R&D and knowledge dynamics in university-industry relationships in biotech and pharmaceuticals: an agent-based model

Giorgio Triulzi*

UNU-MERIT,
Keizer Karelplein 19, 6211TC,
Maastricht, The Netherlands
and
Department of Economics,
Maastricht University,
P.O. Box 616 6200, MD, Maastricht, The Netherlands
E-mail: triulzi@merit.unu.edu
*Corresponding author

Andreas Pyka and Ramon Scholz

Chair for Economics of Innovation,
Economics Institute,
University of Hohenheim,
Wollgrasweg 23, D-70599 Stuttgart, Germany
E-mail: a.pyka@uni-hohenheim.de
E-mail: ramon.scholz@uni-hohenheim.de

Abstract: In the last two decades, university-industry relationships have played an outstanding role in shaping innovation activities in biotechnology and pharmaceuticals. Nevertheless, there still is an intensive and open debate concerning their short and long term effects on the research system in life sciences. This work introduces a new way to analyse university-industry relationships (UIRs) which makes use of an agent-based simulation model. We analyse knowledge interactions among heterogeneous actors and we show that: 1) universities tend to shift from a basic to an applied research orientation as a consequence of relationships with industry; 2) universities' innovative capabilities benefit from industry financial resources but not so much from cognitive resources of the companies; 3) biotech companies' innovative capabilities largely benefit from knowledge interaction with universities; 4) adequate policies in terms of public basic research funding can counteract the negative effects of UIRs on university research orientation.

Keywords: university-industry relationships; UIRs; knowledge dynamics; agent-based modelling; ABM; university patenting; technology transfer; biotech; biotechnology; pharmaceuticals; basic research funding policies.

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Biographical notes: Giorgio Triulzi is a PhD candidate in Economics at UNU-MERIT and Maastricht University. He received his Master degree in Economics of International Markets and New Technologies from Bocconi University (Milan). He has a variety of research interests within the broad field of evolutionary economics. Simulations and network analysis are his favourite research tools.

Andreas Pyka is a Full Professor of Innovation Economics at the University of Hohenheim, Germany. He publishes in the fields of innovation networks, agent-based modelling, complexity economics, neo-Schumpeterian economics, industrial dynamics, biotechnology industries and R&D policies. He is involved in several international research projects. He also is the Editor of the International Joseph A. Schumpeter Society and Advisory Editor of the *Journal of Evolutionary Economics*.

Ramon Scholz received his Diploma degree in Economics from the University of Augsburg and worked in the European NEMO project afterwards. His main research interests are agent-based models.

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1 Introduction

In the past 35 years, science-based industries have been strongly influenced by a radical scientific breakthrough, namely the development of the recombinant DNA technique by Stanley Norman Cohen and Herbert Boyle in 1973 (Cohen et al., 1973), and by a major institutional change, namely, the surge in university patenting (see Kortum and Lerner, 1999; Saragossi and van Pottelsberghe de la Potterie, 2003; Balconi et al., 2004; Breschi et al., 2007; Lissoni et al., 2007). Consequently, the way innovation is pursued in the biomolecular industries has been crucially affected. On the one hand, the advent of the biotechnology paradigm has forced pharmaceutical incumbents to deal with a radically different set of capabilities than organic chemistry, upon which pharmaceutical firms' core-knowledge was grounded. This has pushed large diversified firms (LDFs) in the pharmaceutical industry to adopt an innovation strategy characterised by interaction with both primary generators of new relevant scientific knowledge, namely dedicated biotech firms (DBFs) and universities. On the other hand, the spreading of university patenting has further increased the importance of universities as a source of new knowledge and basic research findings, not to mention the role of universities as biotechnological start-up incubators. The joint effects of these two breakthroughs led to a dramatic strengthening of university-industry relationships (UIRs). Indeed, both the biotech and pharmaceutical industries widely rely on universities, as well as on public research institutions, to acquire mainly fundamental, but in part also applied, external knowledge.

The growing importance of UIRs in the innovation system of life sciences led to a growing awareness of economic and medical literature on this central topic. Nevertheless, the costs/benefits debate concerning the short and long run effects of UIRs on the innovativeness of the research system in pharmaceuticals and biotech is still open and intense.

Therefore it is of primary importance to understand whether UIRs are a phenomenon which intrinsically presents short-term benefits and long-term drawbacks or whether there are different and additional effects to be considered. In the former case, UIRs should not be furthered at all, because short-run and self-reinforcing effects would induce universities to rely more and more on these relationships as source of funding, even though this would generate harmful effects for the long run innovativeness of the research system as a whole. In the latter case, the two effects are opposed and depending on their relative strength, the total effect on the innovativeness of the research system could be positive.

The lack of a generally accepted evaluation of UIRs, despite their long tradition, can be traced back to one main shortcoming: the complexity of these relationships makes it difficult to analyse their multiple correlated effects. In particular, because of this complexity it is more and more important to consider the role of all the actors which are engaged in the biotech and pharmaceutical innovation systems and to analyse how these relationships affect each of them. When we analyse UIRs in the biotech and pharmaceutical sectors, we have to consider that they are embedded into a broad innovation system where, besides universities and industry, also the government plays an important role (e.g., Niosi, 2010). In particular there is a growing debate in the literature and in the media on the nature and role of public funding with respect to academic research. Several studies highlight complementarities between public and private R&D while others claim a substitutive relationship between these two sources of research funding (for a comprehensive literature review, see David et al., 2000).

In the attempt to contribute to the formation of a more widely accepted perspective on UIRs' total short and long run effects, we apply agent-based modelling (ABM) to investigate this phenomenon (for an overview of ABM's advantages and characteristics see Triulzi and Pyka, 2011). Due to their focus on multi-agents' micro-interactions, agent-based models (ABMs) are explicitly suited to analyse UIRs and generate new insights to the UIRs debate. Furthermore, this class of models can be meaningfully applied to study phenomena where data cannot be easily collected – in our case knowledge dynamics – and allows for studying self-reinforcing mechanisms. Therefore, by building an agent-based UIRs model, we aim to provide a new dimension for the discussion of UIRs long run effects on the production of innovative new drugs based on the interaction of the different agents and on the underlying knowledge dynamics. For this purpose we draw on an extensive and growing literature about simulation models of innovation networks (Gilbert et al., 2001, 2007; Pyka et al., 2002, 2007, 2009; Ahrweiler et al., 2004a, 2004b, 2011; Pyka and Scholz, 2008) which guided us in our research and lays the foundations of our model.

The paper is organised as follows: The theoretical framework and the hypotheses to be tested are introduced in Section 2. Then a description of the methodology (Section 3) and of the agent-based UIRs model follows (Section 4). Finally, the results generated by simulation experiments are introduced (Section 5) and discussed (Section 6).

2 Theoretical framework and hypotheses

The biotech and pharmaceuticals' system of innovation is grounded on complex interactions among many different actors. Several studies analysed UIRs focussing only on the effects that these relationships have on single classes of actors, generating very useful insights but loosing the overview on the systemic nature of these relationships. Nevertheless, these detailed and specific insights and concerns are helpful in setting up a general model of the biotech and pharmaceuticals system of innovation centred on UIRs. In the following, we will very briefly review these studies and their conclusions, whose stylised facts underlie the theoretical framework of our model. From these arguments some hypotheses are extracted. We grouped them by actors: universities, industry and government.

2.1 UIRs' effects on universities

In the life sciences, the generation of new scientific discoveries and the achievement of highly innovative and patentable research results strongly depend on a sound understanding of a particular disease. In order to have a chance of finding an innovative and effective drug for a certain disease, it is critical to study the disease in question in depth. Only in this way can one understand how the human body is affected and how to 'attack' the causes and the effects of the disease. This is, generally speaking, what basic research deals with (Angell, 2004). Therefore, the generation of innovative medical solutions can be attained more easily by those actors which are characterised by having a fundamental research orientation, i.e., universities[1].

On the cost side, many authors (e.g., Angell, 2004; Ding, 2004; Geuna, 2001; Blumenthal et al., 1996) suggest that UIRs can potentially damage the long run innovativeness of the research system in life sciences. Following this literature, UIRs have modified the reward system for academic researchers and for universities in general, introducing a personal and institutional incentive to do more applied research. From this point of view, the possibilities to increase industry funding stemming from the commercialisation of academic research potentially push universities away from pure basic research in favour of a more applied research, in order to increase the probability of ending up with patentable research outcomes. This result might be harmful to the system because it could potentially lead to a situation in which fewer scientists and fewer academic institutions are engaged in pure basic research, which is a fundamental component of the whole system necessary for generating scientific discoveries which open new research areas.

In particular, the most common forms of UIRs are

1 LDFs sponsorships to universities

2 university patents licensing

3 joint research projects between universities and DBFs (Blumenthal, 2003).

Industry-sponsored research is often focused on achieving the goals of the sponsor rather than on the goals of the researcher or the sponsored academic institution (Association of University Technology Managers, 2007). Therefore, projects of this nature tend to involve applied research instead of fundamental research, as argued by Poyago-Theotoky et al. (2002). The considerable financial resources which accompany licensing also

strengthen the incentive to focus on applied research. Universities may be induced to put stronger emphasis on those research projects which offer a higher probability of achieving patentable outputs. Finally, the same shift of the research direction may be caused by an increase in the number of joint research projects with DBFs, due to the influence of knowledge exchange with actors whose research interests are more commercially-oriented (especially in the case of frequent and long interactions). Therefore, we postulate:

H1 University relationships with industry, in terms of sponsored research, university licensing and joint research projects, cause a shift from basic to applied research in the research direction of universities.

On the other hand, according to the US National Science Board, the reason why UIRs increased tremendously are the potential positive effects of these relationships on the availability of university research funding, on the speed of technology transfer and on economic development in general (NSF, 1997). Indeed, many studies (e.g., Meyer-Krahmer and Schmoch, 1998; D'Este et al., 2005) showed that access to additional financial resources and to industry skills and facilities, as well as the search of research applicability are among the reasons why university researchers interact with industry. Some authors (Breschi et al., 2007; Fabrizio and Di Minin, 2008; Azoulay et al., 2004) postulate the existence of a *resource effect*: interactions with industry, providing larger cognitive and financial resources, increase the productivity of academic scholars and university institutions in terms of publishing and patenting, thus increasing their visibility, fame and reputation. By this, a self-reinforcing virtuous circle is generated which ultimately boosts research productivity. In particular, sponsorships, licensing and joint research projects, provide a unique balance of financial support, expertise and knowledge exchange which creates a prolific atmosphere for applied research that may result in an increase of patentable outputs by the university compared to basic programs supported by government or by universities themselves. Following this reasoning, we formulate the second hypothesis:

H2 The access to *cognitive* and *financial* resources coming from industry increases university productivity in terms of truly innovative outputs.

2.2 UIRs' effects on the industry

In pharmaceuticals and biotech, basic research plays a fundamental role. Of course, in order to produce commercially meaningful outputs, basic research needs to be matched with adequate applied research. Considering both, the narrowness of resources as well as the limited competences of actors, it is easy to understand that no actor is able to manage the entire research process, from basic to applied research, and to keep pace with the innovation process and the rate of new knowledge production in isolation. Therefore, biotech and pharmaceutical firms specialise in one area of research and in selected parts of the knowledge space, thus, relying on interaction with other actors in order to complete the research process (Arora and Gambardella, 1990, 1994; Powell et al., 1996; Pyka and Saviotti, 2005). A halt to relationships with universities would significantly affect the expansion of companies' knowledge base, with a negative effect on firms' productivity in terms of truly innovative patents and drugs. This holds in particular for DBFs because, due to their limited financial resources, they have to specialise in a narrower part of the

knowledge space (Pyka and Saviotti, 2005) and hence can substantially benefit from interaction with universities. From this the third hypothesis follows:

H3 Interaction with universities increases DBFs' productivity in terms of truly innovative outputs.

2.3 The role of government and the impact of its research funding policies

UIRs in biotech and pharmaceuticals have to be placed in the broader context of the triple-helix system of research (Leydesdorff and Etzkowitz, 1996; Etzkowitz and Leydesdorff, 1997, 2000) which also includes government agencies. In several countries, government plays a crucial role in the biotech and pharmaceuticals' system of innovation, as main funders of academic research. Due to the growing importance of industry as an additional source of funding for universities, the role of public R&D funding with respect to private R&D has increasingly gained attention (see, David et al., 2000). Several econometric analyses (Jaffe, 1989; Adams, 1990; Acs et al., 1991; Toole, 1999a, 1999b), as well as historical case studies (Link and Scott, 1998; National Research Council, 1999) demonstrate that public R&D has positive spillover and stimulating effects on private R&D and beneficial effects on the generation and diffusion of new technologies. In particular, in the case of UIRs, an increase in public research funding for basic research can reduce the pressure on universities to search for external funding from industry, thereby reducing the potential negative effects of these relationships. A brief overview on the historical evolution of UIRs in the USA seems to confirm this hypothesis. Blumenthal (2003) observed that a cut in US Government investments in basic research, as in the mid-1970s, led US universities to increasingly search for industry partnerships. Vice-versa, when public funding was widely available, such as was the case directly after World War II, relationships with industry were considered to be less crucial. Therefore, we believe that government funding policies more favourable to basic research allow for mitigating the potential negative effects on university research orientation caused by interactions with industry. If this hypothesis is proved to be correct, our findings will also confirm the idea of complementarities between public and industry research funding. The hypothesis is formulated as follows:

H4 An increase in government basic research funding prevents the shift of university research direction from basic to applied research.

3 Methodology

To investigate the long-run effects of UIRs on innovative capabilities and to analyse the knowledge dynamics among the involved actors, an agent-based model was developed. The model is characterised by the interactions among different actors which lead to modifications of the agents' knowledge bases. The model allows for tracing the knowledge dynamics for each class of actors as well as their patenting behaviour.

The methodology used is particularly suitable for providing new insights for the costs/benefits debate concerning UIRs. In fact, as Dawid and Fagiolo (2008) pointed out, the fundamental characteristic of agent-based computational models is their ability to explicitly capture "the relationship between structured interaction of heterogeneous individuals and the emerging patterns at the macroeconomic level, and to incorporate

different types of boundedly rational individual behaviour". Furthermore, ABMs allow testing hypotheses that could not be analysed with traditional tools, expanding the range of situations in which we can study a particular problem. For instance, empirical papers cannot study the evolution of a system in situations different from the ones in which it actually developed. Conversely, modelling allows to make experiments, for example eliminating some classes of actors from the population, which are able to provide insights that could not be generate by the solely observation of reality.

Our hypotheses are tested with simulation experiments in which we make use of a standard and various alternative scenarios. Results are then compared and tested for statistical significance. In order to reduce the random component of the results and to increase their trustworthiness, we ran sets of 20 Monte Carlo simulations for 100 periods and then computed the average values for each of the variables under observation. The comparison of the results from different simulation experiments proves a fair level of stability of the model with respect to those parameters that were not modified exogenously.

4 The model

The model is a multi-agent simulation which reproduces R&D and knowledge dynamics in the biotech and pharmaceutical sectors, with a particular focus on the role of UIRs[2]. We draw on a theoretical model of innovation networks originally developed by Gilbert et al. (2001) (see also Pyka et al., 2002). This model is further refined in subsequent works in which it has been applied to study knowledge dynamics between innovation networks' agents (Ahrweiler et al., 2004a, 2004b), to investigate the impact of different learning activities on agents' knowledge stocks (Gilbert et al., 2007), to highlight the persistency of cooperation activities in knowledge intensive industries (Pyka et al., 2007) and to investigate the existence and channels of knowledge spillovers among agents (Pyka et al., 2009). Further works have applied a modified version of the model to study the governance of EU-funded innovation networks (Pyka and Scholz, 2008) and to explore the role of science-technology links for innovation diffusion (Ahrweiler et al., 2011). We extend the original theoretical model to reproduce the innovation system of biotech and pharmaceutical industries, explicitly taking into account different classes of agents moved by diverse aims and rewards (universities, biotech and pharmaceutical firms), multiple channels of interactions (research collaborations, licensing and sponsored research) and different research outputs (three classes of patents and drugs).

4.1 The agents

The model's population is composed of universities (UNIs), LDFs and DBFs. There are two further actors, a National Research Agency (NRA) and venture capitalists (VCs). These latter agents are, however, funding bodies (of universities and biotech firms respectively) which are not actively engaged in research. Agents' research efforts follow different aims. However, a common feature of firms and universities is that they both undertake research and want to produce the 'best' research outcomes.

In particular, universities' main aim is to expand their knowledge and to spread it among society. In order to pursue their mission, they are engaged in research and licensing, which can be seen as the major form of technology transfer. Their research

activities lead universities to get in contact with industry also through joint research projects or by performing sponsored research. Universities can also obtain government research funds by applying for public funding granted by the NRA. In this case, universities set up a research project proposal and send it to the NRA for evaluation. The NRA funding criteria are based on the research direction of the proposal (basic projects are favoured) and on the variance of the capabilities involved. Additional information on these criteria can be found in Appendix A.1.

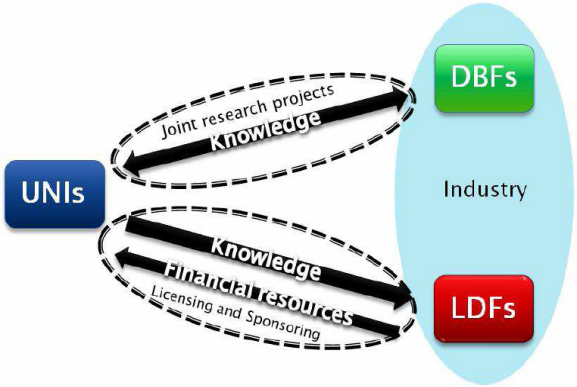
LDFs are actors with a large capital stock and a broad specialisation pattern (as the name suggests). LDFs' aim is to produce as many new drugs as possible, filling up their pipeline. For this reason, besides own research, LDFs intensively screen the market for research, searching for new patents to acquire from other agents through licenses. LDFs also rely on sponsorships of university research as an alternative source of patents.

Finally, DBFs are private actors with a small capital stock compared to LDFs. DBFs are specialised in a small subset of capabilities and abilities, due to the narrowness of their financial resources. In order to survive in the long run, DBFs are forced to apply for venture capitalists' funding. VCs will invest only in those companies who proved to have strong research skills, i.e., in those companies that hold a large cumulated number of patents. Their efforts to produce innovative outputs also induce biotech companies to approach universities, in order to gain access to academic knowledge. Moreover, DBFs are engaged in extensive licensing activities with LDFs, which provide large additional resources that are crucial for their survival.

4.2 University-industry relationships

Interactions among agents lead to the rise of UIRs. In particular, universities interact with DBFs through joint research projects in which knowledge is mutually exchanged. Mixed teams of university and LDF researchers working on a joint research project are unlikely to be observed in reality (Poyago-Theotoky et al., 2002). Therefore, we designed the interaction between universities and LDFs in a twofold way as licensing or sponsoring relations. In both cases, knowledge is transferred from universities to LDFs which reward universities through a corresponding transfer of financial resources. These relationships are depicted in Figure 1.

Figure 1 The design of UIRs in the model (see online version for colours)



If a university research project eventually leads to a patent, the university tries to find a LDF partner in order to grant an exclusive license that increases the university capital stock through periodical royalties. Similarly, through sponsorships universities receive funding from LDFs to perform selected research projects. It is important to note that the cumulated number of patents held by a university plays a crucial role. The more patents a university holds, the easier it is to access industry funding. Indeed, only the most productive universities in terms of patents are eligible for LDF sponsorships. Furthermore, LDFs only sponsor applied research projects (i.e., projects for which the research direction value (RD) is above a certain threshold – see paragraph 4.6 and Appendix A.4). Consequently, universities which obtain a sponsorship shift the research orientation of the sponsored research project in a more applied direction. This is because UNIs know that it could be difficult to receive further funding if they do not prove themselves able to produce a patentable outcome.

In other words, both in the case of licensing and sponsorships, the patent can be considered as a powerful tool that is able to produce the so-called *resource effect* (Breschi et al., 2007). Basically, the patent is a signal of the academic researchers' abilities. A strong signal allows for attracting more funds from industry as well as from the NRA (whose funding allocation criteria favour universities which are engaged in patenting[3]). The increased amount of financial resources allows the receiving university to undertake more research projects, increasing the probability of being able to file new patents and, in turn, increasing university resources.

4.3 The model's dynamics

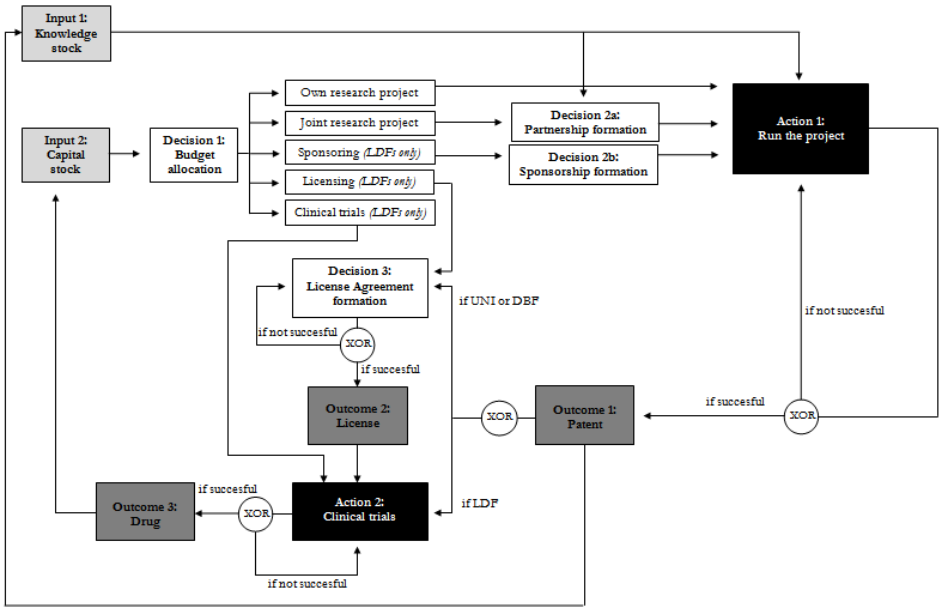
Figure 2 shows the model flowchart. We distinguish between stock inputs (light gray boxes), decisions (white boxes), actions (black boxes) and outcomes (dark grey boxes). Each simulation run consists of several iterations, i.e., cycles of research. A cycle starts with the agent's decision on how to allocate their budget (that is the amount of their capital stock to finance the starting cycle of research). Agents have different options. Universities and DBFs can allocate their budget between own research projects and joint research projects[4]. LDFs can additionally invest part of their budget in sponsoring universities' research projects, acquiring licenses and performing clinical trials. Afterwards, those agents which have decided to undertake a joint research project and/or a partnership move to the process of partnership and/or sponsorship formation, while the others directly jump to the running of the project. Projects last several periods. Agents are allowed to refine their project and run it again if the first attempt is not successful. If the project is successful a patent is granted (outcome 1). If the patent is granted to a university or a DBF, the patent holder searches for possible licensees among LDFs. If a license agreement formation (decision 3) is successful, a license is granted (outcome 2) and the LDF has to pay the associated royalties to the licensor. Alternatively, if the patent is originally granted to a LDF, the firm can directly perform clinical trials (action 2) and try to develop a new drug (outcome 3) to earn revenues from it. Eventually the actors re-invest the money that they have gained at the end of the research cycle (from the license royalties or the sales of the new drug) in new research projects and a new cycle begins.

As Figure 2 shows, agents have to make decisions. In this, they are aided by some decision rules which exhibit some elements of adaptive intelligence (i.e., agents learn from their past decisions). Since the way cooperation and interactions are built is key for

the main hypotheses of the paper, we will focus in the following on the process of budget allocation (§4.4), partnership formation (§4.5) and sponsorship formation (§4.6).

Besides decision rules, agents also follow some rules of the game, which can be grouped based on the three outcomes of our model: how to obtain a patent (§4.9 and §4.10), how to obtain a license and how to obtain a drug. For the sake of simplicity, we will only explain how patents are generated, as our hypotheses and experiments focus on this outcome. We leave the role of licenses and commercialisation of drugs for future work, and hence do not provide further detail concerning these parts of the model in this paper.

Figure 2 The model's flowchart



Finally, it is crucial to notice that knowledge drives the dynamics of our model. Knowledge has multiple roles throughout all the cycle. It directly affects the process of partnership formation (through the characteristics of the knowledge base of the possible partners) and indirectly affects sponsorship formation (through the number of accumulated patents). Furthermore, the knowledge base of the project determines (excluding the influence of random events) whether the project is successful or not. We provide details about the knowledge base of the agents in sub-Section 4.7, on how knowledge is upgraded through research in paragraph 4.8 and on the process of patent generation in sub-Sections 4.9 and 4.10.

4.4 Budget allocation

Agents have to decide

1 how much to invest each period

2 how to allocate their budget among the different activities.

It is evident that no actor can invest his whole capital stock in only one period, so agents have to decide the amount of their *periodic budget*. This decision is initially set randomly within the range 10%–30% of their capital stock. In the following periods the actors follow a process of adjustment of the size of their investment budget which is based on market feedbacks. If they are successful (i.e., between the top 20% of their sector ranking – UNIs, LDFs or DBFs) they will maintain the same amount of investments in the next period, otherwise they will increase their periodic budget by 10%.

Once a periodic budget has been set, actors have to choose how to allocate it through the different options. First, budget allocation must respect a constraint which refers to the maximum number of projects per period that an actor is able to sustain. This number depends on the size of the actor (we use the size of the capital stock as a proxy). The larger the capital stock that an actor has, the larger number of projects per period they are able to undertake.

The *budget allocation process* is slightly different between firms and universities. For firms, initially the periodic budget is split among the different activities ('own research', 'joint research', 'sponsoring', 'licensing' and 'clinical trials' for LDFs; 'own research' and 'joint research' alone for DBFs) through a random process. Then a particular market feedback mechanism is implemented. This mechanism follows Simon's principle of *satisficing behaviour* (Simon, 1956), rather than optimising behaviour, as applied by Nelson and Winter (1982) in their evolutionary model of firms' behaviour. Periodically each firm (both LDFs and DBFs) compares its allocation strategy with the average allocation of the most successful firms (top 15%) of its own sector in terms of annual profits (total annual earnings of new drugs + total annual royalties of the licensing activity – total annual research costs). If the firm is successful (i.e., it is within the top 15%) it does not change its allocation strategy. If the firm is not successful it will modify its strategy as follows. The activity for which the average allocation strategy of the most successful firms is highest, will receive 10% more of the budget in the next period. The 10% increase will be financed by a corresponding 10% reduction of resources allocated to the other activities.

Universities apply a similar budget allocation process to firms except for two important differences. First, UNIs are only engaged (as DBFs) in own and joint research projects. Second, the budget allocation process does not really decide how much of the universities' capital is invested in own research or in joint research. In fact, through the same comparative process with the most successful universities (in terms of patents held), a certain university decides how many projects to undertake on their own and how many to undertake jointly with other actors; but this does not necessarily imply that the project will be financed with university's own capital. In fact, universities first try to get their projects funded by the NRA, then through a LDF's sponsorship and only if they are not successful with these two possibilities they will finance research projects with their own capital.

4.5 Partnership formation

When an agent decides to enter in a partnership with one or more other agents in order to undertake a joint research project, she applies a particular partnership strategy in order to select the 'right' counterpart. Two partnership strategies exist:

1 a *conservative strategy* in which the actor looks for a similar partner according to its knowledge base

2 a *progressive strategy* in which the actor looks for a dissimilar partner.

The actors that choose the former aim to undertake an incremental research project, therefore they prefer less risk and a common understanding. In this case the variance between the knowledge bases of the partners is small, which increases the probability of success but on the other hand reduces the potential magnitude of the project outcome (see sub-Section 4.9). Actors that, on the other hand, choose to follow a progressive strategy aim to undertake a radical research project. In this case the variance between the knowledge bases is high, with a positive effect on the potential innovativeness of the project outcome but with a negative effect on the probability of success. Hence, the decision rule in the model is grounded on the different aims of the agents and on a mechanism based on similarities and complementarities with respect to the agent's knowledge base. This rule of selection is supported by recent literature on partner selection in innovation networks (Balconi et al., 2009).

It is also important to add that, regardless of the partnership strategy, in all cases agents first look for partners among the list of agents with which they had a successful cooperation in the past. If there are no agents satisfying the requirements of the chosen partnership strategy then they extend the search to the other agents. This reflects the aim to increase the probability of success of the partnership and is in line with well documented evidence that accumulated network resources arising from firm participation in the network of prior alliances are influential in firms' decisions to enter into new alliances (Gulati, 1995, 1999).

4.6 Sponsorship formation

The sponsorship procedure is introduced in Table 1. The first step is the creation of two rankings. In the first one, LDFs are ranked according to their sponsorship budget. In the second one all UNIs who have projects that have not been sponsored by the NRA are ranked according to their cumulate number of patents. Then, a matching procedure starts. The first university of the ranking gets the sponsorship from the first LDF that has enough remaining sponsorship budget to finance the research project (all the UNIs' research projects have equal cost, which is exogenously fixed).

Table 1 The sponsorship mechanism

Private agent	*Sponsorship budget*	*Remaining sponsorship budget*	*Who will the sponsor be?*		*Public agent*	*Cumulate patents*	*Project cost*
LDF_1	20	0	**X**		**UNI_1**	**10**	**5**
LDF_2	15	0	**X**		UNI_2	6	5
LDF_3	10	5	√	←	UNI_3	3	5
…					…		
LDF_N	5	5			UNI_M	0	5

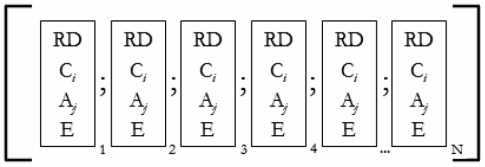
It is important to notice that the accumulated number of patents held by a university, as well as the size of the LDF's sponsorship budget play a crucial role. The more patents a

university holds, the easier it is to access industry funding. This is one of the different ways in which the so-called resource effect is implemented in the model. Of course, the largest firms in terms of sponsorship budget are able to get in contact with the best universities (the high number of accumulated patents is considered evidence of the research competencies of the agent). Another important aspect of sponsorship is the size of LDFs' sponsorship budget. If a LDF wants to increase the probability of sponsoring a successful university, it has to increase its sponsorship budget, which on the other hand leads to a reduction in the funds that the budget sets apart for the other activities. This choice can be considered profitable by the LDFs only if the probability that the sponsored university will develop a patent (whose intellectual property, under the sponsorship agreement, is held by the sponsor LDF) is high. For this reason, LDFs sponsor applied research projects rather than basic research projects. Furthermore, those universities that obtain a sponsorship will shift the research directions of part (2/3) of their innovation hypotheses' quadruples toward a more-applied direction during the running of the sponsored project. This is due to the fact that UNIs know that it could be difficult to obtain sponsorships in the future if they do not prove themselves able to produce a patentable outcome.

4.7 The agent's knowledge base

The model's representation of the agents' knowledge builds on the concept of 'kene' developed by Gilbert (1997) and applied in previous simulations of knowledge dynamics in innovation networks (Gilbert et al., 2001, 2007; Pyka et al., 2002, 2007, 2009; Ahrweiler et al., 2004a, 2004b). In the model we used the notion of kene, the knowledge base of an agent, as it has been developed further by Pyka and Scholz (2008). In this version, *kene* elements also include the research orientation of the actors. Figure 3 shows the concept of *kene* graphically.

Figure 3 The *kene* concept



The knowledge base of each agent consists of a vector containing different 'units of knowledge' consists of a vector containing different 'units of knowledge' between universities (mainly engaged in basic research) and firms (mainly engaged in applied research), a capability (C) which stands for the particular technological discipline in which actors are engaged (pharmaceutical or biotechnology), an ability (A) which reveals the actor's specialisation in his/her capability field and an experience level (E) which shows for how long an agent has been active in a certain ability. The research direction is represented by an integer. It can take values from 0 (pure basic research) to 9 (pure applied research). In the model biotechnology covers the array of capabilities from 1 to 60, whereas the range from 61 to 100 stands for pharmaceutical capabilities. The range of abilities, instead, spans from 1 to 10. Finally, the experience level depends on the use of knowledge in research projects: if the knowledge is applied in a certain research project

(individually or jointly with other actors) the experience level of the respective actor's kenes increases by 1 each period; if the knowledge is not used, the experience level reduces each period, if it reaches 0 the respective knowledge is forgotten. The initial distribution of the kene variables for the different agents is provided in Appendix A.5.

4.8 Learning and cooperation

The actors choose whether to conduct research on their own, to collaborate with other actors or both, according to the budget allocation explained in sub-Section 4.4. As in Gilbert et al. (2001) (see also Gilbert et al., 2007; Pyka et al., 2002, 2007, 2009; Ahrweiler et al., 2004a, 2004b) the process of own and collaborative research endeavours is based on the combination of selected elements of agent's knowledge base which form so-called innovation hypotheses (IH).

When agents choose to undertake research on their own they focus on some selected research interests which are designed as a subset of their kenes. Project innovation hypotheses are periodically derived from these research activities. Once the project is completed, the experience level of the abilities involved in the IH are increased by 1 while the experience level of those quadruples of the kenes that are not involved in the IH are reduced by 1. This represents learning by doing and forgetting.

In the case of joint research, the project knowledge base is a combination of parts of the knowledge bases of the involved agents. Some quadruples of the agents' kenes are randomly recombined to form a project innovation hypothesis. If the project is successful, the actors with an absorptive capacity (Cohen and Levinthal, 1990)[5] above a critical threshold acquire the knowledge of the joint innovation hypothesis which has been contributed by the project partner(s) with a reduced experience level.

4.9 Transforming knowledge inputs into project outcomes

Whether a research project is successful or not and which outcome is eventually produced is decided by two equations which determine the 'value of success' and 'probability of success'. The former decides on the type of potential outcomes, the latter decides if the outcome is actually generated or not. These two equations are different for own and joint research projects. Furthermore, joint research projects are evaluated in two different ways following the partnerships strategy that actors have applied. This way, we are able to consider different aims which drive the partnership. A detailed description of these formulas can be found in the appendix.

Basically the 'value of success' and the 'probability of success' functions are based on four variables:

1 the *knowledge distance* among the IH's quadruples, used as a measure of heterogeneity of the knowledge applied in the project

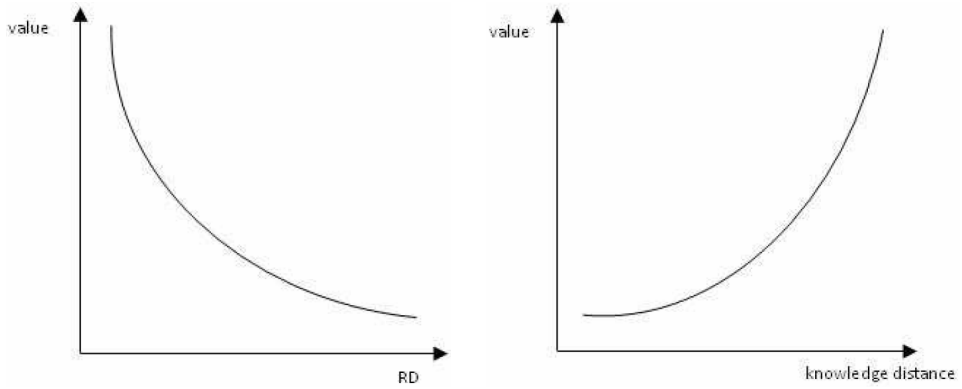
2 a *research direction factor*, which accounts for the IH's quadruples average research direction

3 the *experience* of the actor(s)

4 a so-called *technical factor* (only for own research projects), which take into consideration the quality of the physical capital available to the project runner.

The 'value of success' is affected by the research orientation of the agents and by the heterogeneity of knowledge. A basic research direction increases the potential magnitude of the innovation. This is due to the fact that it is mandatory to deeply understand the causes and effects of a disease in order to discover a new molecular entity which produces a significant improvement in the treatment (as will be explained in the next subsection, this is how we define the most innovative patents). Therefore such a result is more likely to be achieved by an actor whose research focus is the study of the disease, i.e., by an actor who is predominantly engaged in basic research. On the other hand, an applied research direction reduces the potential magnitude of the innovation. In fact, in this context, for an agent who is engaged only in applied research it is harder to generate an output with a very high innovative potential. As argued by Angell (2004), the discovery of a new application for an already known molecule, or minor modifications of an already existing drug are more likely outcomes. The 'value of success' also depends on the variance in the capabilities involved: the higher (the lower) the variance, the higher (the lower) the potential magnitude of the innovation. The underlying idea is that the potential novelty is higher if many different capabilities are involved, as discussed by Nooteboom et al. (2007) and Wuyts et al. (2005). The effects of the research orientation and of the heterogeneity of knowledge in terms of capabilities on the value of success are shown in Figure 4.

Figure 4 The relation between the 'value of success' and the kene-related variables

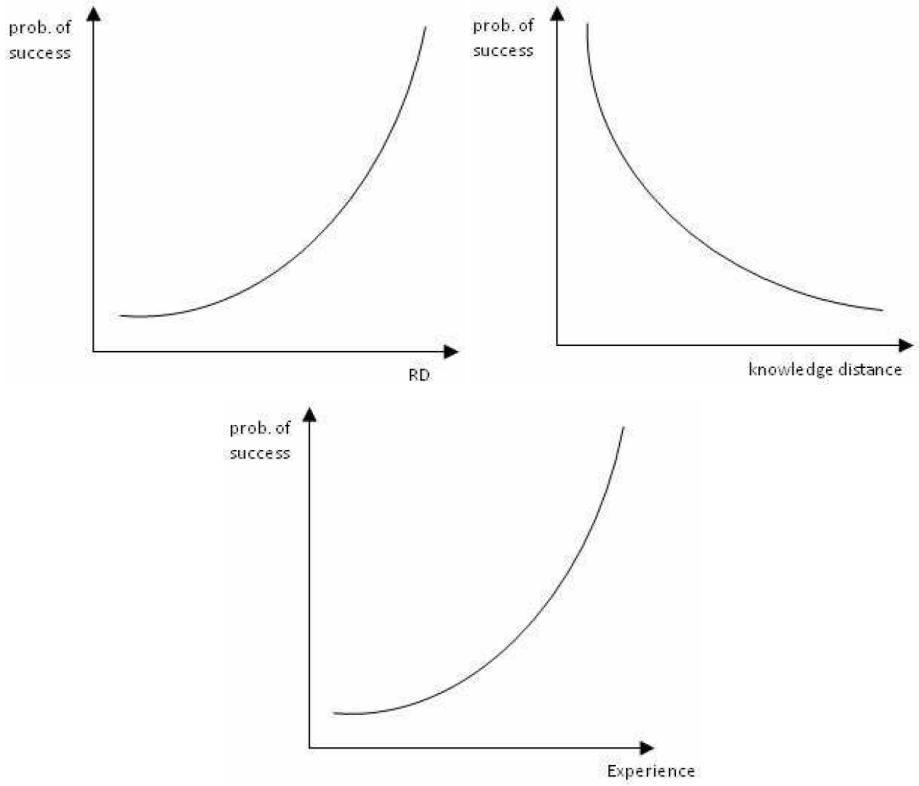


The relation between the 'probability of success' and the kene-related variables 'research direction', 'knowledge distance' and 'experience' are graphically depicted in Figure 5.

The 'value of success' function predicts which kind of innovations can be potentially generated. Whether this innovation is actually successfully generated or not, is decided by the 'probability of success' equation. This equation depends on the same variables as the 'value of success' but in an opposite way. A basic research direction decreases the possibilities of a project being successful (i.e., to end up with a patent). The same holds for a high maximum distance between the kene elements of the project's innovation hypothesis, which is used as a proxy for the heterogeneity of involved capabilities and abilities. This definition of the probability of success reflects two difficulties: Basic research is truly uncertain by definition, therefore an applied research direction provides a higher probability of ending up with concrete results than a basic research one does. The other obstacle on the road to success depends on the difficulties combining

heterogeneous knowledge in a single project. This surely increases the novelty of a potential outcome but, at the same time, reduces the possibility of achieving the desired result[6]. Finally, the 'probability of success' is also influenced by the experience level of the actors, which obviously positively affects the likelihood of generating a patent. The experience level does not affect the 'value of success' because the novelty value of a project can be high even if the participants are not experts. Indeed new comers are keener to think out-of-the-box and to overcome what the literature calls *learning traps* (Levinthall and March, 1993, see also Christensen, 1997) which are due to a certain rigidity of thinking coming from overembeddedness in a particular field and path dependency of the learning process. On the other hand, experienced agents can also contribute much to the novelty of a project due to their larger endowment of knowledge. Hence the experience level has no direct impact on the value of success but rather a strong influence on the probability of success.

Figure 5 The relation between the 'probability of success' and the kene-related variables



4.10 Research outcomes

In this work we focus on a single research outcome: patents. Although in the 'real world' universities are obviously widely engaged in publishing, tracing the publication activities is beyond the scope of our model. However, patents are not a uniform category. Even if they are identical from a legal point of view, huge differences exist with respect to their

economic value. In the case of drugs, the differences are related to the newness of the related molecule and to the effectiveness of the treatment. In the model we distinguish between three kinds of patents (from the most to the least innovative):

1 A-class patent

2 B-class patent

3 C-class patent.

We define our three patent classes drawing on the US Food and Drug Administration (FDA) classification of new drugs as introduced in Angell (2004). The FDA is the US federal agency which decides whether a new drug can be commercialised or not. Once the FDA receives the request for commercialisation based on a certain patent, the agency classifies the potential drug (thus, implicitly, the related patent too) according to two criteria:

1 the newness of the molecular entity

2 the improvement in the treatment of the particular disease.

The drug can be characterised by a molecular entity which is completely new (in this case the drug is assigned with a '1') or already discovered in the past (in this case FDA assigns the drug with a '0'). Moreover the new drug can provide a significant improvement in the treatment (in this case FDA proceeds with a privileged analysis – 'P') or a similar treatment as an old drug (in this case the agency proceeds with a standard analysis – 'S'). It is important to notice that the discovery of a new molecular entity does not necessarily imply that the related drug provides a significant improvement in the treatment. On the other hand, a molecular entity already discovered in the past could be successfully used to treat another disease. For these reasons we propose the following patent classification:

- A-class patent: combination (1)-(P)
- B-class patent: combinations (0)-(P) and (1)-(S)
- C-class patent: combination (0)-(S).

In our view only the combination (1)-(P) deserves to be labelled as a truly innovative patent (A class) because it is both *new-to-the-world* and meaningful for the final users. Combinations (0)-(P) and (1)-(S) can be considered having a semi-innovative value because they lack one of the two characteristics of truly innovative patents. Finally, combination (0)-(S) is surely the least innovative, since it is little more than an imitation (so-called me-too drugs and generics) of an already existing drug which, moreover, does not provide any significant improvement in the treatment. Table 2 shows the 'value of success' thresholds which generate the different patents. The calibration of these values has been carried out relying on empirical evidence on the classification of 'real-world' production of drugs (see Appendix A.6) combined with insights gained through a sensitivity analysis of the model itself. As can be noticed from the table, a research project is not successful if it does not generate a value larger than 0.5. One can interpret this as a threshold below which a research project may produce publications or working papers (which we do not take into consideration in the model) without being able to generate any patentable outcome.

Table 2 'Value of success' and patent classes

$0.5 \leq v < 0.63$	$v = C$
$0.63 \leq v < 0.71$	$v = B$
$0.71 \leq v$	$v = A$

As explained in sub-Section 4.9, the probability to generate A-class patents is not the same for all actors. Besides the element of luck element (the random components of the equations – see Appendices A.2 and A.3), necessary conditions in order to discover a new molecular entity which is also effective are: a fairly basic research orientation, a sufficiently high variance of the capabilities involved and a good level of experience.

5 Results

For testing the hypotheses introduced in Section 2, we first develop a standard scenario. In the following steps, we run different experiments with alternative scenarios for each hypothesis and compare the results with the standard scenario.

5.1 UIRs' effects on universities

The first hypothesis postulates that university relationships with industry, which are reproduced in the model through joint research projects, sponsorships and licensing, cause a shift of university research orientation from basic to applied. To test this effect of UIRs, we compare the results in terms of university average RD (for both the kenes and the current research interests quadruples) from the standard scenario with those generated by a scenario whose population is composed solely of universities. Figure 6 shows the comparison of the UNIs' RD mean values in the different scenarios.

Figure 6 Scenario comparison (see online version for colours)

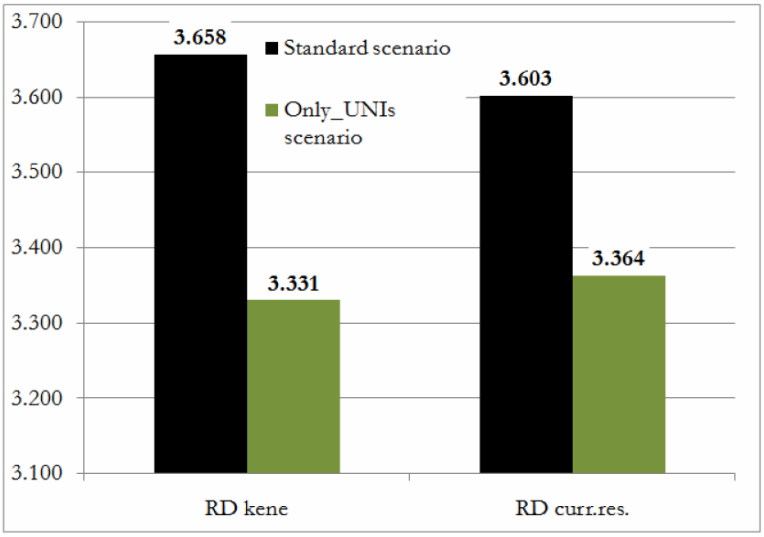
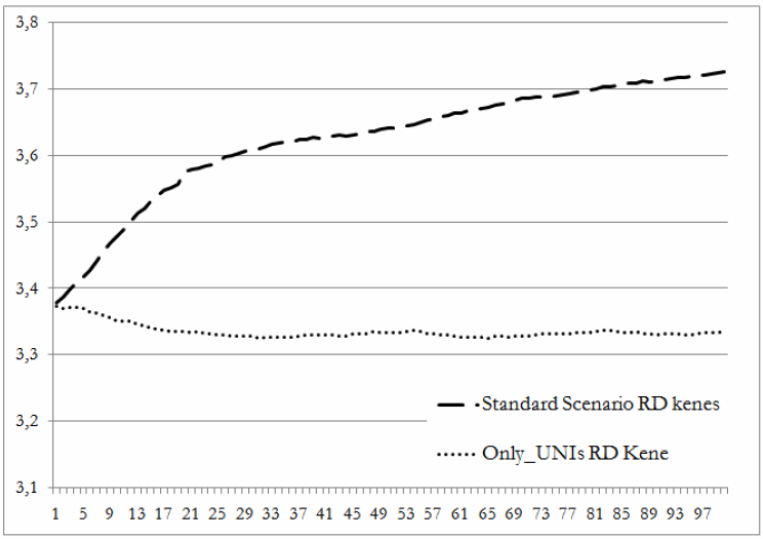
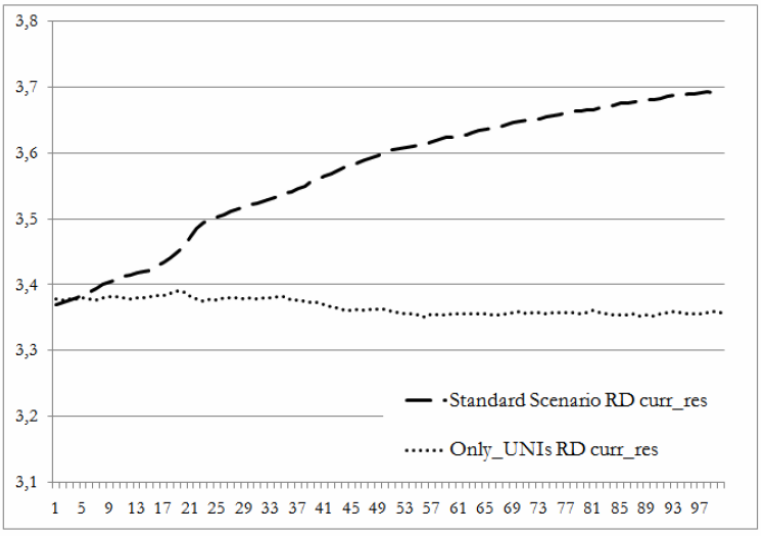


Figure 7 Differences in the evolution of the average research direction between the standard scenario and the 'only UNIs' scenario, (a) kene (b) current research



(a)



(b)

The t-test confirms the statistical significance of the differences in the mean values ($p < 0.001$). Accordingly, the presence of university interactions with industry increases the university focus on applied research. In particular, the average research direction of the kene elements increases by 8.93%, whereas the current research orientation increases by 7.12%. Additionally, the standard deviation for the mean values of the university research direction is higher in the standard scenario than in the 'only UNIs' case (0.09 vs. 0.008 for the kenes and 0.105 vs. 0.005 for the current research). This confirms that the interaction with industry increases the heterogeneity of universities' knowledge bases and

research interests. In Section 4.9, we argued that this has a positive effect on the magnitude of the university research outcomes, though contrasted by an increase of the RD factor, but, on the other hand, also reduces the probability of success (this issue will be considered below).

Furthermore, the differences in the evolution of the average research direction between the standard scenario and the 'only UNIs' scenario, shown in Figure 7, demonstrates that the average university RD is not only higher in the case of interaction with industry but also continuously increasing, whereas in the 'only UNIs' scenario the university research orientation stays almost constant. Therefore, these findings fully confirm H2.

The second hypothesis deals with the potential positive effects that interaction with industry generates for universities in terms of a higher access to cognitive (i.e., higher degree of knowledge heterogeneity) and financial (i.e., larger capital stock) resources. In particular, the third hypothesis can be split in two parts. First, according to H2, joint research projects with DBFs are expected to increase the heterogeneity of universities' knowledge bases due to the underlying knowledge exchange processes. A larger innovativeness of university research outputs is expected if the positive effect on the 'value of success' stemming from an increase in the variance of universities' knowledge is stronger than the negative effects caused by the decrease of the RD factor (due to a shift to more-applied research, as confirmed by H1) and by a reduced probability of success. To test this first part of H2 related to the increase in university cognitive resources, we compare the standard scenario with the results of a scenario in which DBFs are excluded from the population. The second part of H2 claims that university patenting benefits from the availability of extra financial resources coming from LDFs' research sponsorships and from license agreements. To test this aspect of H2, we compare the standard scenario with an alternative scenario in which LDFs are excluded from the population.

The results from the comparisons between the standard and the 'without DBFs' scenarios are shown in Figure 8. The differences in the percentages of A-B-C classes between the two scenarios are statistically significant ($p < 0.005$).

The results suggest a rejection of the first part of H2. The 'without DBFs' scenario generates better results in terms of the percentage of university A and B-class patents compared to the standard scenario. Accordingly, university productivity in terms of truly innovative patents is negatively affected by extensive interactions with DBFs. Furthermore, this test of H2 has revealed another important aspect: As shown in Figure 9 joint research projects with DBFs reduce the total number of patents produced by universities for each class.

This finding is in line with the insights provided by the tests of H1. As explained above, the knowledge exchange between UNIs and DBFs leads to an increase in the heterogeneity of the university knowledge base, due to a higher variance of university capabilities and abilities, but these positive effects on the ´value of success´ seem to be overcompensated by the negative effects given by the decrease of the research direction factor, the increase in the knowledge distance and the decrease in the experience level, which reduce the probability as well as the value of success (see Section 4.9).

Figure 8 Scenario comparison in terms of relative number of A-B-C patents (see online version for colours)

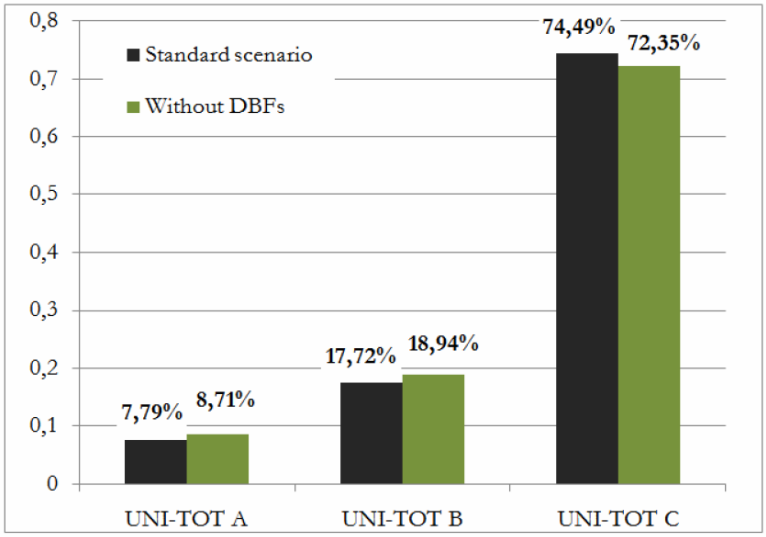
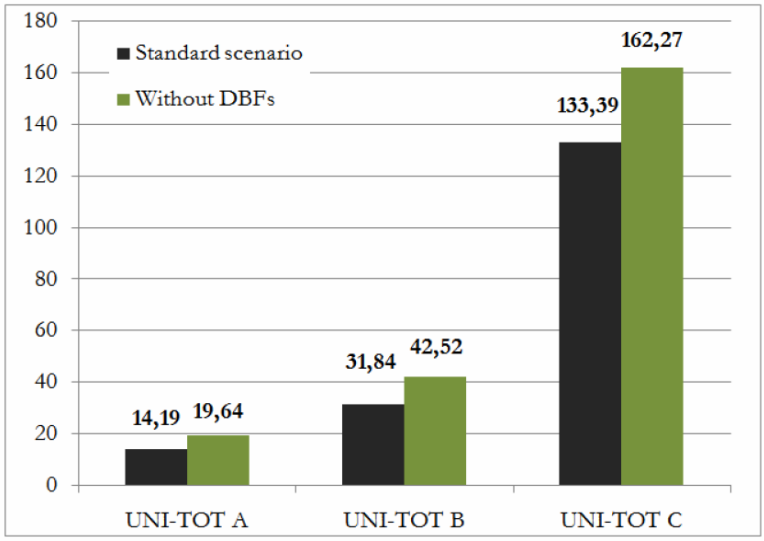
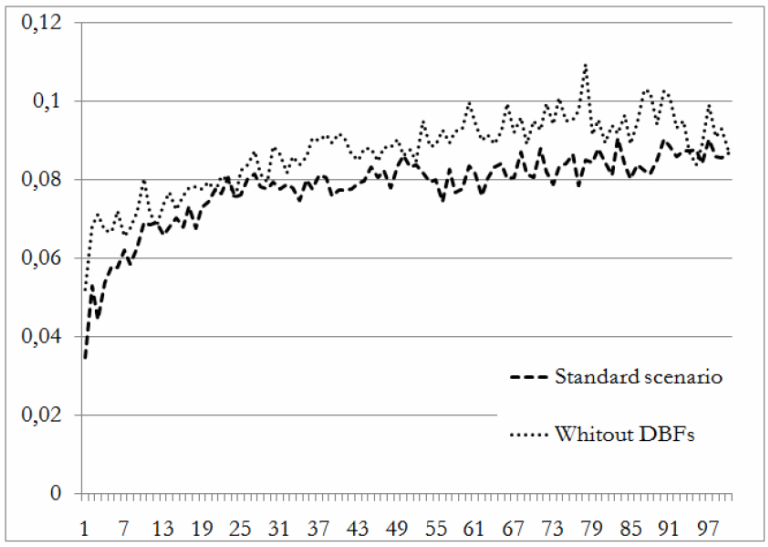


Figure 9 Scenario comparison concerning the total number of A-B-C patents (see online version for colours)



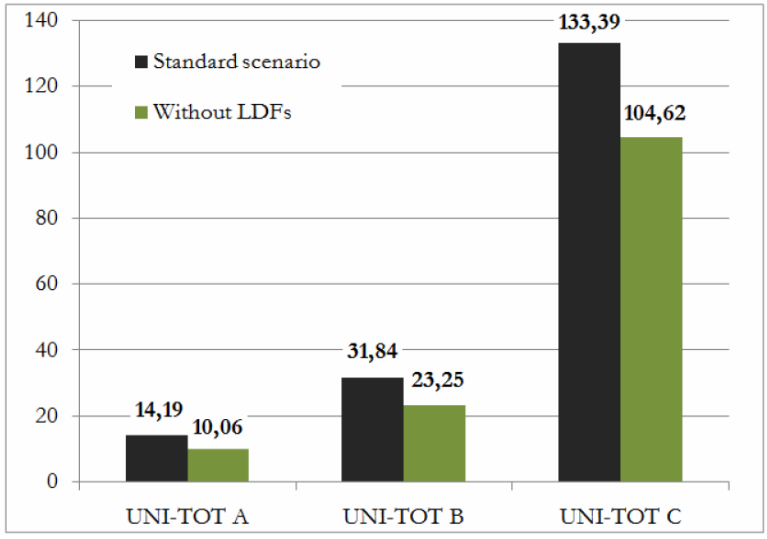
The comparison between the evolution of the relative production of A-class patents in the two scenarios, which is shown in Figure 10, further confirms the rejection of the first sub-part of H3.

Figure 10 The evolution of the relative production of A-class university patents in the two scenarios



The second sub-part of H3 is partially rejected as well. The differences in the relative number of AB-C university patents between the 'without LDFs' scenario and the standard scenario, are not statistically significant ($p > 0.005$). Nevertheless, the difference in the total number of university patents generated by the two simulations was proven to be significant ($p < 0.05$). In particular, as Figure 11 shows, the total number of A-B-C university patents is always higher in the standard scenario than in the 'without LDFs' one.

Figure 11 Scenario comparison in terms of total number of A-B-C patents (see online version for colours)



The exclusion of the possibility for universities to rely on sponsorships and on licensing revenues, reduces significantly the number of projects that universities are able to undertake, thus, generally reducing the number of patentable research outputs. Therefore, a financial resource effect seems to emerge, but this has a general influence on the number of university patents without specifically affecting the most innovative ones. On the one hand, this is due to the fact that there is no direct knowledge exchange between universities and LDFs, hence the 'value of success' is not directly affected by this interaction. On the other hand, as we have explained in sub-Section 4.6, sponsorships provide incentives to universities to shift their research direction, hence the relative number of A-class patents should decrease. Our results suggest that the former effect is stronger than the latter. In other words partnerships with LDFs increase universities' capital stocks, leaving their knowledge stock substantially unchanged. The larger availability of financial resources allows universities to increase the number of projects that can be undertaken, thus, increasing the total number of patentable outcomes.

5.2 UIRs' effect on industry

The third hypothesis focuses on the industry side of the relationship. In particular a positive influence of UIRs on DBFs' knowledge base and patent production is hypothesised. To test this hypothesis we compare the results coming from an alternative scenario in which universities were excluded from the population (thus, impeding interactions with DBFs) with the results of the standard scenario.

The difference in the percentages is statistically significant ($p < 0.005$). DBFs widely benefit from knowledge exchange with universities. The percentage of A and B-class patents generated by DBFs own research and in cooperation with other DBFs in the standard scenario is about 4.6% higher than in the 'without UNIs' scenario (see Figure 12). The same results hold for the total number of A and B-class patents (see Figure 13). These findings confirm H3 and show that interactions with universities in terms of two-way knowledge exchanges sharply increase DBFs' innovative potential.

Figure 12 Scenario comparison in terms of relative number of A-B-C patents (see online version for colours)

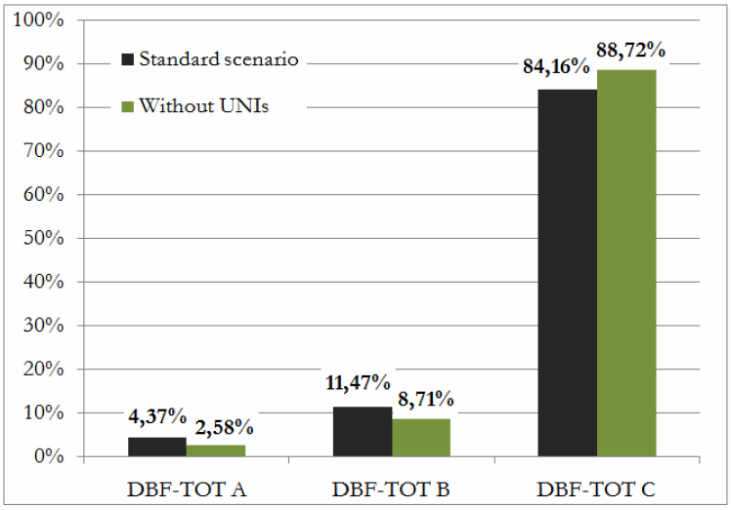
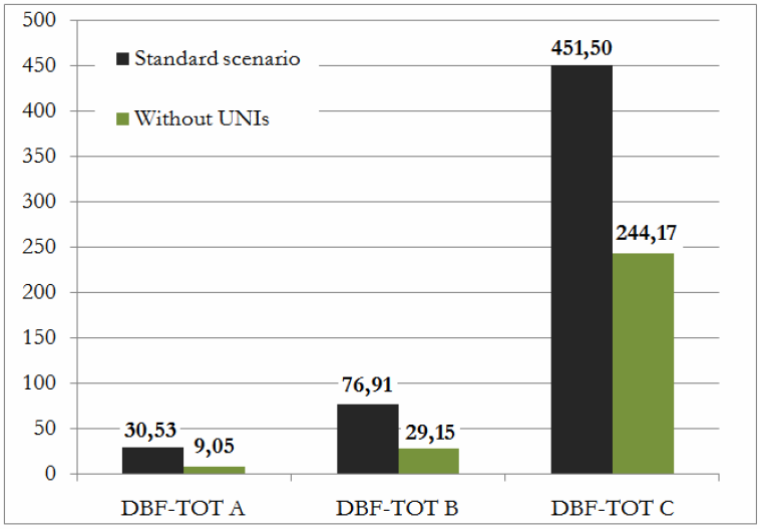
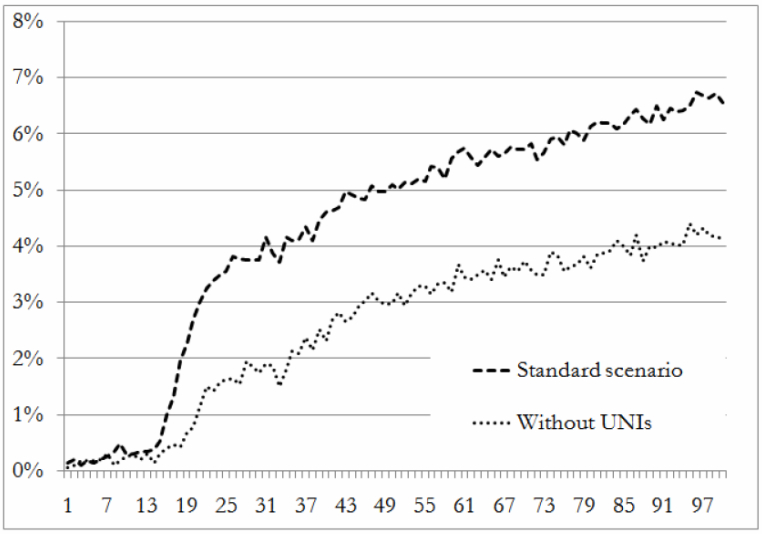


Figure 13 Scenario comparison in terms of total number of A-B-C patents (see online version for colours)



Finally, Figure 14 shows the evolution of the relative production of A-class patents by DBFs in the two scenarios.

Figure 14 The evolution of the relative production of A-class patents by DBFs in the two scenarios



Until about period 15, the percentages of DBFs' A-class patents are very similar. The first periods are usually considered as an initial adjustment time of the simulation in

which actors increase their experience and build their network of collaborators. The following surge in A-class patents in the standard scenario is interpreted as a signal that once DBFs have developed an adequate experience in collaboration, interactions with universities start to achieve their true potential on the industry side. In fact, DBFs, thanks to their high experience level, are able to apply the new kene elements, gained through joint research projects with universities and characterised by a basic research orientation, in their own innovation hypothesis in more fruitful and productive ways. As the figure shows, after the adjustment time, the trend of DBFs' A-class patents is constantly about two percentage points higher in the standard scenario than in the 'without UNIs' scenario.

5.3 The government's role and the impact of research funding policies

The test of the first two hypotheses shows that UIRs negatively affect university research orientation. The fourth hypothesis theorises that government funding policies more favourable to basic research (through a larger public funding budget) might be able to prevent this shift. We test this hypothesis by comparing the standard scenario with three alternative scenarios in which NRA's funding policies were progressively shifted toward a larger basic research funding budget and a reduction of the RD threshold to be eligible for NRA's funds (MAX_NRA_rd5/4/3). As no further changes are implemented in the alternative scenarios, the impact of relationships with industry on universities' research direction and patent production is exactly the same as in the standard scenario. A comparison of the scenarios in terms of mean values of the average university research direction and of the relative number of A-B-C patents are shown in Figures 15 and 16, respectively.

Figure 15 Scenario comparison in terms of average RD

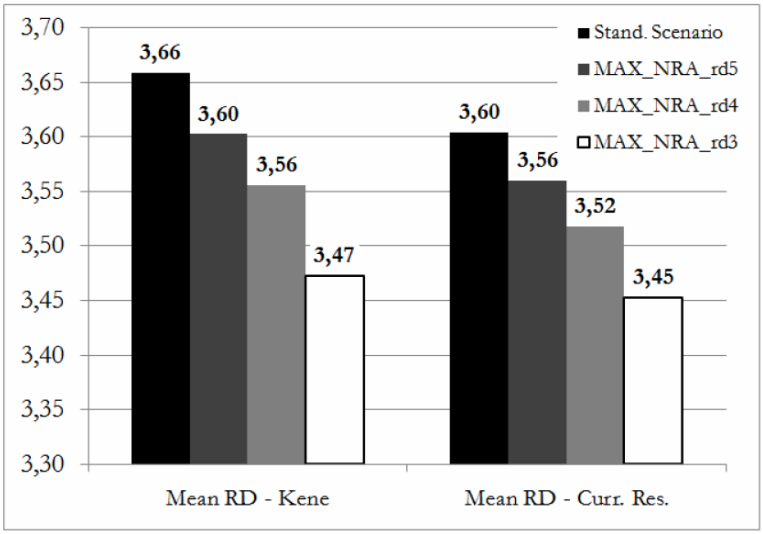
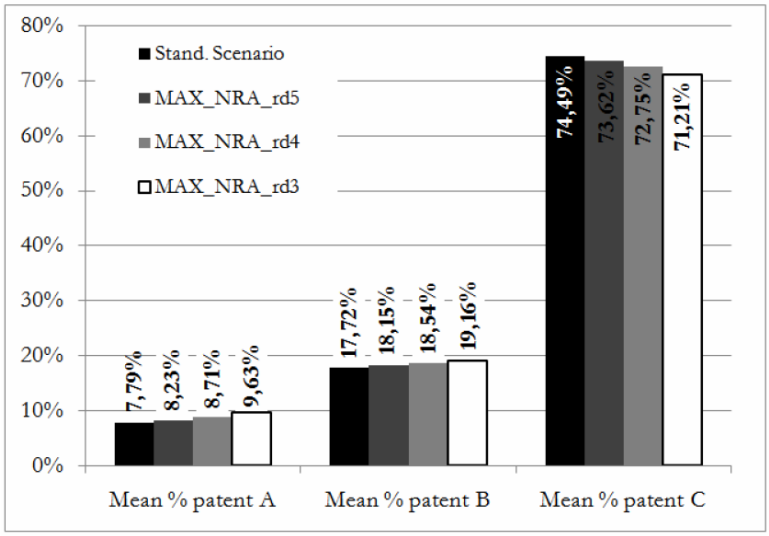


Figure 16 Scenario comparison in terms of relative number of A-B-C patents



The differences between the RD (Figure 15) and patents variables (Figure 16) among the different scenarios (statistically significant at the 1% level) confirm H4. An increase in government basic research funding prevents the shift of university research orientation from basic to applied research. This also causes an increase in the relative number of A and B-class patents which academic research is able to generate. It is important to notice that even a small reduction in the mean value of RD leads to a considerable increase in the percentage of A and B-class patents. Between the standard scenario and the most favourable scenario for basic research funds (MAX_NRA_rd3) the mean value of the average RD is reduced by 0.19 which, nevertheless, leads to an increase of about 3% in the relative number of A and B class patents.

Figures 17 and 18 illustrate the comparison of the evolution of the average university RD for both kenes and current research among the alternative scenarios.

The figures visually support what the analysis of the mean values in Figure 15 suggests. An increase in the government research funding budget avoids a shift of universities towards more applied research, thus, increasing the relative number of truly innovative patents. Therefore, hypothesis 4 is confirmed by the results.

6 Discussion and conclusions

Today innovation activities are undertaken in extremely complex systems which are characterised by heterogeneous actors, multi-dimensional interactions and multiple knowledge flows. This increasing complexity is creating new challenges for scholars. In order to understand multifaceted phenomena such as UIRs, and to capture their overall, global effect, it is no longer possible to solely rely on traditional methods of analysis. The application of the agent-based simulation methodology allows for analysing and generating new insights of such complex phenomena.

Figure 17 Scenario comparison in terms of evolution of the average RD – kenes

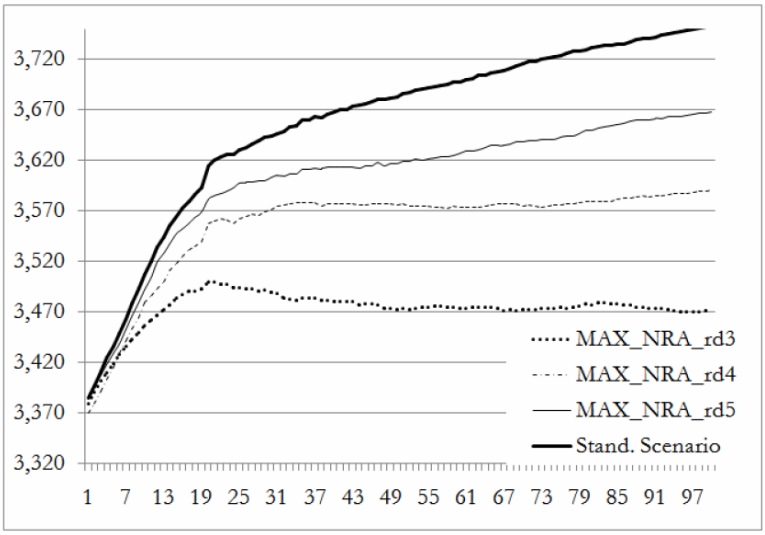
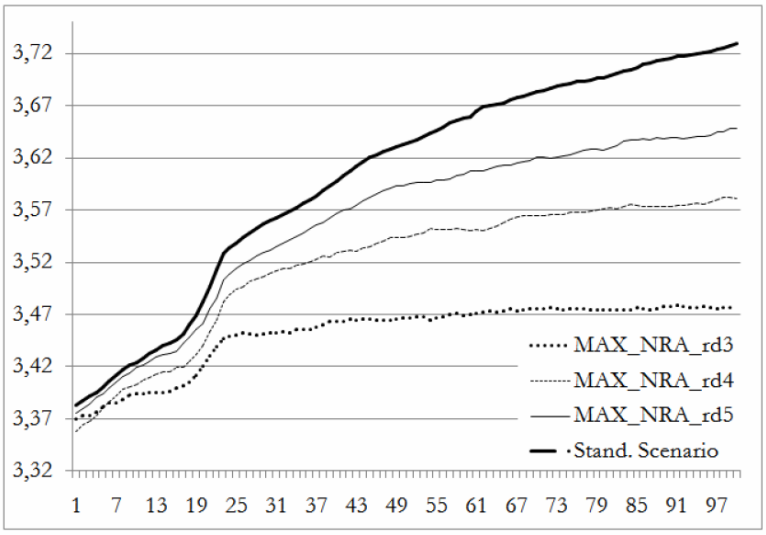


Figure 18 Scenario comparison in terms of evolution of the average RD – current research



First, according to our simulation experiments, relationships with industry modify the reward and incentive schemes for universities, as Stephan (1996) and Nelson (1959) argued, thus affecting the research orientation of universities (H1). In order to generate highly innovative pharmaceutical solutions, a strong understanding of scientific knowledge is necessary. Therefore, universities have to keep a basic research direction, alongside more applied-oriented joint research projects with industry. The 'traditional' division of scientific labour (universities engaged in basic research and industry devoted to applied research) should not be radically broken. Besides interacting with each other and building a mutual understanding, university and industry should still keep their own

identities. Otherwise, we may face an unpleasant slowdown in the growth of scientific knowledge and in the improvement of the treatments of known and less-known diseases, which can only be realised through the development of new innovative drugs, for which truly innovative patents are a crucial input.

Second, our experiments reject the hypothesis of a positive influence of a cognitive resource effect on university innovative patents productivity and partially reduce the influence of the financial resource effect (H2). Nevertheless, knowledge exchange processes are still a crucial characteristic of UIRs. Intensive interactions between universities and DBFs do not produce an increase in universities' innovative capabilities. Instead, they reduce the total number of patents coming from academic research. The reduction of the amount of university patents that is observed when universities interact with DBFs (H2) and consequently shift to applied research (H1), is due to the fact that when the average research orientation becomes more applied. This is because there are fewer universities that are eligible for NRA research funding, because the research projects of many universities in this case no longer fulfil the agency's requirements concerning the basic research orientation. Consequently there is a reduction of patents stemming from NRA-funded projects which generates a vicious circle. A decrease in the amount of patents affects the reputation of universities in terms of their research productivity, decreasing the flow of industry funds generated by sponsorships, thus, further reducing the number of university patents.

Even if universities do not take advantage, from a cognitive point of view, of interactions with DBFs, this does not mean that the relevance of these partnerships for universities should be disregarded. Joint research projects between universities and biotech firms allow for an exchange of the successful innovation hypotheses' quadruples. The newly acquired capabilities and abilities expand university knowledge bases, thereby increasing heterogeneity, yet this is not sufficient for increasing universities' patent productivity. Universities also need to be able to effectively combine the new knowledge in their research projects. As Ahrweiler et al. (2011) explain, the relation between knowledge inputs and technology outputs is not linear. Different actors follow different scientific and technological trajectories, and for universities, as for any other actor, there is no guaranteed success. For instance, many universities might very simply not have the right skills for dealing with applied research. As we show in Section 4.9, the probability of success positively depends on the average experience level of the innovation hypothesis and negatively on the heterogeneity of the knowledge base. The capabilities and abilities which biotech firms transfer to universities when they work together are related to an applied research orientation. On the one hand, this increases the heterogeneity of the university knowledge base, augmenting the potential magnitude of the research outcomes. On the other hand, universities are not experienced[7] enough to successfully deal with these new capabilities. This dynamic is confirmed by the insights provided by the test of the second hypothesis, which shows that new knowledge acquired from interactions with DBFs is not effectively applied by universities.

Our findings also show that when a complex phenomenon like UIRs involving heterogeneous actors is analysed, one has to consider all of its multi-facetted aspects. Even if we found that the existence of a 'resource effect', generated by UIRs, is limited to financial resources and excludes cognitive resources, the importance of the knowledge transfer between university and industry is not reduced. Instead, our results show that UIRs cause a significant increase in the innovative potential of biotech firms. This is due to a threefold effect. First, interactions with universities expand DBFs' knowledge bases,

allowing biotech firms to absorb new kene elements focusing on fundamental research. Second, they also increase the variance in their capabilities and, third, they have a positive effect on DBFs' networking experience. Therefore, our results highlight the importance of UIRs concerning technology and knowledge flows. Moreover, from society's point of view, it is not important who develops an innovative new drug, but whether this drug is developed or not. Our findings suggest that, besides universities, new scientific knowledge (symbolised by A-class patents) is increasingly generated by biotech firms. The creation and diffusion of this knowledge could be seen as a sort of *second mission* of biotech firms (the first one being, obviously, achieving commercial success), which complements the so-called *third mission* of universities, defined as the commercialisation of academic knowledge (Etzkowitz and Leydesdorff, 1997). We argue that biotech firms' *second mission* cannot be accomplished without close interactions with universities, which, as a matter of fact, have characterised biotechnology since its early days. Indeed, although our model has an explorative nature and not an history-friendly one (see Malerba and Orsenigo, 2002; Malerba et al., 1999), its results in terms of UIRs' effects on DBFs' innovative potential seem to reproduce the historical development of biotechnology. In fact, during the first periods of the simulation made with the standard scenario, universities play the leading role in the production of new scientific knowledge (A-class patents). Then, after some periods of collaboration with universities, DBFs have expanded their knowledge base sufficiently, including also basic research interests, to be able to widely generate truly innovative science-based research outputs. This shows that what Gibbons et al. (1994) called 'the Mode2' of knowledge creation, namely a co-production of scientific knowledge between different agents, emerges from our simulation.

Finally, the application of a systemic perspective on innovation in biotech and pharmaceuticals shows that the negative effects of such an environment to universities can be mitigated by public policies in favour of basic research. David et al. (2000) argue that the rational for government support to (academic) research is "the correction of the market failures in the production of scientific and technological knowledge, arising from the incomplete private appropriability problems identified by Nelson (1959) and Arrow (1962)" [David et al., (2000), p.501]. Our results show that government grants for basic research are crucially important in counterbalancing the different aims and incentives provided by industry which further contribute to market failure, especially in the long run. Accordingly, government research policies should be oriented toward increasing the public research funding budget with the aim of ensuring that an adequate amount of fundamental research is undertaken by universities. This counteracts the harmful effects of UIRs and while still relying on the positive effects.

These findings are in line with the results of econometric analysis (Jaffe, 1989; Adams, 1990; Acs et al., 1991; Toole, 1999a, 1999b) and historical case studies (Link and Scott, 1998; National Research Council, 1999; Angell, 2004), surveyed by David et al. (2000), which show that government funded R&D generates beneficial spillover effects and stimulates commercial innovations. More specifically, in our model government funding has a twofold role. First, it creates and strengthen capabilities in the universities. These capabilities allow for the creation of new scientific knowledge which, in the long run, spread in the system through interactions with other agents. Second, government grants increase the amount of innovative patents which circulate in the system. As a consequence, the ultimate number of innovative drugs is positively affected.

A summary of our findings suggests that, if properly complemented by an increase in government basic research funds, UIRs in the biotech and pharmaceutical sector have a positive total effect for society through the development of new innovative patentable outcomes. If not matched with applied research, basic research is not valuable for society. However, there is nothing left to be applied if basic research does not constantly generate new scientific discoveries. Therefore, it is of essential importance that the different actors engaged in research cooperate to produce new scientific discoveries as well as new innovative drugs. Our results show that joint research projects with universities are an important source of knowledge for industry. Possibilities to prevent harmful effects of the interactions between universities and firms exist and are relatively easy to be implemented for governments. Accordingly, policy makers should not legitimise a reduction in public support to academic basic research as a consequence of an increase in industry funding to universities, as frequently happens (e.g., see Blumenthal, 2003). Our results suggest that these two sources of university funding have different but complementary aims and address different needs. This strongly highlights the importance of a coordinated and harmonious innovation system as a platform which sustains innovation both in the short and long run.

Although data on drugs production, R&D investments, university patenting and licensing revenues have been used as a benchmark in obtaining orders of magnitudes in calibrating, our model is not specifically grounded on empirical evidence. Since our aim was not to develop a history-friendly model (see, for instance, Malerba et al., 1999) but rather a theoretical model applicable to the analysis of hypothetical scenarios, a detailed process of empirical validation would have been unnecessary and irrelevant, if not impossible given the complexity of the model (which includes 17 parameters in the equations and 23 initial conditions, as listed in Appendices A.3, A.4 and A.5). Nevertheless, as our analysis focused on the comparison of several scenarios in terms of production of A, B and C-class patents, it is important that the standard scenario of our model is able to reproduce the stylised facts concerning the trends and the relative numbers of the three classes of innovative outcomes. As shown in Appendix A.6, the difference in the relative number of A, B and C patents in the model resembles those that we observe when looking at the distribution of A, B and C-class drugs in the real world. The trends also appear similar, even though those from the real world fluctuate much more than the artificial ones. This is unavoidable as random events have a stronger importance in reality. Therefore, the model is able to replicate the distribution of innovative outcomes that we observe in the biotech and pharmaceuticals innovation system. The comparative nature of our experiments, which was limited to the investigation of the effects of alternative scenarios on the generation of innovative outcomes, makes this relatively simple calibration strategy sufficient to provide reliable insights.

Besides the calibration of the equation parameters and initial conditions, there are other possible aspects which can influence the results. These are: the assumptions made about the particular functional forms of the equations governing the production of patents and about the nature of the budget allocation process and the mechanisms of partnership and sponsoring formation. It is crucially important to notice that these assumptions were not expression of the particular tastes of the authors but solidly grounded on theories and empirical evidences which can be found in the literature, as we have argued in different subsections of the paper. This is a fruitful area of complementarity between ABMs and

'traditional' research tools which have to be exploited more heavily in the future of the discipline.

What has been left over from our analysis are the micro-processes whose aggregation lead to the emergence of macro phenomenon. Despite the micro-foundation of our model we preferred to focus on the aggregate variables, even though we can differentiate between the single agents whose interactions are responsible for the generation of the macro-based evidence we observed. We made this choice because we believe that this kind of analysis would have required a much larger amount of data to validate the results of the model at the micro-level. These data are not at our disposal. Furthermore, several modifications to the principles of the model would need to be made to accomplish this task. However, we are aware of the importance of closely looking at the micromacro interactions in this context. Additional and extremely interesting results could be provided, concerning for instance the distinction and the characterisation of successful and un-successful agents. Efforts to collect sufficient data to calibrate and validate future versions of the model at a micro-level will be carried out and such analyses will be performed in future endeavours.

Finally, there are other features of the model which have not been exploited in this work. For instance, the analysis of the functioning of the market for research in terms of university licensing and its effect on the innovation system are also other interesting notes on the agenda for future avenues of research.

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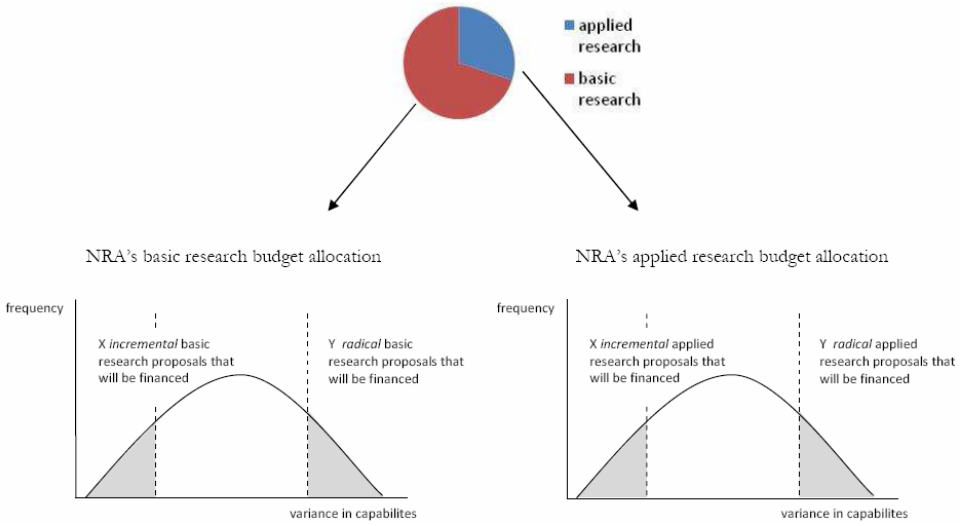
Appendix

A.1 The NRA

The behaviour of the NRA in the model aims to reproduce, in a simplified version, the role played by the US National Institutes of Health (NIH), and by some smaller European national agencies, in the real world. The NIH is the largest life sciences research funding body in the world (Angell, 2004). Although the NIH also invests a minor part of its annual budget in research programmes designed for industry (small business innovation research and small business and technology transfer programmes), the larger part (more than 83%) of the NIH's funding is granted to universities, medical schools and other research institutions, whereas about 10% of NIH's budget supports projects conducted in the institute's laboratories (*NIH Grants Policy Statement*, 2003). In the model, the NRA is purely a funding body which does not conduct research on its own. Furthermore we only allow the NRA to finance universities; LDFs and DBFs have others source of funding (production of new drugs and licensing).

Figure A.1 NRA's annual budget allocation (see online version for colours)



The allocation process of the NRA's funding is designed as follows. Universities can apply for funding both for own research projects and for joint research projects with other universities. If they want to undertake a joint research project, universities will start to look for partners according to their partnership strategies. Afterwards (or as a first step in the case of own research projects) a project proposal has to be set up. The project proposal is constructing by mixing part of the agents' kenes constituting the project knowledge base. Then all the proposals are sent to the NRA. The agency has an exogenously fixed annual budget, which is divided in two parts. The largest one is designated to finance basic research projects (whose average research direction value is equal or less than an exogenously set threshold), and the smallest one is set aside for applied research projects. The former is bigger than the latter due to the specific aim of the NRA to support and provide incentives for basic research. Within the two budgets,

not all the proposals are accepted and financed. First the proposals are assigned to their respective budget category (either basic or applied), then they are ranked according to the number of different capabilities each proposal contains. In this way, incremental and radical research projects can be distinguished. For each of the budget categories, only a selected number of incremental and radical (basic or applied) research projects are financed. Figure A.1 illustrates on this process.

A.2 'Value of success' and 'probability of success' for own research projects

The 'value of success' and 'probability of success' for own research projects depend on four knowledge variables:

1 the knowledge distance among the IH's quadruples, used as a measure of the un-relatedness of the knowledge applied in the project

2 a 'research direction factor', which accounts for the IH's quadruples average research direction

3 a so-called 'technical factor'

4 the experience of the actor.

Before we introduce to the 'value of success', and 'probability of success' functions, we briefly explain these four variables.

The distance between two kene elements is calculated as follow:

$$d = \alpha \cdot \left|C_1 - C_2\right| + \beta \cdot \left|A_1 - A_2\right| \tag{1}$$

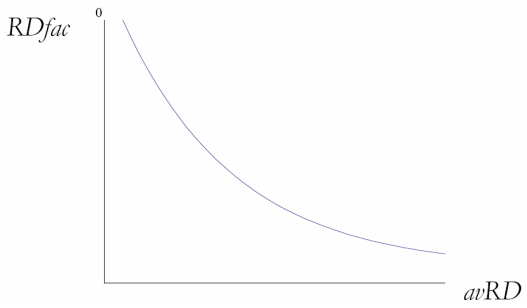
where d is the distance and α and β are used to weight the single distances between the kene elements. The average of all the distances d between all kene elements can be interpreted as a measure of the un-relatedness in the components of project's knowledge base, i.e., of the heterogeneity of project's innovation hypothesis quadruples.

The research direction factor, to be included in the 'value of success' and in the 'probability of success' formulas is calculated as:

$$\mathrm{RD}fac = e^{-\left(\frac{10}{3}\cdot av\mathrm{RD}\right)+\frac{1}{2}} \tag{2}$$

where '*av*RD' is the average research direction of the project's kene elements. Figure A.2 graphically shows the relationships between '*av*RD' and 'RD*fac*'.

Figure A.2 The research direction factor (see online version for colours)



The figure shows that the higher the average research direction of a project is, the higher the RD factor becomes, which leads to a higher value of success [see (3)].

For the evaluation of own research projects, we also account for a technological factor. When actors decide to *go-it-alone*, they can only rely on their own resources. Although some exceptions exist, in general, universities have less valuable and sophisticated technical instruments and machinery than firms. Furthermore, they do not have the competencies to improve the research devices on their own. Due to their larger amount of financial resources, LDFs have more powerful and accurate research instruments. Therefore, we introduced a technological factor in the 'value of success' function for own research projects, in order to account for the differences in the technical equipment of actors. In particular, the relationship is as follows: the higher the technological factor, the higher the value of success. It has to be noticed that differences in the technical equipment no longer matter once actors decide to undertake research in cooperation with other agents. The technological factors (TF) for each agent class were calibrated relying on a sensitivity analysis and can be found in Table A.1.

Table A.1 The technological factors

Agents	*TF*
UNIs	0.9
DBFs	1.1
LDFs	1.2

The effects of the knowledge distance, the research direction factor and the technological factor are combined together in the 'value of success' function for own research projects, which is introduced in (3):

$$v = TF \cdot a_1 \cdot \frac{(\min d + \max d) \cdot \mathrm{av}d}{\tau_1 \cdot \delta_1} + a_2 \cdot \frac{\mathrm{RD}fac}{\tau_2} + \sigma_1 \tag{3}$$

'*TF*' is the technological factor, 'min*d*' is the minimum distance in the knowledge-space between the kene elements of the innovation hypothesis, 'max*d*' is the maximum distance and 'av*d*' is the average distance among the kene elements of the actor's current work[8]. *RD* factor is the research direction factor. 'τ_1' and 'τ_2' standardise the output within the expected knowledge space depending on the research orientation. 'a_1' and 'a_2' weight the contribution of the knowledge distance and the research direction factors, with $a_1 < a_2$. Finally, δ_1 is a scaling factor and σ_1 is a randomly distributed variable.

Whether the potential outcome from the value of success formula is generated or not is decided by the 'probability of success' formula (4). The project is successful – i.e., the output from (3) is generated – if:

$$\frac{\varnothing E}{a_3} > \sigma_2 + \tilde{\sigma}_2 \cdot \frac{\max d}{\tau_1 \cdot \delta_2} \cdot \frac{\mathrm{RD}fac}{\tilde{\tau}_2} \text{ and } v > 0.5 \tag{4}$$

On the left side of the first condition we find the weighted average experience of the contributed quadruples ($\varnothing E$ / a_3). In order to have a successful project, the experience factor must be higher than the right side of the equation. On the right side we have σ_2, which is a Poisson-distributed random variable, $\tilde{\sigma}_2$ which is a normal-distributed random variable, the knowledge distance factor, standardised with τ_1 and weighted with δ_2, and

the standardised research direction factor. The second condition to be respected, $v > 0.5$, has been added in order to specify that some projects can be successful but nevertheless do not generate a patentable output (see § 4.7).

A.3 'Value of success' and 'probability of success' for joint research projects

The process through which a joint research project innovation hypothesis is transformed into an outcome is equivalent to that for the own research projects and is based on the two functions, 'value of success' and 'probability of success'. Nevertheless there are significant modifications to these functions. Moreover, joint research projects are evaluated in two different ways according to the chosen partnerships strategies. Another main difference is that the quadruples of the project innovation hypothesis come from different agents' kenes. This means that there is a greater array of possibilities for improving the project's IH if the project is not successful, because the new quadruples can come from different actors, i.e., the project knowledge base is larger. This is the main advantage of a joint research project compared to a research project in isolation, together with the opportunity to link complementary competences and research directions and to the expansion of actors' knowledge bases. If the project is successful, in fact, each participating actor will acquire the quadruples of the IH which have been contributed by the project partner(s) in his own kene. The functions for the 'value of success' and the 'probability of success', for both the conservative and progressive strategies, are introduced in the following paragraphs.

Conservative strategy

In the case of conservative strategy the 'value of success' function has been designed as follows:

$$v = \frac{\min d}{\tau_3} \cdot a_4 + \frac{\max d}{\tau_4} \cdot a_5 + \frac{RDfac}{\tau_2} \cdot a_6 + \sigma_1 \cdot a_7 \tag{5}$$

As usual, τ_2, τ_3 and τ_4 are used to standardise the output within the knowledge space, a_4, a_5, a_6 and a_7 weight the contributions of the different elements and σ_1 is a Poisson-distributed random variable. The variable 'min*d*' is the minimum distance between the innovation hypothesis kene elements of the joint research project, whereas 'max*d*' is the maximum distance. Finally RD*fac* is as in (2). Compared to own research projects, here the interpretation and the importance of the minimum and the maximum distance is different, because the project involves many actors. The 'shortest' distance is the distance between the two most related quadruples of two actors and can be interpreted as a proxy of the *absorptive capacity*. Instead, the 'longest' distance is the largest distance between two quadruples in the knowledge space of two actors and can be interpreted as a measure of the knowledge un-relatedness. As Pyka and Scholz (2008) argue, if two actors have very related knowledge in parts of their kenes, the shortest distance is small. Thus, the absorptive capacity is high and, accordingly, they should be able to communicate easily with each other. Consequently, the 'value of success' is likewise high. On the other hand, combining un-related knowledge (i.e., high 'longest' distance) also increases the potential magnitude of the project output. If the agents select their partners following the conservative strategy, they try to minimise the knowledge

distance between them, therefore we can assume that they consider absorptive capacity to be more important than knowledge heterogeneity. Consequently in the 'value of success' functions for the conservative strategy the contribution of the 'mind' term is larger than that of 'max*d*' ($a_4 > a_5$).

The 'probability of success' for the conservative strategy is as follows:

$$\frac{\varnothing E}{a_3} \cdot \sqrt{\varnothing net} > \sigma_2 + \tilde{\sigma}_2 \cdot \frac{\min d}{\tau_3} \text{ and } v > 0.5. \tag{6}$$

The standardisation factor (a_3) and the random variables (σ_2 and $\tilde{\sigma}_2$) are the same as in (4). The most interesting difference with the research project in isolation is the presence of '$\varnothing net$', which stands for the average value of the networking experience of the cooperating agents. It is important to notice that this term is always larger than 1, therefore if agents decide to cooperate, they always have a higher probability of success than if they would have undertaken the same research project alone. In fact, the left side of the equation in (6) is always greater than in (3), *ceteris paribus*. Furthermore, the right side of (6) is smaller than in (3) because in the 'probability of success' for the joint research project we do not account for the RD factor. In fact, we assume that, when it comes to collaborate with other agents, the knowledge distance between partners is much more important than the research direction to decide whether a project is successful or not (nevertheless the research direction is still crucial for the value of success).

Progressive strategy

The 'value of success' and 'probability of success' functions for the progressive strategy have been designed as follows:

$$v = \frac{\min d}{\tau_5 - \tau_6} \cdot a_8 + \frac{\max d}{\tau_5 - \tau_6} \cdot a_9 + \frac{\mathrm{RD}fac}{\tau_2} \cdot a_{10} + \sigma_1 \cdot a_{11} \tag{7}$$

$$\frac{\varnothing E}{a_3} \cdot \sqrt{\varnothing net} > \sigma_2 + \tilde{\sigma}_2 \cdot \frac{\min d}{\tau_5 - \tau_6} \text{ and } v > 0.5. \tag{8}$$

Besides minor changes in the standardisation factors, the most important difference between (5) and (6) is that the contribution of max*d* is larger than that of min*d* ($a_8 > a_7$). In fact, when agents apply a progressive strategy, they aim to collaborate with very dissimilar partners. Consequently, we assume that they consider un-relatedness of the knowledge (max*d*) to be more important than absorptive capacity (min*d*).

A.3 List of (exogeneous) parameters and standard scenario's settings

Parameter	*Equation*	*Meaning*	*Range*	*Standard scenario*
α	Distance between kene elements (1)	Weight the distances between the kene elements	0–1	0.5
β	Distance between kene elements (1)	Weight the distances between the kene elements	0–1	0.5
TF	Value of success for own research project (3)	Technological factor	0.5–1.5	UNIs = 0.9; DBFs = 1.1; LDFs = 1.2
a_1	Value of success for own research project (3)	Weight the contribution of the knowledge distance	0–1	0.4
a_2	Value of success for own research project (3)	Weight the contribution of the research direction	0–1	0.6
a_3	Probability of success for own research project (4)	Weight the contribution of the experience level	0–1	0.25
a_4	Value of success for joint research project – conservative strategy (5)	Weight the contribution of the minimum distance	0–1	0.3
a_5	Value of success for joint research project – conservative strategy (5)	Weight the contribution of the maximum distance	0–1	0.2
a_6	Value of success for joint research project – conservative strategy (5)	Weight the contribution of the research direction	0–1	0.3
a_7	Value of success for joint research project – conservative strategy (5)	Weight the contribution of the random variable	0–1	0.2
a_8	Value of success for joint research project – progressive strategy (7)	Weight the contribution of the minimum distance	0–1	0.2
a_9	Value of success for joint research project – progressive strategy (7)	Weight the contribution of the maximum distance	0–1	0.3
a_{10}	Value of success for joint research project – progressive strategy (7)	Weight the contribution of the research direction	0–1	0.3
a_{11}	Value of success for joint research project – progressive strategy (7)	Weight the contribution of the random variable	0–1	0.2
v_A	Value of success	Threshold for A-class patents	0–1	0.71
v_B	Value of success	Threshold for B-class patents	0–1	0.63
v_C	Value of success	Threshold for C-class patents	0–1	0.5

A.4 List of initial conditions

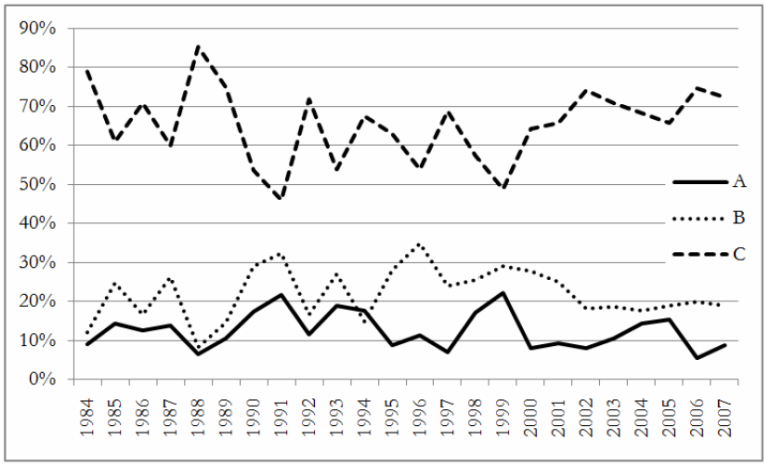
Initial condition	*Parameter*	*Standard scenario*
Population	Number of UNIs	150
	Number of DBFs	400
	Number of LDFs	14
NRA settings	Research direction basic/applied threshold	5
	Number of incremental basic research project financed by the NRA per period	3
	Number of radical basic research project financed by the NRA per period	3
	Number of incremental applied research project financed by the NRA per period	1
	Number of radical applied research project financed by the NRA per period	1
Sponsorship settings	University research direction required by LDF to sponsor	≥ 4

A.5 Initial distribution of agent's kene elements

Agents	*Kene quadruple's element*	*Distribution*
UNIs	*RD*	70% of UNIs' kene quadruples have a research direction randomly distributed within the range 1 and 3;
		30% of UNIs' kene quadruples have a research direction randomly distributed within the range 2 and 7.
	C	80% of UNIs' kene quadruples are distributed around 3 to 5 capabilities focal points, the rest is randomly spread.
DBFs	*RD*	10% of DBFs' kene quadruples have a research direction randomly distributed within the range 1 and 4;
		80% of DBFs' kene quadruples have a research direction randomly distributed within the range 3 and 6;
		10% of DBFs' kene quadruples have a research direction randomly distributed within the range 5 and 9.
	C	90% of DBFs' kene quadruples are randomly distributed within the range of capabilities from 1 to 60;
		80% of this 90% is distributed around a +/–5% range of the first capability;
		10% of DBFs' kene quadruples are randomly distributed over the whole range of capabilities (1-100)
LDFs	*RD*	20% of LDFs' kene quadruples have a research direction randomly distributed within the range 1 and 9;
		10% of LDFs' kene quadruples have a research direction randomly distributed within the range 2 and 4;
		70% of LDFs' kene quadruples have a research direction randomly distributed within the range 5 and 9.
	C	60% of LDFs' kene quadruples are distributed within the range of capabilities from 61 to 100 with focal points with group 3–5 kene elements;
		40% are distributed over the whole range of capabilities (1–100) with focal points with group 3–5 kene elements.

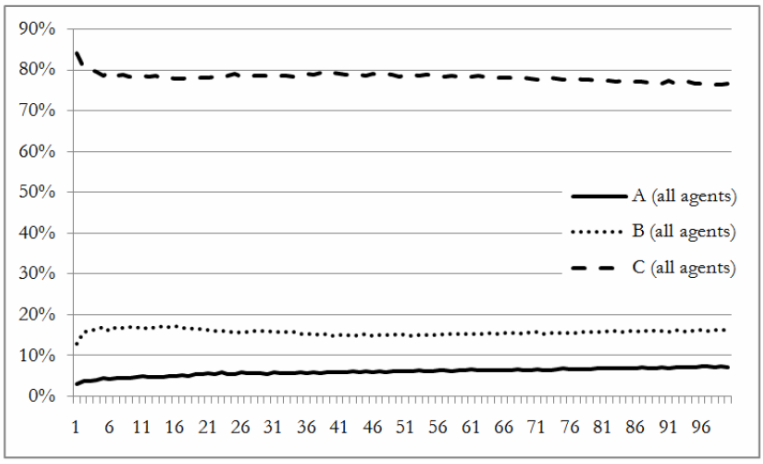
A.6 Empirical validation of the results

Figure A.3 Classification of A/B/C drugs from the Food and Drugs Administration



Source: Own elaboration of FDA's data available at http://www.fda.gov

Figure A.4 Generation of A/B/C patents in the model's standard scenario



Notes

1 This is what we assume in our model, along with the empirical evidence showed by Angell (2004).

2 The NetLogo code of the model is available upon request to the first author.

3 This is a common trend in many countries, as the allocation of government funds has been increasingly driven by criteria of competition (Clark, 1998; Vincent-Lancrin, 2004).

4 As mentioned in sub-Section 4.1, universities' own and joint research projects with other universities can also obtain funding from the NRA. In this case universities do not have to use their capital stock to finance their research projects.

5 As a proxy of the agents' absorptive capacities we apply a measure of un-relatedness (i.e., the variance) of their knowledge base, which is calculated as the average distance between all own kene elements.

6 Therefore, the relation between the innovative output and the knowledge distance, which is jointly determined by the combination of the two equations for the 'value of success' and the 'probability of success', has the shape of an inverted U. This is in line with the recent literature on knowledge distances and innovation (Nooteboom, 1992, 1999; Nooteboom et al., 2007; Wuyts et al., 2005).

7 The low expertise level of the newly acquired capabilities reduces '∅E', the average agent's experience related to the IH's quadruples – see (4), (6) and (8) in Appendices A.2 and A.3 – thus decreasing the probability of success.

8 For actor's current work, we mean the sum of all the innovation hypothesis applied in all the research project that the actor is simultaneously running in a certain period.