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πSim: Proposed simulation of pharmaceutical innovation

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1 Introduction

There is substantial interest in various policies that could have a major impact on the development of new pharmaceuticals. Given this interest, it may be of value to develop a model of pharmaceutical innovation to be used to evaluate the impact of policy proposals. To that end, this paper proposes a policy simulation based on a hurdle model of pharmaceutical manufacturer decision making. This model has been used in DiMasi et al. (2016) and Adams and Brantner (2006), among other papers, to analyze the "cost" of new drug development.

Consider the firm's problem of deciding whether or not to take a drug into Phase III development. Phase III clinical trials are generally "pivotal" to getting approval from regulatory authorities such as the US FDA. They generally require a large number of patients, often over a thousand, take many years and require a lot of money. DiMasi et al. (2016) reports that a subset of pharmaceutical firms spend an average of $255m per drug in Phase III. The firm must weigh these expected costs against the expected returns associated with the successfully getting approval.

In the model presented below, the firm is assumed to make a "go/no-go" decision before taking the drug into Phase III. The firm's marketing people, economists, statisticians, doctors and biologists, meet to discuss the likely success of the drug, the likely revenue and the likely costs. With all this information gathered, the firm decides whether it will be profitable to begin Phase III trials.

The firm is assumed to make a similar "go/no-go" decision at the beginning of Phase II and the beginning of Phase I. However, there is an important distinction between these problems and the Phase III problem. That is, in the earlier problem there is an "option value." When making the Phase II decision the firm recognizes that it has an option at

*Thanks to Anna Anderson-Cook, Meg Blume-Kohout, Joe DiMasi, Pierre Dubois, Craig Garthwaite, Evan Herrnstadt, Jeff Kling, Ellen Werble for helpful suggestions. All errors are my own.

Phase III. If at that future point, the firm expects to get negative returns then they will stop. This means that positive returns tend matter a lot more than negative returns.[1]

To model this decision problem we need estimates of the success probabilities, the expected developments costs, expected time in development, capital costs, and expected revenue. Unfortunately, we don't observe all of these values. Therefore, the proposed model makes functional form assumptions and calibrates the parameters of interest using observed distribution of returns for drugs in Medicare Part D and survey results presented in DiMasi et al. (2016). We assume the observed distributions are related to the distributions of interest through the go/no-go decision problem. This idea is similar to the way the observed female wage distribution is related to the unobserved female wage *offer* distribution through a decision problem (Heckman and Honore, 1990). In particular the paper uses a parametric Roy model to identify the joint distribution of returns and costs from the marginal distributions of each and the semi-observed probability of choosing to enter into the phase.[2] We implement the estimation/calibration using simulated General Method of Moments (GMM) to match "moments" of the observed distributions to the simulated distributions that have been filtered through the decision problem. To be clear this is a calibration exercise, not an estimation exercise. While some parameters are identified given the data observed, structural assumptions and parametric restrictions, other parameters are not identified and their values are assumed.

The proposed simulation approach is an alternative to directly using elasticity estimates from the literature. Dubois et al. (2015) estimate an elasticity of 0.25 for policies that increase expected market size. That is, if a policy increases expected market size for a new drugs by 10% then this leads to a 2.5% increase in the number of new drugs on the market.[3] So, for example, the CBO estimates that a bill called HR 3 will decrease the expected market size by approximately 20%, so Dubois et al. (2015) suggest a 5% decrease in the number of new drugs.[4] At a rate of 300 new drugs in a ten year period, this would mean 15 fewer drugs. Dubois et al. (2015) updates a similar study by Acemoglu and Linn (2004) which estimated the elasticity to be 4, corresponding to a 80% reduction in the number of new drugs. The estimates from the model presented below are in between, although much closer to the Dubois et al. (2015) estimates.

The analysis presented below points out that any relationship between some policy change and the number of new drugs entering the market cannot be constant across time. The change is likely to be quite small for the first few years as new drugs enter the market

[1] I am grateful to Craig Garthwaite and Evan Herrnstadt for their insight and assistance in modelling this.

[2] In the standard parametric Roy model we observe the marginal distributions of outcomes in the two sectors, relative prices and the market share of the two sectors. Given the parametric restrictions we can identify the joint distribution of outcomes. Here the "relative price" is 1 by definition, and we observe a bound on share of firms that enter.

[3] A new drug refers to a new molecular entity, that is a new active ingredient. It does not refer to a new delivery mechanism or flavor of the drug.

[4] urlhttps://www.cbo.gov/publication/55936

based on decisions made years earlier. However, this change will substantially increase as decisions in earlier phases of development affect later phases and finally the drugs that reach the market.

To some extent this analysis is closer to Blume-Kohout and Sood (2013). The authors look at the impact of the introduction of Medicare Part D, called the Medicare Modernization Act (MMA), on drugs in the different phases of development. The authors estimate a long run increase of about 60% in the number of drugs in pre-clinical trials and a 50% increase in the number of drugs in Phase 1 trials. The authors estimates on Phase I are similar to the results presented below. However, we do not account for changes in pre-clinical trials. Also, the authors point out that some care needs to be taken in interpreting effect for pre-clinical and early phase trials because of the way the data is collected.

The analysis below suggests a way to interpret the results presented in Blume-Kohout and Sood (2013). An observed change in a particular phase of development is determined by two different effects. First, there is a change in the decision problem. Given the current available candidates for the next phase of development, it becomes more or less profitable to enter the phase. Second, there is a change in the decisions for the previous phase leading to a change in the available candidates for the next phase. The first change is likely to occur immediately, while the second will take time to have an impact. We could thus interpret the Blume-Kohout estimate of a 27% immediate increase in Phase I trials as due to the first and the long term effect of a 50% increase as the combined effect of the first and second. Similarly, the authors find that the initial impact on Phase III trials is small, but becomes much larger as decisions from the earlier phases show up in changes in the number of Phase III trials. In the results presented below, we present estimates of the initial immediate effect on the decisions given the available candidates. In the policy analysis we account for both effects.

The analysis presented below also attempts to measure the impact of a policy aimed at increasing research and development. In particular, we consider a policy that permanently increases NIH funding by 2.5%. The analysis relies on Blume-Kohout (2012) and her estimate of a long-term elasticity of 0.45. That is, a permanent increase of NIH funding of 10% would lead to a 4.5% increase in Phase I trials twelve years later. Here we assume that the lagged effect builds over the twelve years according to a function that increases at an increasing rate. The results show that a 2.5% increase in NIH funding has only a small impact on the number of new drugs getting to market, and the impact isn't felt within the first twenty years.

2 Hurdle Model

The simulation is based on a hurdle model. Before deciding to enter the phase (phase k), the firm (firm i) is assumed to observe a signal of its "type" which we will denote θ_{ik}. This signal provides the firm with expectations over the likelihood of success, returns once on

the market and costs of developing the drug. The firm will enter the phase of development if net expected returns are positive. Firm i enters phase k if and only if the following inequality holds.

$$E(y_{ik}R_{ik} - C_{ik}|\theta_{ik}) > 0 \tag{1}$$

where $y_{ki} \in \{0, 1\}$ is an indicator of whether the firm will successfully complete the phase, R_{ki} are the returns associated with successfully completing the phase and C_{ki} are the costs associated with the entering the phase. Equation (1) states that the firm will enter the phase ("go") if and only if the expected returns are greater than the expected costs, given the expected probability of success in the trial.

Importantly, this is not a choice model. Firms are assumed to take every profitable candidate into the next phase. That said, the return from the next best alternative is captured by the cost of capital parameter, which is assumed to be 0.081 annually for all firms.[5]

For simplicity it is assumed that there is one drug per firm. So i denotes a drug "candidate." Let N_k denote the number of candidates available to potentially take in to Phase k. Then M_k are the number of candidates that actually enter Phase k.

$$M_k = \sum_{i=1}^{N_k} 1(E(y_{ik}R_{ik} - C_{ik}|\theta_{ik}) > 0) \tag{2}$$

where 1() is an indicator function that is 1 if the inequality holds and 0 otherwise. The probability of entering Phase k is $\frac{M_k}{N_k}$. Lastly N_{k+1} denotes the number of candidates that successfully complete Phase k and are available to enter the following phase. The probability that a drug candidate i that enters Phase k, successfully completes Phase k is given by p_{ik}.

Note that each of the decisions are linked in that following relationship holds.

$$R_{i(k-1)} = E(y_{ik}R_{ik} - C_{ik}|\theta_{i(k-1)}) \tag{3}$$

The expected returns for Phase II is determined by the Phase III model. Firm i does not know its returns for Phase k when making a decision for Phase $k-1$. The firm knows its expected returns from the next phase but not its actual returns. In the notation above, the signal at the beginning of the phase $k-1$ ($\theta_{i(k-1)}$) may be different from the signal at the beginning of the next phase (θ_{ik}).

3 Identification

In the simplest version of the model there exists a return R_i and a cost C_i and a decision problem in which the firm enters if and only if $R_i - C_i > 0$. This is an example of a

[5]This is based on the nominal weighted average cost of capital for the pharmaceutical and biotech industries, from here: `http://people.stern.nyu.edu/adamodar/New_Home_Page/datafile/wacc.htm`. The nominal rate is adjusted to a real rate assuming an inflation rate of 0.024.

Roy model. If we observe the marginal distribution of R_i and the marginal distribution of C_i, the $\Pr(R_i - C_i > 0)$ and assume the two random variables are from a bivariate normal, then the model parameters are identified. Given the parametric restriction there is a known copula function that maps from the observed marginals to the joint distribution. The correlation parameter is tied down by observing the probability that $R_i > C_i$.

The model used below is more complicated. In particular, the joint distribution has four marginals, success rates, revenue, costs and time. Given this, a number of restrictions are placed on the model. The success probabilities for each phase and the distribution over time are assumed to be independent of the other factors. The phase success rates observed by the decision maker are assumed to be equal to the observed success rates presented in DiMasi et al. (2016). In addition, the distribution of costs observed by the decision maker is assumed to be the same as that presented in DiMasi et al. (2016). These two assumptions are consistent with the results of simulation exercises.

3.1 Capitalized Expenditures

DiMasi et al. (2016) provides information on the actual expenditure in each of the phases of development by drug. But these amounts do not account for the actual costs of the development, because they don't account for the opportunity cost of the money. Money invested in human clinical trials could have been invested in some other project.

The capitalized expenditures are calculated in two steps. First, the expenditures are assumed to be uniformly spread out over the period. This assumption is approximated by rounding the time in phase to the nearest year and assuming that equal fractions are spent at the beginning of each year. These amounts are discounted to the end of the phase and summed. Second, capitalized expenditure in the phase is discounted to the expected time on market.

Note that all dollar amounts are discounted to point where the drug enters the market. This is done in order to correctly compare the various expenses that occur during the drug's development process and the revenue that the drug receives while on market.

$$C_{ik} = \left(\sum_{t=1}^{t_{ik}} \left(\frac{\tilde{C}_{ik}}{t_{ik}} \right) (1+\beta)^t \right) (1+\beta)^{T_{i(k+1)}} \tag{4}$$

where $\tilde{C}_{ik}$ is the observed expenditure of firm i in phase k, β is the discount rate (time cost of money), t_{ik} denotes time in phase k and T_{ik} denotes time to market from the beginning of phase k.

3.2 Options and Expectations

The inequality represented by Equation (1) represents expected values over success probabilities, return and costs. Moreover, in Phase I and Phase II, the distribution of returns

is censored. That is, a firm will never undertake a project with negative expected returns. It is more accurate to represent the go/no-go decision as the following inequality.

$$E(p_{ik})E(\max\{0, R_{ik}\} - c_{ik}|\theta_{ik}) > 0 \tag{5}$$

In the actual simulation presented below, these expectations are approximated by taking a small set of draws from the true distribution. With just one draw, the firm has perfect foresight of its returns from the phase, with a large number of draws, the firm has little or no information regarding its idiosyncratic returns. The simulation below assumes that expectation in Phase II is determined by 5 draws, this increases to 10 for Phase I. The increase accounts for the degradation in information as the firm moves back through the dynamic decision process.

3.3 Parametric Restrictions

In order to simplify the problem we make a number of parametric restrictions. In general, these restrictions are made in order to take advantage of the multivariate normal.

$$\{\log(R_{ik}), log(\tilde{C}_{ik}), log(t_{ik})\} \sim \mathcal{N}(\mu_k, \mathbf{\Sigma}_k) \tag{6}$$

where $\mu_k = \{\mu_{Rk}, \mu_{Ck}, \mu_{tk}\}$, and

$$\mathbf{\Sigma}_k = \begin{bmatrix} \sigma^2_{Rk} & \rho_{RC}\sigma_{Rk}\sigma_{Ck} & 0 \\ \rho_{RC}\sigma_{Rk}\sigma_{Ck} & \sigma^2_{Ck} & 0 \\ 0 & 0 & \sigma^2_{tk} \end{bmatrix} \tag{7}$$

Revenue, costs and time are assumed to be log normally distributed. For the later two, the actual observed distributions are based on the supplemental analysis to DiMasi et al. (2016).

The goal of the calibration exercise is to determine μ_k and $\mathbf{\Sigma}_k$.

4 Data

The model uses two main sources of data. First, the revenue data comes from publicly available Medicare Part D expenditure on brand name drugs. Second, the expenditure information comes from DiMasi et al. (2016). That paper reports results from a survey conducted by the authors of drugs being developed by ten pharmaceutical companies.

4.1 Revenue Estimates

We are interested in knowing the distribution of expected revenue. We don't observe it, but we do observe the revenue for various drugs in various years. To go from what observe to what we want, we estimate life cycle earnings of a drug. To do this we use publicly available

data from 2011 to 2015 from the Medicare Part D "dashboard." This a short panel, but when combined with information on the "age" of the drug, we can regress revenue on a polynomial of age.

$$r_{i4t} = \alpha_1(t - t_{0i}) + \alpha_2(t - t_{0i})^2 + \alpha_3(t - t_{0i})^3 + \upsilon_{it} \tag{8}$$

where t_{0i} is the launch year of drug i and r_{i4t} is the observed revenue of drug i in year t. Equation (8) is a cubic without an intercept term.

In order to estimate Equation (8) we combine the revenue data set with information on the launch data of the drug. Here this merger is done using the names of the drugs.[6]

```
> x <- read.csv("Copy of Medicare Drug Spending PartD All Drugs YTD 2015, 12_06_2016.csv",
> y <- read.csv("products.csv", as.is = TRUE)
> x$name <- gsub("[/ | -]","",gsub(" ","",tolower(x$Brand.Name)))
> x$name2 <- gsub("[/ | -]","",gsub(" ","",tolower(x$Generic.Name)))
> y$name <- gsub("[/ | -]","",gsub(" ","",tolower(y$PROPRIETARYNAME)))
> y$name2 <- gsub("[/ | -]","",gsub(" ","",tolower(y$NONPROPRIETARYNAME)))
> y1 <- y[!duplicated(y$name),]
> y2 <- y[!duplicated(y$name2),]
> x <- as.data.frame(x)
> y1 <- as.data.frame(y1)
> y2 <- as.data.frame(y2)
> w <- merge.data.frame(x,y1, by = c("name"))
> w$name2 <- w$name2.x
> w$name2.y <- w$name2.x <- NULL
> v <- merge.data.frame(x,y2, by = c("name2"))
> v$name <- v$name.x
> v$name.x <- v$name.y <- NULL
> z <- rbind(w,v)
> z <- z[!duplicated(c(z$name,z$name2)),]
> z <- z[is.na(z$name)==0,]
```

Given this matched data the next step is to create the data set to be used in the analysis. In the code the difference between the current year and the launch date is called `lag`.

```
> brand_name <- sort(unique(z$name))
> mat_brand <- matrix(NA,length(brand_name)*5,4)
> # Includes years 2011 to 2015.
> k <- 1
> for (i in 1:length(brand_name)) {
```

[6] It would be preferable to do the merger on NDC or some other commonly used code.

```
+   brandi <- brand_name[i]
+   starti <- min(as.numeric(substr(z[z$name==brandi,]$STARTMARKETINGDATE,
+                                   1,4)), na.rm = TRUE)
+   for (j in 1:5) {
+     yearj <- 2010 + j
+     lagj <- yearj - starti
+     if (lagj >= 0) {
+       partdj <- sum(z[z$name==brandi,3+j], na.rm = TRUE)
+       mat_brand[k,1] <- brandi
+       mat_brand[k,2] <- yearj
+       mat_brand[k,3] <- lagj
+       mat_brand[k,4] <- partdj
+     }
+     k <- k + 1
+     #print(k)
+   }
+ }
> colnames(mat_brand) <- c("BrandName","Year","Lag","PartD")
> mat_brand <- as.data.frame(mat_brand)
> mat_brand$Lag <- as.numeric(as.character(mat_brand$Lag))
> mat_brand$PartD <- as.numeric(as.character(mat_brand$PartD))
```

In order to estimate a *distribution* of revenue we do quantile regression.

```
> quant_reg <- function(beta, Y, X, const=TRUE, tau=0.5) {
+   Y <- as.matrix(Y)
+   if (const) {
+     Xb <- as.matrix(cbind(1,X))%*%beta
+   } else {
+     Xb <- as.matrix(X)%*%beta
+   }
+   Y1 <- Y[is.na(rowSums(cbind(Y,Xb)))==0]
+   Xb1 <- Xb[is.na(rowSums(cbind(Y,Xb)))==0]
+   return(sum(ifelse(Y1 < Xb1, (tau-1)*(Y1-Xb1), tau*(Y1-Xb1))))
+ }
> # initial parameters
> lm1 <- lm(PartD ~ Lag + I(Lag^2) + I(Lag^3) -1, data=mat_brand)
> y1 <- mat_brand$PartD
> x1 <- cbind(mat_brand$Lag,mat_brand$Lag^2,mat_brand$Lag^3)
> mat_quant_coef <- matrix(NA,99,4)
> for (i in 1:99) {
```

```
+   taui <- i/100
+   ai <- optim(par=lm1$coefficients,fn=quant_reg,Y=y1,X=x1,
+               const=FALSE,tau=taui)
+   mat_quant_coef[i,1] <- taui
+   mat_quant_coef[i,2:4] <- ai$par
+   #print(i)
+ }
> ave_TAR <- matrix(NA,20,100)
> for (i in 1:20) {
+   ave_TAR[i,1] <- (i-1)
+   ave_TAR[i,2:100] <- (i-1)*mat_quant_coef[,2] +
+     ((i-1)^2)*mat_quant_coef[,3] + ((i-1)^3)*mat_quant_coef[,4]
+   #print(i)
+ }
> ave_TAR[,2:100] <- ifelse(ave_TAR[,2:100]<0,0,ave_TAR[,2:100])
> write.csv(ave_TAR,"ave_TAR.csv")
```

In order to compare apples to apples we need to discount the drug's expected returns back to date of launch. The following calculates this "prize" assuming a discount rate of 8.1%. In net present value terms, the average drug returns $214m from Part D. In order to get an estimate of global expected revenue, this distribution is scaled up by 6.7. This accounts for both Medicare Part D's share of US revenue, average rebates in Medicare Part D and the US share of the global revenue.

```
> npv_list <- function(A,delta) {
+   return(sum(unlist(lapply(1:length(A), function(x) A[x]*delta^x))))
+ }
> wacc <- 0.081
> prize <- c()
> for (i in 2:100) {
+   prize <- c(prize,npv_list(ave_TAR[,i],(1 - wacc)))
+ }
```

Figure 1 presents the distribution of the "prize" associated with successfully getting a drug to market. This distribution is based on the quantile regression estimates above. The lifetime earnings of the drug is discounted back to the date of launch using a 8.1% discount rate.

4.2 Expenditure Estimates

We don't have access to any similar data base to estimate the expenditures associated with bringing a drug through the development process. Given this, we rely on information

```
> plot(density(log(prize)),type="l",col=1,lwd=3,
+      xlab="Log of $",ylab = "density",main="")
```

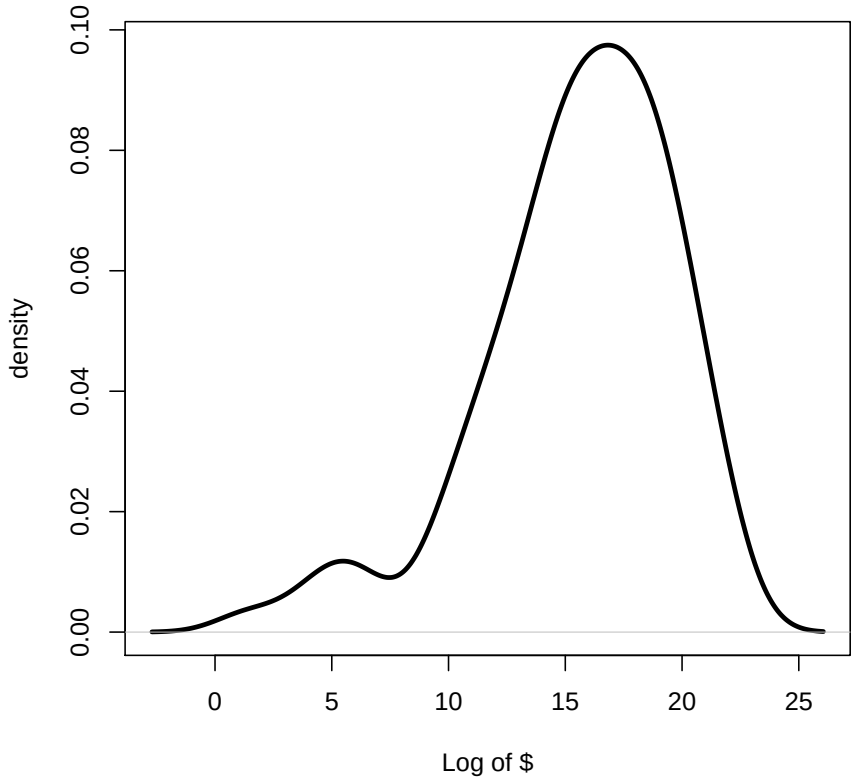

Figure 1: Density of log of revenue. This is the net present value at the time of launch using a 8.1% discount rate. This distribution is based on estimates from the quantile regressions.

reported in DiMasi et al. (2016) regarding a survey conducted by the authors. The survey data comes from ten multinational firms of various sizes. The authors selected a sample of approximately 100 drugs and requested information expenditure associated with these drugs in each of the stages of development.

Table 1 shows that the distribution of expenditures is skewed. In the supplement to their 2016 paper, the authors present fitted log-normal distributions for expenditures and time in phase. The paper uses these fitted parameters for each of the three phases of

Phase	Mean	Median	Std. Dev.
I	25.3	17.3	29.6
II	58.6	44.8	50.8
III	255.4	200.0	153.3

Table 1: Expenditure distributions in $m for each phase from DiMasi et al. (2016).

development.

4.3 Other Observed Distributions

While the revenue and expenditure distributions are the most important, the model also needs estimates for success rates of drugs through clinical trials and the amount of time spent in each phase. Here we use the reported results in DiMasi et al. (2016). These numbers are from a sample of over 1,400 drug candidates that were initially tested in humans between 1995 and 2007.

5 Estimation

As stated above, the values of interest are the expected revenue and expenditure distributions. However, we don't observe these distributions. We observe distributions that have gone through the decision making "filter" described above. To calibrate/estimate the model parameters we therefore solve a Generalized Method of Moments problem.

The moments of interest are as follows.

$$\begin{aligned} &Q(\hat{r}_{i(k+1)}) = Q(r_{i(k+1)}) \\ &Q(\hat{t}_{ik}) = Q(t_{ik}) \\ &E\left(\frac{\hat{M}_k}{N_k}\right) \geq \frac{M_k}{N_{k-1}} \end{aligned} \tag{9}$$

where $Q()$ refers to a quantile of the distribution and $\hat{r}$ denotes the distribution of returns generated by the model and model parameters. The model uses quintiles and all the moments are weighted equally.

The moment function is as follows. Note this function is "wrapped" in order to use the same function for both the parameter calibration and the policy analysis.

```
> require(mvtnorm)
> offer_fun <- function(par,N,mu_r,sd_r,shift_r,
+                 mu_c,sd_c,shift_c,mu_t,sd_t,shift_t,
+                 go_l,p,wacc,T_k,alpha=0,alpha_cut=0.75,alpha_slope=0.1) {
+
```

```
+   # Set up parameters
+   set.seed(123456789)
+   # expected revenue
+   rho_rc <- exp(par[5])/(1 + exp(par[5]))
+   sigma <- cbind(c(exp(par[2])^2, rho_rc*exp(par[2])*sd_c),
+                  c(rho_rc*exp(par[2])*sd_c,sd_c^2))
+   rc <- rmvnorm(N,mean=c(par[1],mu_c),sigma=sigma)
+   r1 <- exp(rc[,1]) - shift_r
+   c1 <- exp(rc[,2]) - shift_c
+   t1 <- (exp(rnorm(N, mean=par[3], sd=exp(par[4]))) - shift_t)/12
+   t2 <- round(t1)
+   t2 <- ifelse(t2 < 1,1,ifelse(t2 > 15,15,t2))
+   c2 <- unlist(lapply(1:N, function(x)
+     sum(rep(c1[x]/t2[x],t2[x])*(1 + wacc)^(c(1:t2[x])))))
+   c2 <- c2*(1 + wacc)^T_k
+   if (alpha > 0) {
+     index <- round(runif(1000, 1, length(r1)))
+     a1 <- unlist(lapply(r1, function(x) mean(ifelse(r1[index] < x, 1, 0))))
+     r1 <- ifelse(a1 < alpha_cut, r1,
+              ifelse(a1 < alpha_cut + (1-alpha_cut)/5, r1*(1 - alpha),
+                     ifelse(a1 < alpha_cut + 2*(1-alpha_cut)/5,
+                            r1*(1 - (alpha + 0.25*alpha_slope)),
+                            ifelse(a1 < alpha_cut + 3*(1-alpha_cut)/5,
+                                   r1*(1 - (alpha + 0.5*alpha_slope)),
+                                   ifelse(a1 < alpha_cut + 4*(1-alpha_cut)/5,
+                                          r1*(1 - (alpha + 0.75*alpha_slope)),
+                                          r1*(1 - (alpha + alpha_slope)))))))
+   }
+   go <- ifelse(p*r1 - c2 > 0, 1, 0)
+   go_prob <- sum(go)/N
+   r2 <- r1[go==1]
+   t2 <- t1[go==1]
+   rs <- exp(rnorm(N,mean=mu_r,sd=sd_r)) - shift_r
+   ts <- (exp(rnorm(N,mean=mu_t,sd=sd_t)) - shift_t)/12
+   quant_r1 <- quantile(rs,c(1:5)/5)
+   quant_t1 <- quantile(ts,c(1:5)/5)
+
+   g <- c(rep(1/5,5) - c(mean(ifelse(r2 < quant_r1[1], 1, 0), na.rm = TRUE),
+       unlist(lapply(c(2:5), function(x)
+         mean(ifelse(r2 > quant_r1[x-1] &
+                       r2 < quant_r1[x], 1, 0), na.rm = TRUE)))),
```

```
+   rep(1/5,5) -
+     c(mean(ifelse(t2 < quant_t1[1], 1, 0), na.rm = TRUE),
+       unlist(lapply(c(2:5), function(x)
+         mean(ifelse(t2 > quant_t1[x-1] &
+                       t2 < quant_t1[x], 1, 0), na.rm = TRUE)))),
+   go_prob - go_l)
+   W <- g%*%t(g)
+   sos <- t(g)%*%W%*%g
+
+   return(list(sos=sos,go_prob=go_prob,
+               ereturn=p*ifelse(r1 < 0, 0, r1) - c2))
+ }
> offer_wrap_fun <- function(par,N,mu_r,sd_r,shift_r,
+                 mu_c,sd_c,shift_c,mu_t,sd_t,shift_t,
+                 go_l,p,wacc,T_k,alpha=0,alpha_cut=0.75,alpha_slope=0.1) {
+   return(offer_fun(par,N,mu_r,sd_r,shift_r,
+                 mu_c,sd_c,shift_c,mu_t,sd_t,shift_t,
+                 go_l,p,wacc,T_k,alpha=0,alpha_cut=0.75,alpha_slope = 0.1)$sos)
+ }
```

Note that the function itself is not dependent upon whether we are considering Phase III or Phase I decisions. However, the inputs into the function will change with the different phases. In particular, the earlier phases will assume to take the results from the later phases as given.

5.1 Phase III Decision

Consider the Phase III go/no-go problem. The observed returns that come out of this problem are assumed to be equal to 6.7 times the net present value of Part D revenue. Other observed variables are described above and their actual values are presented below.

```
> N <- 100000
> M3 <- 1
> prize_draw1 <- 0.8*8.325*prize[round(runif(N*M3,min=1,length(prize)))]/100000
> # tranformed into millions of dollars of global revenue.
> er4 <- prize_draw1[prize_draw1 > 2]
> shift_r <- 0
> r4_mean <- mean(log(er4 + shift_r))
> r4_sd <- sd(log(er4 + shift_r))
> p3_mean <- 0.62   #estimated
> p4_mean <- 0.93   #estimated
> t3_mean <- 3.495 # DiMasi et al (2016) Supplemental
```

```
> t3_sd <- 0.325 # DiMasi et al (2016) Supplemental
> t3_shift <- 3.916
> T3 <- 16/12 # DiMasi et al (2016) Supplemental
> # note the last is adjusted for difference between average time in phase
> # and average time to next phase.
> c3_mean <- 5.204  # DiMasi et al (2016) Supplemental
> c3_sd <- 0.928 # DiMasi et al (2016) Supplemental
> c3_shift <- 10.880  # DiMasi et al (2016) Supplemental
> # this shift is negative (it enters as a negative in the function)
> #go3 <- 150/(450*0.355)  # Based on Blume-Kahout and Sood (2003)
> go3 <- 0.5
> par3 <- c(r4_mean-2,log(r4_sd-1),t3_mean+2,log(t3_sd+1), log(2))
> a_p3 <- optim(par=par3,
+            fn=offer_wrap_fun,
+            N=N, mu_r=r4_mean,sd_r=r4_sd,shift_r=shift_r,
+            mu_c=c3_mean, sd_c=c3_sd, shift_c=c3_shift,
+            mu_t=t3_mean, sd_t = t3_sd, shift_t=t3_shift,
+            go_l=go3,p=p3_mean*p4_mean,wacc=0.081,T_k=T3,
+            alpha=0,alpha_cut=0.75,
+            control = list(trace=0, maxit=10000))
> write.csv(a_p3$par,"a_p3_par_v9.csv")
```

We assume that the policy has a large impact on drugs that expect to earn more revenue than drugs that expect to earn lower down the distribution. We assume that the policy affects drugs that expect to earn in the top 20% of revenue. Moreover, the policies effect increases from a 15% reduction in global revenue to a 25% reduction for the highest expected earners.

```
> # Policy analysis
> alpha2 <- 0.15
> a2_cut <- 0.8
> a2_slope <- 0.1
> b_p3_before <-
+   offer_fun(a_p3$par, N=N, mu_r=r4_mean,sd_r=r4_sd,shift_r=shift_r,
+            mu_c=c3_mean, sd_c=c3_sd, shift_c=c3_shift,
+            mu_t=t3_mean, sd_t = t3_sd, shift_t=t3_shift,
+            go_l=go3,p=p3_mean*p4_mean,wacc=0.081,T_k=T3,
+            alpha=0,alpha_cut=0.75)
> b_p3_after <-
+   offer_fun(a_p3$par, N=N, mu_r=r4_mean,sd_r=r4_sd,shift_r=shift_r,
+            mu_c=c3_mean, sd_c=c3_sd, shift_c=c3_shift,
```

```
+            mu_t=t3_mean, sd_t = t3_sd, shift_t=t3_shift,
+            go_l=go3,p=p3_mean*p4_mean,wacc=0.081,T_k=T3,
+            alpha=alpha2,alpha_cut=a2_cut,alpha_slope = a2_slope)
> b_p3_before$go_prob*p3_mean*p4_mean

[1] 0.2747153

> b_p3_after$go_prob*p3_mean*p4_mean

[1] 0.2744674

> (b_p3_before$go_prob*p3_mean*p4_mean -
+     b_p3_after$go_prob*p3_mean*p4_mean)/(b_p3_before$go_prob*p3_mean*p4_mean)

[1] 0.0009025271
```

Such a policy has a small effect on the number of drugs entering from Phase III conditional on the number of candidates available.

Figure 2 presents a density of returns before and after the policy change. Note that everything has been shifted up. The policy takes away some of the top part of the return distribution. But the figure shows that there is little action around the zero profit level due to the policy.

5.2 Phase II Decisions

As stated above, the estimator is the same for all the decision problems. However, the inputs into the problem are different. In particular, the Phase II decision takes expected returns from the Phase III model. Note that this expected distribution is censored at 0 to account for the option value of entering Phase II. In the code the distribution is shifted up in order to take logs.

```
> N = N
> M2 = 5
> er3 <- b_p3_before$ereturn
> index_er3 <- round(runif(N*M2,1,length(er3)))
> ER3 <- matrix(er3[index_er3],nrow=N)
> er3 <- rowMeans(ifelse(ER3 < 0, 0, ER3))
> shift_r <- 1
> r3_mean <- mean(log(er3 + shift_r))
> r3_sd <- sd(log(er3 + shift_r))
> # Fixed Paramters
> p2_mean <- 0.355   #estimated
```

```
> shift_r <- min(b_p3_before$ereturn)
> plot(density(log(b_p3_before$ereturn - shift_r)),lwd=3,main = "",
+      xlab="log of $ (shifted right)",xlim=c(9.4,9.9))
> lines(density(log(b_p3_after$ereturn - shift_r)),lwd=3, col=2)
> abline(v=log(-shift_r),lwd=3,lty=2)
> legend("topright",c("Before", "After"),col=c(1,2),lwd=3)
```

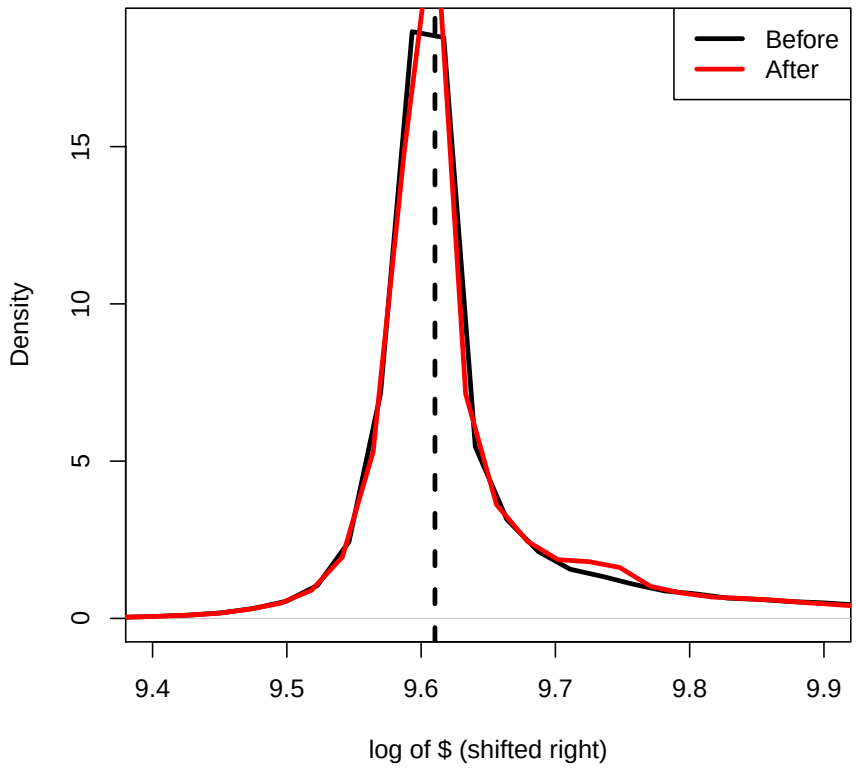

Figure 2: Expected returns for drugs going into Phase 3, before and after a policy that reduces the top 20% of revenue by an average of 20%. The dashed vertical line is the zero-profit level.

```
> t2_mean <- 3.371
> t2_sd <- 0.447
> t2_shift <- 1.629
```

```
> T2 <- (37.9 - 30.5 + 45.1)/12
> c2_shift <- 8.879  # note change in sign
> c2_mean <- 4.007
> c2_sd <- 0.792
> go2 <- 0.5
> par2 <- c(r3_mean-2, log(r3_sd), t2_mean+1, log(t2_sd+1), log(2))
> a_p2 <- optim(par=par2,
+            fn=offer_wrap_fun,
+            N=N, mu_r=r3_mean,sd_r=r3_sd,shift_r=shift_r,
+            mu_c=c2_mean, sd_c=c2_sd, shift_c=c2_shift,
+            mu_t=t2_mean, sd_t = t2_sd, shift_t=t2_shift,
+            go_1=go2,p=p2_mean,wacc=0.081,T_k=T2,
+            alpha=0,alpha_cut=0.75,
+            control = list(trace=0, maxit=10000))
> write.csv(a_p2$par,"a_p2_par_v9.csv")
```

We can again illustrate the policy effects the top part of the distribution. Note that due to expectations the impact of policy is felt more broadly across the distribution.

```
> b_p2_before <- offer_fun(a_p2$par,
+            N=N, mu_r=r3_mean,sd_r=r3_sd,shift_r=shift_r,
+            mu_c=c2_mean, sd_c=c2_sd, shift_c=c2_shift,
+            mu_t=t2_mean, sd_t = t2_sd, shift_t=t2_shift,
+            go_1=go2,p=p2_mean,wacc=0.081,T_k=T2,
+            alpha=0,alpha_cut=0.75)
> er3_a <- b_p3_after$ereturn
> ER3_a <- matrix(er3_a[index_er3],nrow=N)
> er3_a <- rowMeans(ifelse(ER3_a < 0, 0, ER3_a))
> quantile(er3_a,c(1:20)/20)/quantile(er3,c(1:20)/20)

       5%       10%       15%       20%       25%       30%       35%       40%
0.9816799 0.9903923 0.9926317 0.9894104 0.9843041 0.9596628 0.9115907 0.8753206
      45%       50%       55%       60%       65%       70%       75%       80%
0.8546899 0.8302297 0.8179365 0.8065480 0.7929556 0.7827976 0.7792726 0.7773843
      85%       90%       95%      100%
0.7595293 0.7528056 0.7513402 0.7500482

> b_p2_after <- offer_fun(a_p2$par,
+            N=N, mu_r=r3_mean,sd_r=r3_sd,shift_r=shift_r,
+            mu_c=c2_mean, sd_c=c2_sd, shift_c=c2_shift,
+            mu_t=t2_mean, sd_t = t2_sd, shift_t=t2_shift,
+            go_1=go2,p=p2_mean,wacc=0.081,T_k=T2,
```

```
+            alpha=0.05,alpha_cut=0.25,alpha_slope = 0.20)
> b_p2_before$go_prob

[1] 0.48899

> b_p2_after$go_prob

[1] 0.46719

> (b_p2_before$go_prob - b_p2_after$go_prob)/b_p2_before$go_prob

[1] 0.04458169
```

The impact on Phase II decisions is much higher than for Phase III decisions. There is about a 4% reduction in the number of trials. Part of the explanation may be the option value, part may be due to the fact that the decision maker has less information about the value of their drug.

5.3 Phase I Decision Problem

Like the Phase II decision, the Phase I decision takes the distribution of expected net returns from the previous model as given. Again, there is an option value associated with entering Phase I.

```
> N = N
> M1 = 10
> er2 <- b_p2_before$ereturn
> index_er2 <- round(runif(N*M1,1,length(er2)))
> ER2 <- matrix(er2[index_er2],nrow=N)
> er2 <- rowMeans(ifelse(ER2 < 0, 0, ER2))
> shift_r <- 1
> r2_mean <- mean(log(er2 + shift_r))
> r2_sd <- sd(log(er2 + shift_r))
> # Fixed Paramters
> p1_mean <- 0.595   #estimated
> t1_mean <- 3.012
> t1_sd <- 0.529
> t1_shift <- 3.411
> T1 <- (33.1 - 20)/12 + 45.1/12 + 37.9/12
> c1_shift <- 2.112  # note change sign
> c1_mean <- 2.977
> c1_sd <- 0.956
```

```
> go1 <- 0.5
> par1 <- c(r2_mean-1,log(r2_sd-1), t1_mean+1, log(t1_sd+1), log(2))
> a_p1 <- optim(par=par1,
+            fn=offer_wrap_fun, N=N, mu_r=r2_mean,sd_r=r2_sd,shift_r=shift_r,
+            mu_c=c1_mean, sd_c=c1_sd, shift_c=c1_shift,
+            mu_t=t1_mean, sd_t = t1_sd, shift_t=t1_shift,
+            go_l=go1,p=p1_mean,wacc=0.081,T_k=T1,
+            alpha=0,alpha_cut=0.75,
+            control = list(trace=0, maxit=10000))
> write.csv(a_p1$par, "a_p1_par_v9.csv")
```

Again we can look at the effect of the policy on the number of Phase I trials. Again the effect is larger due to the fact that firms have less information about where in the distribution they are likely to end up.

```
> b_p1_before <- offer_fun(a_p1$par,N=N, mu_r=r2_mean,sd_r=r2_sd,shift_r=shift_r,
+            mu_c=c1_mean, sd_c=c1_sd, shift_c=c1_shift,
+            mu_t=t1_mean, sd_t = t1_sd, shift_t=t1_shift,
+            go_l=go1,p=p1_mean,wacc=0.081,T_k=T1,
+            alpha=0,alpha_cut=0.75)
> er2_a <- b_p2_after$ereturn
> ER2_a <- matrix(er2_a[index_er2],nrow=N)
> er2_a <- rowMeans(ifelse(ER2_a < 0, 0, ER2_a))
> quantile(er2_a,c(1:20)/20)/quantile(er2,c(1:20)/20)

       5%       10%       15%       20%       25%       30%       35%       40%
0.7085523 0.7305941 0.7356650 0.7333891 0.7310911 0.7320209 0.7320921 0.7333944
      45%       50%       55%       60%       65%       70%       75%       80%
0.7338610 0.7353216 0.7359032 0.7376206 0.7385240 0.7402841 0.7423169 0.7432242
      85%       90%       95%      100%
0.7440379 0.7471045 0.7476484 0.7499702

> b_p1_after <- offer_fun(a_p1$par,N=N,mu_r=r2_mean,sd_r=r2_sd,shift_r=shift_r,
+            mu_c=c1_mean, sd_c=c1_sd, shift_c=c1_shift,
+            mu_t=t1_mean, sd_t = t1_sd, shift_t=t1_shift,
+            go_l=go1,p=p1_mean,wacc=0.081,T_k=T1,
+            alpha=0.25,alpha_cut=0,alpha_slope = 0)
> b_p1_before$go_prob

[1] 0.52293

> b_p1_after$go_prob
```

```
[1] 0.48794

> (b_p1_before$go_prob - b_p1_after$go_prob)/b_p1_before$go_prob

[1] 0.06691144
```

The estimated impact of Phase I is much larger than for the later phases.

6 Policy Effects On New Drug Development

In order to see the impact of the policy changes on the number of new drugs we can use the model estimates to simulate a policy that reduces expected revenue in period 20. In the simulation, the policy has a compounding effect because it reduces both the incentive to enter Phase III trials but also the incentive to enter Phase II trials. In the model the impact of reduced Phase II trials is to reduce the number of drug candidates available to go into the Phase III trials.

Note that in addition to the impact on expected revenue, we may be interested in a policy that increases NIH funding. In the analysis below, we model a small (2.5%) increase in NIH funding. The elasticity estimates of the impact of the increase in Phase I trials come from Blume-Kohout (2012).

```
> nih_bk <- read.csv("nih_elasticity.csv", as.is = TRUE)$Elasticity
> nih_hr3 <- 10/(39*10)
> nih <- rep(0, 60)
> nih[41:60] <- nih_hr3*nih_bk
> num_ave <- 150000
> entry_p1_mat <- matrix(0,200,3)
> for (i in 1:60) {
+   indexi <- round(runif(num_ave,1,N))
+   p1i <- p1_mean
+   reti <- b_p1_before$ereturn[indexi]
+   goi <- ifelse(reti > 0, 1, 0)
+   T1i <- (exp(rnorm(num_ave,mean=a_p1$par[3],sd=exp(a_p1$par[4]))) -
+             t1_shift)/12
+   enteri <- ifelse(runif(num_ave) < p1i & goi==1,1,0)
+   yeari <- ifelse(i + round(T1i[enteri==1]) < 200,
+                   i + round(T1i[enteri==1]),NA)
+   tabi <- table(yeari)
+   entry_p1_mat[i,1] <- i
+   entry_p1_mat[1 + as.numeric(names(tabi)),2] <-
+     entry_p1_mat[1 + as.numeric(names(tabi)),2] + tabi
```

```
+   if (i > 40) {
+     indexj <- round(runif(num_ave,1,N))
+     p1j <- p1_mean
+     retj <- b_p1_after$ereturn[indexj]
+     goj <- ifelse(retj > 0, 1, 0)
+     goj[goj==0] <- ifelse(runif(length(goj[goj==0])) < nih[i],1,0)
+     T1j <- T1i
+     enterj <- ifelse(runif(num_ave) < p1j & goj==1,1,0)
+     yearj <- ifelse(i + round(T1j[enterj==1]) < 200,
+                     i + round(T1j[enterj==1]), NA)
+     tabj <- table(yearj)
+     entry_p1_mat[1 + as.numeric(names(tabj)),3] <-
+       entry_p1_mat[1 + as.numeric(names(tabj)),3] + tabj
+   } else {
+     entry_p1_mat[,3] <- entry_p1_mat[,2]
+   }
+   #print(i)
+ }
> entry_p2_mat <- matrix(0,200,3)
> for (i in 1:50) {
+   num_ave <- entry_p1_mat[i+10,2]
+   indexi <- round(runif(num_ave,1,N))
+   p2i <- p2_mean
+   reti <- b_p2_before$ereturn[indexi]
+   goi <- ifelse(reti > 0, 1, 0)
+   T2i <- (exp(rnorm(num_ave,mean=a_p2$par[3],sd=exp(a_p2$par[4]))) -
+             t2_shift)/12
+   enteri <- ifelse(runif(num_ave) < p2i & goi==1,1,0)
+   yeari <- ifelse(i + round(T2i[enteri==1]) < 200,
+                   i + round(T2i[enteri==1]),NA)
+   tabi <- table(yeari)
+   entry_p2_mat[i,1] <- i
+   entry_p2_mat[1 + as.numeric(names(tabi)),2] <-
+     entry_p2_mat[1 + as.numeric(names(tabi)),2] + tabi
+   if (i > 30) {
+     num_ave <- entry_p1_mat[i+10,2]
+     indexj <- round(runif(num_ave,1,N))
+     p2j <- p2_mean
+     retj <- b_p2_after$ereturn[indexj]
+     goj <- ifelse(retj > 0, 1, 0)
+     T2j <- T2i
```

```
+     enterj <- ifelse(runif(num_ave) < p2i & goi==1,1,0)
+     yearj <- ifelse(i + round(T2j[enterj==1]) < 200,
+                     i + round(T2j[enterj==1]),NA)
+     tabj <- table(yearj)
+     entry_p2_mat[1 + as.numeric(names(tabj)),3] <-
+       entry_p2_mat[1 + as.numeric(names(tabj)),3] + tabj
+   } else {
+     entry_p2_mat[,3] <- entry_p2_mat[,2]
+   }
+   #print(i)
+ }
> entry_mat3 <- matrix(0,100,3)
> for (i in 1:40) {
+   num_ave <- entry_p2_mat[i+10,2]
+   indexi <- round(runif(num_ave,1,N))
+   p3i <- p3_mean*p4_mean
+   reti <- b_p3_before$ereturn[indexi]
+   goi <- ifelse(reti > 0, 1, 0)
+   T3i <- (exp(rnorm(num_ave,mean=a_p3$par[3],sd=exp(a_p3$par[4]))) -
+             t3_shift)/12
+   enteri <- ifelse(runif(num_ave) < p3i & goi==1,1,0)
+   yeari <- ifelse(i + round(T3i[enteri==1]) < 100,
+                   i + round(T3i[enteri==1]),NA)
+   tabi <- table(yeari)
+   entry_mat3[i,1] <- i
+   entry_mat3[1 + as.numeric(names(tabi)),2] <-
+     entry_mat3[1 + as.numeric(names(tabi)),2] + tabi
+   if (i > 20) {
+     num_ave <- entry_p2_mat[i+10,3]
+     indexj <- round(runif(num_ave,1,N))
+     p3j <- p3_mean*p4_mean
+     retj <- b_p3_after$ereturn[indexj]
+     goj <- ifelse(retj > 0, 1, 0)
+     T3j <- T3i
+     enteri <- ifelse(runif(num_ave) < p3i & goi==1,1,0)
+     yearj <- ifelse(i + round(T3j[enterj==1]) < 100,
+                     i + round(T3j[enterj==1]),NA)
+     tabj <- table(yearj)
+     entry_mat3[1 + as.numeric(names(tabj)),3] <-
+       entry_mat3[1 + as.numeric(names(tabj)),3] + tabj
+   } else {
```

```
+     entry_mat3[,3] <- entry_mat3[,2]
+   }
+   #print(i)
+ }

> (mean(entry_mat3[20:24,2] - entry_mat3[20:24,3]))/mean(entry_mat3[20:24,2])

[1] 0.05115132

> (mean(entry_mat3[25:29,2] - entry_mat3[25:29,3]))/mean(entry_mat3[25:29,2])

[1] 0.1942978

> (mean(entry_mat3[30:34,2] - entry_mat3[30:34,3]))/mean(entry_mat3[30:34,2])

[1] 0.2270552

> (mean(entry_mat3[35:39,2] - entry_mat3[35:39,3]))/mean(entry_mat3[35:39,2])

[1] 0.2693861
```

The 20% reduction in revenue from the top of the distribution leads to 6% fewer drugs in the first 5 years after the policy. This increases substantially in the second 5 years, then again to 23% fewer drugs in the third 5 years finishing with around 30% fewer drugs in 15 to 20 years after the policy.

Figure 3 presents a visual description of the policy where we account for the impact on each of the phases. It shows that the policy has a negligible impact in the first 5 years after the policy. The policy effect increases to about 10 to 15 years after the policy change.

7 Conclusion

The proposed pharmaceutical innovation model provides a way to think about how various policies affect new drug entry. The model considers the firm's decision at the start of the various phases of human clinical trials. The firm considers the expected cost and the expected returns of entering the phase. As an example the paper considers what happens when a policy is introduced that reduces the top decile of revenue by 20 to 30%. The model estimates that such a policy reduces the number of drugs entering the market by 30%. Due to a compounding affect through the phases, the policy takes over ten years to be fully felt.

```
> a1 <- mean(entry_mat3[10:40,2])/30
> plot(entry_mat3[,1],entry_mat3[,3]/a1,col="red",lwd=3,
+      ylim=c(0,50),xlim=c(10,40),xlab="Year",ylab="New Drugs")
> lines(entry_mat3[,1],entry_mat3[,2]/a1,type="p",col=1,lwd=3,pch=2)
> abline(v=20)
> abline(v=30, lty=2)
> legend("bottomleft", c("Baseline","Policy"),col=c(1,2),
+        lwd=3)
```

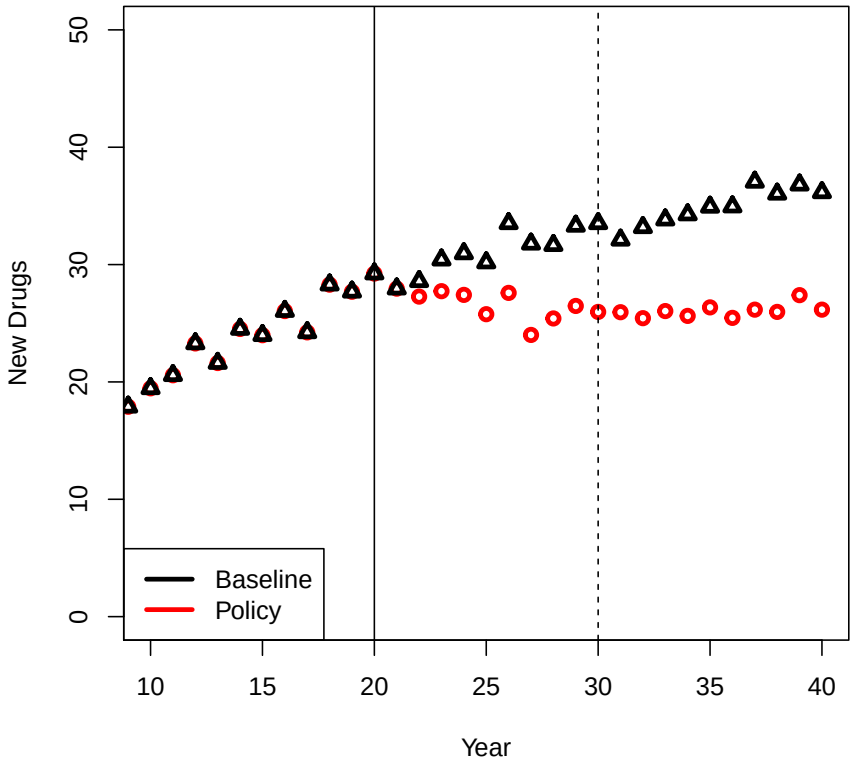

Figure 3: Plot of the impact of the policy, where the policy arrives in period 20. The policy impacts between 20% and 30% of revenue for drugs that expect to be in the top 10% of the revenue distribution.

References

D Acemoglu and Joshua Linn. Market size and innovation: Theory and evidence from the pharmaceutical industry. *Quarterly Journal of Economics*, 119:1049–1090, 2004.

Christopher P. Adams and Van Brantner. Estimating the cost of new drug development: Is it really $802 million? *Health Affairs*, 25(2):420–428, 2006.

Margaret E. Blume-Kohout. Does Targeted, Disease-Specific Public Research Funding Influence Pharmaceutical Innovation? *Journal of Policy Analysis and Management*, 31 (3):641–660, 2012.

Margaret E. Blume-Kohout and Neeraj Sood. Market Size and Innovation: Effects of Medicare Part D on Pharmaceutical Research and Development. *Journal of Public Economics*, 97:327–336, 2013.

Joseph DiMasi, Henry Grabowski, and Ronald Hansen. Innovation in the pharmaceutical industry: New estimates of r&d costs. *Journal of Heath Economics*, 47:20–33, 2016.

Pierre Dubois, Olivier de Mouzon, Fiona Scott-Morton, and Paul Seabright. Market size and pharmaceutical innovation. *RAND Journal of Economics*, 46(4):844–871, 2015.

James Heckman and B Honore. The Empirical Content of the Roy Model. *Econometrica*, 58:1128–1149, 1990.