Ex situ collections in microbial research: The contribution of public networks to knowledge accumulation

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Abstract

Microbes constitute key inputs for basic and applied research and product development. Microbial ex-situ collections hold microbial diversity as a public good to provide tangible use value for private and public companies and research organizations in addition to significant option value given their capacity to store genetic information for potential use in the future. Changes in the financial and technological context are altering the conservation priorities of some collections, and potentially creating a new global scenario in which the ex-situ microbial gene pool is conserved further away from the public domain. This paper addresses the factors that lay behind the collections' preferences to conserve such gene pools, with a special focus on knowledge accumulation. We use primary data collected through a worldwide survey of microbial collections. Results show that broad public research infrastructures are associated with specialisation type strains which have particular knowledge accumulation properties. Moreover, this infrastructure is the basis for distribution of inputs for both basic and applied research by academia and industry alike.

Keywords: Ex-situ biodiversity conservation, life science research, public research institutions, knowledge networks, microbial commons

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1. Introduction

Microbes are the smallest life forms, but together they represent the single largest mass of life on earth, which is inextricably intertwined with the functions they perform (Schaechter et al. 2004). For example, micro-organisms are critical to maintaining the health of organisms that depend on them for nutrients, minerals, and energy recycling, while conversely, causing infectious disease when they overlap with susceptible hosts. Microbes manifest the greatest diversity of all living creatures, using biological and chemical processes that exist nowhere else in nature. Consequently, we can look to the microbial world as a vast, mostly untapped[1] resource of biotechnological potential, and we can study microbes to understand the bulk of life processes so as to further unravel the basic mechanisms of life on earth.

With 92,000 strains of microbes and other cell isolates, the American Type Culture Collection (ATCC) is the largest public service (ex-situ) microbial collection (PSMC). However, the majority of biomaterials are conserved in a worldwide network of public service collections with an estimated total number of 1 389 656 strains (WFCC 2005). Several collections from other than Organization for Economic Co-Operation and Development (OECD) countries have a substantial number of PSMCs, while OECD countries have generally centralised their collections into large PSMCs. Geographically, among the ten countries which hold the largest number of PSMCs, Thailand and Brazil lead with 57 and 46 collections each, followed by Australia (34), France (28), Japan (22) and the USA (21).

PSMCs link academia, industry, government and international knowledge providers and users of microbial material. As such they are knowledge hubs for the life sciences (sensu Stern, 2004) that support innovation by facilitating acquisition of and access to existing research materials through a worldwide network of centralised deposit and access services. As knowledge aggregators, they can be considered as the research libraries for bio-materials. However, as knowledge hubs, they increasingly perform

[1] Today, less than 1% of microbial biodiversity has been identified, and that microbial biodiversity is best preserved in ex situ collections, which presents a formidable challenge for the current network of Biological Resource Centers (OECD 2001).

research and provide services in bioinformatics, biosecurity and biodiversity preservation.

Specifically, PSMCs certify the quality of the microbes as research materials. Such certification supports knowledge production since subsequent researchers can use the same certified material, thus avoiding duplication of effort. This paper addresses the economic and institutional conditions that contribute to the management of microbial material that supports knowledge accumulation in the research sector by PSMCs. The governance challenge is to achieve high international diffusion of biological material without compromising the quality of the research materials. This requires a well designed strategy. High diffusion is generally associated with decentralised management mechanisms among the distributed network of PSMCs, while more centralised governance may be thought to better assure quality.

To address this question empirically in this paper we analyse data gathered through a worldwide survey of 499 PSMCs. The analysis supports the idea that, in order to better govern the access and diffusion of microbes associated with knowledge accumulation across PSMCs, the strategy should be to strengthen the public international research infrastructure of PSMCs, as this enhances the investment in basic research materials and their availability both for public and private research. In this way, PSMCs facilitate both diffusion and quality control, in addition to internalising the public good benefits that for a private provider would be associated with costly exclusion. General purpose microbes, such as type strains, which support cumulative knowledge generation, have important public good properties. Here the empirical results call into question the role of markets in assuring the appropriate provision of such biological materials in a global context. Furthermore, the analysis shows that private industry also relies on the broad public research infrastructure of which PSMCs form part.

The paper is organised as follows: the next section places the microbial collections in their scientific context and examines their role in providing basic infrastructures for life science research. This is followed by the development of the conceptual framework from which a specific hypothesis about PSMCs' conservation and distribution strategies is derived. The general hypothesis from this conceptual framework is that the PSMCs' strategy is shaped by the microeconomic institutional environment which houses the public collection. This hypothesis is then tested using a unique dataset from a survey of PSMCs. The last section provides results and policy implications.

2. Increasing importance of material exchanges for microbial research

By making available biological materials and information of guaranteed identity and quality, PSMCs serve an essential infrastructural function for scientific investigation and R&D (OECD 2001). The availability of materials in public, certified repositories, instead of minimally curated, in-house private collections, is a condition for building upon previously validated knowledge. Using certified materials from culture collections diminishes the cost of mistakes in cumulative research (Furman and Stern 2006) and decreases the search costs for finding appropriate materials (Evenson and Kislev 1976; Gollin et al. 2000; Visser et al. 2000).

This basic infrastructure function was a key element in the development, in the 1960s, of many research fields that rely on living cultures of micro-organisms, such as virology or the study of fermentation processes and still plays an important role today in these fields. However, it is important to stress its increasing crucial role in the context of the contemporary life sciences, because of the significant synergies between research infrastructures in microbial and genomics research.

For instance, two recent sequencing programs had to be extended after the completion of the full human genome in 2001, because the competing laboratories arrived at different sequence results. In both cases, a partnership between the competing laboratories was set up to compare the original biomaterials, in order to determine errors due to the sequencing machines and those due to mutations in the strains acquired by different culture collections in the US and the EU (Harvey and McMeekin 2007). In other cases, such as the race to discover the cause of AIDS between the Robert Gallo Laboratory at the National Cancer Institute, US, and the Institut Pasteur in France, in the late 1970s, human retroviruses were exchanged informally between the competing laboratories. Although the French team first isolated the correct virus, laboratory-to-laboratory material exchanges resulted in nearly a decade of confusion about the precise nature of the virus and the allocation of credit for its initial discovery.

Moreover, some fields of research depend on the availability of large amounts of original and/or derived biomaterials. This is the case for high throughput screening of the activity of small molecules against drug targets (Parry 2004; Rai et al. 2008). For instance, the availability of large amounts of human cell lines at the Coriell Institute for Medical Research in New Jersey, U.S. (collected amongst a high-incidence population in Venezuela) was crucial in identifying the location of the RSS1 gene responsible for Huntington's disease in 1993 (Stern 2004).

Finally, sequencing projects (even of one single human gene or a single bacteria) generate tens of thousands of new biological entities (OECD 2001) that have to be preserved, identified and duplicated for the replication of research findings in other laboratories and for creating cumulative research in genomics on well recognized models (Furman and Stern 2006). These so-called "derived" biological entities include the replicable parts of organisms, such as plasmids, rDNA or viruses. High-throughput sequencing has, then, dramatically increased the amount of materials to be preserved by the culture collections and available for follow on research.

In sum, despite the increasing importance of disembodied research that accompanied the advent of bioinformatics and synthetic biology, the availability of large amounts of both original and derived certified biomaterials generates an important set of scientific pay-offs and future opportunities for public and private life sciences research.

3. The role of PSMCs

The role of PSMCs is based on the acquisition, authentification and distribution of living microbes and their replicable parts (e.g., DNA, genomes, plasmids, viruses) along with important information about their properties. PSMCs' specific added value consists not only in identifying the taxonomic nature of a microbe, but also in characterising their biological function, and increasingly, sequencing them to identify the genetic code.

Such information is organised in databases with molecular and physiological information diffused on PSMCs' internet sites (Arora et al. 2005; Sigler 2004; Stern 2004).

The scientific infrastructure of which PSMCs form a part induces diffusion of new findings, since academic researchers deposit evidence of their microbial findings in PSMCs prior to publication in scientific journals, although not always in a systematic manner.[2] Similarly, in the private domain deposits to PSMCs are required by the 'Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purpose of Patent Procedure' in order to gain a patent (Winter and Adam 2001). In the case of bacteria, biohazard concerns lie behind compulsory PSMC deposits of newly identified and described bacteria.

Of course, users of microbes can also turn to sources other than PSMCs. The largest collections of microbes are held by the industry itself (Furman and Stern 2006). However, starting in the mid-1990s, the pharmaceutical industry has changed its basic research focus, and as a result many of their in-house collections have been abandoned or outsourced. As a result, small niche public service collections also provide more specialised services to the industry under conditions of relative secrecy. This is important as property rights to microbes are changing (Smith 2003) and there are concerns that profits generated by specialised services to industry turn collections away from the objective of conserving sufficiently large stocks of general purpose biological materials. This would be a problem given that their services are public goods, depending on a predictable and sufficient income flow (Baker 2004).

With the complexity of the structure of large PSMCs there is a need for investment in costly expertise among staff, as well as sophisticated storage equipment. For example, the cost of creating a new collection of about five thousand strains is approximated to USD 1 million, excluding the substantial costs of storage, maintenance and use (Baker 2004). The high costs of operating collections frequently lead to mergers and grandfathering of abandoned collections. Funding for PSMCs is most frequently provided by governments and universities, and to a much lesser extent by semi-

[2] The compliance with this 'best practice' depends to a large extent on the editorial policy of the scientific journal.

governmental organisations, industry, and self-financing (WFCC 2005). The two main categories of the 423 collections classified within the database of the World Federation of Culture Collections are held by universities and governments, with 42 and 41 percent of the PSMCs respectively, the remaining categories being semi-governmental (8 percent), private (4 percent), industry (1 percent) and inter-governmental (1 percent). In parallel, while strains have traditionally been distributed free of charge and some governments expressively prohibit PSMCs from charging a fee in exchange for providing strains, PSMCs in general are increasingly charging handling fees to cover the marginal cost of distribution of the strains.

4. Choices for investing in microbial resource accumulation and diffusion

PSMCs form a key role in the interface between basic and applied research, by linking public sector mandates to public policy outcomes. Therefore their choices have to be situated in the microeconomic institutional and organisational environment which houses the PSMC (King 2005; Mowery and Rosenberg 1998; Rosenberg and Nelson 1994). In this section, we develop a more specific hypothesis about the key drivers of conservation choices among PSMCs, which is the focus of this paper. Based on the literature on public goods and positive network externalities we construct a hypothesis for the determinants of PSMCs' investment in conservation and diffusion of basic biological research materials.

4.1 The case for public investment in general purpose microbial research materials.

Here we pay attention to one particular value of biological resources for knowledge accumulation, which has received little attention; namely, certified research materials. To this end we focus on a category of microbes called '*type strains*' (TS henceforth). By scientific standards, TS refers to microbes that are the reference strains used for taxonomic purposes. They are subject to strict quality management and are also particularly well described. Due to these properties TS are important building blocks for knowledge accumulation since they constitute the reference library against which any new microbial species has to be compared in order to certify its novelty. As such, while all microbial material contains potentially useful information for research, TS hold specific features that make them a particularly vital tool for knowledge accumulation. Typically, TS holdings will be important in so-called taxonomic collections which specialise in building a reference library, but research collections will also need a basic stock of TS as part of their overall holdings (c.f. Table 1).

[TABLE 1]

Characterising TS along the public-private good continuum has some important implications for trying to understand the drivers of conservation in ex-situ microbial collections. TS are a mixed good consisting of both the biological resource as well as well-documented information about their properties, such as reactivity with cancer cells. The biological component is characterised by relatively low cost of exclusion and relatively low rivalness since it can be reproduced at low cost. However, their information content is nonrival. Through institutional design to achieve broad diffusion, and capturing of coordination benefits, TS' information contents are by convention placed in the public domain in scientific journals and PSMCs' internet portals,[3] and the biological resource made widely available through replicas in several PSMCs.

As such, broad diffusion of TS is central to knowledge accumulation. The economics literature has highlighted the option value of biodiversity that is associated with the means to enhance the search for useful compounds as applied both to *in situ* biodiversity conservation and bioprospecting activities (Goeschl and Swanson 2007; Rausser and Small 2000; Simpson 2002; Simpson et al. 1996), as well as to *ex situ* conservation (Evenson and Kislew 1976; Gollin et al. 2000; Visser et al. 2000). Based on this literature, and having seen the public good properties of TS as basic research material, we can expect that public investment is required for enhancing investment in TS for research and product development. We hypothesize that public investment by the social planner is important for building larger TS collections. In particular, one can expect that PSMCs which specialise in TS holdings will depend on a sufficient level of public research funding. This would be the case of specialised taxonomic collections. At

[3] The broader dissemination (and thus lower rivalness) of type strains is reflected in that non type strains are held in 1.2 collections on average while type strains can be found in up to eight collections (Personal communication, June 2007, Peter Dawyndt; analysis done with the Straininfo Bioportal software, www.straininfo.net).

the same time it can be expected that research collections will to a certain degree invest in type strains but will also develop a broader portfolio of biological materials. In those cases a more diversified funding strategy will be required. Moderate support from the social planner to support the conservation funding is expected to be important as well; whether through direct funding or indirectly through statutory basic income stream such as the formation of a patent deposit authority.

In section 6 we set out to test the conservation hypothesis. Indeed, while industry has an incentive to invest in applied research and product development, it will not invest sufficiently (from a social point of view) in TS, due to their public good characteristics and resulting problems regarding the private internalisation of coordination benefits (positive externalities from basic research are easier to exploit by coordinated action at the country level). Consequently, support in basic research by a social planner is needed as a way to stimulate investment in TS. Similar findings are expressed in the literature on innovation and public goods (Cornes and Sandler 1996; Evenson and Kislew 1976; Jaffe 1986; Nordhaus 1969).

4.2 The importance of formal and informal exchange networks

The question dealt with in section 4.1, regarding PSMCs' strategy of investing in high quality strains for knowledge accumulation, should be complemented and extended to the subsequent important question of distribution, especially to non-commercial entities. In a context of commercialisation it is of particular interest to explore the uses of PSMCs' microbial holdings in general, whether they are TS or not, and in particular to explain the factors behind the spillovers to industry.

Increased commercial pressure has led many PSMCs to adopt formal measures of microbe exchange rather than the informal networks which are the traditional means of microbe transfer among collections. The charging of fees for specialised services to industry[4], providing guarantees of formal property right through the Budapest Treaty,

[4] Although fees for contract research and other services may be important, for the great majority of PSMCs the commercial incentives from industry that are explicitly linked to distribution of microbes are limited. The fee that most collections charge for provision of strains is low in relation to the associated cost of acquisition and maintenance, and especially low when considering the upstream research effort

and formal quality-signalling through Industrial Standardization Organization (ISO) certificates, all form part of such a pattern (King 2005).

Most of these measures are simply a formalization of the traditional role of PSMCs as knowledge hubs. For instance, fees are far below the real costs of curating the microbes in the culture collections and roughly reflect the marginal cost of distribution[5]. Indeed, restrictive licensing of basic research materials is ill-suited to cumulative processes of knowledge that are based on networks of innovation. This is especially the case when such networks include public organisations, such as in microbial research. Instead, where marginal cost of diffusion is low, and, when network effects generate benefits from a high level of diffusion that exceeds those of restrictive licensing, non-restrictive access regimes offer increased efficiency (for similar conclusions, see Fowler et al. 2001; Gollin et al. 2000; McCabe and Snyder 2004a; Visser et al. 2000).

In this context, networks refer both to the formal exchange patterns and the informal networks of culture collection managers and researchers. The latter can be understood as loose structures of actors, coordinated in a voluntary, reciprocal, horizontal way for communication and exchange (Alkaby 2008). When there is sufficient incentive to produce information and there are mutual benefits from exchange, networks based on non-restrictive access regimes offer lower negotiation costs,[6] and fast knowledge accumulation, especially when users are spatially dispersed, as for PSMCs. Furthermore, the dispersal of PSMCs is coherent with economies of scale through specialisation, as well as risk spreading and importantly, transaction costs. While the information content in TS may lend itself to centralisation, the physical nature and the frequency of use of the microbial mixed-good research input is only manageable through local and national supply complemented by international supply (Visser et al. 2000).[7] Some research processes need microbes with different genetic resource properties that are available only in specific geographical zones (for the case of crop

that lies behind these microbes. Some collections also receive donations of technology, such as nitrogen freezers. However such support is often aimed at storage of industry holdings of microbes.

[5] Cf. footnote 4 supra.

[6] Open access provides lower search costs than barter, in which a suitable exchange partner and item must be identified.

[7] Furthermore since the end of the 1990s a new barrier has made international microbe transfers costly: security concerns caused the implementation of strict biosafety rules on international transfers of microbial material for exchanging TS among collections.

GR, see Fowler et al. 2001). Networks of PSMCs can thus offer an efficient means to achieve both diffusion and high quality of TS and associated services.

Networks favour diffusion with lower negotiation costs by inducing higher levels of standardisation in both taxonomic terms and transfer mechanisms. They may also impede monopolistic situations in which provider complacency encourages monopolistic abuses (Furman and Stern 2006). For example, a study of the pricing structure at ATCC suggests that high pricing of certain biological material impedes its diffusion (Furman and Stern 2006).

Hence it is possible to hypothesise that acquisition, authentification and distribution of TS holdings will benefit from large structured networks of sharing of materials and related information.

5. Data

This section gives a brief introduction to the data used in the next sections' empirical analysis.

The population consists of all 499 PSMCs that are members of the World Federation of Culture Collections (WFCC) or MIRCEN[8]. In order to assure a high response rate a pilot questionnaire was circulated to 12 microbial PSMCs. Based on the pilot survey the final survey instruments were constructed, consisting of three separate questionnaires designed together with representatives of WFCC and MIRCEN, and distributed electronically with a two-month interval to all the members of WFCC and MIRCEN networks from Europe, Africa, the American continent, Asia and Oceania. Additionally, for the first questionnaire a posted questionnaire and follow-up telephone-based survey targeted at a subset of 170 randomly selected PSMCs stratified by OECD membership of the country of origin was conducted. For the purpose of the analysis, information on 103 of those PSMCs is used, since these provided the most complete information on the variables that are associated with the hypothesis mentioned above.

[8] United Nations Educational Scientific and Cultural Organisation Microbial Resources Network

Some collections were started up with the explicit aim of having many type strains (Smith, Pers.Comm.). However, researchers often prefer to deposit their TS in high-profile collections, since that gives prestige and higher diffusion for the researcher. Hence the strategy to focus on TS is induced by more than the size of the public collection and its reputation. Indeed, analysis of our data reveals that the group of collections with a high ratio of TS is very heterogeneous, both in the size, geographical origin and scope of the collection. Hence the group includes some of the largest high-profile collections of the category of experimental collections (c.f. Table 1), with more than 15,000 strains. However, it also includes medium-sized and small PSMCs with fewer than 250 strains, with incidental and taxonomic collections in both universities and medically oriented organisations. The PSMCs with high TS ratios are located mainly in OECD countries, but also in Brazil, India, China, Senegal and Egypt. Only one US collection is represented in the dataset.

The sample of PSMCs is reasonably representative in terms of the size of the collections[9] and in our sample TS constitute approximately 10% of the microbe stock among all PSMCs. From table 2 it can be seen that PSMCs located in OECD countries have on average considerably larger stocks of microbes. The majority of collections receives heavy public funding and only a small share has adopted the formal quality ISO standardisation. Table 3 describes, and provides descriptive statistics for, the variables used in subsequent models.

[TABLE 2]

[TABLE 3]

6. Modelling the PSMCs' management of type strains

Here we focus on the public good properties of the basic microbial research materials and related information, which have consequences for the underlying incentives of

[9] It should be noted that while 52% of PSMCs in the population belong to OECD countries, our sample contains 67% of such collections, thus over representing them in the analysis.

PSMCs to manage microbial knowledge. We set out to test empirically whether public investment is required for enhanced investment in accumulation of TS, used both in research and as reference strains in product development. By answering this question we can shed light on PSMCs' conservation strategies.

In order to address these questions we estimate the effect of various factors, described in section 4, on the PSMCs' conservation focus, i.e. the predicted ratio of microbes that facilitate knowledge accumulation particularly well (i.e. type strains) compared to total number of microbes (*CONSERV_RATIO*). Table 3 provides a description of the variables used in the analysis.

In order to model the distribution policy we construct a variable denoting the proportion of a collection's distributed microbes that go to private industry, as opposed to distributed to other traditionally more public sector affiliated users such as academia or public hospitals (we call this variable *"OUTFLOW_IND"*). It is expected that *OUTFLOW_IND* is correlated with the ratio of search tools (*CONSERV_RATIO*) since, as described, industry needs large quantities of TS.

As described above the demand for strains by basic research and industry is becoming increasingly interlinked. This is manifested by industry's dependence on PSMCs in order to gain access to the gene flow, and, industry's influence in the decision making of public collections. Hence both the conservation strategy and distribution focus of PSMCs are interlinked in a joint decision process shaped by the PSMC microeconomic institutional context (Smith, Pers.Comm.). From the point of view of the PSMC, two decisions have to be made: the conservation strategy (*CONSERV_RATIO*) and distribution policy (*OUFLOW_IND*). The bivariate Tobit model allows incorporating the PSMCs joint conservation and distribution decisions by estimating the two decisions simultaneously, and testing the hypothesis that the covariance across the two equations is not zero (Greene 2003). The correlation coefficient (*Rho*) shows the correlation between the error terms in the two Tobit equations. The model can also be estimated in two independent regressions, but this would provide lower efficiency of the estimates since it ignores the correlation between the error terms (Greene 2003).[10]

To address the question regarding the public mandate effect on the collections' conservation strategy, variables are included to denote the social planner's influence over the collection (*PUBLIC_HI*, *PUBLIC_MED* and *PUBL_LOW*). Namely, the PSMC faces a choice between which microbes to focus on. Since budgetary constraints on PSMCs may impose limits to investing in specialized personnel, storage space and maintenance, an increase in TS implies an opportunity cost of forgone benefits from storing fewer of the other kind of microbes. Further, since search tools are used both by industry and academia, but have public good characteristics and important positive externalities we expect that collections specializing in TS will adopt a mixed funding strategy. On the one hand, it is expected that PSMCs with a strategy towards investing more in strains for distribution to industry only would be more likely to be dependent on private funding. On the other, for collections specializing in a wide variety of strains used in basic research projects, without specializing in the general research tools, one expects a much higher level of public funding. We thus hypothesize that specialization in TS will be characterized by a mixed funding strategy, even if a slightly higher level of public funding is expected to be associated with PSMCs that are investing in systematic collections of type strains, which can be used by industry and academia alike, here proxied by the share of TS. The variable *PUBLIC_HI* denote that the PSMC received between 61 and 80 percent of its funding from public bodies. *PUBLIC_MED* denotes that the collection received between 41 and 60 percent of its funding from public bodies and PUBLIC_LOW between 21 and 40 percent. These variables are compared with PSMCs that receive no public funding.[11]

Of course, this hypothesis cannot be tested if one cannot control for other key factors influencing the conservation strategy of PSMCs. For instance, we expect a positive

[10] The bivariate Tobit model we use addresses left-hand censored variables (Barslund 2007). As described our dependent variables are both left and right-hand censored. However, the right-hand censoring is weak (only one and five unitary observations in the first and second equation, respectively) and we do not expect it to significantly affect the results. A bivariate probit model was also used, with the dependent variables transformed to dichotomous variables, with similar results.

[11] The threshold of 80% is used to discriminate between highly public sector influenced collections and other more commercially influenced collections. Together with the other threshold, no public funding at all (PUBL 0), we have two polarised control groups to compare to the group of collections that receive some but below heavy public funding.

effect on the provision of search tools of being part of a broader public research infrastructure. We control this by adding an explanatory variable that represents PSMCs' network affiliation. TS's public good properties would motivate maximum diffusion of TS among PSMCs within social networks. Hence, it is expected that PSMCs that form part of such networks are more likely to acquire and hold such search tools. Thus, we expect, for example, that being part of exchange networks of strainsn, which are both formal and informal, would affect positively the ratio of type strains in stock. Hence the variable "*INFLOW*" is included to measure this network effect, which consists of actual acquisition of microbes from other PSMCs. This, ceteris paribus, is expected to increase the proportion of TS, since TS to a larger extent than other strains are a product of the broad research infrastructure. In addition, an explanatory control variable (called "*PR*") denotes if the handling of any of the microbes acquired was subject to a formal contract or material transfer agreement. Hence, this variable reflects the institutional environment in which the PSMC operates; the traditionally reciprocity-based tier or a more formal and legalistic environment. We do not have an a priori expected effect on the conservation strategy.

As mentioned above, in order to quantify the potential positive effect of forming part of a public research infrastructure on the PSMCs' specialisation on TS, other key control variables need to be included in the model. Another characteristic of the PSMCs to bear in mind refers to their scale of operation as it is also likely to affect conservation decisions. The collection's scale is approximated by the covariate "*STOCK*" which stands for the aggregate stock of type and non type strains. While a collection may be more conservation-oriented in absolute terms by having a large stock of type strains, it generally has also a significantly much larger stock of non-type strains, and thus larger PSMCs are expected to have a lower proportion of type strains. As such, adding the variable *STOCK* in the model also controls for this dilution effect. Lastly, since it is expected that OECD countries would on average have a higher proportion of privately owned research collections, as compared to more general purpose collections that tend to prioritise type strains, a variable is included to indicate whether the collection is located in an OECD country.[12] Among the OECD countries, the USA is non-representative due to its special research funding characteristics, especially in the life

[12] To proxy the presence of demand from biotechnology industry in different countries Mexico and Turkey are coded as non-OECD, while Brazil, China and India are coded OECD.

sciences, scale economy factors which have lead to the presence of high degree of centralization of culture collection facilities and property rights regime. The variable *"USA"* is included to control for such heterogeneity. Finally, we included a set of variables to control for the various categories of microbes that are held in the collections and which were reported in the survey (FUNGI, YEAST, ALGAE and BACTERIA).

[TABLE 4]

The bivariate Tobit estimates are reported in Table 4. The upper half of the table presents the estimated results for the conservation strategy regression, and the lower half provides the estimates for industry orientation. The first question of interest is whether or not PSMCs jointly set their conservation and distribution strategies. The correlation coefficient (*rho*) on the covariance term across the two equations is statistically significant and positive.[13] There are two implications of this result: firstly, the statistically significant *rho* shows that the bivariate model increases efficiency of the estimated parameters, as compared to deploying two separate tobit models in which the correlation between the error terms of the two regressions is not accounted for. Secondly, the positive sign of rho, i.e. of the correlation between the error terms, means that, holding all else constant, collections that hold a larger percentage of TS (*CONSERV_RATIO*) also provide a higher percentage of microbes in general to industry (*OUTFLOW_IND*), and vice versa.

The hypothesis concerning the broad influence that public investment sources has on PSMCs (thus related to a social planner's objectives) by affecting investment in search tools (based on the ratio of type strains in stock, *CONSERV_RATIO*) is supported by the data. That is, *PUBLIC_MED*, is associated with a significant and positive coefficient in the bivariate Tobit model, thus indicating that it affects positively the ratio of search tools in stock, as compared to receiving no funding from public bodies. It follows that a mix of funding from a social planner and funding sources from industry characterizes collections that prioritise investment in TS. It also suggests that although PSMCs traditionally operate within the framework of a social planner's mandate, this mandate

[13] Rho is significant and with a medium strong positive correlation between the two dependent variables CONSERV_RATIO and OUTFLOW_IND (the likelihood ratio test of rho is significant, rho21 = 0: chi2(1) = 7.33, Prob > chi2 = 0.007).

works through the actual financial influence that the social planner exercises on the collection.

Secondly, the use of networks, as expressed by acquisition of microbes from other PSMCs (*INFLOW),* is significant. Its positive sign is consistent with the idea that PSMCs that receive strains from other microbe collections may be more oriented towards type strains. Location in the USA is significant and negative, which due to the inclusion of the OECD variable means that USA collections have lower TS ratios as compared to collections located in non OECD countries. This result may be related to the USA's particular institutional environment in which the broad public research infrastructure in the life sciences has long operated in a more business-oriented way.

Also, the property rights variable *PR* has a positive effect, suggesting that a more formal approach to sharing information, i.e. with a legalistic mechanism to control the use of the resource, is associated with a higher ratio of microbial search tools. This suggests that the traditional tier, as represented by strong public influence and focusing on public good search tools, is influenced by a more formal regime of managing microbes. However, this may indeed not be enclosure, unless the specific terms of the Material Transfer Agreements (MTA) are restrictive.

As far as the overall goodness of fit of the models is concerned, the Wald test suggests that taken together the variables explain the variability in the dependent variables in a satisfactory way. This suggests a rather high explanatory power of the explanatory variables on the dependent variables.

7. Spillovers from public to private sector research

The question regarding PSMCs' strategy of investing in high quality strains for knowledge accumulation should be complemented by and extended to the subsequent important question of distribution, not only to traditionally public but also to commercial entities. In the same vein, a lot of collections, especially the research collections (c.f. Table 1), invest in a vast variety of strains, and the TS are only one part of their holdings. In order to analyse in a tentative way the determinants to the distribution choice of a broader set of collections and investment strategies, we constructed a second part of the model to test jointly with the first. The second part deals with the industry orientation of the PSMCs. As described above, a censored variable is used to proxy industry orientation. We expect that a heavily publicly funded collection is less likely to pursue an industry oriented strategy, i.e. to distribute strains to industry, since the social planner is expected to prioritise basic research rather than industry. We are therefore interested in evaluating the potential spillover effect of investment in public general-purpose collections. In this second part of the model we also analyse how the kind of collection affects distribution focus.

One variable is expected to have an important impact here, which is the variable reflecting whether a collection charges a fee (*"FEE"*) when distributing strains from its own collection, as opposed to distributing the strains for free. [14] Further, fees are charged by PSMCs that provide to industry and collections that provide to other users. In fact, fees tend to be relatively low and thus do not become an obstacle for industry. However, a collection that charges a fee signals that the collection is more commercially oriented and may thus offer lower transaction costs for industry to deal with. As such, fee status would signal a policy orientation rather than a direct income strategy. Thus, the potential endogeneity bias is not expected as it is not likely that the supply of strains to industry would induce collections to take the decision to charge a fee. Instead we would expect the relationship to be the other way around. The variable PR denotes another aspect of a more formal approach to microbial sharing, with an expected positive effect on industry provision.

The other control variables are given by the relative distribution to academia and hospitals, which are expected to be negatively associated with industry orientation by representing categories that traditionally have been associated with public research as opposed to private research.[15] The variable *OECD* is expected to positively affect industry orientation, due to a perceived higher industry demand in such countries.

[14] It should be noted though that charging a fee does not automatically signal commercialisation or a de facto industry orientation, but rather whether the collection has decided on an industry orientation policy or not.

[15] Note that the sort of demanders, industry versus academia plus hospitals, are not mutually exclusive, sine PSMCs also provide much microbes to other recipients not included in these categories.

The first result is that, as described in the first part of section 6., the ratio of TS is correlated with the predicted ratio of industry orientation (lower half of Table 3.). This suggests that PSMCs with a larger proportion of microbes representing search tools, are associated with industry orientation.

The coefficient of the public funding variables supports the hypothesis that a social planner would be slightly less inclined to prioritise provision to industry. The coefficient for the variable denoting medium public funding (*PUBLIC_MED*) has the expected positive sign, but the results of this second regression are less clear cut then the previous one. Indeed, the other funding variables also have a positive sign. This reflects a much more diversified funding strategy for industry oriented collections. However, the overall result is consistent with the first regression in indicating that a strong public service mandate, as reflected by heavy public funding, is associated with an orientation towards other users than industry.

The fee variable is significant and supports the expectation that charging a fee signals that the collection adopts a more formal regime and thus is also prepared to serve their commercial clients through a market institution rather than an informal and reciprocity-based governance mode. However, the *PR* variable is not significant. In addition, higher relative provision to academia and hospitals (*OUTFLOW_ACAD)* appears to decrease the ratio of microbes to industry, hence supporting the idea that industry and other sectors have structurally different preferences and needs. It follows that it is not necessarily the case that any high demand for microbes from a PSMC, irrespective of who makes the demand, signals that the collection offers high quality and thus also attracts demand from industry. Rather, more traditional users such as academia and hospitals may have different preferences than industry, related to issues such as governance mechanisms regarding microbe transfers or the content and quality of microbes and associated information. As such, the data also suggest that PSMCs on average tend to specialise in providing strains to either the traditional sector or to industry, while at the same time being more flexible in distributing to other PSMCs.

The OECD variable is statistically significant, suggesting that PSMCs in countries with high level of industry development respond to industry demand by channelling some of their flow to industry. The scale of the collection (*STOCK*) does not have any significant effect on the ratio of industry orientation.

8. Conclusion

To the best of our knowledge this paper addresses for the first time the factors, at the meso-economic level, affecting biological resource management and flow from ex-situ microbial collections. The principal interest has been to shed light on the conservation choices for such resources, as expressed through microbial collections' stocks of what we term search tools versus microbes with other properties. The focus has also been on what sectors collections supply to. Qualitative and quantitative analysis of primary data gathered from a world-wide survey on culture collections conducted in 2005 confirms the important role that these collections play as holders and distributors of microbe tools for research. Specifically, such collections are the basis for distribution of inputs for both basic and applied research by academia and industry alike.

The empirical analysis of conservation strategies for ex-situ microbes tends to support previous conclusions from crop-breeding analyses (Gollin et al. 2000, Visser et al. 2000), namely, consistent with public good theory as well as search theory, society relies on public investment for the provision of diversity that otherwise would be underprovided by markets alone. Another finding is industry's reliance on knowledge spillovers from such public infrastructure. Furthermore, the results highlight the interlinkages between basic research-oriented and the commercially-oriented governance frameworks for PSMCs: firstly, collections simultaneously choose which kind of microbes to conserve, and whether and how much microbes to distribute to industry. Moreover, there is a positive correlation between specialisation in microbes with public good properties, and provision to industry. Also, cost-sharing between public and industry sources appears to be associated with specialisation on microbes with public good properties.

PSMCs play a critical role in the national and international research infrastructure by providing certified knowledge and microbial genetic resources from today's researchers upon which subsequent research can be done. Moreover, their scope has multiplied due to information technology and other innovations. Traditionally, exchange of microbial genetic resources between the scientific community and microbial collections has been governed by informal rules and supported by international institutions such as the WFCC. However, the changes brought about by an increasingly commercialised atmosphere call for a review of this system in order to create the incentives for continued production not only of niche collections but also of the the above mentioned general search tools' collections, given the considerable cost of rebuilding collections once they have ceased their activities, and the irreplaceability of strains.

We hope that this paper provides novel insights about the way that public-service microbial collections constitute a very heterogeneous group of institutions. It is important to distinguish between the different underlying incentives of collections, and from that undrestanding to guarantee the kind of conservation strategies needed to support different services such as providing insurance for solving future biological threats as well as to offer solutions to current problems such as waste water treatment and catalyzing ethanol production as a sustainable energy source (Canovas and Iborra 2003). In this sense policy makers need to ensure that the ex-situ collections' conservation strategies balance the current needs of applied research and the requirements for basic research. As such microbial collections provide different aspects of international common good properties that need public support, from solutions to large-scale economic problems in industrial countries, such as wheat plagues, to problems that are more important in developing countries, such as plagues in minor crops such as cassava. Furthermore, supported by the result that international commons properties are related to the availability of basic microbial search tools, collaboration and the presence of spillovers to industry appear to be relevant not only nationally, but internationally in order to continue to sustain global complementarity among collections.

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List of acronyms

ATCC	American Type Culture Collection
ECCO	European Culture Collections Organization
ISO	Industrial Standardization Organization
MIRCEN	United Nations Educational, Scientific and Cultural Organisation Microbial Resources Network
MTA	Material Transfer Agreement
OECD	Organization for Economic Co-Operation and Development
PR	Property rights
PSMC	Public service (ex-situ) microbial collection
TS	Type strains
WFCC	World Federation of Culture Collections

TABLES

Table 1. Typology of PSMCs' conservation focus (table by the authors, typology based on Scott Stern, Pers. Comm. and own survey data).

Kind of PSMC	Conservation aim	Example	Kind of biological material
Incidental	What the laboratory happens to produce	Hospital that deposits arbitrarily	Characterised by depth instead of breadth
Taxonomic	Reference library	A reference collection for one kind of strains	Specialisation in type strains
Experimental	Research collection	ATCC, DSMZ	Importance of breadth of scope (large portfolio)

Table 2. Summary statistics for the sample used in the analysis: for selected main variables (mean and standard deviation)

PSMC located in OECD country	Average number of strains, variable: *STOCK*)		Average of non-type strains		Average of type strains		Percentage of PSMCs with ISO certificate, variable: *ISO*	Percentage of PSMCs with high public funding, variable *PUBLIC_HI*
	Mean	Sd	Mean	sd	Mean	Sd	Mean	Mean
OECD[a]	5 877	13 294	5 349	12 876	527	1 206	17%	61%
Non-OECD	2 775	3 562	2 561	3 545	214	450	9%	41%
Total	4 853		4 429		424		14%	54%

[a] OECD denotes that the PSMC is hosted by an OECD country (excluding Turkey and Mexico, but including Brazil, India and China). Note that for the purpose of analysing the OECD vs. non OECD stratas here USA is included as an OECD country (in the econometrics analysis USA is instead represented by an own variable). High public funding means that the PSMC received more than 80% of its funding from public sources.

N: 103 observations. Further detail appears in the appendix.

Source: Own survey

Table 3. Description and summary statistics of the variables showed in table 2 and used in the econometric model [a]

Variable	Description	Mean	Std. dev	Min – Max
Dependent variables				
CONSERV RATIO	Ratio of type strains over total number of strains in the PSMC's holding	0.15	0.25	0-1
OUTFLOW_IND	Share of the distributed microbes that are provided to the private sector	0.23	0.26	0-1
Explanatory variables				
CATEGORIES	Number of categories of microbes held by the collection (1-5, denoting if the collections hold bacteria, fungi, yeast, algae, other)	2.11	1.07	1-4
PR	Latent variable representing whether the collection received any strains regulated by Material Transfer Agreement (MTA) or contract. The variable is constructed from predicted probabilities of three instruments.	0.38	0.24	0-1
STOCK	Natural log of number of strains in the collection's stock (type strains and non-type strains)	7.40	1.54	3-11.29
INFLOW	Interval variable: percentage of received strains that the PSMC sourced from other PSMCs, as opposed to from for example academia and hospitals (0%, 1-20%, 21-40%, 41-60%, 61-80%, 81-100%)	1.17	1.20	0-5
OUTFLOW_ACAD	Share of the distributed microbes that are provided to academia and hospitals	0.60	0.34	0-1
Dummy explanatory variables				
PUBLIC HIGH	Of the funds that the collection had to its disposal for spending in 2005, more than 80 percent came from public bodies as opposed to private donors (yes = 1, 0 otherwise)(1)	0.54		0-1
PUBLIC MED	the PSMC receives between 1% and 80% of its funding from public bodies (yes = 1, 0 otherwise) (1)	0.23		0-1
PUBLIC 0	The PSMC receives no funding from public bodies (no funding from public bodies= 1, 0 otherwise)	0.15		0-1
OECD	Collection is hosted by an OECD country (excluding Turkey, Mexico and USA, including Brazil, India and China) (yes = 1, 0 otherwise)	0.82		0-1
ISO	The PSMC is ISO certified (yes = 1, 0 otherwise)	0.14		0-1
ECCO_ISO	Interaction variable: collection is member of ECCO which is a European network of microbe collection, and, has an ISO certificate which is a quality certificate	0.07		0-1
USA	Collection is located in USA (yes = 1, 0 otherwise)	0.10		0-1
FEE	The collection does charge a per unit fee for provision of microbes (yes = 1, 0 otherwise)	0.67		0-1

N. observations: 103; [a] Values correspond to the year 2005. (1) The survey data distinguishes between ranges of public funding (0, 1-20, 21-40, 41-60, 61-80, 81-100). The categories between 1 and 81 percent public funding are merged due to low number of observations in some of these categories

Table 4. Estimates of the ratio of type strains in stock, and, the ratio of distribution to industry of microbes in general (bivariate Tobit).

	Coefficient CONSERVATION _ RATIO	Standard errors
PUBLIC HIGH	0.07	0.06
PUBLIC MED	0.16 *	0.08
ECCO ISO	0.19 *	0.10
ISO	- 0.10 *	0.05
INFLOW	0.06 ***	0.02
PR	0.34 ***	0.10
STOCK	- 0.03 *	0.02
USA	- 0.17 *	0.10
OECD	0.03	0.07
CONSTANT	0.07	0.16

	Coefficient OUTFLOW_IND	Standard errors
PUBLIC HIGH	- 0.10 **	0.05
PUBLIC 0	- 0.06	0.08
FEE	0.19 ***	0.07
STOCK	0.01	0.02
OECD	0.15 ***	0.05
OUTFLOW ACAD	- 0.56 ***	0.08
CATEGORIES	0.08 ***	0.02
ISO	0.02	0.06
PR	- 0.05	0.10
CONSTANT	0.07	0.17
Rho12	0.31	0.09

*** significant at 99 percent level, ** significant at 95 percent level, * significant at 90 percent level
Number of observations = 103
Wald chi2(18) = 179.73; Prob > chi2 = 0.0000
Likelihood ratio test of rho21 = 0: chi2(1) = 7.33, Prob > chi2 = 0.007