Source: Christine Cooper

E. SOCIAL, ECONOMIC AND CULTURAL CONSIDERATIONS ASSOCIATED WITH THE COMPONENTS, ORGANISMS AND PRODUCTS RESULTING FROM SYNTHETIC BIOLOGY TECHNIQUES

This section discusses potential positive and negative impacts of the components, organisms and products resulting from synthetic biology with regard to social, economic and cultural considerations. Table 2 at the end of this section provides examples of potential positive and negative impacts in the context of biosecurity, economic, health, ethical and intellectual property.

9. BIOSECURITY CONSIDERATIONS RELATING TO BIODIVERSITY

A common definition of biosecurity is an effort to "prevent misuse or mishandling of biological agents and organisms with an intent to do harm" (PCSBI 2010). Synthetic biology presents potential challenges to biosecurity, as well as potential tools to aid in security efforts.

Biosecurity concerns related to biodiversity include the use of synthetic biology to create destructive pathogens targeting agriculture or other natural resource bases. Existing livestock and crop diseases could be made more lethal, and novel pathogens designed to impact agricultural biodiversity (Kaebnick 2009).[52] Mukunda *et al*., writing from MIT and Boston University, predict that biological weapons customized to attack specific groups are highly likely in the long term (10 or more years) (Mukunda *et al*. 2009).

There is heated debate as to the level of threat of biological weapons, but broad consensus that advances in biotechnology are likely to increase the dangers posed by biological weapons (Mukunda *et al*. 2009). Mukunda *et al*. (2009) classify potential impacts of synthetic biology on offense as primarily increasing capabilities for acquisition of biological weapons and, in the long term, the effects of such weapons, including enhanced lethality and infectiousness.

Infectious viruses have been created using what some consider as synthetic biology techniques; it is predicted that the creation of bacterial pathogens may be possible. In 2005, researchers at the US Centers for Disease Control and Prevention (CDC) constructed a virus with the complete coding sequences of the eight viral gene segments of the extinct 1918 Spanish influenza virus, following genomic RNA retrieved from autopsy materials and the remains of a victim found buried in the Alaskan permafrost (Tumpey *et al*. 2005). An infectious poliovirus was produced in an American laboratory in 2002, using oligonucleotides ordered from a commercial supplier (Cello *et al*. 2002).[53] Mukunda

52 *Most literature on biosecurity considerations of synthetic biology focuses on human targets, but this analysis applies to biodiversity-associated biosecurity as well.*

53 *These two examples are frequently noted when discussing synthetic biology (see Douglas & Savulescu 2010; Mukunda et al. 2009; RAE 2009). However, one organization commented on an earlier draft of this document that some argue the techniques used in both of these cases are not synthetic biology. Both of these projects involved sequencing parts or all of the target viral genome, and then synthesizing the necessary oligonucleotides (Cello et al. 2002; Tumpey et al. 2005). Tumpey et al. (2005) generated the influenza viruses using a "reverse genetics system." Cello et al. (2002) assembled the poliovirus entirely from oligonucleotides.*

et al. rate the synthesis of viruses as "relatively easy" at present, and thus synthetic biology may be expanding the pool of actors able to acquire agents for biological warfare. In the medium term future, they anticipate the creation of new organisms with novel properties (Mukunda *et al*. 2009). This aligns with the 2007 analysis by Garfinkel *et al*. that synthesizing highly pathogenic viruses will become easier, and that pathogenic bacteria may eventually be possible. At the time, Garfinkel *et al*. (2007) noted that over the next five years, "constructing an infectious virus [would] remain more difficult than obtaining it from nature or from laboratory stocks," but that this could be reversed within 10 years.

Synthetic biology could provide tools for responding to biosecurity risks. The US PCSBI claims it is "easy to anticipate potential benefits" of synthetic biology to biosecurity, such as identifying biological agents of concern and countering biosecurity threats (PCSBI 2010). Synthetic biologist Drew Endy urges that synthetic biology be understood in terms of its "net contribution to risk exposure and not only risk creation" (Endy 2005, Fig. 3). Thus, although synthetic biology can be used to create threats, tools such as DNA synthesis can help identify and respond to biological threats, for example by accelerating the ability to analyze the pathogen and more rapidly synthesize vaccines or vaccine precursors (Endy 2005). Similarly, Mukunda *et al*. point out that synthetic biology could be used for defense, such as improved surveillance to detect pathogenic agents, accelerate vaccine production, and provide therapies for some pathogens (Mukunda *et al*. 2009).

10. ECONOMIC CONSIDERATIONS RELATING TO BIODIVERSITY

The global market for synthetic biology products is growing rapidly, as are investments in synthetic biology research. As seen in section 1, the global synthetic biology market is expected to grow to $11.8 billion in 2018. While smaller than the estimated global market for nanotechnology ($20.1 billion in 2011, $48.9 billion in 2017), synthetic biology's predicted compound annual growth rate of 45.8% outshines nanotechnology's 18.7%.[54] The WWICS Synthetic Biology Project estimates that the US and European governments funded over a half billion USD in synthetic biology research between 2005 and 2010 (WWICS 2010).

There is no clearly agreed definition or scope to the term "bioeconomy"; definitions either focus on the tool of biotechnology or on the use of biomass as a fuel and raw material. The 2009 OECD document *The Bioeconomy to 2030: Designing a Policy Agenda* defines bioeconomy as "a world where biotechnology contributes to a significant share of economic output." (OECD 2009). The United States' White House's *National Bioeconomy Blueprint* similarly defines bioeconomy as "economic activity that is fueled by research and innovation in the biological sciences" (US White House 2012). The European Commission's definition of bioeconomy is broader: "an economy using biological resources from the land and sea, as well as waste, as inputs to food and feed, industrial and energy production. It also covers the use of bio-based processes for sustainable industries" (EC 2012).[55] Civil society groups' definitions of the bioeconomy are similar to that of the European Commission.[56] The Global Forest Coalition describes it as a post-fossil fuel economy, "heavily based on the use of biomass, both as a fuel and as a raw material from which to manufacture a wide range of products, including plastics and chemicals" (Hall 2012). The ETC Group sees the bioeconomy as relying on three inter-related and reinforcing concepts: the biomass economy, moving from fossil and mineral resources to biological raw materials; the biotech economy, in which genetic sequences are the building blocks for designed biological production systems; and the bioservices economy, in which new markets in ecosystem services enable trading of ecological credits (ETC 2010).

States, industry, and civil society identify synthetic biology as playing a potentially significant role in the bioeconomy. The Government of the United States of America names synthetic biology as an emerging technology that "holds vast potential for the bioeconomy, as engineered organisms could dramatically transform modern practices in high-

54 *See http://www.bccresearch.com/report/nanoparticles-biotechnology-drug-development-delivery-bio113a.html. Accessed on 17 April 2013.*

55 *The EC's Strategy describes the bioeconomy as including the sectors of "agriculture, forestry, fisheries, food and pulp and paper production, as well as parts of chemical, biotechnological and energy industries" (EC 2012b).*

56 *For all of these actors, the bioeconomy is a narrower concept than UNEP's "Green Economy" (an economy "that results in improved human well-being and social equity, while significantly reducing environmental risks and ecological scarcities") (UNEP 2011).*

Source: Macroscopic Solutions, LLC

impact fields such as agriculture, manufacturing, energy generation, and medicine" (US White House 2012). Industry analysts see a "bright future" in the bio-based economy for developers of biochemicals, biomaterials, bioactive ingredients, and processing aids (Huttner 2013). The ETC Group describes synthetic biology as a "game-changer," expanding the "commercial possibilities for biomass" (ETC 2010).

State-led policies and strategies are driven by the anticipated benefits of an expanded global bioeconomy. The EC is pursuing the bioeconomy to "reconcil(e) demands for sustainable agriculture and fisheries, food security, and the sustainable use of renewable biological resources for industrial purposes, while ensuring biodiversity and environmental protection" (EC 2012a, 1). The European Commission three-part Action Plan includes: investing in research, innovation and skills; reinforcing policy interaction and stakeholder engagement; and enhancing markets and competitiveness (EC 2012b). The US Obama Administration is prioritizing the bioeconomy "because of its tremendous potential for growth" as well as its potential to "allow Americans to live longer, healthier lives, reduce our dependence on oil, address key environmental challenges, transform manufacturing processes, and increase the productivity and scope of the agricultural sector while growing new jobs and industries" (US White House 2012). Brazil is aligning its strategies to become the "No.1 Global Bioeconomy," building on its natural resources base and extensive biodiversity.[57] And States that have not yet developed bioeconomy-specific strategies are adopting the language of the bioeconomy, such as the Malaysian Minister of Natural Resource and Environment identifying bioeconomy as key to transforming Malaysia into a high-income country.[58]

Engagement by some civil society groups on synthetic biology is significantly motivated by anticipated dangers of an expanded global bioeconomy. Some civil society groups have expressed deep concern over the methods by which a transition from fossil fuels to renewable resources is proposed. As described in section 5.1, a major concern is that the necessary scale of extraction and use of biomass for a global bioeconomy is ecologically unsustainable (Hall 2012; ETC 2011; ICSWGSB 2011; FOE *et al*. 2012). The new bioeconomy also potentially threatens "older "bio-based" economies represented by billions of people with preexisting claims on the land and coastal waters where biomass grows" (ETC 2011). The ETC Group cites the World Health Organization statistic that 3 billion people depend on firewood as the primary source of fuel for heat and cooking, and that 2 billion people rely on animals as the main source of power for agriculture and transport (ETC 2011). Many civil society groups express concern that these biodiversity-based economies depend on the same natural resource as the new bioeconomy, and therefore stand to be displaced by land and resource grabs (ETC 2011; ICSWGSB 2011; Hall 2012).

Many of the first wave synthetic biology commercial applications replicate naturally-occurring molecules that are expensive or difficult to source outside the laboratory or produce in the laboratory using synthetic chemistry (Wellhausen and Mukunda 2009). Product displacement can potentially ease negative pressures on wild or cultivated species, but it can also displace cultivation practices, often in topical and sub-tropical regions.

The anti-malarial semi-synthetic drug artemisinin is a high-profile example of the complicated trade-offs that may result from product substitutions. The artemisinin project of Prof. Jay Keasling of UC Berkeley has been the most popular example of the promise of synthetic biology, and particularly of synthetic metabolic engineering, for the past seven years (Collins 2012; Garfinkel *et al*. 2007; Garfinkel and Friedman 2010; Heinemann and Panke 2006; PCSBI 2010). The shrub *Artemisia annua* has been used in China for centuries to treat a variety of illnesses, including malaria (White 2008). Although announced to the rest of the world in 1979, global politics and issues of price kept artemisinin largely inaccessible. It was not until 2004 that the World Health Organization (WHO) and Global Fund for AIDS, Tuberculosis and Malaria switched to Artemisinic-based Combination Therapy (ACT) (Enserink 2005; Milhous and Weina 2010; White 2008). Since then, the availability - and thus price - of artemisinin has varied wildly, as a combination of bad weather and a glut of new producers has led to year-to-year price swings (Peplow 2013). The Gates

57 *See http://www12.senado.gov.br/internacional/05-18-2012/brazil-can-become-a-leader-in-bioeconomy-says-director-of-national-industry-confederation; http://www.iica.int/Eng/prensa/IICAConexion/IICAConexion2/2012/N13/secundaria4.aspx; and http://www.process-worldwide.com/management/markets_industries/articles/345478/. Accessed on 23 April 2013.*

58 *See http://www.mysinchew.com/node/81046. Accessed on 23 April 2013.*

Source: Macroscopic Solutions, LLC

Foundation gave two grants totaling $53.3 million to the Institute for OneWorld Health to help Prof. Jay Keasling of UC Berkeley engineer the molecular production of artemisinic acid from yeast (Sanders 2013). In 2006, Keasling's group announced their success in engineering the metabolic pathway of yeast using 12 new synthetic genetic sequences to produce high levels of artemisinic acid (Ro *et al*. 2006). OneWorldHealth, Amyris (a commercial synthetic biology company co-founded by Keasling), and pharmaceutical company Sanofi partnered to produce semi-synthetic artemisinin. The term "semi-synthetic" is used because Sanofi has developed a proprietary photochemical method to convert artemisinic acid into artemisinin (Sanders 2013). In 2013, Sanofi announced the launch of large-scale production upon regulatory approval, with plans to produce 35 tons of artemisinin that year and 50 to 60 tons by 2014, the equivalent of 80-150 million ACT treatments (Sanofi and PATH 2013). Thus far, Sanofi has exported approximately 400 kg of semi-synthetic artemisinin to India, the bulk in one shipment worth US$ 350/kg.[59]

There are potential public health benefits from semi-synthetic artemisinin. For seven years, synthetic biology has been described as a cheaper and more efficient way to produce artemisinin than its natural plant source, although a price still has not been named (Garfinkel *et al*. 2007; PCSBI 2010; RAE 2009).[60] Because production of artemisinin is following a "no profit, no loss" model and UC Berkeley included humanitarian use terms in the intellectual property license, it has been expected to be affordable and lead to a "stable cost and steady supply" (Sanders 2013; US PTO 2013). Many analysts anticipate that this will lead to positive public health outcomes (Wellhausen and Mukunda 2009; Peplow 2013). Keasling has also argued that, because individual Artemisia growers sometimes sell to producers of artemisinin monotherapies (which can lead to artemisinin resistance), semi-synthetic production will lead to a more easily controlled market (Thomas 2013).

Semi-synthetic artemisinin may displace cultivation of *Artemisia* by tens of thousands of small-scale farmers. *A. annua* is primarily cultivated on farms in China, Vietnam, East Africa and Madagascar; the average crop area per farmer in China and Africa is around 0.2 hectares (A2S2 2013). Sources within the Artemisinin trade estimate that up 100,000 people (smallholders and wild pickers) depend upon artemisinin for their livelihoods, with a wider social impact when families are factored in to calculation (ETC Group 2013; Charles Giblain[61] 2014 pers. comm.). Initially, semi-synthetic artemisinin was described as a complement to natural cultivation. For example, at the 2013 annual artemisinin conference, the semi-synthetic artemisinin consortium communicated their production was intended to be a complementary source to supplement plant-based artemisinin, that the estimated price would be between US$ 350 and 400, and that the semi-synthetic product would act as a price regulator.[62] But, at an April 2013 conference on synthetic biology and conservation, Keasling noted that "moves are afoot to replace the entire world supply [of artemisinin]". Civil society organizations have long been concerned that this might be an impact of semi-synthetic artemisinin (Thomas 2013; FOE *et al*. 2012). Thomas (2013) noted that "early on, it was not about replacing the agricultural form […] and now I think it is nearly inevitable that it will shift over". The ICSWGSB agrees that malaria drugs must be accessible and affordable, but they question the value of pursuing a high-tech solution over decentralized, sustainable approaches such as supporting expanded smallholder production (ICSWGSB 2011). Moreover, Marris (2013) notes that a crucial issue in the debate between the potential health benefits of artemisinin and the potential loss of income and livelihoods for farmers growing *Artemesia* bushes as a crop is that the hoped-for health benefits for local populations do not simply depend of an increased supply of artemisisin (synthetic or not), but also require a complex set of interrelated political, economic and social conditions.

As noted in several comments on an earlier draft of this document, the displacement of small-scale farmers' crops is not an impact unique to synthetic biology, nor are the experiences of these farmers pre-determined. Indeed, the displacement of natural products by synthetic-biology produced versions follows a "tradition of major technological advances that have displaced former methods of production" (Wellhausen and Mukunda 2009). Wellhausen and Mukunda see semi-synthetic artemisinin and other commercial synthetic biology applications as possibly

59 See: http://www.infodriveindia.com/, accessed 21 Feb. 2014.

60 According to A2S2's tracking of artemisinin imports into India, the average monthly price of artemisinin has been dropping over the past two years, down to US$ 267.51/kg (excl. duty) in December 2013. See: http://www.a2s2.org/market-data/artemisinin-imports-into-india.html, accessed 21 Feb. 2014. Thus far, Sanofi imports of semi-synthetic artemisnin to India have been for more than this.

61 Giblain, CEO of Bionexx in Madagascar, calculated this number based on the Madagascar and Chinese workforces engaged with production and wild picking of Artemisia.

62 See: http://www.a2s2.org/upload/5.ArtemisininConferences/1.2013Kenya/2013ArtemisininConferenceFinalReport.pdf, accessed on 21 Feb. 2014.

improving health and thus the standard of living in developing countries, while simultaneously displacing laborers, exports, and the tax base of those same countries (*Ibid*.). Using the historical examples of natural rubber and indigo dyes' competition with chemically produced alternatives, they explain that sometimes displacement results in impoverishment and sometimes the natural version continues to hold on to some share of the market (*Ibid*.). They see a role for national governments in facilitating industrial restructuring and redistributing any benefits to the "economic losers" (*Ibid*.). The ETC Group has described *Artemisia* growers as the "canaries in the coalmine," providing an early example of the risks that synthetic biology production poses to smallholder producers (ETC 2010). The ETC Group asks what benefits developing countries will experience when the product being displaced is not medicine for a tropical disease. They point to synthetic-biology produced isoprene (rubber), currently in development by Genencor and Goodyear, which could displace smallholders in Asia producing natural rubber (ETC 2007; 2010).

Although artemisinin is a more high-profile example, other synthetic biology versions of natural products are on the near-term horizon. The near-term commercialization of synthetic-biology-produced lauric acids could compete with production from coconut and palm kernel oils (ETC Group 2013). Coconut is a major export crop for the Philippines, primarily from owner-operated farms averaging 2.4 hectares (ETC Group 2013). Palm kernel oil from oil palm primarily comes from large industrial farms in Indonesia and Malaysia. Unilever's investment in Solazyme is related to a desire to move away from the environmentally destructive crop (ETC Group 2013). Tamiflu producer La Roche produces some of its shikimic acid with modified *E. coli*, as opposed to star anise (ETC Group 2013; Rawat *et al*. 2013).

Some are optimistic for developing countries in the global bioeconomy; those who express concern have differing degrees of confidence that harm can be mitigated or avoided. The US PCSBI sees synthetic biology as bringing potential benefits to developing countries, "where health, access to resources, and economic stability are closely linked to one another and to disparities in health and welfare" (PCSBI 2010). The example of artemisinin is frequently put forward as an example of how synthetic biology can significantly improve the health, and thus economies, of developing countries (Ibid.; Garfinkel *et al*. 2007; RAE 2009). A biotechnology-led bioeconomy could also, however, reinforce trends towards the dominance of knowledge-based economies, and the further consolidation of international trade by a few rich states and trans-national corporations (Rhodes 2010). The civil society *Principles for the Oversight of Synthetic Biology* insists that the development of synthetic biology must "not deepen economic and social injustices" through product displacement, increased biomass cultivation and extraction, or the further privatization and control of naturally occurring processes and products (FOE *et al*. 2012). Others recognize the potential that developing countries might fail to benefit from or even be harmed by synthetic biology's role in the global bioeconomy, but see ways that these potential harms can be mitigated. For example, the UK Royal Academy of Engineering recognizes the potential for global inequalities to be "exacerbated" by synthetic biology through product displacement of developing country exports (RAE 2009). Garfinkel and Friedman see many potential synthetic biology applications, such as treating neglected tropical diseases, as potentially most useful to those who can least afford it (Garfinkel and Friedman 2010). But in both cases, these are considered challenges that can be addressed through product-specific arrangements (such as the Gates Foundation's support of artemisinin research and the Sanofi-Aventis no-profit/no-loss model of production) and engagement with the public (Garfinkel and Friedman 2010; RAE 2009).

11. HUMAN HEALTH CONSIDERATIONS RELATING TO BIODIVERSITY

Through the CBD's cross-cutting programme on "health and biodiversity," it is recognized that "we cannot have healthy societies without biodiversity" (CBD 2012). Biodiversity provides sources of medicine, food, clean air and fresh water; loss of biodiversity can negatively impact human health through increased contact with diseases and the loss of substances used as medicines or in medical research (*Ibid*). Synthetic biology may be used for advanced medical interventions but also could have unintended impacts on health and biodiversity.

Classic genetic engineering has been used for over three decades to engineer bacteria to produce molecules such as insulin and vaccines (PCSBI 2010). As with other areas of current and potential future synthetic biology applications, researchers and industries deploying synthetic biology tools are building on the history of established biotechnology, and the lines between "synthetic biology" and classic genetic engineering are not always clear.

Health applications are a major focus of synthetic biology research; much of it is still at the stage of basic research, but some is in commercialization. According to WWICS (2013a), the top application focus of biological systems designers and manufacturers conducting synthetic biology research is medicine. Synthetic biology may provide tools for better understanding disease mechanisms by "rebuilding and studying them in a context isolated from their high degree of natural interconnectivity" (Lienert *et al*. 2014). For example, the oft-cited study synthesizing the 1918 Spanish influenza virus provided insight into the pathogen's virulence factors (Tumpey *et al*. 2005; Weber & Fussenegger 2012). Synthetic biology may be used in drug discovery through developing drug screening platforms (Pauwels *et al*. 2012). One of the expectations for xenobiology is that XNA could be used in diagnostic tests (PCSBI 2010). One focus of synthetic biology research and development is the design of organisms to produce drugs and vaccines. As discussed in more detail in section 4.2.2, semi-synthetic artemisinin for the treatment of malaria is already being produced using metabolic engineering techniques that many consider to be synthetic biology (Sanders 2013). In 2013, researchers at Novartis and Synthetic Genomics published an approach to rapidly generate influenza vaccine viruses, using an enzymatic, cell-free gene assembly technique, producing an accurate vaccine more quickly than previously possible (Dormitzer *et al*. 2013). J. Craig Venter, founder and CEO of Synthetic Genomics, refers to this as "reverse vaccinology" (Industrial Biotechnology 2014). Another approach referred to as "SAVE" (synthetic attenuated virus engineering) (Coleman *et al*. 2008) was used to rationally redesign the genome of an influenza virus, resulting in an attenuated virus with hundreds of nucleotide changes (Mueller *et al*. 2010). Still at the research stage are synthetic biology devices that would provide therapeutic treatment, for example through reprogramming mammalian cells to tackle diseases through prosthetic gene networks, controlling the timed delivery of drugs, more controlled approaches to gene therapy, and engineering micro-organisms to target, penetrate regress tumors (Forbes 2010; Khalil & Collins 2010; Wieland & Fussenegger 2012). In December 2013, two companies using synthetic biology techniques, Intrexon and Agilis Biotherapeutics, LLC, announced a collaboration focused on DNA-therapeutics for Friedreich's ataxia (FRDA), a rare genetic neurodegenerative disease (Intrexon Corp. 2013a). The RAE (2009) anticipates that in the longer term (10 and 25 years) synthetic biology will help to make personalized drugs and highly adaptive vaccines and antibiotics.

It is difficult to anticipate specific negative impacts, but broad categories of potential concerns have been identified related to human health impacts. As discussed earlier, synthetic biology may have negative ecological impacts related to biosafety (section 6), which could then negatively impact human health. Accidental release of organisms resulting from synthetic biology could possibly also have negative impacts on human health (PCSBI 2010; RAE 2009). As was noted by the European Group on Ethics in Science and New Technologies, it is hard to predict the "long-term health-related risks associated with the ecological effects" of synthetic biology (EGE 2009). The coalition of civil society groups that developed *Principles for the Oversight of Synthetic Biology* (FOE *et al*. 2012) as well as the US Presidential Commission for the Study of Bioethical Issues (PCSBI 2010) identify synthetic biology laboratory workers as potentially at risk because of accidental exposure. There is also the possibility that medicines and therapies resulting from synthetic biology techniques may trigger unanticipated adverse effects on human health (König *et al*. 2013; PCSBI 2010). Indirect negative effects to human health could arise if medicines and therapies produced with synthetic biology technologies are inaccessible to some countries because of broad patents and patent "thickets" (see section 13) (König *et al*. 2013).

12. ETHICAL CONSIDERATIONS RELATING TO BIODIVERSITY

Ethical considerations of biodiversity and of how humans relate to biodiversity are recognized as important in the context of the CBD. For example, CBD COP10 established the *Tkarihwaié:ri Code of Ethical Conduct to Ensure Respect for the Cultural and Intellectual Heritage of Indigenous and Local Communities* (Decision X/42). The *Tkarihwaié:ri Code* identifies general ethical principles, including: prior informed consent and/or approval and involvement of ILCs; the fair and equitable sharing of benefits with ILCs; and the precautionary approach, including relevant ILCs and the use of local criteria and indicators in the prediction and assessment of potential harms to biodiversity (Decision X/42, Annex A, Section 2(A)).

Starting as early as 1999, ethicists have actively engaged with the new tools and techniques of synthetic biology (Cho *et al*. 1999). Common considerations have included the ethical debate on whether to ban publications of dual use science discoveries and whether synthetic biologists are

"playing God" (Boldt and Müller 2008; Douglas and Savulescu 2010; Kaebnick 2009; RAE 2009). This section focuses on ethical considerations that relate to biodiversity.

Ethicists disagree whether synthetic biology introduces "new" ethical issues based on the ability to create life rather than modify existing organisms. Ethicists Joachim Boldt and Oliver Müller see synthetic biology as having crossed a threshold from the mere manipulation of life to its "creation" from scratch, thus potentially changing our approach to nature (Boldt and Müller 2008). They are concerned that the ability to design significant portions of organisms may "lead to an overestimation of how well we understand nature's processes and our own needs and interests" (*Ibid*.). Ethicist Christopher Preston invokes Aristotle's distinction between the natural and artifact, arguing that *de novo* organisms, "with no causal chain of viable organisms connecting […] with the historical evolutionary process" should have less value (Preston 2008). A number of commentators counter that such arguments overestimate the current abilities of synthetic biology. Scientists have thus far replicated existing genomes and modified existing cells; this is different from creating a novel organism from scratch (Garfinkel and Friedman 2010; Kaebnick 2009). Social scientists Claire Marris and Nikolas Rose caution against engaging in "speculative ethics" on the assumption that the scientific feat of life-from-scratch is already accomplished (Marris and Rose 2012). Philosopher Beth Preston (2013) argues that synthetic biology presents no new ethical issues; she considers the advent of agriculture as the truly revolutionary moment in human society, and synthetic biology as simply continuing the kinds of human relationships to the natural world established by agriculture. On the other hand, Parens *et al*. (2009) find it important for society to start conversations around the ethics of molding the natural world.

Some areas of synthetic biology research are based on a reductionist view of the world; there is disagreement on the ethical implications of this. Reductionism is the idea that complex entities can be completely explained by the properties of their component parts (Calvert 2008). With the discovery of DNA, the biological sciences took a reductionist turn, attempting to explain life by breaking it down to chemical and physical processes (Cho *et al*. 1999). In recent years, epigenetics has expanded understanding of genes to acknowledge that environmental context has important impacts on gene expression. In some areas of biological sciences, reductionism is seen as a dated and misguided theory that ignores biological complexity. Some synthetic biologists use synthetic biology to try to bypass this complexity, using reductionist logic to design organisms that are less complex (Calvert 2008; EGE 2009). It is an empirical question whether emergence and complexity can be avoided by biological design, but there are also ethical implications of a commitment to reductionism. A reductionist view of life might undermine the special status of living things, if life is seen as "producible, controllable and at our disposal" (Boldt and Müller 2008; Cho *et al*. 1999; ECNH 2010). A similar concern is that synthetic biology moves humanity towards instrumentalism, by which organisms are assigned value based on their instrumental use (EGE 2009). A common counterpoint to these arguments is that life does not necessarily hold such a special status; for example, bacteria are not generally given moral status (ECNH 2010; Douglas and Savulescu 2010). Also, there is not yet evidence that reductionist synthetic biology science has led to a 'slippery slope' of valuing others less (ECNH 2010). Whether an instrumental view of life is problematic depends on how anthropocentric one's ethical stance is (EGE 2009).

Synthetic biology raises ethical issues around harms, benefits and risks. Anderson *et al*. say: "The ability to create synthetic organisms, combined with our inability to control them with solid guarantees, raises the need to consider the ethical implications" (2012). Considerations of biosafety and biosecurity are sometimes discussed as ethical questions of weighing and balancing potential harms and benefits (Boldt and Müller 2008; Cho *et al*. 1999; Douglas and Savulescu 2010; EGE 2009). Some risks might be deemed not morally acceptable because of the severity of harm and/or the probability of harm occurring (Schmidt *et al*. 2009). This raises questions about what level of predictability should be required, and how to weigh possible negative impacts against positive impacts (Anderson *et al*. 2012). The distribution of potential harms and benefits related to synthetic biology products and technologies is also an ethical matter (Schmidt *et al*. 2009; Nuffield 2012; Parens *et al*. 2009). What would be an equitable distribution of synthetic biology related harms and benefits, and how can that distribution be achieved? Ethical issues around harms and benefits also incorporate discussions on global justice, and the potential impacts of synthetic biology on the "technology divide" (EGE 2009).

Questions of synthetic biology's impact on attitudes to biodiversity and conservation are being asked. The US Presidential Commission for the Study of Bioethical Issues (PCSBI) brings up the concern of the "broader effect on how society views and protects biodiversity" (PCSBI 2010). The conveners of a 2013 conference "How will synthetic biology and conservation shape the future of nature?" ask how synthetic biology will change public perceptions of

what is natural, and if it will "challenge the ethical basis for conservation action" (Redford *et al*. 2013). Philosopher Brian Norton speculates that synthetic biology could "encourage an inaccurate model of biodiversity protection as maintaining an inventory of biological units" (Norton 2010). Building on this, Redford *et al*. note the increasing importance of ecosystem services in valuing biodiversity, and ask what will happen if ecosystems with synthesized elements are able to out-compete natural ecosystems, "delivering more services with less biodiversity" (Redford *et al*. 2013). More optimistically, renowned physicist and mathematician Freeman Dyson (2007) imagines a future in which biotech will "give us an explosion of diversity of new living creatures […] Designing genomes will be a personal thing, a new art form as creative as painting or sculpture." Dyson paints this as a largely positive direction for our world, although one with dangers that will need to be managed.

Synthetic biology is seen by some to raise ethical issues related to intellectual property (IP) rights; others consider synthetic biology as a way to avoid ethical challenges to 'patenting life.' Considerations of justice include the distribution of material and non-material goods. The application of intellectual property rights to synthetic biology, such as patents on DNA sequences or organisms resulting from synthetic biology, could restrict the global distribution of products and knowledge (ICSWGSWB 2011; Schmidt *et al*. 2009; ECNH 2010). Civil society groups strongly critique the way that IP regimes have been used in agricultural biotechnology to concentrate power with a few corporations, and they see similar patterns of use occurring in synthetic biology (ETC 2010; FOE 2010; ICSWGSWB 2011) Using synthetic biology to design and synthesize DNA sequences is also, however, seen by some as a way to avoid ethical and legal challenges – particularly those related to patenting the sequence information of naturally occurring DNA (Torrance 2010).

13. INTELLECTUAL PROPERTY CONSIDERATIONS RELATED TO BIODIVERSITY

Intellectual property rights for synthetic biology has been described as a potential "perfect storm"; biotechnology and software already pose serious challenges to the patent system, and synthetic biology's combination of those two areas presents significant challenges (Rai and Boyle 2007). In the field of biotechnology, patents have created an "anti-commons" problem, where broad, ambiguous patent claims restrict the innovation of others (Oye and Wellhausen 2009; Henkel and Maurer 2009; Torrance 2010). Narrow patents, on the other hand, can cause patent "thickets," where complex designs that incorporate many individual parts face an unmanageable number of patents (Rutz 2009; Henkel and Maurer 2009; Rai and Boyle 2007). There is also the possibility that, like with electronics and software, a tipping dynamic will lead to one solution dominating an industry because it is the first to establish common standards (Henkel and Maurer 2007; Henkel and Maurer 2009).

As the field of synthetic biology develops, two main models of intellectual property (IP) for synthetic biology components, organisms, products, and techniques seem to be forming (Calvert 2012). The first heavily relies on patents and is exemplified by the approach of the J. Craig Venter Institute (JCVI) (Gibson *et al*. 2008; Gibson *et al*. 2010; Glass *et al*. 2007). While working at the US National Institutes of Health in the 1980s, J. Craig Venter attracted attention and criticism for leading patent applications of thousands of short DNA sequences (Calvert 2012). In the 1990s, his Institute of Genomic Research (now part of JCVI) sequenced and patented one of the smallest known bacterial genomes, *M. genitalium*. In 2007, scientists at his institute applied for a "minimal bacterial genome" patent (Calvert 2012; Glass *et al*. 2007). This is still pending; NGOs and commentators have expressed concern at its attempted breadth (ETC 2007; ETC 2011; Calvert 2012). The other main model is the BioBrick™ system, modeled on open-source software. On the iGEM's Registry of Standard Biological Parts, contributing researchers post their BioBrick™ parts (DNA-sequences that incorporate standardized sections) on pages accessible to the general public, which allows users to exchange parts and share their experience. Following a similar philosophy of exchange, the BioBricks Foundation has independently developed a BioBrick™ Public Agreement that is essentially a contractual agreement between "Users" and "Contributors" of parts. Contributors may hold patents on the parts, but they promise not to assert any present or future proprietary rights against Users. Unlike open source software, Users have no obligation to openly share the devices or parts they make with the BioBricks™. They can patent novel devices if they want to, meaning that they can build private, proprietary systems on the open platform (Calvert

2012; BioBricks Foundation 2013). As in open-source software, proponents consider this approach as more likely to lead to innovation as well as furthering transparency and openness (Calvert 2012).

IP regimes for synthetic biology could have a variety of impacts on biodiversity and related considerations. In the USA, each patent application costs $10,000 (Henkel and Maurer 2009). If patenting becomes established as the necessary method of claiming of intellectual property rights on synthetic biology, the high cost could influence the kinds of applications of synthetic biology that are pursued (high profit applications targeting wealthy populations), as well as the types of organizations (continuing concentration of ownership and control in large transnational corporations) (ICSWGSB 2011; ETC 2007; Redford *et al*. 2013). If patent "thickets" form in certain areas of synthetic biology applications, this could also restrict its accessibility by less wealthy countries (Redford *et al*. 2013). A strong concern of civil society groups is that strong IP regimes could also restrict access to information for carrying out independent, effective risk assessments (ICSWGSB 2011). Finally, it is possible that an additional challenge for conservation biologists and synthetic biologists to work together could be that the types of biological knowledge used by synthetic biologists are "much more restricted" (Redford *et al*. 2013).

Table 2. Examples of potential positive and negative impacts of synthetic biology with regard to social, economic and cultural considerations

Social, economic and cultural considerations	Possible positive and negative impacts of synthetic biology
Biosecurity	Synthetic biology techniques may provide tools for better detecting and identifying pathogenic agents, and responding to biosecurity threats, for example through accelerated vaccine production (Endy 2005; Mukunda et al. 2009; PCSBI 2010)
	Synthetic biology techniques may raise a "dual use" challenge, in that the substances used by research for positive ends may also be used for damaging results, such as creating destructive pathogens that target natural resources (Kaebnick 2009; Mukunda et al. 2009)
Economic	Synthetic biology is widely anticipated to play a significant role in the bioeconomy, which could benefit the economic growth (and human health and environment) of countries (EC 2012a; US White House 2012) Synthetic biology alternatives for natural products may lead to product displacement in developing countries, but potential harms may be addressed through product-specific arrangements and public engagement (Garfinkel & Friedman 2010; RAE 2009) or the natural version may still hold on to some share of the market, or the benefits of the synthetic biology versions may outweigh the losses (Wellhausen & Mukunda 2009) Products from synthetic biology, such as artemisinin, may improve the health of the people of developing countries and thus their economies (PCSBI 2010)
	Synthetic biology alternatives to natural products may lead to product displacement, harming the economies of developing countries and displacing the livelihoods of small-scale farmers and pickers (ETC 2013a; ICSWGSWB 2011) The necessary scale of extraction and use of biomass for a global economy may be ecologically unsustainable and rely on the same biomass resources as traditional economies (ETC 2011; Hall 2012; ICSWGSB 2011)
Health	Synthetic biology may: • help to study disease mechanisms (Lienert et al. 2014) • aid in diagnostics (PCSBI 2010) • aid in drug discovery through developing drug screening platforms (Pauwels et al. 2012) • help design organisms to produce drugs and vaccines (Dormitzer et al. 2013; Mueller et al. 2010; Ro et al. 2006) • help design therapeutic treatments (Khalil & Collins 2010; Wieland & Fussenegger 2012)

Source: Macroscopic Solutions, LLC

Source: Macroscopic Solutions, LLC

Table 2. continued	Examples of potential positive and negative impacts of synthetic biology with regard to social, economic and cultural considerations
Social, economic and cultural considerations	**Possible positive and negative impacts of synthetic biology**
Health	Synthetic biology applications may result in the possibility of direct harm to patients' health if engineered organisms / viruses trigger unanticipated adverse effects (König et al. 2013; PCSBI 2010) Synthetic biology may result in the possibility of direct harm for workers in synthetic biology laboratories (FOE et al. 2012; PCSBI 2010) Patent thickets and broad patents may restrict access to drugs and therapies (König et al. 2013)
Ethical	*Ethical discussions around synthetic biology are not structured around potential "positive" and "negative" impacts, but rather broad considerations*: Ethical analysis may help determine how to weigh and balance possible negative impacts of synthetic biology against possible positive impacts, as well as explore what equitable distribution of synthetic biology-related harms and benefits would look like and how to achieve this (Anderson *et al*. 2012; EGE 2009; Nuffield 2012; Parens *et al*. 2009) On the one hand, the ability to design significant portions of organisms may change humanity's approach to nature and lead humanity to overestimating our understanding of nature's processes (Boldt & Müller 2008); on the other hand, ethical discussions should not be based on assumptions that synthetic biology is able to do more than it can (Marris & Rose 2012) On the one hand, where synthetic biology research is based on a reductionist view of the world, it may undermine the special status of living things (Boldt & Müller 2008; Cho *et al*. 1999; ECNH 2010), on the other hand, "life" does not necessarily hold special status, and there is no evidence that synthetic biology science is leading to a "slippery slope" of devaluing some forms of life (ECNH 2010)
Intellectual property	A model of IP based on open-source software may lead to greater innovation, transparency, and openness (Calvert 2012) Using synthetic biology to design and synthesize DNA sequences may avoid ethical and legal challenges related to patenting natural DNA sequences (Torrance 2010)
	Synthetic biology may extend private ownership of genetic material, restricting access for public benefit (Redford *et al*. 2013; ECNH 2010; Schmidt *et al*. 2009) Strong IP regimes could restrict access to information for carrying out independent risk assessments (ICSWGSB 2011)

Source: Macroscopic Solutions, LLC