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Complexity and path dependence in biotechnology innovation systems

Jorge Niosi*

In commercial applications of biotechnology, there is no international convergence. On many critical dimensions, the United States is pulling ahead vis-à-vis most other developed or emerging countries, in spite of the efforts made by the potential catching-up nations. The article argues that the explanation lies in the institutional fabric that fosters commercial biotechnology: this institutional structure is too complex and costly, it exists mainly in the United States, and the followers either do not understand it, or are trapped with more inefficient institutions. The paper builds on biotechnology in order to theorize about institutions and their evolution in sectoral innovation systems. It also applies concepts and models from complex system theory.

JEL classification: O31, O32, O33, O38.

1. Introduction

This article started with a simple question: is the world catching up with the United States in the commercial applications of biotechnology? Is the United States first-mover advantage disappearing over time? The answer is negative, as one can judge by several indicators, including Table 1. In an activity where patents are a key indicator of the commercial activity, and where venture capital holds a central role, the United States is at least as dominant as it was 20 years ago, and may still be pulling ahead (Table 2). Neither the European Union nor Japan is catching up.

The next question then is why? And the answer is to be found in the complex web of institutions within which commercial biotechnology develops.

2. Theory

Institutions are increasingly seen as the locus where the residual of economic development lies. Yet, it was 50 years ago that Gunnar Myrdal (1959) argued that the main

*Jorge Niosi, Department of Management and Technology, UQAM Montreal, P.O. Box 8888 Station Centre-Ville, Montreal, Quebec, Canada, H3C 3P8. e-mail: niosi.jorge@uqam.ca

Table 1 Complexity and evolutionary economics versus the traditional view

	Complexity	Traditional
Dynamics	Open, nonlinear, far from equilibrium	Closed static linear systems in equilibrium
Agents	Modeled individually, they are heterogeneous, use rules of thumb to make decisions with incomplete information; learn and adapt over time	Modeled collectively use complex deductive calculations to make decisions, make no errors, do not learn or adapt
Networks	Models interactions between agents; networks change over time	Assumes agents only interact indirectly through market mechanisms
Emergence	No distinction between micro and macro; macro patterns emerge from micro behaviors	Micro and macro-economics remain separate disciplines
Evolution	Co-evolutionary processes of learning, differentiation, selection and reproduction provide the system with perpetual novelty in firms, strategies, technologies, markets	No mechanism for endogenously creating novelty. Growth occurs through increases in productivity.
Institutions	Key mechanisms for the production, retention and diffusion of information. No optimality or trend to optimality	Institutions either do not play any role or are marginal economic factors.

Table 2 Policy instruments for commercial biotechnology

Policy instruments
Higher tax credits for R&D for small firms
Grants for privately held DBF to explore academic and public research (i.e. SBIR, USA)
Academic research grants
Policy support for private venture capital
Policy support for alternative stock markets
Income tax exemptions and other tax advantages to young innovative firms
Public research laboratories
Network policies and grants
IP policies
Regulatory and approval policies
Public and private (tax deductible) research chairs

factors responsible for the vicious circle of underdevelopment were institutional: education, health, and religion were among the main obstacles to development. Since then many institutional explanations have been proposed including democratic institutions, the rule of law, intellectual property, and good governance (Breznitz, 2009).

In the last 20 years, the innovation system perspective (Freeman, 1987; Lundvall, 1992; Nelson, 1993; Edquist, 1997, Cooke, 2001, Niosi, 2002, Malerba, 2004) has moved closer to the center of theoretical and policy debates about economic development, with its emphasis on *science, technology, and innovation institutions*. However, some of its concepts still require more refining, and it needs yet to adopt a more formal approach and develop policy-making theory. This article addresses some of these issues, by analyzing the concept of institution and proposing the use of models of complexity to clarify the causal relationships at stake. The case of biotechnology innovation systems is used as an example.

The systems-of-innovation approach has successfully emphasized the role of science, technology, and innovation (STI) institutions in economic development. These institutions play a key role in the creation, absorption, diffusion, and retention of technology, and they form systems. Thus, the production of human capital needs to be somehow coordinated with the incentives aimed at increasing the demand for such capital, particularly in the private sector. Incentives for innovation in large corporations such as tax credits for R&D must be complemented with subsidies for R&D in smaller firms, and inducements for the creation of a venture capital industry. The perspective has first and mostly emphasized *national* innovation systems (NIS), which are defined as sets of institutions:

> The network of institutions in the public and public sector whose activities and interactions initiate, import, modify and diffuse new technologies. (Freeman, 1987)

> A set of institutions whose interactions determine the innovative performance . . . of national firms. (Nelson, 1993)

In what is called the "narrow" perspective of the NSI, Nelson and Rosenberg (1993) made clear that the major institutional actors they are writing about are firms with R&D capabilities, research universities and government laboratories, and more generally all financial institutions that have an impact on innovation. The "broad" perspective is that of Lundvall (1992) where all users and producers of innovation are part of the system.

Institutions and technology co-evolve (Nelson, 1994). Yet, it may happen that the co-evolution does not occur or only occurs in an incomplete way. Second, the nature of these institutions in innovation systems is still a debated issue. The term "institution" usually includes such different things as customary norms, beliefs, organizations (i.e. universities, public laboratories, and private firms), laws and policies,

organizational routines, and more (Nelson, 2005). Institutions are important because they are the cradles and the repositories of knowledge from which agents draw their information. All authors agree that the term is fuzzy and needs more elaboration. Institution is a vague term. North (1991) distinguished between institutions that are "rules of the game" and organizations. In this article, I elaborate on this perspective and distinguish four different types of institutions in the NSI, also on the basis of origins, evolution and nature. The four types are:

(a) *Organizations*. They are social units deliberately constructed to seek specific goals (Aldrich, 1999). Participation in organizations is most often voluntary. In order to operate efficiently, organizations create routines. Firms, universities, government departments and research institutes, venture capital partnerships, and new technology-based start-ups are in this category. Organizations develop inertia (resistance to change) over the course of their lives. Organizations are modular and most often decomposable in other second-level organizations (i.e. university departments, company divisions, and the like). At the lowest level of disaggregation, organizations are made of modules that we call "routines." Organizational change most often consists of the modification, addition, or subtraction of routines.

(b) *Routines*. They consist in repetitive patterns of action within organizations (Cohen *et al.*, 1996). Routines allow organizational learning, adaptation, production, as well as enrollment of new organizational members. Not only organizational competencies, but also organizational rigidities, are based on routines. Members of organizations must comply with routines. Routines also change slowly in organizations, as they carry enormous inertia.

(c) *Norms or customs*. Patterns of social action based on common attitudes, beliefs, expectations, religion, and the like. They may decide which members of society are educated, which will enter the labor pool, or be nominated to leading positions. Such norms usually change gradually via social processes. They may sometimes change owing to legislative action (i.e. a religion may be outlawed). Customs usually structure action through guilt and disapprobation (Shevell, 2002).

(d) *Laws or policies*. That is, rules of conduct imposed by a national or regional authority. They evolve through the legislative action of governments, usually but not solely following policy evaluation. They structure human behavior under the threat of public, legal, and sanctions. Policies are often aimed at inducing organizational change in firms. Cases in point are procurement policies giving priority to companies with some level of quality control (i.e. ISO 9001 or 14,001) and those aiming at fostering R&D activities in private firms (tax credits) or universities (research councils).

These four types of institutions are neither optimal nor converging toward optimality. There is no selective pressure toward increasingly improved institutions. No "visible hand" guides institutions toward any optimum (David, 1993).

Government meddling may both implement deficient policies or reorient existing policies in the wrong direction. But managers can also implement the wrong routines with a view to advance their own interests.

National and international diffusion of policy innovations is well evidenced by policy specialists (Mintrom, 1997, Simmons *et al.*, 2004). Such diffusion often takes place among neighbor AND culturally close states (i.e. among American states; from France or Italy to Spain or Portugal). Geography per se is not a good predictor of diffusion. Witness the institutional convergence between United States and Canada, but not between the United States and Mexico. If this is true, a continent such as Europe with 20 and more different languages and cultures will experience "sub-regional" institutional convergence: that is, Nordic countries, Latin countries, and Baltic countries.

In addition, institutional evolution, like biological evolution, works with the materials at hand. This material includes imperfect information and deficient incentive systems, more or less efficient public and private sector bureaucracies, and differential specific groups that may gain or lose from those institutions. An example will illustrate the issue. Universities in Continental Europe or Latin America suffer from many ailments; one is inbreeding in faculty selection. Such hiring routines are socially uneconomical. But the general public is often not aware of such practices and their social consequences, and does not participate in these selection processes. Then, there is "the logic of collective action" (Olson, 1965). The cost for an individual within a large group to change these socially harmful patterns of action is far higher than the rewards the same individual may expect from his participation in any corrective behavior. Thus, inefficient institutions subsist under imperfect information, and small-group coalitions impose these institutions to unorganized and/or badly informed majorities. Besides, institutions are part of larger adaptive complex economic systems. And these complex economic systems, including innovation systems, are difficult to understand.[1]

I have suggested elsewhere that in socioeconomic systems plagued by market and system failures, institutions with variable efficiency and effectiveness, and with bounded rational agents *who* do not maximize, benchmarking may be the predominant evolutionary method of finding and adopting best practices from superior organizations and systems (Niosi, 2002). Benchmarking is the search for best practices that lead to superior performance. Benchmarking is now practiced in private firms, public administrations, and universities.

2.1 What are complex adaptive economic systems?

Systems dynamics is one of the methods of both modeling an evolutionary economic system and developing theory. It is radically different from pure theoretical models

[1]We have recently witnessed private firms sometimes keep routines that reward managers with generous bonuses when the large corporations they run are on the verge of bankruptcy.

of neoclassical economics. Table 1 compares the complexity and evolutionary perspective with traditional economics (Arthur *et al.*, 1997; Beinhocker, 2006: 97).

I would argue that the innovation systems approach has much to gain from adopting a complexity and dynamic perspective. A system is complex "when there are strong interactions among its elements, so that current events heavily influence the probabilities of many kinds of events" (Axelrod and Cohen, 2000: 7). Complex adaptive systems are those characterized by dispersed interaction among heterogeneous agents, continuously adapting their strategies, none of which controls the system, and where perpetual novelty in markets, technologies, behaviors, and institutions occurs. The dynamics of such a system is out-of-equilibrium (Arthur *et al.*, 1997). In such complex adaptive systems, co-evolutionary processes take place. The economy and its innovation system is a classic example of such complex adaptive structures.

An NIS is a complex adaptive system, which includes many different organizations such as private firms, government departments, universities, public labs, and industrial associations, as well as laws such as public STI policies. In addition, it includes customary norms and many financial, technological, personal, and commercial interactions (Niosi *et al.*, 1993).

The elements of this system are under continuous change, due among other things, to learning. Organizations change their missions and their routines. Thus, in the last 20–30 years, universities have created offices of technology transfer and intellectual property routines that were previously inexistent. Venture capitalists who were experienced in information technologies learned about biotechnology in the 1980s. Also, customs and laws evolve, the first through several influences, including the information explosion linked to the diffusion of Internet. New products, new process and new markets emerge, new routines are diffused, and agents adopt them gradually.

Under such conditions, there are no optimal policies, routines, or organizations, only more or less efficient ones. Efficiency and adaptive institutions are context dependent. Inefficient institutions can survive in any such innovation systems. The reason is that systems have some resistance to adaptation. These include the *mental models* of those who inhabit these institutions. If academics think their role is only to teach and publish papers, they will resist any attempt to create spin-off firms, to patent technology, or license it out. Also, the very complexity of organizations makes them fuzzy even to insiders.

2.2 Why do inferior STI institutions subsist in innovation systems?

2.2.1 Path dependence

Inferior STI institutions may experience path dependence, and remain locked *in* inferior practices for several reasons (David, 1993, 1994, 1998).

- *Winners and losers*: inferior institutions may bring gains to small well-organized groups, while being detrimental to the majority of society (Puffert, 2004) everybody

else's losses. The winners and losers problem is also evident in university hiring. Several short papers published in *Nature* by Spanish scholars calculate that the rate of inbreeding in Spanish universities is close to 90%. It was 91% in Portugal, 78% in Italy, 73% in Austria, 65% in France (Soler, 2001). Aghion *et al.* (2007) arrive to lower figures but the percentage of faculty with in-house PhD is still very high. In such an environment, losers are young scholars not educated at the same university where they apply, and society as a whole. Winners are senior professors recruiting their own students, who will never challenge them.

- *Contracts*: local academic contracting is less effective than international hiring, but less expensive and easier to operate. Yet once signed, contracts are rock solid and very difficult to change. Again, evolution works with the materials at hand; in the United States, Australia, and Canada the massive influx of Europeans and other immigrants provided "human capital material" for research universities to hire international scholars. A positive reinforcing loop takes place: international hiring produces higher standards and more international recruitment.
- *Imperfect information*: policymakers, as well as company and university managers are not always aware of the precise factors behind the sustained superior capability of other regions, countries, or organizations. Causal ambiguity is a central element of the imperfect information syndrome. Besides causal ambiguity, combinatorial complexity makes information still more imperfect and difficult to assess (Ryall, 2008). In addition, innovation systems are characterized by a large number of organizations, policies, and networks. And these innovation policies are complementary and supermodular (Mohnen and Röller, 2005): the efficiency of each policy depends on the presence or absence of other policies. Also, the inefficiencies of specific policies often go unchanged for long periods of time, as Tassey (2007) has shown for the US tax credit system.
- *Networks* (Owen-Smith *et al.*, 2002): in the United States, there are large interregional networks of universities, R&D active companies and public laboratories. The United States has many advantages over Europe, including a unique language, high mobility of personnel, and policies favoring interregional cooperation; all these factors support the building of large interregional networks. In Europe, on the contrary, there are smaller regional networks, only connected through a few large international linkages. Most European researchers live in a region within a single European country. Over 20 major languages and dozens of regional ones do not help networking either, even if the situation has improved thanks to EU programs for networking such as DIME. Smaller networks may lead to group think traps. Thus, inferior STI policy institutions are the norm, rather than the exception. According to David:

> Rather than be the robust epiphenomena of a new organum of intellectual inquiry, the institutions of open science are independent and in some measures fortuitous social and political constructs. (David, 1993: 20)

2.2.2 Insufficient investment

An additional factor in the survival of inefficient institutions is insufficient public and private investment. More efficient institutions may be more costly. In order to avoid the ineffective use of tax credits based on fixed annual amounts, governments would need to "open the doors" to a far larger number of proposals and hire a large number of financial inspectors to control R&D claims. This superior solution is more costly than allowing a fixed amount every year for tax credits. Also, more research in the EU will require more research funds. In sum, high-level R&D may be "unaffordable" to poorer countries (Chang, 2003).

Under conditions of causal ambiguity, combinatorial complexity, and long-term returns, it is not surprising that policymakers and private firms tend to underinvest in STI institutions. In many OECD countries, governments pay lip service to R&D, higher education, innovation, and technical progress but most often these areas have low priority. Similarly, because of externalities and long-term and uncertain return on investment, private firms tend to allocate reduced internal funds to R&D and innovation. Figure 4 shows the public expenditures for biotechnology R&D as calculated by the European Commission in 2005. The EU-15 plus Iceland, Norway and Switzerland spent US$3.8 billion PPP. The United States spent $US 23.2 billion (six times more). Japan spent $1.9 billion, South Korea 1.2 billion, and Canada and Singapore 0.6 billion (EC 2007 and Figures 4 and 5).

2.3 Why is STI policy evolutionary, complex, and path dependent?

STI policy in innovation systems is evolutionary because in such risky, uncertain, and medium to long-term return activity, both governments and firms move cautiously. Also, STI institutions, as all institutions, tend to suffer from inertia. Take the case of universities. Over the centuries, most universities have been undergraduate and teaching institutions. Teaching is a more manageable and less costly activity than research. It requires fewer investments in libraries, laboratories, assistants, highly skilled academics, and intellectual property management. Many higher education institutions never evolve, for these reasons, from undergraduate teaching organizations to research ones. Some of them do, and it takes years, if not decades to incorporate the routines and personnel required to conduct advanced research. Government policy (i.e. national funding councils) may change the academic system but many countries are slow in investing in order to create incentives for academic R&D.

The evolution of government laboratories is similar. Most government labs are agricultural or industrial extension organizations: they teach good agricultural and industrial practices, such as metrology; they train company personnel in quality control, just-in-time systems; or counsel them on technology adoption. R&D public laboratories are much more costly and difficult to run than purely extension units. Yet, some public research institutes move toward advanced research under

government incentives. But seldom do governments apply a large set of different STI policies in a short period of time. Usually they implement some policies, learn through exploration and ex-post assessment the effects of these policies, and eventually modify them or add new ones. Complementarities or combinatorial complexity make the trial and error search much less effective and more costly and time-consuming, and require permanent attention and evaluation.

3. Biotechnology

The growth of commercial biotechnology is an evolutionary, complex, and path-dependent process. National systems of innovation in biotechnology have been analyzed for over a decade (Bartholomew, 1997; Dohse, 2001; Kim *et al.*, 2007). Biotechnology is a science-based activity, heavily dependent on public research conducted in universities and government laboratories.

Biotechnology is not an industry, like pharmaceutical manufacturing or agriculture, but a set of technologies used in many different industries. Dedicated biotechnology firms are conducting research on these technologies, aimed at one or several applications. When they get products, they either license them out or become themselves a manufacturing, commercial or agricultural company. Pharmaceutical industries produce drugs, active ingredients and processes. Some of them are based on genetic engineering, thus using a set of biotechnologies.

Also, as Bartholomew (1997) has pointed out, the commercialization of its research results is a function of the specific economic and institutional structure of the country, i.e., how much absorptive capacity the industrial sector has accumulated in order to adopt these technologies, the development of a venture capital industry, the missions of research institutions, and the sophistication of national, sectoral, and regional STI policies. Bartholomew finds eight elements in the institutional structure of biotechnology that need to be considered. They are:

(a) the level and patterns of national funding of basic research;
(b) the linkages with foreign research institutions;
(c) the national tradition of scientific education;
(d) the degree of commercial orientation of research institutions;
(e) labor mobility between university and industry;
(f) the venture capital market;
(g) the role of government in technology diffusion; and
(h) technological accumulation in related sectors.

These factors determine the flows and stocks of knowledge in industry and *in* research institutions. Kim *et al.* (2007) insisted on the role of US universities in the biotechnology innovation system. Among these factors, this article suggests that

Table 3 Main agents in the biotechnology innovation systems

Agent	Role
Universities	Produce and transfer cutting-edge knowledge through world-class teams of mobile researchers
Star scientists	Lead cutting-edge teams and patent commercially useful knowledge
Venture capital	Selects promising project and funds DBFs
Patenting offices	Provide rapid and adequate IP protection for useful knowledge
Regulatory offices	Provide fast analysis and authorization for new GMOs, functional food or ingredients
Pharmaceutical corporations	Select, fund, and market promising new drugs
Public laboratories	Produce and transfer cutting-edge knowledge. Make available state of art laboratories to DBFs
Consumers	Accept and buy biotechnology products
Farmers	Plant and breed GMOs
Mining corporations	Use genetically modified bacteria for soil clean-up
Health departments	Provide fast analysis and authorization for new drugs
Science parks	Host DBF, public labs and other agencies

university and policy institutions are key because they may have an impact on all the others.

3.1 Complexity

Biotechnology policy is complex because it involves the interplay between many different agents such as research universities and public laboratories, venture capital firms, government agencies such as national and regional patenting offices (USPTO, EPO) and regulatory agencies (FDA), pharmaceutical and large seed-producing corporations, consumers, and farmers. Table 3 summarizes the most important of these.

First, these organizations display different levels of organizational change and inertia, and diverse strategies that are not always aligned.

Governments in industrial and emerging nations want to exploit at least some of the opportunities provided by new technologies, and at the same time diversify the economy. For instance, 41 states in the United States have created programs for the promotion of biotechnology, as have almost all European and many developing countries.[2] Governments create biotechnology programs through the founding of

[2]The UN FAO website lists public policies for agricultural biotechnology in such countries as Argentina, Australia, Brazil, Canada, Chile, European Union, Finland, India, Ireland, Jamaica,

public laboratories, new business R&D funding programs, policies for academic research, venture capital, science parks, incubators, and programs aiming at the repatriation of scientific stars.

Universities became aware of the new potential source of income, and created offices of technology transfer, university–industry liaison offices and/or intellectual property offices. With time, they improve the management of the intellectual property created *on* their own campuses. However, universities sometimes resist these new government programs, or adopt them using their preexisting hiring, research and publication routines. Their routines may preclude academic mobility, patenting, and the recruitment of star scientists, or create obstacles to the launching of academic spin-offs. They may hinder university/industry cooperation such as in Japan (Kneller, 1999) and in Italy (Orsenigo, 2001). In Latin Europe, academic institutions were created for teaching. A different set of research-only institutions were launched between the wars in France, Spain, and Portugal, and in Germany after WWII: they are the Italian CNR (1923), French CNRS (1938), Spanish CSIC (1939), and Portuguese CNIC (1982). In the 1950s and 1960s, Latin American countries copied this institutional scheme with similar (adverse) results. Teaching was divorced from research. Graduates had little contact with academic R&D. Researchers had little contact with graduates. Universities had little contacts with industry. The main mechanism for technology transfer from public research to industry was thus severed.

Venture capital firms, which emerged slowly in the 1950s and 1960s, and whose importance increased with the birth of information technologies in the 1970s, became interested in biotechnology in the 1980s after the successful launch of Genentech in the United States (Kenney, 1986). Angels and angel organizations complement the private funding of the new biotechnology firms, but the size of their investment funds varies from country to country, the largest being in the United States and Canada.

Second, systems failures slow down the building of the complex biotechnology innovation system. Such failures include the lack of demand for some types of biotechnology products, burdensome regulatory, science and IP policies, among other factors (Calvert and Senker, 2004). In addition, the venture capital environment makes a major difference: US venture capital firms not only have more funds to invest, partially due to a better policy incentive system, but they are also more experienced and benefit from more exit avenues than their European or Asian competitors (Haar, 2001). A study analyzing venture capital investments from 2003 to 2004 found that the United States "remains the global biotech leader by a significant

Malaysia, Namibia, the Netherlands, New Zealand, Nigeria, Peru, South Africa, and Thailand (www.fao.org/biotech/country.asp). The list is incomplete. Other countries include Italy in 1987 (Orsenigo, 2001) and Germany (in 1995) (Dohse, 2000).

margin, raising 80% of venture capital (VC) margin in that period" (Ang, 2006). The new data for 2008 do not alter the picture.

Besides, these agents change their strategies over time, and government policies also adjust (i.e. from reduced IP protection and subsidies for academic R&D and private dedicated biotechnology firms (DBFs) to increased IP protection, increased academic management of IP generated in universities and public R&D, such as Bayh–Dole, increasing numbers of OTT in all OECD countries). Some of these characteristics are common to all OECD countries. Most are not. For instance, in 1980, the United States implemented the Bayh–Dole Act, which, as Mowery *et al.* (2001) showed, did not play a key role in the rise of biotechnology; the majority of OECD countries did not implement a similar policy.

Regulatory issues contribute to the slow evolution of the system, take tissue engineering, and advanced therapy. Not until April 2007 did the European Parliament approve a new regulatory framework for gene therapy, somatic cell therapy, and tissue-engineered products *for* human use. Yet, each member state is free to enact its own legislation forbidding or adding regulatory requirements to one or all of these advanced therapy medical products (Sanzenbacher *et al.*, 2007). The regulatory framework would become law in 2009. In the United States, three federal agencies are regulating GMOs and biotechnology products: the US Department of Agriculture, the FDA, and the Environmental Protection Agency. Its regulations are much older, while some (i.e. stem cell products) need to be rewritten. The white biotechnology approaches in the United States and the EU are a sort of model for what is going on. In the United States, the DoE and DoA, consulting with academia and industry, centrally coordinated this model. The emphasis was on an early start (in 1999) to compete successfully with foreign countries. A guiding national procurement approach and massive public research funding were implemented. In the EU, it was a bottom-up approach initiated in 2004 by the chemical industry against strong environmentalist movements and reduced public support. Besides, a highly regulated agricultural sector is opposed to many forms of biomass and bioenergy research and field trials (Lorenz and Zinke, 2005).

Finally, US public investment in biotechnology is unmatched in the European Union or anywhere in the world. Simply recall the annual budgets of the NIH (over $31 billion), add the budgets of the National Science Foundation for academic research (6.9 billion per year), include the tax credit for R&D (some US$10 billion in 2010) where many biotechnology DBF and biotechnology users are financed, include the SBIR program (2.2 billion in 2010) that supports many small firm biotechnology projects, and one starts measuring the size of public investment in US biotechnology.

3.2. Evolution

Biotechnology is the subject of a myriad of selection processes. Governments must decide which technology areas they will try to develop. Universities must select which

areas of biotechnology application (human health, animal health, ag-bio, environment, nutraceuticals, or other) they will prioritize in their programs, and how they will recruit top scientists to lead such programs (through industrial or public research chairs, through normal hiring processes, or other options). Venture capital firms must decide whether they will build a biotechnology portfolio, and in that case, which applications they will select. Entrepreneurial DBFs have to select personnel, strategies, specific applications, as well as product and process technologies. Pharmaceutical and chemical companies must select which DBFs they will cooperate with. DBFs must also select which networks they link with. The development of commercial biotechnology depends on these selection processes, how they are made, how many resources the selectors invest in collecting information in order to guide their choices.

Also, only a fraction of these selection processes is successful. Not all positions available are filled with star scientists; in Eastern Europe for instance, academic salaries are low and research grants very low compared to Western countries, which constitutes a major obstacle to the recruitment of high-level scientists (Samson, 2004). Also, not all VC-backed DBFs grow, and not all DBF-pharmaceutical alliances are successful (Owen-Smith *et al.*, 2002). Some of these university–industry links are blocked by the lack of a culture of cooperation between academia and business (Samson, 2004). Institutional impediments to scientific personnel mobility in Europe (where academics are often civil servants) create a further obstacle to university–industry linkages.

The science-based sectors, such as bio and nanotechnology, are continuously and rapidly changing. Institutions display inertia, what Hodgson (1989) would call "ossification." Inertia is part of the structure of organizations due to the very existence of routines (Larsen and Lomi, 2002). Organizational change is risky, because it disrupts the routines on which organizational competencies are built.

4. Biotechnology: why do so many countries fail?

In most OECD countries, the adoption of commercial biotechnology is a case of slow growth due to a thousand "breaks." The scientific frontier moves very fast (Pisano, 2006). Institutions may get locked into inferior practices through several mechanisms. The co-evolution between technology and institutions just does not take place.

4.1 Winners and losers

Some routines may be useful to some agents and harmful to others, without the latter being aware of the trade-offs involved, or the gains and losses for all the parties. Spanish tax credits on R&D are supposed to be among the most generous in the world. Yet, few companies take advantage of them. BERD is low in Spain, and few small companies claim it. As in the case of Mexico, the explanation may lie in the

specific regulations of the program. In the UK, in contrast, as in most OECD countries, a company claims R&D fiscal credits in its annual tax return, at the end of its accounting period. In Spain, a company must first be recognized as an innovator to claim tax credits. Large companies are better able to bypass the requirements of the law. Biotechnology firms are usually out of the game.

4.2 Contracts

Contracts consolidate and freeze routines. As was previously explained, in Continental Europe lower salaries and lower research funds are often aggravated by the fact that academics and government researchers are public servants. Thus, they usually need to be national citizens and they are hired in national competitions for professorships, which seldom produce satisfactory results. Once hired, the interregional mobility of scholars is difficult and international mobility is almost impossible. With such low salaries, stars tend to move abroad and low salaries accord with lower (on average) efforts.

4.3 Networks

Knowledge flows through networks. In the United States, there are large interregional networks of PROs and life sciences companies. In European biotechnology there are smaller regional networks, mostly connected through large pharmaceutical corporations. In the United States, there is a highly mobile labor force of scientists and engineers, moving from academia to industry (Owen-Smith *et al.*, 2002).

4.3.1 Imperfect information diffusion

Twenty-two or more national languages do not favor the diffusion of information, even if, in Europe, English has become the lingua franca of science.[3] Paul David makes the point clear as to the key role of institutions: "What one is left with, instead, is a mixture of the intended and unintended consequences of an undirected historical process on which the various interests of many parties, acting at different points in time, have left an enduring mark" (David, 1993: 21).

Over 20 major languages, plus dozens of regional ones dividing Europeans, represent as many barriers to exploration of other people's ideas, and restrict interaction to pools of homogeneous researchers and research results (Axelrod and Cohen, 2000: 81). Besides, English, the language in which two-thirds of global scientific publication takes place, is the official language of only two European countries.

[3]Yet just 13% of Europeans have English as their native language, and another 38% declare being able to have a conversation in English.

4.3.2 Insufficient investment

Niosi and Reid (2007) suggested that biotechnology requires large public investments. But public investment is not enough: countries with imperfect institutions will not catch up, even if they are big spenders. Between 1991 and 1999, the US venture capital market invested 6.3 billion while the Europeans invested 2.2 billion (OECD, 2001: 28). The distance is now 5 to 1 dollars in favor of the United States, while it was less than 3 to 1 in 1991–1999. Also, the US angel investor funds in the United States are 50 times *greater* than in Europe, due to differences in tax systems (*The Economist*, March 14, 2009: 13).

Public investment also lags. A recent Parliamentary report in France (Le Déaut, 2005) on biotechnology indicates that the most recent increase in NIH budgets (4 billion US $ for annual total over 31 billion) was larger than the entire French budget for health research. The report calculates that, in per capita terms, the US federal government spends six times more than the French on health R&D. It produces similar figures for the EU, and concludes that neither France nor Europe plays on level fields compared to the United States. He concludes that even if Europe has more DBF than the United States, none of them has the size of the largest US companies**;** the American biotechnology sector has twice the number of employees compared to Europe (195,000 against 82,000) and there are almost four times more American DBFs quoted on the stock exchanges than there are in Europe.

4.4 Catching up?

In the early 1980s, the United States introduced biotechnology as an industrial activity. In this sense, it enjoyed a first-mover advantage vis-à-vis other scientifically advanced nations such as the UK, Canada, and several countries in Continental Europe. This article argues that commercial biotechnology is a case of international nonconvergence in spite of the many efforts deployed by most industrial and emergent nations. The efforts of the catchers-up are evident in biotechnology publication (Figure 1 and OECD, 2006, Ch. 3).

But the commercial backwardness of the would-be catchers-up is evident in patents, sales, and venture capital, in the relative size of dedicated biotechnology firms (DBFs), in land cultivated with GMOs, as well as in the continuous investment of European pharmaceutical MNC in US and Canadian biotechnology (Sharp, 1999). Figure 2 shows the number of patents of a selected group of countries.

The article hypothesizes, as did David (1993, 1994, 2000) and Henrekson and Rosenberg (2001) and Orsenigo (2001), that in most OECD countries—and most LDCs—institutions have not been designed to cope with such fast-changing and complex science-based industries as biotechnology. Prevezer (2001) has enumerated five advantages of US commercial biotechnology over its European competitors.

1. Substantially more academic research funds in the United States than in Europe.
2. Easier for US academics to found start ups while retaining their academic posts.

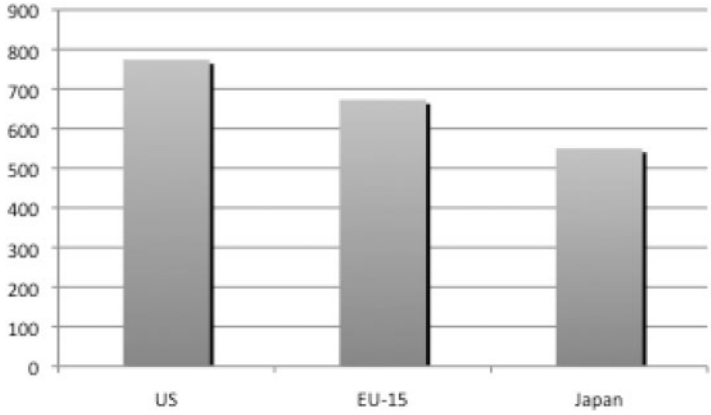

Figure 1 Scientific publication per million population, 2002, selected countries and regions. *Source*: EC (2003): *Toward a European Research Area*, Key-Figures, Brussels, p. 61.

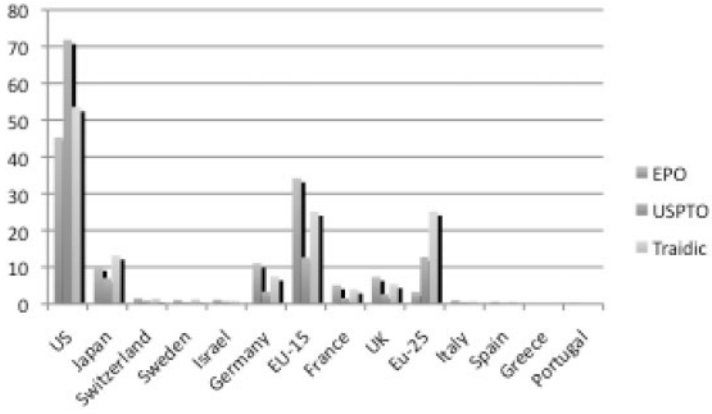

Figure 2 Thousands of USPTO, EPO and triadic biotechnology patents, up to 2003, selected countries and regions. *Source*: EC (2003): Toward a European Research Area, Key-Figures, Brussels.

3. US start-ups have been concentrated in human health and ag-bio, where commercial potential was higher.
4. Financing and managerial conditions were easier in the United States in terms of venture capital, stock market admissibility and access to managerial expertise.
5. Greater access of US DBFs to alliances with large pharmaceutical corporations.

We may add other factors. First, the European Patent System is less receptive to biotechnology. In December 2008, the EPO has refused the first patent for stem cells

on the basis of morality. Plant and animal varieties are also excluded from patenting, as well as biological processes for the production of new plants or animals.[4]

Second, in the United States and Canada, universities recruit their faculty all over the world, many of those recruited being foreign-born students who have completed their PhDs in the United States or Canada. The European university system is much more endogamic, *except in Switzerland and the UK*.

Third, competition between universities for faculty and students does not exist outside the United States (as well as Canada and the UK, up to a certain point) (Mowery and Sampat, 2004).

Fourth, in a comparison between US and Swedish science-based entrepreneurship, Henrekson and Rosenberg (2001) uncovered several weaknesses in the Swedish incentive structure: few inducements to become an entrepreneur, insufficient incentives to adjust university curricula, and human capital investment. This is probably true *in several countries* in the EU.

Fifth, a comparative study of 52 USA and 272 EU biotechnology research centers (independent public and university) found that "European centres do not seem focused enough to become serious players . . . . The various obligations are often put forward by policy makers that want a return on scarce or even declining (public) investment" (Peter, 2004).

In the United States, consumers and farmers accept biotechnology products, many universities have adopted some of the best hiring practices, government funds biotechnology R&D in academia and private firms at both the national and the state levels, the university system is large, decentralized and competitive, IP protection is strong, the venture capital market is the most experienced and large in the world thanks to government support since the late 1970s (Lee and Dinber, 2005), public laboratories are large and productive.[5] Bayh–Dole may not have been a policy bonanza in biotechnology (Mowery *et al.*, 2001), particularly because Canada has a similar experience without Bayh–Dole. But SBIR, ATP, and SSTR may be part of the explanation. And Rosenberg has underlined the established university–industry relationship in the United States (Rosenberg and Nelson, 1994; Mowery and Rosenberg, 1998). Kenney (1986) has emphasized the key role of the U-I complex

[4]http://www.epo.org/topics/issues/biotechnology.html

[5]At over US $31 billion in F2010, NIH budgets are larger than most countries' total R&D expenditures. More than 80% of it supports almost 50,000 competitive grants to more than 325,000 researchers, and about 10% of it supports projects conducted by its 6000 researchers in NIH labs (www.nih.gov/about/budget.htm). With a similar number of researchers as the French INSERM budget for 2008 is 658 M €. The 2008 UK combined national budget for medical research and health and medical R&D within NHS is 1.65 billion £ (2465 billion USD) including 992 M £in NIHR and 682 M £in the MRC. The CIHR budget for 2008-9 is C$960 M (788 M USD). In per capita terms (divided by population), such budgets are equivalent to 98 USD (in the US), 40 USD (in the UK), 24 USD (in Canada), and 14 USD (in France).

in biotechnology. Orsenigo (2001) explains why Italy and Europe lag behind in biotechnology.

> Structural weaknesses in the industrial base, in the research system and at the institutional level hindered the development of biotechnology" (Orsenigo, 2001: 77).

This institutional complex may not exist anywhere else in the world. Owen-Smith *et al.* (2002) have also emphasized the importance of biotechnology networks and the US first-mover advantage. In the United States, one language, a national legal environment, and vast research funds both private and public favor the development of interregional networks through which knowledge flows easily.

In Europe, such networks are less frequent. The tax and legal environments are less conducive to the development of a venture capital industry. Consumers are not in favor of most products in the ag-bio sector, hiring practices at universities are mostly local (Soler, 2001; Navarro *et al.* 2001; Bas and Van der Ploeg, 2006), patenting practices are less widespread in universities and public laboratories both in general and in biotechnology, regulatory agencies are slower. Table 4 summarizes some of the thousand cuts.

The latest hurdle documented is the 2004 European Clinical Trials Directive. Since its implementation, the number of noncommercial clinical trials has been reduced by 50% in leading countries such as the UK (Cressey, 2009).

Under such constraints, Continental European companies are restricted to a reduced list of products and services. The pipeline of each individual company is limited. Nature Biotechnology puts it succinctly: "three key factors affecting the competitiveness of European biotechnology: the limited availability of risk capital, a fragmented patent system, and environments that do not foster a connection between science and business" (Nasto, 2008).

In sum, in the last 30 years, many EU countries have introduced academic programs in biotechnology, if one judges by the increase of scientific publication. They have also invested in incubators, science and technology parks, funding programs for new DBFs, and the like (Enzing *et al.*, 2008). But when it comes to commercial applications, the results are often disappointing. The institutional systems display enormous inertia, *particularly in Southern and Eastern Europe.*

5. Models of complexity in biotechnology policy

Influence diagrams of different countries and regions, including the USA (the leader), and Western Europe, show differences in agents, strategies, investments, selection mechanisms, and outcomes (Figure 3).

In the United States, the foundation of new DBFs is the result of the combined efforts of research universities and venture capital firms. Public funds support basic

Table 4 EU compared to the US institutional base: introduction to the thousand brakes

	European Union, particularly South and East Europe	USA
Customs	Over 20 major languages Dozens of regional languages	One language
	Public attitude opposed to biotechnology (van Reenen, 2002)	Public attitude favorable to biotechnology
Organizations	Little interorganizational mobility	High mobility
	Academics are public servants	Academics are not public servants
	Mental models of academics reluctant to industrial or publicly funded chairs	Mental models in favor of public and industrial chairs
	Universities weakly connected with industry	Universities strongly linked to industry
	Universities founded as teaching organizations	Universities conducting teaching and research
	Mental models against university patenting and in favor of publication	Mental models in favor of academic patenting and publication
	Mental models against private universities and academic entrepreneurship	Mental models accept private universities and academic entrepreneurship
Routines	Academic hiring tainted by inbreeding	Hiring often excludes inbreeding
Policy	Overregulation of biotechnology	Softer regulation
	National patenting predominant	US and EPO patenting dominant
	Failure of industrial demand due to low BERD (Calvert and Senker, 2004)	Strong industrial demand due to high BERD
	Some national patent systems are not easily accessible (Moreadel, 2008)	Patent registers easily available
	Scant public funding of research	Abundant public funding of research
	Low salaries for faculty	Comparatively reasonable salaries
	Cumbersome legislation on clinical trials	Fairly straightforward legislation (Cressey, 2009)
	Few exit avenues for venture capital	Several exits available for venture capital
	Few experienced angels and venture capitalists	Experienced angels and venture capitalists
Other	EU specialized in low-to-medium technology industry (EC, 2008)	United States more specialized in pharmaceuticals (EC, 2008)
	EU conducts 20% to 30% of global BERD in pharmaceuticals	US industry represents over 50% of BERD in pharmaceuticals
	Banking centered financial systems	Stock market centered financial systems

Table 5 Biotech market comparison in 2007: United States versus Europe

	United States	Europe
Public companies	386	181
Private companies	1116	1563
Total companies	1502	1744
IPO financing (USD millions)	1238	1010
Follow on /other offerings	14,689	4880
Venture financing (USD millions)	5464	1604
Total financing	21,391	7494
Total employment	130,600	39,740

Source: Ernst & Young (2008): *Beyond Borders. Global Biotechnology Report.*

research at the university and applied and commercial research at the DBF. With abundant venture capital and public funds, DBF built a portfolio of patents and developed new products. They organize research alliances with large pharmaceutical corporations, allowing them to pursue clinical trials, and request approval of products. Kenney (1986) was the first to expose the process (Table 5).

In Western Europe, particularly in Continental Europe, there is much less venture capital. The latest account finds 2350 DBF in Europe in 2006, which collected US$1.175 billion in 2006 in 156 deals and $1.704 billion in 2007 in 151 deals (around 11 million USD per deal). This represents one third of biotech venture capital funds in the US, where the number of companies is around 1500 and the venture capital fund for biotechnology is over $5 billion (Nasto, 2008). In Europe, most DBFs are not spin-offs but start-ups (Bigliardi *et al.* 2005). The connection between academia and commercial biotechnology is much weaker than in North America. The opportunities for learning and networking are much reduced in Europe. With little venture capital and reduced public support, the norm is slow growth and a proliferation of small firms.

6. Conclusions

In the innovation system perspective, technical change occurs in organizations structured by routines and influenced by policy incentives. Complex adaptive innovation systems are ever-changing configurations, in which it is sometimes difficult to assess success factors, best institutions and practices. Yet these systems can be harnessed, i.e. their underlying structures can be understood and their evolution can be guided

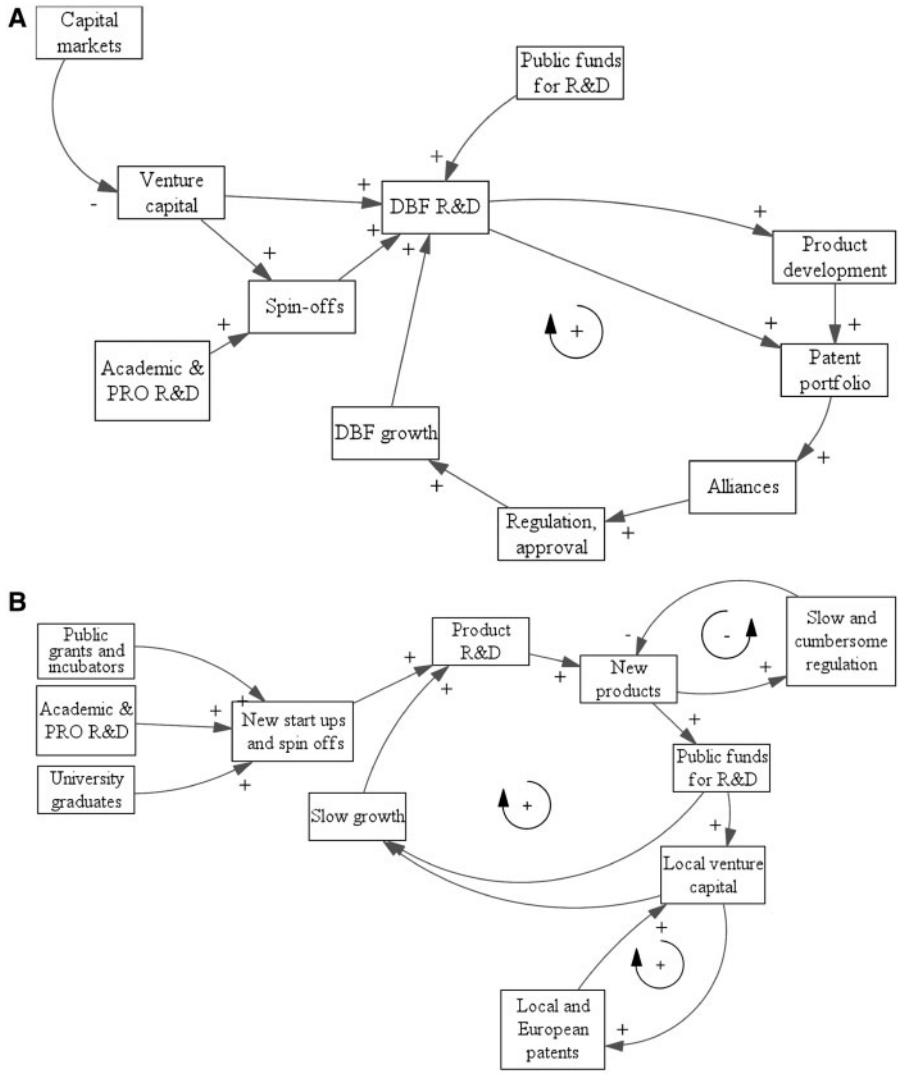

Figure 3 (**A**) US commercial biotechnology. (**B**) EU commercial biotechnology.

through public policy in order to increase *their* performance (Axelrod and Cohen, 2000).

This article brings more evidence in favor of the hypothesis that innovation systems and their STI institutions are characterized by variety, multiple equilibriums (many of which are very inefficient), and continuous change. There are no optimum policy sets, but a few fairly efficient ones, and many fairly inefficient ones.

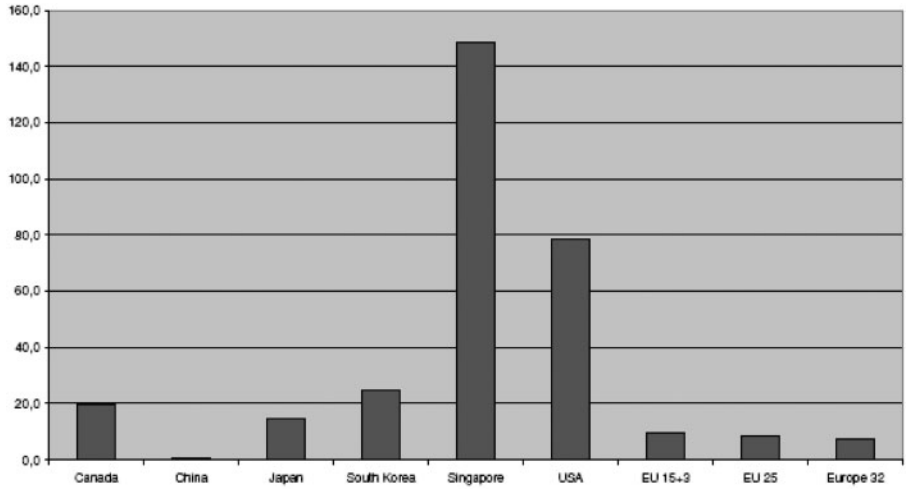

Figure 4 Total public funding of biotechnology 2005, selected countries and regions in US$ PPP, per million population (EC, 2007). *Source*: EC (2007: 22).

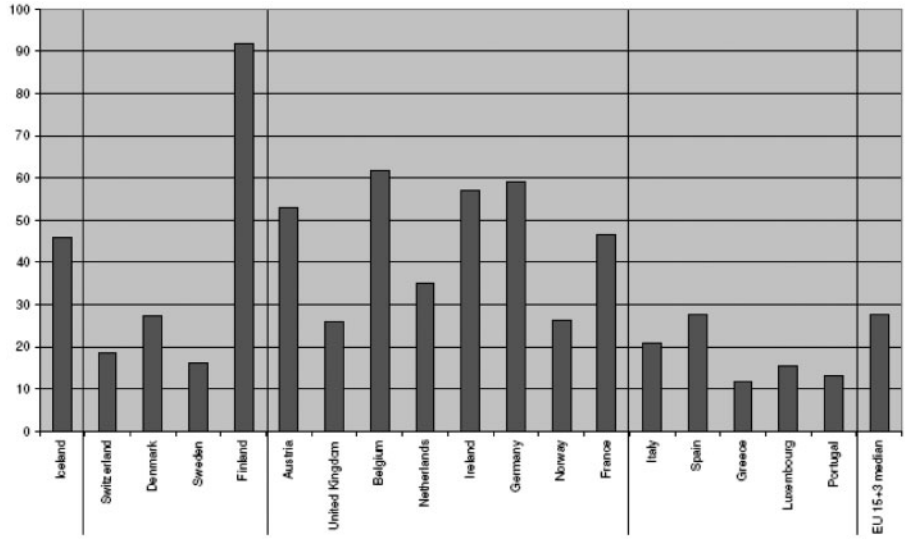

Figure 5 EU public spending on biotechnology, in $PPP pMC, 2002–2005. *Source*: EC (2007: 22).

A second theoretical conclusion is that national systems of innovation are long-standing and are not disappearing in the face of technoglobalism. National, regional and sectoral institutions restrain technological convergence. Institutions change slowly. The sectoral system of innovation approach has put the emphasis

on the international similarities between technologies, actors and institutions within a given sector. This contribution is very important. However, institutions are national, and sometimes subnational, because of their history. Universities in North America are different from those in Europe, Japan, or Latin America. They will not easily change to accommodate a new sector such as biotechnology. The historical division between universities conducting mainly teaching, while research is centered in specialized institutions where there are no students (CNRS/CSIC/Max–Planck type), is *not* conducive to the development of biotechnology. Institutions—as David (1994) has put it—are the carriers of history, not of sectoral systems.

> Organisations that recruit members on ascriptive grounds (whose family do you belong to? In what territory where you born?) are likely to find it more difficult to implement meritocratic procedures for the internal promotion or separation of individual members . . . "In this way the organisational structure can become 'locked in' to a comparatively narrow subset of routines, goals an future growth trajectories" (David, 1994: 214).

The third theoretical conclusion is that convergence should be pictured not simply as a macroeconomic phenomenon, as it has most often been. This article suggests that convergence is above all sectoral, and macroeconomic convergence is a result of what occurs at the sector level. Germany may keep its leadership in chemicals, but it is not catching up in biotechnology. The United Stares is falling behind in the car industry, but remains ahead in biotechnology.

Technology and evolution co-evolve, but this co-evolution is far from perfect. Just as France never caught up with electrical (and later electronic engineering), it may never catch up in biotechnology if its institutions remain locked in inferior practices.

Finally, system dynamics provides a useful tool for modeling causal links and interactions in any system, and most interestingly in complex ones such as innovation systems.

There are also several policy implications. The first is that sector- and technology-specific institutions must be reintroduced into growth analysis, as many of us have been suggesting. But policies have to be studied and implemented within systems, and not in isolation, due to complementarity. Public investment in human capital without taking care of the demand side (i.e. that companies hire the bearers of such capital, and apply them in crucial innovative routines through R&D policies directed at the private sector) may result in the waste of such capital, or in brain drain.

The second policy implication is that institutional change is not to be taken for granted, it does not occur by "natural selection" of the best routines, organizational forms or policy recipes, and the simultaneous abandonment of less efficient ones. Institutional change is the result of human action. Benchmarking helps in the task of implementing institutional change, and it must be considered a privileged method for policy implementation in evolutionary economics. Institutional action must then

take place: benchmarking is not just survey and study; it is done with the purpose of action, including the understanding of inertia and the ways to overcome it.

Another policy implication is that all four types of institutions are slow to evolve, but—among them—private and public sector incentives are the most likely to evolve and allow moderately fast system changes. STI Policies are less prone to inertia and less dependent on contracts and routines, and may accelerate organizational change. They do so by promoting the adoption of new modules and routines in private and public organizations. Also, these policies will take decades to produce the desired changes, due to the great inertia of the other relevant organizations (universities, government laboratories, and private firms). Grand plans for changing university systems or government laboratories (the French attempt taking place these days) seldom work because of existing mental models, routines and contracts in those organizations. However, new studies show that greater funding, greater autonomy, and greater competition are part of the solution. Aghion *et al.* (2007, 2009) suggest that European universities should be free to hire whomever they deem reasonable and live in a competitive world with the result of their choices. They also found fairly high endogamy, particularly in smaller countries and southern ones.

The information revolution has produced "information contagion" in biotechnology techniques without a similar diffusion in their underlying institutional setting. Among the would-be catchers-up, the four types of institutions conspire against fast growth. In terms of beliefs, the public attitude is against many biotechnology applications and products. Science and technology organizations (universities, government laboratories, specialized markets and venture capital firms) often suffer from inferior routines and practices, Sweden, Switzerland and the UK being among the exceptions. European and national policies supporting biotechnology are sometimes innovative, but the public financing of research—in academia, public research organizations and private firms—is reduced compared to US levels.

Let me add two final observations. First, it is interesting to find out that since at least the late 1980s social scientists have identified institutions, and particularly those involved in the generation, diffusion and use of science and technology, as the basis of economic development. Yet, they have not refined the analysis of such institutions in order to understand different classes of institutions, different forms of evolution, and different levels of efficiency and effectiveness. My guess is that this drawback is due to the fact that it was economists who discovered the key role of institutions. But their training (economics does not study institutions) did not allow them to go beyond the general identification of their role within the "residual" of economic development.

Second, institutions are more difficult to understand because they are located at the intersection between culture, psychology, history, and society. One example: why do people want to develop (not simply keep) and expand the use of such languages as Bask, Catalan, Irish, Galician, and perhaps resuscitate the 30-odd dialects that exist in

Italy, 12 of which already have official recognition since 1999? This is enigmatic and is anything but "rational" in the traditional sense, if it is true that the world is converging toward five or six major languages (according to the UN). Maybe it is a way of protecting themselves against the strong international winds fuelled by the European Union in the midst of globalization. University hiring is similar: why give prestigious and well-paid positions to foreigners and not to our own children and nephews? Why is it that the principle "hire the best from around the globe" is evident for the managers of the Barcelona Football club, but is not evident for the University of Barcelona? Lack of competition among academic institutions is part of the answer. But more knowledge is needed to understand the issue and provide solutions. Similarly, the determinants of a vibrant venture capital industry include mental models and other institutions such as banking regulations and capital gains taxation.

Will Europe attain the critical mass and institutional fine-tuning required to take advantage of biotechnology? The short history of high technology in postwar Europe proves that nothing is to be taken for granted in terms of catching up. Biotechnology will offer many business and other welfare opportunities in the future, but today the only country that seems institutionally ready to take advantage of them is the United States. Yet, it is also true that every backward country was relatively inefficient when it started to catch up with the leader. It is not written anywhere that Europe will not catch up with the United States in biotechnology. But catching up is not settled either. The issue is whether the European Union is able to make its institutions co-evolve with this fast moving set of technologies.

References

Academic Career Observatory (ACO) (2007), *Report 2008*. European University Institute: Fiesole, Italy.

Aghion, P., M. Dewatripont, C. Hoxby, A. Mas-Collell and A. Sapir (2007), *Why Reform Europe's Universities*. Bruegel Policy Brief: Brussels, Issue, 4.

Aghion, P., M. Dewatripont, C. Hoxby, A. Mas-Collell and A. Sapir (2009), 'The governance and performance of research universities,' Cambridge, MA, NBER WP 14851.

Aldrich, H. (1999), *Organizations Evolving*. Sage: London, UK.

Allen, P. A. (2001), 'Knowledge, ignorance and the evolution of complex systems,' in J. Foster and J. S. Metcalfe (eds), *Frontiers of Evolutionary Economics, Competition, Self-Organization and Innovation Policy*. Cheltenham: Elgar, pp. 313–350.

Ang, S. H. (2006), 'Country of origin effect of VC investment in biotechnology companies,' *Journal of Commercial Biotechnology*, **13**(1), 12–19.

Arthur, W. B., S. N. Durlauf and D. Lane (1997), 'Introduction,' in W. B. Arthur *et al.* (ed.), *The Economy as an Evolving Complex System II*. Perseus: Reading, MA, pp. 1–14.

Axelrod, R. (1984), *The Evolution of Cooperation*. Basic Books: New York, NY.

Axelrod, R. (1997), *The Complexity of Cooperation*. Princeton University Press: Princeton, NJ.

Axelrod, R. and M. D. Cohen (2000), *Harnessing Complexity*. Basic Books: New York, NY.

Barkley Rosser, J. Jr (2003), 'Complexity in Economics,' in J. Barkely Rosser, Jr (ed.), *Complexity in Economics*. Cheltenham: Elgar.

Bartholomew, S. (1997), 'National systems of biotechnology innovation: complex interdependence in the global system,' *Journal of International Business Studies*, **28**(2), 241–267.

Bas, J. and F. Ven der Ploeg (2006), 'Guide to reform of higher education: a European Perspective,' *Economic Policy*, **21**(47), 535–592.

Beinhocker, E. (2006), *The Origin of Wealth*. Harvard Business School Press: Boston, MA.

Bigliardi, B., A. Nosella and C. Verbano (2005), 'Business models in Italian biotechnology: a quantitative analysis,' *Technovation*, **25**, 1299–1306.

Breznitz, D. (2009), 'National institutions and the globalised political economy of technological change: an introduction,' *Review of Policy Research*, **26**(1–2), 1–11.

Bruton, G., V. Fried and S. Manigart (2005), 'Institutional influences on the worldwide expansion of venture capital', Entrepreneurship,' *Theory and Practice*, **29**(6), 737–760.

Calvert, J. and J. Senker (2004), 'Biotechnology innovation systems in two small countries: a comparison of Portugal and Ireland,' *Science and Public Policy*, **31**(5), 359–371.

Chang, H. J. (2003), *Kicking Away the Ladder. Development Strategy in Historical Perspective*. Anthem Press: London.

Cohen, M. D., R. Burkhart, G. Dosi, M. Egidi, L. Marengo, M. Warglien and S. Winter (1996), 'Routines and other recurring patterns of organizations: contemporary research issues,' *Industrial and Corporate Change*, **5**(3), 653–699.

Commons, J. H. (1931), 'Institutional economics,' *American Economic Review*, **21**, 648–657.

Cooke, P. (2001), 'Regional innovation systems, clusters and the knowledge economy,' *Industrial and Corporate Change*, **10**(4), 945–974.

Cressey, D. (2009), 'European clinical trials under fire,' *Nature*. March 13, 2009 (Epub ahead of print; doi:10.1038/news.2009.163).

David, P. A. (1993), 'Intellectual property institutions and the Panda's Thumb: Patents, copyrights and trade secrets in economic theory and history,' in M. Wallerstein, M. Mogee and R. Schoen (eds), *Global Dimensions of Intellectual Property Rights in Science and Technology*. National Academy Press: Washington, DC, pp. 19–61.

David, P. A. (1994), 'Why are institutions the carriers of history?: Path dependence and the evolution of conventions, organizations and institutions,' *Structural Change and Economic Dynamics*, **5**(2), 205–220.

David, P. A. (1998), 'Common agency contracting and the emergence of "open science" institutions,' *American Economic Review*, **88**(2), 15–21.

Dohse, D. (2000), 'Technology policy and the regions: the case of the BioRegio contest,' *Research Policy*, **29**, 1111–1133.

Dosi, G., P. Llerena and M. Sylos Labini (2006), 'The relationship between science, technologies and their exploitation: an illustration through the myths of the so-called "European Paradox",' *Research Policy*, **35**, 1450–1464.

Ederer, P. (2006), *Innovation at Work: The European Human Capital Index*. The Lisbon Council: Brussels, Belgium.

Edquist, C. (ed.), (1997), *Systems of Innovation*. Pinter: London.

Enzing, C, A. van der Giessen, S. van der Molen, R. Lidner and J. Senker (2008), 'Dynamics in biotechnology policy making in Europe in the period 1994–2008,' *International Journal of Biotechnology*, **10**(4), 283–302.

Ernst & Young (2008), *Global Biotechnology Report*. London, UK.

European Commission (EC) (2007), 'Competitiveness of the European biotechnology industry' Working Paper.

European Commission (EC) (2008), *A more research-intensive and integrated European Research Area*. Directorate General for Research: Brussels: Belgium.

Florida, R. and M. Kenney (2002), 'Creating an environment for venture capital in India,' *World Development*, **30**(2), 227–253.

Fox, R. (1993), 'France in perspective: education, innovation and performance in the French electrical industry, 19880-1914,' in R. Fox and A. Guagnini (eds), *Education, technology and performance in Europe, 1850–1939*. Cambridge University Press: Cambridge, pp. 201–224.

Freeman, C. (1987), *Technology Policy and Economic Performance*. Pinter: London, UK.

Gompers, P. A. (1998), 'Venture capital growing pains: show the market diet,' *Journal of Business and Finance*, **22**(6–8), 1089–1104.

Haar, B. (2001), 'Venture capital funding for biotech pharmaceutical companies in an integrated financial services market: Regulatory diversity in the EC,' *European Business Organization Law Review*, **2**(3/4), 585–602.

Hayek, F. (1973), *Law, legislation and liberty*, Vol. 1, Routledge: London.

Henrekson, M. and N. Rosenberg (2001), 'Designing efficient institutions for science-based entrepreneurship: lessons from the US and Sweden,' *Journal of Technology Transfer*, **26**, 207–231.

Hodgson, G. (1989), 'Institutional rigidities and economic growth,' in G. Hodgson (ed.), *The Economics of Institutions*. Cheltenham: Elgar.

Hodgson, G. (2009), 'On the institutional foundations of law: the insufficient foundations of custom and private order,' *Journal of Economic Issues*, **43**(1), 143–167.

Kaiser, R. and H. Prange (2004), 'The reconfiguration of national innovation systems: The example of German biotechnology,' *Research Policy*, **33**, 395–408.

Kenney, M. (1986), *Biotechnology: the University-Industry Complex*. Yale University Press: New Haven, CT.

Kim, K., H. Byung Hwan and S. Chung (2007), 'US national innovation system in biotechnology from the Korean perspective,' *PICMET Proceedings 2007*. Portland.

Kneller, R. (1999), 'University industry cooperation in biomedical R&D in Japan and the US: implications for biomedical industries,' in L. W. Branscomb *et al.* (ed.), *Industrializing Knowledge*. MIT Press: Cambridge, MA, pp. 410–438.

Kuemmerle, W. (2001), 'Comparing catalysts of change: evolution and institutional differences in the venture capital industries in the US, Japan, and Germany,' *Research on Technological Innovation, Management and Policy*, **7**, 227–261.

Larsen, E. and A. Lomi (2002), 'Representing change: a system model of organisational inertia and capabilities as dynamic accumulation processes,' *Simulation Modelling Practice and Theory*, **10**, 271–296.

Le Déaut, J. Y. (2005), 'Rapport sur la place des biotechnologies en France et en Europe,' Assemblée nationale, Paris, 12th Legislature, Parliamentary Document #2046.

Lee, D. P. and M. D. Dinber (2005), 'The rise of venture capital and biotechnology in the US and Europe,' *Nature Biotechnology*, **23**(6), 672–677.

Lorenz, P. and H. Zinke (2005), 'White biotechnology: differences in US and EU approaches,' *Trends in Biotechnology*, **23**(12), 570–574.

Lundvall, B.-A. (ed.), (1992), *National Systems of Innovation*. Pinter: London.

Malerba, F. (ed.), (2004), *Sectoral Systems of Innovation*. Cambridge University Press: Cambridge, UK.

Mintrom, M. (1997), 'Policy entrepreneurs and the diffusion of innovation,' *American Journal of Political Science*, **41**(3), 738–770.

Mohnen, P. and L.-H. Röller (2005), 'Complementarities in innovation policy,' *European Economic Review*, **49**, 1431–1450.

Moreadel, G. (2008), 'Patent information in Italy,' *World Patent Information*, **31**(1), 19–31.

Mowery, D. and N. Rosenberg (1998), *Paths of Innovation*. Cambridge University Press: Cambridge, UK.

Mowery, D., R. R. Nelson, B. Sampat and A. Ziedonis (2001), 'The growth of patenting and licensing by US universities: An assessment of the Bayh-Dole Act of 1980,' *Research Policy*, **30**, 99–119.

Mowery, D. C. and B. Sampat (2004), 'Universities in national innovation systems,' in J. Fagerberg, D. C. Mowery and R. R. Nelson (eds), *The Oxford Handbook of Innovation*. Oxford University Press: New York, NY, pp. 209–239.

Myrdal, G. (1959), *Economic Theory and Under-Developed Regions*. Duckworth: London, UK.

Nasto, B. (2008), 'Chasing biotechnology across Europe,' *Nature Biotechnology*, **26**, 83–288.

Navarro, A. and A. Rivero (2001), 'High rate of inbreeding in Spanish universities,' *Nature*, **410**(6824), 14.

Nelson, R. R. (1994), 'The co-evolution of technology and institutions,' in R. W. England (ed.), *Evolutionary concepts in Contemporary Economics*. University of Michigan Press: Ann Arbor, MI.

Nelson, R. R. (2001), 'Co-evolution of institutions and technologies,' in R. Foster and J. S. Metcalfe (eds), *Frontiers of Evolutionary economics, Competition, Self-Organization and Innovation Policy*. Elgar: Cheltenham, UK.

Nelson, R. R. (ed.), (1993), *National Innovation Systems, a Comparative Analysis*. Oxford University Press: New York, NY.

Nelson, R. R. (2005), *Technology, Institutions and Economic Growth*. Harvard University Press: Cambridge, MA.

Nelson, R. R. and N Rosenberg (1993), 'Technical innovation and national systems,' in R. R. Nelson (ed.), *National Innovation Systems, a Comparative Analysis*. Oxford University Press: New York, NY, pp. 3–21.

Niosi, J. (2002), 'National systems of innovation are x-efficient (and x-effective): why some are slow learners,' *Research Policy*, **31**(2), 291–302.

Niosi, J., P. Saviotti, B. Bellon and M. Crow (1993), 'National systems of innovation: In search of a workable concept,' *Technology in Society*, **15**(2), 207–227.

Niosi, J. and S. Reid (2007), 'Biotechnology and nanotechnology: Windows of opportunity for LDCs?' *World Development*, **35**(3), 426–438.

North, D. (1991), 'Institutions,' *Journal of Economic Perspectives*, **5**(1), 97–112.

OECD (2001), 'Biotechnology Statistics in OECD Member Countries: Compendium of Existing National Statistics,' DSTI, STI Working papers 2001/6, Paris, France.

OECD (2006), *Innovation on Pharmaceutical Biotechnology, Comparing National Innovation Systems at the Sectoral Level*. Paris: France.

Olson, M. (1965), *The Logic of Collective Action*. Harvard University Press: Cambridge, MA.

Orsenigo, L. (2001), 'The (failed) development of a biotechnology cluster: the case of Lombardy,' *Small Business Economics*, **17**, 77–92.

Owen-Smith, J., M. Riccaboni, F. Pammolli and W. W. Powell (2002), 'A comparison of US and European University–Industry relations in the life sciences,' *Management Science*, **48**(1), 24–43.

Patel, P. and K. Pavitt. (1994), 'The nature and economic importance of national innovation systems,' *STI Review*, **14**, 9–32.

Perotti, R. (2002), 'The Italian university system: rules versus incentives,' First Conference on Monitoring Italy, Rome, Italy.

Peter, V. (2004), 'International benchmarking of biotech research centres: lessons and perspectives,' *Nature Biotechnology*, **22**(5), 633–635.

Pisano, G. (2006), *Science Business*. Harvard Business School Press: Boston, MA.

Prevezer, M. (2001), 'Ingredients in the early development of the US biotechnology industry,' *Small Business Economics*, **17**, 17–29.

Puffert, D. J. (2004), 'Path dependence, network form and technological change,' in T. W. Guinnane, W. A. Sundstrom and W. C. Whitley (eds), *History Matters*. Stanford University Press: Stanford, CA, pp. 63–95.

Radzicki, M. and J. Sterman (1994), 'Evolutionary economics and system dynamics,' in R. W. England (ed.), *Evolutionary concepts in Contemporary Economics*. University of Michigan Press: Ann Arbor, MI, pp. 61–89.

Rosenberg, N. and R. R. Nelson (1994), 'American universities and technical advance,' *Research Policy*, **24**, 323–348.

Ryall, M. D. (2008), 'Causal ambiguity, complexity and capability-based advantage,' *Management Science*, **55**, 389–403.

Samson, C. (2004), 'EU expansion: Enlarged horizons or false dawn?' *Nature Biotechnology*, **22**(5), 501–504.

Samuels, W. J., A. A. Schmidt and J. D. Shaffer (1994), 'An evolutionary approach to law and economics,' in R. W. England (ed.), *Evolutionary concepts in Contemporary Economics*. University of Michigan Press: Ann Arbor, MI, pp. 93–110.

Sanzenbacher, R., A. Dwenger, M. Schuessler-Lenz, K. Cichutek and E. Flory (2007), 'European regulation tackles tissue engineering,' *Nature Biotechnology*, **25**(10), 1089–1091.

Senker, J., C. Enzing and T. Reiss (2008), 'Biotechnology policies and performance in central and eastern Europe,' *International Journal of Biotechnology*, **10**(4), 34–362.

Sharp, M. (1999), 'The science of nations: European multinationals and American biotechnology,' *International Journal of Biotechnology*, **1**(1), 132–162.

Shevell, S. (2002), 'Law versus morality as regulators of conduct,' *American Law and Economics Review*, **4**(2), 227–257.

Simmons, B. A. and Z. Elkins (2004), 'The globalization of liberalization: policy diffusion in the international political economy,' *American Political Science Review*, **98**(1), 171–189.

Soler, M. (2001), 'How inbreeding affects productivity in Europe,' *Nature*, **411**, 132.

Stevens, P. (2004), 'Academic salaries in the UK and the US,' *National Institute Economic Review*, **190**, 104–113.

Storz, C. (2008), 'Dynamics in innovation systems: evidence from Japan's game software industry,' *Research Policy*, **37**(9), 1480–1491.

Tassey, G. (2007), 'Tax incentives for innovation: time to restructure the R&E tax credit,' *Journal of Technology Transfer*, **32**, 605–615.

Van Reenen, J. (2002), 'Economic issues for the UK biotechnology sector,' *New Genetics and Society*, **21**(2), 109–130.

Appendix A

Table A1 US biotechnology patents 1985–2006 main region and country

Country/ region	Number of patents 1985–95	World patents 1985–1995 (%)	Number of patents 1996–2006	World patents 1996–2006 (%)
USA	8868	60.8	37,625	65.95
EU	2056	17.2	9965	17.46
Japan	2290	15.70	4416	7.7
Germany	840	5.76	2525	4.42
Canada	680	4.66	1928	4.22
UK	491	3.37	2044	3.58
France	365	2.5	1712	3
The Netherlands	163	1.12	747	1.31
Denmark	101	0.69	745	1.31
Belgium	82	0.56	525	0.92
Sweden	134	0.92	517	0.91
Italy	134	2.6	379	0.61
Austria	52	0.36	252	0.44
Finland	68	0.47	213	0.37
Spain	27	0.34	121	0.21
Singapore	1	0.01	62	0.1
South Korea	31	0.21	408	0.72
World	14,586	100	57,044	100

Source: NSF (2008): *Science and Engineering Indicators*, Vol. 2.

Table A2 EPO Patents in biotechnology, 1985–2006, selected countries and regions

Country/ region	Number of patents 1985–1995	Number of patents 1996–2006	World patents 1985–1995 (%)	World patents 1996–2006 (%)
USA	2720	6281	35	39.7
EU-27	2850	6070	36.7	38.33
Germany	1046	2031	13.5	12.8
UK	526	1202	6.8	7.6
France	482	931	6.2	5.9
Belgium	93	257	1.2	1.6
Austria	74	160	1.0	1.0

(continued)

Table A2 Continued

Country/ region	Number of patents 1985–1995	Number of patents 1996–2006	World patents 1985–1995 (%)	World patents 1996–2006 (%)
Netherlands	162	419	2.1	2.64
Finland	37	138	0.48	0.87
Denmark	114	289	1.47	1.82
Italy	135	265	1.74	1.67
Sweden	113	245	1.47	1.55
Spain	21	85	0.27	0.53
Japan	1740	2076	22.4	13.1
Singapore	1	13	n.	n.
South Korea	10	104	0.13	0.65
World	7756	15,833	100	100

Source: NSF (2008): *Science and Engineering Indicators*, Vol. 2.

Table A3 PCT Patent applications in biotechnology, 2000 and 2005, selected countries and regions

	Total		Percentage (%)	
	2000	2005	2000	2005
USA	4719	2718	49.2	39.7
EU-27	2299	1701	24.0	24.9
Japan	774	1195	8.1	17.5
Canada	235	223	2.5	3.3
South Korea	119	156	1.2	2.3
Australia	129	151	1.3	2.2
Israel	113	101	1.2	1.5
China	911	88	9.5	1.3
Switzerland	91	87	0.9	1.3
Singapore	27	53	0.3	0.8
India	28	50	0.3	0.7
Russia	21	30	0.2	0.4
Norway	24	20	0.3	0.3
South Africa	5	7	0.1	0.1
World	9590	6842	100	100

Source: European Commission (2008): *A more research-intensive and integrated European Research Area*, Brussels, p. 68.