Trends in Ecology & Evolution

CellPress

Opinion

Is It Time for Synthetic Biodiversity Conservation?

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Evidence indicates that, despite some critical successes, current conservation approaches are not slowing the overall rate of biodiversity loss. The field of synthetic biology, which is capable of altering natural genomes with extremely precise editing, might offer the potential to resolve some intractable conservation problems (e.g., invasive species or pathogens). However, it is our opinion that there has been insufficient engagement by the conservation community with practitioners of synthetic biology. We contend that rapid, large-scale engagement of these two communities is urgently needed to avoid unintended and deleterious ecological consequences. To this point we describe case studies where synthetic biology is currently being applied to conservation, and we highlight the benefits to conservation biologists from engaging with this emerging technology.

Trends

Synthetic biology can change genomes, and this power can be utilized towards solving the intractable problems of biodiversity conservation.

Conservation biologists need to engage and collaborate actively with synthetic biologists to ensure that this power is utilized in way that protects biodiversity and minimizes negative consequences.

The opportunity to resolve biodiversity issues may depend on a sea-change of philosophy in the conservation movement to incorporate the application of adapted genomes into the wild.

Synthesizing Biodiversity?

Despite decades of conservation action and two global initiatives under the auspices of the Convention on Biological Diversity, current indications are that we have been unable to slow the rate of loss of **biodiversity** (see Glossary) [1–3]. Even with increasing terrestrial and marine areas under some form of protection, current protected-area networks are considered to be insufficient to stem biodiversity loss [1,4]. Further, degradation of protected areas, the impacts of invasive species, emerging infectious diseases, and even societal denial of biodiversity loss, threaten to turn back the progress that has been made [1,5]. Consequently there have been calls for bolder conservation thinking [6], such as engagement with new technologies, including those emerging from the field of **synthetic biology** [7,8].

Synthetic biology is a rapidly expanding field where engineering principles are applied to the construction of biological parts and systems, resulting in new and desired traits they would not have in their original or natural state [9,10]. Recently, the field of synthetic biology has stimulated technological advances by adding the powerful technique of **genome editing** through deleting a target gene and/or inserting a synthetic one, typically using **CRISPR/Cas9 technology** [11,12] (a graphical illustration of this technique can be found in Figure 3 of [12]). This, paired with harnessing the power of **gene drives**, which can be synthesized or occur naturally [13], and other new synthetic techniques, brings the efficacy of genetic modification to a new level. Further, such genetic modification is cheaper, easier, more precise, and more rapid than ever before, and is thus widely accessible. It has become apparent that synthetic biology holds tremendous potential across numerous fields, including conservation biology. With such tools in hand conservation of biodiversity could become proactive rather than reactive. What if we could

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Table 1. Major Conservation Problems with Possible Solutions Through the Application of Synthetic Biology

Conservation issues	Biodiversity issues	Synthetic biology solutions	Refs
Invasive species	Mice and rats on islands	See Box 1	[8,17,40,41]
	Brown tree snake (*Boiga irregularis*) in Guam	Use Y chromosome alterations and gene drives to stop reproduction in this species	[17]
Pathogens	Avian blood parasites in Hawaiian birds	See Box 2	[5,40,42]
	Fungal pathogens: white-nose syndrome in North American bats and chytrid fungus in amphibians and snakes	Engineer genetic resistance to fungal diseases	[17,18,40]
	Plague in black-footed ferrets	Use CRISPR/Cas9 to cut out part of genome that is susceptible to disease and replace with genetic code for disease resistance	[18]
Habitat conversion	Palm oil	Use other plants or systems to produce man-made palm oil and take pressure off current production methods, and thus reduce tropical forest conversion	[2]
	Productivity of soils reduced from pesticides and herbicides or by mining practices such as gold or strip mining	Synthetically restore microbiome of soils for habitat restoration, engineer plants that require less pesticides/herbicides for production	[5]
	Extraction and use of fossil fuels	Provide alternative solutions and thus alleviate pressures on such resources and the damage they cause, such as habitat loss and pollution. Create and modify microorganisms to consume hydrocarbons to clean up oil spills	[17,40]
Loss of biodiversity	Agriculture and its limitations to feed and house (forests) a growing human population	New food sources or ways to produce food without pesticides and large tracts of arable land	[2,8]
	Loss of faunal and floral biodiversity	Create ecological proxies, restore ecological functions	[2]
	Revive and restore extinct species	'De-extinction' (e.g., woolly mammoth): the use of an existing species (e.g., elephant) whose genome is altered to incorporate genetic code from the extinct species, thereby creating a proxy species that hopefully fills the same ecological role as the extinct species	[17,40]
Overexploitation	Rhino horn ivory and deep sea sharks for squalene	Produce a material that is a substitute and can be man-made	[40,43]
	Pet trade and feral domestic animals	Produce sterile pets	[40]
	Fish species	Improve aquaculture for higher protein production	[44]
Pollution	Replacing things made from petroleum and synthetic rubber	Engineer plants to make the same products	[40]

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Table 1. (continued)

Conservation issues	Biodiversity issues	Synthetic biology solutions	Refs
	Pesticide use	Increase resistance to pests	[45]
	Emissions of CO_2 or other greenhouse gases	Biofuels from synthetic algae	[5,17]
	Pharmaceuticals in the environment	Create or modify microorganisms to consume or degrade pharmaceuticals	[17]
	Micro-plastics in oceans and soils	Create or modify microorganisms to consume or degrade micro-plastic	[2,46]
	Water pollution	Create and modify algal or bacterial species that consume or degrade pollutants	[2]
	Coral reef bleaching	Alter the coral reef genome for resistance by borrowing pathways from coral species that withstand increased temperature and/or acidity	[2,17,47,48]

engineer mosquitoes, which are invasive in Hawai'i, with a synthesized gene or genetic pathway such that they are no longer capable of transmitting the avian blood parasite that has devastated endemic bird populations [14]? Or, perhaps, using the techniques of synthetic biology, scientists could produce male mosquitoes that produce only male offspring when they breed with wild-type females, thus driving local populations extinct [15]. What if burgeoning human populations could be fed with reduced or minimized impact on biodiversity [2]? Through these examples and others presented here (Table 1) the potential of synthetic biology to aid biodiversity conservation efforts is apparent. However, lack of understanding of the technology, the speed of developments, the potential for unforeseen outcomes, and the prospect of altering natural systems have held conservation biologists back from engaging with synthetic biology. In fact, some conservation activists have recently called for a moratorium on research into gene drives [16].

Some conservation biologists have recognized the potential of synthetic biology for biodiversity conservation, and have called for dialogue between the conservation and synthetic biology communities [8,17,18]. Initially, members of the two communities met formally in April 2013 [17] at a workshop in Cambridge, UK, with the explicit goal of exploring areas of mutual interest and identifying concerns. Subsequently, some of the same participants, together with new members from both communities, took part in a workshop in Sausalito, California, in April 2015. This workshop had three goals; (i) to educate conservationists about the application of these new tools and their potential benefits and risks, (ii) to inform synthetic biologists about urgent conservation problems that have thus far been intractable to conservation efforts, and (iii) to identify a subset of the cases presented at the meeting that offer the best opportunity for tool development and application (http://longnow.org/revive/meeting-report/). This was the first attempt at identifying real-world problems that traditional conservation approaches have been unable to solve, but that might realistically be addressed by synthetic biology.

Most recently, in December 2015, a meeting was held between conservation and synthetic biologists at the Rockefeller Foundation Bellagio Center in Bellagio, Italy. This meeting was led by the International Union for Conservation of Nature (IUCN) and sought: (i) to understand the relevance of synthetic biology to the mission and vision of IUCN, (ii) to identify ways in which

Glossary

Biodiversity: biological diversity, the sum of variation in ecosystems, species, and genes.

CRISPR/Cas9 technology: biochemical method using clustered regularly interspaced short palindromic repeats (CRISPR) guide RNA in conjunction with Cas9 (CRISPR-associated 9) nuclease to efficiently cut and edit DNA.

De-extinction: the development of functional proxies for species which have previously become extinct.

Gene drive: technique for spreading selected, usually recombinant, DNA sequences (genes) through wild populations with the aim of eliminated unwanted characteristics of an organism or adding desired characteristics. This is a naturally occurring process of 'selfish-genes' that is now being harnessed to rapidly spread genome edits through a population.

Genome editing: making targeted changes to the genome of an organism, predominantly by using site-specific endonucleases such as CRISPR/Cas9.

Genetically modified (GM): also known as genetically engineered (GE); see also GMO.

Genetically modified organism (GMO): also known as 'living modified organism' (LMO), an organism whose characteristics have been changed by genetically engineering (contrasting classical selection experiments or naturally by mating and/or recombination).

International Genetically Engineered Machine (iGEM) Foundation: organization dedicated to education and competition, advancement of synthetic biology, and the development of an open community and collaboration (http://igem.org/Main_Page).

Release of insects carrying a dominant lethal (RIDL): release into the wild of insects carrying a dominant lethal gene or genetic system.

SRY mice: *Sry* is a sex-determining gene that regulates testis differentiation; in SRY mice this gene is placed on an autosome and offspring are only male.

Sterile insect technique (SIT): a technique in which sterile individuals of a species are generated in the lab (e.g., through radiation) and then released into the wild.

synthetic biology might have a positive impact on conservation issues, and also to address potential negative impacts and ways to mitigate these, and (iii) to discuss the future of synthetic biology, its role in international biodiversity conservation, and ways to influence the trajectory of the application of synthetic biology to conservation. As participants in the Bellagio meeting we identified an urgent need for immediate and broad engagement of the conservation community with synthetic-biology practitioners. We focus here on two case studies of currently intractable conservation problems where synthetic-biology solutions are being sought (Boxes 1 and 2). Further, we consider other biodiversity problems in detail (Table 1), identify likely risks, uncertainties, points of concern within the conservation community, and potential mitigation of these concerns. Our goal is to stress the crucial need for conservation biologists to apply their expertise in investigating the use of synthetic biology as a possible tool to add to the biodiversity conservation toolbox [19]. Further, we emphasize that synthetic biology will be applied to global environmental issues with or without the expertise of conservation biologists. However, the robust science needed to ensure safe and successful application will be more assured with the participation of conservation biologists. We conclude by suggesting some guiding principles for the integration of synthetic biology and conservation biology. Considering the moral, ethical, and esthetic issues associated with intentional direct human modification of a wild species, we call for the development of a robust decision-making, risk-assessment framework, and for research to be conducted on the application of synthetic biology to conservation issues.

Conservation Crisis

Biological diversity is the currency of conservation, but by all indications we are losing the battle to slow biodiversity loss. An evaluation of the outcomes of a 2002 major global commitment to slow the rate of biodiversity loss showed that, by the 2010 deadline, key indicators of biodiversity had declined, while pressures on natural systems had increased [1]. In 2010, given the continued

Sterile male: sterile males are released into nature such that, when mating with wild females, there are no offspring. Males are sterilized either through radiation or by genetic manipulation.

Synthetic biology: the application of science, technology, and engineering to facilitate and accelerate the design, manufacture, and/or modification of genetic materials in living organisms [61].

Box 1. Eradication of Invasive Rodents

Only 147 of the more than 2000 species of rodents worldwide are considered to be pests, and of these three species alone (black rat *Rattus rattus*, Norway rat *Rattus norvegicus*, and house mouse *Mus musculus*) have by far the greatest negative impact on the systems they invade, particularly on endemic fauna on island systems [49]. Rodent invasions of islands have resulted in the extinction of hundreds of species of native birds [50], particularly seabirds, thereby disrupting the flow of nutrients from the ocean to the land [51].

Invasive mammal eradication on islands is a major conservation tool, and rodents are the most common targets for eradication [52]. The principal approach to rodent eradication on islands involves the use of poisons, particularly the aerial broadcast of non-selective anticoagulants [53]. Although there are alternative techniques that do not require toxins (e.g., [54]), toxicants are still considered the most effective. There are concerns about the development of anticoagulant resistance in target species, and about the effects of poisons on non-target species, but it has been suggested that the search for alternative techniques has not yet been fruitful [49].

Experimental work currently underway is exploring the feasibility of a synthetic biology solution to the problem of invasive rodents through the creation of mice with a gene from the Y chromosome inserted onto chromosome 17 (autosome) that results in the production of only male offspring (Figure I). The release of these modified mice (**SRY mice**) into a natural population therefore has the potential to eventually breed that population out of existence as males predominate, reproduction ceases, and the remaining animals die of old age. The numbers of modified inoculants that would need to be released, and the time frames to extinction, remain uncertain. The risks of such an approach include the accidental translocation or natural dispersal of **genetically modified** (GM) rodents to other, non-target rodent populations; possible hybridization between GM individuals and endemic rodent species; public opposition to the environmental release of a GM animal; and unanticipated ecosystem effects following successful rodent eradication. Mitigation of risks could entail a focus on isolated oceanic islands that have no human inhabitants nor endemic rodents, but to which access can be strictly regulated. Many such islands exist in the Oceania region, on which invasive rodents have heavily impacted on the endemic fauna. Early field-trial success on oceanic islands might facilitate public acceptance of synthetic biology solutions to conservation challenges, and would additionally enable the refinement of lab and field protocols, and the specificity of risk–cost assessments. Strategies for mitigation might include the use of reversible gene drives, or the traditional application of rodenticides.

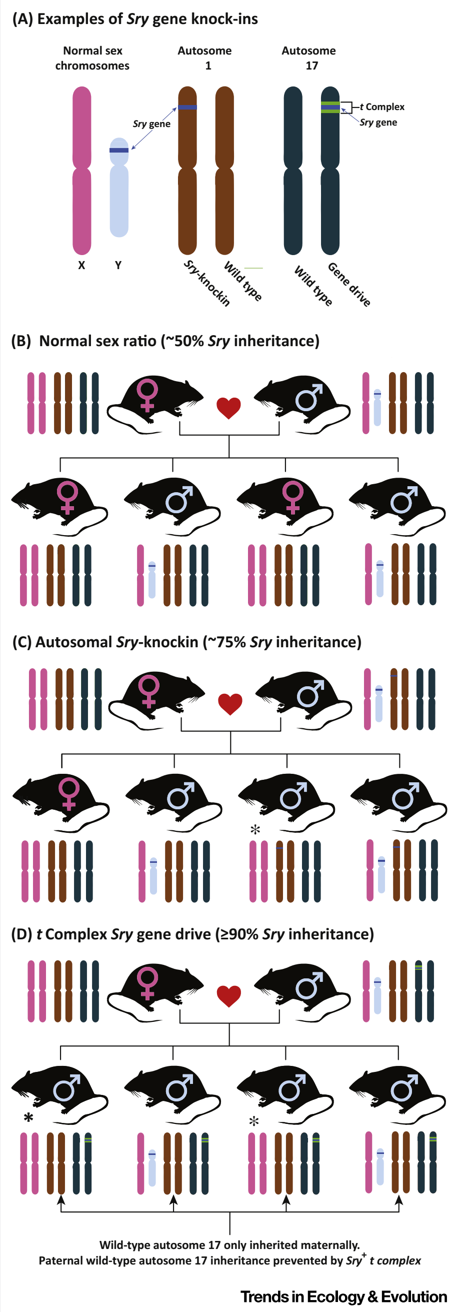

Figure I. *Sry* Gene Drive in Mice. To skew sex ratios in naturally breeding populations, the male-determining gene (*Sry*), normally found on chromosome (Chr) Y, can be inserted into a naturally-occurring gene-drive element on Chr 17 known as the *t* complex. The *t* complex is passed down to greater than 90% of the offspring through the paternal side. (A) The X and Y chromosomes are shown, with the *Sry* gene on Chr Y, as well as on any autosome (autosome 1 is shown as an example) and in the *t* complex. (B) In normal breeding scenarios the *Sry* gene is located only on Chr Y, and thus only mice inheriting Chr Y are male – therefore approximately 50% of the offspring are XY (male) and 50% are XX (female). (C) In a breeding scenario where the *Sry* gene has been added to an autosome, approximately 75% of the offspring will be male and 25% will be female. The * denotes the scenario where the mouse is chromosomally female but phenotypically male. (D) In breeding scenarios where the male carries the *Sry* gene within the Chr 17 *t* complex, over 90% of offspring will inherit the *t* complex-containing autosome. It is predicted that fewer than 10% of the offspring will be XX (female), with the remaining being phenotypically male, including either XY (male) or XX (sterile male).

loss of biodiversity, another attempt was made to secure global agreement on a set of ambitious biodiversity-related 'Aichi Targets' to be achieved by 2020 [20]. However, interim analyses indicate that, despite some local successes, as well as improved responses and policies, rates of biodiversity loss have not slowed, and thus the 2020 targets are unlikely to be achieved [3]. While protecting geographic areas is a major focus of biodiversity conservation [5], other conservation tools take a single species management approach or regulate drivers of biodiversity loss such as pollution, invasive species, land-use change, and climate change. The estimated cost of protecting, monitoring, and managing terrestrial conservation sites for a single animal taxon, such as birds, is in excess of US$65 billion annually [21]. Most countries cannot sustain such economic costs. Although the overall rate of biodiversity loss has not been slowed, without current efforts many more species would be threatened and/or extinct [22].

Conservation and Synthetic Biology

Most conservationists acknowledge that more tools will be necessary to slow the loss of biodiversity. In fact, there have been attempts to adopt more risky, and therefore controversial, conservation interventions such as assisted colonization to mitigate climate-change-induced habitat alterations [23], or ecosystem restoration using ecological replacements [24]. But these have been resisted by some within the conservation community owing to justifiable concerns about unanticipated deleterious impacts on recipient ecosystems and/or further alterations to natural systems [25,26]. Given that conservation biologists have been characterized as scientists 'wishing to pool their knowledge and techniques to solve problems' [27], and to seek novel interdisciplinary connections and practices, why have they, as a community, generally 'paid little

Box 2. Controlling Avian Malaria in Hawai'i

More than 90% of bird extinctions during historic times have occurred on islands, and the Hawaiian Islands have lost a greater proportion (34%) of their endemic bird species than any other system [55]. It is estimated that 71 of the 113 endemics became extinct, and over three-quarters of those left are endangered. Further, range contraction of endemic birds of Kaua'i has appeared to accelerate since 2000, and multiple extinctions are predicted in the next decade [56]. While significant losses occurred as a result of the impacts of invasive species, and owing to exploitation and habitat destruction following the arrival of humans, it is believed that after the 1920s the principal cause of extinction and decline has been avian malaria, caused by protozoan parasites in the genus *Plasmodium*, that is transmitted by the mosquito vector *Culex quinquefasciatus* that was introduced to the islands in 1826 [57]. Global warming is predicted to increase the impact of avian malaria in Hawai'i as mosquitoes expand their range into high-altitude refugia [58]. Traditional approaches to the control of mosquito-borne disease have focused on reducing the abundance of vectors through removal of larval habitat, chemical control of adults and larvae, or biological control using predators or microbial pathogens [59]. Such approaches are difficult to apply over large areas of rugged terrain, and/or would have unacceptable impacts on native invertebrates, therefore calls have been made for innovative techniques to control avian malaria transmission [58].

A synthetic biology solution to avian malaria vector control takes the form of a variation on the traditional **sterile insect technique** (SIT), whereby the DNA of invasive male mosquitoes is damaged, for example through irradiation, and the mass release of **sterile males** overwhelms the invasive wild population. A more precise synthetic biology solution uses genetic modification to disrupt normal cell function. The **release of insects carrying a dominant lethal** (RIDL) technique entails the release of GM male mosquitoes whose offspring will inherit a self-limiting gene and die before becoming functional adults (Figure I). Field trials of mosquito vector control using the RIDL technique have been conducted since 2009, and have successfully suppressed target populations of *Aedes aegypti* in the Cayman Islands, Brazil, and Panama [42]. To date, trials have used a self-limiting approach, requiring repeated mass release of GM males. But a self-sustaining control would be possible using a gene-drive system, eliminating the need for ongoing releases, although potentially being harder to monitor and adjust in a natural population [42,60]. Some conservation biologists believe this might be an effective management tool for the endemic birds of Kaua'i [56].

Risks from using a gene-drive approach to the control of avian malaria in the Hawaiian Islands include loss of efficacy through the evolution of resistance to the lethal gene [42]; escape of transgenic mosquitoes to other natural systems; disruption of any process whereby endemic species acquire natural immunity to *Plasmodium* infection; and societal resistance to the environmental release of a GMO. The challenge, and opportunity, is for the conservation community to work with synthetic biologists to design the appropriate approach: disrupt the ability of the vector to transmit the parasite or drive the vector to local extinction?

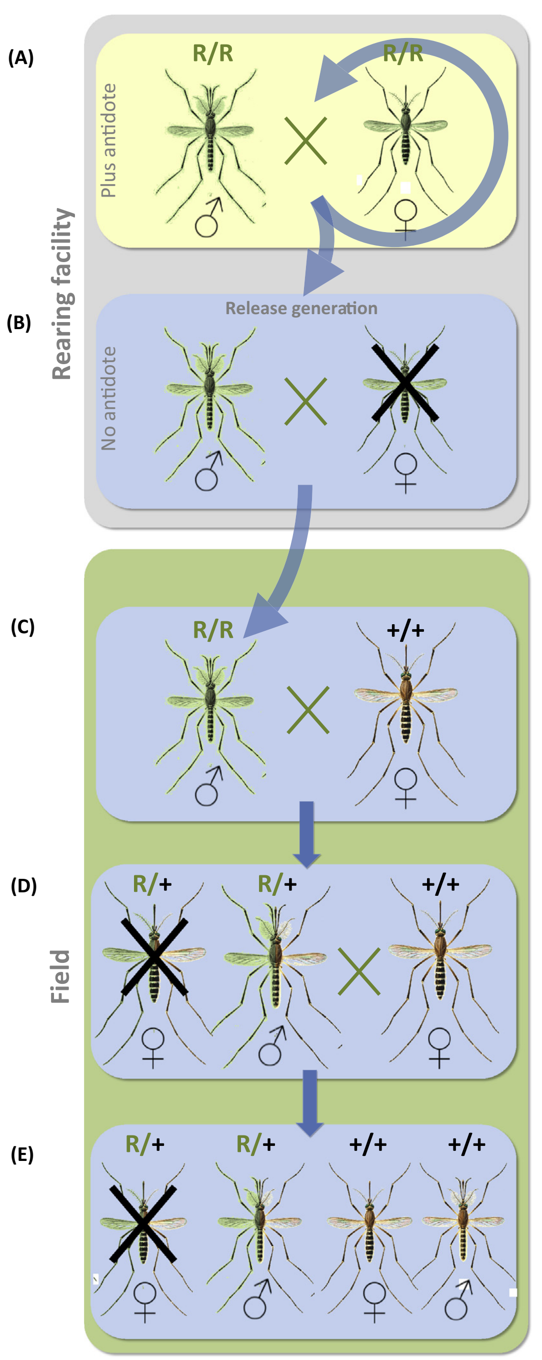

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Figure I. Engineering Sterile Mosquitoes. (A) A population homozygous for a repressible female-specific lethal (R/R) can be mass-reared by providing the repressor (chemical 'antidote') during rearing. (B) Cohorts intended for field release are reared in the absence of the repressor, and thus females die. This rearing could be in the production facility, as depicted, or in the field if eggs are released, perhaps into artificial larval habitats. (C) The males are released to court and mate with wild vector females. (D) The offspring of such matings are heterozygous for the dominant female-lethal gene (R/+), and females therefore die. (E) Heterozygous males can mate with additional wild females, inducing some further female mortality. The female-lethal effect means that the construct has a high fitness cost and will disappear rapidly from the population unless replaced by periodic release of additional homozygous males (A–C).

attention to synthetic biology', and have been 'timid' to engage in this body of knowledge and techniques [7]? Instead, as the conservation community has become aware of synthetic biology, there has been resistance and fear from some, although not all, sectors [7,28].

We see several points of contention that have emerged from those that call for synthetic biology to be in abeyance: (i) technology has been responsible for many of the plights of the natural world, and it is unlikely that technology can also address these plights; (ii) once we start making human-made changes to genomes, natural selection may take over and begin to modify the modifications we have made; (iii) representing a value-based position, the idea of synthetic biology applied to conservation is often accused of being equivalent to 'playing God'. This represents a philosophical rather than scientific view about the importance of leaving nature alone; (iv) synthetic biology technologies might be patented, and we would then be left with difficult decisions about how to separate profit-driven motives from public-good initiatives. Questions then arise such as: who will 'own' endangered species modified by patented technologies? (v) Approaches driven by synthetic biology might spread modified genes to wild relatives, and might also create land-use changes that will further stress endangered ecosystems; (vi) the development of new and modified crops grown to provide feedstock for synthetic biology-altered microorganisms (especially those developed for fuel production) might have an impact on both ecosystems and the rural poor. We acknowledge all of these concerns and we do not dismiss them, but we suggest that they are not facts, but instead hypotheses to be tested with rigorous science. We argue that answers to these questions lie in the scientific engagement of experts from conservation biology and other fields, robust research, and ecological risk assessments [29].

The concerns listed above are not new – there have been over 40 years of genetic modification of organisms, and synthetic biology is part of this continuum. What is unique about synthetic biology is its ease of application. The US National Academies of Sciences, Engineering, and Medicine recently observed that research on gene drives has already greatly exceeded the pace of research on population genetics and ecosystem dynamics [29]. These subjects are clearly within the purview of conservation biology, and must continue to be advocated for, especially in relation to proposed releases of organisms with modified genomes. It is improbable that calls for moratoria will slow the advances or applications of synthetic biology. In fact, it would be a disservice to the goal of protecting biodiversity if conservationists do not participate in applying the best science and thinkers to these issues. Several international organizations are striving towards frameworks and regulations for synthetic biology [29–31]. However, we have not even begun to debate the role of synthetic biology in biodiversity conservation although, at the IUCN World Conservation Congress in September 2016, Resolution 095 was passed by consensus, with calls for the IUCN to develop an approach for engaging with the synthetic biology community [32]. We hope by presenting our opinion that this necessary conversation will begin and that robust scientific engagement will follow.

Synthetic biology hybridizes engineering and biology, and has two main areas: (i) genome redesign for new and desired traits, and (ii) faster and more reliable fabrication techniques for parts and systems that do not exist in the natural world. The discovery of techniques such as gene drives and CRISPR has led to an explosion of synthetic biology research in the past few years. Recently, not only have synthetic biology research projects increased exponentially, but so too has interest in the economic potential of bio-products from the application of synthetic biology methods [33]. The economic motivation to develop and deploy these technologies is driving a rapid pace of development. Events such as emerging infectious diseases, and the effects of climate change, will constitute even stronger incentives. While researchers have been able to work with **genetically modified organisms** (GMOs) for about four decades, the cheap, easy, and precise tools now available through synthetic biology make it possible to alter the genetic codes of organisms or even create novel organisms rapidly and inexpensively. Synthetic biology is characterized by extremely fast technological developments and a mindset that the future need not look like the past, including future biological systems. This perspective stands in stark contrast to that of conservation biology currently, which, despite the value of sustainable use being acknowledged, is essentially preservation-minded [7]. We argue that 21st century conservation philosophy should embrace concepts of synthetic biology, and both seek and guide appropriate synthetic solutions to aid biodiversity.

Synthesis of Conservation and Synthetic Sciences

We suggest that it is necessary to adapt the culture of conservation biologists to a rapidly-changing reality. The current paradigm is not accomplishing radical positive change nor adequately slowing anthropogenic destruction of habitat and biodiversity. To make progress we need to continue to press for more of the same solutions that we know can succeed (e.g., a greater proportion of the planet being set aside for protection, as per [6]). But we must also embrace new technologies and methodologies. There is a consequent immediate need for the conservation community to more fully engage with synthetic biology: (i) to understand potential and identify risks through applying their expertise to robust risk assessments, (ii) to advise synthetic biologists of environmental concerns and issues, (iii) to head off possibly ecologically damaging initiatives, and (iv) to identify the most appropriate conservation problems for the development and implementation of acceptable synthetic biology solutions. In fact, synthetic biology approaches are already being applied to some intractable conservation issues (Boxes 1 and 2). These examples represent flagships for many conservation issues (i.e., invasive species and emerging diseases) but also demonstrate that the application of synthetic biology to conservation issues is occurring presently. Further, the application to wild systems has been outlined and a roadmap developed [12].

Guiding Principles for the Way Forward

We offer the following guiding principles not only to assist those involved in biodiversity conservation to recognize their responsibility in participating in synthetic biology but also as recommendations for scientifically rigorous application of this technology to conservation problems.

Responsible Stewardship

The Presidential Commission for the Study of Bioethical Issues outlined five guiding principles for their evaluation of synthetic biology, one of which was ‘responsible stewardship’ [34]. We reiterate this concept here because we believe it is one that the conservation community should adopt wholeheartedly. For responsible stewardship, as defined in [35], it is our responsibility as humans and stewards of the natural world to avoid taking extreme stances regarding new technologies. We should neither embrace them completely nor set out to block them for fear of unintended consequences. ‘Responsible stewardship rejects positions that forsake potential benefits in deference to absolute caution and positions that ignore reasonably foreseeable risks to allow unfettered scientific exploration’ [35]. We do not think this is incompatible with the precautionary principle of conservation. The way forward is to acknowledge the potential benefit of new technologies, make measured decisions to integrate new technologies into conservation solutions, and implement ongoing oversight. Further, conservation and synthetic biologists must be open and willing to educate themselves about their respective fields so as to identify ways to bridge the gap and achieve integration. Such an effort would be a powerful, interdisciplinary way to achieve responsible stewardship.

Look to the Past

With the advent of classical biological control (CBC) and ecological restoration, many of the same concerns about altering natural processes and ecosystems were discussed as are being raised today in the context of synthetic biology applications in the wild. Others have suggested that detailed risk assessments, as are regularly used in CBC to evaluate risks and benefits, are of use in conservation applications of synthetic biology [29,36]. We advocate this view, and further urge conservation biologists and synthetic biologists to apply the decision frameworks and risk assessments developed for the application of CBC and ecological restoration [37,38] to intractable conservation issues so as to make informed and thoughtful decisions about the ecological, political, and biological aspects of each project before deciding the validity of applying synthetic biology to such issues. Having a framework, including risk assessments and adaptive management [19], for decision-making will serve to highlight conservation issues that are inappropriate candidates for application of synthetic biology and will provide legitimacy for projects that pass the rigors of the framework.

Early and Often

There has been insufficient engagement between the conservation biology and synthetic biology communities. We are concerned that the accelerated application of synthetic biology to wild systems is outpacing our level of understanding and input. Robust scientific studies need to happen early and often. Further, this research needs to be transparent and 'engage the public early and often'; this message was a common denominator of each of the workshops mentioned earlier. It is likely that the public, including other scientists, is the greatest source of knowledge about the potential pitfalls of applying synthetic biology to specific conservation issues, and public opinion is likely to be the biggest hurdle for any project, such as the case studies (Boxes 1 and 2). Without a guiding principle of 'early and often' it is likely that synthetic biology will be applied to conservation issues without broad engagement of conservation experts and without appropriate stakeholder involvement.

Concluding Remarks

Humanity has a responsibility to reduce the rate of loss of biodiversity. For this we need to use integrated strategies. It is time for the conservation community to consider the application of synthetic biology and other new genomic tools. Engagement is urgently needed, and it should be based on a series of guiding principles and with a robust decision framework to understand the pros and cons built on existing and new science to maximize biodiversity benefits and minimize biodiversity harm. The conservation community should reach out to the synthetic biology community – and with them jointly engage in broad conversations with communities, scientists, and regulators across the globe. The future of nature may depend on our efforts at this crucial nexus of biodiversity conservation and technology (see Outstanding Questions).

Acknowledgments

We would like to thank the Rockefeller Foundation for making the workshop at Bellagio Center possible, and all participants for stimulating discussions. Our sincerest thanks to Ben Novak for his tireless help on one of the figures. The conclusions in this article are those of the author(s) and do not necessarily represent the views of the US Department of Agriculture.

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Outstanding Questions

How can conservation biologists interact with synthetic biologists, including the next generation of scientists who are interested in both new technologies and conserving biodiversity? Conservation biologists can benefit from stimulating initiatives such as the **International Genetically Engineered Machine (iGEM) Foundation** competition where teams of young lay-persons interact in creating biological systems. There is a need for judges and sponsors within this program, and conservation biologists could thus influence the direction of synthetic biology in biodiversity conservation immediately and into the future through their active participation.

How can the conservation community increase knowledge and confidence about understanding the pitfalls and benefits of synthetic biology approaches? Several workshops have already taken place, but this is still a good forum for more active engagement of synthetic biologists with the conservation community, and of conservation biologists within the synthetic-biology community, particularly through future conferences and in specific workshops (http://syntheticbiology.org/).

How can conservation biologists be involved in decision making when evaluating planned synthetic-biology applications to biodiversity conservation? From an early stage of a proposed project involving synthetic biology, conservation biologists should play an active role in risk assessments.

When a species or an individual is altered through the application of synthetic biology, what is the entity that is being conserved/protected? This question has been intensively discussed in the current **de-extinction** debate, and the conservation biology community can provide their expertise [39].

How can we facilitate public engagement and ensure transparency in decisions around the application of synthetic biology to biodiversity conservation, which is crucial from a very early stage? This is one of the biggest and most important issues facing any new technological advance that could be applied to conservation biology. We advocate an 'early and often' approach to working with the public. Further, an interdisciplinary approach involving human dimensions experts is crucial for this step.

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