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REVIEW ARTICLE

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Culture collections over the world

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Abstract Culture collections have the crucial role of providing the authenticated biological material upon which high quality research is based. Importantly, they serve as repositories for strains as part of patent deposits, providers of safe and confidential services to store key organisms for research and industry, and sources of organisms cited in scientific papers that can be used in the confirmation of results and for further study. The demands upon culture collections change as new technologies and uses of organisms are discovered. Many are becoming Biological Resource Centres, as defined by the OECD Biological Resource Centre (BRC) Initiative, in that they operate according to international quality criteria, carry out essential research, enhance the value and applications of strains and provide a vital information resource. In a changing international scientific environment, many collections are under threat of extinction because of inadequate funding, changing government support strategies and the cost of new technologies. We are also suffering a decline in the number of biosystematists, who are needed to form a sound base for molecular technologies and to aid in identifying, and characterizing microbial diversity. In this environment, collections must work together to make the best use of new technologies and to contribute to the description of the 1.4 million fungi yet to be discovered. At the current rate, this will take 700 years. New technologies and novel ways of funding this task must be engaged and, above all, scientists must collaborate. Common policies are necessary to address the regulatory demands on collections, to control access to dangerous organisms, and, in particular, to enforce the Convention on Biological Diversity. Countries that hold the majority of biodiversity require support in building the facilities required to explore their hidden resource. The World Federation for Culture Collections (WFCC) and, in Europe, the European Culture Collection Organisation (ECCO) have a key role to play. The world must benefit from its microbial diversity, which is crucial to solving increasing problems in food provision, public health and poverty alleviation.

Keywords Biodiversity · Biological Resource Centres · Culture collections

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Introduction

The tasks that face microbial culture collections are enormous, whilst funding for them and the associated biosystematics and fundamental research are on the decline. There are estimated to be over 1.5 million fungi in the world but less than 100,000 are described [5]. At the current rate of discovery, it will take 700 years to describe them all. However, there is also strain diversity to be considered, making the potential numbers huge. Genomics, post-genomics and other developing areas in bioinformatics are placing enormous demands on researchers and collections, making it imperative that information generation and maintenance of ex situ microbial diversity are coordinated and that tasks are shared. The OECD Biological Resource Centre Initiative is examining how collections can be networked to form a global 'virtual' BRC and a proactive role is defined for them. Details on this initiative can be found in the OECD report *Biological Resource Centres—Underpinning the Future of Life Sciences and Biotechnology* [http://oecdpublications.gfi-nb.com/cgi-bin/oecdbookshop.storefront].

It is recognized that microorganisms can provide solutions to world problems in public health, food, environment and poverty [8, 13, 15]. They are vital components of the world's biodiversity, contributing immense value ecologically and economically. They are fundamentally important in ecosystems, breaking down complex animal and plant remains in soil and thus releasing essential nutrients for plant growth; they form beneficial mutualistic relationships with various plants, for example, nitrogen-fixing rhizobia with leguminous plants and mycorrhiza with forest trees; and they have also been harnessed for the benefit of humankind, producing valuable drugs, being used as biocontrol agents for pests and pathogens as well as in the detoxification of wastes and waste breakdown. It is thus crucial that the microbial diversity of the world is not lost and that it is identified, characterised and exploited in a sustainable way for the benefit of humankind.

The safeguarding of microbial diversity for future use and exploitation is of vital importance for wealth creation. The potential for discovering the new penicillin or finding organisms that have industrial uses is enormous. However, this is not as easy as it first looks and investment is necessary to discover such products. The chemicals and drugs currently on the market originating from microorganisms are often the results of limited screening, and microbiologists can improve and accelerate the search. CABI, an intergovernmental organization [http://www.cabi.org], encompasses in its mission the support of developing countries and in particular the 41 CABI member countries who own it. It has developed marketable products that are generating income for support of biodiversity initiatives, fundamental research, biosystematics and collection development and maintenance. Such examples can be followed to make best use of the world's hidden resource, its microorganisms. Culture collections have an important role in providing the biological resource to underpin research and development. There is not one collection on its own that can conserve representatives of all microorganisms, yet there is little coordination of activities. Areas of the world rich in biodiversity have few facilities for the ex situ conservation that is essential for compliance with the requirements of the Convention on Biological Diversity (CBD) and that enable them to take advantage of the potential of microorganisms. Culture collection organizations, such as the World Federation for Culture Collections (WFCC) and the European Culture Collection Organisation (ECCO), act as fora for discussion by bringing together a critical mass of collections and users to try and co-ordinate activities as well as to exchange information and technologies that will facilitate progress in this vital task.

The World Federation for Culture Collections

The WFCC was founded in 1963 and is a multidisciplinary commission of the International Union of Biological Sciences (IUBS). Since the separation of the International Union of Microbiological Societies (IUMS) from IUBS in 1979, it has operated as an interunion commission [http://www.wfcc.info] that seeks to promote activities supporting the interests of culture collections and their users. Member collections of the WFCC register with the World Data Center for Microorganisms (WDCM), and there are currently approximately 470 member collections [13]. The WFCC has a total membership of around 700 from 62 countries. A congress is held every 4 years to discuss advances in technology and common policies with regard to biodiversity and the role of culture collections. The WFCC keeps its members informed on matters relevant to collections in its newsletter and has standing committees reporting on patent depositions; postal, quarantine and safety regulations; the safeguarding of endangered collections; education, publicity, standards and biodiversity. Since 1986, the WFCC has overseen the activities of the WDCM and it is now the data center for the WFCC and Microbial Resource Centers (MIRCENs) Network. Established in 1966, the WFCC produced the first hardcopy volume of the *World Directory of Collections of Cultures of Microorganisms*, in 1972, whilst based at the University of Queensland, Australia. The WDCM relocated in 1986 to RIKEN, Saitama, Japan, and then again in 1999 to the National Institute of Genetics, Japan. The *World Directory* [13] illustrates some of the data held on the Web site [http://wdcm.nig.ac.jp]; it has indexes by country, main subjects studied, cultures held, culture availability, their staff, and services offered. The WDCM collections hold in excess of 1 million strains (see distribution by continents in Table 1), 44% of which, are fungi, 43% bacteria, 2% viruses, 1% live cells, and 10% others (including plasmids, plants, animal cells and algae).

European Culture Collection Organisation

The European culture collections have collaborated together since 1982, when the European Culture Collection Curators Organisation was established to bring the managers of the major public service collections in Europe together to discuss common policy, exchange technologies and seek collaborative projects. The organization opened itself to staff and users of microorganisms and is now named the European Culture Collection Organisation (ECCO). There are currently 65 members, including 57 collections that hold over 350,000 strains. Members have helped produce practical approaches to international rules and regulation. Initiatives led by the Belgian Coordinated Collections of Microorganisms (BCCM) have led to a code of practice for collections to operate within the Budapest Treaty (1983) and the Microorganisms, Sustainable Access and Use, International Code of Conduct (MOSAICC), which provides guidelines for compliance with the CBD [http://www.belspo.be/bccm/mosaicc]. There have been several collaborative projects involving ECCO members that have placed the European collections at the cutting edge of culture collection activities and research. The most recent, European Biological Resource Centre Network (EBRCN), follows on from the Common Access to Biological Resources and Information (CABRI)

Table 1 World Data Centre for Microorganisms (WDCM)

Country	Number of collections	Number of strains	Percent of total number of strains
Africa	10	8,540	0.8
Asia	152	215,992	20
Europe	152	470,860	44
America	111	296,496	27
Oceania	46	89,973	8.2
Totals	471	1,081,861	

electronic catalogue project [http://www.cabri.org]. This project is setting operational standards for the operation of European biological resource centres and is working in close collaboration with the OECD BRC initiative and the WFCC. Information on the members, activities and meetings can be accessed via the ECCO Web site [http://www.eccosite.org].

Microbial diversity

Europe and America hold 56% of the collections and 71% of the microorganisms (Table 1), whereas most diversity lies outside these regions. There are many examples of biodiversity-rich countries and it is not unreasonable to find that 20–30% of isolations in tropical and extreme environments are new to science. Malaysia is one of the 12 countries of megadiversity that together hold 60–70% of the world's biodiversity, but little is known about the microbial component. It has 12,500 known flowering plants, and using Hawksworth's formula of an estimated six unique fungi per plant [5], potentially 75,000 associated fungi. Yet there are only five microbial collections registered with the WDCM and together these hold 2,108 strains. Similarly, China has a huge biodiversity. China ranks third behind Malaysia and Brazil in numbers of species of plants [http://www.biodiv.org]. The China National Reports and Biodiversity Action Plan reveals that there are 83,000 species in total, excluding soil organisms, microorganisms and insects. The country is a vast territory of complex climates and very diverse geography, with tropical forest covering only 0.5% of land but holding 25% of China's species. It is one of the largest agricultural countries of the world with 30 species of grain, 200 types of vegetables and 300 types of fruit trees. The associated microbial diversity includes 8,000 species of fungi, 5,000 species of bacteria and 500 algae. However, according to Hawksworth's [5] formula, for the 30,000 flowering plants there are possibly 180,000 fungi and therefore some way to go to identify the remainder. The Chinese microbial culture collections have made some inroads into storing representatives of the microflora: there are 14 collections registered with the WDCM with some 30,000 strains of bacteria and fungi and a total of 13,500 species held in ex situ collections (Table 2).

Table 2 The microbial and cell culture collections of China

Organisms held	Number of strains
Algae	4,141
Animal cell lines	617
Animal hybridomas	121
Bacteria	15,953
CDNA	88
Fungi	14,205
Plasmids	404
Protozoa	3
Vectors	150
Viruses	1,252
Yeasts	3,981
Patent strains	733
Total	41,288 (13,500 species)

Conservation of microorganisms

In addition to ex situ conservation, microorganisms can be maintained in situ. However, it is difficult to assess the effectiveness of in situ conservation when we have so little information on the extent of microbial diversity. Microorganisms are subject to relatively rapid evolution and adapt and change to environmental factors that in some cases can eliminate some of them. There are many plants on the endangered species list but it is likely that for every flowering plant that is lost the six associated species of fungi are lost, too. The application of modern genomic techniques to assess microorganisms presents problems, e.g. limited information [1] and the fact that population genetics for fungal communities can be difficult as DNA is not always easily released from the fungal cell [2]. Additionally, WDCM data show that 50% of holdings are represented only in one collection. It is not always possible to go back to a location and isolate the same species with exactly the same properties. There are so many threats to biodiversity, including habitat loss, conversion of forests to farmland and the over-exploitation of natural resources such as harvesting lichens from rainforest. However, today it is more likely that industrial pollution has the greatest effect on numbers of species.

BRCs have a role to play in the ex situ conservation of organisms by providing a living resource to underpin the life sciences [6]. They accept deposits subject to publication to enable confirmation of results and further studies, and offer safe, confidential and patent deposit services. BRCs not only supply strains but also provide reference and standard strains along with the associated information, and they carry out preservation research to ensure that strains are preserved without change [12]. Organisms held by BRCS are necessary for teaching and research and can provide microbial solutions for many of today's problems. Crop losses can be reduced by integrated pest management programs that include the use of natural enemies to control pests and diseases. Crop wastes can be degraded and converted into compost or useful products through the use of carefully formulated microbial communities. Microorganisms play an important role in soil fertility and plant health as nitrogen fixers and mycorrhizal symbionts to give plants access to nutrients and water they would not normally get. Microorganisms are being increasingly used in bioremediation of industrial waste. Through many different uses they can lead to poverty alleviation, for example by production of active and marketable molecules and through biotechnological applications. Studying the ancestors of resistant disease organisms held in collections from times before antibiotics and some forms of chemical pollution will help provide solutions to public health problems.

Microorganisms have value that can be assessed in several different ways. At CABI Bioscience, the value of the 28,000 strains held can be based on their replacement cost ($12 million), the curation costs over the last 50 years ($21 million) or the revenue from sale of all stocks ($40 million). This equates to between US$429 and US$1429 each. Microorganisms can also be valued on the basis of cost to society and industry, for example, up to 40% of the world rice crop is lost to pests and diseases [http://www.riceweb.org/research/Res_isspests.htm]. World rice production in 2002 was expected to be 384.4 million tons. worth US$ 73 billion at a cost of US$ 190 per metric ton. A 40% loss would therefore be valued at almost US$ 30 billion [http://www.foodmarketexchange.com/datacenter/product/grain/rice/detail/dc_pi_gr_rice0602_01.htm]. Microorganisms can also be valued based upon their products, for example a detergent enzyme raised US$ 0.5 billion in one year, 42% of sales of the 25 top-selling drugs worldwide are either biological, natural products or entities derived from natural products [14]. Bioremediation of soil in the European Community in 2000 was considered to be worth US$ 60 billion. Fungal-derived drugs are extremely valuable, for example cyclosporin raised US$ 1.2 billion, clarithomycin, US$ 1.35 billion and amoxicillin US$ 1.5 billion [14]. As it is not uncommon to find that 15–30% of fungi found in the tropics or in unexplored environments are unknown to science, the potential is enormous. However, biotechnology discovery is not so simple. There are many different estimates on the chances of getting a product to market, and the time frame can be 10–15 years. There is maybe 1 chance in 250,000 for an unknown chemical reaching the market; for active compounds this increases to between 1 in 5,000 to 1 in 10,000 [3]. Microbiologists can increase chances ten-fold through manipulation of metabolism, and chances increase when working in countries rich in biodiversity.

The Convention on Biological Diversity

The CBD [http://www.biodiv.org] affects accesses and benefit sharing for which collections can provide transparency. The three key objectives of the CBD are: (1) conservation of biodiversity; (2) sustainable development of genetic resources; and (3) fair and equitable sharing of resultant benefits.

The CBD has been ratified by over 185 countries but it has yet to be fully implemented, and to date few collections have implemented policy to comply. Governments have not issued guidelines on access to ex situ collections, although the Bonn Guidelines were adopted as a voluntary code in 2002 [http://www.biodiv.org] There have been a few case studies to attempt to develop procedures for compliance, for example, MOSAICC and the Common Policy Guidelines (CPG) for Botanical Gardens, but these have been hampered by the lack of information, e.g. on the granting of prior informed consent (PIC), and the fact that the translation of national biodiversity strategies into action plans is not very advanced. Countries, politicians and scientists alike are uncertain of how to make progress without affecting scientific advancement or the environment. Tackling compliance independently can put collections at a disadvantage. When CABI Bioscience introduced their policy to ensure that material transfer agreements were in place for all organisms supplied this resulted in a significant drop in the use of the collection. However, the CBD does present an opportunity for collections such as CABI Bioscience to help provide solutions to some of the problems that exist.

Key requirements of the CBD

Identification and monitoring of biodiversity (Article 7). Ex situ conservation, preferably in-country (Article 9). Establishment of education and training programs for identification, conservation and sustainable use of biodiversity with attention to the needs of developing countries (Article 12). Promotion of research and the use of scientific advances (Article 12). Access to genetic resources; sovereign rights over resources is given to the country of origin with the understanding that they will allow access for environmentally sound use (Article 15). Access to, and transfer of, technology—a two way flow of technology is encouraged, high technology and taxonomic expertise balanced with in-country traditional knowledge (Article 16). Fair and equitable sharing of benefits on mutually agreed terms (Article 16). Exchange of information (Article 17). Technical and scientific cooperation (Article 18). Handling of biotechnology and the distribution of its benefits (Article 19).

Collections must work with their CBD National Focal Points [http://www.biodiv.org] as they can provide mechanisms to help implement national policies. Collections must organize themselves nationally in order to play an effective role and to prevent access to biological materials becoming too bureaucratic thus impeding research and development. In the UK, the UK National Culture Collection (UKNCC) has been formed to co-ordinate activities of the UK national collections as well as to develop uniform approaches to international requirements and allow them to become more cost effective. CABI Bioscience UK Centre runs the UKNCC Secretariat [http://www.ukncc.co.uk]. There are over 20 national federations that can also develop enabling mechanisms not just for the CBD but also by acting as national nodes in many international initiatives.

Utilization of microorganisms for sustainable development

It is clear that microorganisms do, and will continue to, provide solutions to societal problems, and they have a role in sustainable development. Culture collections can play a capacity-building role to help biodiversity-rich countries better understand and utilize their microbial diversity. They can help initiate targeted isolation programs, aid in the characterisation of strains and establish ex situ conservation programs to utilize preservation technologies to retain properties and introduce modern methodologies to add value to strains. Introducing screening programs to collections will give biodiversity-rich countries ownership and through partnerships allow them to benefit from exploitation of the microbial diversity they hold. However, to achieve these ends there is a need for collaboration.

The importance of collaboration is also exemplified by the decline in biosystematics around the world at a time when the need to harness biodiversity to help provide solutions to problems in the environment, health and agriculture is at a high. Common policy for compliance with legislation must be established, as there are so many rules and regulations that impact on the operations of culture collections [11]. Common policy and practical solutions to comply are essential while enabling the continuation of research for the benefit of humankind.

Commercialisation

Adequate funding is crucial to support culture collections, not only their continued maintenance but also their future development [7]. There is no single model that can be applied to the financing of a collection. However, a formula for sustainability must include government support for services provided by collections to them with respect to conservation, advancing life science research and meeting biodiversity obligations. Traditional products must be extended by the provision of new products to meet the needs of today's users, for example, DNA, enzymes, metabolites and other derivatives from authenticated strains. Collections can move beyond this by developing commercial products through the provision of biotechnological solutions and active compounds, funding such initiatives through public/private investment and the establishment of spin-off companies. CABI Bioscience has been moving in this direction since the 1990s, when direct UK government funding ceased in 1989.

CABI identified the need for a rapid test kit to detect fungal contamination in kerosene as the detection methods of the time took 3–10 days. The company Conidia Bioscience [http://www.conidia.com] was established to develop the FUELSTAT resinae detection kit, which has attracted substantial interest from aircraft fuel providers and airlines. The use of the kit is recommended in the Boeing Aircraft Maintenance Manual. It is not beyond culture collection staff to come up with solutions to current microbial problems and to establish similar companies whose profits can be partly used to support biosystematics, biological collections and fundamental research. There will be a need to develop new products, and Conidia Bioscience plans to develop further kits for the detection of bacteria and yeast in fuel that can be used in storage complexes, marine vessels and land fleets. CABI Bioscience has also been involved in developing biocontrol agents and one particular success has been *Green Muscle*, used for control of African locust [4]. Profits from the sale of this product go into a fund to support biodiversity initiatives in Africa.

Not only do collections need to find novel ways of funding, they also need to keep abreast of and harness new technologies to produce information on the strains, adding to their value with the aim of providing today's users with the information they need. It is not always possible to establish these technologies in-house but it is possible to establish partnerships with manufacturers, other collections or institutions with the expertise and the facilities. Bioinformatics is of increasing importance to the operation of collections, and new ways of collecting, storing, analyzing and presenting data are required to make best use of biodiversity information. Molecular techniques to differentiate between strains and to aid in their identification are increasing in use. Recent work at CABI has shown through PCR fingerprinting of replicates of an isolate of *Metarhizium anisopliae* that polymorphisms were introduced as a result of non-optimized preservation techniques [9]. Therefore, at the very least collections should be adopting molecular techniques to determine whether they are preserving strains without change.

Summary

Science has moved at an extremely rapid pace since collections first started to maintain examples of microorganisms over 100 years ago [10]. The collections of today must adapt and change to meet new demands and they must work together to meet the enormous tasks ahead. Lands rich in microbial diversity must explore, maintain and utilize their genetic resources but need human resources and technologies to do so. Capacity-building in these areas is underway through the activities of collections such as CABI Bioscience and through the collection organizations such as the WFCC. How can this be funded? As described here, microbial diversity has enormous value; it can provide solutions to environmental, food and health problems and produce high-value products. Collections must harness new technologies and form partnerships to find novel funding mechanisms. Ex situ microbial resource collections have an important role to play in the conservation, understanding and utilization of the world's microbial diversity.

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