Bio-Commons Whitepaper

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View out of the Bio-Commons conference hall, Vartiosaari island, Finland

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Content

Preface

At the Pixelache Unconference in Helsinki, June 2014, a discussion was initiated during the Bio-Commons workshop setting out to identify the requirements and conditions of Open-Source and Citizen-Science concepts to realize Responsible Research and Innovation (RRI) in the Life Sciences. In this whitepaper the results of the scenario thinking workshop and brainstorm discussions on the topic of the Bio-Commons are presented. As a way to realize these concepts, a hypothetical licensing model termed Bio-Commons (in analogy to the Creative-Commons) was discussed. The ideas were worked out by participants with a professional background ranging from life sciences, engineering and arts to philosophy and law. Some of them associate themselves with the European DIYbio scene. Although the participants were mostly professionals in one or the other subject, no single person was an expert on all aspects of the Bio-Commons topic due to its transdisciplinary character. Therefore, participants are further simply referred to as 'citizens'. Citizens taking part in the discussion came from a broad range of countries from across Europe and south-east Asia. The report does not reflect any personal opinion unless otherwise stated, but serves as a summary of various ideas and concepts that were discussed.

Abstract

With increasing knowledge and technical skill, the sphere in which intentional intervention in nature are possible will further be expanded. Alternative IP regimes such as open-access and open-source could in future help to leverage the cost for research and development in the life sciences, mobilize unused knowledge and become more adaptable to spark new inventions. Citizens proposed a 'Bio-Commons' license model to put biological innovation into service to society and at the same time limit the potential misuse of knowledge and material. Taking the antibiotic resistance problem as an example, this whitepaper aims to demonstrate the necessity and feasibility of a Bio-Commons approach. Overuse of the available antibiotics and subsequent evolutionary pressure has led to the development of multi-resistant bacteria. Bacteria are under selective pressure and evolve mechanisms to avoid the antimicrobial effects of the antibiotics. Once developed, the genes for the resistance rapidly spread, and even cross over between different species - a process called horizontal gene transfer. It is therefore necessary to continuously develop new antibiotics to keep up pace with resistant bacteria. The reason for an exacerbation of the antibiotics problem into an antibiotics crisis is a market failure due to a lack of financial incentives for the pharmaceutical industry to develop new drugs like antibiotics with a small profit margin. Citizens thought of three possible scenarios of how to detect antibiotic substances from samples collected in the field. In a citizen science project dubbed 'Biostrike', people around the globe could contribute to the solution to the antibiotics problem by raising awareness on the issue. Citizens and Scientists could participate in a global community around Biostrike, collaborating to find new antibiotics. Specialists from all fields of expertise could put together their knowledge to build the tool sets – that is wetware, hardware and software - to enable decentralized research on antibiotics. The Bio-Commons license could make licensing of innovation and discovery easier for researchers and thereby stabilize global collaborations that will help overcome market failure situations as they exist in antibiotics research. A widely accepted regulatory framework would be required to provide legal security and reliability as well as equal, transparent, and fair terms for all participants. Before creating a legal framework for the Bio-Commons, the social relations and assumptions underlying an idea of the Bio-Commons need to be addressed. Opening up the Bio-Commons discussion and introducing democratic decision making will make everybody a stakeholder. To successfully initiate a broader discussion about the underlying principles for the Bio-Commons, a mutually understandable bio-language is needed that adequately describes the biological reality in digital form. The development of this bio-language in turn opens the possibility for responsible research and innovation already at the earliest stages in the development of a new living system. Citizens also looked for technical solutions and defined a number of requirements for software to handle the data generated under a Bio-Commons license. It was thought that the blockchain technology could in future comprise the technical infrastructure for the Bio-Commons.

Introduction: The commons

Common goods are not owned by individuals and allow for the use by everyone. Examples for common goods are natural commons such as air to breathe, fish in the oceans or a public meadow shared by farmers to feed their animals. With the increasing insights of the life sciences into the fundamental setup of nature, the idea of natural goods can also be applied on organisms, cells, genes, pathways and any conceivable resources found in any organisms. The concept can be further enlarged with the advent of genetic engineering and its successor: synthetic biology. Now, discoveries, inventions and man-made creations such as genetic codes, algorithms, novel metabolic pathways and molecular processes designed for and realized in biological media and even entire organisms can be considered as natural goods. When looking for historic comparison of an extension of the commons to inventions and man-made creations, the most similar and recent problem was faced by the software developers during the 80s and 90s of the twentieth century. The debate in the computer science on the subject of what nature digital algorithms are – physical or abstract, a creation, invention or mathematical discorveries - and how to make best use of them resulted in the formulation of a variety of digital licenses. Among those are the widely used examples like the creative common licenses, the GPL and GNU license frameworks. Today, these licenses allow the creative and inventive potential of the programmer to be directly placed into the commons as a resource meant to be shared by all. The availability of decentralized creative commons in the internet enabled a community of private and corporate software developers and users to construct complex and open systems such as Wikipedia and the Linux. These systems allow a great number of people and private enterprises to make use of sophisticated tools and knowledge at little to no cost – depending on the license model. Such fundamental mechanisms help to avoid a classical market failure, a scenario in which all resources are commoditized, and no party has any incentive to contribute to a development which competitors may profit from at no cost. Despite the substantial success of commons in the digital world, there exists no similar licensing model for the life sciences. Citizens expressed the need to conceptualize the idea of a new intellectual property (IP) -regime for life-sciences to allow for a more productive use and generation of knowledge and innovation, further called “Bio-Commons”.

Excursus: Bio-language

“If it is not true it is very well invented.” (Giordano Bruno) [1]

To fruitfully initiate a broader discussion about the underlying principles for the Bio-Commons, a mutually understandable bio-language needs to be developed which allows all stakeholders to address relevant questions. To develop such a language, stakeholders need to become familiar with the materialistic and the abstract aspects of living systems. A living system here means any life-form consisting of a single or multitude of cells and the corresponding matter it requires for sustained survival. According to the concept of ‘Code Duality’ by Jesper Hoffmeyer, the code of life appears as a ‘digital’ redescription of an ‘analog’ function and structure. Or in other words: life can be considered software and hardware in one. The analog structure and function themselves are thus the materialistically pronounced version of the digital code, while the digital code has no meaning without its analog counterpart. Jesper Hoffmeyer writes:

„For a system to be living, it must create itself, i.e. it must contain the distinctions necessary for its own identification as a system. Self-reference is the fundament on which life evolves, it is its most

[1] http://en.wikiquote.org/wiki/Giordano_Bruno

basal requirement. […] *But what is the basis of this self reference that is at the basis of life? We shall suggest here that the central feature of living systems allowing for self-reference- and thus the ability to select and respond to differences in their surroundings – the the code-duality, i.e. the ability of a system to represent itself in two different codes, one digital and one analog.* […] *Thus, self reference clearly depends on some kind of re-description. The system must somehow be able to construct a description of itself in order to perpetuate itself. This description furthermore must stay inactive in – or at least protected from – the life processes of the system, lest the description should change and thereby ultimately die with the system. In other words, the function of this description is to assure the identity of the system through time. It is the memory of the system.* […] *Eventually the* [living] *system will survive long enough to pass on its own copy of the digitalized memory (or part of it) to a new generation; this corresponds to a back-translation of the message to the digital form.* […] *This codification, however, is necessarily analog – since it has to interact with the physical surroundings, and this must share with these surroundings, the properties of physical extension and contiguity. The chain of events that sets life apart from nonlife –i.e., the unending chain of responses to selected differences – thus needs at least two codes: one code for action (behavior) and one code for memory*.[…] *A digital code is 'outside' the sender and the receiver and mediates their relationship; an analog code is the relationship which mediates them*" (Jesper Hoffmeyer)[2]

A recent development emerging at the intersection of synthetic and systems biology is to describe the digital code in form of biological programming languages. The goal of this approach is to find adequate hierarchies of abstraction, modularization and standardization to make biological design easier. A future bio-designer should thus be able to code the properties of a living system on a computer by simply describing the desired features in the biological programming language. The program will then compile a genetic code, which is subsequently synthesized, transformed into an organism and then tested and debugged in the living system – the analog counterpart of the digital code. To date it is hardly possible to blueprint functional genetic parts that work in the real world ab initio. Evolutionary selection mechanisms are needed to achieve the desired functional outcome. The same is true for genetic elements of any size, cells and entire organisms. It can be assumed that this gradually improve with new abstraction layers that are underlying future Bio-languages under constant development. However, the efficiency and speed with which an idea is translated into biological reality will dramatically increase, as well as it will be able to automate its testing and thus extend the quantity of designed organisms. Eventually, humans will refine the Bio-language to a point at which we will 'speak' it fluently, intuitively understanding the essential underlying mechanisms of the analog and digital code of living systems.Such an approach is not reductionist and cannot be deterministic, but is an iterative and highly creative process. Erich Berger from the Finnish Society of Bioart correctly notes that

"*there is [also] a realization of the kinship between art and science. Artists recognize that both are creative practices exploring our world through common core processes with a mutual interest in questions of philosophy, ethics and politics.[…] One fundamental reason [for artists to involve in biology] is the realization that life sciences and technology are among the most potent forces transforming our life-world. Genetically modified organisms, synthetic biology, and environmental concerns lead artists to engage with the sciences behind these developments to find a cultural response to new emerging questions and issues concerning society.*" (Erich Berger)[3]

[2] Jesper Hoffmeyer; 2008; Biosemiotics: signs of life and life of signs; University of Scranton Press; ISBN 978-58966-169-1

[3] Erich Berger and Laura Beloff; Five years of *art&science* work by the Finnish Society of Bioart at Kilpisjärvi Biological Station; Ars Bioarctica; unpublished material

Intellectual property in the life sciences

To date, most societies rely mainly on intellectual property (IP) in form of patents as means to enable and secure innovations in the life sciences. This whitepaper is grounded on the ad-hoc hypothesis that the productive use of intellectual property regimes based on patents today has reached its limits. During the discussion at the Bio-Commons workshop, citizens questioned the usefulness of the concept of patents for the natural resources unraveled through modern life science technologies. Citizens asked, whether patents, such as the current IP regime, actually meet the nature of biological innovations. Precisely, how a genetic sequence, which was considered a digital code (a detailed examination of the 'Code Duality' see chapter 'Bio-languages'), could fall under the protection of patents at all. Especially the fact, that genetic code is highly redundant and the correlation to the actual function of its corresponding protein is rather weak. In enzymes for example, the same catalytic activity can be achieved by a variety of protein sequences, as only a few amino acid residues of the chain are evolutionary conserved. Furthermore, does not the composition of a genetic code made by man equate better to a creative procedure than to an actual invention and thus some kind of copyright based approach would eventually suit better? To apply for a patent, high costs for a patent search and international registration done by specialists have to be mounted by the inventor. To defend a patent has become equally difficult and expensive and thereby often a patent creates more legal and financial insecurity than it provides security. A single patent becomes an asset as part of patent pool, far removed from its actual invention and its potential applications. Simultaneously, there is a tendency of patents to become increasingly 'weak', meaning is less focused on an actual invention and often simply applied for out of strategic considerations by big companies. The long lifetime of a patent (up to 20 years) further increases the difficulty to safely introduce new inventions to the market. The legal costs and risks can prevent small companies from securing their intellectual property through patents, limiting them in their abilities to cooperate and others in their abilities to build upon their work. Today, products are becoming increasingly complex depending on a large number of inventions. Further, the speed of innovation, especially of that in life sciences had dramatically increased since the inception of the patent system. Therefore, patents can hinder the development and establishment of a new idea from early on, limiting the option to innovate to large corporations that can afford the legal costs incurred by the patenting process. Taken together, these tendencies lead to the creation of monopolies and subsequently induce market failure. A prominent and dangerous outcome of such a development in the medical sector is the decline of usable antibiotics in the market. In the chapter 'Biostrike', a brief scenario will be drawn investigating potential technological innovations to allow for decentralized and commons based drug discovery on the example of antibiotics.

Market failure: antibiotic resistance

In various citizen scientist communities around the world, the problem of the post-antibiotic era was repeatedly addressed.[4,5] The WHO reports that the last new antibiotic was developed 1987 and since then, no new drug was introduced to the market.[6] An overuse of the available antibiotics and subsequent evolutionary pressure led to the development of multi-resistant bacteria. By now, the situation is becoming urgent, as very few effective drugs are left to treat infections.

[4] http://brmlab.cz/project/biolab/biostrike
[5] http://www.longitudeprize.org/prize
[6] Antimicrobial Resistance - Global Report on Surveillance; 2014; World Health Organization
http://www.who.int/drugresistance/publications/infographic-antimicrobial-resistance-20140430.pdf?ua=1

"*Antibiotic resistance is a worldwide problem. New forms of antibiotic resistance can cross international boundaries and spread between continents with ease. Many forms of resistance spread with remarkable speed. World health leaders have described antibiotic-resistant microorganisms as "nightmare bacteria" that "pose a catastrophic threat" to people in every country in the world*" (CDC)[7]

It has been reported that to date 60% of clinically isolated *Staphlococcus aureus* are resistant to methicillin, while in 1990 it was only 25%.[8] Similar numbers exist for most of the known antibiotics. [9] Antibiotic resistance development is a natural process. Bacteria are under selective pressure and evolve mechanisms to avoid the antimicrobial effects of the substances. Once developed, the genes for the resistance then rapidly spread and even cross over between different species - a process called horizontal gene transfer. It therefore is necessary to continuously develop new antibiotics to keep up with resistant bacteria.[10]

"*The European Centre for Disease Prevention and Control estimates that antimicrobial resistance (AMR) results each year in 25 000 deaths and related costs of over €1.5 billion in healthcare expenses and productivity losses."*(European Comission)[11]

"*If we fail to act, we are looking at an almost unthinkable scenario where antibiotics no longer work and we are cast back into the dark ages of medicine where treatable infections and injuries will kill once again."* (David Cameron)[12]

Latest reports revealed that there are resistant genes against even the latest version of antibiotics spreading in the environment. [13] Citizens noted that the reason why no new antibiotics were introduced to the market is not due to a lack of potential substances or scientific inability. Citizens believed that the main reasons for this development lie in the existing organizational structures predominating in public and private life science and research. One reason is a lack of public research efforts to tackle big societal challenges – despite a general availability of skilled personnel and infrastructure. The existing publication model is based on competition of scientists to publish first in a journal of high renown. This incentive though hinders a free exchange of knowledge due to paywalls and a reluctance to share results prior publication, as this could impair the chances of the scientists on research funds and career opportunities. This attitude prevents a wider collaboration and open sharing of results and thus makes a global effort to develop new antibiotics extremely difficult. Another, even more problematic reason is a classical market failure in the pharmaceutical branch. Apart from the costs associated with regulation and cautious clinical testing of new pharmaceuticals – based on sound arguments – market mechanisms contribute significantly to the increase in costs of drug research and development. The effect was described as 'Eroom's Law', which refers to the Moore's Law of the computer chip industry, stating a doubling of efficiency of the

[7] *Antibiotic resistance threats in the United States, 2013;* Centers for Disease Control and Prevention; http://www.cdc.gov/drugresistance/threat-report-2013/

[8] Fix the antibiotics pipeline; Matthew A. Cooper, David Shlaes; Nature 472,32; 07 April 2011; doi:10.1038/472032a

[9] http://en.wikipedia.org/wiki/Staphylococcus_aureus

[10] *Antibiotic resistance threats in the United States, 2013;* Centers for Disease Control and Prevention; http://www.cdc.gov/drugresistance/threat-report-2013/

[11] Communication from the Commission to the European Parliament and the Council; Action plan against the rising threats from Antimicrobial Resistance; Directorate-General for Health & Consumer, European Commision; 15 November 2011; http://ec.europa.eu/health/antimicrobial_resistance/policy/index_en.htm

[12] British Prime Minister on BBC; 02 July 2014 http://www.bbc.com/news/health-28098838

[13] Steve Connor; The Independent; 19 July 2014 http://www.independent.co.uk/environment/drugresistant-bacteria-sewagetreatment-plants-described-as-giant-mixing-vessels-after-scientists-discover-mutated-microbes-in-british-river-9615850.html

technology at the same costs at a given time interval. Eroom's Law (Moore spelled backwards), describes exactly the opposite phenomenon. Despite a steady exponential increase of available scientific information in form of peer reviewed publications [14] and digital database sizes[15], the number of new drugs which were introduced to the market per billion dollar spent fell exponentially.

"*Eroom's Law indicates that powerful forces have outweighed scientific, technical and managerial improvements over the past 60 years, and/or that some of the improvements have been less 'improving' than commonly thought. The more positive anyone is about the past several decades of progress, the more negative they should be about the strength of countervailing forces."*[16]

Due to the high costs and the risky nature of drug development, there is a tendency to push for even higher shareholder revenue from a newly developed drug. Thus there is a lack of financial incentives for the pharmaceutical industry to get involved in the development of drugs with a small profit margin.

"*Pharma industry is profit driven and interested only in chronic diseases, the costs of any research/clinical trials are high and they are also strategizing because they know governments will have to come and offer them money for this type of research, which is already happening in the US and EU. They simply wait so they can milk the governments. In 1990 there were 18 companies developing new antibiotics, by 2011 there were only 4. In 1990 10 new antibiotics were licenced, in 2011 only 2.*[17] *In 2013 Glaxo and the U.S. Department of Health and Human Services agreed to work on new antibiotics. And the government could pay Glaxo as much as $200 million over the next five years, if things go well in EU* [18,19]" (Denisa Kera)[20]

Dr. Charles Knirsh, V.P. Clinical Research for Pfizer for example explains why Pfizer cannot continue their research into drug-resistant bacteria:

"*These are portfolio decisions about how we can serve medical need in the best way.[…] We want to stay in the business of providing new therapeutics for the future. Our investors require that of us. I think society wants Pfizer to be doing what we do in 20 years. We make portfolio management decisions*." (Dr. Charles Knirsh) [21]

In near future, this market development is not going to change dramatically.[22] That is especially problematic regarding the situation of available antibiotics. The WHO reports:

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[14] Citation Counts by Year of Publication; MEDLINE; U.S. National Library of Medicine; November 2013; http://www.nlm.nih.gov/bsd/medline_cit_counts_yr_pub.html

[15] Growth of GenBank and WGS; National Center for Biotechnology Information, U.S. National Library of Medicine; Jun 2014; http://www.ncbi.nlm.nih.gov/genbank/statistics

[16] Fix the antibiotics pipeline; Matthew A. Cooper, David Shlaes; Nature 472,32; 07 April 2011; doi:10.1038/472032a

[17] http://www.ann-clinmicrob.com/content/12/1/22

[18] http://www.pharmatimes.com/article/12-05-24/EU_industry_223_7M-euro_fund_to_tackle_antibiotic_resistance.aspx

[19] http://online.wsj.com/news/articles/SB10001424052702304707604577423683954355876

[20] Interview with Denisa Kera

[21] We Are In The Era Of "Nightmare" Bacteria And Nobody Seems To Care; Meg Marco; Consumerist; 22 October 2013 http://consumerist.com/2013/10/22/we-are-in-the-era-of-nightmare-bacteria-and-nobody-seems-to-care/

[22] Diagnosing the decline in pharmaceutical R&D efficiency; Jack W. Scannell, Alex Blanckley, Helen Boldon and Brian Nature Reviews Drug Discovery 11, 191-200; March 2012; doi:10.1038/nrd3681

"In a field which offers little or no financial incentive to the major pharmaceutical companies, innovations are urgently needed to stimulate the research and the discovery of antimicrobials and vaccines, and to devise funding arrangements and partnerships to support research and development" (WHO) [23]

The problem of antibiotic overuse is made even worse through market mechanisms. Companies that develop antibiotics need to market the use of their drugs in order to get the necessary revenue to compensate their investments. However, the more they sell, the faster multi-resistant bacteria develop. As a countermeasure, users, distributors and producers of antibiotics should be obliged to be prudent with marketing and consumption of the antibiotics. Fewer sales and less consumption, however reduce profit margins and lead to increased product costs. Thus, the incentives for private companies are further lowered to invest into antibiotics development. [24]

Tragedy of the Anticommons

Even though the patent system was meant to provide investment-incentives for commercial developments serving the need of society, antibiotics is one of the areas in which this has failed. The situation turns out to be a classical market failure. [25] However, market failure is not the only explanation of the antibiotics-crisis. It is equally a problem of the overuse of a common, termed "Tragedy of the commons". This means that non-managed common goods, such as natural resources, can be exploited by everyone. For example, all fishers overfish the oceans and thus destroy the foundation of their own livelihood. Widely available and cheap antibiotics can be considered as a common good, too. And the overuse of antibiotics creates resistant bacteria which can affect everyone. A 'Market Failure' in combination with the 'Tragedy of the Commons' thus becomes the 'Tragedy of the Anticommons'.[26] The Anticommons problem arises when ambiguous and conflicting intellectual property claims offer worst of both worlds by deterring sharing and weakening investment incentives.

Bio-Commons

How to overcome this breakdown of innovation and in the same time fix the urgent antibiotics problem? The innovation process has to become more efficient to leverage the development costs. New technology platforms could be used to align research procedures and enhance synergy effects and make the use of knowledge and technology as convenient as possible.[27] Citizens believed, due to the shortcomings of the concepts of patents to foster life science innovations, actual legal innovation might become necessary. Alternative IP regimes such as open-access and open-source could in future help to leverage the costs for research and development in the life sciences, to mobilize unused knowledge, spark new inventions, be more adaptable to actual innovation speed and thus overcome the market failure situation. The bios organization states:

[23] The evolving threat of antimicrobial resistance Options for action; World Health Organization; 2012; ISBN 978 92 4 150318 1; http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf?ua=1
[24] EU Joins Widening Push to Find New Antibiotics; Sten Stovall; The Wall Street Journal; 24 May 2012; http://online.wsj.com/news/articles/SB10001424052702304707604577423683954355876
[25] https://en.wikipedia.org/wiki/Market_failure
[26] https://en.wikipedia.org/wiki/Anticommons
[27] Non-market innovation through the co-production of public services; Michel Bauwens; 12th July 2014; P2P Foundation; http://blog.p2pfoundation.net/non-market-innovation-through-the-co-production-of-public-services/2014/07/12

"*Extraordinary efficiencies occur when the tools of innovation are shared, are dynamically enhanced, have increased levels of confidence (legal and otherwise) associated with their use, and are low or no-cost.*" (Richard Jefferson)[28]

A Bio-Commons license which puts discovery and inventions in the life science under a common regulation, can serve to decentralized biological innovation, while at the same time allow for bigger cooperative projects. In consequence, the Bio-Commons license could even replace the need for patent thickets. Therefore, global and decentralized collaboration of scientists and citizens should be encouraged to speed up the development of new antibiotics. Such a new, decentralized way to handle the vast amounts of knowledge created in the life-science, raise questions on how to deal with intellectual property in general.

"*Could the development of new antibiotics be encouraged by the government? By simplifying how they are licensed and providing financial incentives, more drugs could be discovered.*" (Liz Bonnin) [29]

Ethics Imprinting

Concerning the life sciences, the general weakness of the prevailing IP system is further complicated by ethical problems arising through the advancing technical interventions in the foundations of biological existence – especially that of human life. To date it is not entirely clear, how far the interventions will go and where the limit of technological control over living systems lies. However, it should be assumed that with increasing knowledge and technical skill, the sphere in which intentional interventions are possible will be expanded further. An exponential development of key technologies such as DNA-sequencing, DNA-synthesis and also automation, miniaturization and decentralization of laboratory practices underlines this prospective assumption. Anyways, it is common practice to patent inventions made in the life sciences. With the proposed Bio-Commons license model, biological innovation should be put into service to society and at the same time limit the potential for misuse of knowledge and material. Before creating a legal framework for the Bio-Commons, the social relations and assumptions underlying an idea of the Bio-Commons need to be addressed. Citizens considered the Bio-Commons as relationship and agreement between people, as eventually, the concept of property comes into conflict with ethical values. Thus, there will have to be a decision on where to draw the divisive line between a fact- and value based reference system for the Bio-Commons. It will have to be determined to what extent biological innovation can be seen as a cultural good and in how far it is a product subject to market mechanisms. Fundamental ideas as right of self-determination, the definition of individuality, the human rights (Compare the universal declaration of human rights articles 1- 5 [30]) and the ontology of life itself need to be renegotiated or reinterpreted when formulating the ethical principles for the Bio-Commons.

[28] Science as Social Enterprise; Richard Jefferson; innovations; 2006; http://www.bios.net/daisy/bios/3067/version/default/part/AttachmentData/data/INNOV0104_pp13-44_innovations-in-practice_jefferson.pdf

[29] Human vs. superbug: Too late to turn the tide?; Liz Bonnin; BBC; http://www.bbc.co.uk/guides/z8kccdm

[30] http://www.un.org/en/documents/udhr/

Biostrike: open source antibiotic discovery

"Oh dear! Oh dear! I shall be too late!" (White Rabbit)[31]

In the following, a R&D scenario dubbed 'Biostrike' is presented. It was developed by the citizens during the Bio-Commons workshop, addressing technological and managerial innovations to mitigate the antibiotic-resistance-crisis. The aspiration of the citizens was to highlight the problem of the post-antibiotic era, but also to offer practical solutions. Biostrike was started as a science-art based educational project. It was chosen to be developed further into a lighthouse project for the Bio-Commons and to address the technical, social and legal questions around the Bio-Commons. In a citizen science project, people around the globe could contribute to the solution of the antibiotics problem by identifying new antibiotics in a crowd-sourced research approach. Decentralizing the screening for antibiotics around the world could on one hand reduce the costs of research as more people would contribute voluntarily and on the other hand increase the chances to discover new compounds, as citizens of a diverse range of countries have direct access to a wide variety of ecosystems and local knowledge around the globe. The Biostrike project would ideally be aligned with related international projects such as the Indian initiative "open source drug discovery"[32], private initiatives such as open-source pharma[33] and others[34,35], the European commission projects[36,37] e.g. SYNMOD[38] or combact[39,40] and international projects lead be the WHO[41].

[31] Alice's Adventures in Wonderland; Lewis Carroll; 26 November 1865; Macmillan; http://en.wikipedia.org/wiki/White_Rabbit
[32] http://www.osdd.net/
[33] http://www.opensourcepharma.net
[34] http://www.reactgroup.org/
[35] http://www.jpiamr.eu/
[36] http://www.pharmatimes.com/article/12-05-24/EU_industry_223_7M-euro_fund_to_tackle_antibiotic_resistance.aspx
[37] http://online.wsj.com/news/articles/SB10001424052702304707604577423683954355876
[38] http://www.esf.org/coordinating-research/eurocores/running-programmes/eurosynbio/projects-crps/synmod.html
[39] http://www.imi.europa.eu/webfm_send/914
[40] http://www.imi.europa.eu/content/combacte
[41] http://www.nature.com/news/policy-an-intergovernmental-panel-on-antimicrobial-resistance-1.15275

Scenarios

Citizens thought of three possible scenarios of how to detect antibiotic substances from samples collected in the field (Fig.1). The three ways are: I) the classical molecular biology approach, II) the systems biology approach and III) the synthetic biology approach.

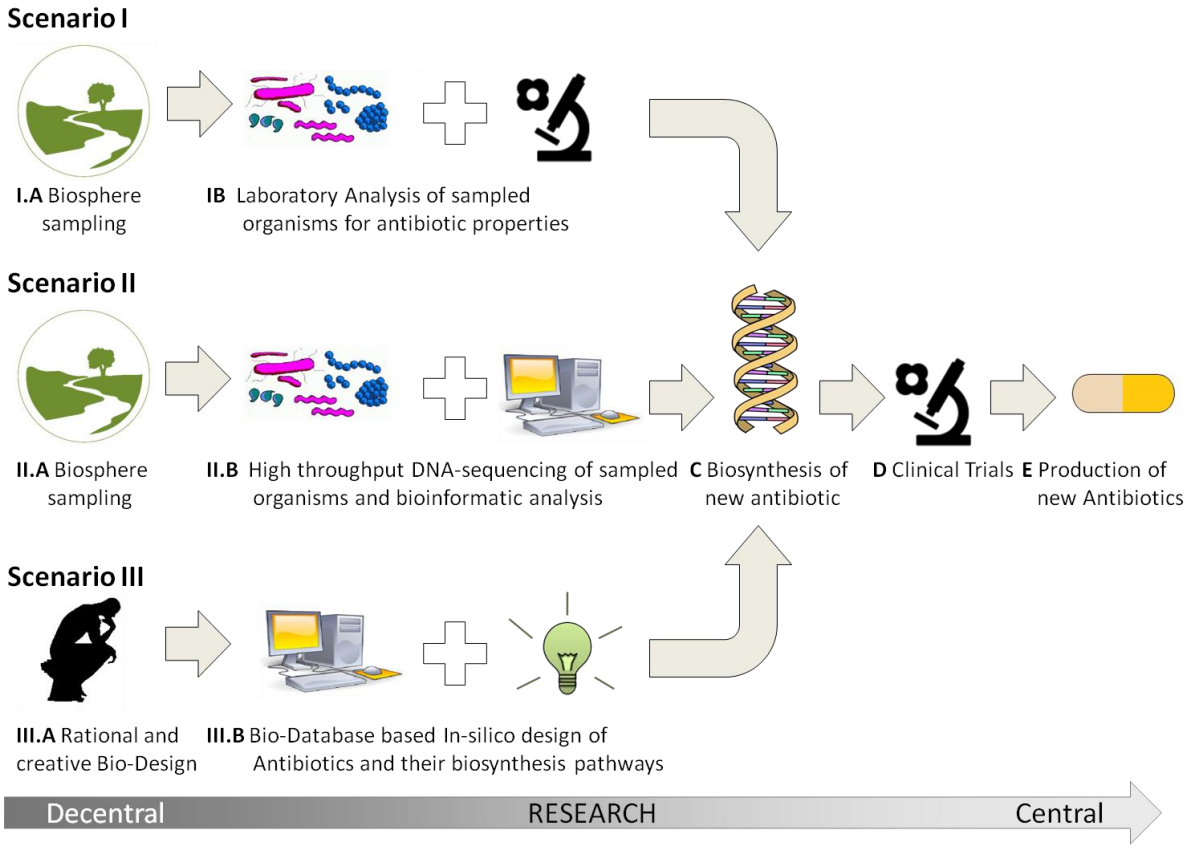

Fig. 1: Three scenarios for Biostrike antibiotics discovery. Description of scenarios see table 1 to 3

To successfully decentralize the screening, a platform technology to standardize methods and ways to analyze experimental results needs to be developed. This is true for all the scenarios described. Such a technology has to be cheap, easy to distribute around the world, usable on-site where the samples are taken and connected to a 'Bio-Commons' database for further analysis of the sampled data. Ideally, the tool-set would give feedback to the researcher right away whether a screened substance has antimicrobial properties or not, to allow the researcher on the site to screen as many samples as possible. To allow for further refinements of the methods, the platform technology should be flexible and adaptable. Beside these hardware and wetware challenges, the skills and crafts to make good use of the data need to be transferred to all the researchers involved. Subsequent to the decentralized screening, centralized analysis of the findings is needed. To date, there is no technology available to decentralize DNA synthesis. Therefore, all steps after the identification of a promising biosynthetic pathway of an antimicrobial substance need to be made in specialized laboratories able to perform high throughput cloning, transformation, and especially analysis of the synthesized substances. If the screening is successful and the specialized laboratories manage to synthesize the substance of interest, clinical trials can be launched. If these, too, are successful, new antibiotics can be produced. Eventually, the centralized methods described in the presented scenarios can also be decentralized. With progressing technology, laboratory equipment will become smaller, more efficient, and cheaper. There are predictions that before 2030, the most

Tab. 1: Scenario I – classical molecular biology approach:	
Decentral	**Central**
Samples could be gathered by researchers in various ecosystems around the world (Fig.1, I.A). The samples could be taken from any biological material, as long as simple and standardized extraction methods are defined. All contained substances could then be isolated using standard biochemical and organic chemistry extraction methods. These substances / the extracted fractions containing them would then be tested on a standardized microbial target (e.g. E. coli) to see whether it affects their growth. Growth could be monitored using a standard E. coli plate and applying the substances on them to see if they inhibit the propagation of the cells or by monitoring the change of the optical density in a liquid culture before and after adding the substance. The DNA of the sample would be extracted and analyzed on the spot using qPCR or similar methods. Of special interest are the sequences of e.g. enzyme clusters that are involved in polyketides[46] biosynthesis pathways or other genes known to be involved in the synthesis of biologically active secondary metabolites. Degenerated primers that match with the conserved elements of the polyketide could be used to detect these gene clusters. As soon as a positive hit is confirmed through any of the screening methods, the DNA would be handed over to a specialized laboratory for further analysis.	A central laboratory would have to precisely identify the active substance and its producing organism / the sequences of genes involved in the biosynthesis that were found in the decentralized screening. The gene cluster of interest could be extracted, the open reading frames of the genes of interest copied and inserted into a standard laboratory strain for protein expression (e.g. E. coli or yeast). These strains would then produce the compound in higher quantities which could be then tested in detail for biological activity on a set of to-date multiresistant pathogens. Following the preclinical tests, a series of clinical trials and subsequent mass production of the antibiotic could be initiated.
Pro	**Con**
• active substances would be detected right away • all types of biologically active substances can be detected • simplicity of the method (required technology widely available) • safety and security measures are hardly needed	• it will be largely unknown what type of substance has been found / very little information can be retrieved about the nature of the substance • it will not be possible to figure out what organism / gene cluster is producing the active compound • only substances which appear in high concentrations in the sample will show significant activity and thus many interesting substances would be neglected • low grade of decentralization of labwork and collection of information - a big workload would lie with the specialized laboratory

Tab. 2: Scenario II - systems biology approach:	
Decentral	**Central**
Soil samples could be gathered by the researcher and the DNA of the sample extracted. The entire genomes of the given sample would then be sequenced on the spot using Nanopore[42] or a comparable sequencing technology. The resulting genetic information would be uploaded to a database protected by the Bio-Commons license. Subsequently, researchers all around the world could analyze the data using bioinformatic tools. Of special interest are the sequences of e.g. enzyme clusters that are involved in polyketides[43] biosynthesis pathways or other genes known to be involved in the synthesis of biologically active secondary metabolites. A metagenomic analysis to screen the entire microbiome of the sample could be perfomed to identify the organism of interest. Relevant genetic information would then be handed over to a central laboratory for further analysis.	In a specialized laboratory, the open reading frames of the gene cluster of interest detected in the decentralized screening would then be synthesized. The synthesized DNA would be inserted into a standard laboratory strain for heterologous expression (e.g. E. coli or yeast). These strains would then produce the compound in higher quantities which could be tested in detail for its biological activity on a set of to-date multiresistant pathogens. Following the preclinical tests, a series of clinical trials and subsequent mass production of the antibiotic could be initiated.
Pro	**Con**
• the organism of interest would be known right away and in great detail, including entire biosynthesis pathways • the digitalization of all data allows decentralized processing of the information • simplicity of the method (assuming nanopore sequencing works reliably) • safety and security measure are hardly needed	• only sequences which are known to be included in the biosynthesis of biologically active substances can be found • low grade of decentralization of labwork - a big workload would lie with the specialized laboratory (cloning and testing of biological activity of compounds) • heavy dependence on price and availability of nanopore sequencing • difficulty to reconstitute the biosynthetic pathway

[42] https://www.nanoporetech.com/

[43] Polyketides are a class of secondary metabolites which are very heterogeneous in their chemical structure and pharmacological effects. Polyketides are synthesized by a common biosynthetic pathway. The genes of this pathway have certain conserved elements that only vary slightly, but the resulting enzymes are still able to produce a great number of bioactive compounds. Many pharmaceuticals are derived from or inspired by polyketides, among them a range of antibiotics. Examples are Tetracycline , Erythromycin, but also cancer drugs like Doxorubicin and Epothilone, as well as the antiparasitec drug Avermectine. Beside the Polyketides there is a couple of other known biosynthetic pathways, which could also be included into the analysis. The following example-scenarios are only referring to the polyketides, but could just as well be extended to other compound classes. https://de.wikipedia.org/wiki/Polyketide

Tab. 3: Scenario III - synthetic biology approach:	
Decentral	**Central**
Point of care diagnostic analysis: the resistant bacteria could be collected by medical personnel. The results would then be gathered in a central database. The databases would be accessible to a global community of researchers that shares the task to design a case specific treatment. By rational and creative design of biosynthetic pathways, entirely new antibiotics could be designed. For example, the polyketide synthesis could be altered, so that it creates new classes of molecules. Another approach could be, to design bacteriophages that specifically target one multiresistant bacteria strain and then injects molecular scissors like the CRISPR/cas9, to degrade the chromosome of the bacteria.[44]	After a pathway or phage has been designed through the decentralized community effort, the constructs would be synthesized in combination with high throughput testing. The synthesized DNA would be inserted into a standard laboratory strain for heterologous expression (e.g. E. coli or yeast). These strains would then produce the compound in higher quantities which could be tested in detail for its biological activity on a set of to-date multiresistant pathogens. Following the preclinical tests, a series of clinical trials and subsequent mass production of the antibiotic could be initiated.
Pro	**Con**
• all kinds of diseases could be approached • treatments would be individualized • In-Silico bio-design could lead to a reduction of costs for medical innovation • Could create a new, digital bio-economy	• To date not realistic • Will require new technologies • Will create new hierarchies and dependencies • Will require fundamental adjustments of science policies

advanced laboratory equipment available today will be scaled down to hand held devices[45]. This would then also include DNA-synthesis, heterologous production of compounds and their analysis. Ultimately, only the clinical trials would have to be organized by a central agency, while all other steps can be done in a decentralized and global collaboration of scientists. However, such a way of organizing science will require – besides the already discussed legal innovation – fundamental adjustments of funding schemes and regulatory oversight to prevent accidents and the abuse of knowledge and technology.

Bio-Commons and Biostrike

The concept presented in Fig. 2 is one possible way to use a Bio-Commons license in order to foster open source antibiotic drug discovery. It can be considered a template which may be redesigned to fit any particular need. Citizens and Scientists could participate within a global community around Biostrike, collaborating to find new antibiotics. Specialists from all fields of expertise would put together their knowledge to build the tool sets – that is wetware, hardware and software – to enable decentralized research on antibiotics. Governments, citizens, NGOs or companies could provide the necessary funding to the community to conduct the research. To coordinate the research activities and to allocate the funding in a productive way, the community would be organized in a democratic manner, voting on which projects should be supported. Any digital redescription of discoveries or

[44] Perspective: The age of the phage; Shigenobu Matsuzaki, Jumpei Uchiyama, Iyo Takemura-Uchiyama & Masanori Daibata; Nature 509, S9; 01 May 2014; doi:10.1038/509S9a

[45] Dr. Blaney, Postdoc at Broad Institute, Assistent Prof. MIT Bioengineering http://www.youtube.com/watch?v=66Oc8fLKXlE (unpublished graph)

inventions of the research activities would be collected in a common database. All data of this database would be under the protection of the Bio-Commons License.

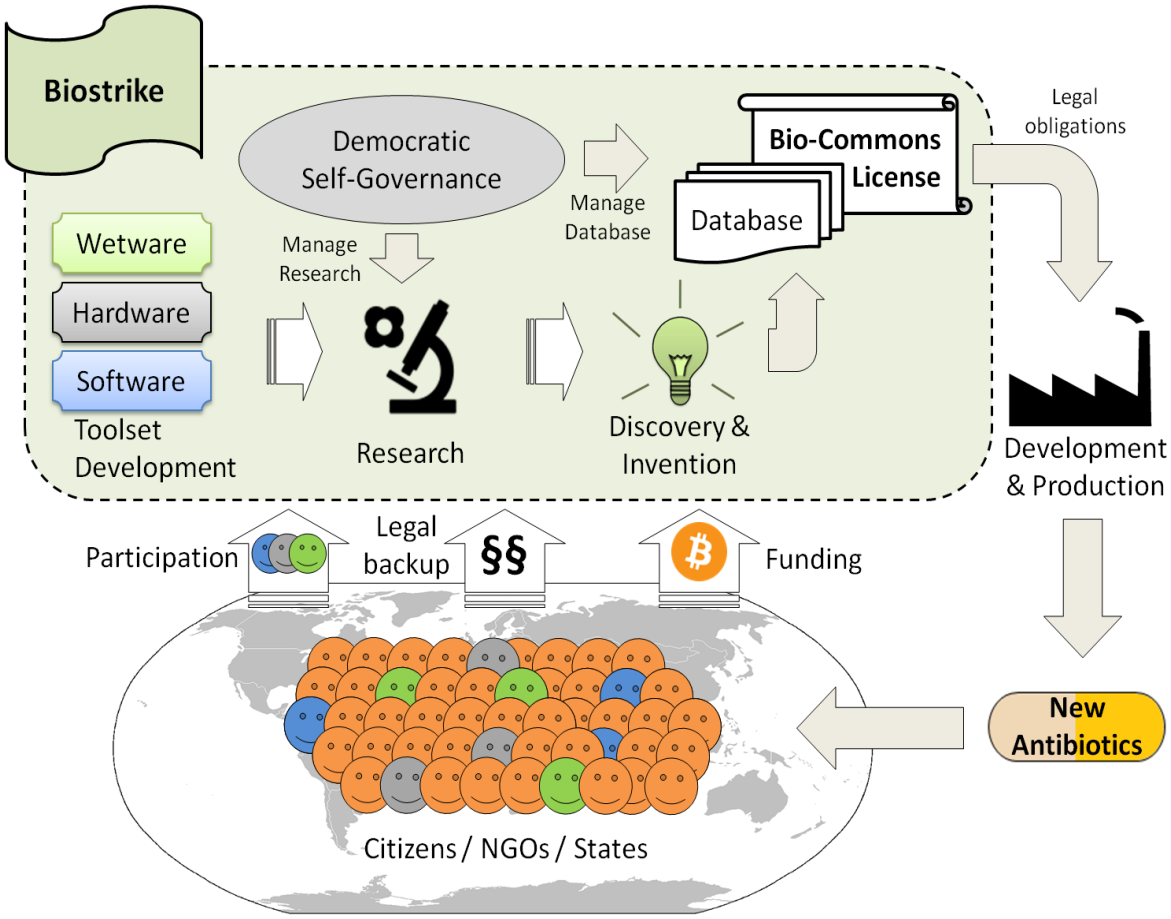

Fig. 2: An example of how a Bio-Commons license could be applied to encompass the decentralized and global research project Biostrike for overcoming the antibiotics crisis. Description see text.

To translate the database knowledge into industrially produced drugs, the Biostrike community could negotiate the conditions with private corporations to take over product development, production and sale. A Bio-Commons license could for example make obligations for companies seeking to use the generated knowledge under its protection. Here, ethical norms could aid in the prevention of abuse of knowledge contained in the database. However, the scope of the license and the conditions for the use of knowledge is yet to be determined. Various license models with different conditions can be formulated. To realize a decentralized, community-based drug discovery project, the Bio-Commons license must be legally valid in as many countries as possible. Governments could support the project by helping to formulate the license models and adjust by their laws internationally to encompass new IP regimes that are better adapted to the life sciences.

Democratic Self-Governance

Due to the inherent ability of living systems (be it genetic elements or organisms) to autonomously proliferate, these can have effects which are out of the control of the user, posing problems for the liability of individuals. Despite these problems, it could eventually be a goal of society to make use of the functionality of a given living system in a non-contained manner. Citizens thought that

democratic decision making is the best way to figure out whether or not this is the case. Opening up the Bio-Commons discussion and introducing democratic mechanisms will thus make everybody a stakeholder. By making use of decentralized crowd-review processes, as well as a democratization of scientific procedures, in-depth control of the applications of data in the Bio-Commons could be achieved. At this point, the idea of democratic self governance within the science remains speculative. A couple of questions arise with it – for example how to guarantee a fair functionality of the science governance.

Software solutions

Many of the described topics on life science research and the management of the knowledge are, from a practical perspective, all about the handling of data. The results of scientific experiments create data, the registration and management of IP is based on data, the distribution of materials (like new antibiotics) requires data and the governance of all this is based on decisions about available data. It is therefore a logical conclusion to look for software in order to solve these questions and problems that are based on the handling of data. Citizens looked out for technical solutions and specified a number of requirements for software with which to handle knowledge under a Bio-Commons license. The list may yet be incomplete:

- Network neutrality: it needs to be operable by a decentralized community of users
- Scalability: it has be able to handle and store huge amounts of data (e.g. acquired by high throughput experimentation)
- Universality: it has to be able to handle any type of data and code (see Biostrike scenario and Bio-language)
- Historicity: any addition or change of data has to be provable for all times – to allow for contracts, citations, references and authorship etc.
- Reliability: storage and handling of data must be safe
- Resilience: the software must be resilient against accidental or intentional damage
- Efficiency: the software must be efficient in terms of operation costs
- Convenience: the software must be convenient to use

Furthermore, mechanisms like reputation systems, voting, personal authentication or secure anonymity for e.g. medical data would be useful features for Bio-Commons projects such as Biostrike. Eventually, a Bio-Economy could be created around Bio-Commons databases. Therefore, the possibility to digitally buy and sell data would be useful additions. There are ongoing software developments based on the blockchain cryptography technology that might match these needs. The blockchain is an algorithm that allows for time-proofed, decentralized transference of data. It was part of the invention of the internet cyptocurreny bitcoin.[46] Bitcoin has, since its inception, spawned a number of promising new software scripts. Just to give the reader an idea of the type of possible services, in the following a few examples are briefly introduced:

- To take the financial burden of scientific discovery and product development away from researcher, projects could in future be funded through crowdfunding campaigns based on decentralized blockchain technology:

[46] https://bitcoin.org/bitcoin.pdf

"*Swarm is a crowdfunding platform powered by Bitcoin 2.0 technology. It allows the users of a product to also be its investors. Everyone benefits as the platform grows*." [47]

- To make contracts between industry partners and the Bio-Strike community project, blockchain based platform Ethereum could be used. It is especially interesting as it promises to allow for the foundation of so called "decentral autonomous organization" able to manage data as well as digital currencies through voting by its members.

  "*Ethereum can be used to codify, decentralize, secure and trade just about anything: voting, domain names, financial exchanges, crowdfunding, company governance, contracts and agreements of most kind, intellectual property, and even smart property thanks to hardware integration. Ethereum borrows the concept of decentralized consensus that makes bitcoin so resilient, yet makes it trivial to build on its foundation.*" [48]

- To process and store scientific data safely in the cloud, the Maidsafe software as an encrypted, decentral storage and computation instance could be used:

  "*MaidSafe is a fully decentralized platform on which application developers can build decentralized applications. The network is made up by individual users who contribute storage, computing power and bandwidth to form a world-wide autonomous system.*"[49]

- DNA.bits promises the handling of sensitive data like a patients genome through encryption. The concept will make the genetic information fully accessible to the researchers who need it, while using strong private keys to maintain digital DNA-wallet privacy and individual anonymity.[50]

Despite the promises that software solutions based on cryptography hold, it should be kept in mind that these are still under development. Setting up a project like Biostrike on such a service would thus be highly experimental. Nevertheless, it might, after some time of development and evaluation constitute, the necessary infrastructure for a global, trustworthy and decentralized scientific research collaboration that is democratically controlled by a community of citizens and scientists.

Conclusion

The 'classical' examples of natural commons often end in tragedy: due to a lack of management, individuals act egoistically and overuse the resource, e.g. fish in the ocean, until it is finally depleted. The result is contrary to the interest of the community and also to the disadvantage of the individual. However, this argument does not apply on digital goods that are copyable. The only physical limit for digital goods is the available computation power and the energy needed for computation. As long as these factors are available in abundance, a 'classical' tragedy of the digital commons is highly unlikely, and the digital goods are practically inexhaustible. The code duality of living systems allows for a digital redescription of genetic code. This digital information can be copied and shared in the internet at almost no cost. When translated back into the analog counterpart, meaning the phenotype of a cell, e.g. by synthesizing the DNA and transforming a cell, the digital information that comes for free can be converted into highly valuable substances. The value of the substance can be monetary but does not need to be. In case of antibiotics, it would be a life prolonging therapy at almost no cost.

[47] http://swarmcorp.com/
[48] https://www.ethereum.org/
[49] http://maidsafe.net/
[50] http://www.dna-bits.com/

Biological 'phase shift'

The presented Biostrike scenarios can be considered an example for what type of data is created in life sciences. In scenario I, collected data in forms of publications, texts, machine readouts and pictures would be uploaded on a database and protected under the Bio-Commons license. Scenario II would yield a lot of DNA-sequences of yet undiscovered organisms. Depending on the sophistication of the sequencing technology, its market price and global availability, theoretically, an enormous number of organisms could be digitally analyzed and uploaded. Looking ahead, a "phase shift" from analog to digital biological information will happen. Vast numbers of biological systems will be digitalized by high throughput sequencing and parameterization of biological samples. To date, many ecospheres like coral reefs are recognized as a world heritage and thus belong to the natural commons. In future, these could become digitalized, quantified and eventually monetized. [51,52] Under a Bio-Commons license, the digital redescription of these ecospheres could be kept in the commons and also managed by a large community, preventing overuse and misuse alike. Equally, the results yielded by the use of bioinformatic tools applied on the datasets need to be covered.

The designed biosphere

In future, there will be software solutions that allow for global and decentralized use of Bio-languages for community driven In-Silico design of novel biological systems. Ultimately, the digital redescription of the natural world will be mixed with human inventions and creations that will become increasingly indistinguishable and interdependent. The Bio-Commons license should therefore be able to cover natural, rational and creative In-Silico bio-designs generated by the community of researchers as a whole. The development of a new Bio-language opens the possibility for responsible research and innovation already at the stage of the design of a new living system. To address the social and ethical implications of Bio-design is not only the responsibility of the scientists, but requires involvement of a wide variety of stakeholders. As the development of bio-languages is in a very early phase, there is plenty of room for involvement of new stakeholders to influence the way in which these language will develop. A Bio-language is exactly the point, where human culture, the digital and the analog aspect of biological systems intersect. A new bio-language thus could allow a new type of 'cultural coding', hardwiring ideas such as ethical values by design, but also allowing for better feedback of biological discovery into the societal context. Besides, a Bio-language could be directly regulated by societies with legal instruments. A regulatory approach addressing the use of Bio-languages would allow societies to precisely shape their biological realities. The risk in regulating such a language is that imposed restrictions could result in an incomplete and dysfunctional description of the factual reality of nature. Bio-languages remain inherently anthropocentric and thus the danger of overlooking crucial e.g. ecological relations is present. However, it is to date the most progressive and promising approach to the design of life.

[51] http://portal.unesco.org/en/ev.php-URL_ID=42855&URL_DO=DO_TOPIC&URL_SECTION=201.html

[52] http://whc.unesco.org/en/list/?search=reef&searchSites=&search_by_country=&region=&search_yearinscribed=&themes=&criteria_restrication=&type=&media=&order=country&description=

Managing the Bio-Commons

Although the classical tragedy of the commons is highly unlikely with digital information, this does not mean that Bio-Commons should remain unregulated. A regulatory framework is required to prevent a market failure in the digital world. Furthermore, new knowledge in the life sciences may create ethical and social problems that need to be addressed. The Bio-Commons license could make licensing easier for researchers and thereby stabilize global collaborations that will help to overcome the 'Tragedy of the Anticommons' as described for the situation around antibiotics research. A widely accepted regulatory framework would be needed to provide legal security and reliability as well as equal, transparent, and fair terms for all stakeholders. All participation of stakeholders should be entirely voluntary and the knowledge falling under the license protection must not be in violation to other types of IP. However, as the knowledge basis in the life sciences is growing at exponential rates, there will be enough new information generated in the near future to quickly build up comprehensive databases. Knowledge to date still protected by closed source IP systems will thus become relatively unimportant in the context of the speed of knowledge gain. Besides these practical goals, Bio-Commons licenses could be used to protect and manage any type of biological knowledge in order to curtail possible misuse, e.g. for experiments that are unethical or to produce harmful substances. The larger the community of people contributing to the Bio-Commons, and the better it is backed by societies, the more effective the protection of knowledge under a Bio-Commons license will become. Even though the cost for the development of new substances like antibiotics could be reduced, there are still costs for the underlying research that has to be mounted. New modes of funding could be explored by communities as they were proposed to manage the Biostrike project. To guarantee a fair distribution of funding and have a most productive research management, Citizens proposed democratic decision making procedures. There are a number of problems arising with the use of such a democratic mechanism and the Bio-Commons concept. It is foreseeable that there will be a hierarchy around the Bio-Commons, with interest groups trying to influence the use of the Bio-Commons. This could subsequently lead once more to a technology lock-in and create a similar problem to the one society faces it today with patent based IP. Before creating a democratically controlled Bio-Commons, a couple of questions need to be addressed: who is going to decide on the distribution of the Bio-Commons? Who is going to define the meaning of Bio-Commons, and how? Is there a limit to the number of people involved? What are the pragmatic problems associated with the everyday use of Bio-Commons? What to do in case of a conflict of interest? The reflections on how to manage Bio-Commons are surely not yet complete and will have to be intensified in an ongoing process in the near future. One essential point, though, has already been defined by the citizens: Commons are transitory by nature and resist conclusive definition. The future use of life science knowledge needs to remain open, multi-directional and exitable. At the current speed of life science development, the half life of a license will therefore most likely be rather short. Thus, it needs flexibility to adapt regulation to upcoming challenges. Independent of how well the Bio-Commons license will be conceptualized, there has to be a clearly defined exit-option describing what is happening with the contained knowledge and values, when the license model becomes outdated. In future, there can be a great number of licenses and organizational models around it, allowing for all sorts of underlying ethical principles, rules for regulation and market models. By using platforms based on the blockchain technology, these license regimes could even overlap or have defined interfaces, mutually allowing for use of contained knowledge. It will depend on the legal authorities of societies to decide which ones to promote and which ones to block. Licenses with a solid ethical foundation, smart and convenient knowledge handling, low costs

of maintenance and a widely accepted legal basis will be most attractive. Eventually, policy makers of national states might need to adapt some exiting regulation to encompass these new licensing regimes (compare Fig. 3). Policy makers are welcome to consult with citizens to set out for new and experimental forms of handling life science knowledge, help to build a civil society around the Bio-Commons and to find the best way to make use thereof.

Fig. 3: Scan of a Gustave Doré Engraving from "The Ingenious Hidalgo Don Quixote of La Mancha" – 1863.[53] A historic analogy to the failure of outdated regulatory concepts in times of fundamental technological change.

53 https://commons.wikimedia.org/wiki/Category:Don_Quixote?uselang=de#mediaviewer/File:202_025_quijote_cap07.jpg

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