

Exploring and exploiting microbiological commons: contributions of bioinformatics and intellectual property rights in sharing biological information.

Introduction to the special issue on the microbiological commons

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1. Objectives

As scientists and user groups become better connected with each other, particularly through the Internet, and as research focuses on issues of global importance, such as climate change, human health and biodiversity, there is a growing need to systematically address data access and sharing issues beyond national jurisdiction and thereby create greater value from international co-operation. The goal should be to ensure that both researchers and the broader public receive the optimum return on public investments, and to build on the value chain of investments in research and research data (Stiglitz *et al.* 2000). Data sharing of microbiological information is essential for expedited translation of research results into knowledge, products and procedures to improve matters of general interest such as the exploration, conservation and exploitation of biodiversity. At present the widespread national, international and cross-disciplinary sharing of research data is no longer merely a technological matter, but also a complex social process in which researchers have to balance different pressures and interests. Purely regulatory approaches to data sharing are not likely to be successful without consideration of these factors, as technology itself will not fulfill the promise of e-science. Information and communication technologies provide the physical infrastructure. It is up to national governments, international agencies, research institutions and scientists themselves to ensure that the institutional, financial and economic, legal, and cultural and behavioral aspects of data sharing are taken into account (Arzberger *et al.* 2004).

In an attempt to point out the different technological shortcomings and conflicts of interest – and find ways to overcome the opposing forces that prevent sharing of biodiversity data – it is timely to bring together the information shareholders. The current workshop will address the problematic nature of data sharing for the particular case of microbes. Microbes are the smallest life forms, but together they represent the single largest mass of life on earth. As a result they are often stepmotherly treated in general biodiversity projects, but analogous to the

role of dark matter that is invisibly hidden across the universe, microbes cannot be neglected for the creation, maintenance and restoration of balance in virtually all ecosystems. All life on earth is inextricably intertwined with microorganisms as they are critical to maintaining the health of organisms that depend on them for nutrient, mineral and energy recycling, while conversely some microorganisms can cause infectious disease when they overlap with susceptible hosts. Microbes have the greatest diversity of all living creatures, using biological and chemical processes that exist nowhere else in nature. Consequently, we can look to the bacterial world as a vast, mostly untapped resource of biotechnological potential, and we can study microbes to understand the majority of life processes to further unravel the basic mechanisms of life on earth.

This interplay of the microorganisms with their surroundings – from individual cells to entire ecosystems – strongly appeals to be translated into a technology platform that seamlessly integrates all available knowledge, enabling the construction of dynamic self-learning systems for automated information acquisition and knowledge creation. As such, the workshop on “exploring and exploiting the microbiological commons” is part of a pilot project aiming at gathering expertise and new ideas in the build-up process of a European Biological Resources Platform¹. In particular, its goal is to constitute a reference group for a strategic research program on a cross-cutting theme of interest to the platform as a whole.

For several reasons, the bacterial world seems an ideal prototype to focus on as a starting point for the evocation of a biodiversity data exchange platform. Notwithstanding their broad metabolic diversity, there are at present no more than 6000 validly described species names which result in a fairly limited number of anchor points for an information system. Moreover, the polyphasic approach underlying most microbial screening studies has made available large data sets on standardized observational features that reflect the phenotypic and genotypic diversity encountered among bacteria. In addition, the limited genome size that is the groundwork of bacterial life has been a strong factor leading to sequencing the complete genome of some 200 bacterial organisms, with a least another 650 complete genome sequencing projects reaching their final stage in the near future (www.genomesonline.org).

Integrated and combined access to this multifaceted information realm opens perspectives for the implementation of new applications. Moreover, this new set of tools for studying biological building blocks and pathways will lay the foundation for even more complex future

projects. These may include the complete mapping of an organism's protein and metabolism networks, as well as the creation of biological models that can pave the way for theoretical models on bacterial speciation and their complex ecological dynamics (Gevers *et al.* submitted). The development of tools for automated species identification undoubtedly requires access to sets of skills that are not typically encountered among systematists or within the departments and institutions in which the bulk of formal taxonomic identifications are conducted. Developing solid approaches requires novel collaborations between microbiologists, engineers, mathematicians, computer scientists and personnel who have significant knowledge of both applied biology and computing science, as not to forget the legal aspects of sharing biological resources and software tools in the public domain. By engaging seemingly unrelated disciplines, traditional gaps in terminology, approach and methodology might be gradually eliminated. With roadblocks to potential collaboration removed, a true meeting of minds can take place: one that broadens the scope of investigation into biodiversity problems, yields fresh and possibly unexpected insights, and may even give birth to new hybrid disciplines that are more analytically sophisticated.

2. State of the art

The implementation of such a cross-cutting research program only makes sense on the basis of a common diagnosis of the problems that have to be faced and the elaboration of a fundamental hypothesis that guides the research.

Relying on recent *Colloquia Reports* of the American Society of Microbiology (www.asm.org), one can already point to some key elements that are part of such a diagnosis. The enhanced recourse to genetic screening and bio-informatics within microbiology is causing a profound change in the organization of research and development in biotechnology. In particular biological resources are increasingly explored through computational means and information is extracted through the combination of a wealth of data, coming from different sources and scales of interaction. Also, contemporary research shows the necessity to move towards a systems biological perspective: the way the genes are expressed in an organism depends on the ecosystemic properties of its environment. In the analysis of properties of micro-organisms, genetic information has to be combined with behavioral and environmental data. Moreover, in such diverse fields as antibiotics, food research or bio-security important new insights are to be expected from the possibility of enhancing our knowledge on the

principles behind the generation of microbiological diversity through new computational and experimental techniques.

As a consequence of this re-organization of research and development in biotechnology, users and scientists have become more interconnected in the innovation chain. Three factors play a key role in the necessity of this dynamic user-scientist interaction.

First, the adoption of a systems biological perspective requires combining information coming from a broad range of actors. In particular, knowledge of the behavioral properties of the organisms in the real-world requires gathering data from a diverse set of “information shareholders”, ranging from traditional communities for data on slow ecosystems variables, to physicians for data on antibiotics resistance or industries for data on fermentation processes. For instance, a study on the genetic diversity of *Vibrio cholerae* strains, isolated in different geographical regions of Brazil, has revealed the close evolutionary lineage between different cholera causing strains in completely different geographical regions (Thompson *et al.* 2003). This study relied on a combination of clinical data on cholera, environmental data on *Vibrio cholerae* and genomic fingerprinting data of the collected strains. As this example shows, organizing and combining information from different information shareholders has become a key issue.

Second, the multi-actor nature of the information gathering process has also raised new social issues. Indeed, public concerns have been raised about the appropriate protection of the rights of the information shareholders, for example in the use of clinical data or in bioprospecting. In this context, opting for a certain mode of organization of the information gathering process is not only a technical choice, but is also a choice for a certain set of social values, such as prior informed consent, privacy protection or benefit sharing. Therefore, the path of technical innovation in biotechnology has become more “reflexive” (Beck 1997, pp.11-19), in a similar manner to what has happened in other fields such as the Internet (Dedeurwaerdere 2002). Moreover, in this multi-actor process, protecting the rights of the shareholders cannot be the sole responsibility of the scientist, but depends also on the distribution of the bundle of rights granted to the intermediaries in the process of data sharing and the end users of the data.

Finally, the recourse to bio-informatics and database management also introduces a new type of technical « actor » in the process: the information and communication technologies (ICT).

Indeed, the role of ICT goes far beyond its use as a passive tool for data gathering and exchange. Instead, it provides an active contribution to the process of knowledge generation itself. For instance, in the case of integrated strain databases, self-learning systems organize data across different scales and show new types of linkages in an unanticipated manner (Dawyndt *et al.* in press). Also, computer simulations based on self-organizing networks produce new patterns of biodiversity out of existing data sets, allowing to extend our knowledge beyond the existing culturable microorganisms (Kohonen 1990 ; Abe *et al.* 2003). The self-organisatory character of these computational processes also requires a closer interaction between the provider and the user of the information. Indeed, these processes produce a plurality of possible paths of development and the user plays a key role in producing the appropriate feedback information for the selection between these paths.

The fundamental hypothesis of the research, drawing on these insights, is that this re-organization of the innovation chain implies a *reversible interaction* between scientists and innovators on the one hand and the end users of the new products (food, drugs, environmental technologies, etc ...) on the other:

- on the one hand, the combination of information coming from genetic screening, bio-informatics, know-how and traditional knowledge, etc. generates new knowledge and different possible paths of innovation, often in an unpredictable manner
- on the other hand, end users should (1) provide the criteria for *selecting* between the different paths of development (2) provide input to the innovation process by bringing information from the behavioral environment of the products and (3) provide appropriate guarantees for the protection of the rights of the information shareholders.

Some projects have already been developed relying on such a reversible interaction between users and scientists, such as the Iceland Health Sector Database (IHD), which combines health sector databases with genealogical and human genomics data in order to generate knowledge about the interplay between genes, environment, disease, treatment and outcomes in an innovative way². No study has been undertaken in a more systematic way on the generic concept of a global microbial information system for knowledge generation as such. That is why in this pilot project, we want to focus on one particular case study where a sufficiently comprehensive dataset already exists, allowing to deal with these issues in a more systematic way.

The pilot project on « exploring the microbiological commons » focuses on one main component of this ongoing transformation of the innovation chain. This is the role of bioinformatics and intellectual property rights for knowledge generation, data access and data sharing. As has been mentioned above, one of the advantages of focusing on this case is the existence of available large data sets on standardized and reproducible observational features, both of genetic and phenotypic nature. Moreover, from the point of view of intellectual property rights, it is also one of the key areas where the most advanced experiments with institutions for exchange and sharing of data and biological material have been developed (such as public sequence databases³, the Mosaics⁴ project, etc.). These new institutions emerged as collaborative efforts creating appropriate data sharing for the exploration of the microbiological commons.

3. Bioinformatics for knowledge generation

The use of “bioinformatics” in the building of global databases in microbiology aims at pinpointing the key technologies and necessary building blocks that should make it possible to i) build an accumulative knowledge repository that captures the reams of experimental data and meta-data about micro-organisms, and to ii) develop general data mining tools for knowledge discovery within this data-rich environment, in order to iii) establish dynamically updated and flexible portals upon the observed bacterial diversity and related biotechnological innovations, with the ultimate goal of iv) valorising newly discovered insights as new applications or end-products. This leitmotiv is schematically represented in Figure 1. The reality is that all of those involved in the initial stages of the design of automatic and dynamic models upon the raw material that is at the heart of bio-discovery research are in a period of intense experimentation, the outcome of which is difficult to predict. However it is strongly believed that – although some of the visions may change in their details – prototyping and lack of dogmatism are undoubtedly the way forward. One of the primary goals of the bioinformatics sessions is to streamline some of these pioneering initiatives and mould the different insights they have produced into a more integrative approach.

[fig 1. about here]

With the rapid emergence of data formats and applications in bio-informatics supporting a veritable cottage industry of databases and web-services, the design of commonly accepted and implemented data formats and interrogation languages becomes paramount to support holistic scenarios. The issue of querying databases in environments where the distributed data sources have different schemas has been addressed extensively in literature, and is known as the *schema integration* problem. Multiple common schema design initiatives for the standardization of data exchange between distributed microbial data providers have arisen over the past two decades: Microbial Information Network Europe (MINE) and Common Access to Biotechnological Resources and Information (CABRI) are standard schemas designed specifically for disseminating information on microorganisms, while the Global Biodiversity Information Facility (GBIF) supports both Access to Biological Collection Data (ABCD) and Darwin Core as standard schemas to cover all information about the complete biodiversity on earth. Standards for managing biodiversity content have hardly been a riveting topic for researchers. But they are key to a host of issues that affect scientists and user groups,

such as searching, data mining, functionality and the creation of stable, long-term archives of research results.

Successful database integration does however not only require the development of common schemas which allow searching the different information sources from a logical single point of access, but also urges that the collected information is normalized and corrected wherever necessary. Database annotations lack the prestige of published papers, as their value is largely ignored by citation metrics, and their upkeep is often regarded as a thankless task. Database curation has consequently lacked the quality control typical of good journals. These *data integration* issues are complementary to their schema integration counterparts, but do not seem to have been fully addressed within the problem domain of microbiology or that of the life sciences in general. Instead of striving for one single physical knowledge base containing a large amount of the accumulated information gathered on the bacterial diversity, it should be anticipated that the future microbial information landscape might see a large number of high added-value information providers evolving as overlays to vast but largely automated knowledge archives and databases. This observation urges the need to establish a solid divide and conquer strategy for the management of distributed microbial information providers. Such a holistic data integration strategy is sensible as it acknowledges the fact that the value and nature of scientific information are heterogeneous.

The most prominent user-added value resulting from the integration process of microbiological commons is the establishment of information gateways that seamlessly glue together related pieces of the puzzle of common knowledge. As such, they are capable of enhancing manual navigation between distributed and heterogeneous microbial information sources, cross-checking and fusion of the information disseminated by different data providers, automated execution of dynamic distributed queries and exploitation of large scale data mining activities for the discovery of new patterns and principles behind the bacterial diversification processes. This quest requires the design of objective exploratory data analysis strategies with evident applications in biotechnological innovation. As such, mathematics and computer science might increasingly benefit from their involvement with biology, just as mathematics and computer science have already benefited and will continue to benefit from their historic involvement with physical problems (Cohen 2004). By breaking down terminological barriers between disciplines, this should also enhance interdisciplinary understanding and serendipity.

Despite the slew of unresolved issues, it is anticipated that the people and the ideas brought together during the workshop might give further impetus to some global action in the integration of microbial data sources, instead of just wishful thinking. Getting there will require novel forms of collaboration between microbiologists, mathematicians, computer scientists and other stakeholders. After all it would be unwise to put all of one's eggs in the basket of any one 'solution'. Diversity is the best bet.

4. Intellectual property rights for data access and sharing

Our hypothesis of a reversible interaction between user groups and scientists, in the exploration and exploitation of the microbiological commons, calls for innovative answers in the field of intellectual property rights and institutions for data access and sharing.

Microbial biodiversity in nature shares some of the properties of private goods, as it is a depletable good, and some properties of public goods, as it is *de facto* public in consumption or often kept in public access in order to ensure its sustainable use. As such, it can be appropriately described as a « common pool resource » (Polski 2005). However, the growing importance of the digital infrastructure in the exploration and exploitation of the microbiological commons and the related possibility to make access to data more exclusive, calls for the creation of a second type of « commons », a microbiological information commons.

Within the field of microbiology, initiatives for sharing knowledge through databases, gathering knowledge from different fields exist, such as within the CABRI network or the ongoing GBIF project⁵. From a governance perspective, these networks face the increasing pressure from the development of global markets. In particular, the development of global intellectual property rights has led to a competition for the ownership of previously shared resources. In the same time, the role of the state in the provision of services of general interest, such as public collections and databases, is gradually shifting from direct intervention to regulation of markets or *quasi*-markets. In the context of this new role of the state, cost effective access can for example be guaranteed through introducing a general research exemption for database access for non-commercial research. In a similar manner, exchange of biological material can be regulated through compulsory clauses in the contractual

arrangements for the exchange of biological material, specifying the origin of the resource and / or prior informed consent.

In this special issue, we will analyze the institutional conditions for the development of database sharing in this context of global intellectual property rights. In particular, we will rely on contemporary insights in theories of governance, which show the necessity to develop new forms of collective action in order to deal both with the insufficiencies of market solutions and the limits of the new forms of regulation, in the context of the construction of a research commons for scientific data (Reichman 2003 ; Hess and Ostrom 2003). For instance, within the field of digital communication the development of E-print repositories such as arXiv.org and BioMedCentral or the development of trusted digital repositories for knowledge of general interest is based on the coordination between groups of scholars and information specialists for the building of a common knowledge pool. What is new in these initiatives is that authors are participating in an international epistemic community that is committed to building an interoperable global scholarly library –with the goal to obtain higher joint benefits and to reduce their joint harm from the enclosure process. In the case of database fusion in the field of microbiological resources, the recourse to such collaborative arrangements seems also necessary, in order to deal with the problems of uncertainty and complexity of the innovation process. In particular, collective arrangements in the knowledge networks seem necessary to go beyond market insufficiencies created by the unpredictable character of the automated knowledge creation process and to create new partnerships between the diverse set of both public and private actors that are involved in the entire innovation chain.

These insights in contemporary governance theory allow also to cast the stake of intellectual property rights in an entirely different perspective. Indeed, if we look at the innovation process as it has been represented in the pyramid of figure 1 above, we see that the value of a biological resource is created progressively through the various steps of the process of value creation – from the extraction and accumulation of the information on the biological resources, through the laboratory screening and modeling process, to product development and new applications. However, the current intellectual property right system only creates an incentive at the top end of the pyramid – the applications – and does not address the stake of addressing the entire innovation chain. Under such conditions, it seems more appropriate to adopt a dynamic framework to economic valuation (Driesden 2003). Such a dynamic

approach incorporates the conditions of bounded rationality and also takes into account the dynamics of economic change outside the view of a static equilibrium situation. Accordingly, in this framework, the focus shifts from a concern about the optimal allocation of existing resources, to a concern about issues of adaptive efficiency, such as knowledge acquisition throughout the entire process of value creation and incentives for the preservation of future option value under conditions of uncertainty (Dedeurwaerdere 2004).

The diagnosis on the necessity of taking into account a dynamic conception of economic efficiency in the definition of intellectual property rights joins the analyses of authors such as Jerome Reichman or Timothy Swanson, for whom the necessity for new tools of regulation is not only due to the adaptation of the existing regime of intellectual property rights to a new situation, but also reveals a change in the underlying beliefs of the classical paradigm of intellectual property rights (Reichman 1994 ; Swanson 1997).

These authors distance themselves from the position that only sees the difficulties posed by intellectual property rights on genetic resources as a simple technical legal issue. In order to capture the originality of the new legal tools that are required, another reading of current changes is necessary—a reading which does not reduce them to a simple technical adjustment by sector of activity. For this, the proposal of new legal tools, within the biodiversity regime, that aim at complying with the need for a more dynamic approach of efficiency should receive serious consideration and be worked out in more detail. For example, Reichman proposes to evolve from a paradigm that functions by hybridization of existing tools, based essentially on patent and copyright, to a paradigm in terms of a liability regime, allowing the *ex post* compensation of the prior link in the innovation chain (Reichman 2000, pp.1776-1796). Others have proposed the creation of collection societies of traditional knowledge and / or know-how, for creating both a wide diffusion of knowledge and appropriate protection (Drahos 2000). These alternative proposals need still a long way to go in order to become fully operational for data sharing within the microbiological commons, but they are certainly the way forward in the creation of incentives for innovation throughout the entire process of value creation.

5. The workshop format

This special issue gathers a set of original papers that were discussed at the first workshop that has been organized on the Microbiological Commons. As a new field of research, it has since been further developed at meetings of the International Association of Common Property (IASCP) and within European and Belgian interuniversity research networks. In a series of two parallel sessions, the workshop aimed to gather the relevant expertise for furthering the development of a prototype for information fusion (the bioinformatics sessions) and designing the appropriate intellectual property rights and institutions for database sharing (the governance sessions).

Fashioning complex computational concepts is one thing, but bringing them into practice is yet another issue. Therefore, the technical sessions of the workshop discussed prototypes for landscaping the microbial world, i.e. the development of automated, dynamic and interactive information systems for knowledge accumulation, exploration and exploitation. Many practical questions remain open and were the discussed at the major topics of the first series of sessions of the workshop (the “bio-informatics” sessions): i) what are the key ICT technologies that power the construction of distributed information networks, ii) what are the necessary services for implementation of an integrated biological information framework established as a community-wide effort and iii) how can state-of-the-art data mining methods lead to knowledge discovery in databases and what are the precursors for their application in the biotechnological innovation chain.

The analysis of the role of intellectual property rights and collaborative knowledge networks for the development of appropriate data access and sharing in microbiology was the subject of the second series of sessions of the workshop (the governance sessions). The session was be organized in three sub-sessions, dealing respectively with (a) case studies of the existing institutions for collaborative database management (public sequence databases, GBIF and CABRI) (b) new approaches for developing appropriate bundle of rights for database fusion and information sharing (cooperative license agreements, *sui generis* database protection, etc. ...) (c) institutional design of the microbiological information commons, drawing on a list of necessary databases that should be combined in the realization of the pilot project (taxonomic data, biological resource data, scientific literature, observational data (16S rRNA, FAME, MLSA,), DNA stocks, etc.). This special issue is based on a substantial reworking of the

original papers presented in this second session on the social science and institutional challenges of the microbiological commons.

Notes

1. The initiative for this platform results from consultations between participants of several European research projects (EBRCN, EUROGENTEST, MOSAICC, TEDDY, ...). A proposal has been submitted to the EU in December 2004, in the context of a consultation on future Technology Platforms. Several meetings are planned in 2005 in order to gradually enlarge and compose the core group of the Platform.

2. The IHD database will collect information from patient records which have undergone de-identification by coding from Iceland's National Health Service and store the data in a computer system for clinical and statistical analysis, with legal protection against infringement or abuse. The IHD can be linked to an existing genealogical database. The initiative also permits to cross-reference IHD data with genomics data, which has been obtained and analyzed with the informed consent of Icelandic donors (OECD 2000, p.37).

3. International Nucleotide Sequence Database, publicly accessible through the DDBJ (www.ddbj.nig.ac.jp/Welcome.html), EMBL (www.ebi.ac.uk/embl/index.html) and GenBank portals (www.ncbi.nlm.nih.gov).

4. Cf. <http://www.belspo.be/bccm/>

5. Cf. www.cabri.org and www.gbif.org

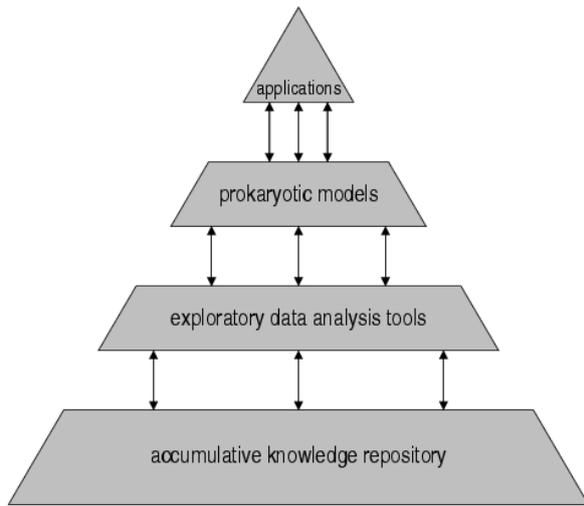


Figure 1: innovative biotechnological applications currently reach so far, because they are standing on the shoulders of giants, i.e. the scientific merits of many researchers that paved the way.

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