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EVALUATING R&D ALLIANCES UNDER UNCERTAINTY: A REAL OPTIONS APPROACH

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Chapter 1

Introduction

1.1 Introduction

Technology-intensive landscape has changed and new business models, based on research and development (R&D) alliances, are increasingly being adopted. Particularly in high-technology sectors, R&D alliances - contractual asset pooling or resource exchange agreements between firms - appear to have become a routine strategic initiative (Stuart, 1998). Partnerships between airlines, joint ventures between car manufacturers, co-development contracts between pharmaceutical and biotechnology companies, production sharing between oil majors and national oil companies, collaborations between telecommunications and mobile technology companies, are just some examples of industries where alliances are significant drivers of value (Savva, 2006). As a matter of fact, R&D collaborations are argued to offer multiple benefits such as access to complementary resources, taking advantage of more business opportunities, as well as sharing of both development costs and risks (Hagedoorn 2002; Gassmans, 2006; Du et al. 2013). These agreements represent one of the most important Open Innovation practices. Chesbrough (2003) coined the term "open innovation" to indicate how big companies changed their traditional way of new business development by opening the firm's boundaries to external inputs and combining external and internal technology development. This new paradigm suggests that organizations should put even greater emphasis on R&D collaborations. Accordingly, R&D alliances – that gained increased popularity in the 1990s with more than 20,000 new alliances formed in the U.S from 1987 to 1992 (Harbison and Pekar, 1998) - have continued to rise by as much as 25 percent every year (Deloitte 2008) and they are expected to grow in future (Deloitte 2012). However, as stated in Lukas (2008, p. 3), the overall growth of technology alliances, is somewhat odd since firms have hitherto preferred to internalize their R&D activities. In fact, on the one hand, collaborations with other firms could help to access complementary resources (such as information, tangible and intangible resources, technological knowledge), which are critical to foster the introduction of innovations, and give the opportunity to share the risks and costs involved in the process (Powell et al., 1996). On the other hand, there might be different reasons to reach the final market with products whose revenue are not shared with the partner in order to appropriate higher

profits. In fact, the income coming directly from the alliance as well as all the benefits it could offer are likely subject to significant uncertainty from each partner's perspective, especially in the initial stage of their joint operation. For instance, two firms may establish an alliance to develop some new technology that is expected to benefit both. However the outcome of their joint effort may turn out to suit one partner's needs much better than the other partner's (Chi, 2000, p.6). As a result, firms are constantly being confronted with the decisions whether to develop a particular technology in-house, or whether to source it externally (Vanhavarbeke et al. 2008).

Given these considerations, it is interesting to understand under what conditions R&D alliances would perform better than the corresponding activity traditionally conducted in house. Yet, surprisingly, there has been very little attention to this important issue. As a matter of fact, according to Huizing (2011), a decent cookbook, i.e. an integrated framework that helps managers to decide when and how to deploy open innovation practices (R&D alliances in particular), is missing. This consideration is especially true if a portfolio of R&D collaborations is considered. In fact, little is known on how to manage several R&D collaborations simultaneously. Studying the challenges of simultaneous management of multiple R&D collaborations is a neglected issue in both research and managerial practice (Harbison and Pekar, 1998; de Man and Duysters, 2002). Financially constrained decision-makers should select projects accurately, being sure to choose the most promising, and must consider new paradigm solutions including next-generation licensing and effective precompetitive collaborations with other companies (Dhankhar et al., 2012), without neglecting interdependencies among products and strategic goals. However a framework that helps managers in making this critical decision is missing. Also, the stage of the innovation process where collaboration is the most effective is still not very clear and it is currently one of the key issues debated in the open innovation literature (Huizing, 2011).

This thesis attempts to contribute to these issues. Generally speaking, it enhances our understanding of when, and under what circumstances it is advantageous for firms to engage in the use of either in-house R&D activity, or R&D alliances. On the one hand it discusses the implications of managing a portfolio of R&D projects, with the main aim of investigating the key factors that influence the important choice to develop them resorting to an internal or an external path. On the other hand, this work sheds light on

when, i.e. in which stage (if any) of the innovation process, collaboration is the most effective, by taking into account the important role of competition. Moreover, since these kinds of decisions are traditionally made in a stochastic environment, I address these issues by adopting a real options approach. The results have also important practical implications for business professionals involved in alliance process management.

1.2 Research context, motivation and thesis outline

An *alliance* can be defined as any independently initiated cooperation between firms. It involves an exchange, sharing or co-development of capital, technology, or firm-specific asset, and is performed by either joint ventures, marketing and distributions agreements, or technology licensing or transfer agreements (Gulati 1995, Lukas 2008).

Usually, R&D alliances[1] not only generate stochastic benefits (*uncertainty*) but also bring sunk costs (*irreversibility).* In addition, a key element in these agreements is *flexibility*: firms have the opportunity, not the obligation to sign an alliance, or sometimes the right to renew an existing one. In other words they can wait to form an alliance when more information is available. Therefore, analyzing these kinds of alliances in *a real options* framework can precisely capture these important three aspects (Nischide and Tian, 2011). As a matter of fact, real options analysis (ROA) has been recognized to evaluate investments which involve a significant amount of both uncertainty as well as irreversibility (Dixit and Pindyck, 1994). Traditionally, ROA has been concerned with the valuation of projects with real options owned exclusively by one firm. However this assumption is often unrealistic: more frequently, projects are developed by a consortium of firms (Savva, 2006). Very little research has focused on the evaluation of uncertain R&D partnerships through ROA (Lukas, 2008) and it traditionally dealt with the evaluation of the single R&D partnership. Several interesting aspects have not been sufficiently investigated.

First, it is very interesting to take a holistic point of view and model the whole R&D portfolio of the alliances as a series of options whose exercise depends on the performance of all the constituent parts of the portfolio. While valuing portfolios of options is one of the most important problems in both real options and corporate

[1] Throughout the thesis I adopt the terms: alliance, partnership, collaboration without distinction.

finance in general, it has not been satisfactorily addressed (Brosch, 2008). Obviously, managers are financially constrained and then they cannot buy all the options: as a consequence, a portfolio perspective is needed to properly allocate the limited budget and to consider the interdependencies among projects. Considering R&D collaborations in a projects portfolio management, is a key for any corporation facing strategic resources allocation decisions. Also, when considering entry into a new R&D project development, firms must first make a decision between separate and cooperative operations with other firms (Nischide and Tian, 2011), i.e. between developing projects on their own or adopting new paradigm solutions. In this context, interesting questions arise that have not yet found any answer.

i. *What are the managerial implications of considering an R&D collaboration in a portfolio of R&D projects?*
ii. *Under which conditions do R&D alliances perform better than the traditional innovation practices conducted in house, when the whole projects portfolio is considered? (What are the portfolio parameters that push to an open way (by signing partnerships) rather than to a closed way to innovate?)*

Second, since R&D project development is a dynamic process (Pinto and Prescott, 1988) during which partnerships are initiated, developed or terminated at different point of time, one important aspect of R&D collaborations is the optimal timing to sign a partnership during the R&D development process. Very little is known on the optimal timing to establish an R&D alliance. Extent research focused on this issue (Kalamas et al. 2002; Nicholson 2005; Rogers et al. 2005; Lukas 2008), but it does not consider the important role of the competition. Savva (2006, p.3) states that " In a number of industries, firms that undertake investments have an impact on market price and thus affect the profits of all firms in the industry. These firms must base their decisions not only on the stochastic underlying, but also on the actions of other firms in the industry." As a consequence, it is more realistic to incorporate the possible re-action of competitors in the decision-making process. Given this important consideration, interesting questions that have not yet found any answer are:

i. *In which stage of the uncertain innovation process is (if any) R&D collaboration most effective, when competition is taken into consideration?*
ii. *What are the factors that induce firms to welcome or disregard the opportunity of collaborating with other firms in a competitive and uncertain environment?*

By adopting a real options approach, I attempt to answer these research questions. Specifically, the present research focuses on the evaluation of R&D alliances under uncertainty in two research areas of practical importance: portfolio management literature and alliance timing literature. Accordingly, in the first part of this dissertation (chapter 3 and chapter 4) I analyze how R&D alliances impact projects portfolio decisions, whereas in the second part (chapter 5) I analyze how competition impacts alliance timing decisions. Particularly, in my analysis, I refer to the biopharmaceutical industry. As a matter of fact, the pharmaceutical industry has experienced the advent of biotech newcomers in an increasing number of R&D collaborations (Gupta et al., 2007). In this industry, strong portfolio management is pivotal in helping to focus company resources effectively on the most attractive projects, especially in the very uncertain first stages of the R&D development process (Betz, 2011). In addition, the biotechnology industry is characterised by the presence of many competitors (Deloitte, 2005; FierceBiotech, 2007). Deloitte survey reports that a solid majority of both large and small companies in this industry believes that the alliance market will become even more competitive (Deloitte, 2005). By contrast, research that includes competition in the dynamic setting of biopharmaceutical collaborations is missing. These apparent *lacunae* motive the present Ph.D. dissertation. In details, I organize this thesis around the following chapters.

Chapter 2 provides a wide discussion of the existing literature on the main topics covered in this thesis, in order to highlight the gap this research aims at filling and collect necessary elements for the models proposed in the further chapters. Specifically, the first section of Chapter 2 provides an overview of the theoretical background on the investments under uncertainty, illustrating the main real options approaches used to evaluate R&D investments. In the second section, an extensive discussion of relevant studies - including ROA based contributions - in portfolio management literature is offered. The third section discusses that part of option analysis which combines with

game theory, that is, the ROG (real options game) literature is discussed. Section 2.4 points the attention to the benefits of open innovation that can be partly explained by applying the real option approach, while in section 2.5 a discussion of relevant studies in alliance literature – with a particular focus on theoretical modeling in the setting of R&D alliances- is offered. Finally, in section 2.6, the goal this research aims to reach is also provided.

Chapter 3 is the outcome of the collaborative work with Giovanna Lo Nigro and Gianluca Enea (Lo Nigro et al. 2014) and deals with R&D collaborations managed simultaneously in a pharmaceutical R&D portfolio. By taking the perspective of pharmaceutical firms, I introduce a stochastic portfolio optimization model for making optimal project selection decisions when potential R&D alliances with biotechnology firms are considered. Indeed the developed model is able to select which R&D projects to finance and how to carry them out- that is, developing them in-house or in alliance with a biotechnology company, which represents an operative way to deploy open innovation practices. In addition, the self-financing option is modelled, that is, once commercialized, some products can finance other projects in the pipeline. Research findings suggest that considering R&D collaborations in the analysis makes an important contribution to the value of the chosen portfolio. In fact, the results obtained for the developed numerical case suggest the selection of a multi-balanced portfolio: the most valuable products that have reached the last stage of the development process are chosen in-house, in order to maintain their total ownership. Conversely, R&D collaboration is preferred in the case of products at their early stages of development (and thus characterized by higher uncertainty) and that will not necessarily come to market: the pharmaceutical company shares both development costs and potential revenues of these projects with the biotechnology company. Interestingly, the mix between in-house activity and R&D collaborations as well as the presence of a self-financing policy, cause an overall increase of the real option value of the portfolio compared to its value estimated without considering the alliance option and the self-financing option.

Chapter 4 is the outcome of joint work with Giovanna Lo Nigro and aims at understanding what are the portfolio parameters that would push to a strategy of open innovation rather than to a closed one, which means under which conditions

pharmaceutical companies should collaborate with biotechnology companies when the whole portfolio of real options is considered. To this aim, starting from the model illustrated in the previous chapter, a DSS (Decision Support System), more and more used in literature to answer to similar questions, is proposed. Research findings show interesting managerial and academic implications: the main driver in product robustness (resilience in the optimal portfolio) and in determining the way the product is developed (in-house or in alliance) is the Net Present Value (NPV) of cash flows that result from the commercialization of the product (that represents the underlying of the related real option): specifically, the higher this value, the higher the convenience to select the project and develop it in house. Also the potential added value from the partner plays an important role in product selection: indeed, as it increases, the convenience to select and develop the product in alliance increases, confirming the importance of complementary resources in open innovation literature.

Chapter 5 is the outcome of collaborative work with Giovanna Lo Nigro, Serena Robba and Paolo Roma (Lo Nigro et al. 2013) and focuses on the time aspects of R&D biopharmaceutical collaborations in presence of competition. Some authors highlight the optimal time to sign a partnership during the R&D biopharmaceutical process (Kalamas et al. 2002; Nicholson 2005; Rogers et al. 2005), but they do not consider competition. However, it is more realistic to incorporate the possible re-action of competitors in the decision-making process, especially in the biotechnology industry, which is characterised by the presence of many competitors (Deloitte, 2005; FierceBiotech, 2007). In this part of the thesis I introduce and analyse the effect of competition in biotechnology industry by modelling the decisions of whether and when ally with a pharmaceutical company through a two-stages real options game. Research findings suggest that the timing decisions depend on the level of the competition, synergies obtained through the alliance and contract terms offered by the pharmaceutical company as well. Interestingly, I also show that the first mover might not always pre-empt the follower in partnering with the pharmaceutical company.

Finally, chapter 6 concludes and presents the main theoretical contributions and managerial implications of this dissertation. It also outlines the limitations of this work and suggests further research developments. Among the others, a very interesting development could aim at testing some results of this research in laboratory through an

experimental laboratory approach. Does real options theory describe actual investment behaviour? Recent studies (Yavas and Sirmans 2005; Oprea et al. 2009; Anderson et al. 2010) focused on this issue, considering investments decisions. Therefore, future research could aim at investigating human choice behaviour in R&D alliance decisions, by developing quantitative models in order to predict and explain behaviour in this particular context.

Chapter 2
Literature review

2.1 Real options analysis: theoretical background

A major advance in development of R&D project selection tools came with the application of options reasoning to R&D. The evaluation of investment projects is generally done by using discounted cash flows based methods such as the net present value (NPV). However, in the field of R&D projects, where high uncertainty and risks are prominent, these methods lose a large amount of their effectiveness. In fact they fail to correctly assess the real value of these projects which results, among other things, from the flexibility possessed by the management and from the several opportunities these kinds of investments offer (Myers 1987, Dixit and Pindyck 1994, Trigeorgis 1988, Trigeorgis 1995, Smit 1996). Although traditional methods are still the most frequently used to evaluate R&D projects (Hartmann and Hassan 2066), the enormous pressure to innovate, especially in the knowledge-intensive industries, forces the companies to use sophisticated instruments which are more accurate in evaluation of chances and risks of R&D projects, in order to choose the right ones and avoid the risk of missing profitable opportunities. Therefore, in recent years, the evaluation of R&D projects through real options based methods has gained growing attention. As a matter of fact, real options methods are able to model the uncertainty and the flexibility embedded in the R&D process and to consider the value of future opportunities.

A real option is "the right, but not the obligation, to take a specific action in the future" (Amram and Kulatilaka 1999, p. 5). A real option gives the right, but not the obligation, to undertake a business decision, which generally is the chance to make, abandon, expand, or contract a capital investment. To use Trigeorgis (1996) words, "the owner of a discretionary opportunity has the right -but not the obligation- to acquire the present value of expected cash flows by making an investment on or before the anticipated date when the investment will cease to exist" (Trigeorgis 1996, p. 124).

Real options are options whose underlying asset is a real asset and not a financial instrument. As with financial options, it is possible to distinguish between real *call options* giving the right to buy the underlying asset at a predetermined price and real *put options* giving the right to sell the underlying asset at a given price. For example, the

opportunity to invest in the expansion of a firm's production capacity if the market grows is a call option, whereas the opportunity to abandon a project can been seen as a put option (Munari and Oriani 2011). In this dissertation the focus is on real options in R&D that are a precondition to open up opportunities for future growth, i.e. call options. In addition, another distinction is between American or European put and call options dependently if it is possible to exercise the option before or at a fixed date respectively.

The real options analysis (ROA) applies the financial options evaluation techniques, like the Black & Scholes formula (Black & Scholes, 1973) or the binomial model (Cox et al., 1979) to capital budgeting decisions (Brealey and Myers, 2000). These financial options models usually require input variables such as the *underlying value*, the *exercise price*, the *volatility*, the *time to maturity*, as well as *the riskless interest rate*. These input variables have real counterparts in actual capital investments, as shown in Table 1, and have to be estimated before valuing a real option.

Variable	**Financial option**	**Real option**
Underlying	Current value of the stock	Present value of project expected cash flows
Exercise price	Stock price	Current value of project investment cost
Time to maturity	Expiration date of the stock	Length of time in which the investment opportunity exists
Volatility	Volatility of returns on stock	Project value volatility
Interest rate	Riskless interest rate	Riskless interest rate

Table1: Input variables used in financial options and real options evaluation.

When valuing investments as real options, generally these input parameters can easily be observed or approximated (Lint, 2004). For instance, the *riskless interest* rate can be derived from government bonds that have the same time to maturity as the R&D option. The *exercise price*, i.e. the expenditure required to acquire the project asset, can be a known exercise price or a stochastic exercise price. According to Lint (2004), the exercise price is relatively short-term oriented since it is possible to obtain reasonable

estimates of this cost by means of the interviews with managers involved in the R&D process. Literature offers also some contributions, such as that provided by McDonald and Siegel (1986), which consider the exercise price not known in advance. In such a case, it has to be replicated as a stochastic variable. Computing the *time to maturity* could be not easy. The time to maturity generally is the time to go to market. It can be can be a fixed date (as in European options) or a not known date (as in American options). In the latter case, different circumstances can influence its value. According to several authors, in absence of competition, delaying the market introduction (delaying the exercise of the option) is beneficial, in order to obtain more information in the future that makes the option more valuable. However, under competitive circumstances, a company may anticipate the market entry for first-mover reasons (this issue is discussed more in details in section 2.3). In such cases, the R&D option should be considered as an American option, whose evaluation is more complicated than European options. As a matter of fact, many applications of R&D option valuation focus on projects modeled as European options, i.e. with a fixed time to maturity, and assuming that the option will be exercised at that date (Lint 2004). Another important key parameter is represented by the *underlying value*, which is the present value of expected future cash flows upon commercialization of the project. The underlying is treated as a stochastic variable[2] with a given *volatility*, i.e. the volatility of the same expected cash flows. Both underlying and volatility, are hard to measure. The former is generally estimated through managers' interviews. As far as the volatility is concerned, depending on the specific case to model, managements estimates as well as past data from the volatility of completed R&D projects, have been used as an approximation[3] (Lint 2004; Perlitz et al. 1999).

Different options methods have been used in literature to evaluate R&D investments and they can be classified, according to some classifications proposed in literature (Cassimon et al. 2011b; Munari and Oriani 2011), in *numerical approaches* such as the

[2] Different approaches have been used in literature to model the stochastic process of the underlying and one has to distinguish between continuous time and discrete time contemplation of the underlying movements. In particular, if the continuous time approach is applied, several processes are conceivable: the Diffusion-Process (such as the Brownian Motion), the Jump-Process and the Mean Reverting process (Dxit and Pindyck 1994).

[3] For example, Merck (the first pharmaceutical company that has explicitly embraced real option pricing to R&D in order to evaluate its investments process), uses the historic volatility of a biotechnology index of related stocks which are traded at NASDAQ (Nichols, 1994).

binomial model and *closed-form solutions* such as the Black and Sholes (B&S) formula and the Geske model, based on B&S, which is able to evaluate compound options (a set of subsequent options that are dependent on each other).
In the following sub-sections I first briefly review some of the above-mentioned models used to evaluate *call options* and, secondly, I show both weaknesses and strengths in using numerical and closed-form methods respectively.

2.1.1 The Black and Sholes formula

Black and Sholes analyze the option pricing problem in a continuous-time framework by assuming that the value of the underlying asset (S in the following formulae) follows a geometric Brownian motion. The geometric Brownian motion assumption corresponds to assuming a lognormal distribution for the underlying at the end of any finite interval time (please refer to Figure 1). Other assumptions of the model are (Black and Sholes 1973, p. 640):

- The riskless interest rate is known and is constant through time;
- The variance rate of the return on the stock is constant;
- The stock does not pay any dividend;
- The option is "European", that is, it can only be exercised at maturity;
- There are no transaction costs in buying or selling the stock;
- It is possible to borrow any fraction of the price of a security to buy it or to hold it, at the riskless interest rate;
- There are no penalties to short selling. A seller who does not own a security will simple accept the price of the security from a buyer, and will agree to settle with the buyer on some future date by paying him an amount equal to price of the security on that date.

Under these assumptions, the value of the option will depend only on the price of the stock (i.e. the underlying), on time and on variables that are taken to be known constants (the riskless rate, the volatility as well as the exercise price). Specifically, the value of a call option - C in equation (1) - in terms of the Black and Sholes parameters is:

$$C = SN(d_1) - Ke^{r(T-t)}N(d_2) \quad (1)$$

With:

$$d_1 = \frac{\ln\frac{S}{k} + (r + 1/2\,\sigma^2)(T-t)}{\sigma\sqrt{(T-t)}}\ ; \quad (2)$$

$$d_2 = d_1 - \sigma\sqrt{(T-t)}. \quad (3)$$

Where:

S = the price of the underlying;

K= the exercise price;

r = the riskless interest rate;

T= the time to maturity;

t = the current time;

σ = the standard deviation of the stock's returns;

N(.) = the cumulative normal density function.

Let me illustrate how the model works. Figure 1 represents the underlying process according to a geometric Brownian motion which originates a lognormal distribution at the maturity, with mean and variance equal respectively to (Dixit and Pindyck 1994):

$$E[S(T)] = Se^{rT} \quad (4)$$

$$Var[S(T)] = S^2e^{2rT}(e^{\sigma^2T} - 1) \quad (5)$$

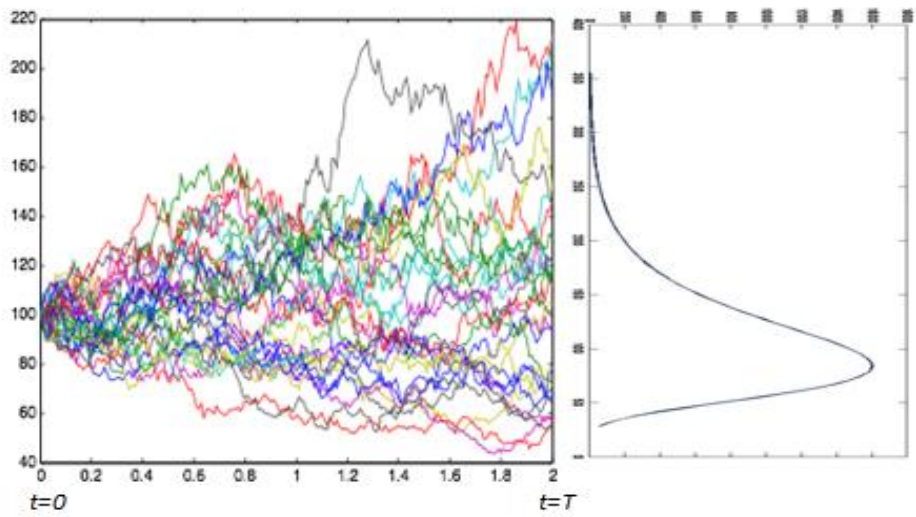

Figure 1: Replications of the underlying process of a project according to a GBM. On the right side the lognormal distribution at maturity obtained with 10.000 replications.

There are two important points in time: the current time t=0 and the time to maturity T=2 (see Fig. 1). At t=0, the holder of the option acquires the right, but not the obligation, to make another investment at maturity T=2, i.e. to exercise the option at maturity. In fact, at maturity new information is available, i.e. the realization of S at T (S_T) from the lognormal distribution is known. The option will be exercised only if the net payoff at maturity is positive, that is only if S_T will exceed the exercise price K (in such a case the option is called "in the money"). Accordingly, the payoff at maturity will be:

$$C_T = max\{0, S_T - K\} \tag{6}$$

Of course we have to compute an expected value of the option at t=0, so that we can obtain the formulation as in equation 1. According to Nielsen (1993), it is useful to split the call value in equation 1 in two components. A first component is the payment of the exercise price, contingent on the option finishing in the money. In equation 1, $N(d_2)$ is the probability, P, that the event of the option will finish in the money, i.e. $N(d_2)=P\{S_T > K\}$. As a consequence, the expected payment at maturity is $-KN(d_2)$ and the present discount at t=0, is $-KN(d_2)e^{-rT}$.

The second component is the receipt of the stock, again contingent on the option finishing in the money and thus is exercised. The expected future value of this component is not simply the conditional expectation of the stock price given exercise. Rather it is the conditional expectation of the stock price given exercise times the probability of exercise. In mathematical formulation it is:

$$E[S_T/S_T > K]\, P\{S_T > K\} = e^{rT} SN(d_1)^4 \quad (7)$$

and so the current value at t=0 is $SN(d_1)$(Nilesen, 1993 p. 5and 6).

By putting together the values of the two components, it is straightforward to get the Black and Sholes formula as in equation 1.

An important consideration is that the investment at t=0, is a sunk cost, i.e. it does not affect the option value, but decreases this value.

Finally, the B&S formula for a call option can be seen as a simple option, or a 1-fold option (Cassimon et al. 2004). In other words, this model works very well in a general R&D environment where the decision to exercise the option is made only once at maturity, that is, the simple option is characterized by one expiration date and one exercise price.

2.1.2 The Geske model

To better evaluate sequential R&D projects, in which the staged process allows the management to move a product development into the next stage only if the expected results appear to be satisfactory, the Geske model should be adopted, well known to evaluate European compound options.

In fact, the R&D process of a generic project is a series of consecutive phases from the research phase to the commercialization phase, where each phase represents an option on executing the following phase, i.e. a compound option.

Starting from the Black and Sholes formula, Geske derived in 1979 a closed-form solution for the evaluation of an option on an option, or a 2-fold compound option. According to Geske model, the holder of the compound option makes decisions in two

[4] In formula 7 note that $P\{S_T > K\}$ is not equal to $N(d_1)$

separate dates. Specifically the compound option is characterized by two expiration dates and two exercise prices. If the first expiration date arrives and the 'inner' option's market price is over the agreed exercise price the first option will be exercised, giving the holder a further option at final maturity. Important assumptions of this model are (Geske, 1979 p. 68):

- The changes of the value of the stock follow a random walk in continuous time with a variance rate proportional to the square root of the value of the firm;
- Investors are unsatiated;
- The security markets are perfect and competitive;
- The riskless interest rate is known and is constant through time;
- The trading takes place continuously in time,
- The firm has no payouts.

Under these assumptions, the value of the option will again depend only on the price of the stock (i.e. the underlying), and time and on known and constant variables. Specifically, the value of a call option - C in equation (8)- in terms of the Geske parameters is:

$$C = SN_2(a_1, a_2;\ \rho) - K_2 e^{r(t_2 - t)} N_2(b_1, b_2;\ \rho) - K_1 e^{r(t_1 - t)} N(b_2) \tag{8}$$

With:

$$b_1 = \frac{\ln \frac{S}{\bar{S}} + (r - 1/2\ \sigma^2)(t_1 - t)}{\sigma\sqrt{(t_1 - t)}}\ ; \tag{9}$$

$$b_2 = \frac{\ln \frac{S}{K_2} + (r - 1/2\ \sigma^2)(t_2 - t)}{\sigma\sqrt{(t_2 - t)}}\ ; \tag{10}$$

$$a_1 = b_1 + \sigma\sqrt{(t_1 - t)}; \tag{11}$$

$$a_2 = b_2 + \sigma\sqrt{(t_2 - t)}; \tag{12}$$

$$\rho = \sqrt{\frac{t_1 - t}{t_2 - t}}; \tag{13}$$

$\bar{S}$ = the solution of $C_1(S, t_1) - K_1 = 0$.

Where:

S, r, σ, t, N(.) assume the same meaning as in the previous section. Also, let me define:

t_1= time to maturity of the compound option C;

t_2= time to maturity of the underlying call option;

K_1= exercise price of the compound option C;

K_2= exercise price of the underlying call option ;

N_2 = bivariate cumulative normal distribution function with a_1 and a_2 as upper limits and ρ as the correlation coefficient between the two variables.

Let me provide an application of the Geske formula, available in literature (Perlitz et al. 1999), that clarifies how the model works. Assume the evaluation of a project in the pharmaceutical industry. For the sake of simplicity, consider the R&D process, traditionally divided in several phases from research to market introduction, as split into 3 main phases (see Fig. 2). Phase 1 serves to identify active substances out of numerous possible compounds. Once a substance has been identified as promising enough, the testing Phase can start (generally this phase includes four sub-sequent testing phases). If this phase turns to be successfully completed, then the pharmaceutical company can make an ulterior investment in production capacity and market introduction. Two options can be identified in this setting: the option to invest in testing is the first option, whereas the second option is represented by the investment in production capacity and market introduction. Taken together, both opportunities form a compound option, or better, a 2-fold option that can be well evaluated by the Geske model.

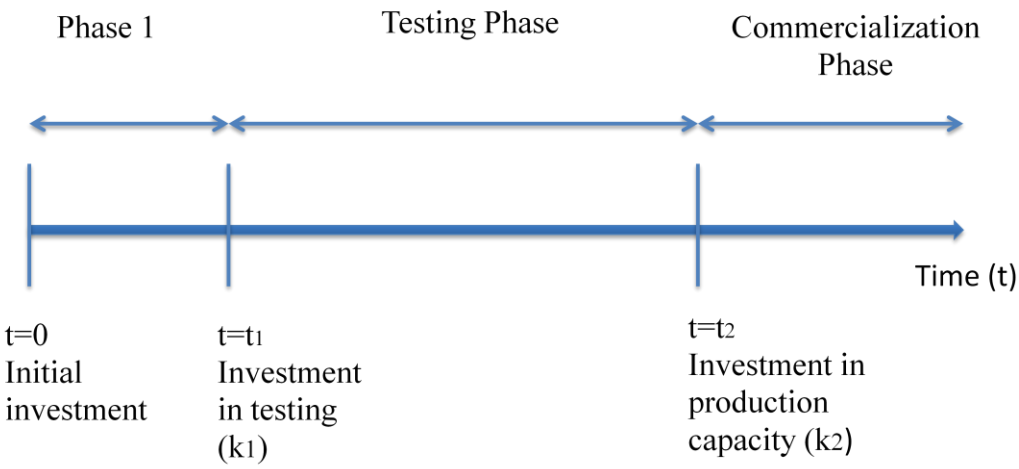

Figure 2: Simplified illustration of the pharmaceutical R&D process

As in the case of the simple call option discussed in the previous section, at t=0, the company makes an initial investment (again a sunk cost that does not affect the compound option value) to buy the compound option to make further investments later (K_1 and K_2 in equation 8), based on successfully completion of both the Phase 1 and the testing Phase, in two fixed dates (t_1 and t_2). In other words, if the asset value at time t_1, exceeds the investment cost K_1 (or alternatively, if the current asset price at t_1 is over $\bar{S}$, as defined above), the first option is exercised and the company buys the right to exercise the second option at t_2. At that date, if the asset value exceeds the production and market cost K_2, the pharmaceutical company will exercise the second option too, that is, the compound option is exercised.

2.1.3 The binomial model

A simpler, discrete time analysis, which in the limit of very small time steps yields the continuous time results obtained by Black and Sholes, was proposed by Cox et al. (1983). The key assumption on which this approach, known as the binomial pricing approach, is based is to make discrete the continuous-time stochastic process for the underlying S and then use dynamic programming to compute the option value C. In such a way, the underlying S follows a multiplicative binomial process as shown in Figure 3. As a consequence, the first step to solve the model is to build a tree of all possible discrete values that S can assume in future.

Let me illustrate the stochastic process of S after just one period. As Figure 3(a) shows, the current stock price S at the end of one period can assume two values: Su if S goes up with probability q and Sd if S goes down with probability (1-q); with:

$$u = e^{\sigma\sqrt{\Delta t}} \tag{14}$$

$$d = e^{-\sigma\sqrt{\Delta t}} = 1/u \tag{15}$$

Where σ is the standard deviation of the underlying S and Δt is the discrete time interval. If n is the number of time steps between 0 and T (the maturity of the option), Δt is computed as T/n and represents the length of each interval that constitutes the tree. In the illustrated case Δt is equal to T, since just one time-step is considered.

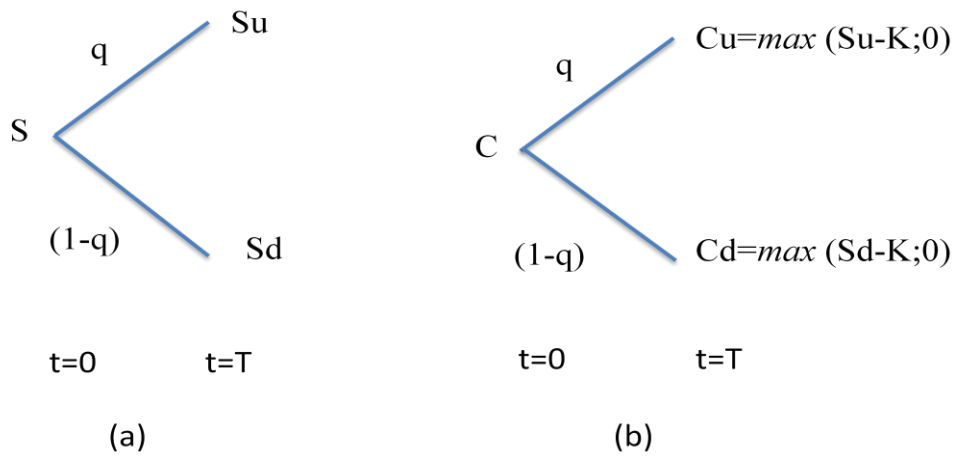

Figure 3: Binomial pricing tree for underlying value (a) and call value (b)

In the model, the risk neutral probability q of an up movement is given by:

$$q = \frac{e^{r\Delta t} - d}{u - d} \tag{16}$$

where r is the riskless rate.

Once the tree and the values of the underlying are computed, it is possible to calculate the option value C, by recurring to dynamic programming. The value of the option in the last period (Cu or Cd in Figure 3(b)), is computed as:

$$C(i) = \max(S(i) - K; 0) \; \forall i = u, d \tag{17}$$

where K is the exercise price.

As a matter of fact, the option is exercised only if the net payoff at the end of the first period is positive. The value of the call option C is thus obtained by discounting back the two possible values of C (Cu and Cd), weighted by their risk-neutral probabilities (q and (1-q) respectively), and using the riskless rate r as the appropriate discount factor.

$$C = e^{-r\Delta T}(qC_u + (1-q)C_d) \tag{18}$$

It is possible to extend the process of the underlying S over multiple time periods, solving the model by dynamic programming in order to obtain the call value C at t=0. For small enough values of ΔT, i.e. considering a huge number of time steps *n*, the discrete approximation of C will converge to the Black-Scholes continuous-time value.

2.1.4 Numerical approaches vs Closed-form formulae: a comparison

Binomial approaches show a somewhat misleading intuitive simplicity because they still use a discrete numerical method. According to Cassimon et al. (2004, 2011a), two problems may arise by adopting binomial approaches. The first problem is that it is not known how many time steps are necessary in order to obtain an accurate option price. In general, binomial prices converge to an analytical result. However, theory does not say how many periods are needed to obtain a good level of accuracy (Cassimon et al., 2004, p. 49). The second problem is the choice of the up (u) and down ratios (d) and the risk of neutral probabilities (q), which are computed using the formulae for pricing stock options based on the binomial model provided by Cox et al. (1979). Chriss (1997, p. 238) demonstrates that, under given input parameters, the Cox, Ross and Rubenstein binomial tree does not work[5].

As above said, a real option gives the right, but not the obligation, to undertake a business decision, which generally is the chance to make, abandon, expand, or contract

[5] Particularly, Chriss (1997) refers to Kellogs and Charnes's (2000) work, The authors applied the Cox et al. (1979) approach to evaluate a pharmaceutical company. Chriss (1997, p. 238) demonstrates that, under given input parameters which are used to obtain u, d and q, the Cox et al. (1979) binomial model leads to calculate a value of q equal to 3,005632, which is an invalid probability.

a capital investment. These options can be modeled by American or European put and call options dependently if it is possible to exercise the option before or at a given date respectively. Whereas numerical expressions are able to model all types of the above options, the main limit of closed-form formulae is their inability to solve the American put option. However, since the focus of this dissertation is on the growth options (modeled as call options), this limitation would not apply.

Another limitation is represented by the assumed distribution for the underlying: in closed formulae this is the Brownian Motion. This particular motion implies a continuous arrival of information that changes the underlying value (Pennings & Lint, 1997). However, information that affects the underlying value (the NPV of future cash flows) arrives at discrete points of time and this means that the managers, in real markets, do not continuously adjust the underlying value, but rather do so, i.e. only when information with strategic impact arrives (Pennings & Lint, 1997). In order to overcome this limitation, several authors propose jump-process models, where discrete value changes are superimposed on a Brownian process following exponentially distributed intervals (Merton 1976; Lint and Pennings 1997).

In addition, an important consideration is about the risk that characterizes the innovative R&D process. This total risk is usually divided in two components, namely economic (or commercial) risk and technical risk. The former deals with factors that increase market uncertainty, like interest rates, inflation and changes in industry prices. This kind of risk is systematic because a company can't affect it. On the other hand, the latter, i.e. the technical risk, stems from the lack of certainty about the process success. Technical risk deals with factors related to the projects such as approval probability and uncertainty in development costs. Whereas numerical approaches are able to capture the technical uncertainties and commercial risk of the R&D process, closed-form solutions, such as B&S or Geske model, capture only the economic risk. However, Cassimon et al. (2011a) incorporated the technical risk, in the n-fold compound option model, preserving the closed-form formula.

Finally, while the binomial model allows for the widest range of applications and is very robust under different conditions, it has some methodological problems. The reason has to be searched in the way of contemplation of the underlying: in the binomial model the underlying is discrete rather than continuous as in the closed

formulae. The continuous time assumption of Black and Sholes and Geske model, allows for closed-form solutions that makes the handling easier (Perlitz et al. 1999, p 264). However, according to Munari and Oriani (2011), the choice of the model may be very idiosyncratic to the specific problem to address and no unique recipe can be provided ex ante.

2.2 Critical review of portfolio selection methods

The portfolio selection problem has been one of the most important issues in modern finance since the 1950s. The first model for portfolio optimization was developed by Markowitz in 1952. In this model the return on the portfolio is measured by the expected value of the random portfolio return, while the associated risk is quantified by the variance of returns' distribution. Optimization requires selecting the portfolio with the highest expected return for a given level of risk, or, alternatively, the lowest risk for a given level of expected return.

The concept of building business portfolios emerged in the late 1950s and evolved through the 1970s (Souder and Mandakovic, 1986) to become an established planning tool. During the 1980s and 1990s, companies extended the use of portfolio management into new products selection and R&D resource allocation. While the tools have changed over time, the basic need remains the same: companies must allocate a limited set of resources to projects in order to obtain a balanced portfolio, i.e. diversifying the projects in the portfolio in terms of various trade-offs such as high risk versus sure bets, internal versus outsourced work, etc (Cooper et al. 1998; Dickinson *et al*. 2001). Methods and techniques for selecting projects have appeared in the literature for at least 40 years and there have been hundreds of published studies. Approaches tend to be either quantitative and qualitative, ranging from rigorous operations research methods to social-science-based interactive techniques (Henriksen &Traynor, 1999). Overviews on the topic of R&D portfolio selection are provided by Henriksen &Traynor (1999), Chien et al. (2002) and Iamratanakul et al. (2008). An update overview of the R&D portfolio selection literature is presented in Table 2: in particular, for each paper, the evaluation approach and the contribution to the literature are shown.

Authors (Year)	Title	Evaluation Approach	Contribution
Markowitz (1952)	Portfolio selection	Mean-variance approach	The authors propose the concept of "considering a portfolio as a whole".
Sharpe (1964); Mossin (1966)	Capital asset prices: a theory of market equilibrium Equilibrium in a capital asset market.	Capital asset pricing model	Find the relation between risk of an asset and its expected return.
Golaby et al.(1981)	Selecting a group of dissimilar projects for funding.	Hybrid approach • Multi attribute theory utility (MAU) • Mathematical programming	Use MAU in portfolio selection by transforming the utilities into measurable value functions and then combined the value functions into a portfolio index.
Fox et al. (1984)	Economics models for R&D projects selection in the presence of project interactions.	Mathematical programming	Take indirectly into account interactions between projects (both cost and outcome interactions) in a mathematical optimization model with budgetary constraints. The present value interrelations is assessed indirectly by explicitly modeling R&D project impacts on profitability.
Keeney (1987)	An analysis of the portfolio of sites to characterize for selecting a nuclear repository.	Mean-variance approach	Apply the mean-variance approach in order to obtain different portfolios of three sites for selecting a nuclear repository
Bard et al. (1988)	An interactive approach to R&D project selection and termination.	Hybrid approach • Screening • Mathematical programming	Develop a new 2-steps methodology (i, screening; ii, mathematical programming) to adequately address the qualitative aspects (organizational,

			environmental, and technical) in the projects selection.
Liberatore (1989)	An extension of the analytic hierarchy process for industrial R&D project selection and resource allocation.	Hybrid approach • AHP • Mathematical programming	The purpose of this paper is explore the applicability of an extension of the Analytic Hierarchy Process (AHP) for priority setting and resource allocation in the industrial R&D environment. Cost-benefit analysis and integer programming are used to assist in the resource allocation decision.
Peerenboom et al. (1989)	Selecting a portfolio of environmental programs for a synthetic fuels facility.	Hierarchical decision framework	The authors propose a hierarchical decision framework to establish research priorities and budget allocations within five environmental projects.
Kocaoglu, and Iyigum (1994)	Strategic R&D project selection and resource allocation with a decision support system application.	Hybrid approach • AHP for criterion weights • Scoring for project screening • Delphi for information on requirements • NPV for analysis of benefit interactions • Mathematical programming with heuristic for resources allocation	Develop an integrated DSS helps searching alternative solutions to strategic and operational R&D problems.
Blau et al. (2004)	Managing a Portfolio of Interdependent New Product Candidates	Hybrid approach: • Simulation optimization; • Genetic	Combine discrete simulations with bubble-chart diagrams and genetic algorithms

	in the Pharmaceutical Industry.	algorithms • Bubble-chart diagrams	to obtain a robust portfolio to changing economic conditions, acceptable risk, and resource levels.
Rogers et al. (2002)	Real options based analysis of optimal pharmaceutical research and development portfolios.	Real options Optimization	Integrate ROA (real options analysis) in a stochastic optimization model to select the optimal portfolio, given a set of limited resources.
Rogers et al. (2005)	Valuation and design of pharmaceutical R&D licensing deals.	Real options Optimization	Starting from Rogers et al.'s (2002) model, the authors propose an approach by which to select the best licensing strategy for each product in the R&D portfolio.
Bardhan et al. (2006)	Optimizing an It Project Portfolio With Time-Wise Interdependencies	Real options Optimization	Integrate ROA (real options analysis) in a dynamic multi-period portfolio optimization model, where inter-dependencies between projects are considered.
van Bekkum et al. (2009)	A real options perspective on R&D portfolio diversification.	Real Option Simulations	Introduce a real options perspective on R&D portfolio diversification. The study supplements the Markowitz (1952) approach in that it explicitly considers real option characteristic. The authors demonstrate that correlation among R&D products with Real Options characteristics act differently than usually and in particular negative correlation only slightly reduces portfolio risk.

Table 2: R&D Portfolio Selection Literature Summary

The review of the literature in this field highlights that different methods (third column) can be used to construct the optimal portfolio. According to Henriksen and Traynor (1999) R&D project selection methods can usually be classified in different categories such as *Scoring, Mathematical programming, Financial/economic models, Decision analysis*. So, as shown in Table 2, any logical combination of the indicated techniques can be used to construct an organization's "optimal" R&D portfolio. For example, scoring may be used to carry out preliminary screening, financial models to evaluate single projects and, finally, mathematical programming to allocate resources and to select the optimal portfolio. In fact, the most recent trend has been to combine the different approaches into an integrated, interactive, manager-friendly, computer-based decision support system (DSS) (Chu et al. 1996; Henriksen and Traynor, 1999; Ghasemzadeh and Archer, 2000).

Moreover, though different tools have been used to select an R&D portfolio, according to Cooper et al. (2001) and Zapata and Reklaitis (2011), most of them incorporate financial performance. Specifically, Cooper et al. (2001) provided a survey to IRI (Industrial Research Institute) member companies participating in an ongoing best practices study. The results of this study highlight that Financial methods (please refer to Figure 4) dominate portfolio management and project selection approaches. Specifically, the different portfolio tools considered in the survey are:

- *Financial methods.*
- *Business's strategy*. The business's strategy as the basis for allocating money across different types of projects is the second most popular portfolio approach. In this case, accordingly to the strategy achievement, money is allocated across different types of projects considered in the portfolio
- *Bubble diagrams*. Two-axes diagrams are typically used to display the trade-off between two criteria: e.g., risk versus reward, probability of success versus value, or ease of implementation versus attractiveness.
- *Scoring models.*
- *Check lists*: Projects are evaluated on a set of Yes/No questions. Each project must achieve either all Yes answers, or a certain number of Yes answers to proceed. The number of Yes's is used to rank decisions.

- *Others.*

The results of the survey highlight that financial models are the most popular with 77,3 % of businesses using them, and 40,4 % relying on them as the dominant portfolio decision tool. A total of 64,8 % of businesses use a strategic approach to select their portfolio of projects: for 26,6 % of businesses, this is the dominant method.

Bubble diagrams or portfolio maps have received attention in recent literature, since a total of 40,6 % of businesses use portfolio maps; however only 5,3 % of businesses use this as their dominant method. Moreover, a total of 37,9 % of businesses use scoring models and in 13,3 % this is the dominant decision method while only 20,9 % of businesses use check lists and in only 2,7 % is the dominant method. Finally, 24% of businesses indicate that they use some "other method", i.e. variants or hybrids of the above methods (Cooper et al. 2001)

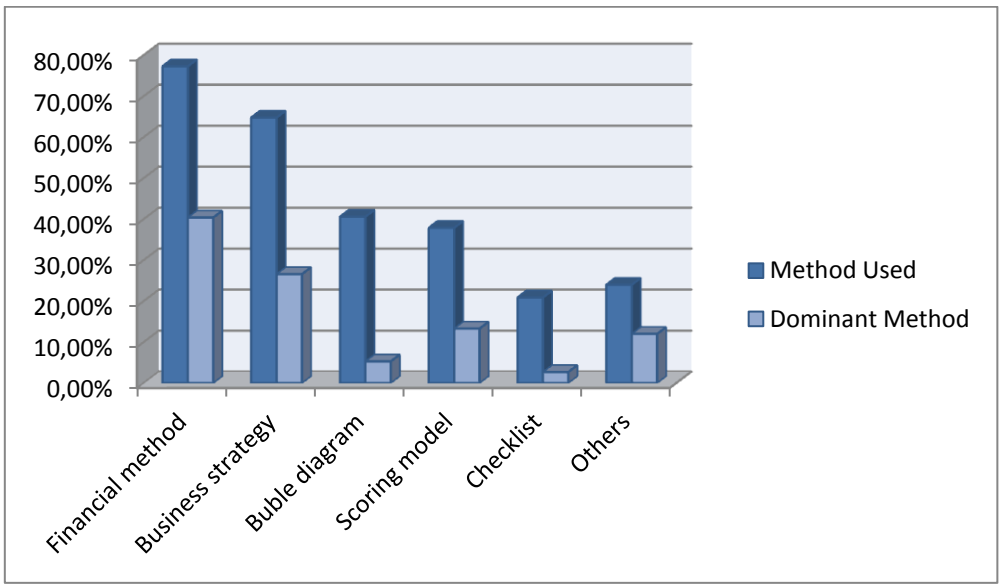

Figure 4: Popularity of Portfolio Methods Employed (Source: Cooper et al. 2001)

The commonly used financial portfolio valuation methods are mainly based on the standard application of the net present value. Although the simple NPV method is very simple to use, it is not able to adequately capture risk and uncertainty of the R&D investments. This is not a trivial question. As a matter of fact, as pointed out by Poh and Buy (2001), uncertainty and risk of a project, have become important factors when the

effectiveness of an evaluation tool is considered. Specifically, Poh and Buy (2001), in a comparative analysis of R&D project evaluation methods conducted by an AHP framework, show that seven mayor criteria are important in determining the effectiveness of R&D evaluation methods. The seven criteria in this considered study are:

1. *Simplicity.* This criterion refers to simplicity of the evaluation method.
2. *Multiple objective*. This criterion refers to the ability of the evaluation method to deal with multiple objectives.
3. *Risk and uncertainty*. This criterion refers to the ability of the evaluation method to incorporate risk and uncertainty in the analysis.
4. *Cost of implementation*. This criterion refers to cost of implementing the evaluation method
5. *Adaptivity*. This criterion refers to the ability of the evaluation method to incorporate knowledge and experience of different decision-makers.
6. *Nature of data*. This criterion refers to nature of data (both qualitative and quantitative) that are needed by the evaluation method
7. *Availability of data.* This criterion refers to the availability of data required by the evaluation method

The result of the analysis[6] (please refer to Table 3) indicates that the two most important criteria are "multiple objective" and "risk and uncertainty".

Classification	Criterion	Relative importance
I	*Multiple objective*	0,309
II	*Risk and uncertainty*	0,254
III	*Simplicity*	0,141
IV	*Availability of data*	0,099
V	*Adaptivity*	0,094
VI	*Nature of data*	0,064
VII	*Cost of implementation*	0,039

Table 3: Classification of criteria with respect to the goal. (Source: Poh and Bai, 2001)

[6] Poh and Buy (2001) developed an AHP approach where the hierarchical levels consist of the goal (identification of the best project evaluation), followed (level 2) by the criteria contributing to the goal and, finally, the alternatives (evaluation methods) at the lowest level. Particularly, I refer to level 2 in the analysis.

As the same Poh and Buy (2001) underline, "the evaluation R&D methods which can deal explicitly with the risks and uncertainty of projects, will be more effective and therefore preferred to those methods that do not". This important consideration reinforces the need to evaluate the R&D projects portfolio through real options analysis, since - as widely discussed in section 2.1- ROA is acknowledged as a powerful tool to evaluate uncertain projects that have an intrinsic flexibility (Dixit and Pindyck, 1994). In the last decade, as shown in Table 2, mathematical ROA-based models have also been developed to evaluate an R&D projects portfolio (this topic is addressed in more details in the following section). However, organizations, as pointed out by Hartmann & Hassann (2006), while recognizing the importance of ROA, do not apply it very often because it is perceived as a complex concept. The complexity of many R&D project-selection methods is another important issue. Referring once again to Poy and Buy's study, "simplicity" is another important criterion (see Table 3) considered in evaluating the best method to select projects. The next section reviews in details ROA methods to evaluate an R&D portfolio and draws attention to the important fact that, from a practical standpoint, most of these models are very difficult to implement. It follows that future studies in the projects portfolio selection should be direct towards the integration of ROA and various methodologies in order to obtain a manageable tool, useful to select a balanced portfolio.

2.2.1 Real options Analysis in a Portfolio Context

"Valuing portfolios of options embedded in investment decisions is one of the most important and challenging problems in real options and corporate finance in general. Although the problem is vitally important in the value creation process of almost any corporation, it has not been satisfactorily addressed" (Trigerogis words in Brosch 2008). As a matter of fact, most of real options methods are limited to the evaluation of a single project. Conversely, according to several authors, it is better to evaluate the entire R&D project portfolio of a company instead of its single projects, in order to consider the relations and the interdependencies between them. These interdependencies, which are ignored if projects are evaluated one by one, usually deal with limited resource consumption, risk balancing and company strategies. However,

while there is a large amount of literature on project evaluation using ROA, in practice the method has been used effectively only to evaluate single projects (Brosch 2008; Zapata and Reklaitis 2011).

	R&D portfolio evaluation
Numerical approaches	Rogers et al., 2002; Smith and Thompson 2004; Rogers et al., 2005; Wang and Min 2006; Brosch 2008; van Bekkum et al. 2009; Rafiee and Kianfar 2011; Zapata and Reklaitis 2011.
Closed-form solutions	Luherman 1998; Bardhan et al. 2004.

Table 4 : Classification of selected references about ROA based models to evaluate an R&D portfolio

In Table 4, I summarize some literature contributions on ROA approaches in a portfolio context in accordance with the particular approach used, i.e. numerical methods, and closed-form solutions. To the best of my knowledge this is the first attempt to classify literature on real options methods used to evaluate an R&D portfolio. Among the others, I consider contributions such that offered by Luherman (1998), which is notable for stressing the important intuition of adopting a portfolio perspective, even if he didn't consider limited resources allocation. Particularly the author adopts the B&S formula to evaluate each of the six projects in the portfolio and provides a comparison with the traditional NPV methodology. The analysis produces a very different assessment of the portfolio: instead of accepting only two projects and rejecting four, the options framework - that accounts of uncertainty and flexibility- suggests to reject just one project, accept immediately another project and wait and see for the other fours. Similarly, Smith and Thompson (2004), Wang and Min (2006) and van Bekkum et al. (2009), do not address the important problem of allocating scarce resources. On the other hand, these works shed light on how correlation between options can be coped with in a rigorous valuation framework. Specifically Wang and Min (2006) develop a methodology for valuing a portfolio of power generation projects that are market correlated. In Smith and Thompson's (2004) work, the options considered in a given portfolio are assumed to be dependent, in that exercise of any one is assumed to

produce, in addition to some intrinsic value based on its underlying asset, further information concerning the value of other options based on related assets. van Bekkum *et al.* (2009) show that correlation among R&D products with real-options characteristics acts differently than it usually does in evaluation contexts that use traditional methods such as the NPV, and, in particular, negative correlation only slightly reduces portfolio risk. Though correlation between projects is a very significant source of interaction, in R&D portfolios it is dominated by resources constraints (Zapata and Reklaitis 2011). Other contributions take into account the very important aspect of the limited budget and they don't consider other forms of interdependences among projects. Among these, given a set of limited resources, Rogers et al. (2002) develop a stochastic optimization model to select the optimal portfolio. In order to model both technological and market uncertainty, the authors adopt a quadranomial approach (a two-variable binomial tree) and model each project development as a series of continuation/abandonment options, deciding at each phase whether to proceed further or stop the development. Similarly, in Zapata and Reklaitis's (2011) work, the evaluation of each project considered in the portfolio is represented by a quadranomial tree. Starting from Rogers et al.'s (2002) model, Rogers et al. (2005) propose an approach by which to select the best licensing strategy for each product in the R&D portfolio.

All of these contributions (except for Lueharman 1998) adopt numerical approaches in evaluating the entire portfolio. The main limitation in using such approaches is their implementation. According to Cassimon et al. (2004), it can easily become difficult to manage discrete approaches because of the rapidly increasing number of trees with the size of the portfolio. In fact, increasing the number of the underlying assets as well as the number of time-steps makes the model more realistic, but increases the dimensionality of the problem (Brosch 2008). As a result, not surprisingly, most of the above-mentioned references have considered the valuation of portfolios constituted by two or three projects. When the size of the portfolio increases (for example in the case study proposed by Rogers et al. (2002) that considers twenty candidate projects), the mathematics of the model becomes too complex including 893 binary variables and 12,843 continuous variables. In such a case, companies may find it hard to identify an optimal project portfolio to solve a problem with a lot of constraints and several dozen

thousands of variables. A step towards simplifying this model was made by Rafiee and Kianfar (2011), who propose the same stochastic model of Rogers et al. (2002), but involving a smaller number of both scenarios and projects considered in the portfolio.

Moreover, a rigorous valuation framework for portfolios of real options is offered by Brosch (2008). The author adopts a discrete approach to model *n* underlying assets and their *inter*- and *intra*-projects interactions. As a matter of fact, on the one hand he models different real options on the same underlying (*intra*-projects interactions), so that a compound option type approach is adopted. On the other hand, interactions created by the use of shared resources and operational constraints are also taken into account (*inter*-projects interactions). In addition, a key future of the model is the dynamic global budget equation which has the form of a balanced equation. Funds that are not spent can be invested in later periods and funds freed up from disinvestment can be plowed back (Brosch 2008, p. 133). To the best of my knowledge, this is the most exhaustive real options portfolio optimization model which, from a theoretical point of view, handles several important portfolio futures that have not been covered so far in literature. However, from a managerial point of view, since its mathematical formulation is very complex, the model presents several weaknesses and it is very hard to implement. The same author, when illustrates the proposed portfolio approach, highlights that he didn't focus on the efficiency of implementation of the model.

As far as closed-form solutions proposed to evaluate a projects portfolio are concerned, only few models appear in literature. As Lueharman (1998), Bardhan et al. (2004**)** integrate the Black and Sholes formula in a dynamic multi-period portfolio optimization model, where different inter-dependencies between projects are considered. For example, in their model, hard dependencies between two projects exist when a capability for one project is also required by one or more of the other project(s).

Finally, there are a number of contributions which include fuzzy variables in the real options portfolio evaluation. Among these, Wang and Hwang (2007), Hassanzadeh et al. (2011), Hassanzadeh et al. (2012) propose closed-fuzzy option models, while Arastheh et al. (2014) and Carlsson (2007) propose discrete fuzzy approaches. However, the discussion of these last models is beyond the scope of this dissertation.

2.3 Real Options Games

ROG (real option games) approach combines real option analysis and game theory, thus allowing an economic actor to make decisions, which take into account both exogenous uncertainty (nature) and (re)-actions of economic actors that can affect his payoffs. In the managerial field, to use Chevalier-Roignant et al. (2011) words, ROG examines the tradeoff between managerial flexibility and commitment in dynamic competitive setting under uncertainty.

The main principle underlying game theory is that economic actors involved in strategic decisions are affected not only by their own choices but also by the decisions of others.

The games studied in game theory are well-defined mathematical objects. To be fully defined, a game must specify the following elements: the players of the game, the information and actions available to each player at each decision point, and the payoffs for each possible outcome (Kreps, 1990). The players are also assumed to be rational, i.e., each player is aware of the rationality of the other players and acts accordingly (Azevedo and Paxson, 2010). A game theorist typically uses these elements, to deduce a set of equilibrium strategies for each player such that, when these strategies are employed, no player can profit by unilaterally deviating from their strategy. These equilibrium strategies determine an equilibrium to the game (Kreps, 1990). According to Azevedo and Paxson (2010, p. 3), the two most common investment games are the *pre-emption game* (where it is assumed that there is a first mover- advantage that gives the economic actor an incentive to be the first to invest) and the *attrition game* (where it is assumed that there is a second mover-advantage that gives the economic actor an incentive to be the second to invest). Furthermore, the actor's advantage to invest first/second is, usually, assumed to be partial, i.e. the investment of the leader in the preemption games or the follower in the attrition games does not completely eliminate the revenues of its opponent. Also, in these kinds of games, firms are allowed to invest only once either sequentially or simultaneously, or both.

In the last two decades, the literature combining game theory aspects with real options analysis has been very active[7]. In fact, as game theory aims to provide a framework for modeling situations in which players, in making investment decisions, take into account

[7] Grenadier (2000a) and Smit and Trigeorgis (2006) provide very good summaries of existing literature on real options games.

other players' possible reactions, and real options theory is appropriate for most investment decisions, a merger between these two theories appears to be a logic step (Smit and Trigeorgis, 2007; Azevedo and Paxson, 2010). The existing literature offers a wide range of ROG models which, among the others, present the following characteristics: the underlying value of investment is treated as a variable which follows a known stochastic process (for instance, the above-mentioned geometric Brownian motion); the investment cost is sunk; players are not financially constrained; the investment problem is studied in isolation (i.e., the game is played on a single project); the number of players which hold the option to invest is traditionally two (duopoly) (Azevedo and Paxson, 2010, p.3).

Particularly, this stream of research starts with Trigeorgis (1991) who studies the impact of competition on the optimal timing of project initiation. Smit and Ankum (1993) investigate the timing investment decisions in a discrete time-real options model. They illustrate the influence of competition on both project value and investment timing. Similarly, Lambrecht (1999) and Joaquin and Butler (1999) analyze timing decisions by presenting models where competing firms have opportunities to invest in discrete investment projects. Dixit and Pindyck (1994), chapter 9, deal with similar research questions by introducing a real options continuous-time model for duopoly market. Grenadier (2000b) and Bouis et al. (2009) study competitive investments in new markets where more than two potential competitors are present, i.e. in oligopoly market. Smit and Trigeorgis (2007) highlight the importance to combine real options analysis and game theory, by implementing their proposed discrete-time model in electronics and telecommunications. In such a way, the authors can help guide managerial judgment in deciding whether and when it is more profitable to pre-empt the rival and when participation in strategic alliances is the preferred route. Readers can refer to Azevedo and Paxson (2010) for an exhaustive overview of ROG models.

Although several different ROG models have been developed, the pre-emption game is one of the most common used in the real options literature. In addition, this kind of game is mainly modeled in duopoly market (Bouis et al. 2009; Azevedo and Paxson 2010). The focus is on studying the trade-off between the value of waiting (as suggested by real options literature about single decision maker models) and the incentive to preempt the competitor. As a matter of fact, in single decisions maker problems, i.e.

when an investor has a monopoly over an investment opportunity, real option theory shows that in presence of irreversible investment costs and uncertain revenues, there is an option value to wait until more information is available an delay the investment opportunity more than the classical net present value method suggests. The reason is that once more information becomes available over time, the decision maker can make better decisions at a later date (Dixit and Pindyck 1994; Trigeorgis 1996). For instance, as stated in Smit and Trigeorgis (2007), in 1990 *Digital* faced a timing decision as to when to commercialize its Alpha microprocessor chip and decided to wait because of uncertainty over which product standard would prevail (Smit and Trigeorgis, 2007, p. 87). However, in a duopoly game, when competition is taken into account in the analysis, the option to delay the investment becomes less valuable. The presence of competition may have an erosion effect on the option value that may justify an earlier investment. For example, in consumer electronics, Philips and Sony's strategy to commercialize the Digital Video Disk was affected by the competitive decisions of Toshiba and Ti-Warner, and vice-versa (Smit and Trigeorgis, 2007, p. 91). It follows that, depending on the decision problem managers may face, we can distinguish between two different kinds of real option games, (Smit and Trigeorgis, 2007):

- *Games against nature*, where managers make investment decisions when commercial prospects are uncertain, i.e. in the face of random fluctuations of the project value.
- *Strategic games against competition*, where managers make investment decisions recognizing, in addition to the kind of uncertainty present in the games against nature, possible reactions of competitors that would in turn impact the value of their investment opportunity.

As shown in the first chapter, this thesis addresses the important issue of the alliance timing decisions in a dynamic setting, by introducing a real option game, which provides insights on timing alliance in biopharmaceutical industry (please refer to chapter 5). In order to become more confidential with the proposed model for alliance timing problem, let me illustrate in Figure 5 and Figure 6 an example of both a traditional *Games against nature* (the monopoly case) and a *Strategic games against*

competition (specifically the duopoly case) that deal with the investment timing decisions under uncertainty. Specifically, in both cases, a two-stages discrete-time model is represented, in which the choice to "invest" or to "defer" is made in two possible moments by firm A in the monopoly case and by both firm A and firm B in the duopoly case. To make the mathematics as simple as possible, it is common to divide the entire project development process in two stages (stage I and stage II in Fig.5 and Fig. 6), such as the R&D phase and the commercialization phase. Then, the investment (or not) decisions are made at the beginning of the stage I and at the beginning of the stage II, i.e. at t=0 and t=1 in both Figures. Note that just a qualitative representation of the problems is given, that is the computation of payoffs is not provided.

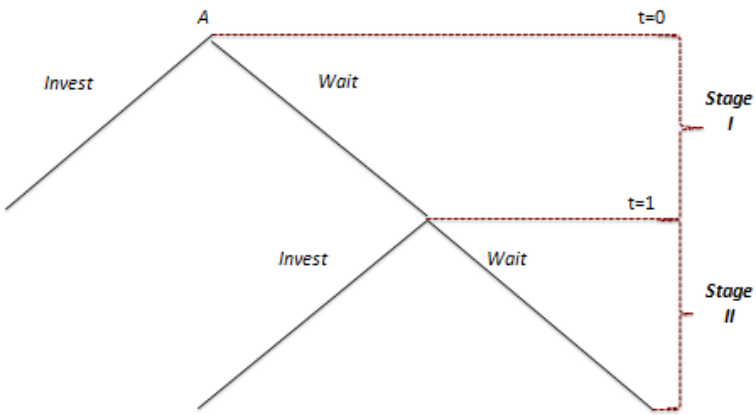

Figure 5: Two-stages Investments decisions (Monopoly case)

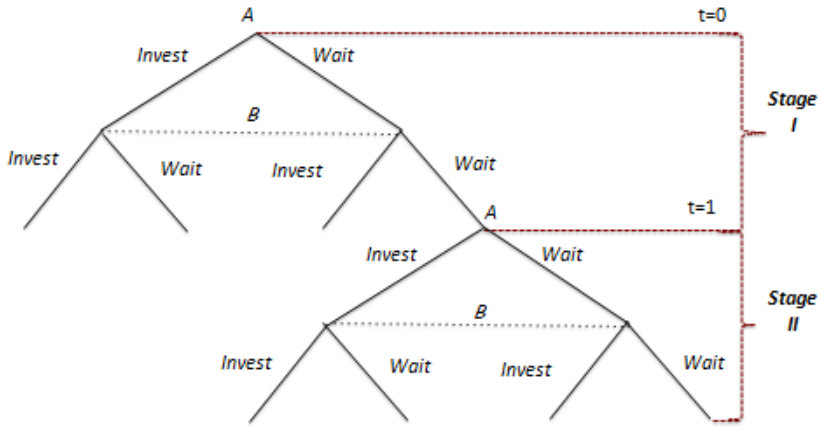

Figure 6: Two-stages Investments decisions (Duopoly case)

2.4 Open Innovation and Real Option

Open innovation is defined as 'the use of purposive inflows and outflows of knowledge to accelerate internal innovation, and expand the markets for external use of innovation, respectively' (Chesbrough et al., 2006, p. 1). According to this definition, depending on its business model, a firm decides if or not external and internal knowledge is valuable to be further developed and commercialized into a new business. For instance, when the project is expected not to be profitable enough, the firm will not simply dismiss the project (as in the closed innovation framework), but she will try to license or to sell it to other firms who can use the innovation productively because they have different business models (Vanhavarbeke et al. 2008, p. 253). As a result, unlike the closed innovation model, the open innovation paradigm highlights the spectrum of alternatives available to firms during the R&D process; indeed, at any phase of the process, firms can decide to start, continue, partner with others firms or dismiss the project completely. At the same time, there are different kinds of real options which may be embedded in a project, namely: the growth option, the option to defer an investment project, the option to contract, expand or temporarily shut down an investment, the option to abandon an investment project (Perlitz and al. 1999). So, as Vanhavarbeke et al. (2008) state, it is surprising that scholars do not pay attention to the existing synergy

between ROA and OI. Starting from this important consideration, though there are many studies that have focused on various aspects of the open innovation process, in this section- consistently with the goal of this dissertation- I discuss some contributions that point the attention to the benefits of open innovation that can be partly explained by applying the real option approach (Van de Vrande et al., 2006; Vanhavarbeke et al. , 2008) .

As companies strive both to maintain their annual revenue-growth rates and to be more competitive, the emphasis is on investing in new business opportunities. The creation of new businesses inherently involves a high level of uncertainty, especially in the early stages of new business development. One way that have firms to handle uncertainty associated with new business development is making small investments in multiple options on technology (Vanhavarbeke et al., 2008). As it should be clear from the section 2.1, real options reasoning is a recognized tool in literature to reduce the uncertainty of innovation projects as well as corporate venturing (Miller & Arikan, 2004). As a matter of fact, making a small, initial investment under high levels of uncertainty allows firms to create an option to wait until the uncertainty about the opportunity has decreased. When the uncertainty has decreased, the investing firm can decide whether to make a further investment or whether to dismiss the project (Adner & Levinthal, 2004; McGrath & Nerkar, 2004). In these early phases with high levels of uncertainty (both technological and market uncertainty), firms can create options through learning investments: establishing research alliances with partners is just one possibility to explore business opportunities in the first uncertain phases (Vanhavarbeke et al. ,2008). By investing in collaborative research firms learn about this opportunity and in this way decrease the huge uncertainty related to the initial investment. Once the learning investments result in an improved understanding of the technology and uncertainty has reached an acceptable level, innovating firms could invest in more substantial ways using other external governance modes such as equity alliances or joint ventures (Van de Vrande et al., 2006). As a consequence, the real options approach offers a framework to better explain the sequential investment rounds in new technologies. Accordingly to Vanhavarbeke et al. (2008) there are several advantages in adopting the innovation practices in terms of real options compared to the closed innovation ones. In particular, their study shows how the real option approach can

explain the benefits of one of the most common open innovation practices, i.e. of external corporate venturing. *In primis*, open innovation allows innovating firms to access to several externally developed inventions by participating, for instance, in venture capital funds. The main advantage of this strategy is that companies make small investments and learn about new technologies or projects with uncertain payoffs. Once uncertainty is solved or it is at an acceptable level, companies can decide to invest more. In addition, investing in external technologies enhances the potential of the real option because the company can scan a wide range of interesting ideas and projects. In real option terms, open innovation allows companies to build a portfolio of projects, instead of just writing options on internal projects alone. *Second*, innovating firms also benefit from delayed entry. Whereas in closed innovation models firms can only start with an internally developed project and pull it through the funnel, open innovation practices offer firms more flexibility about when to start the innovation process: firms could prefer to invest in technologies at a later stage when the level of uncertainty has decreased. *Third*, open innovation offers firms the advantage of an early exit : as a matter of fact, firms can always license or sell technologies that are not promising enough if they are developed internally (for instance they do not fit with their core competencies), but they might be valuable as they come to be developed in partnership (Vanhavarbeke et al. , 2008 p. 253, 254).

These considerations reinforce the need to adopt a real options approach when evaluating R&D alliances.

2.5 Research on R&D alliances

This section presents a review of alliance literature with a particular focus on the literature that considers theoretical modeling in the setting of R&D alliance activity under uncertainty. The literature on alliances is vast and most of it has examined the formation process of the R&D alliances, which includes the important decisions of both whom to ally with (Li et al. 2008; Lavie et al. 2012) and the appropriate governance structure (Powell 1990; Das and Teng, 2001). The most popular theories that have been used to analyze several key aspects involved in the alliance process, such as partner selection or governance choice, are the Transaction Cost Economics (TCE) (Williamson 1985), and the Resources-based View (RBV) (Zollo, 2002). Recently,

Real Options Theory has started to attract significant interest also in the field of strategic management (Kogut, 1991). In fact, for at least a decade, work on investment under uncertainty - summarized by the seminal book by Dixit and Pyndyck (1994) - has significantly shaped the research on sequential investments and created a fruitful paradigm for its treatment (Lukas, 2008). As widely discussed in the previous section, the initiation of an R&D alliance is just a first step, which generates subsequent options in the next stages. These real options rights have been recognized in R&D alliance literature. Accordingly, there are a number of empirical studies that emphasize that option characteristics are of particular importance for the formation of R&D alliances and especially for the choice of the appropriate governance structure (Kogut 1991; Folta and Leiblein, 1994; Folta 1998, Santoro and McGill 2005; Van de Vrande et al. 2009).

By contrast, according to Lukas (2008), there are a comparatively small number of papers that consider theoretical modeling in the setting of R&D collaborations adopting a real options approach. In other words there has been limited effort to scrutinize the properties of options in R&D alliances (e.g., options to acquire, divest and expand) through rigorous theoretical modeling (Chi 2000). Thus, in accordance with the focus of this thesis, I mainly review the very little literature strand which deals with theoretical modeling in the setting of R&D partnerships under uncertainty (Savva, 2006; Lukas 2007; Lukas 2008; Chi 2000). By way of anticipation, these works provide important insights on the effect of uncertainty and flexibility on the collaborations contracts (how partners share the value project in a stochastic environment), on the timing aspects of the collaborations as well as on their duration and terminations strategies, that previous research has neglected. Specifically, Savva (2006) focused on partnerships contracts under uncertainty, but with clauses that admit downstream flexibility, whose value is captured by the partner(s) who own the right to exercise, and analyzes the effect of this flexibility on the contract. The author distinguishes between cooperative options and non-cooperative options: the former are exercised jointly by the partners who enter the alliance in the interest of maximizing the total contract value, whereas the latter are exercised unilaterally and in the interest of the option holders' payoff. He also provides a framework that captures the effect of optionality on partnerships synergies.

Lukas (2007) highlights the importance of modeling the dynamics of market entry by developing a real options framework that gives insight into the expansion, dissolvement, and optimal timing of international joint ventures. In line with real options logic, the initial entry strategy serves as a platform allowing the firm to make subsequent investments to exploit host-country advantages. He precisely allows for this by taking a three-step expansion strategy explicitly into account, so that a compound option is modeled. The results suggest that uncertainty, size of equity share and future investment/divestment opportunities play an important role when it comes to transit from export to the first phase of the foreign direct investment commitment. In a similar way, Lukas (2008) adopts an option framework to model a joint venture-induced market entry under both economic and technology uncertainty in a continuous time setting. He presents critical thresholds for timing and termination strategy in the domain of joint ventures and finds that technology uncertainty promotes the formation of joint ventures. Consistently with this literature, Chi (2000) develops a model that is used specifically to examine the option to acquire or divest a joint venture, both in the case where the acquisition/divestiture price is specified *ex ante* in the initial contract and in the case where the price is to be negotiated *ex post*. The results derived from the model show how the value of the option and each partner's payoff from the venture vary with the structure of the option.

An important consideration on the theoretical modelling in this environment is that, the nature of an option (e.g., its values to the "buyer" and "seller") varies markedly with its structure (e.g., the structure of uncertainty and terms of the option contract): therefore it is difficult to figure out an option's implications without modelling its structure precisely. For instance, options in joint venture possess some unique structural attributes that are not incorporated in any existing option models (Chi, 2000, p. 3).

Finally, I want to highlight that this literature deals with the evaluation of the single R&D alliance and one can easily imagine further developments in this context.

2.6 Research Goal

The above sections provided a general overview of prominent research which combines real options analysis with portfolio management, competitors interaction as well as with alliance literature. It is important to highlight the most of the literature presented in

section 2.2.1 and 2.3 deals with investments under uncertainty, i.e. it concerns with the evaluation of real options owned exclusive by one firm. Surprisingly, as the previous section highlights, there is little theoretical work on alliances under uncertainty (Savva, 2006; Lukas, 2008), i.e. assuming that projects are developed by two or more firms, which is a more realistic assumption in today's landscape. Several interesting aspects in the alliance's domain have not been sufficiently addressed by real option theory. For instance, how should the partners share the value of a project in a stochastic environment? How do uncertainty and the associated flexibility affect the value of the contract for two or more partners? Specifically, I address these questions by assuming a portfolio perspective on the hand and a dynamic perspective in a competitive environment on the other hand. In such a way, I find important key factors that influence the important choice of when and whether to develop projects in-house, or externally.

In particular, I contextualize this work looking at the collaborations established between pharmaceutical firms and young biotechnology firms. Different reasons leaded me to this choice. First, the biopharmaceutical industry is absolutely one of the industries with the highest rate of formation of alliances; second it has recognized the importance of real option approaches (see the next chapter where a description in detail of the biopharmaceutical industry is provided). However, as the following chapters will highlight, both the portfolio management and the alliance timing decisions are open debates. As a matter of fact, questions such as: "Which projects are more promising than other ?" or "What is the optimal stage to sign an alliance ?" are more and more frequent in this industry and still not well addressed, especially in a situation where the level of uncertainty is particularly high (Betz 2011). Therefore the present dissertation aims to answer to these important questions and, in addressing these themes, I cannot neglect some important considerations coming from the literature review presented in the previous sections. First, most of the real options models, used to evaluate an R&D portfolio, are based on numerical approaches and are very difficult to implement. Conversely, I adopt closed-solutions that greatly make the implementation of the portfolio model easier (see the next chapter). Second, following the most recent trend in the portfolio management literature that combines different approaches to select an optimal projects portfolio, a decision support tool which integrates the real options

approach with screening tools and mapping tools, is also proposed (chapter 4). Third, section 2.3 shows the importance to combine the real options valuation technique with game theory concepts. However no extant research considers this important link by focusing on the choice of the alliance timing (rather the focus has been on the investment timing decisions). By contrast, the chapter 5 of this thesis sheds light on this important issue, taking explicitly into account the important role of competition.

Finally, although the research context is the biopharmaceutical field, the results and insights provided by this thesis apply more generally to R&D environments that have the following characteristics:

- Firms present in the industry resort to R&D partnerships to carry out their innovation process (traditionally partnerships between a small innovator and an established mayor);
- Projects under the alliance are staged and are subject to significant uncertainty over market, which is resolved progressively as the project advances through the development stages (Savva and Sholtes 2014);
- Industries are characterized by competition, that is, for example, when a small firm is signing an alliance with a giant, there are other small firms that aim at firming the same agreement.

Chapter 3
The value of R&D alliances in a pharmaceutical drugs portfolio

3.1 Introduction

New drug development has become considerably challenging in recent years: while length and cost of research and development (R&D) have been growing, chances of success have become extremely low. As a matter of fact, pharmaceutical companies have invested more than $500 billion in research and development into medical innovations since 2000, with an estimated $48.5 billion only in 2012 – the largest R&D investment of any sector in the US economy (PhRMA, 2013). In contrast, only 43 new medicines were approved by the U.S. Food and Drug Administration (FDA) in 2012, being the highest number in the last 15 years (PhRMA, 2013). The pharmaceutical industry is also the sector with the highest ratio of R&D investment to net sales. Nevertheless, big pharmaceutical companies cannot avoid relying on R&D activities, and keep considering them as a major source of value creation, in spite of their intrinsic risks. The emphasis is on increasing both new drugs in the development pipeline and the number of commercial launches every year (Rogers et al. , 2005). To achieve these goals, pharmaceutical companies more and more consider new paradigm solutions including next-generation licensing (Kleyn and Kitney, 2007) and effective pre-competitive collaborations with other companies (Dhankhar et al., 2012). One fundamental element to complete the picture is related to the advent of biotechnology, which has significantly impacted the pharmaceutical industry. In fact, since the eighties, pharmaceutical companies more and more have partnered with the newcomers, i.e., the biotechnology companies, in order to pool their complementary assets along the drug R&D and commercialization processes, and succeed in the winner-takes-all patent race. While the “raw material” is located in biotech firms, pharmaceutical companies have expertise in managing advanced phases in new drug development (i.e., clinical stages, approvals, marketing and production) and considerable amounts of financial resources, of which biotech firms are lacking (Gupta, 2007). Therefore, the emergence of biotechnology has helped change the “closed innovation” business model traditionally

adopted by most of the pharmaceutical companies to the "open innovation" (OI) business model (Cooke, 2005; Chesbrough and Crowther, 2006; Chiaroni *et al.*, 2008; Bianchi *et al.*, 2011; Lo Nigro *et al.* 2012).

In this scenario, financially constrained pharmaceutical decision-makers, should select projects accurately, being sure to choose the most promising. This important choice is also made more complex by the option to sign agreements with biotechnology companies. This consideration implies a proper evaluation of every single project, the enrolment of an open innovation paradigm in the manager's agenda, and the adoption of a portfolio perspective that is able to incorporate strategic issues into the R&D decisions. However, in this environment, strong portfolio management is pivotal in helping to focus pharmaceutical company resources effectively on the most attractive projects (Betz, 2011). In addition, the pharmaceutical R&D process has a long and dynamic life, and further investments depend on the success/failure of previous ones, which then also represent an ideal field of application for ROA. As a matter of fact, as it will be discussed in section 3.3 of this chapter, in recent years, the real options approach has begun to receive attention in biopharmaceutical industry, even if its use has not been very widespread[8] (Hartmann & Hassan, 2006), especially in a portfolio context.

The aim of this chapter is to set up a manageable real options model (Open OptFolio Light (OOL)) that is able to support pharmaceutical R&D decision-makers in the portfolio selection process by suggesting which projects should be undertaken, the best means by which to develop them (through an open- or a closed-innovation paradigm, i.e. licensing-in or not), and the cross-financing policy. Indeed, in order to obtain a balanced portfolio, the model takes into account different aspects, including the possibility of adopting OI solutions to develop each project, as well as a self-financing policy. As illustrated in the next section, the literature fails to deal with these "needs" simultaneously, and managers have highlighted this lack (Hartmann and Hassan, 2006): this part of the dissertation aims to fill this literature gap.

In the following section, a literature analysis is conducted to highlight the scientific support of the above mentioned research goal. Section 3.3 focuses on the

[8] A survey conducted by Hartmann & Hassan, 2006 into the most important pharmaceutical firms in 2005, which aimed to investigate the methods used by companies in the evaluation of their R&D projects, finds that ROA use is not very widespread, mainly because of: (i) perceived technique complexity; (ii) lack of acceptance by the decision makers; and (iii) lack of transparency.

biopharmaceutical R&D portfolio evaluation. The OOL model, which is based on OptFolio (a model available in the literature (Rogers et al., 2002)), is presented in section 3.4; in section 3.5 OOL is compared to other real options models that are available in literature to highlight its characteristics, and in section 3.6 OOL is applied to a numerical example. In section 3.7, conclusions are drawn, the research findings are summarized, and further developments are anticipated.

3.2 Literature Overview

Previous research acknowledges ROA as a powerful tool to evaluate biopharmaceutical R&D projects (Cassimon et al., 2004); nonetheless, the evaluation of a single project would not be consistent with a firm strategy that usually assumes a more comprehensive point of view. In order to overcome this limitation, the whole portfolio of R&D projects should be considered. This is especially important in the context of the biopharmaceutical industry, which is characterized by very high failure rates of new drug candidates, and by long times to complete the entire R&D process (Rogers et al., 2002).

Project portfolio selection is crucial in many organizations, which must make decisions on investment, where the appropriate distribution of investment is complex due to varying levels of risk, resource requirements, and interactions among the candidate projects (Berzinsh et al., 2006). In addition, R&D activities have become increasingly costly and risky; hence, measuring their performance and contribution to value is critical **(**Lazzarotti et al., 2011). As discussed in the previous chapter (section 2.2), while the portfolio management methods employed in different organizations vary greatly, the objectives that managers are trying to achieve are quite similar (Eilat et al., 2006). According to Cooper et al. (1998), an objective that usually dominates this decision process is that of obtaining a balanced portfolio, i.e. diversifying the projects in the portfolio in terms of various trade-offs such as high risk versus sure bets, internal versus outsourced work, etc. Open Innovation practices provide an invaluable tool by which to balance an innovation portfolio and share risk; in the meantime, an actively managed portfolio demands judgments calls. The judgments may well be based on quantitative values and careful measurements, but the shadow of false positive and false negative judgment persists (Bingham & Spradlin, 2011) and can be mitigated by

adopting an evaluation method that is able to overcome the underrated problem inherent in the net present value methodology (false negative in the case of flexible alternatives) such as the ROA method. Therefore, OI reinforces the usefulness of ROA in this context. However, organizations, while recognizing the importance of ROA, do not apply it because it is perceived as a complex concept. This consideration is especially true when the whole R&D projects portfolio has to be evaluated. As widely discussed in the first part of this thesis (section 2.2.1), most of the real options models available in literature to evaluate an R&D portfolio, are hard to implement mainly because they are based on discrete approaches. Such approaches if, on the hand, are more intuitive than closed-solutions, on the other hand, are difficult to manage as the size of the portfolio increases. Conversely, closed-solutions could appear as black-box tools, but show a major easiness of implementation (please refer to the section 3.5) and provide more accurate solutions (Chance, 1998).

The main contribution to the literature of the present chapter is to propose a closed ROA model that is easy to implement, in order to support two critical aspects: (i) R&D projects selection; and (ii) how to carry out the selected projects (internally or externally). Such a tool would represent an operative way to deploy OI. The targeted balance is multifaceted: behind open vs. closed means by which to decline innovation, the equilibrium between products able to produce cash flows and products that need financial sustain is pursued. Therefore, the model also aims to contribute to the available models, considering the possibility to create a financially balanced portfolio, since it includes a self-financing policy. According to Kamien & Schwartz (1978), the self-financing of R&D for a company is urgent for two reasons. First, external financing may be difficult to obtain without substantial related tangible collateral that can be claimed by the lender if the project fails; an R&D project that fails generally leaves behind few tangible assets of value. Second, the firm might be reluctant to reveal detailed information about the project that would make it attractive to outside lenders, fearing its disclosure to potential rivals.

The output of the model, named Open OptFolio Light (OOL), is the composition of the pharmaceutical portfolio, and, for each selected drug, it is able to suggest whether it should be developed in-house or through an alliance with a biotechnology company, and if (and to what extent) it will finance other projects in the pipeline when it is

commercialized. Moreover the model is able to deal with variables that take into account the business strategy (the choice of therapeutic areas in which to invest) as well as characteristics of possible partnership (level of synergy, profit sharing policy, etc.), and it has been tested through a case study taken from the literature (Rogers et al., 2002).

3.3 Pharmaceutical R&D Project Evaluation

Discounted cash-flow-based methods, such as NPV, are generally used to evaluate investment projects. However, in the field of R&D pharmaceutical projects, where high uncertainty and risks (both economic and technical) are prominent, these methods lose a large amount of their effectiveness. In fact, as discussed in details in section 2.1, they fail to correctly assess the real value of these projects, which results, among other things, from the flexibility possessed by the management and from the several opportunities these kinds of investments offer. Thus, the real options approach has begun to be used in biopharmaceutical industry: however, while there is a large amount of literature on pharmaceutical project evaluation using ROA, in practice the method has been used effectively only to evaluate single projects (Copeland & Antikarov, 2001).

3.3.1 Single pharmaceutical R&D project evaluation

This section reviews some contributions to the literature that adopts ROA method as a tool to evaluate single pharmaceutical projects. Several papers propose different solutions for modeling the multi-phase (bio)pharmaceutical process, and I can classify these according to the chosen method to evaluate the project, i.e. numerical approaches or closed-form solutions. While a first group uses a binomial lattice approach, (Kellog & Charnes, 2000; Shockley et al., 2003) or decision tree (Loch & Bode-Greul, 2001), a second group solves this problem with closed-form models. Particularly, as Bowman & Moskowitz (2001) point out, the first application of ROA in the evaluation of a pharmaceutical R&D project was carried out by Merck, one of the most important pharmaceutical companies, in the early 1990s. Merck adopts the B&S option-pricing model to determine the option value of an investment project. Since this first attempt, many scholars have devoted their attention to these closed-form solutions, and they

refer to more accurate models such as the aforementioned option model (Geske, 1979). Among these, I can mention the two-fold compound approach (Perlitz et al., 1999) or the generalized *n*-fold version of this (Cassimon et al., 2004; Cassimon et al., 2011a). Moreover, in order to more realistically evaluate the pharmaceutical process, several authors adopt "adjusted" formulae (specifically jump-diffusion models) based on the B&S formula (Brach & Paxson, 2001) or on the Geske model (Pennings & Sereno, 2011).

Finally, Sereno (2010) applies both a lattice method and a closed-form solution (a three-fold compound option) to evaluate a pharmaceutical patent and, as Sereno points out, it is easy to demonstrate that by increasing the number of time steps in the binomial model, the solution converges to the closed-continuous time one – for the compound option as well.

3.3.2 Pharmaceutical R&D portfolio evaluation

However, according to several authors, it is better to evaluate the entire R&D project portfolio of a company instead of its single projects, in order to consider the relations and the interdependencies among them. These interdependencies, which are ignored if projects are evaluated one by one, usually deal with limited resource consumption, risk balancing and company strategies. A great contribution in this field to scientific literature has been made by Rogers et al. (2002), who, as discussed in section 2.2.1, developed a stochastic optimization model (OptFolio), based on a quadrinomial tree method, which is able to identify the most valuable projects among the entire R&D project portfolio of a pharmaceutical company. Starting from this real options optimization model, Rogers et al. (2005) proposed an approach by which to select the best licensing strategy for each product in the R&D portfolio. Specifically, the OptFolio model is based on the binomial tree method. Despite being close to reality, the implementation and use of OptFolio turns out to be very complex and difficult to manage. As a matter of fact, a pharmaceutical company may find it hard to identify an optimal project portfolio to solve a problem with a lot of constraints and several dozen thousands of variables, with only 20 candidate drugs. A step towards simplifying this model was made by Rafiee and Kianfar (2011), who propose the same stochastic model of Rogers et al. (2002), but involving a smaller number of both scenarios and projects

considered in the portfolio. As far as closed-solutions models are concerned, they have been adopted by Wang & Hwang (2007) who developed a closed fuzzy compound option model to estimate the value of each R&D project in a pharmaceutical company pipeline. Enea and Lo Nigro (2011a, 2011b) used closed-solutions to develop an OptFolio Light (OL) model inspired by OptFolio that addresses OptFolio issues in a way that is very easy to implement. However, neither of the above models considers an aspect very important in terms of a balanced portfolio: i.e. the decision to license-in or to internally develop selected projects. The next section illustrates in details the proposed model OOL, which takes into account this issue.

3.4 The Open OptFolio Light (OOL) model

In order to maintain their annual revenues and growth rates, pharmaceutical companies aim to increase both new drugs in the development pipeline and the number of commercial launches each year. Consistently with these goals, they are augmenting their product pipelines by also licensing-in the proprietary compounds by biotechnology companies (Rogers et al. , 2005). Licensing-in is a form of inbound OI (Dahlander & Gannb, 2010), and typically consists of an initial payment, milestone payments based on the successful completion of an R&D stage, and royalty payments upon product commercialization. According to Rogers et al. (2005), the pattern of these partnerships is easily assimilated to a real option: so, after an initial up-front payment to the biotechnology company, the pharmaceutical company has the right – but not the obligation – to make a milestone payment at each stage of development to continue the alliance. Furthermore, financial interdependencies existing among the projects of a product portfolio have to be underlined. This could mean that selecting a drug to be developed may deduct financial resources from the development of other drugs, and also that it may provide funds to feed the development of new products. In fact, if a drug manages to be commercialized and to achieve satisfactory economic results, a company might use part of its incomes to finance other R&D projects. This is, as a matter of fact, one of the prominent features of blockbuster drugs.

These considerations highlight the importance for a pharmaceutical company to select a balanced R&D portfolio, in terms of drugs selected at different stages of development (both drugs in their early stages and successful ones able to provide profits, as well as to finance new drug development), and drugs selected internally (in-house) or by

licensing-in (in alliance with a biotechnology company). Therefore, I propose a closed-form model, Open OptFolio Light (OOL), based on the OL model (Enea and Lo Nigro, 2011b), which considers R&D alliances to select the optimal R&D portfolio.

Mathematical formulation of OOL

Sets and Parameters

The proposed model uses the following parameters to describe the problem of portfolio optimization projects:

i=1,2,...,M products/drugs/molecules (in the following drugs)

s=1,2,...,S stage of the process of drug development

t=1,2,...,T year of the portfolio planning horizon

For each of the candidate drugs, as also suggested by the OptFolio model, the impending stage at the present time t=0 is classified as s = 1, regardless of where the candidate drug is in its development. Subsequent development stages are numbered in ascending order until termination at product launch. Let me also define:

V_{0i} = NPV of future incomes for drug i at t = 0

σ_i = estimated annual market volatility for drug i

r = risk-free interest rate

$T_{i,s}$ = length in years of stage s of drug development for drug i

$I_{i,s}$ = investment cost of developmental stage s for drug i

Θ_{is}= probability of technical success in stage s of development for drug i

B_t = budgetary constraint for year t

C_i = value of drug i if it is developed in house

C_i' = value of drug i if it is developed in alliance with a biotech company

F_i = annual cash flow of drug i made in house

F'_i = annual cash flow of drug i made in alliance

r_{ph} = rate of return in the pharmaceutical industry

n = drugs commercial life

$X_i^{R\&D}$ = percentage of cash flows of drug *i*, developed in house, invested in R&D

$X'^{R\&D}_i$ = percentage of cash flows of drug *i*, developed in alliance, invested in R&D

Specifically, V_{0i} represents the estimated value of drug *i*, based on the NPV of all cash flows that result if the drug is commercialized, at time $t = 0$ of the planning horizon. This value is an aggregate of the projected sales revenue of the drug minus production, distribution, and marketing costs and all other expenses (Rogers et al., 2002). The market volatility σ_i is the standard deviation of V_{0i} , which is usually estimated using historical sales data of similar products. The risk-free interest rate, *r*, corresponds generally with an observable market rate, such as US Treasury Bills. Every development stage *s* of each candidate drug *i* could have a different length $T_{i,s}$ as well as a different investment cost to be carried out $I_{i,s}$ and probability of technical success Θ_{is}. The budgetary constraint B_t is the total amount of financial resources that a company can spend for its R&D projects in the year *t*.

Model assumptions

The drug value D_i (i.e. C_i or C_i' depending if it is developed in house or in alliance respectively) is calculated by different closed expressions depending on the number of phases left. In order to capture this important aspect, let me briefly represent the pharmaceutical process. Specifically, as Figure 7 shows, the development of a new drug is a step-wise process that starts with a pre-clinical test phase, followed by three clinical test phases (phase I, phase II and phase III) and concluding with FDA (Federal and Drug Administration) approval phase. Particularly, each phase is an option on the following one: if the preclinical phase turns to be successful, the first clinical Phase (Phase I) can start. This means that the preclinical phase is an option on the first clinical test. In the same way, the first clinical phase is an option on the second one, which is an option on the next test and so on, until the FDA phase (Cassimon, 2004).

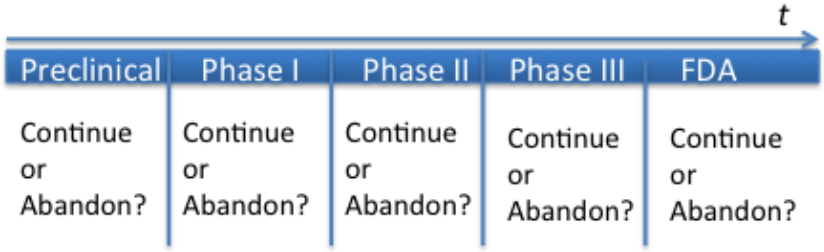

Figure 7: Pharmaceutical R&D decision making process

In the context of this framework, as above mentioned, different closed-solutions are adopted, depending on the number of phases left.

Specifically if a drug has successfully completed the last clinical phase (phase III) and has only one phase left to pass through (i.e. the FDA approval phase), the simple NPV can be adopted because no more option is available.

The B&S formula is used for a candidate drug that is about to complete its R&D process, and has one development phase left (i.e. the Phase III) before the FDA approval phase. As a matter of fact, the Phase III is an option for the FDA phase: thus the B&S formula , which is a 1-fold option formula, is ideal to model this situation.

Let me recall the B&S formula introduced in the first chapter:

$$D_i = S_i N(d_{i1}) - K_i e^{r(T-t)} N(d_{i2}) \tag{19}$$

Specifically, in this context, as it will be clearer later in the next section, the underlying S_i and the exercise price K_i of the generic product *i*, will vary accordingly to the modeled scenario, i.e. dependently if the "alliance" scenario or the "in-house" scenario is modeled.

For candidate drugs in earlier phases of their development and that precisely have to pass their phase II, the Geske formula is used. Once again, the Phase II is an option on the phase III which is an option on the FDA phase, i.e. it is a 2-fold compound option. The Geske model, which is a 2-fold options formula, is ideal to model this situation.

Similarly as the B&S formula, let me recall the Geske formula introduced in the first chapter:

$$D_i = S_i N_2(a_{i1}, a_{i2};\ \rho) - K_{i2} e^{r(t_2-t)} N_2(b_{i1}, b_{i2};\ \rho) - K_{i1} e^{r(t_1-t)} N(b_{i2}) \tag{20}$$

Once again, the underlying S_i and both the exercise prices K_{i1} and K_{i2} will vary according to the modeled scenario.

Finally, for drugs with more than three phases left, the aforementioned extended Geske model, i.e. the *n*-fold options model developed by Cassimon et al. (2004), would be necessary. For example, following the same logic of above, a drug which is in its phase

I and, consequently, has other four stages left, would better modeled by a 3-fold options model. However, in order to simplify the analysis (for example in a spreadsheet where an *n*-variate cumulative normal distribution is hard to implement) and to keep the mathematics as simple as possible, the traditional Geske expression can be used. To do so, $s = 2$ and $s = 3$ stages, for instance, could be merged if the decision to undertake both of them is made at the beginning of the $s = 2$ stage. This allows the drug to appear as it has only three stages left instead of four. The investment/exercise price of this new single stage can be calculated as:

$$I_{i2,3=}I_{i2} + I_{i3}e^{-rT_{i2}} \quad (21)$$

Computing payoffs: The "in-house" scenario

To better understand the mathematics present in the model, let me present the payoff of the pharmaceutical company in the simplest scenario, in which alliance is not considered. The net value of the generic drug in the portfolio, is given by (C_i - I_{i1}), where C_i is the drug value without alliance, calculated at t=0 using NPV/B&S/Geske formulae and I_{i1} is the initial cost at t=0, necessary to buy the option to invest in further stages if successfully completed. Therefore I_{i1} is a sunk cost and does not affect the option value, but decreases the total project value. Successive investments in different stages, $I_{is,s\neq1}$ affect the real options value C_i: in fact, they represent the exercise prices of the call C_i, with underlying value equal to V_{oi} (please refer to table 6).

Computing payoffs: The "alliance" scenario

To gain insight into how the proposed real options framework takes into account the alliance option, as suggested by Rogers et al. (2005), I introduce the concept of indifference for the biotech company in developing the drug in alliance with the pharmaceutical company or on its own. In this way, I can obtain the licensing conditions: i.e. payments offered by the pharmaceutical company and royalties. In fact, as above mentioned, the alliance agreement consists of an initial payment, milestone payments based on the successful completion of an R&D stage, and royalty upon product commercialization.

Assuming that a biotech company has the resources to develop the drug *i* independently, she will grant the license to a pharmaceutical company if the alliance alternative offers a value that is at least equal to the one if the biotech develops the drug on its own.

$$C_i\left(\text{Biotech}\right)license + P_{i1} - I_{i1} = C_i\left(\text{Biotech}\right)nolicense - I_{i1} \qquad (22)$$

The terms $C_i\left(\text{Biotech}\right)nolicense$ and $C_i\left(\text{Biotech}\right)license$, are calculated using again the formulae mentioned above (B&S/Geske/NPV). In particular, the underlying asset value of $C_i\left(\text{Biotech}\right)nolicense$ is $V_{oi}\ \gamma_i^{'}$ where the initial value of the drug is multiplied by the amplification factor $\gamma_i^{'}$ (>1), which takes into account the possible added value from the biotech firm.

On the other hand, if the biotech company will license the drug, the underlying asset becomes $V_{0i} \cdot \gamma_i \cdot (1-\alpha_i)$ (see Table 5). In such a case, i.e. when the biotech company signs the agreement with the pharmaceutical company, the pharmaceutical company will transfer an upfront payment (P_{i1}), interim payments $(P_{is,s\neq 1})$ and a percentage of the revenues $(1-\alpha_i)$ to the bio-company, with $0<\alpha_i<1$. The amplification factor γ_i, which is greater than $\gamma_i^{'}$, represents the measure of value added to the project by the bio-pharmaceutical alliance (the NPV of the alliance future incomes becomes $V_{0i} \cdot \gamma_i$ and $(1-\alpha_i)$ is the part held by the biotechnology company whereas α_i is the part held by the pharmaceutical company). A large pharmaceutical company, which has advanced marketing resources, is able to double the value that would generate a small biotech company for a drug license (Rogers et al., 2005). According to Nicholson et al. (2005), if an experienced pharmaceutical firm works with a biotech company, some of the development costs will be lower or expected revenues will be higher. This causes an increasing drug value.

As I_{i1}, P_{i1} is the up-front payment at t=0, necessary to the pharmaceutical company to buy the option of signing the alliance with the biotechnology company. If later development stages will be successfully completed, the pharmaceutical company will contribute with further payments $(P_{is,s\neq 1})$. As a consequence, the exercise price

considered in the term $C_i\left(\text{Biotech}\right)license$, will not be the whole investment cost of developmental stage *s* for drug *i* (I_{is}), but a lower value: stage by stage the biotech firm will invest ($I_{is} - P_{is}$) (see Table 5), with $P_{is} \leq I_{is}, \forall\, i, s \neq 1$

	Variable	$C_i\left(\text{Biotech}\right)nolicense$	$C_i\left(\text{Biotech}\right)license$
Biotechnology company	Underlying asset value (S_i)	$V_{0i} \cdot \gamma_i^{'}$	$V_{0i} \cdot \gamma_i \cdot (1-\alpha_i)$
	Exercise price(s) (K_{is})	$I_{is,s\neq 1}$	$I_{is} - P_{is}$, $s\neq 1$

Table 5: Input variables used in biotech real options evaluation

In particular, I impose among the payments the same proportionality of the corresponding investments. Specifically, I refer to the "hedging investment policy" (Rogers et al., 2005), which consists of smaller up-front payments and larger milestone payments in later stages of development. Imposing the indifference condition we can obtain, for each *i*, a value of α_i and the corresponding payment P_{i1} (the other payments are functions of P_{i1}), that satisfy equation (22): in fact, the problem admits ∞^1 solutions. Once obtained the above payments, the payoff of the pharmaceutical company in the alliance scenario, can be easily computed. The net value of the generic drug is given by (C'_i - P_{i1}), where C'_i is the drug value in alliance, calculated using NPV/B&S/Geske formulae and the aforementioned P_{i1} is the up-front payment at t=0, necessary to buy the option to ally and represents a sunk payment that does not affect the option value, but decreases the total project value. Successive payments in different stages, $P_{is,s\neq 1}$, affect the real options value C'_i since they represent the exercise prices of the call C'_i, with underlying value equal to $V_{oi}\ \gamma\ \alpha_{i.}$(please refer to table 6).

	Variable	**C_i (in-house scenario)**	**C_i'(alliance scenario)**
Pharmaceutical company	Underlying asset value (S_i)	V_{oi}	$V_{oi}\,\gamma_i\,\alpha_i$
	Exercise price(s) (K_{is})	$I_{is,s\neq 1}$	$P_{is,s\neq 1}$

Table 6: Input variables used in pharmaceutical real options evaluation

Model formulation

The model includes four dichotomous variables, with the following meanings:

$$H_i = \begin{cases} 1 \text{ if the drug, developed in house, is selected for the optimal portfolio} \\ 0 \text{ if the drug, developed in house, is NOT selected for the optimal portfolio} \end{cases}$$

$$L_i = \begin{cases} 1 \text{ if the drug, developed in alliance, is selected for the optimal portfolio} \\ 0 \text{ if the drug, developed in alliance, is NOT selected for the optimal portfolio} \end{cases}$$

$$h_i = \begin{cases} 1 \text{ if part of the cash flow of the drug developed in-house is reinvested} \\ 0 \text{ if part of the cash flow of the drug developed in-house is NOT reinvested} \end{cases}$$

$$l_i = \begin{cases} 1 \text{ if part of the cash flow of the drug developed in alliance is reinvested} \\ 0 \text{ if part of the cash flow of the drug developed in alliance is NOT reinvested} \end{cases}$$

Clearly, if a drug is developed in-house by the pharmaceutical company, it cannot be licenced-in. Mathematically, this condition can be expressed with the following constraint, which also considers the possibility that the same drug is not selected:

$$H_i + L_i \leq 1 \qquad \forall i \tag{23}$$

As mentioned before, further assumptions are needed to achieve a balanced R&D portfolio. The first, which concerns the annual revenue distribution of a marketed product, assumes that, after its commercialization, a drug provides a company with uniform cash flows, F_i, for n years. The value of these annual incomes for drug i, developed in-house, is:

$$F_i = V_{0i}\,\frac{(1+r_{ph})^n\, r_{ph}}{(1+r_{ph})^n - 1} \tag{24}$$

If the drug is developed within the alliance, the value of the cash flows turns out to be:

$$F'_i = V_{0i} \cdot \gamma_i \cdot \alpha_i \frac{(1+r'_{ph})^n r'_{ph}}{(1+r'_{ph})^n - 1} \tag{25}$$

More precisely, I assume r'_{ph} lower than r_{ph} because of the risk sharing coming from the agreement. In order to consider the possibility of reinvesting the cash flows of a drug, other constraints are needed. The self-financing by the commercialized drugs is allowed only if the drug has been selected to be part of the optimal portfolio. In mathematical terms, these concepts can be expressed with the following constraints:

$$h_i \leq H_i \qquad \forall i \tag{26}$$

$$l_i \leq L_i \qquad \forall i \tag{27}$$

However, only a share $X_i^{R\&D}$ or $X_i'^{R\&D}$ (depending on the adoption of a closed rather than open paradigm, respectively) of annual cash flows is potentially reinvested to fund the development of further drugs. Thus, the actual amount of financial resources, deriving from the commercialization of drug *i* and planned to be invested yearly in R&D, is:

$$RF_i = X_i^{R\&D} F_i \qquad \text{if drug } i \text{ is developed in house} \tag{28}$$

$$RF'_i = X'^{R\&D}_i F'_i \qquad \text{if drug } i \text{ is developed in alliance} \tag{29}$$

$$0 \leq X_i^{R\&D} \text{ and } X'^{R\&D}_i \leq 1 \tag{30}$$

The resulting mathematical model is as follows:

$$\max ROV = \sum_i \left(C'_i - P_{i,1}\right) L_i + \sum_i \left(C_i - I_{i,1}\right) H_i - \sum_{i,t} \frac{\omega_{it} RF'_i}{(1+r'_{ph})^t} l_i - \sum_{i,t} \frac{\omega_{it} RF_i}{(1+r_{ph})^t} h_i \tag{31}$$

s. t.:

$$\sum_{i,s} \left(P_{i,s} \theta_{i,s-1} w_{ist}\right) L_i + \sum_{i,s} \left(I_{i,s} \theta_{i,s-1} w_{ist}\right) H_i \leq B_t + \sum_{i,s} \left(\omega_{it} RF'_i\right) l_i + \sum_{i,s} \left(\omega_{it} RF_i\right) h_i \; \forall t \tag{32}$$

constraints of equations 23-30.

with: $H_i, L_i, h_i, l_i \in [0,1]$

The objective function (eq. 31) can be decomposed into two parts: the first concerns the selection of a drug candidate to be included in the optimal portfolio (considering the possibility of developing this through an alliance with the biotech firm), and the second concerning the possibility of using part of the income of a selected drug to fund additional R&D projects. The binary parameter ω_{it} allows the contribution of drug *i* in the period *t* to be considered only if the drug has already been introduced to the market in that period. As far as the budget constraint (eq. 32) is concerned, the first part of the equation is related to the expenses necessary for the development of drugs, while the second part includes the financial contributions brought to R&D by those commercialized drugs whose revenues have been partially allocated for this specific purpose. Finally, the binary parameter w_{ist} appears (in the OptFolio model too) and makes it possible to include in budgetary constraints only those drugs (*i*) beginning a stage of development (*s*) in the period *t* (a phase can be longer than one year).

In addition, the mathematical formulation above can be simplified; for example, some binary variables can be omitted if, *a priori*, their value is known (products in the earlier phases of development cannot finance other products in the time horizon considered).

3.5 Optfolio and OL: a comparison

In order to highlight the importance to use closed-solutions, especially from an implementation standpoint, let me provide a comparison between OL (the closed model I refer to) and Optfolio model, that has been used in literature to evaluate a pharmaceutical portfolio too, but, conversely, uses numerical approaches.

The aim of OptFolio (Rogers et al., 2002) and OL is to determine the optimal drug developmental portfolio that maximizes the real options value (ROV), which is the overall value of the portfolio given a set of candidate drugs in various stages of development. To estimate the value of the single project/drug, OptFolio uses a quadranomial approach (a two-variable binomial tree) and models each project development as a series of continuation/abandonment options, deciding at each phase whether to proceed further or stop the development (Rogers et al., 2002). However, according to Copeland & Antikarov (2001) and Cassimon et al. (2004), decision tree methods can easily become difficult to manage because of the rapidly increasing

number of trees with the size of the portfolio. As a matter of fact, the resulting OptFolio formulation, as pointed out by the same authors, involves a large number of binary variables and causes the objective function to no longer be a linear function. Thus, in order to achieve a more tractable approach in a linear form, the authors must solve a sub-problem with no budgetary restrictions. This linearization procedure reduces the number variables, but complicates the global problem resolution. Several constraints are present in the model, such as budgetary constraints or others that are used to enforce the precedence between the different development phases of a drug and to prevent a drug which has been abandoned in an earlier stage from being selected. Using this approach, the mathematical model for the case study considered (the same presented in section 3.6) includes 893 binary variables and 12843 continuous variables.

To reduce OptFolio's complexity, OL (Enea and Lo Nigro, 2011a; 2011b), introduces some alterations, while the goal is the same. The first is the way in which the R&D process is modeled: OL opts for closed-form formulae instead of the binomial method, making the computational burden lighter. Particularly, the B&S formula is used for candidate drugs which are about to complete their R&D processes and have only two development phases left, while the Geske formula is used for candidate drugs in earlier phases of their development. Lastly, if a drug has only one phase left to pass through, which is generally the approval phase, the NPV can be adopted. As a consequence, an important difference from the OptFolio model is that the real options drug values are input parameters in the proposed mathematical model, while in OptFolio they are an output of the mathematical programming (they are considered in the objective function). This is an important issue because it greatly reduces the implementation complexity. Moreover, OL foresees, inside the closed solution, the possibility to further or stop investments (Perlitz et al., 1999) during the pharmaceutical R&D if the outcome of any phase is or not satisfactory (indeed, in this case, the corresponding single real options, as shown earlier in chapter 2 assume values equal to 0). On the other hand, a drug can be dismissed because of budgetary constraints. These two assumptions allow OL to use a binary variable for each drug, with only one subscript to model whether a drug is selected to be part of the optimal portfolio. In this mode, the same case study proposed by Rogers et al. (2002), can be solved with only 40 binary variables and 20 continuous variables.

Actually, binomial approaches show more clearly how the value of the real asset can evolve over time. However, as widely discussed earlier in this dissertation, they can be more complicated in terms of implementation, especially in a portfolio context. Also, as discussed in Chapter 2, another limitation consists in the " arbitrary granularity", i.e. the arbitrary in choosing the number of sub-trees.

On the other hand, a possible shortcoming of OL, could be the assumption of a diffusion process (the Geometric Brownian Motion) for the underlying. This implies a continuous arrival of information that changes the underlying value (Pennings & Lint, 1997) while, in a research environment information tends to arise at discrete points of time, causing that that the managers, in real markets, do not continuously adjust the underlying value, but only when information arrives (Pennings & Lint, 1997). In addition, for drugs that are in early phases of their development, OL is based on Perlitz et al.'s (1999) approach, which models the complex R&D process in two phases (eq. 21). This simplification is addressed to keep the mathematics as simple as possible, because in this way the two-period compound option model of Geske (1979) can be used. Using a generalization of Geske's compound options Cassimon et al. (2004) derive a closed-form solution for the n-fold compound option model. However, this model, while being a better fit for the pharmaceutical process than Perlitz et al.'s (1999) model, is more complicated from a mathematical point of view. In addition, Cassimon et al. (2011a) present a valuation of a project (Vitosha project) using both the two-fold compound option approach and the n-fold compound option approach: the results do not seem to be very different.

Table 7 summarizes the similarities, key assumptions, weaknesses and strengths of OptFolio and OL.

	OptFolio	OptFolio Light (OL)
Similarities • Goal • Financial option used • Portfolio optimiziation tool	Pharmaceutical R&D portfolio optimization Call option Mathematical programming formulation	Pharmaceutical R&D portfolio optimization Call option Mathematical programming formulation
Key assumptions • Real option model • Means of contemplation	Quadranomial approach Discrete	Closed solutions (B&S/Geske); NPV Continuous
Weaknesses	Huge number of variables and constraints Arbitrary granularity (number of sub-trees)	Not applicable in the case of American put Continuous change in the underlying value due to Brownian motion
Strengths	Transparency of the binomial tree approach	Easy implementation Flexibility (possibility to take into account open innovation and self-financing)

Table 7: A comparison between OptFolio and OL

3.5.1 OOL: a comprehensive comparison

To better highlight the unique futures that make OOL very attractive, let me provide a briefly comparison with other models that have been adopted in literature for the pharmaceutical portfolio management. To the best of my knowledge, in addition to Optoflio model (Rogers et al., 2002) and OL model (Enea and Lo Nigro 2011a; 2011b), other models (Rogers et al., 2005; Wang & Hwang, 2007; Rafiee and Kianfar (2011)) are available to select the optimal pharmaceutical portfolio. Particularly, Rogers et al. (2005) and Rafiee and Kianfar (2011) use the same model developed by (Rogers et al., 2002), that has been thoroughly described in the previous section. As far as Wang and Hwang's (2007) model is concerned, it adopts the same case study (Rogers et al. 2002) I use to test OOL (please refer to the following section). Therefore, it is even more

interesting to show a comparison between this model and OOL to understand how the latter differs from it. Specifically, Wang and Hwang (2007) adopt a fuzzy real options valuation method that is based on the method proposed by Carlsson & Fullér (2003). They use the Geske compound options valuation model for all 20 drugs considered in the portfolio, but I believe that the method (Geske, B&S, or the simple NPV) should depend on the remaining phases. Moreover, the authors formulate the R&D portfolio selection problem as a fuzzy zero-one integer programming model with the aim of maximizing an objective function, subject to budgetary constraints or constraints on the availability of human resources and other mathematical constraints. Specifically, the objective function is the total ROV (fuzzy real option value) of selected projects, minus all development costs in the planning horizon. However, according to Hassanzadeh et al. (2011), deducting the total development costs of selected projects from their ROVs in the objective function implies that the total benefit of the portfolio is doubly affected (because they are also considered as exercise prices in the real options evaluation) by development costs (except for the initial cost).

Moreover, neither of the above models (Rogers et al., 2005; Wang & Hwang, 2007; Rafiee and Kianfar, 2011) considers two aspects that are very important in terms of a balanced portfolio: i) the self-financing option and ii) the decision to license-in or to internally develop selected projects. Finally, the model has been tested using a spreadsheet (as described in the following section), so it can be implemented and used in a simple way: this characteristic could bring managers to adopt a ROA-based tool.

3.6 An OOL Numerical Example

The low computational burden of OOL allows its implementation in a Microsoft Excel spreadsheet. Any pharmaceutical company interested in evaluating and selecting its R&D projects could create its own optimal products portfolio simply by entering the drug information and clicking a button. Specifically, the model requires inputs regarding budget limitations as well as candidate drugs, such as their expected current values, volatilities, technical success rate and investment costs for each stage and type, which indicates what the impending development stage of a drug is at the time of portfolio selection. Thus, the spreadsheet identifies whether the B&S, Geske or NPV approach is needed for each drug, and eventually calculates the options parameters,

which are useful for estimating the real options values C_i and $C_i^{'}$. Ultimately, it is sufficient to click on a macro button, which launches the Excel solver to find the balanced optimal portfolio composition. Of course, if the drug is developed jointly through an alliance with a biotech company, among the input parameters the payments that the pharmaceutical company will pour into the biotech company during the agreement will substitute the investments. To calculate payments and royalties by the above indifference condition (eq. 22), it is therefore necessary to introduce additional input parameters such as the values of γ_i and $\gamma^{'}_i$, as shown in Figure 8.

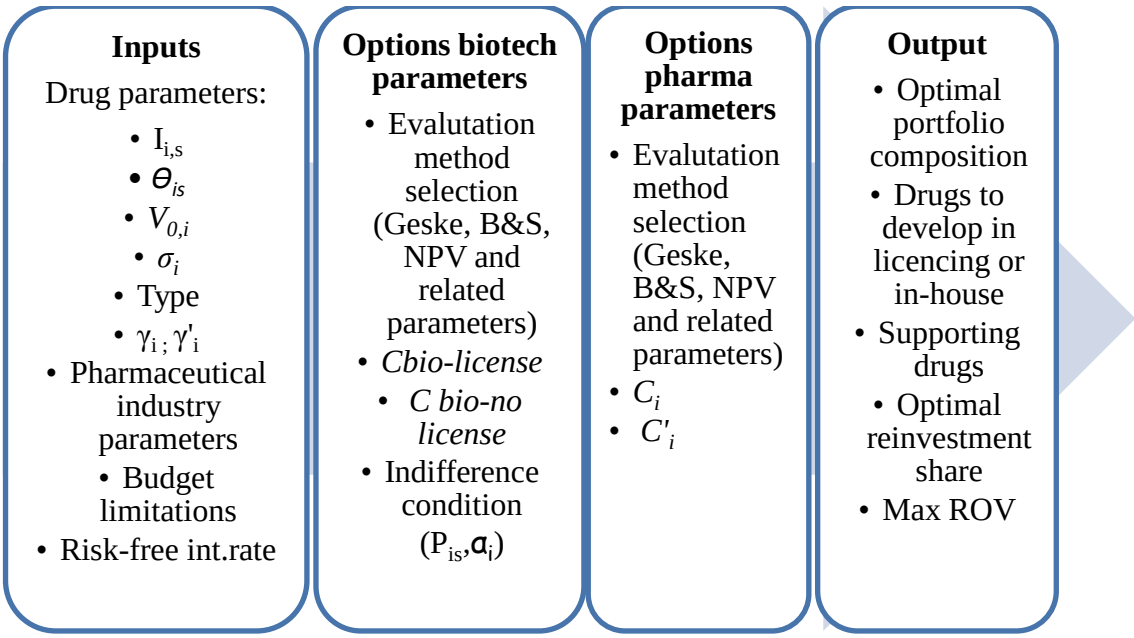

Figure 8: Optimal portfolio selection process using OOL spreadsheet

As an illustrative example of the model OOL, I use the case study presented by Rogers et al. (2002), which concerns the portfolio selection of a pharmaceutical company with 20 drug candidates (M) for an R&D portfolio. Each of them is classified into six categories, depending on which stage of development it is at (Table 8).

Type	Beginning phase	Candidate drugs (M)	Evaluation method	Development stages left
1	Phase I	1, 2, 3, 4, 5, 6	Geske	4
2	Phase II	7, 8, 9, 10, 11	Geske	3
3	Phase III	12, 13, 14	B&S	2
4	2^{nd} year Phase III	15, 16	B&S	2
5	1^{st} FDA Approval	17, 18	NPV	1
6	2^{nd} FDA Approval	19, 20	NPV	1

Table 8: Candidate Drugs

In particular, drugs of type 1, 2 and 3 are all placed in the clinical phase, which is divided into three sub-phases (phase I, phase II, phase III). Moreover, drugs of type 5 and 6 have only the commercialization phase (or phase IV) left. The length of phases I and II have been assumed to be equal to one year each, while the length of phase III and FDA approval is equal to two years each, resulting in an overall length of six years for the R&D process. Budget limitations have been considered as M$ 400 for the first year and M$ 800 for the remainder, with a planning horizon of five years (Rogers et al., 2002). In order to obtain from the V_{0i} the annual cash flow F_i / F'_i which represents the available self-financing from the commercialized drugs developed, a value of r_{ph} equal to 12% was also assumed, as suggested by DiMasi et al. (2003), along with a lower value for r'_{ph} (due to the risk sharing) equal to 11%. .

Finally, the risk-free interest rate, *r*, has been set at 5%. This corresponds to an average observable market rate (e.g. US Treasury Bills as used by Rogers et al., 2002), which has been adopted to compare part of the numerical example results. In addition, the life of a drug after its commercialization, *n*, has been considered as equal to 10 years, since after this lapse of time a drug normally loses its patent protection, causing its annual incomes to fall dramatically.

Some of the input parameters (Table 9) of the model, such as the present value of future cash flows of drugs, the probability of technical success, as well as investments for each

drug, and volatility, have been estimated based on historical and industry data (Rogers et al., 2002), and the biotech investments are supposed as equal to the pharmaceutical ones.

M	Type	V_{0i}	σ_i (%)	I_{i1} (M$)	I_{i2} (M$)	I_{i3} (M$)	I_{i4} (M$)	θ_{i1}	θ_{i2}	θ_{i3}	θ_{i4}
1	1	50	80%	2	10	20	30	0.6	0.7	0.8	0.95
2	1	100	70%	3	10	40	45	0.65	0.55	0.75	0.9
3	1	200	50%	10	15	60	100	0.7	0.8	0.9	0.9
4	1	200	60%	5	15	50	170	0.5	0.7	0.8	0.9
5	1	600	50%	20	40	45	200	0.6	0.6	0.8	0.9
6	1	100	20%	15	15	25	45	0.85	0.9	0.9	0.95
7	2	80	50%	10	25	30	-	0.6	0.8	0.95	
8	2	100	70%	20	35	50	-	0.6	0.8	0.95	
9	2	180	55%	20	55	80	-	0.75	0.7	0.85	
10	2	380	35%	30	55	120	-	0.6	0.8	0.95	
11	2	80	45%	10	25	30	-	0.6	0.8	0.95	
12	3	100	80%	30	60	-	-	0.8	0.9		
13	3	400	30%	75	180	-	-	0.8	0.9		
14	3	700	40%	90	280	-	-	0.6	0.85		
15	4	500	35%	50	100	-	-	0.8	0.95		
16	4	300	100%	80	150	-	-	0.7	0.9		
17	5	350	60%	180	-	-	-	0.75			
18	5	550	30%	220	-	-	-	0.9			
19	6	800	60%	250	-	-	-	0.7			
20	6	1150	20%	350	-	-	-	0.9			

Table 9: Inputs parameters

Among the input parameters, some reflect the pharmaceutical strategy and the agreement characteristics ($P_{is=1,4}$, α_i, γ_i, $\gamma_i^{'}$, the therapeutic area); these are summarized in Table 10 (Ncore refers to a non-core therapeutic area). Moreover, for the sake of clarity, Table 10 also shows the drug values (C_i and $C_i^{'}$). Finally, for drugs 17-20,

which are in the FDA phase, possible alliance with a biotech company is not considered. The therapeutic area (core or non-core) influences the choice of factor $\gamma_i^{'}$, which considers the possible added value from the biotech company to the value of the drug produced by the pharmaceutical company. As can be observed from Table 10, higher values are assumed for the drugs allocated in the early stages of the process, in which the biotech enterprise has more expertise than the pharmaceutical company. More precisely, as suggested by empirical analysis on the adoption of open innovation in the bio-pharmaceutical industry (Bianchi et al., 2011), a larger value of $\gamma_i^{'}$ is assumed for a drug placed in a non-core area, whereby the biotech firm has more specialized competencies than the pharmaceutical industry, thus increasing the value of the project. This explains the high value for γ_i , which is the value added from collaboration within the project, which, for some drugs, equates to double the amount achieved without collaboration.

M	α_i	$\gamma_i^{'}$	γ_i	**Ther. area**	C_i	C_i'	P_{i1} **(M$)**	P_{i2} **(M$)**	P_{i3} **(M$)**	P_{i4} **(M$)**
1	0.54	1.5	2	Ncore	16.97	25.05	1.52	7.61	15.23	22.84
2	0.54	1.5	2	Ncore	37.55	52.30	2.43	8.10	32.43	36.48
3	0.48	1.3	1.8	Core	69.37	99.23	5.04	7.56	30.24	50.41
4	0.57	1.3	1.8	Core	62.033	92.75	3.61	10.83	36.12	122.82
5	0.50	1	1.4	Core	371.1	252.67	14.78	29.57	33.26	147.86
6	0.39	1.5	2	Ncore	26.76	54.80	4.811	4.81	8.01	14.434
7	0.50	1.4	1.9	Ncore	33.85	45.53	6.151	15.37	18.45	-
8	0.53	1.4	1.9	Ncore	40.56	58.63	12.23	21.41	30.59	-
9	0.40	1	1.3	Core	72.72	60.11	11.86	32.62	47.44	-
10	0.46	1.2	1.7	Core	225.1	207.07	17.27	31.66	69.08	-
11	0.50	1.4	1.9	Ncore	32.91	45.72	6.13	15.34	18.4	-
12	0.66	1.3	1.7	Ncore	59.96	71.30	29.75	59.51	-	-
13	0.68	1	1.2	Core	228.07	159.00	74.79	179.5	-	-
14	0.53	1.2	1.5	Core	440.47	309.88	89.84	279.5	-	-

15	0.34	1.1	1.2	Core	396.85	99.96	49.75	99.51	-	-
16	0.62	1.2	1.4	Ncore	182.88	149.55	79.73	149.5	-	-
17	-	-	-	Ncore	350	-	-	-	-	-
18	-	-	-	Ncore	550	-	-	-	-	-
19	-	-	-	Core	800	-	-	-	-	-
20	-	-	-	Core	1150	-	-	-	-	-

Table 10: Strategic input parameters and real option values of drugs

Bounded by a specific budget for the R&D process, the pharmaceutical company has to decide which drugs should be allocated development finance in later years. The same budget limitations and values of other common input parameters used in the aforementioned case study (Rogers et al., 2002) have been considered.

3.6.1 Analysis of results

In order to compare the proposed model to the OptFolio model (Rogers et al., 2002), which represents the benchmark, I start the analysis simplifying OOL by neglecting both the license possibility and the self-financing possibility: in this way, OOL gives the same output typologies as the benchmark model. Table 11 shows a comparison of the optimal portfolio selected by the OptFolio model and that selected by the OOL model, referring to the same case study (Rogers et al. 2002) as that mentioned above.

	Optimal portfolio (drugs selected)
OptFolio model	15, 20
OOL	1, 2, 4, 5, 10, 14, 15, 16, 19 (ROV= M$ 2003.03)

Table 11: OptFolio vs OOL without the licensing option and the self-financing possibility

It is clear from the above that the proposed OOL model suggests selecting as many as nine drugs, unlike the original OptFolio which selected only the two that were closest to commercialization. In fact, it replaces drug 20 with eight products that less profitable at the decision time, but which have greater growth opportunities (drug 19 excepted).
Table 12 shows the optimal portfolio selected, *ceteris paribus*, in the case of license possibility and the self-financing possibility are considered.

Drugs selected	In alliance	In-house	Supporting drugs	ROV (M$)
11	2, 3, 4, 6, 7, 10	5, 14, 15, 16,19	0	M$ 2213.74

Table 12: OOL: The optimal portfolio composition and the overall ROV (OOL model)

In general, drugs that have reached the last stage of the development process have a higher value, as their market launch is more likely. However, investment and marketing costs associated with their launch are significant, and limit the number of products that pharmaceutical companies can bring to market. The size of the optimal portfolio therefore balances the desire to launch drugs that are most valuable and that are in the FDA approval phase, with investments into drugs that are potentially valuable in the early stages of the development process. The model results seem to satisfy this desire: 11 drugs are selected, with four allocated in the latter stages (FDA) of the process and seven placed in the early stages (clinical phases). Moreover, the most valuable drugs, which are allocated within the core therapeutic area (drug 16 excepted), are selected in-house, while alliances are allocated drugs which are in different stages of the development process and are in core (3,4,10) and non-core therapeutic areas (2, 6, 7), in order to exploit the complementary skills of the biotech company (Bianchi et al., 2011). Comparing Table 11 with Table 12, we can observe that OI makes an important contribution to the value of the chosen portfolio: in fact, the most valuable drugs (5, 14, 15, 16, 19) continue to be chosen in-house, in order to maintain their total ownership (α_i =100%), and six potentially valuable drugs are selected in alliance, causing an overall increase of ROV. This result is very important in terms of risk held by the pharmaceutical industry: drugs that are in the early stages of the process (and are thus characterized by higher uncertainty) and will not necessarily come to market, are chosen in alliance; so the pharmaceutical company can share the risk with the biotech company.

Table 13 shows the results of optimal portfolio selected when, *ceteris paribus*, budget constraints are more stringent (M$ 400 for the first year and M$ 100 for the remaining

ones). Once again, to highlight the importance of collaborations, a comparison between OOL with and without the licensing option is provided.

This numerical example highlights even more benefits from the adoption of open innovations. In fact, the most valuable drugs (5, 15, 20) continue to be chosen in-house, and are all placed in core therapeutic areas, while drug 10 is chosen in alliance (even if $C'_{10} < C_{10}$, because the alliance allows some budget to be freed up and thus allocated to other products), and two new products (2, 6) are selected in alliance and placed in non-core therapeutic areas, causing an overall increase of ROV. So, open innovation contributes in a twofold way: *in primis* it makes the optimal portfolio more balanced (drugs which are in different stages of the process are selected) and more diversified (drugs are in both core and non-core areas), and on the other side, drugs that are less likely to be launched on the market are chosen in alliance, thereby reducing the risk for the pharmaceutical company. For these products, also, the pharmaceutical company makes lower development investments since they are shared with the biotech company.

	# of drugs selected	**In alliance**	**In-house**	**Supporting drugs**	**R&D share**	**ROV (M$)**
OOL with licensing	7	2, 6, 10	5, 15, 20	15, 20	15=89.29% 20=1.9%	1730.12
OOL without licensing	4	-	5, 10, 15, 20	15, 20	15=37.29% 20=3.44%	1650.87

Table 13: The optimal portfolio composition and the overall ROV with a more stringent budget

In particular, as suggested by Rogers et al. (2002), drugs 15 and 20 are selected in both scenarios because they have a very large V_{0i} and a high chance of being successfully launched on the market, compared to the other potential drugs; these two products in Rogers et al.'s (2002) study show a robustness compared to the budgetary constraints (they are always chosen when the budget varies).

Finally, an important contribution is provided by the possibility of self-financing of the drugs selected. It is indeed worth noting that if this problem had been solved with the

same budget constraints, but without any chances of self-financing, it would have led to a lower overall ROV, which is equal to M$ 1.515,49 (see Table 14):

	# drugs selected	In alliance	In-house	ROV (M$)
OOL without self-financing	7	2, 6, 7, 10, 11	15, 20	1515.49

Table 14: The optimal portfolio composition and the overall ROV without self-financing

The ROV decreases and less profitable drugs are selected – i.e. 7 and 11, rather than 5. In fact, just the reinvested market revenues of drugs 15 and 20 would allow for the development of the profitable drug 5, leading to a higher portfolio ROV.

3.7 Discussions and Conclusions

This chapter addresses an issue that is related to three literature streams: open innovation, real option analysis and R&D portfolio selection. R&D portfolio selection, especially in some industries, cannot avoid taking into consideration the OI alternative, and in the meanwhile dealing with the intrinsic uncertain and flexible nature of the process. As a result, the ROA method becomes a must in this field. The managers perceive ROA adoption as a complex task, so they prefer to use a simple and easily manipulated means by which to evaluate investments (NPV most of all). The main contribution to the literature is to propose a closed-form model that is easy to implement (but not to manipulate) in order to select which R&D projects to finance and how to carry them out – that is, developing them in-house or with an alliance that represents an operative way to deploy OI. The proposed model, moreover, considers the self-financing option: every portfolio should be composed of elements able to produce cash flows and others that need financial support; usually, these will finance new entries into the portfolio (according to the life cycle of the element). The biopharmaceutical industry is characterized by a long, uncertain, expensive and strategic R&D function, which thus represents an ideal benchmark for the proposed model, even though it can be customized according to the industry considered. In the developed biopharmaceutical numerical example, each potential drug that reaches the market has an implicit option consisting of financing drugs in the pipeline, and this option cannot

be taken into consideration without a portfolio perspective. Finally, the considered portfolio has been selected assuming a strategic perspective: actually, the R&D decisions have a significant impact on the firm's future performances: so the firm's weaknesses and strengths should impact on these decisions. The proposed model takes this aspect into account through the core/non-core nature of the drugs. The results obtained for the developed numerical case suggest the selection of a multi-balanced portfolio: this is composed of drugs of different types (that are at different stages of the pipeline), which are developed both in-house and in alliance; thus, the model gives the best mix of closed-open innovation patterns in terms of risk control, and some of the selected drugs are able to self-finance the portfolio. In addition, the model can be easily extended to consider other kinds of open innovation solutions.

Further developments aim to test the model in other R&D-based industries; moreover, a sensitivity analysis allows the obtained results to be generalized in order to obtain further insight into the optimal selection of the R&D portfolio from an inter-industry perspective. Finally, building on the findings of Vassolo et al. (2004), further developments aim to investigate the interactions between projects.

Chapter 4

A DSS to select an optimal biopharmaceutical R&D portfolio

4.1 Introduction

The research findings of the previous chapter provide support for the managerial implications of considering R&D collaboration as a way to carry out the development of a project, considered as a part of a projects portfolio. As a matter of fact, the proposed real options model provides insight on the fact that R&D alliances make an important contribution to the value of the chosen portfolio, since – as shown in chapter 3 - they contribute to make a more balanced portfolio. This consideration is especially true for the biopharmaceutical industry, which has been making a rich use of alliance activity. In fact, pharmaceutical companies are increasing their product pipelines by both developing drugs on their own and collaborating with biotechnology companies (Rogers et al. 2005). As a consequence, since the R&D process can last more than 10 years, with the pharmaceutical pipeline consisting of several drugs in different phases of development, financially constrained pharmaceutical companies must to be sure to select the most promising ones along their best development path (i.e. developing the selected drug on their own or collaborating with a biotechnology company). Yet, surprisingly, there has been very little attention given to whether and under which conditions R&D alliances would perform better than the traditional innovation practices conducted in house, especially when the whole portfolio of R&D projects is considered; as a consequence an integrated framework that helps managers to decide when to deploy open innovation practices is missing (Huizingh, 2011). In this chapter, starting from the model illustrated in the previous chapter, I propose a Decision Support System (DSS) in order to answer to the following research question:

i) *What are the portfolio parameters that induce firms (in particular pharmaceutical firms) to welcome or disregard the opportunity to collaborate with other companies (such as biotechnology companies)?*

Specifically, the proposed tool provides pharmaceutical managers with an optimal set of drugs to be developed (suggesting to resort or not to open innovation for each of them) and supports this decision with a *what if* analysis, useful to understand what would happen to the best selected portfolio if some candidate drugs parameters change. Then, the analysis of the results coming from the *what if* analysis allows to draw up "what-if" rules helpful in getting managerial insights about the convenience to develop the drug on their own or cooperating with a biotechnology firm.

In addition, as already discussed in chapter 3, pharmaceutical R&D has a long and dynamic life and further investments depend on the success/failure of previous ones; then, its evaluation represents an ideal field of application for real options analysis. Literature discussed in the previous chapter offers interesting examples of mathematical models, based on ROA, that are able to support managers in the selection of the best R&D pharmaceutical portfolio also considering, as illustrated in the same chapter, OI and self-financing. However, these methods do not support managers in a *what if* analysis. As a matter of fact, in order to evaluate each product, several parameters are involved such as the underlying value (i.e. the current value of future incomes from drug's commercialization) and the estimated annual market volatility of the product as well as the potential value added by a biopharmaceutical alliance. In fact, these key-variables represent the major value-drivers of the real option that evaluates the single project (Cassimon *et al.*, 2004); however, the contribution of this chapter is to highlight their impact not only on the single related real option, but especially on a considered portfolio of R&D options. To this aim, a three-step DSS is proposed: starting from the ROA-based optimization model illustrated in the previous chapter, (1) I solve the model several times in order to test the optimal portfolio sensitivity to given input parameters; (2) I provide a Pareto Analysis of products to concentrate the analysis on a narrow number of projects; and (3) I elicit *what if* rules, and map results in an effective way.

By way of anticipation, the proposed DSS suggests that whether the drug development process is conducted in-house or in alliance depends mainly on the value of future incomes from the drug's commercialization, as well as on the potential value added to the drug by a biopharmaceutical alliance.

The contribution aims also at having a strategic implication, since R&D portfolio selection represents a strategic activity in any pharmaceutical firm. Strategy sets the framework within which future decisions will be made, but at the same time it leaves room for learning from ongoing developments, as well as for the discretion to act based on what is learned (Luehrman, 1998). Luehrman sees strategy as a portfolio of real options, and his vision fits perfectly with the decision process I want to handle with. The best decision would be to bet to the safest options, i.e. the ones that are successful whatever the context will vary. Each option is like an avenue that a manager would walk through and the avenue attractiveness depends on the knowledge about the future. Promising avenues could deteriorate as managers continue their strategic walking, because knowledge evolves and forecasts, based on it, could therefore turn out to be incorrect. Some avenues maintain their attractiveness no matter how the knowledge evolves: managers would want to walk along these ones. Obviously, managers are financially constrained and then cannot buy all the options, but at the same time, they could avail the possibility to sign partnerships that can help in building up some avenues making them more rewarding: the proposed DSS takes into account these strategic issues.

The remainder of the chapter is organized as follows: the next section reviews the literature about portfolio selection methods and pharmaceutical portfolio models based on real options and in this framework strengthens the contribution of the research; section 4.3 introduces the research methodology along with the numerical example I will refer to; section 4.4 illustrates the obtained results for each step of the DSS; and, finally, section 4.5 focuses on the paper's findings and further developments.

4.2 Portfolio-selection literature overview

The present chapter aims at developing a simple tool to support the complex decision-making process of R&D portfolio selection in the pharmaceutical industry. In this respect, it combines two streams of research: portfolio theory, as well as ROA, to select an optimal portfolio in the biopharmaceutical industry. First of all, let me highlight the recent trend of increasingly using decision-support tools in the R&D in general and in pharmaceutical setting in particular.

As already discussed in chapter 2, different methods have been used to select an optimal portfolio. Though different classifications have been proposed in literature, one has particularly influenced this part of the dissertation (please refer to section 4.4), i.e. the classification proposed by Cooper *et al.*'s (1998). According to these authors, the R&D projects portfolio-selection models can be divided into three main categories: i.e. *mathematical programming*; ii. *classical tools* that include scoring and sorting models and checklists; and iii. *mapping tools* that use graphical and charting techniques to visualize a balanced portfolio. Two-axes diagrams are typically used to display the trade-off between two criteria: e.g. risk versus reward or probability of success versus value (Dickinson *et al*., 2001). However, any logical combination of the indicated techniques can be used to build up an "optimal" R&D portfolio and the most recent trend has been to combine the different approaches into an integrated and manager-friendly DSS that can then be used directly by decision makers to analyse *what if* scenarios for different parameter sets and portfolio compositions (Chu *et al.*, 1996; Henriksen and Traynor, 1999; Ghasemzadeh and Archer, 2000).

Moreover, given the high costs and risks associated with drug development, and the huge potential future cash flows, different frameworks have been developed to assist decision-making in biopharmaceutical industry. Among these, Blau *et al.* (2004) proposed a DSS to manage a pharmaceutical portfolio of interdependent new candidate products. Specifically, they combine discrete simulations with bubble-chart diagrams and genetic algorithms to obtain a robust portfolio by maximizing expected financial returns at an acceptable level of risk for a given level of corporate resources. Closer to the spirit of this chapter, Rajapakse *et al*. (2005) generated a prototype for a computer-aided tool to find out, among different input parameters, which ones had the biggest effect on the net present value (NPV) of a pharmaceutical portfolio. However, neither of these works considers ROA to evaluate properly the highly uncertain as well as flexible pharmaceutical R&D process. Actually, as already discussed in the previous chapter, in recent years, mathematical ROA based models have been also developed to evaluate pharmaceutical portfolio[9] (Rogers *et al.* 2002; Rogers et al. 2005; Wang and Hwang 2007; Rafiee and Kianfar 2011). Among these, a few models consider open

[9] Readers can refer to chapter 3 an exhaustive overview of pharmaceutical portfolio models based on real options analysis.

innovation solutions. In particular, Rogers et al. . (2005) propose a numerical approach by which to select the best licensing strategy for each product in the R&D portfolio. A closed-form model has been also developed in the previous chapter to select a balanced optimal R&D pharmaceutical portfolio, as well as the best way to develop each of the chosen products following a closed or an OI path, i.e. developing the product in-house, or through an alliance with a biotechnology firm. However, there is a lack of research explicitly integrating this stream of literature and the literature that considers decision-making activities that have been recently used in biopharmaceutical industry. As a matter of fact, neither of the above models can support managers in estimating the effect of input-parameters variation on the optimal solution. Thus, it lacks a DSS that, using ROA to select the optimal portfolio, can support managers in achieving the following: a deeper knowledge about the selection process; the individuation of the most important products, whatever the parameters scenario; and knowledge about how the selected optimal portfolio (and the paths to develop it) changes as the assumed context varies. This is an important issue, mainly when the OI paradigm is considered. Many studies have focused on various aspects of the OI process, offering useful insights and proposing various frameworks to support managerial decision-making (Huizingh, 2011). Nevertheless, Gassmann *et al.* (2010) recently noted that the internal process by which companies manage open innovation is still more trial-and-error than a professionally managed process. In fact, as above-mentioned, an integrated framework that helps managers to decide when and how to deploy open innovation practices is missing (Huizingh, 2011). Moreover, a DSS could help managers become less fearful of the errors associated with choosing the wrong portfolio: more confident managers are more inclined to consider a larger spectrum of alternatives, even if they are not well-known due to uncertainty. One of the most important barriers to OI implementation is represented by the lack of confidence in this kind of collaborations, so the exploration of the range of outcomes (varying input parameters) can encourage its adoption.

In order to fill the aforementioned gap, I propose a ROA-based decision-support tool for pharmaceutical R&D managers who are tasked with selecting, from a set of candidate drugs, those most suitable for development. Specifically, in order to build the DSS, I refer to the aforementioned closed-solutions based model proposed in chapter 3.

In fact, despite being particularly close to reality, implementation and use of numerical approaches turn out to be very complex, due to the significantly rapid increase in the number of selection and sequencing decisions related to the size of the portfolio (Copeland and Antikarov, 2001; Brosch 2008). Conversely, Chapter 3 highlights the benefits (in terms of implementation) in using closed-solutions in a portfolio context.

4.3 A numerical example

In order to better understand the tool, let me briefly recall the numerical example used in the previous chapter, which I refer to. The numerical considers 20 candidate products. Table 15 shows, for each product (P), the data of interest for the DSS and used to test it: the type, the impending phase and the involved input parameters. The type indicates the impending phase; V_{0i} (i.e. the call option underlying that evaluates the product) is represented, as above mentioned, by the NPV of the cash flows coming from the product's commercialization; σ_i is the estimated annual standard deviation of product *i* return based on the cash flows distribution; γ_i' the value added to the drug by the biotechnology company and γ_i, the value added to the drug by the biopharmaceutical alliance. Realistic values, based on historical studies of the pharmaceutical industry, are chosen for the data used in this example (Rogers *et al.* 2002) as summarized in Table 15. In practice, these parameters would be based on historical data and market research (PhRma 2013; EFPIA 2014). As in Rogers *et al.* (2002), the set of 20 candidate drugs represents a variety of product characteristics. Volatility estimates range from 20% for low-risk drugs to 100% for high-risk drugs, with a typical market volatility of 50%/year.

P	*Type*	*Impending phase*	*Eval. tool*	V_{0i} *(M$)*	σ_i	γ_i'	γ_i
1	1	Phase I	Geske	50	80%	1,3	1,8
2	1		Geske	100	70%	1,3	1,8
3	1		Geske	200	50%	1,5	2
4	1		Geske	200	60%	1,5	2
5	1		Geske	600	50%	1,5	2
6	1		Geske	100	20%	1	1,4
7	2	Phase II	Geske	80	50%	1	1,3
8	2		Geske	100	70%	1,2	1,7

9	2		Geske	180	55%	1,4	1,9
10	2		Geske	380	35%	1,4	1,9
11	2		Geske	80	45%	1,1	1,5
12	3		B&S	100	80%	1	1,2
13	3	1st year Phase III	B&S	400	30%	1,3	1,7
14	3		B&S	700	40%	1,3	1,6
15	4	2nd year	B&S	500	35%	1,2	1,4
16	4	Phase III	B&S	300	100%	1,1	1,2
17	5	1st year FDA	NPV	350		1	1,1
18	5	Approval	NPV	550		1	1,2
19	6	2nd year FDA	NPV	800		1	1,1
20	6	Approval	NPV	1150		1	1,2

Table 15: Input parameters for the baseline solution

In particular, for the numerical example at hand, managers could be interested in understanding how robust the obtained solution is for the considered input data (the last four columns of Table 15). The relationship between each of these parameters and the selected portfolio cannot be made explicitly because I am faced with a constrained optimization problem. It is therefore not possible to specify *ex ante* whether a change in a certain parameter will increase or decrease portfolio value (Brosch, 2008). Thus, as Ghasemzadeh and Archer (2000) suggest, the model should be re-solved several times in order to test its sensitivity to particular parameters. This is the main goal of the proposed DSS, which is illustrated in details in the following section.

4.4 The proposed DSS

Particularly, a spreadsheet-based DSS has been built: by changing cell values and having all cell values re-evaluated, a user performs *what if* analysis and can observe the effects of these changes (Power and Sharda, 2007). Moreover, according to Novak and Ragsdale (2003), there are different advantages with using Microsoft Excel. As a matter of fact, it is the most widely distributed spreadsheet software package in the world, and it is very user-friendly when it comes to solving various optimization problems (Novak and Ragsdale, 2003).

Specifically, the proposed decision-support tool has been built in three steps. As Figure 9 shows, after running several times the afore-illustrated OOL (see chapter 3) in order to test the portfolio sensitivity to given input parameters (STEP 1), a Pareto Analysis has been implemented to concentrate further analysis on a narrower number of projects

(STEP 2). Then, by matching and analyzing the results of STEP 1 and STEP 2, I'm able to formulate *what if* rules and map results in an effective way (STEP 3). In particular the general structure of the DSS covers with the three portfolio selection model classes suggested by Cooper *et al*. (1998):

STEP 1: Mathematical programming;
STEP 2: Screening and sorting;
STEP 3: "*What if" rules and mapping*.

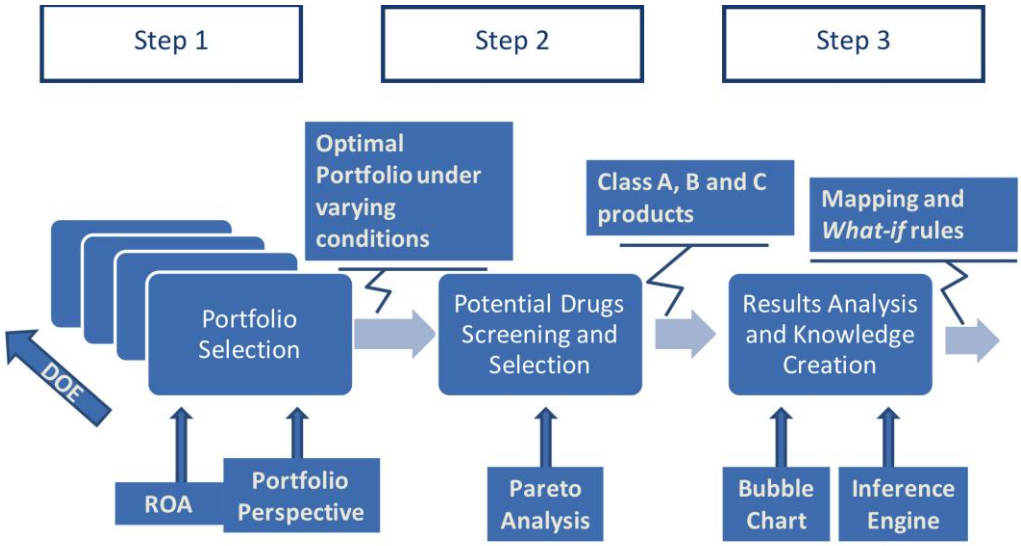

Figure 9: Graphical representation of the proposed DSS

STEP 1: Mathematical programming

In order to become more familiar with the model optimization logic, I use Design of Experiments (DOE) to build experiments to test how, varying the input parameters, the optimal portfolio composition changes. The range by which to vary the input parameters is set according to their expected values.

Without loss of generality, the input parameters have been varied by the range proposed in the numerical example: for each drug's type (type1-type6) I individuated the minimum and maximum value of the input parameters considered (V_{0i}, γ_i'-γ_i, σ_i) obtaining, consequently, 112 experiments (Table 16). For products 17-20 (those in the

last phase of development), the NPV evaluation method was used, so that σ_i was not relevant.

I ran the ROA optimization model proposed in chapter 3 for all the experiments listed in Table 16. In the following, I will indicate with the term baseline the optimal solution obtained with parameters set out in Table 15, consisting of a portfolio of 10 products: six to be developed by licensing them (P3, P5, P6, P9, P10 and P11), and four to be developed in-house (P14, P15, P16 and P19). Each input has been varied in turn, while keeping the others constant. I analysed the results in order to obtain useful insights for managerial decisions; important considerations were formulated by comparing the baseline with the optimal solution of each of the 112 experiments.

STEP 2 Screening and sorting

As there is a high number of products and parameters involved in the problem, it could be useful to individuate the most important products, i.e. the products that are more frequently chosen, or that offer an important financial contribution to overall portfolio values of the selected portfolio (i.e. the real options value (ROV) in equation 31). Experiments' results highlight some products as belonging to many best portfolios, while others do not: therefore, I find out the "contribution" of each product to the all ROV obtained solutions, and then I sort the products out based on this value (i.e. its own contribution). In this way, I can implement a Pareto Analysis (see Figure 10) and individuate the products that mostly contribute to the best solutions; it is possible to notice that P19-P15-P5-P14 (class A) account for 66 per cent of the overall ROV, P10-P20-P16-P9-P3 (class B) account for 29 per cent, and the remaining ones (class C) account for just 5 per cent. We can observe that the baseline solution contains all the four class A products, all the class B products but P20, and two products (P6 and P11) from class C. For the decision it suggests to put attention on P6 and P11's selection and evaluate the opportunity to substitute them with P20.

	Var. levels	V_0	σ_i	γ_i-γ_i'
	MIN	E1	E2	E3
P1	MAX	E4	E5	E6
	MIN	E7	E8	E9
P2	MAX	E10	E11	E12
	MIN	E13	E14	E15
P3	MAX	E16	E17	E18
	MIN	E19	E20	E21
P4	MAX	E22	E23	E24
	MIN	E25	E26	E27
P5	MAX	E28	E29	E30
	MIN	E31	E32	E33
P6	MAX	E34	E35	E36
	MIN	E37	E38	E39
P7	MAX	E40	E41	E42
	MIN	E43	E44	E45
P8	MAX	E46	E47	E48
	MIN	E49	E50	E51
P9	MAX	E52	E53	E54
	MIN	E55	E56	E57
P10	MAX	E58	E59	E60
	MIN	E61	E62	E63
P11	MAX	E64	E65	E66
	MIN	E67	E68	E69
P12	MAX	E70	E71	E72
	MIN	E73	E74	E75
P13	MAX	E76	E77	E78
	MIN	E79	E80	E81
P14	MAX	E82	E83	E84
	MIN	E85	E86	E87
P15	MAX	E88	E89	E90
	MIN	E91	E92	E93
P16	MAX	E94	E95	E96
	MIN	E97		E98
P17	MAX	E99		E100
	MIN	E101		E102
P18	MAX	E103		E104
	MIN	E105		E106
P19	MAX	E107		E108
	MIN	E109		E110
P20	MAX	E111		E112

Table 16: (Step1) Design of experiments. For each type (type1-type6) the min and max value of the parameters V_0, σ_i and γ-γ', are considered in order to obtain the inputs for the experiments.

The Pareto Analysis on the product's contribution to the ROV of optimal portfolios allows to focus our attention on the products that have an important weight on the overall obtained optimal portfolios. This screening task is useful and helps us to concentrate and then compress the effort of time consuming and expensive analyses – that otherwise, being unaffordable, would be eluded and substituted with a waiting strategy (Rotheli, 1990) - on products belonging to class A and to class B.

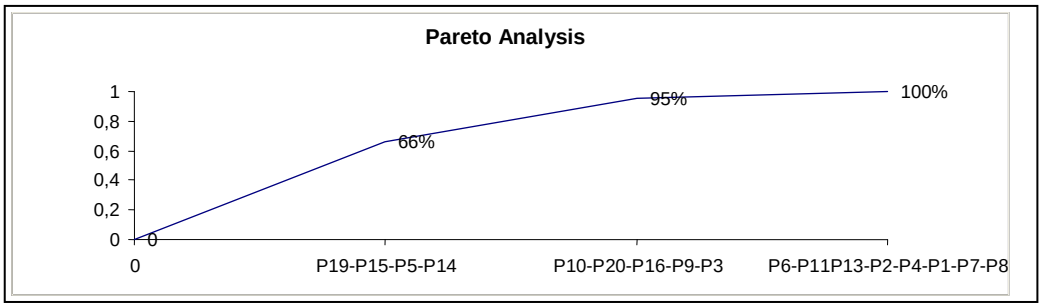

Figure 10: (Step 2) Pareto Analysis of the product portfolio value contribution.

STEP 3: "What if" rules and mapping

The proposed *what if* analysis assumes a portfolio perspective and, to the best of my knowledge, literature has not tackled with it so far.

It is interesting to understand the impact of each parameter on the optimal portfolio: in particular, it is possible to distinguish between direct effect and secondary effect. I refer to direct effect to indicate the impact the product *i* parameter has on the product *i* itself, and I refer to secondary effect to indicate its impact on the nineteen remaining drugs: for example, in E4 (Table 16), the parameter changed is P1's V_{01} that is equal to the maximum of the V_{0i} for type 1's products (V_{0i}=600), and it can influence either product P1's choice (direct effect), or P2-P19's choice (secondary effect). The obtained optimal solution for E4 suggests that P1-P15-P16 and P19 should be developed in-house, and that P2-P5-P9-P10-P11 and P13 should be licensed-in. Comparing this solution to the baseline, I can observe that a higher V_{01} has a direct effect on P1 (P1 in the E4 solution is developed in house while it is not present in the baseline), and a secondary effect on other products (product 3, 6 and 14 no longer belong to the solution, while products 2 and 13 are chosen): it is a kind of substitution effect (Pindyck and Rubinfeld, 2008). The secondary effects are very hard to understand, but to this purpose, the Pareto Analysis (proposed above), combined with the *what if* rules (proposed below), could be helpful.

A direct-effects analysis on the products of the baseline, that belong to class A and class B of the Pareto Analysis, allows to gain some insights. In particular, I can observe that:

- For P15 (E85 and E88), the model recommends in-house development for the maximum value of $V_{015,}$ and the model recommends that the product is licensed in that for the minimum value;
- For P3 for the lowest value of V_{03} (E13), the model recommends exclusion from the optimal portfolio, otherwise (E16, when V_{03} assumes its maximum value) that it should be licensed-in;
- For P5, P10, P16 and P19, no direct effect can be observed, thus they will be included in the portfolio selected, even if secondary effects can be observed;
- For P17, P18, P19 and P20, if selected, they are always developed in-house.

The analysis of direct and secondary effects allows to formulate *what if* rules:

> *Rule 1 The higher the value of the drug i, V_{0i}, the greater the opportunity to select and develop it in-house.*

This is an expected result that agrees with the influence of the underlying (V_{0i}) on the call value, as foreseen by Δ, that measures the rate of change of option value with respect to changes in the underlying asset's price (Gaarder, 2007): the higher the value of V_{0i} of a product, the higher its real options value, which means that for the pharmaceutical firm, it is more convenient to develop the drug in-house and this stands also in a portfolio perspective.

In fact, when we consider the influence of the underlying (V_{0i}) on the option value of a drug developed in alliance, the benefit (the direct influence of V_{0i} on the option) is "mitigated" by the payments and royalties that the pharmaceutical company will give to the biotechnology company during the alliance. Particularly, the higher the V_{0i}, the higher the payments and royalties, which reduce the total value of the option. However, from a portfolio perspective (with budget constraints), the alliance alternative could be more convenient than the in-house alternative (see P3), simply because could require lower net investments leaving room for other investments to develop other products. It seems that, in the case of a product that displays the characteristics best-suited to being developed in alliance, as V_{0i} grows, an ordered

preference arises among "do not develop", "licence in" and "develop in-house" (with in-house being the most convenient for higher values of V_{0i}).

As far as γ_i'-γ_i is concerned, for the products that, in the baseline, are developed in alliance (*licensable drugs*), a lower value of γ_i'-γ_i causes the exclusion of the product from the optimal portfolio (for P3, P9 and P11), or the suggestion that it should be developed in-house (P5 and P10).

This is another expected result, because licensing-in is a convenient solution if the alliance adds consistent value to the product. Moreover, the analysis suggests that it would be valuable to keep products P5 and P10 in the portfolio, and to develop them in-house if licensing is not a convenient alternative (low value for γ_i'-γ_i); furthermore, the other products (P3, P9 and P11) do not remain in the optimal portfolio if the licensing solution is no longer convenient.

These considerations allow to formulate the following *what if* rule:

> *Rule 2 The higher the value of* γ_i'-γ_i, *the higher the convenience of selecting licensable drugs and of licensing them in.*

The influence of σ_i is limited to two cases: we can conclude that, for the considered example, the baseline is robust if σ_i varies.

The results can also give interesting suggestions on the portfolio mix. Figure 11 shows a four-quadrant bubble chart; the four quadrants are obtained combining two variables (product type and development path) with two levels each: Quadrant 1 (Q1) refers to products of type 1 or 2 developed in alliance; Quadrant 2 (Q2) refers to products of type 3, 4, 5 or 6 developed in alliance; Quadrant 3 (Q3) refers to products of type 3, 4, 5 or 6 developed in-house; and Quadrant 4 (Q4) refers to products of type 1 or 2 developed in-house.

For the sake of clarity, let me refer to Q4 in Figure 11 and indicate with $HOSs_i$, the set of optimal solutions in which product *i* is developed in house and with *card*($HOSs_i$) $HOSs_i$ cardinality, how many times product *i* is selected and developed in house. Each bubble in Q4 refers to a product *i* of type 1 or type 2, and to its $HOSs_i$. The bubble is centred according to the average contribution of the product *i* to its $HOSs_i$ (x axis) and to its *card*($HOSs_i$) (y axis), and its area is proportional to the overall contribution of

product *i* to the sum of PV of the considered solutions set ($HOSs_i$) namely the product of its coordinates x and y. Similar arguments hold for the other quadrants.

As shown in Figure 11, comparing Q1 with Q2, we can argue that type 1 and type 2 products – for which the impending phase is one of the first phases considered in the numerical example – are developed by licensing them in, while type 3, 4, 5 and 6 products are developed in-house (Q3 vs. Q4). This result is very important in terms of the risk held by the pharmaceutical firm: drugs that are in the early stages of the R&D process, and that will not necessarily reach the final market, are chosen and developed in alliance so the pharmaceutical company shares the risk with the biotechnology company (Bianchi *et al.*, 2011).

Some exceptions (Q2 and Q4) are represented by the following: P13 (in Q2), which is of type 3 (i.e. it is in Phase III), and, if selected, is developed in alliance (instead of in-house as expected) due to secondary effects; P5 (in Q4), though of type 1 (i.e. it is in Phase I), is developed in-house when γ_i'-γ_i achieve the lowest values (direct effect) or because of secondary effects; P1, P10 (in Q4) and P15 (in Q2) which, for just one experiment, are selected and developed in the opposite way to that expected: P1 and P10, which are developed in-house when V_{01} assumes the highest value and when γ_{10}'-γ_{10} achieve the lowest value respectively (thus the alliance is not a promising alternative), and P15, which is developed in alliance when its V_{0i} is equal to the minimum value (direct effect). Moreover, Figure 11 gives an alternative graphical representation of the Pareto Analysis, according to the mapping methods.

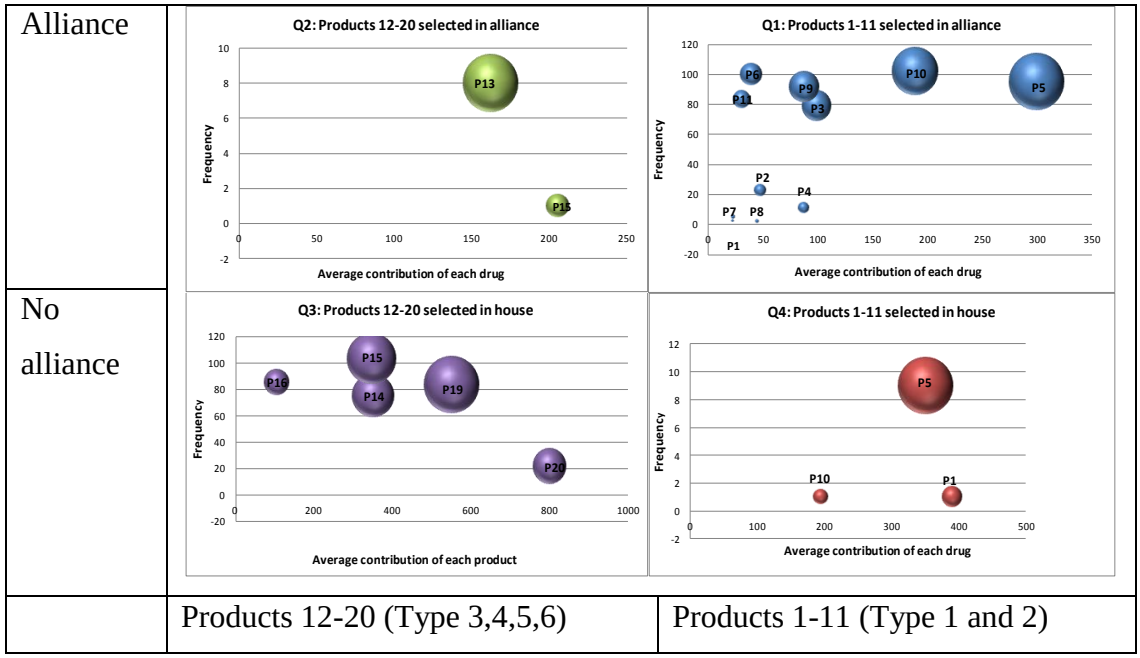

Figure 11 (Step 3): Selected products bubble charts .

The DSS results give some useful insights to managers: in particular, it allows looking at the baseline with greater awareness. The optimal solution, for the case at hand, seems a robust one: if we observe Figure 11, we can notice as products in the baseline are the most selected (they are in the high frequency area of Q1 and Q3). However, decision maker should pay attention to product P20 (belonging to class A and selected only 20 times out of 112) and P13 (selected 8 times, even if in class C). Moreover, three of the selected products, namely P15, P10 and P5 could be developed in an alternative way instead of the suggested one in the baseline. The DSS makes the decision maker more conscious of her/his decision and this allows to overcome barriers in the adoption of ROA based tools.

In addition, the proposed DSS can be used at each decision point when fresh information is available: this is the so-called “rolling view” proposed by Collan and Kyläheiko (2013).

4.5 Conclusions

This chapter aims at supporting managers involved in the selection of the best R&D portfolio in the pharmaceutical industry. This is a constrained problem: limited resources cannot allow the development of all the potential product candidates, and it forces the adoption of a portfolio perspective. Moreover, pharmaceutical R&D process

has characteristics that require advanced evaluation methods, such as ROA. Literature suggests the use of mathematical models to tackle the selection process in the depicted scenario (real option-based R&D evaluation of interdependent projects).

The proposed DSS consists of three steps and is able to: design an experimental plan to test the influence of uncertain parameters of the input data set on the optimal solutions; analyse the results obtained for the experiments individuated in the previous step in order to obtain *what if* rules; and map the results in an effective way. Furthermore, the suggested *what if* rules confirm theoretical knowledge about ROA and OI also in a portfolio perspective: the first rule confirms the importance of the underlying value of each candidate product, both in selecting the product itself and in a portfolio context, while the second rule confirms the importance of complementary resources in OI. In particular, the first rule gives an original contribution to the literature about a controversial issue. Indeed, it states that, even if a product is in its earlier stages of development, and is therefore very risky, it could be better to develop it in-house (rather than sharing the risk with a biotechnology firm) as the reported example for type 1 products shows. This result shows that it could be helpful to analyse the optimal portfolio, considering both risk and return as criteria; indeed, it suggests the existence of a break-even point for the value of the product (which is a proxy of its return), past which it could be better for the pharmaceutical firm to bear a higher risk (developing it in-house and not sharing the risk with a biotechnology firm).

Research findings show interesting managerial and academic implications: the main driver in product robustness (resilience in the optimal portfolio) and in determining the way the product should be developed (in-house or in alliance) is the *underlying value*, i.e. the NPV of cash flows that results from the commercialization of the drug (that represents the underlying of the related call option); also the *added value from the potential partnership*, expressed by γ_i'-γ_i, plays an important role in product selection. The secondary effects need a deeper investigation, which could benefit from a consideration of the correlation between two products: it is possible to argue that the correlation between product *i* and product *j* can affect the impact of product *i* parameter changes over product *j* decision (products also have a generic interdependency one another because of budget constraints that we took into account).

By integrating real-options analysis with portfolio optimization, this chapter offers also an important contribution from a methodological perspective. At the same time, the proposed methodology offers general guidelines for building a DSS that can be applied to mathematical programming with a goal similar to the one we dealt with.

Further developments aim at investigating the diversification side of the problem, and then at obtaining a risk-return efficient frontier: in order to accomplish this task, correlation between each couple of products should be known. This is an interesting task because, as discussed in Chapter 2, in van Bekkum *et al.* (2009), correlation among R&D products with real-options characteristics acts differently than it usually does in evaluation contexts that use NPV, and, in particular, negative correlation only slightly reduces portfolio risk.

Chapter 5

The role of competition in an alliance timing game

5.1 Introduction

While Chapter 3 and Chapter 4 shed light on important aspects on R&D alliances in a portfolio context, this chapter focuses on the time aspects of R&D collaborations, in presence of competition. As shown in Chapter 1, since project development is a dynamic process (Pinto and Prescott, 1988) during which partnerships are initiated, developed or terminated at different points of time, one important aspect of R&D collaborations is the optimal timing to sign R&D collaborations. Specifically, I consider potential collaborations between biotech and pharmaceutical firms, by taking the perspective of biotech firms facing the decision of whether and when to collaborate with a pharmaceutical firm. Alliance timing has, in fact, become a critical decision process. As a matter of fact, several empirical studies highlight its important role in R&D performances (Niosi, 2003; Du et al., 2013). More importantly, whether and when a biotech firm should ally with big pharma is currently one of the key issues debated in the industry world. Some industry insiders suggest that biotech firms should set aside their dreams of becoming the next Amgen or similar firms, which have become big successful companies. Rather, they need to partner with pharmaceutical companies very early in the development process to succeed (Napodano, 2009). It is argued that numerous biotech startups, which had the opportunity to do it but waited in hopes of obtaining bigger payoffs later, did not succeed, remaining at a micro-cap status. On the other hand, other experts highlight that many biotech firms have realized they do not need the support of big pharma to bankroll their clinical trials and marketing efforts, given the more easily available financing. Actually, such firms, e.g., Gilead, are monetizing the success of their product in the final market and evolving from being targets of big pharma to be acquirers (Toonkel, 2013). An industry survey conducted by giant consulting company Deloitte also suggests that, in recent years, the focus of small biotech firms has shifted from simply looking for capital to fund pre-commercialization development to building clinical development and product marketing capabilities. As a result, biotech tends to postpone the alliance timing to the later stages of development

and commercialization (Deloitte, 2005). These interestingly contrasting arguments reflect the existing tradeoff, which has been pointed out in the innovation management literature. In fact, taking the viewpoint of a biotech firm, an early arrangement entails a lower level of risk because of the higher quality and more successful R&D activities the biotech firm can conduct thanks to the considerable amount of financial resources coming from the pharmaceutical firm (Gassmann and Reepmeyer, 2005). At the same time, however, an early arrangement has the negative effect of giving even higher bargaining power to the pharmaceutical company in determining the payment amount, which might financially penalize the biotech firm. On the contrary, in spite of higher risks of failure in early stages, a later agreement might help the biotech firm to better monetize from the innovation through higher payment conditions and higher royalties in the final market (Nicholson et al., 2005; Rogers et al. 2005). In general, the dominance of one of these contrasting forces over the other one determines whether a biotech should collaborate in early stages or postpone such a decision as late as possible. The existence of such conflicting forces also helps explain why we observe substantial differences in the timing of real alliances. As a matter of fact, among the top biotech licensing deals in 2012, we can observe a very large heterogeneity in alliance timing (Carroll, 2012). For instance, the agreements between FivePrime Therapeutics and GlaxoSmithKline and between Genmab and Novartis relate to the discovery stage in the new drug development process. On the other hand, the agreement between Enanta and Novartis relates to preclinical phase, whereas the agreement between Galapagos NV and Abbott Laboratories focuses on phase II. Some other agreements, such as that between Thrombogenics and Merck KGaA, concern the stage of application for approval.

While previous studies offer important intuitions about alliance timing in absence of competition among biotech firms, no works are available when biotech firms compete in the same market. However, Biotechnology industry is characterized by the presence of many competitors (FierceBiotech, 2007). Particularly, Deloitte survey reports that a solid majority of both large and small companies in this industry believes that the alliance market will become even more competitive (Deloitte, 2005). In fact, naturally, some competitors end up working in the same therapeutic area. As an example, recent industry voices anticipate the emergence of a “horse race” in the migraine treatments

among a number of biotech firms (Schatzman, 2013). Therefore, it is more realistic to incorporate the possible reaction of competitors in the decision-making process. In this chapter, I introduce competition among biotech firms, which has not considered in previous works on alliance timing in the biopharmaceutical industry. Specifically, I consider two competing biotech firms that can decide whether and when to partner with a pharmaceutical company. In this setting, the alliance is mutually exclusive in the sense that the pharmaceutical company will only contract with one biotech firm. This is consistent with the observation that usually pharmaceutical companies identify and make a selection only among the most promising biotech target. Also, consistent with certain trends discussed above, it is assumed that both biotech firms can reach the market individually, which implies that they are not exactly researching on the same molecule. Therefore, if one biotech firm signs an alliance with the pharmaceutical company, the other can only continue the R&D process individually with some spillover benefits from the competitor's alliance, but with her own financial resources. This scenario is quite reasonable in reality and offers an opportunity to investigate alliance timing decisions from a wider perspective (Rogers et al. , 2005). In fact, in such a case, competition might change the previous considerations about the timing and the profitability of signing the alliance. Intuitively, one could think that the introduction of competition will raise the incentive of each biotech firm to anticipate the timing of collaboration with the pharmaceutical company in order to prevent the opponent from being faster in establishing the alliance. Therefore, the incentive to anticipate might be due to the traditional economics of pre-emption. To some extent, this might be the case of the recent alliance of Forma Therapeutics with Celgene. In fact, the small biotech firm has reached the deal right after several other biotech firms, such as Cleave Biosciences and Proteostasis Therapeutics, entered the field of protein homeostasis (McBride, 2013). However, an opposite effect might arise as well. In fact, there might be a strong competitive pressure to reach later stages or, even, the final market with products whose revenue are not shared with the pharmaceutical company in order to appropriate higher profits and win the competition against the rival. This effect seems to be consistent with several examples of successful biotech firms more and more willing to postpone potential deals in such a competitive arena (Toonkel, 2013). These contrasting viewpoints from the industry world reveal the importance of the alliance

timing issue in a competitive environment. It appears, in fact, still unclear whether a biotech firm should anticipate, postpone or disregard the opportunity of collaborating with a pharmaceutical company. In this chapter I provide an answer to this question adopting a real options games (ROG) approach, in order to account for both exogenous uncertainty, that characterizes the R&D biopharmaceutical process, and (re)actions of possible competitors.

By way of anticipation, the research findings suggest that whether, when and who will ally with the pharmaceutical company depend on the contract terms offered by the pharmaceutical company, the market value increase due to the presence of the pharmaceutical industry, as well as the competitive advantage one biotech firm gains against the competitor due to the alliance. Identifying and understanding the conditions under which specific results arise can be particularly useful to both biotechnology and pharmaceutical companies involved in open-innovation based R&D project decisions in a competitive environment.

The remainder of this chapter is organized as follows. In the next section, previous closely related contributions are discussed in order to highlight the scientific support of this research. In section 5.3, the ROG model and relative solutions are introduced. In section 5.4, I discuss results and relative managerial implications. Finally, in section 5.5, conclusions are drowned and further developments are anticipated.

5.2 Literature Overview

This chapter investigates alliance timing in the biopharmaceutical R&D process in presence of competition. Specifically, from the perspective of biotech firms, I try to understand the conditions under which competing biotech firms should anticipate, postpone or disregard the opportunity of collaboration with a pharmaceutical company.

In this respect, this part of the dissertation combines two streams of research: real option games and alliance timing in the biopharmaceutical industry. On one hand, I utilize ROGs because firms' decisions do not depend only on the nature of competition, but also on the nature of uncertainty. In this respect, ROGs, as widely discussed in Chapter 2 (section 2.3), take into account both exogenous uncertainty (nature) and (re)actions of possible competitors. In particular, once again, I adopt closed-form solutions (specifically the Black and Scholes formula) because of the easiness of

implementation and also because allow to preserve analytical tractability which is very useful in this kind of analysis. In particular I assume that biotech firms can, in turn, decide whether to ally with the pharmaceutical company at the beginning of each development phase, and thus I model the process with a European call.

While there is an amount of literature on Rogs (as presented in chapter 2), in this chapter I refer to specific references in this field, that are more closely related to the proposed model, since they apply ROG to R&D investment decisions in presence of spillovers. Specifically, Martzoukos and Zacharias (2013) demonstrate how two competing firms can act strategically and take advantage of the positive spillovers, or take pre-emptive action against the negative spillovers. They find that, under learning-by-doing hypothesis, strategy shifts are easier to observe in market environments of high growth and high volatility. Mason and Weeds (2005), conversely, find that in duopoly, in the presence of positive externalities, greater uncertainty can actually hasten rather than delay investment. This is because uncertainty can raise the leader's value more than the follower's. Pre-emptive reasoning entails that the leader must act sooner. However these works deal with investment timing, while the model proposed in this chapter deals with alliance timing under a competition setting.

On the other hand, I am also naturally closely related to the alliance timing literature. Actually, some papers highlight the optimal time to ally in R&D biopharmaceutical environment. However they do not consider competition. Among the others, Kalamas et al. (2002), observe how pharmaceutical firms might want to postpone the agreement to reduce the risk of licensing a drug that ultimately fails to win approval from the US Food and Drug Administration (FDA). So they offer much better contract in the later stages of the drug development. Naturally, under these contract terms, biotech companies prefer late-stage deals. Assuming a fair pricing of the agreement, the authors find that it would be better to ally early in the preclinical phases from a holistic perspective, i.e., taking into account both pharmaceutical and biotech perspectives, in absence of competition.

Nicholson et al. (2005) demonstrate that a biotech company profits more by signing a partnership with a pharmaceutical company in the later stages of R&D in order to acquire a greater bargaining power and obtain more favorable conditions in terms of payments and royalties. In addition, Rogers et al. (2005) tackle with similar research

questions from the perspective of the pharmaceutical company, adopting a real options approach. Their results suggest that the timing and financial side of the license depend on the volatility of cash flows coming from the drug commercialization and the value that the partnership is able to add to the developed drug. Specifically, their results indicate that early stage alliances become more valuable when market uncertainty and the value added to the drug by the pharmaceutical companies increase. However, they focus on the optimal alliance design without considering competition.

5.3 The ROG model

For the sake of simplicity, I model the game as consisting of two main stages of the pharmaceutical process: the first stage is the R&D stage, whereas the second stage is the commercialization one. There are two identical biotech firms, namely BIO1 and BIO2, in the market having the opportunity, in each of the two stages of the game, to establish a partnership with a pharmaceutical company. In line with most of the situations in reality, I assume that the pharmaceutical company has the bargaining power to make a take-it-or-leave-it contract offer and maintain such an assumption throughout the chapter. Another important assumption is that the pharmaceutical company selects biotech firms sequentially. That is, a Stackelberg game is modeled, where BIO1 is the first mover and BIO2 is the follower. Also, the alliance is mutually exclusive in the sense that the pharmaceutical company will only contract with one biotech firm. Therefore, if one biotech firm signs an alliance with the pharmaceutical company, the other can only continue the R&D process and reach the market on its own, which implies that they are not exactly researching on the same molecule. Under this setting, BIO1 certainly enjoys a first-mover advantage. However, the focus is in understanding whether and which of the two biotech firms will ally with the pharmaceutical company and the relative timing of such alliance, i.e., first or second stage.

The sequence of the game is as follows. At the beginning of stage 1, BIO1 is selected by the pharmaceutical company. The pharmaceutical firm offers an alliance contract to BIO1 as consisting of an ex-ante payment P_1 poured at the beginning of stage 1 to the biotech firm and the percentage of royalties she will retain equal to a_1. If BIO1 rejects the offer, the same contract is offered to BIO2 due to the perfect symmetric

environment. If, on the contrary, no agreement has been reached in the first stage, the decision game is repeated. The pharmaceutical firm offers a different alliance contract to BIO1 as consisting of an ex-ante payment P_2 poured at the beginning of stage 2 to the biotech firm and a percentage of royalties she will retain equal to a_2. If BIO1 rejects the offer, the same contract is offered to BIO2, due to the perfect symmetric environment. Therefore I assume that the pharmaceutical company is not financial constrained and she is able to offer two different contracts in two different moments.

At the end of the second stage, future cash flows are estimated for both biotech firms under all the possible situations that can arise in this setting. In case of alliance in any of the two stages, the size of the potential drug market increases relatively to the case of no alliance by an amplification factor $\delta > 1$, which reflects the value added to the drug by the synergies derived from the alliance (Rogers et al. , 2005). Figure 12 depicts the extensive form of the game where the payoffs are computed using ROA, as described later in this section.

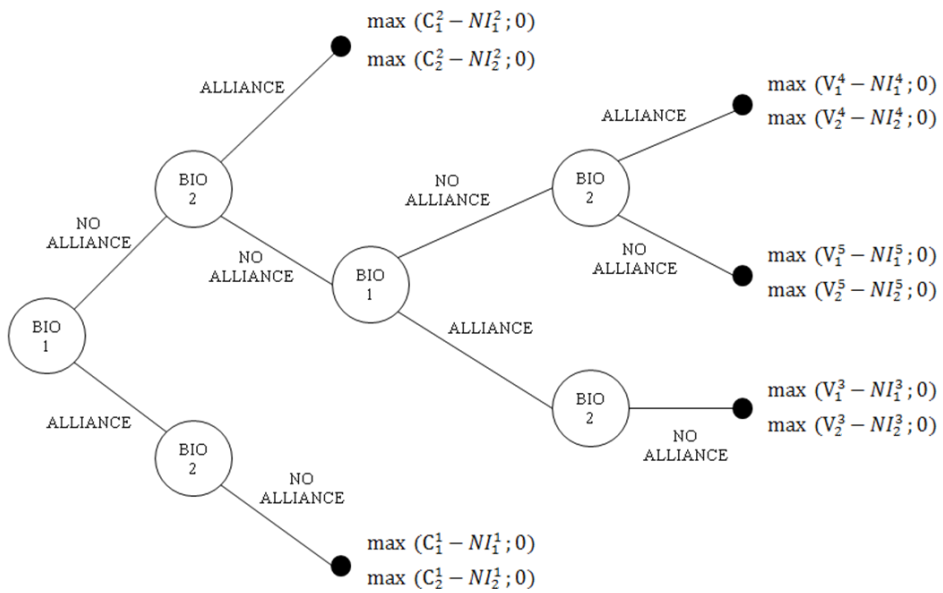

Figure 12**:** Extensive form of the game in presence of competition.

The game can be solved via backward induction procedure. Therefore, I start from the final sub-game where BIO2 has to decide if ally or not with the pharmaceutical company and go back to the first stage involving BIO1's decision, examining all the possible branches of the tree illustrated in Figure 12. Solving the game entirely yields

five possible scenarios of *equilibrium* for the game as shown in Table 17 (e.g., E_1 refers to the equilibrium where BIO1 signs an alliance at stage 1, and so forth).

	Alliance		*No alliance*
	Stage 1	*Stage 2*	
BIO1	E_1	E_3	E_5
BIO2	E_2	E_4	

Table 17: Scenarios of *equilibrium* (duopoly case)

Before computing the payoffs, let denote $i = 1, 2$ the specific biotech involved in the game, and $j = 1, 2, \ldots, 5$ a generic scenario of equilibrium as identified above. Also define:

- I_t = investment cost for stage t;
- σ = volatility of V_0;
- r = risk-free interest rate;
- T= length of the first stage;
- V_0 = value of the project (net cash flows arising after commercialization) at the beginning of the first stage;
- V_T = value of the project (net cash flows arising after commercialization) at the beginning of the second stage.

In case no biotech firm signs the alliance with the pharmaceutical company, they are able to reach the final market individually and they share the total market equally due to symmetry. On the other hand, as mentioned earlier, in case of alliance in any of the two stage, the size of the potential market value of the drug increases relatively to the case of no alliance by an amplification factor $\delta > 1$. Furthermore, the alliance generates spillover effects [10]. That is, not only the biotech signing the alliance with the

[10] R&D spillover effects are significant among different sectors, as discussed in Bernstein and Mohnen (1998). The importance of inter-competitive pharmaceutical companies has been documented in literature (Handerson and Cockborn, 1996).

pharmaceutical company, but also the "lonely" competitor will receive a benefit from rival's collaboration. However, due to presence of competition, the total pie will be split differently between the two biotech firms if one signs the alliance. Specifically a higher portion, say $\beta > 1/2$, of the market will be captured by the company signing the alliance, whereas the competitor will appropriate the remaining portion.

Computing firms' payoffs

In order to understand how the model works, let me consider an environment where only one biotech (BIO) operates in the market, which I refer to as the monopoly case, and describe in details this setting. In addition, considering the monopoly case allows me to highlight the role of competition in the alliance timing decisions. The game structure is similar to the duopoly case. Figure 13 depicts the extensive form of the game in absence of competition. It is straightforward to see that we can obtain three possible scenarios (j) of *equilibrium* for the game. These are (see table 18): BIO's alliance at stage 1 (equilibrium Q1), BIO's alliance at stage 2 (Q2), and no BIO's alliance (Q3).

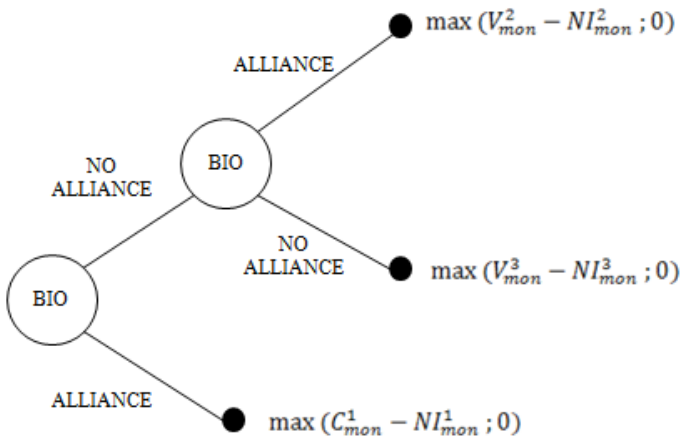

Figure 13: Extensive form of the game in absence of competition.

$Q_{j=1,2,3}$	Q_1	Q_2	Q_3
BIO	Alliance at first stage	Alliance at second stage	No alliance

Table 18: Scenarios of *equilibrium* (monopoly case)

As said earlier, the complex R&D pharmaceutical process, is split in two stages: the R&D stage and the commercialization stage. As a consequence, the R&D stage is an option for the second and final stage. This means that the process can been seen as a 1-fold option. Accordingly, I can model it with the above described Black and Sholes approach, which ensures the flexibility offered by the option to decide further investments when more information is available. As already discussed in the second chapter, adopting such an approach means assuming that the value of the project V_0 at the beginning of the first stage follows a geometric Brownian motion causing that this value, at maturity T (i.e. at the end of the first stage or alternatively at the beginning of the second stage), is a known realization (specifically, as illustrated in section 2.1.1, it is a known realization from a lognormal distribution). As a consequence, the second stage payoffs are function of the known realization of the value of the project at maturity (V_T). As a matter of fact, at the beginning of the second stage, uncertainty is solved and the realization of the underlying is known (see Figure 14, where a possible realization at maturity is indicated). In other words, after the R&D stage, the biotechnology company has more information about the value of cash flows at the moment of commercialization.

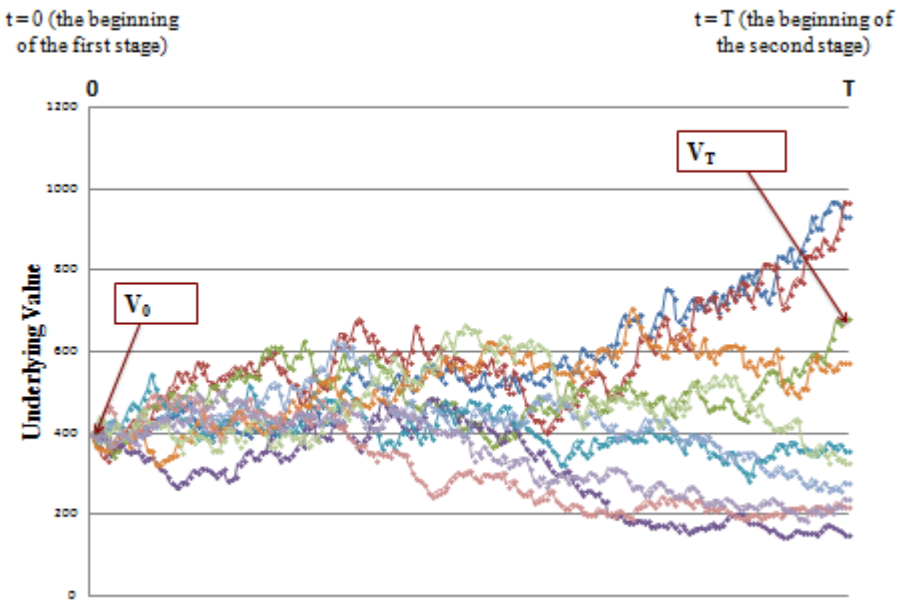

Figure 14: Underlying drug value representation (considering 10 replications) from the beginning to the end of the first stage

In such a way, the payoffs in the first stage are computed as call European options (according to equation 19) in order to take into account uncertainty in this stage. Conversely, the simple NPV is used to compute the second stage payoffs.

Specifically, the first stage payoffs are computed as the difference between the European call option C^j_{mon} (with underlying value S^j_{mon} and exercise price X^j_{mon}, depending of the different j scenario), which represents the gross payoff in the first stage, and the net investments in the same stage, NI^j_{1mon} (see table 19). The latter is actually computed as the difference between the investment needed in the first stage I_1 and the ex-ante payment in case of alliance at the first stage, P_1. Of course, in case of no alliance or an alliance at the second stage, the net investment in the first stage is simply the investment required in the first stage I_1. Note that both I_1 and P_1, as in the model illustrated in chapter 3, are sunk costs that do not affect, but just decrease, the option value. Table 19 reports all the elements necessary to compute first stage payoffs presented in Figure 13 in case of monopoly under all possible scenarios of equilibrium. Note that the exercise price, X^j_{mon} is equivalent to the investment required at the second stage, which, in case of alliance at the second stage, will be decreased by an amount equal to the expected payment E(P2) at the second stage.

As far as the second stage payoffs are concerned, they are simply computed as the difference between the project value realized at maturity under the scenario j (V^j_{mon}), gross of the net investment in second stage, i.e., NI^j_{mon}, where the latter is actually computed as the difference between the investment needed in the second stage and the ex-ante payment in case of alliance P_2. In case of no alliance, the net investment is simply the investment required in the second stage I_2 (see table 20).

Similarly, Table 20 reports all the elements necessary to compute the second stage payoffs . Note that the subscript *mon*. is used in this case, that is, in the monopoly case.

$Q_{j=1,2,3}$	Q_1	Q_2	Q_3
C^J_{mon}	C^1_{mon}	C^2_{mon}	C^3_{mon}
Underlying (S^J_{mon})	$(1-\alpha_1)\delta V_0$	$(1-\alpha_2)\delta V_0$	V_0
Exercise price (X^J_{mon})	I_2	I_2-E(P_2)	I_2
(NI^J_{mon})	I_1- P_1	I_1	I_1

Table 19: Elements necessary to compute first stage payoffs (monopoly case)

$Q_{j=2,3}$	Q_2	Q_3
V^J_{mon}	$(1-\alpha_2)\delta V_T$	V_T
NI^J_{mon}	I_2- P_2	I_2

Table 20: Project value gross of net investments, and net investments in stage 2 (monopoly case)

The game is solved by backward induction. Therefore, starting from the second stage (see Fig.15), it is possible to find the payment P_2 which makes the "alliance" payoff (V^2_{mon} -NI^2_{2mon}) equal to the "no alliance payoff" (V^3_{mon} -NI^3_{2mon}).

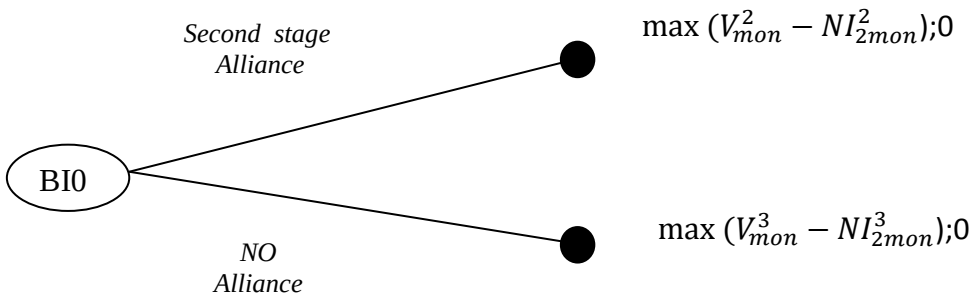

Figure 15: Second stage payoffs (monopoly case)

Referring to table 20, the minimum value of P_2 which satisfies this condition is given by the following expression:

$$P_2 = (V^3_{mon} - V^2_{mon}) = V_T(1 - (1 - \alpha_2)\delta) \quad (33)$$

In fact, in case of alliance, the value of the project is increased by δ and (1-α_2) is the part retained from the biotechnology company.

Note that this payment is linear function of the value of the project V_T.

Clearly, in order to solve the model and find theoretical solutions at t=0, we need to find expected values of V_T and, consequently, of P_2.

Particularly, at the beginning of the second stage (i.e. at t=T) the value of the project V(T), is log-normally distributed with expected value, E(V_T), equal to $V_0 e^{rT}$.

As far as the expected second stage payment E(P_2) is concerned, since P_2 is linear function of V_T, it is given by the following formulation:

$$E(P_2) = E(V^3_{mon} - V^2_{mon}) = E[V_T(1-(1-\alpha_2)\delta] = V_0 e^{rT}(1-(1-\alpha_2)\delta) \qquad (34)$$

Then, if E(P_2)is > $E(V^3_{mon} - V^2_{mon})$, the solution of the sub-game in the second stage is "Alliance at second stage". Backing to the first stage (please refer to Figure 16), we can find the P_1 condition which makes BIO firm indifferent between the first stage alliance ($C^1_{mon} - NI^1_{mon}$) and the second stage alliance evaluated at t=0, computed as a call option ($C^2_{mon} - NI^2_{mon}$).

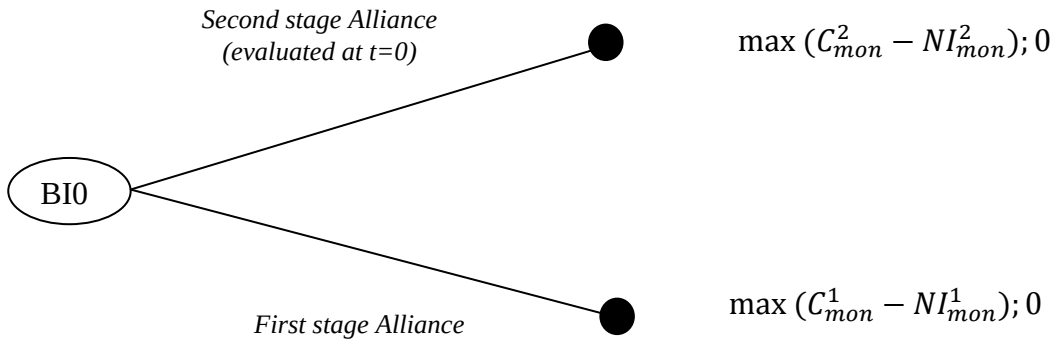

Figure 16: First stage payoffs if the solution of the second stage is "Alliance"(monopoly case)

Referring to table 19, the minimum value of P_1 which satisfies this condition is given by the following expression:

$$P_1 = C^2_{mon} - C^1_{mon} \qquad (35)$$

Therefore, if P_1 is higher than this threshold, the solution of the game will be the first stage alliance, otherwise, i.e. for values of P_1 lower than the same threshold, the solution of the game will be the second stage alliance (see Table 23).

Conversely, if E(P2) is < $E(V_{mon}^3 - V_{mon}^2)$ the solution of the sub-game in the second stage is "No alliance at second stage". Backing to the first stage, we can find P_1 condition which makes BIO firm indifferent between allying at first stage ($C_{mon}^1 - NI_{mon}^1$) or not allying neither at the second stage nor at the first stage ($C_{mon}^3 - NI_{mon}^3$).

$$P_1 = C_{mon}^3 - C_{mon}^1 \tag{36}$$

So, if P_1 is higher than this threshold, the solution of the game will be the first stage alliance, otherwise, i.e. for values of P_1 lower than the same threshold, the solution of the game will be "No alliance" (see Table 23).

It is straightforward to see that the game–solutions (*equilibria)* strongly dependent on both the expected value of the second stage payments, E(P_2) and first stage payments P_1 conditions.

Following this logic, I obtain Payments thresholds for the duopoly case as well (please refer to the next section where all payments conditions are reported in both monopoly and duopoly case). In the sake of space, I do not report all the process conducted to obtain payments thresholds in the duopoly case, but, to the sake of clarity, in Table 21 and Table 22, all elements necessary to compute both second (Table 21) and first stage payoffs (table 22) in case of duopoly are reported. In such a case, the subscript *i=1,2* is used to denote the specific biotechnology company involved in the game.

	$E_{j=3,4,5}$	E_3	E_4	E_5
BIO1	V_1^J	$(1-\alpha_2)\beta\delta V_T$	$(1-\beta)\delta V_T$	γV_T
	NI_1^J	I_2-E(P_2)	I_2	I_2
BIO2	V_2^J	$(1-\beta)\delta V_T$	$(1-\alpha_2)\beta\delta V_T$	$(1-\gamma)V_T$
	NI_2^J	I_2	I_2-E(P_2)	I_2

Table 21: Project value gross of net investments, and net investments in stage 2 (duopoly).

	$E_{j=1,2,3,4,5}$	E_1	E_2	E_3	E_4	E_5
BIO2	C_1^j	C_1^1	C_1^2	C_1^3	C_1^4	C_1^5
	Underlying (S_1^J)	$(1-\alpha_1)\ \beta\delta V_0$	$(1-\beta)\delta V_0$	$(1-\alpha_2)\ \beta\delta V_0$	$(1-\beta)\delta V_0$	γV_0
	Exercise price (X_1^J)	I_2	I_2	I_2-E(P_2)	I_2	I_2
	(NI_1^J)	I_1- P_1	I_1	I_1	I_1	I_1
BIO2	C_2^j	C_2^1	C_2^2	C_2^3	C_2^4	C_2^5
	Underlying (S_2^J)	$(1-\beta)\delta V_0$	$(1-\alpha_1)\ \beta\delta V_0$	$(1-\beta)\delta V_0$	$(1-\alpha_2)\ \beta\delta V_0$	γV_0
	Exercise price (X_2^J)	I_2	I_2	I_2	I_2-E(P_2)	I_2
	(NI_2^J)	I_1	I_1- P_1	I_1	I_1	I_1

Table 22: Elements necessary to compute first stage payoffs (duopoly)

5.4 Game solutions and results analysis

To facilitate the understanding of the role of competition in the timing of biopharmaceutical alliances, the results in case of monopoly, where competition is obviously absent, are firstly presented. Under this setting, the contract terms offered by the pharmaceutical company as well as the value added to drug due to her presence are the fundamental determinants of alliance timing. As a matter of fact, in Table 23, I illustrate the threshold payments, i.e., P_1 and $E(P_2)$, which help understand whether the alliance will be signed in the first stage, in the second stage, or no alliance will be established. In the same Table I also summarize the possible alliance outcomes depending on the level of ex-ante payments received by the biotech firm.

		P_1	
		Low	High
$E(P_2)$	Low	$E(P_2) < E(V^3_{mon} - V^2_{mon})$	$P_1 < C^3_{mon} - C^1_{mon}$ No Alliance	$P_1 > C^3_{mon} - C^1_{mon}$ BIO first stage
	High	$E(P_2) > E(V^3_{mon} - V^2_{mon})$	$P_1 < C^2_{mon} - C^1_{mon}$ BIO second stage	$P_1 > C^2_{mon} - C^1_{mon}$ BIO first stage

Table 23: Threshold payments (P_1 and $E(P_2)$) and possible scenarios of equilibrium in the monopoly game

Specifically, the results suggest that, if the pharmaceutical company does not offer a considerable amount of payment in the initial stage, i.e., P_1 low, the biotech firm might profit more from waiting until the second stage to possibly obtain better payment conditions. In the second stage, in fact, the biotech firm will ally with the pharmaceutical company only under favorable expected payment conditions, i.e., high values of $E(P_2)$. Otherwise, the biotech firm will prefer continue the R&D process on her own. Interestingly, if, in the first stage, the payment conditions are sufficiently high, the biotech company will sign an early alliance independently of any expected value of P_2.

To better visualize these results and provide a practical application of the relative insights, I complement the analytical derivation with a numerical analysis based on a case study available in the literature, which considers a drug in the third clinical phase

(Rogers et al., 2002). Specifically, I consider the following set of parameters: V_0 = \$400M, σ = 30%, r = 5%, I_1 = \$75M, I_2 = \$180M; T=2. In addition, different values of δ (1.1, 2.2 and 2.7 respectively) are assumed to include several scenarios of the value added by the pharmaceutical company. The numerical analysis allows to understand how δ combines with the payment conditions and affects firms' alliance timing decisions. For sake of brevity, I illustrate such influence in case the alliance, if any, can only arise in the first stage, i.e. assuming low values of E(P_2). In this case, Figure 17 identifies the region of alliance as a function of P_1 and a_1. It suggests that when the total market size increases due to the contribution of the pharmaceutical company (δ), the biotech firm has more chances to sign an early agreement with the pharmaceutical company in order to take advantage of the high synergies. These results are consistent with Rogers et al. (2005), who find that early licensing agreements are worthy of consideration as the value added to the developed drug by the partnership increases.

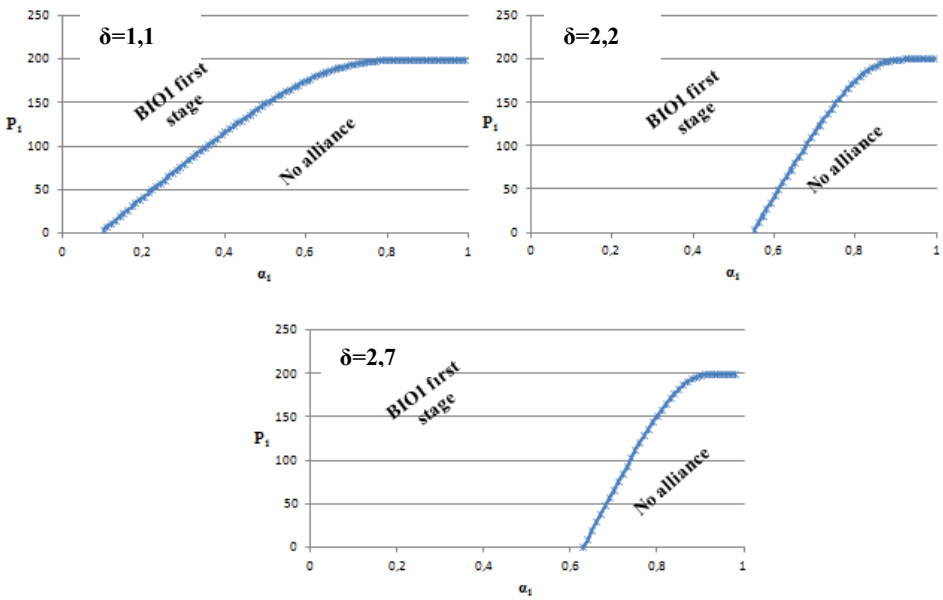

Figure 17: Monopoly thresholds (P_1= C_{mon}^3-C_{mon}^1) when E(P_2) is low and δ varies.

Now I move to the case of competition. Interestingly, the introduction of competition may change the market outcomes significantly. In general, I show the timing decisions depend on the level of the competition β, on the leverage effect of the alliance on the market δ, and on contract terms offered by the pharmaceutical company as well. As a direct consequence of competition introduction, we could

expect that both biotech firms would have an incentive to move quickly and anticipate the rival. In fact, this argument seems to be supported by some real cases, such as the alliance between Forma Therapeutics and Celgene (Toonkel, 2013). Naturally, due to the Stackelberg game setting, one might argue that the first mover, i.e., BIO1, will be able to partner with the pharmaceutical company and pre-empt the follower.

Actually, results show that also the follower might be able to partner with the pharmaceutical company. This occurs when the first mover has a competitive incentive to reach the market individually because of a high spillover effects and low payment conditions. I obtain different scenarios of equilibrium solutions depending on the value of δ, which describes the level of synergy or, alternatively, the contribution added by the pharmaceutical company. Thus, I illustrate them distinguishing between high synergy, i.e., $\delta > (1-\gamma)/(1-\beta)$, and low synergy, i.e., $\delta < (1-\gamma)/(1-\beta)$. Table 24 summarizes the possible alliance outcomes in both cases. For sake of simplicity, I have the C values referred to BIO1. The same condition hold for BIO2: the reported threshold values can be expressed also using C_1^j, I leave the reader to verify the correspondence between C_1^j and C_2^j using Table 22.

Let me start with the high synergy case. I find that all the five scenarios of equilibrium solutions are possible. In this case, the leader firm, i.e., BIO1, might find more profitable that the other biotech, i.e., BIO2, partners with the pharmaceutical company to enjoy generous spillover effects. Specifically, this occurs when both first and expected second stage payments are intermediate or when one of them is low and the other is intermediate. Interestingly, if the first stage payments are intermediate the alliance will be established in the first stage. Alternatively, in presence of intermediate expected second stage payments and low first stage payments, the optimal timing is to ally in the second stage.

Similarly to the case of monopoly, if, in the first stage, the payment conditions are sufficiently high, there is no room for BIO2's alliance, as the first mover will sign an early alliance independently of any value of $E(P_2)$. Moreover, the first mover will pre-empt the rival partnering with the pharmaceutical company in the second stage also when the relative payment is sufficiently high, while the first stage payment is not appealing. Finally, if the pharmaceutical company does not offer attractive

payment conditions in both stages, i.e., P_1 and $E(P_2)$ are low, no biotech firm will find optimal to sign an agreement with the pharmaceutical company.

I use again the data from the same case study as above to unravel how all the parameters of interest combine with each other and affect firms' alliance timing decisions. For sake of brevity, I illustrate such influence in case of low values of $E(P_2)$ and varying the levels of P1, β (0.55; 0.65; 0.75 respectively), δ (2.2; 2.7). Specifically, Figure 18 shows that when the level of competition increases as implies a high value of β, the alliance region for BIO2 is more and more reduced whereas the early alliance region for BIO1 is increased. Figure 19 highlights the role of δ showing how a higher value of the amplification factor δ enlarges BIO2's alliance zone.

$\delta > \frac{1-\gamma}{1-\beta}$ (High synergies)			P1		
			Low	Medium	High
E(P_2)	Low	$E(P_2) < E(V_1^5 - V_1^3)$	$P_1 < C_1^5 - C_1^1$ No alliance	$C_1^5 - C_1^1 < P_1 < C_1^2 - C_1^1$ BIO2 first stage	$P_1 > C_1^2 - C_1^1$ BIO1 first stage
	Medium	$E(V_1^5 - V_1^3) < E(P_2) < (V_1^4 - V_1^3)$	$C_1^2 < C_1^3 \quad P_1 < C_1^2 - C_1^1$ $C_1^2 > C_1^3 \quad P_1 < C_1^3 - C_1^1$ BIO2 second stage	NA $C_1^3 - C_1^1 < P_1 < C_1^2 - C_1^1$ BIO2 first stage	$P_1 > C_1^2 - C_1^1$ BIO1 first stage
	High	$E(P_2) < E(V_1^4 - V_1^3)$	$P_1 < min(C_1^3 - C_1^1; C_1^2 - C_1^1)$ BIO1 second stage	NA	$P_1 > min(C_1^3 - C_1^1; C_1^2 - C_1^1)$ BIO1 first stage

$\delta < \frac{1-\gamma}{1-\beta}$ (Low synergies)			P1	
			Low	High
E(P_2)	Low	$E(P_2) < E(V_1^5 - V_1^3)$	$P_1 < C_1^5 - C_1^1$ No alliance	$P_1 > C_1^5 - C_1^1$ BIO1 first stage
	High	$E(P_2) < E(V_1^5 - V_1^3)$	$P_1 < min(C_1^3 - C_1^1; C_1^2 - C_1^1)$ BIO1 second stage	$P_1 > min(C_1^3 - C_1^1; C_1^2 - C_1^1)$ BIO1 first stage

Table 24: Threshold payments (P_1 and E(P_2) and possible scenarios of equilibrium in duopoly game.

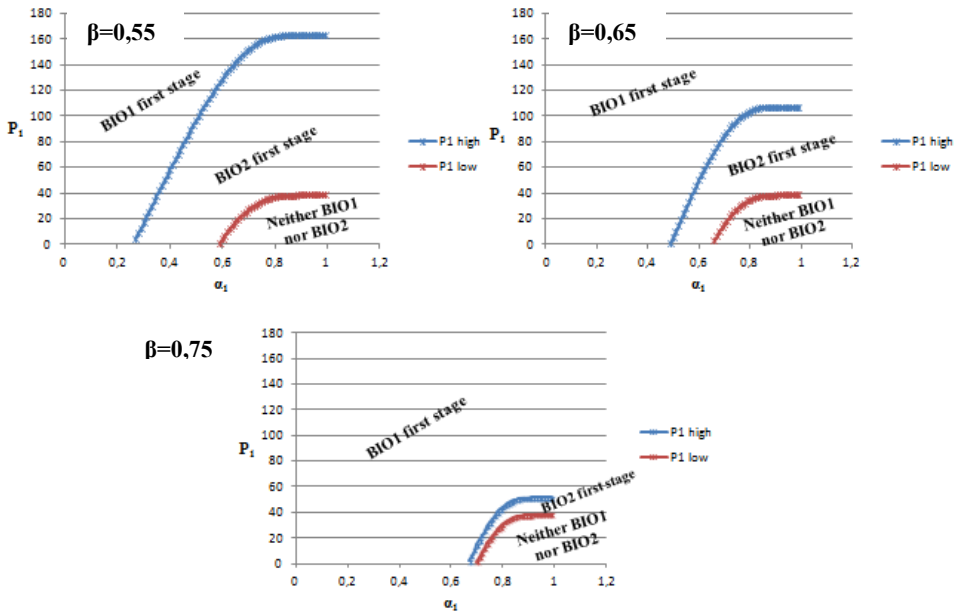

Figure 18: Duopoly thresholds (P_1= C_2^2-C_1^1, if P_1 is high, and P_1 = C_2^5-C_1^1, if P_1 is low) in case of high synergy when E(P_2) is low, δ = 2.2 and β varies.

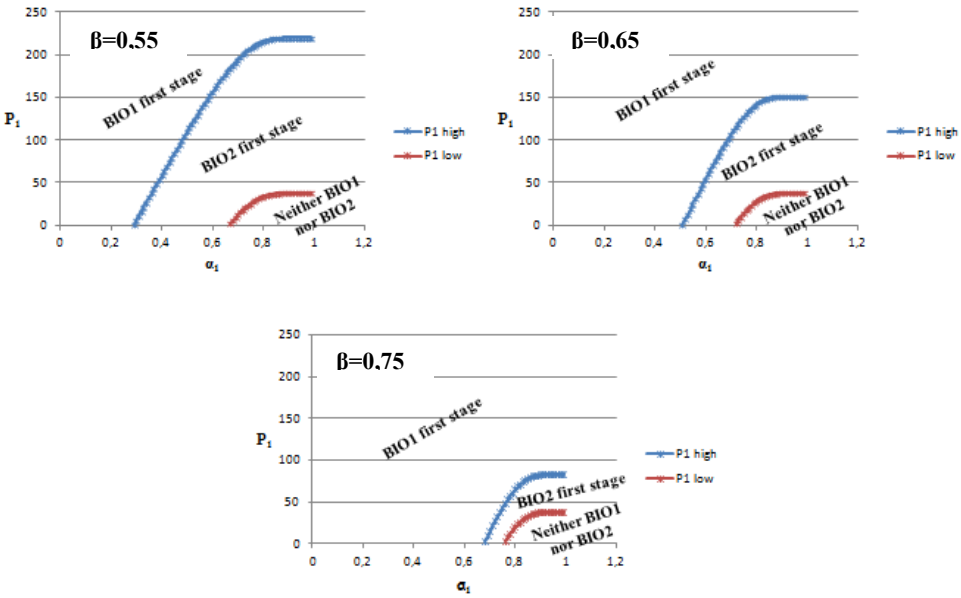

Figure 19: Duopoly thresholds (P_1 = C_2^2-C_1^1, if P_1 is high, and P_1 = C_2^5-C_1^1, if P_1 is low) in case of high synergy when E(P_2) is low, δ = 2.7 and β varies.

Moving to the case of ($\delta < (1-\gamma)/(1-\beta)$[11]), I find that there is no possibility for the second mover to partner with the pharmaceutical company. Interestingly, in this case, the market outcomes are identical to the case of monopoly and similar considerations can be done. The intuition behind this result is that the market pie has not been enlarged enough so that BIO1's competitive advantage of being a first mover more than outweighs the benefits derived from the spillover effect. As a result, the alliance "window" is closed to BIO2. Based on the data of the above case study, in Figure 20, I show how a higher level of β, determines an increase of the region of BIO1's first stage alliance. Furthermore, by comparing Figures 17 and 20, it can be observed that competition leads to lower threshold payments than the monopoly structure. In fact, as the level of competition increases, lower payments are required by the first mover to ally. This result can be demonstrated by comparing the conditions $P_{1\ MONOPOLY} = C_{mon}^{3} - C_{mon}^{1}$ and $P_{1\ DUOPOLY} = C_2^5 - C_1^1$. As the call options have the same exercise price, I can simply compare their underlying values, which are $V_0 - (1-\alpha_1)\ \delta V_0$ in case of monopoly and $\gamma V_0 - (1-\alpha_1)\delta\beta V_0$ in case of duopoly, respectively. Comparison yields that payments are lower in case of competition if the condition $\delta < (1-\gamma)/((1-\beta)(1-\alpha_1))$ holds. It is straightforward to prove that such condition is always satisfied given that the case of low synergy is considered.

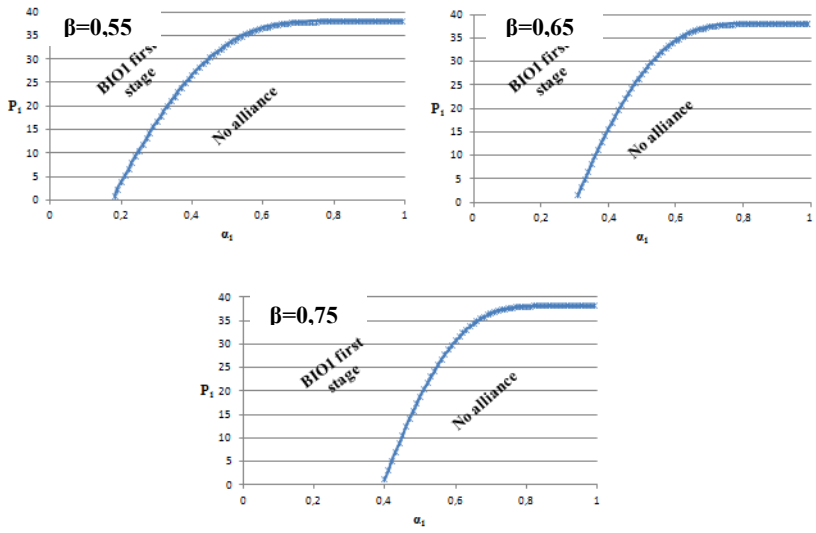

Figure 20: Duopoly thresholds ($P_1 = C_2^5 - C_1^1$) in case of low synergy when E(P_2) is low, δ = 1.1 and β varies.

[11] I impose δ to be greater than 1. Note that the ratio $(1-\gamma)/(1-\beta)$ is always greater than 1, with $\gamma = 0.5$ and $\beta > \gamma$. Thus, feasible values of δ are in the following range: $1 < \delta < (1-\gamma)/(1-\beta)$.

A final important remark is that the ROA offers more opportunities to biotech firms to ally compared to the traditional use of NPV because only positive values of future opportunities are considered. In fact, the region where alliance arises is larger when the ROA approach is utilized. Figure 21 shortly summarizes this implication of ROA flexibility.

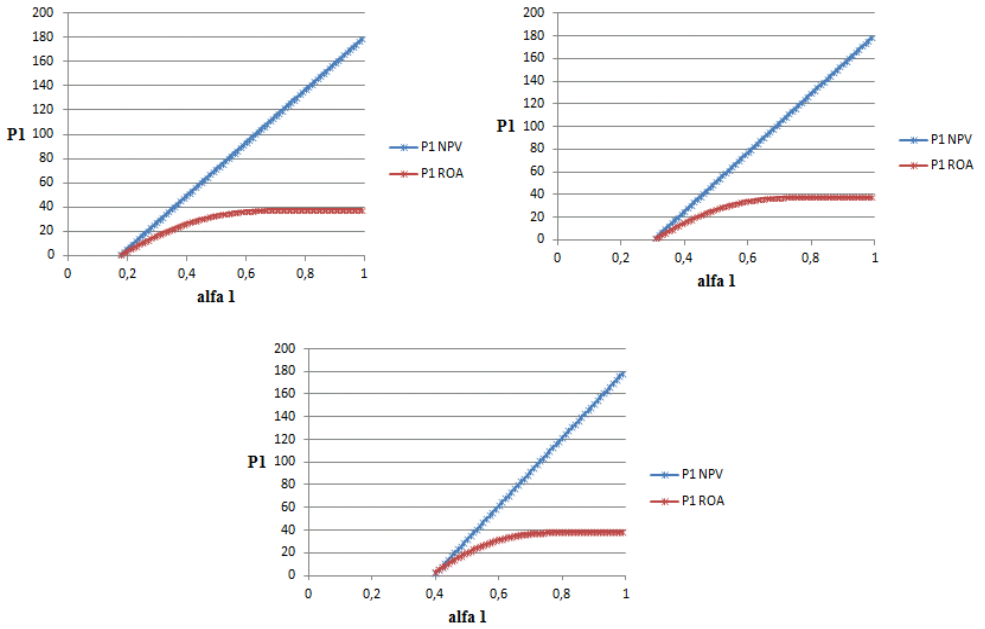

Figure 21**:** P_1 thresholds (the same as in Figure 20) evaluated with both net present value (NPV) and real options analysis (ROA).

5.5 Conclusions

Pharmaceutical companies more and more partner with biotechnology companies to develop new products. The emergence of numerous alliances between these two types of actors poses several relevant questions to the innovation management community. From the perspective of innovative biotech firms, one is certainly related to the alliance timing, which is currently discussed in the biotech industry world. As pharmaceutical companies become more attracted to biotech products and search more collaboration opportunities, biotech firms face decisions such whether and, possibly, when to ally with pharmaceutical companies. Adopting a real options game approach, I have investigated this type of decisions in presence of competition between two biotech firms who can partner with a pharmaceutical company offering a mutually exclusive take-it-or-leave-it contract.

Research findings suggest that under a Stackelberg game, where one biotech firm is the first mover, whereas the other is the follower, whether and when to ally with the pharmaceutical company depend on the contract terms offered by the pharmaceutical company, the market value increase due to the presence of the pharmaceutical industry, as well as the competitive advantage one biotech firm gains against the competitor due to the alliance. Specifically, there are numerous interesting cases. In case the market potential due to the contribution from the pharmaceutical company is high we can notice that all events are possible. The first mover can pre-empt or she can wait for better alliance conditions or she can leave to the follower the possibility to ally, and, in the latter case, the follower might or might not take advantage of this opportunity. The intuition behind the above findings relates to the fact that the first mover in presence of high market potential (or, alternatively, low competition level) allies with the pharmaceutical company when the payment conditions are satisfactory. Otherwise, the first mover prefers to continue the project individually as she can receive indirect benefits from the potential alliance between the follower and the pharmaceutical company. As a matter of fact, what is interesting, however, is that, in the latter case, the follower will not always follow the first mover and compete with her without the support of the pharmaceutical company. Rather, the follower will sometimes prefer allying with the pharmaceutical company, thus determining an increase of the market potential and providing indirect benefits to the first mover. Essentially, under competition, the first mover will not always preempt the follower alliance. On the other hand, if payment conditions are acceptable, the first mover will choose to ally, instead of competing individually, due to the overall benefits that will be generated through the alliance.

A less complex picture is obtained when the market potential due to the contribution from the pharmaceutical company is not high. In this case, only the first mover will partner with the pharmaceutical company: when first-stage payment is high, the alliance will be established in the first stage, otherwise this will happen in the second stage. However, if both first stage and expected second stage payments are low, no alliance will be signed. Under this scenario, as the market potential is not high (or, alternatively, the competition level is very high), the first mover will never leave room to the follower to ally with the pharmaceutical company as the market potential increase is mild. In this

case, the equilibrium scenarios are the same as the monopoly case.

This chapter has provided evidence of contrasting arguments from the industry world on whether and when biotech firms should partner with big pharma. Based on this analysis, none of them is completely right or wrong, in the sense that all alliance timing outcomes are possible. In fact, biotech firms can actually anticipate, postpone or forgo on alliance with big pharma in presence of competitors. However, each outcome will occur under specific conditions. In this regard, the results help provide some guidelines for practitioners with regard to the hot issue of alliance timing in presence of competition. As a matter of fact, in a first mover-follower setting, e.g., the example of Forma Therapeutics vs. new entrants in the protein homeostasis field, the market value added and payments offered by big pharma play a crucial role. Biotech firms, who enjoy first mover advantage, should always anticipate the follower in signing the licensing agreement when the market value does not increase significantly as a consequence of the alliance with the pharmaceutical company. A restricted market potential forces the first mover to adopt always a pre-emptive strategy in order to maintain the competitive advantage over the follower. As discussed earlier, in this case, the amount of payments offered by the pharmaceutical company in different stages determines whether the deal should be signed in the first, in the second stage or never be signed. On the other hand, when the market value added by the presence of big pharma is notably high, first mover should not always choose to partner with big pharma. Rather, when contract terms are not appealing, first mover should let the follower ally to profit more in the final market due to the fact that she does not share the profit with the pharmaceutical company, while still benefiting from positive spillover. Even when the market potential increases due to the presence of the pharmaceutical company, the amount of payments offered by the pharmaceutical company in different stages determines whether the deal should be signed in the first, in the second stage or never be signed.

There are several directions to build upon this work for future research. For instance, I have analyzed alliance timing decisions, where the pharmaceutical company has the bargaining to offer a take-it-or-leave-it contract to the competing biotech firms. However, in some cases, very innovative biotech firms might enjoy some bargaining power, so a more fair negotiation environment (e.g., Nash bargaining game) could be considered in future studies. Also, I considered the competition between biotech firms.

It is of considerable interest and practical relevance to analyze also a setting where two pharmaceutical companies compete to ally with an innovative biotech firm to investigate whether the implications of above are robust in such new environment.

Chapter 6
Conclusions and future developments

6.1 Summary of results and contributions

This thesis deals with the evaluation of R&D alliances under uncertainty. The main objective of this dissertation is to suggest when, and under what circumstances it is advantageous for firms to engage in the use of either in-house R&D activity, or R&D alliances when a stochastic environment is considered. Particularly, the analysis focused on two issues that strongly characterize the turbulent and competitive world in which nowadays firms try to foster innovation. On the one hand the important choice of the optimal R&D projects portfolio including the option to carry out projects through R&D collaborations. On the other hand, assuming a dynamic perspective, the choice of the optimal time to sign an R&D partnership by considering the important role of competition.

This thesis looks at both topics by adopting a real options approach in order to take into account and model uncertainty of the economic environment in which those decisions are made. Therefore, from a theoretical point of view, my thesis contributes to the growing and important stream of research that develops real options valuation models for investments under uncertainty. The particular focus is on R&D alliances. Surprisingly, there is very little specific theoretical work that considers theoretical modeling in the (dynamic) setting of R&D collaborations and it neglects the important issues of above. Specifically the main results of this research are now discussed in details together with the identification of the main contributions. In particular I will briefly discuss both the findings and the major contributions of each chapter, except for chapter 1 (which sets the context and the motivation of this research) and chapter 2 (where a discussion of the relevant literature has related the present dissertation to prior works and has assessed different stands of literature in order to collect necessary elements for the models proposed in the further chapters).

Chapter 3 and chapter 4 give an important contribution to the portfolio management literature. Specifically, Chapter 3 provides a closed-form real options framework for portfolio evaluation which hands important portfolio features that have not been covered so far in literature. The tool aims to contribute to the available models

considering the possibility to create a financially balanced portfolio. In fact, the model is set up as a multi-dimensional real options analysis problem based on n projects (underlying assets) and support two critical aspects: (i) R&D projects selection given a set of limited resources; and (ii) how to carry out the selected projects (internally or externally), that is, the R&D alliance option is included in the model. A self-financing policy is also taken into account. Moreover, since different closed-solutions formulae (NPV method, B&S formula and Geske model) are adopted, the proposed tool presented in chapter 3 gives an important contribution from a methodological point of view. First, the model fits better the R&D environment by distinguishing among projects that are not options, simple options, and compound options, depending on how far the project is from the last phase in its R&D development process (i.e. depending to what extent managers can defer the decision to exercise the option). Second, adopting closed-solutions makes the mathematics of the model less complex than adopting numerical approaches in terms of constraints and variables involved in the problem.

Starting from this model, in chapter 4, a DSS is illustrated to understand which are the portfolio parameters that influence the important choice of conducting R&D activity internally or externally. As widely discussed in the second chapter, which reviews several existing models to evaluate and select an R&D portfolio, the most recent trend in the portfolio management literature, is to integrate both quantitative and qualitative techniques, such as mapping tools, in an integrated decision support system. However such tools neglect real option analysis. To the best of my knowledge, this is the first DSS which includes projects evaluated as real options. In such a way, the research presented in this part of the dissertation gives an important contribution to the real options theory as well. As a matter of fact, while it is well known in literature the impact of the important key variables (the underlying value, the volatility, the interest rate and so on) on the single real option, what is still not known is their impact on a considered options portfolio. The tool proposed in chapter 4 does exactly so and, specifically, sheds light on the influence of some of the above parameters on the important choice of conducting the R&D activity according to a closed or an open innovation strategy. Finally, through the analysis conducted in chapter 5, this thesis also provides insights to the alliance timing literature. Previous research has focused on the optimal alliance design without considering the role of competition. In chapter 5, a two-

stages real options game is presented that includes the effect of the competition in choosing the optimal time to sign a partnership. In fact whether and when ally (i.e. in the first stages of the R&D development process or later) depend on competition, on the value added to the project by the potential alliance as well as on the partnership contracts terms. In addition to this theoretical contribution, the real options game model also presents an important contribution from a methodological standpoint. As shown in chapter 2, literature on real options games offers discrete-time real options games and continuous-time real options games, dependently if the choices to "invest" or to "defer" are made, according to the underlying movements, in a discrete or continuous time respectively. Generally, the former are easier to implement but are solved numerically whereas the latter can be solved analytically but are harder to implement. The modeling involved in the proposed model presents somewhat which is new: since I adopt the closed B&S formula, I assume that the underlying asset follows a continuous process (in particular a geometric Brownian motion) whereas the choices to "invest" or to "defer" are made in discrete points of time. In such a way, I can capture advantages of the above methods, obtaining a model easy to implement that can be solved analytically. Moreover, making decisions in discrete points in time fits better the R&D environment (such as pharmaceutical) where decisions are traditionally made in discrete points, such as at the beginning of a new stage of the R&D development process.

6.2 Managerial Implications

The research provided in this thesis has also several important managerial implications. Overall the analysis conducted offers managerial guidelines and a set of practical recommendations for supporting managers in the important decision of undertaking a new relation with another firm, i.e. when considering enter in partnership with another firm. This important decision is traditionally made in a stochastic environment, characterized by an amount of uncertainty over the future rewards from the investment. On the one hand this research enhances financially constrained managers understanding about important portfolio choices in terms of which factors would influence the selection and the development in alliance of the projects from a considered portfolio. The focus should be given to the underlying value (future value of product commercialization) and the value added from the collaboration to the product.

Specifically, the higher the value of the underlying, the greater the opportunity to select the project and develop it in house. Conversely, the higher the value added from the collaboration, the higher the convenience to select licensable products and to develop them in alliance. On the other hand, assuming a dynamic perspective, this research enhances managers understanding about the alliance timing decisions, by suggesting whether and when they should collaborate with other firms in a competitive environment. In this regard, the results obtained help provide some guidelines for practitioners with regard to the hot issue of alliance timing in presence of competition. Particularly, managers should pay attention to the market value increase due to the alliance, the contract terms offered by the company partner as well as to the level of competition. In fact, supposing that managers enjoy first mover advantage, as the market potential is high enough (or, alternatively, the competition level is very low), they should not always choose to sign licensing agreements. Rather, when contract terms are not appealing, first mover should let the follower ally to profit more in the final market due to the fact that he does not share the profit with the partner company, while still benefiting from positive spillover coming from the follower alliance. Conversely, when contract terms are satisfactory, the first mover should always pre-empt the follower in signing the R&D alliance. Specifically, when early payment conditions are high enough, an early alliance should be established, otherwise managers should wait for better payment conditions in later stages. A less complex picture is obtained when the market potential due to the contribution from the partner company is not high (or, alternatively, the competition level is very high). In this case, a restricted market potential forces the first mover to adopt always a pre-emptive strategy in order to maintain the competitive advantage over the follower. Once again, when early payment conditions are high enough, an early alliance should be established, otherwise managers should wait for better payment conditions in later stages. Finally, in both cases, i.e. when the market potential is high or low, if the payments offered from the partner are very low either in early or in later stages, neither the first mover nor the second mover should sign the R&D collaboration. In such a case, they should prefer continuing the development process on their own.

It is also important to highlight the adoption of the real options methodology (particularly closed-solutions) in this research. From a managerial point of view, the

real options approach has often been criticized for its apparent complexity. This consideration is especially true when applying real options in a portfolio context or when integrating real options aspects with strategic aspects (real option games). Of course, it is important to discuss and structure the option valuation models with managers. However, it could be hard to communicate the valuation framework in details mainly because it presumes a detailed understanding of the underlying option valuation concepts (Brosch, 2008). Therefore making the essence of the model more transparent, that is, in this specific case, making the understanding of the underlying continuous process as clear as possible, could bring managers to be more inclined to accept the model. In fact, once this apparent complex process is clear, adopting closed-solutions makes the implementation of the real options models very easy and simple. As a prove of this, the models presented in this dissertation have been implemented in simple spreadsheets that mangers can easily handle.

6.3 Limitations and further developments

While this research makes important contributions to different research streams, it has also some limitations. At the same time, these limitations represent potential avenues for future researches. From a methodological standpoint, two possible shortcomings arise that, in turn, are attributable to limitations owned by the adopted closed–solutions approaches, i.e. the B&S formula and the Geske model. First, as highlighted earlier in this dissertation, one of the main assumptions of these models is the assumption of the geometrical Brownian motion for the underlying which implies a continuous arrival of information that changes the underlying variable. Actually, information that affects future net cash flows of research projects arrives at discrete points in time, causing that managers not continuously adjust the underlying, but only when information arrives. To overcome the limitation of the Brownian motion, different authors propose jump-process models both for the B&S formula (Brach and Paxson, 2011) and for the Geske model (Pennings and Sereno, 2011). As a matter of fact, a Poisson (jump) process would be able to describe these movements in the underlying variable in a more realistic way. Second, whereas numerical approaches are able to capture the technical uncertainties and commercial risk of the R&D process, closed-form solutions, capture only the economic risk (or alternatively both technical and economic risks are captured by one measure, i.e. the volatility of the underlying). However, Cassimon et al. (2011a)

incorporated the technical risk in the *n*-fold compound option model, preserving the closed-form formula. It follows that, even if it could result more difficult from an implementation standpoint, future research could integrate these models (i.e. Brach and Paxson, 2001; Pennings and Sereno, 2011; Cassimon et al. 2011a) with both portfolio and strategic aspects in order to better address the topics discussed in this dissertation.

Moreover, the present thesis may have limitations from a theoretical point of view. First, in chapter 3 and chapter 4, I considered projects as only budgetary interrelated in the given portfolio. Considering resources limitations is an important issue. However, future research could extend this analysis by integrating other forms of interaction among projects, involving physical or technical properties of the underlying assets. For instance, projects could be mutual exclusive or depend on one another. Also, logic interactions such as precedence constraints may be considered (Brosch, 2008). Similarly, further developments could investigate the diversification side of the problem: in order to accomplish this task, correlation between each couple of products should be taken into account. This is an interesting task because, as discussed in Chapter 2, in van Bekkum *et al.* (2009), correlation among R&D products with real-options characteristics acts differently than it usually does in evaluation contexts that use NPV, and, in particular, negative correlation only slightly reduces portfolio risk.

Second, in chapter 5, alliance timing decisions have been analyzed considering numerous important variables as exogenously given. Future studies could consider endogenous decisions about some of the contract terms offered by the partner firm, or investment levels and research efforts. This kind of analysis is important to provide a complete picture of alliance design and timing decisions.

In addition, R&D collaborations are unstable and, sometimes, they could be problematic to manage. Indeed, when an alliance if formed, a firm becomes exposed, among other ex-post risks, to the unplanned termination (Pangarkar,2009), i.e. the risk of one partner unilaterally withdrawing from the relationship before its objectives have been achieved. Further research could address this important issue by modelling, also in the research context I propose, the exit strategies, i.e. possible divestments highlighting which factors could influence this situation.

Finally, a very interesting development of this dissertation aims at testing some of results in laboratory using experimental methodology in order to investigate human

choice behavior in making alliances decisions under uncertainty. This is a very stimulating issue which deserves a deeper discussion in the following section.

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6.4 Behavioral economics as further development

As Yavas and Sirmanas (2005) point out, in spite of its significant practical implications for various investment decisions, empirical testing of real options has been scarce. To use Moel and Tufano (2002) words, " empirical research on real options has lagged considerably behind the conceptual and theoretical contribution".

This is primarily due to the problems that researchers face in obtaining "key variables" in real options, i.e. reliable data on such components of the real options approach as the current and future value of the underlying asset and the variability of value (Yavas and Sirmanas, 2005; Opera 2009). In addition, even if data are available, very often they are not available in the form that would respect the assumptions of the theoretical models. This is particularly true in individual choice problems and game theoretical analysis (Yavas and Sirmanas, 2005). As a consequence, in the last decade, researches have been using laboratory experiments to generate the data for the analysis and study people's abilities or propensity to follow the dictates of optimal decision policies (Murphy and Knaus, 2011). In Miller and Shapira (2004) work, decision makers are presented with simple binary lotteries and asked to specify the price for selling or buying a call or a put option for the gambles. The results show that the value of the price specified for selling and buying the derivate do not coincide, suggesting inadequacy with the normative model's descriptive power (Murphy and Knaus, 2011). Yavas and Sirmanas (2005) investigate the option "wait and see" in laboratory. The results of their experiments highlight that fundamental insights of real options theory are not so evident to individual investors. As a matter of fact, the majority of subjects tends to invest too early compared to the optimal timing suggested by the theoretical model and thus fails to realize the benefits of waiting. Close to the spirit of this paper, Oprea et al. (2009) investigate behaviour in uncertain investment opportunities governed by Brownian Motion. Their results indicate that people can closely approximate optimal exercise of wait options if they have decent chance to learn from personal experience (Oprea et al. 2009). In fact, while at the beginning investors tend to exercise the option prematurely, over time their average behaviour converges close to the optimum. In Murphy and

Knaus (2011) work, a decision maker must choose how much to invest in a risky environment that evolves over time. Their experimental results contrast predictions from theory.

These findings suggest innate behavioural tendencies that are contrary to the normative dictates since most of the above works highlights that essentially people have biases in their decision-making. In addition, these studies have investigated human choice behaviour in investment decisions under uncertainty. Future studies could investigate human behaviour in R&D alliance decisions in a stochastic environment. For example, it could be very interesting to study the alliance timing decisions -modeled in chapter 5- in an experimental way. This is equivalent to study if individuals make decisions conforming to the theoretical model - thus maximizing potential earnings - both in the simplest case (the monopoly case) and in a more complex case (the duopoly case). In the next and final section a simple possible design of experiment for the monopoly case is provided.

6.4.1 Design of experiment (the monopoly case)

Problem description

To better understand the design of the experiment, let me briefly recall the theoretical model in the monopoly case. Consider a Firm, named Firm A, which is working on a research and development (R&D) project. Also, consider a simple setup in which there are two stages of the development process. In the first stage, the project in its early phases of the development, and in the second and final stage the project is approaching commercialization. At each stage, the firm will have the option to form an alliance with firm B. Firm A can also choose to forgo the alliance and choose to enter the market alone. The sequence of the game is as follows. At the beginning of the first stage (t=0), Firm A's project value is given by V_0. Firm B offers an alliance contract to Firm A as consisting of an ex-ante payment P_1 and percentage of royalties retained by Firm A equal to $1-\alpha_1$, $0<\alpha_1<1$. If Firm A rejects the offer, the decision game is repeated. In the second stage (t=T, with T the length of the first stage), Firm B offers a different alliance contract consisting of an ex-ante payment P_2 and a percentage of royalties equal to $1-\alpha_2$, $0<\alpha_2<1$. If Firm A rejects this offer, the firm proceeds to the final market unassisted.

In each stage i, an investment payment I_i must be made. If an alliance is formed at stage i, the size of the project's market increases relatively to the case of no alliance by an amplification factor $\delta > 1$. This factor reflects the value added to the project by the synergies derived from the alliance. In order to keep the model as simple as possible, I assume royalty payments are the same regardless of when alliance was formed (i.e. $\alpha_{1=} \alpha_{2 =} \alpha$). Thus, if an alliance is signed, the value of the project will be multiplied by K, with K equal to $\delta(1- \alpha)$. As discussed in detail in Chapter 5, I can model the first stage payoffs with the above Black and Sholes approach, which ensures the flexibility offered by the option to decide further investments when more information is available, whereas the second stage payoffs are simply computed with the NPV methodology. This modeling (please refer to figure 22) causes that if Firm A signs an alliance at the first stage, she will receive a sure payment P_1 computed as a difference of two calls options (please refer to the previous chapter, p. 107). Conversely, since the payments in the second stage are linear function of the value of the project (which follows a diffusion process with a log-normal distribution at maturity, i.e. at the beginning of the second stage), if Firm A decides to wait and sign an alliance at the second stage, she will receive a P_2, which is a realization from a log-normal distribution with mean and variance equal to:

$$E[P_2(T)] = V_0(1-K)e^{rT} \tag{37}$$

$$Var[P_2(T)] = (1-K)^2 V_0^2 e^{2rT}(e^{\sigma^2 T} - 1) \tag{38}$$

Therefore, in this decision task, the decision maker (assuming she is playing the role of firm A) has to choose between a sure thing and a risky alternative from a continuous distribution, that is, between a sure payment if she decides to ally at the first stage and a risky payment if she decides to ally at the second stage.

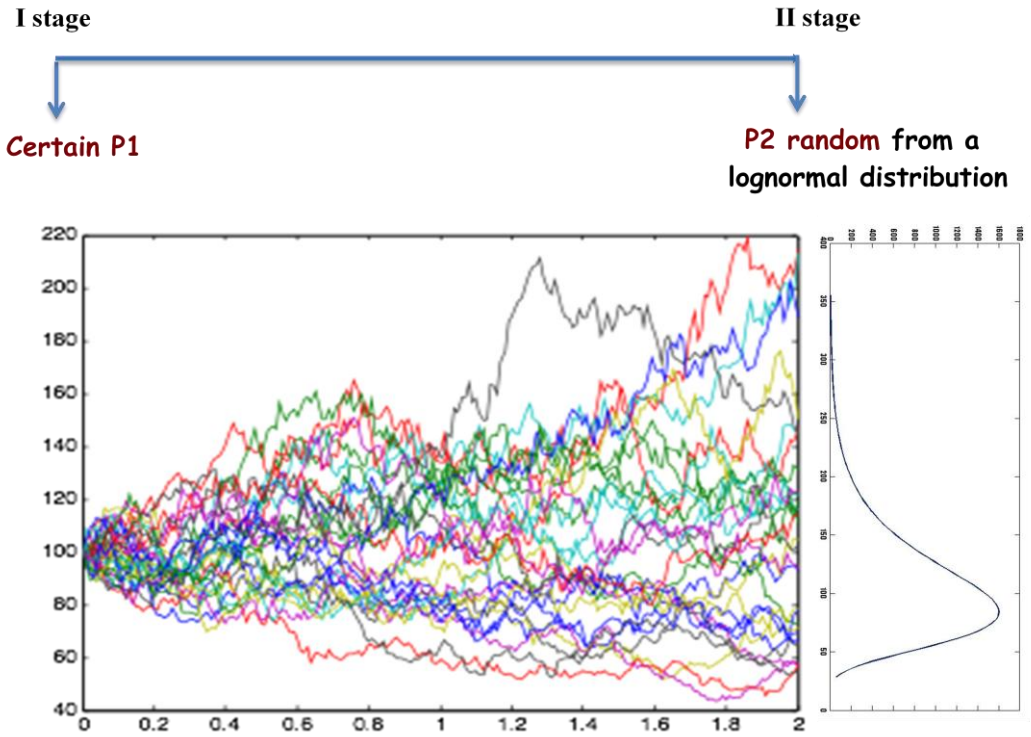

Figure 22: Payments in the two different stages.

Numerical example:

Consider the following set of parameters: V_0 = \$400, σ = 30%, r = 5%, I_1 = \$75, I_2 = \$180; T=2, δ (2.2). With these values, alliance can arise either in the first or in the second stage. Figure 23 identifies the region of alliance as a function of P_1 and α. Therefore, assuming a payment P_1 equal to 17.8 and α =0.6, the theoretical equilibrium of the game is the alliance at the second stage.

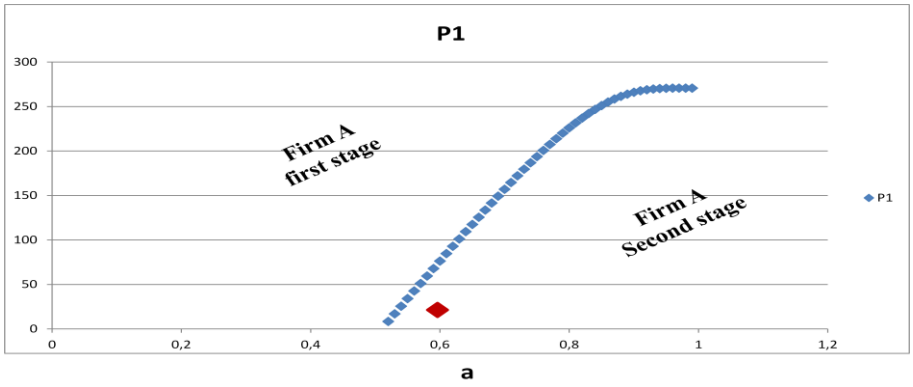

Figure 23: Monopoly P1 threshold when E(P2) is high.

In order to study this specific situation in laboratory, students should be provided with comprehensive instructions describing the task and the interface of the computer program that could be used to administer the experiment. Therefore a possible example of instructions is offered:

Instructions

Welcome! You are about to participate in an experiment in the economics of decision making. If you listen carefully and make good decisions, you could earn a considerable amount of money that will be paid to you in cash at the end of the experiment. The rules for the experiment are as follows. Do not talk or communicate with other participants. Do not attempt to use the computer for any other purpose than what is explicitly required by the experiment. This means you are not allowed to browse the internet, check emails, etc. If you violate any of these rules, you will be asked leave without pay. Feel free to ask questions by raising your hand or signaling to the experimenter. During the experiment your entire earnings will be calculated in points. At the end of the experiment the total amount of points you have earned will be converted to dollars at the following rate:

(Some points)=1$

Your Task

You are in control of a company that is working on a risky R&D (research and development) project with potential significant profit. A large firm that specializes in taking these kinds of projects to the final market will offer to form an alliance with you that will make your profit higher. Specifically, the large company will offer you two different kinds of contracts: a sure contract and an uncertain one. Consequentially, you could receive a certain payoff or a payoff with uncertain outcome, which could be higher or lower than the certain one. Your **TASK** in this game is to choose between a **certain** payoff and a payoff with **uncertain** outcome. You will be shown both the amount of the certain payoff and the distribution of possible outcomes for the uncertain payoff before being asked to make a decision.

The sequence of the game is as follows. At the beginning of each round, the large firm will offer you an alliance contract. You may use to accept this payoff: in which case the round will conclude. However, you may also choose to forgo the guaranteed payoff, and

instead take a payoff tied to the value of your project. Because the development of the project is risky, its value changes random. As a consequence, the alliance contract offered by the large firm –and hence your payoff- changes randomly. This means that it might go higher than the certain payoff, earning you more points. It is also possible that the payoff will be lower, earning you less points. If you choose this option, you will take a payoff randomly picked up from a given distribution, that is shown to you on the screen. You will be playing several rounds of this game, but your decision in a given round **does NOT** affect any other round.

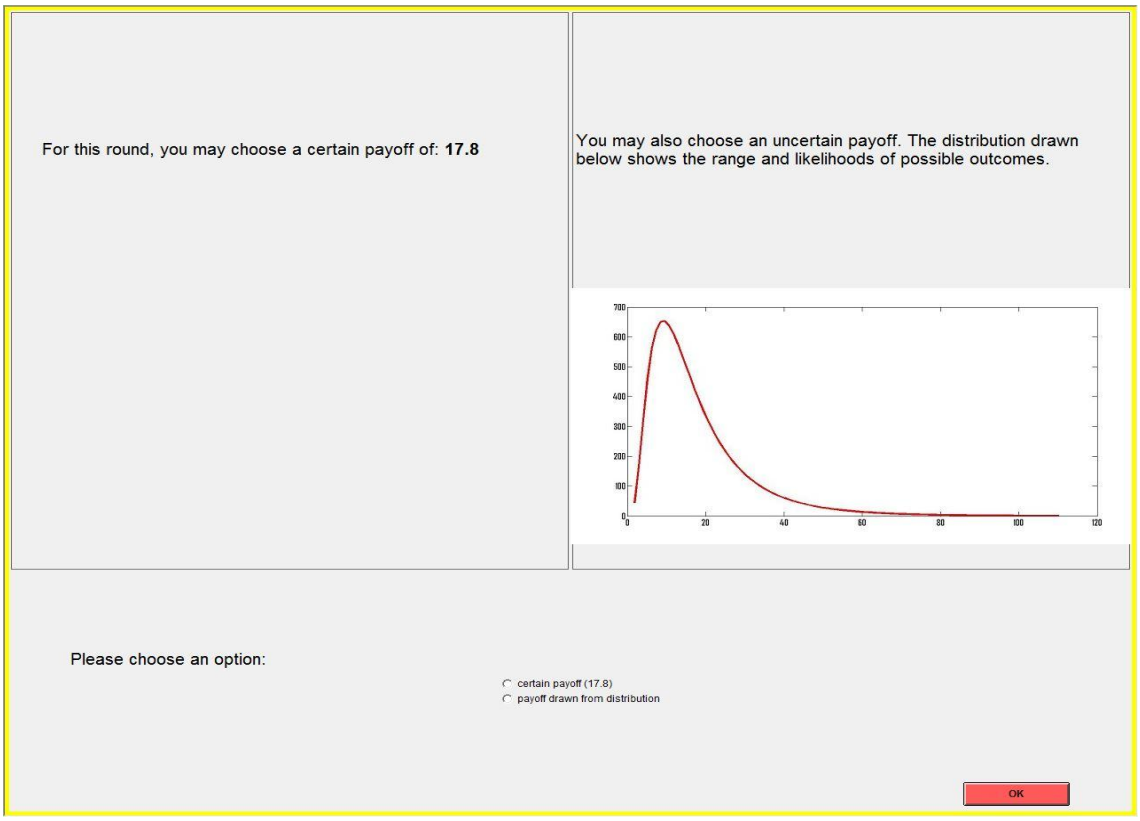

Figure 24: Possible screen to show during the experimental game

Of course, to effectively test the theoretical model, several rounds of the game afore-mentioned should be played. Contracts licensing in the first stage (i.e. payment P_1 and royalties a) should be random selected from the region of alliance illustrated in fig 23, in order to provide different scenarios of equilibrium and observe if people, in average, make decisions according to the theoretical model.

Moreover, the situation above illustrated is just an example, and one can easily imagine other several cases which allow to study empirically the influence of important factors involved in the model. For instance, Figure 17 (in chapter 5) highlights how δ (the total

market size) affects firm' alliance timing decisions. Specifically, it suggests that when the total market size increases due to the contribution of alliance (δ), the firm has more chances to sign an early agreement with the partner company in order to take advantage of the high synergies. Once again, it would be interesting to study how people update their preferences in such a situation.

Finally, a comprehensive work should include the more complex duopoly case, in which people make decision regarding the optimal time considering not only uncertainty due to the nature (such that in the monopoly case), but also uncertainty about reactions of competitors. How does the presence of competition influence people decisions? For instance, it is recognized (see chapter 2) in option pricing literature that, in absence of competition, an incumbent firm would delay project initiation. Conversely, *ceteris paribus*, the presence of competition may speed up a firm's planned investment (Boyer et al. 2004). Under particular values of the input parameters, I find the same situation in the alliance timing problem under uncertainty (see fig. 25). In fact, given the same input parameters, the optimal time to sign the alliance is the second stage when the monopoly case is considered, whereas it is the first stage when the duopoly case is considered.

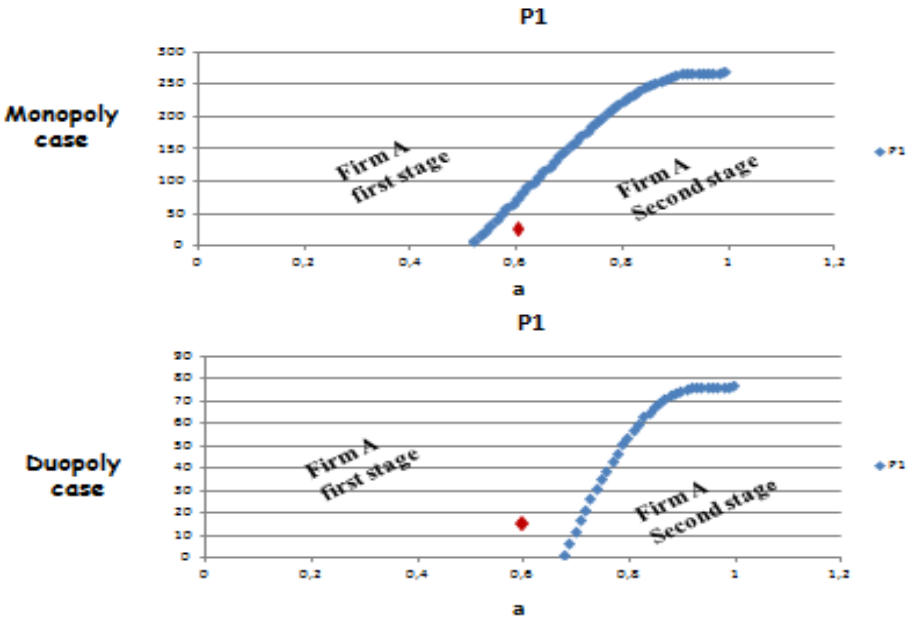

Figure 25: P1 threshold when E(P2) is high (monopoly and duopoly case)

When "waiting" is the optimal strategy in the monopoly case, do investors postpone the alliance decision until uncertainty is resolved (i.e. in the second stage)? Given the same payments conditions in the duopoly structure, does the first mover anticipate the alliance at the first stage in order to pre-empt the follower? It is very interesting to study what it can happen empirically in such a situation. Naturally, several other hypotheses could be tested when also the competition is taken into account.

Of course, in this section I provided some possible examples only referring to the model discussed in chapter 5, but, more in general, future research could integrate the mathematical models illustrated in this thesis with experimental economics methods in order to develop quantitative models that aim at predicting and explaining the decision process, preferences as well as cognitive limitations that the real decision makers exhibit when deliberating over complex options.

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