changed the overall result of the estimation. In effect, the results are robust to different transformations of the data.

7 Conclusion

This paper presents a structural econometric model of "big pharma" companies' investments in innovation for different diseases, using data on clinical trials. These firms learn from each other through out the development pro-

cess of the drugs, but they compete with each other in the market. This paper shows that the negative effect of competition, in absolute terms, dominates the positive effect of knowledge spillovers. As discussed in Section 1, the negative estimate of the interaction term can be interpreted as under-investment in R&D from a welfare perspective.

The model estimated in this paper can be extended to investigate the effect of mergers on innovation. In most merger cases, the antitrust authority has tried to assess potential impacts on innovation but found little guidance in the economics literature (Igami and Uetake, 2019). Mergers in innovative industries represent an opportunity to kill competition and acquire talent. Beyond the trade-off between market power and efficiency, the merger's effect on other firms' innovation should be considered. Previous studies on the effect of mergers on innovation in pharmaceutical industry have numerous flaws. Most importantly, they are unable to address the endogeneity of merger decisions. Moreover, they ignore the effect of mergers on other firms in the market and their innovation. One can overcome this issue by using the estimated model in this paper to simulate the effect of a merger on innovation.

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A Lists

Category	Players
A	Sanofi
A	Merck & Co
A	Takeda
A	Lilly
A	Roche
A	Novartis
A	Allergan
A	Novo Nordisk
A	Daiichi Sankyo
A	AstraZeneca
A	Bausch Health Companies
A	GlaxoSmithKline
A	Johnson & Johnson
A	Kowa
B	Takeda
B	CSL
B	Sanofi
B	Bayer
B	Novo Nordisk
B	Pfizer
B	Kissei
C	Merck & Co

C	Sanofi
C	Novartis
C	Takeda
C	Yuhan
C	Daiichi Sankyo
C	Hanmi
C	Johnson & Johnson
C	Lilly
C	Pfizer
D	Novartis
D	Almirall
D	Maruho
D	Bausch Health Companies
D	Pfizer
D	Dr Reddy's
D	Merck & Co
D	AbbVie
D	Daewoong
D	LEO Pharma
D	Roche
G	Allergan
G	Kissei
G	Astellas
G	Bayer

G	Hanmi
G	Lilly
G	Merck & Co
G	Teva
J	Merck & Co
J	GlaxoSmithKline
J	Gilead Sciences
J	Johnson & Johnson
J	Sanofi
J	Takeda
J	AbbVie
J	Bristol-Myers Squibb
J	Pfizer
J	Bayer
J	CSL
J	Roche
L	Pfizer
L	Novartis
L	Takeda
L	Merck & Co
L	Roche
L	Lilly
L	Amgen
L	AstraZeneca

L	Johnson & Johnson
L	Biocad
L	Celgene
L	Teva
M	Novartis
M	Merck & Co
M	AbbVie
M	Pfizer
M	Sanofi
M	Sarepta Therapeutics
N	Lilly
N	Teva
N	Novartis
N	Merck & Co
N	Roche
N	Alkermes
N	Allergan
N	Lundbeck
N	Pfizer
N	GlaxoSmithKline
N	Gruenenthal
N	Hisamitsu
N	Johnson & Johnson
N	Shionogi

R	AstraZeneca
R	GlaxoSmithKline
R	Merck & Co
R	Novartis
R	Teva
R	Vertex
R	Boehringer Ingelheim
R	Hanmi
S	Novartis
S	Santen
S	Aerie
S	Allergan
S	Bausch Health Companies
T	Lilly
V	Teva
V	Allergan
V	Hisamitsu
V	Johnson & Johnson
V	Bayer
V	Takeda
V	Bausch Health Companies
V	Endo
V	Novartis
V	Pfizer

V Sanofi

Table 7: List of the therapeutic categories and main players in each category.

Players	Revenue	H	Y_0	Y_1	Y_2
AbbVie	28.22	0.072	39	4	2
Aerie	0.02	1.000	12	1	0
Alkermes	0.90	0.157	16	5	0
Allergan	15.94	0.052	57	21	2
Almirall	0.70	0.164	7	4	1
Amgen	22.78	0.087	10	5	1
Astellas	12.06	0.047	13	3	0
AstraZeneca	22.53	0.045	35	17	1
Bausch Health Companies	8.72	0.080	42	12	1
Bayer	42.00	0.050	54	9	1
Biocad	0.20	0.123	12	3	1
Boehringer Ingelheim	20.10	0.047	8	5	0
Bristol-Myers Squibb	20.78	0.062	21	4	0
CSL	5.50	0.153	37	4	1
Celgene	12.82	0.108	10	5	1
Daewoong	0.81	0.160	10	2	0
Daiichi Sankyo	8.79	0.047	34	11	0

Dr Reddy's	1.96	0.140	9	3	0
Endo	3.47	0.125	5	0	1
Gilead Sciences	26.14	0.178	22	1	2
GlaxoSmithKline	38.73	0.056	63	18	2
Gruenenthal	1.44	0.174	17	4	0
Hanmi	0.77	0.086	41	9	0
Hisamitsu	1.50	0.262	22	4	1
Johnson & Johnson	76.48	0.063	91	20	2
Kissei	0.67	0.066	28	5	0
Kowa	0.04	0.102	20	4	0
LEO Pharma	1.55	0.140	6	6	0
Lilly	22.87	0.043	78	21	2
Lundbeck	2.50	0.124	14	7	0
Maruho	0.79	0.143	7	5	0
Merck & Co	39.98	0.030	111	40	5
Novartis	48.34	0.033	92	37	5
Novo Nordisk	16.48	0.190	35	4	2
Pfizer	52.55	0.056	101	20	5
Roche	54.00	0.049	77	18	3
Sanofi	38.65	0.042	79	19	3
Santen	1.81	0.112	9	4	0
Sarepta Therapeutics	0.15	1.000	7	1	0
Shionogi	3.09	0.066	16	5	0
Takeda	15.92	0.038	80	26	3

Teva	23.19	0.091	54	17	1
Vertex	2.49	0.500	12	0	1
Yuhan	1.23	0.157	18	3	0

Table 8: The concentrating their resources in fewer marketsspecification of the players in this model. Revenue is in US$ billions.

B CCP Estimation

I use a parametric approximation to recover CCPs directly from the data. More precisely, I use a flexible ordered logit to define an estimator and use the Expectation-Maximization (EM) algorithm to estimate its parameters. Let $h(x;\phi)$ be a simple first-order polynomial function of the state variable x_m with a vector of parameters ϕ:

$$h(x_m;\phi) = x'_m\phi.$$

I also define a vector of threshold parameters $\eta = \{\eta_1, ..., \eta_J\}$, such that the reduced-form choice probability of player i with state variable x_m, choosing option $y_i = j$ will be

$$P(j|x_m;\phi) = \begin{cases} \Lambda(\eta_1 - h(x_m,\phi)), & \text{if } j = 0 \\ \Lambda(\eta_j - h(x_m,\phi)) - \Lambda(\eta_{j-1} - h(x_m,\phi)), & \text{if } 0 < j < J \\ 1 - \Lambda(\eta_J - h(x_m,\phi)), & \text{if } j = J \end{cases}$$

where $\Lambda(e)$ is the logit function. If we show the right hand side of this equation with $\psi(j, x_m; \phi, \eta)$, we can write the likelihood function for the data as follows:

$$L(y|x) = \prod_{m=1}^{M} \prod_{i=1}^{I} \prod_{j=0}^{J} \psi(j, x_m; \phi, \eta)^{1\{y_{im}=j\}}.$$

Using maximum likelihood, we can estimate $\hat{\phi}$ and $\hat{\eta}$ from the data. As we can see, the model used here is similar to the model described in Section 3, without the interaction term. This means that the estimated parameters in this section will not have any economic meaning, though we can still use them to consistently approximate CCPs. To do that, we substitute the estimated parameters into the estimator and calculate the approximated value of CCPs as follow:

$$\hat{P}_i(y_i|x_{im}) \equiv \psi(y_i, x_{im}; \hat{\phi}, \hat{\eta}).$$