Improving the 'Cancer Megafund' Model: Simulations with Heterogeneity, Infrastructure, & Random Matrices

Won (Ryan) Lee

Abstract

Recently, Fernandez et al. proposed an innovative model of funding high-risk biomedical research by way of securitization. Through this proposed investment vehicle, the pool of all projects in the portfolio would be securitized, and the operational risk of a particular R&D project would be diluted among all investors. To demonstrate the validity of this approach, the paper included a computational simulation of the megafund with promising results. Yet a number of factors were left out of the model, which rendered the simulations less than fully convincing. In this paper, we improve upon the model by adding empirically observed effects to the framework, such as infrastructural synergy between investments, heterogeneity of projects, and stochastic fluctuations in success probabilities at each time point.

Introduction

These are troubling times for biomedical research in the U.S.; indeed, as the director of the National Institutes of Health (NIH), Francis Collins, has noted, "It was the best of times, it was the worst of times." (Rockey and Collins, 2013) While talented and visionary scientists at research universities, national laboratories, and other sites continue to make tremendous progress against ailments such as Alzheimer's disease, cancer, HIV/AIDS, and more, they are quickly being depleted of research funding sources. Most prominently, the budget sequestration of 2013 nearly crippled the NIH's capacity to fund new research projects, and all R&D funding agencies in the U.S. saw their budgets cut by 5-7% in 2013 (Reif and Barrett, 2013). Because the NIH must continue to honor its funding pledges to current projects, Collins and others in the field have warned that the burden of financial austerity will be most heavily borne by younger researchers (Rockey and Collins, 2013). As a result,

there exist significant worries that the U.S. will face a lost generation of research talent, as funding uncertainties and competition from other countries mount.

A number of suggestions have been made to remedy this situation over the years, as funding for science has continued to decline after adjusting for inflation. Recently, scientists have begun relying more and more on charitable foundations and philanthropic donors (Ledford, 2012). Though questions have been raised regarding both the morality of receiving such investments and their propensity to limit and circumscribe academic freedom (Krimsky, 2011), such alternate sources of funding have generally been viewed in a positive light in the scientific research community. In fact, scientists have claimed that securing these nontraditional funding sources allowed them to pursue riskier and non-mainstream projects that would otherwise have not been funded by sources such as the NIH.

Consequently, it has become of interest to determine if other effective models of funding biomedical research can be found or constructed. In particular, the distinct lack of a 'market' for biomedical research has been seen as a concern, especially after recent evidence that very novel and risky innovations may require extensive funding by robust financial markets to be successful (Nanda and Rhodes-Kropf, 2011). This is especially puzzling given the rise of 'big pharma', massive corporations conducting R&D to develop and market pharmaceutical therapies. Fernandez et al. (2012) note a related paradox to the one mentioned in the opening paragraph above: there has been a near doubling of the aggregate R&D budget from 2002 to 2010, yet there has been negligible impact on the sheer number of new drugs and average rate of return on life sciences venture-capital investments in the decade ending in 2010 has been –1%. Indeed, the problem of effective innovation has been noted as the defining challenge for the pharmaceutical industry in the coming years (Paul et al., 2010).

In light of these inconsistencies, the authors propose an explanation in the form of increasing complexity and uncertainty in the biomedical research sector (Fernandez, Stein, and Lo, 2012). First, it is indisputable that the science of biomedicine has become increasingly more complex in recent years. With an understanding of the sigmoid nature of innovation and the technology life-cycle, it is reasonable to expect significantly decreasing returns as a technology matures (Foster, 1986). As a result, the costs of achieving similar innovative output increase over time. Moreover, the authors argue that economic and policy conditions have exacerbated the costs and uncertainty of the biomedical innovation process.

A host of factors have converged to make circumstances much less certain, including the patent cliff of 2012, Vioxx debacle, healthcare reform and its economic repercussions, stock market volatility, and continuing financial uncertainty and illiquidity from the financial crisis. All of these factors result in traditional sources of funding from both public and private entities becoming less effective; increased risk and uncertainty must, in the current situation, be borne by individual institutions and investors, which makes such grants and investments even less attractive.

This prompted the proposal of a 'megafund' structure, which would consist of a portfolio of biomedical research projects at various stages of development funded by this particular vehicle (Fernandez et al., 2012). In doing so, the megafund would achieve two intertwined aims. First, having a single, large portfolio of many disparate research projects would lead to the diversification of risk. Second, this diversification would allow for funds to be raised by issuing both debt and equity. Because debt markets are significantly larger than equity markets ($1 trillion in corporate debt was issued in 2011, compared to $41 in initial public-equity offerings), this approach would allow for the raising of much more capital than through only equity offerings.

The possibility of issuing debt rather than equity is critical for biomedical research in particular, for a number of reasons. Most importantly, debt financing can be structured in such a way as to accommodate the investment horizons of the projects in the megafund's portfolio. Because biomedical research, especially for preclinical projects, requires significantly longer-term horizons than those typically offered by venture capitalists and public companies, the capacity to issue debt with maturities on the order of decades is seminal. Substantial economic value is routinely destroyed in the biomedical research community due to sudden interruptions in funding and other financial constraints; as a result, the megafund's ability to provide continuity and stability in funding would remove such "scientifically perverse but economically rational" effects (Fernandez et al., 2012).

The idea of a megafund builds on trends in the pharmaceutical industry and associated corporations. While securitization is not utilized by any entities in the pharmaceutical industry or life sciences venture capital, but diversification has been an overarching objective for many in the industry, through the pursuit of mergers and acquisitions. Debt financing has also become more common, with Roche Holdings' $16.5 billion bond issuing in 2009 being the second-largest corporate-bond offering of all time.

The megafund stands in contrast to biopharma mutual funds in that both debt and equity can be issued, and investments are made in a much wider range of assets than publically-traded companies. Fernandez et al. (2012) note resemblances to drug-royalty investment companies, which acquire ownership interests in approved drugs' royalty streams, and point out that such investment vehicles have been able to raise debt to finance their operations. Thus, such debt-issue prospects appear feasible for the megafund proposal.

Initial Model

The model originally developed by Fernandez et al. (2012) relies on the securitization of a large number of assets, in the form of biomedical research projects. Dubbing such debt 'research-backed obligations' (RBOs), the authors propose the creation of a special purpose vehicle for the purpose of purchasing the collateral for the debt (namely biomedical R&D projects and licenses, and the profits generated) and issuing the securities. The cash flow generated, mostly from royalties from drugs developed from the projects in the megafund's portfolio, is first used to satisfy the debt obligations, and the residual amount of assets and cash flow is paid out proportionally to equity holders. Securitization also entails the division of these RBOs into different tranches, which are characterized by different repayment priorities. For example, the senior tranche has 'highest priority' in that its obligations are satisfied before any of the lower tranches; similarly, each junior tranche obligation is satisfied in order of its priority. Consequently, the senior tranche is least likely to experience losses or potential default, resulting in the lowest risk and return. This makes such debt attractive to money market funds, banks, and pension funds. Lower-level tranches, which has higher probabilities of losses and correspondingly higher returns, would be more attractive to risk-tolerant investors such as private investors and large pension funds.

To model the performance and feasibility of such a fund, this megafund model was implemented in R and Matlab frameworks in the case of a cancer megafund. Cancer, due to its intrinsically diverse nature, yields greater opportunities for portfolio diversification; moreover, comprehensive databases of cancer drug-development exist. Using these historical industry values, a transition matrix is estimated for projects in each stage of the biomedical research process to the next (preclinical, phase I, phase II, phase III, new drug application,

approval, and withdrawal). The model also allowed for simulations starting and ending at customized points, to allow for the possibility of early-stage or late-stage preferences.

The original paper presents results from simulations of a $5 billion megafund, invested over 7.5 years in 100 preclinical and 100 phase I projects. The initial capital is split into $1.25 billion senior tranche, $1.25 billion junior tranche, and $2.5 billion equity tranche, resulting in a leverage ratio of 2. Over the course of 500,000 simulations, the senior tranche obligations received annual coupons of 5% and were satisfied 99.9% of the time, which would generally be equivalent to highest-rated bonds by Moody's and the S&P. Junior-tranche obligations received annual coupons of 8% and were satisfied 99.1% of the time, while equity investors received 8.9% annually on average. Such numbers would render the fund attractive to more conservative investors; in particular, public pension funds, which totaled $3 trillion in 2012, set a target of 8% annual returns, which could be met by junior tranches or other, more customized securitizations.

Model Improvements

As noted in the closing of their paper, however, the results of this simulation, while definitely promising, depend strongly on the assumptions and parameters used in the model. In particular, a number of features were prominently absent from the model that were empirically evident in the biomedical research industry.

First, despite the megafund's focus on the capacity for diversification among R&D projects, the model ironically did not include provisions for different 'types' of R&D projects. Even in a particular stage for a megafund exclusively focusing on oncology research investments, there exist many different types of potential projects that the fund can invest in. For example, consider the fact that in oncology alone, there exist over 200 different known types of cancers. Moreover, approaches to each individual cancer can be tremendously diverse, ranging from novel tools for diagnosis and screening to techniques and innovations in surgery and chemotherapy. This gamut becomes much wider when viewed in the context of the entire biomedical industry rather than just oncology research. Thus, it appeared more than reasonable to include heterogeneity of projects in the model, with each type of project proceeding along separated paths in the simulation and with different parameters. For the purposes of proof of concept, we included five different types of projects in the model,

which led to a much expanded transition matrix consisting of transition probabilities between stages for each type of investment separately. In light of consistency, however, parameters regarding the pricing of each type of project at each stage were kept the same for illustration. The expanded matrix framework would permit the customization of setting different pricing parameters for each type of project, however.

A second improvement upon the model was suggested by a letter to the editor by Tenenbaum, who noted that with the vast amount of funds pooled by the megafund, it could do more than simply invest in projects (Tenenbaum, 2013). Instead, the megafund could "*change the rules*" by creating an 'ecosystem' of shared services for drug development and patient-based oncology services. This would accelerate the process of drug development and simultaneously allow megafund projects to leverage the resources, successes, and discoveries of other projects. To see how such effects would play out in practice, we implemented infrastructural synergistic effects for projects in the model. The user could specify how much of the initial pool of funds would be used for the purposes of developing this ecosystem, or infrastructure, of oncology research. Based on this investment and its proportion to the total amount of the megafund, additional probabilities were added to the transition matrix for success. For the purpose of illustration, 10% of the proportion of the infrastructural investments to total funds was multiplied by the original probabilities and linearly added to the transition matrix; i.e., if going from phase I to phase II originally had a probability of 0.130, and $500 million from a total of $5 billion (10%) was invested in infrastructure, this would result in an improved probability of 0.143 for the transition. Formally:

$$f_n = \frac{I_n}{T_n} \;\Rightarrow\; p_{n,k} = 0.1 \cdot f_n \cdot p^0_{n,k}$$

where n denotes the particular path of the simulation and k is the stage of the project for which the probability is being computed.

Finally, the model had little stochasticity. While it is true that transitioning between phases was stochastic in this effective Markov model, the probabilities themselves were determined and set by the user at the start of the simulation. Irrespective of financial, political, or scientific conditions, and of whether other projects had already succeeded, the transition probabilities remained identical throughout the entire simulation. We believed that

in order for the simulation to be truly realistic, the transition matrix itself had to be stochastic; in other words, it had to be formulated as a random matrix. This was achieved in the following manner:

1. Each transition probability was drawn from a normal distribution centered at a mean specified by empirical data, set at the deterministic values given by Fernandez et al. (2012).
2. The variation from the mean was computed at each time point by subtracting the mean from the probability drawn.
3. Each 'type' of R&D project received either the full or half the variation, in positive or negative quantities. In our model, the type 1 project always received + variation; type 2 received + 0.5 variation; type 3 received no variation; type 4 received – 0.5 variation; and type 5 received – variation.

Mathematically, we have, for each set of returns:

$$X_i \sim \mathcal{N}(\mu_i, \sigma_i^2)$$

where *i* indicated the particular time point and the values were given by empirical data from Fernandez et al. The variations were calculated as:

$$v_i = X_i - \mu_i$$

and the respective returns were given as follows:

$$\begin{aligned} R_{1,i} &= X_i + v_i \\ R_{2,i} &= X_i + 0.5 \cdot v_i \\ R_{3,i} &= X_i \\ R_{4,i} &= X_i - 0.5 \cdot v_i \\ R_{5,i} &= X_i - v_i \end{aligned}$$

Note that the above does not elevate one type of project over the other, because the variation is symmetric about 0 and could be negative or positive with equal probability. Moreover, the above formulation introduced a negative correlation between projects, which

we felt was more realistic than full independence between projects. Consider projects in oncology, tackling a particular cancer; if one type of project, i.e. blocking a particular biochemical pathway, succeeds, than another type of project, i.e. blocking a competing pathway, will be at least commercially unsuccessful. Thus, it appeared reasonable to negatively correlate different types of projects.

Results & Conclusions

Simulations of the megafund were completed with the parameters provided by Fernandez et al. (2012) and with the specified improvement parameters as provided above. We conducted identical simulations of 500,000 paths using $5 billion total in funds, with $1.25 senior tranche, $1.25 junior tranche, and $2.5 equity investments. The proportion of funds used for infrastructural investment was varied between 5% and 30% of the total fund amount. In nearly every simulation, we obtained results on par with if not better than the results generated by the model in the original paper. In fact, most iterations of the model resulted in significantly improved prospects for investment, especially for the junior tranche and equity holders. The average annual returns were 5.7% was senior tranche RBO holders (compared to 5% for the initial model); 9.1% for junior tranche RBO holders (compared to 8% for the initial model); and 10.2% for equity holders (compared to 8.9% for the initial model). Moreover, the risk was reduced, presumably due to the increased probabilities of at least a certain type of projects succeeding in every iteration. Senior tranche holders could again expect full satisfaction of obligations 99.9% of the time, while junior tranche holders could expect improved prospects of 99.4% (rather than 99.1%).

Thus, it appears that even with the more empirically relevant corrections and improvements made, the returns offered by the model are highly attractive to a wide variety of investors. Moreover, these complications actually improve the prospects of the generated returns and do not remove the possibility of debt financing, which is a key component of the model. Finally, even with the heterogeneity of projects and resulting negative correlations between the various investments, there does not appear to be a significant danger of massive defaulting, which was a major problem of the financial crisis of 2007-2008. Correlations between CDOs, which were not taken into account in predictive models by ratings firms in the 2000s, resulted in a 'systemic failure' of mortgages; the heterogeneity component and

negative correlations between projects take stock of this possibility, yet the probabilities of default on both the senior and junior tranches still remain low. It is expected that this results from the fact that most investments in this fund are expected to fail; consequently, the improved prospects of success of particular types of projects more than offsets then reduced probability of success of negatively correlated types. Thus, we believe that the megafund model is indeed a feasible vehicle for funding biomedical research.

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