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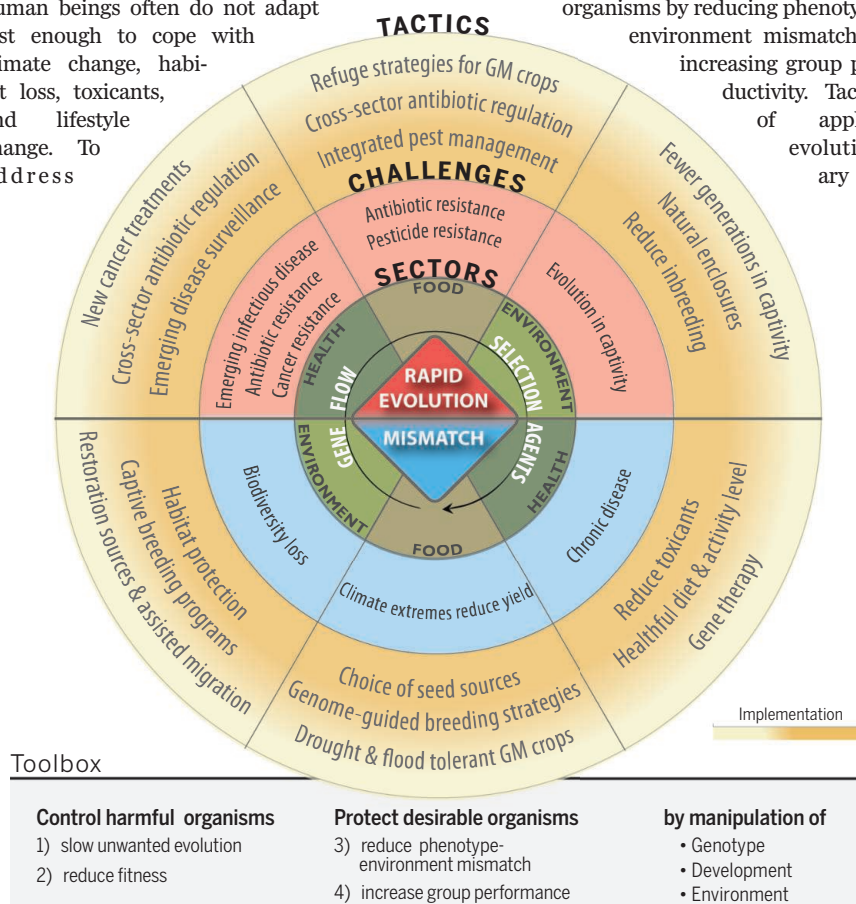
APPLIED EVOLUTION

Applying evolutionary biology to address global challenges

Scott P. Carroll,* Peter Søgaard Jørgensen,* Michael T. Kinnison, Carl T. Bergstrom, R. Ford Denison, Peter Gluckman, Thomas B. Smith, Sharon Y. Strauss, Bruce E. Tabashnik

BACKGROUND: Differences among species in their ability to adapt to environmental change threaten biodiversity, human health, food security, and natural resource availability. Pathogens, pests, and cancers often quickly evolve resistance to control measures, whereas crops, livestock, wild species, and human beings often do not adapt fast enough to cope with climate change, habitat loss, toxicants, and lifestyle change. To address

these challenges, practices based on evolutionary biology can promote sustainable outcomes via strategic manipulation of genetic, developmental, and environmental factors. Successful strategies effectively slow unwanted evolution and reduce fitness in costly species or improve performance of valued organisms by reducing phenotype-environment mismatch or increasing group productivity. Tactics of applied evolutionary biology



Tactics and tools of applied evolutionary biology. (Top) Evolutionary tactics to address the major societal challenges treated in the present study are shown as a wheel. Challenges in the food, health, and environment sectors are caused by rapid contemporary evolution or, in more slowly reproducing or threatened species, phenotype-environment mismatch. Gene flow and selection agents make challenges in one sector dependent on actions in others. Current progress in implementing tactics of applied evolutionary biology to address challenges varies widely. **(Bottom)** Many of these tactics use a common toolbox of strategies to prevent unwanted evolution or to reduce fitness in harmful organisms, as well as to reduce mismatch between organisms and human-altered environments or to increase group performance in desired organisms. Each of these strategies uses a combination of manipulations of the organismal genotype, phenotypic plasticity (development), or environmental conditions.

ology range broadly, from common policies that promote public health or preserve habitat for threatened species—but are easily overlooked as having an evolutionary rationale, to the engineering of new genomes.

ADVANCES: The scope and development of current tactics vary widely. In particular, genetic engineering attracts much attention (and controversy) but now is used mainly

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for traits under simple genetic control. Human gene therapy, which mainly involves more complex controls, has yet to be applied successfully at large scales.

In contrast, other methods to alter complex traits are improving. These include artificial selection for drought- and flood-tolerant crops through bioinformatics, and application of “life course” approaches in medicine to reduce human metabolic disorders.

Successful control of unwanted evolution depends on governance initiatives that address challenges arising from both natural and social factors. Principal among these challenges are (i) global transfer of genes and selection agents; (ii) interlinked evolution across traditional sectors of society (environment, food, and health); and (iii) conflicts between individual and group incentives that threaten regulation of antibiotic use and crop refuges. Evolutionarily informed practices are a newer prospect in some fields and require more systematic research, as well as ethical consideration—for example, in attempts to protect wild species through assisted migration, in the choice of source populations for restoration, or in genetic engineering.

OUTLOOK: A more unified platform will better convey the value of evolutionary methods to the public, scientists, and decision-makers. For researchers and practitioners, applications may be expanded to other disciplines, such as in the transfer of refuge strategies that slow unwanted evolution in agriculture to slow unwanted evolution elsewhere (for example, cancer resistance or harvest-induced evolution). For policy-makers, adoption of practices that minimize unwanted evolution and reduce phenotype-environment mismatch in valued species is likely essential to achieve the forthcoming Sustainable Development Goals and the 2020 Aichi Biodiversity Targets. ■

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REVIEW

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Applying evolutionary biology to address global challenges

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Two categories of evolutionary challenges result from escalating human impacts on the planet. The first arises from cancers, pathogens, and pests that evolve too quickly and the second, from the inability of many valued species to adapt quickly enough. Applied evolutionary biology provides a suite of strategies to address these global challenges that threaten human health, food security, and biodiversity. This Review highlights both progress and gaps in genetic, developmental, and environmental manipulations across the life sciences that either target the rate and direction of evolution or reduce the mismatch between organisms and human-altered environments. Increased development and application of these underused tools will be vital in meeting current and future targets for sustainable development.

Human influence on the biosphere (1, 2) has profound consequences for both the rate and direction of evolution (3). Among the consequences are the challenges billions of people face from the effects of cancers, pests, and pathogens that adapt quickly to our interventions against them. At the same time, humans and other organisms that we value for economic, ecological, or aesthetic reasons are often not able to adapt quickly enough to keep pace with human alterations of the environment. These contemporary dilemmas increasingly threaten human health, food security, and biological diversity (4–12). For example, the World Health Organization (WHO) warns that microbial resistance to antimicrobial drugs threatens the achievements of modern medicine (13). Likewise, more than 11,000 documented cases of pes-

ticide resistance in nearly 1000 species of insects, weeds, and plant pathogens jeopardize agricultural economies and food supplies worldwide (14). Failure to adapt may be equally dire and costly, as in the prevalent mismatch between modern human nutritional and lifestyle behaviors and those of our evolutionary past, which is generally considered a major contributing factor to the high incidence of obesity and associated illnesses such as type 2 diabetes mellitus and cardiovascular disease (15). Meanwhile, the prospect of Earth's sixth mass extinction of species becomes imminent as species are unable to adapt quickly enough to environmental change (16). A growing application of principles from evolutionary biology to challenges such as these may improve our ability to meet many of the most pressing problems of the 21st century (12, 17–19).

Here, we review current and prospective applications of evolutionary biology that may provide solutions for major societal challenges. We examine management approaches that attempt either to improve or to undermine adaptation to modern environments by manipulating the relations between the traits of organisms and the patterns of selection imposed by their environments. These manipulations include tools that may be widely considered evolutionary, such as selective breeding and emerging technologies in genetics, as well as manipulations that are often overlooked as evolutionary, specifically manipulations of development that modify traits independent of genetic change and the altering of environments in ways that can modulate selection itself. A conceptual framework linking all of these genetic, developmental, and environmental manipulations is likely to lead to greater implementation and cross-disciplinary integration of applied evolutionary methods. We highlight how evolutionary strategies may be used to achieve

policy targets of sustainable development for improved human health, food production, natural resource use, and biodiversity conservation, including how stakeholder conflicts may be reduced to achieve desired outcomes. Throughout, we underscore the merits of building a more unified and integrated field of applied evolutionary biology to address global challenges.

Core evolutionary concepts and their relevance to global challenges

Evolution, defined as the change in genetic make-up of a population over successive generations, requires genetic variation, which arises from mutation and recombination (20). Most important for adaptation is genetic variation that affects variation in functional traits (21), such that alternate genotypes produce alternate phenotypes. Selection increases the frequency of genes that improve fitness—the ability to survive and reproduce. The specific genetic basis for most traits is not known, but trait differences among individuals typically have a significant heritable (genotypic) basis. This basis includes heritable aspects of development, which also may evolve and give rise to adaptive phenotypic plasticity (22). A population with low fitness may experience strong natural selection that favors better-adapted genotypes. However, strong selection will not necessarily “rescue” a population if there are too few adapted individuals or suitable genes for the population to persist (23). Movement of genes between populations (gene flow) and random changes in gene frequency in small populations (genetic drift) can also cause evolution and influence the outcome of natural selection (20). These concepts apply not only to organisms from bacteria to humans but also to viruses and cancer cells (24).

The core concepts of evolutionary biology are best known for explaining the unity, diversity, and adaptive characteristics of organisms (17). Phylogenetic methods that establish the relatedness of organisms are central to understanding the patterns and processes of evolution underlying the function and diversity of living systems (25). The practical applications of phylogenetic methods have been thoroughly reviewed by others and include such diverse objectives as reconstructing invasion routes of harmful organisms, conservation planning, and combating crime (17, 26). Here, we focus on the manipulation of processes that determine the adaptedness of individuals, populations, and other biological systems in order to meet management objectives (Fig. 1).

Agriculture, medicine, and conservation address different challenges but, nonetheless, share common strategies to manage phenotype-environment mismatch and the associated risks to populations experiencing strong selection (Fig. 2). Those strategies can be classified as genotypic, developmental, or those related to environmental manipulations. The potential sustainability of such practices may be assessed by comparing the intensity of selection with the adaptive capacity of a target population (27). For example, the widespread use of antibiotics that exert strong selection on

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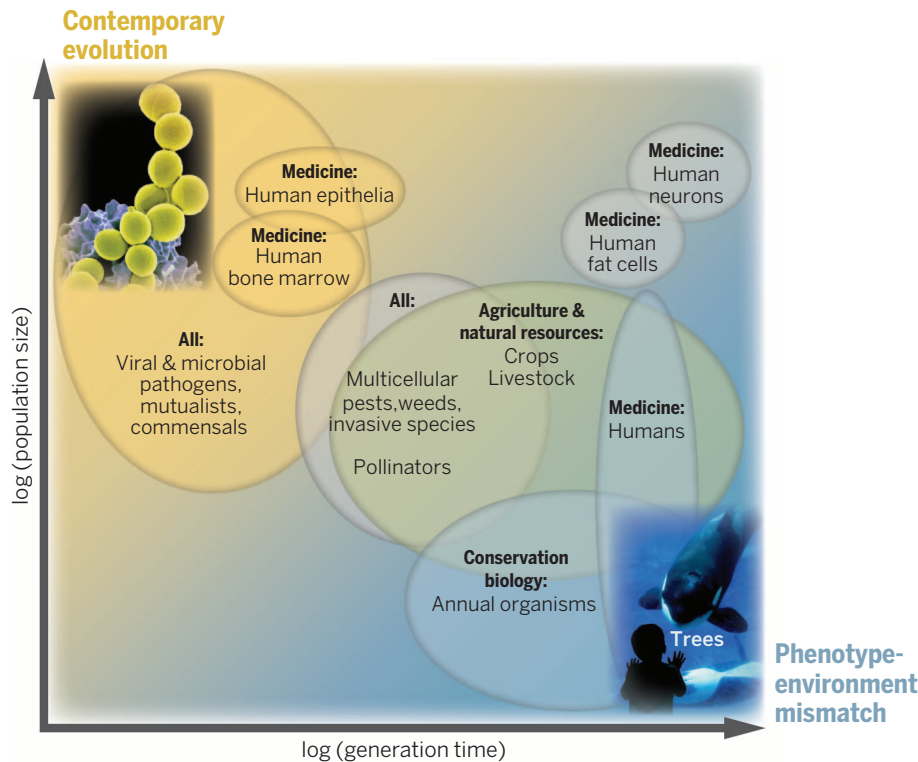


Fig. 1. The two central paradigms of applied evolution are managing contemporary evolution and phenotype-environment mismatch. Managing contemporary evolution is critical for rapidly reproducing organisms with large population sizes, such as the methicillin-resistant *Staphylococcus aureus* (MRSA), pictured top left. Altering phenotype-environment mismatch is most relevant for organisms with relatively long generation times and low population sizes, such as the large mammals shown lower right. Labels in ovals refer to example organisms, viruses, or cell types in specified management sectors. “All” indicates relevance to all management sectors (food, health, and environment). References are provided in table S1.

bacteria is typically not sustainable for controlling highly adaptable microbe populations, because they rapidly evolve resistance (28). Accordingly, the sustainability of antibiotic use can be increased by either reducing selection, for example, through regulated use of particularly strong antibiotics, or by attempts to surpass the adaptive capacity of microbes through drug combinations (29). Below, we review successes and emerging methods in applied evolutionary biology, highlighting commonalities across the sectors of health, food, and environmental management (Fig. 3).

Successes and prospects in applied evolutionary biology

Applied evolutionary biology encompasses widely different manipulations that may together achieve a broad range of goals. From protecting biodiversity with conventional environmental management that increases fitness in wild environments to medical recommendations for traditional diets, some methods of applied evolutionary biology have a long history of use, even if they are not often seen as evolutionary in nature. In contrast, the synthesis of wholly novel genomes with emerging technologies represents obvious evolutionary manipulation that deliberately adds new organisms to the tree of life, but

with little history of application, it involves unknown risks and public controversy. Here, we review some of the most recent successes and leading prospects for the application of evolutionary biology, in a progression from relatively well established methods to underexplored strategies. We first consider manipulations of selection to improve population productivity and individual health and to delay the emergence of resistance (Fig. 2). We then examine less developed methods for the cultivation of populations inherently preadapted to impending environmental changes and for innovative applications of group selection in crops and wildlife. We end this section with urgent considerations for managing evolutionary factors that span disciplinary boundaries, as in cases of emerging zoonotic disease.

Environmental alignment to secure biodiversity and human health

A common application of evolutionary principles is to manage current environments to be more like the historical habitats in which selection shaped the genetic makeup of humans and other species. Conventional habitat protection and restoration recognize that threatened species often adapt poorly to changing environments in the wild (26, 30). Conversely, rapid adaptation

to captive rearing programs used to rebuild populations of rare species contributes to a 50 to 90% failure rate of reintroductions (31). Reintroduction success has been improved with enclosures and rearing methods that mimic wild conditions and by limiting the number of captive generations to minimize adaptation to artificial conditions (32).

Some of the most serious noncommunicable diseases in humans may be prevented by better aligning current environments with those in which our hunter-gatherer ancestors evolved (33). Sedentary modern lifestyles and diets with high-glycemic index processed foods are increasingly implicated in the rapidly rising rates of obesity, diabetes, and cardiovascular disorders (34). These disorders are estimated to contribute to about two-thirds of all deaths in Western societies (35) and to a growing proportion of deaths in developing countries (36, 37). In 2012, the economic burden of type 2 diabetes alone was estimated at \$500 billion globally, nearly 1% of world Gross Domestic Product (38). To restore conditions to which people are better adapted physiologically, while retaining the desired elements of a modern lifestyle (35), public health scientists recommend greater physical activity (39) with reduced consumption of refined carbohydrates (36), that is, diets and activity levels closer to those of the past, to which we are better adapted. More generally, a number of evolutionarily based tools are available to prevent chronic noncommunicable diseases, including the 19% of global cancer incidents that WHO attributes to environmental exposure (40). These tools include life-course approaches, which manage the timing and duration of environmental exposures to minimize risks of subsequent chronic disease (41). From a public health standpoint, environmental approaches to disease prevention may often be most cost-effective when applied outside of health care settings and when simultaneously targeting groups of people rather than one individual at a time, such as through price regulation on goods or public information campaigns (42). Further, systematic population scans that associate disease phenotypes with human genotypes (43, 44) are an important tool for determining the genetic basis of lifestyle diseases and, therefore, in assessing heritable risk and treatment options. Such assessments, however, run the risk of identifying false-positives and underestimating the complexity of genetic and epigenetic regulation (45, 46). For example, it is estimated that 90% of chronic disease risk cannot currently be directly linked to genetic factors but is more likely to be understood in the context of human environmental exposures, such as diet and toxicants (47). Thus, future prevention and treatment of chronic diseases will combine enhanced genotype-phenotype association scans with improved monitoring of toxic compounds in the surrounding environment and in human tissues (47). Such genotype-phenotype association studies search simultaneously for associations across the hundreds of disease phenotypes included in electronic medical registers (45). This

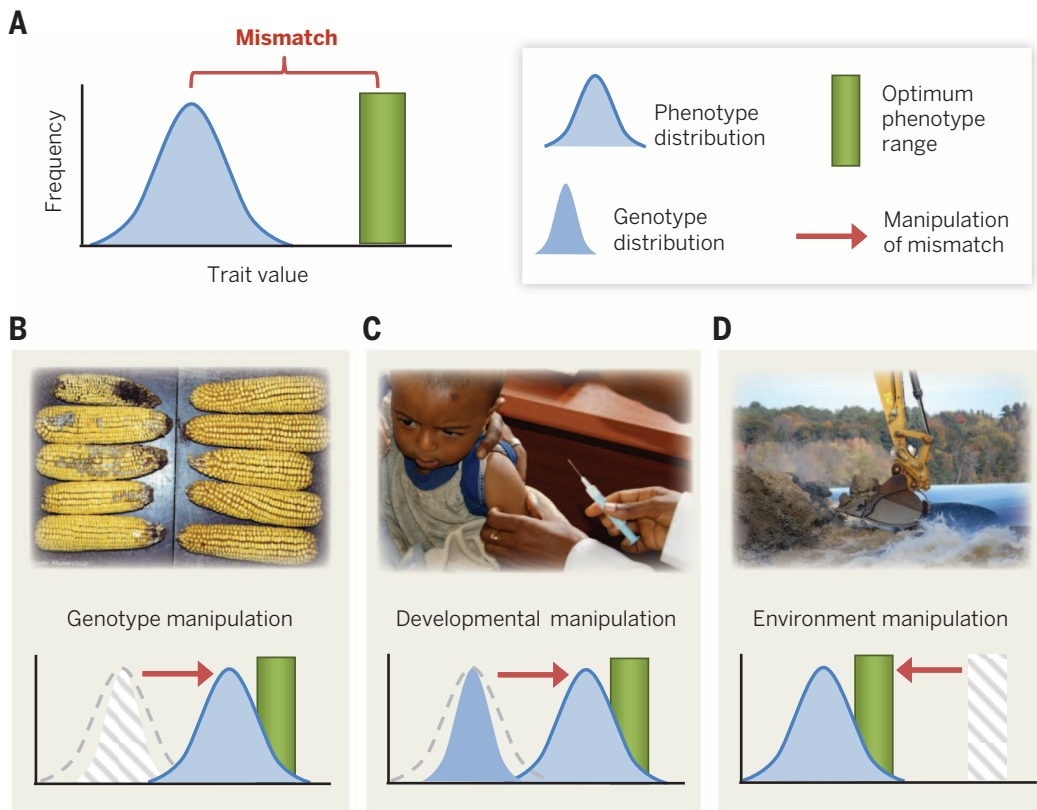


Fig. 2. Phenotype-environment mismatch. (A) Mismatch between phenotypes and an environment occurs when a population's phenotypic trait distribution differs from the optimum; greater mismatch increases selection for adaptation but also implies greater costs through reduced survival and reproduction. (B) Genotypic manipulations reduce mismatch by managing existing genetic variation or introducing new genes. For example, conventional corn is damaged by insect pests (left) that are killed by bacterial proteins produced by GE Bt corn (right). Alternatively, evolutionary mismatch can also be managed by (C) developmental manipulations of phenotypes, such as vaccination to enhance immunity against pathogens, or (D) environmental manipulations, such as habitat restoration. These examples demonstrate methods to reduce mismatch, but these same tactics can be reversed to impose greater mismatch where beneficial to human interests (e.g., pest eradication).

expanded approach reduces the rate of false-positives and helps to identify genetic factors that contribute to multiple diseases, as well as diseases controlled by multiple genes.

Altering genomes for improved food security and human health

Climate change and environmental degradation compromise the productivity of agricultural systems that must feed a rapidly growing human population (48). Genetic modification of crops, through enhanced artificial selection methods and perhaps genetic engineering, will likely be important in meeting these challenges. Genetically engineered (GE) crops were first grown on a large scale in 1996, and during 2013, 18 million farmers in 27 countries planted GE crops on ~10% of the world's cultivated land (175 million hectares) (49). More than 99% of this area was planted with soybean, corn, cotton, or canola into which genes were inserted to confer tolerance to herbicides, protection against insects, or both (50). These engineered varieties are extreme examples of apparently effective genotypic manipulations to reduce mismatch to specific environments. However, societal acceptance is an important factor, and GE

crops remain controversial (51, 52). They have not been adopted widely in some regions, including Europe, where alternative manipulations of evolutionary mismatch, such as use of non-GE lines with some degree of tolerance, pesticide applications, and integrated pest management serve as alternative genotypic and environmental manipulations (53).

An alternative to genetic engineering is enhanced artificial selection and hybridization of superior cultivated varieties with molecular genetic tools that identify individuals and gene regions conveying preferred traits (54). A priority application, where genetic engineering has until now been less successful (55), is to improve abiotic tolerance because of more frequent weather extremes under climate change. For example, flood-tolerant rice, which is grown by two million farmers in Bangladesh and India (49), was developed with marker-assisted breeding by using molecular markers of quantitative traits to identify targets for hybridization and selection (56). At the same time, candidate drought-tolerance genes for GE crops have also recently been identified in rice, as well as corn (57, 58), with corn hybrids putatively tolerant

to both drought and herbicides brought to market in 2013 (55, 59). Regardless, whether produced via artificial selection or genetic engineering, the potential to improve food security by reducing mismatch may be greatest when technology allows growers to select or customize crop varieties for adaptation in their local agroecosystems (60).

In contrast to the advances in agriculture, genetic modification to treat human disease is in a trial phase. Gene therapy is under development mainly for diseases with high heritability and simple genetic control, in which replacing or complementing parts of a patient's genome can improve their health (61–63). Therapies in advanced trial stages include the targeting of retinal cells to prevent expression of heritable blindness (64, 65), and oral administration of p53 gene for tumor suppression (66). However, even as targeted DNA analysis and whole-genome sequencing of patients becomes increasingly routine (67), few efforts have met the promise of their preclinical and clinical trials to reach final approval phase of “postmarketing” surveillance trials (68, 69).

Using environmental heterogeneity to delay the evolution of resistance

One of the most costly and widespread outcomes of efforts to control populations is the rapid evolution of resistance to control measures in insect pests (14), weeds (70), pathogens, and cancers (71). For example, intensive use of the systemic herbicide glyphosate [*N*-(phosphonomethyl)glycine] by farmers, particularly those who grow glyphosate-tolerant GE crops, has selected for resistance in 24 weed species in 18 countries since 1996 (72, 73). In contrast, strategies that vary selection in space or time have delayed the evolution of resistance in some pests (Fig. 3). For example, scientists and farmers have proactively developed and implemented strategies to slow pest adaptation to GE crops that produce insecticidal proteins from *Bacillus thuringiensis* (Bt) (74, 75). The primary strategy employs “refuges” of host plants that do not produce Bt toxins to promote survival of susceptible pests (74). In principle, the rare resistant pests that survive on Bt crops are more likely to mate with the comparatively abundant, susceptible pests from the nearby refuges. If resistance is inherited as a recessive trait, the heterozygous offspring from such matings will be susceptible and will die on the transgenic plants. The U.S. Environmental Protection Agency (EPA) and regulatory agencies in many other countries


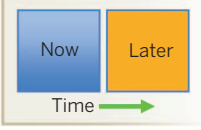



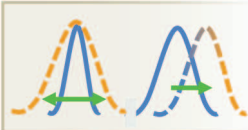
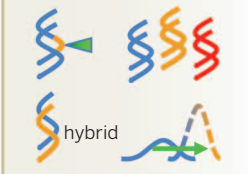

	Strategy	Tactic	Food and fiber	Health	Environment
A Control pests, pathogens and invaders by . . .					
<i>. . . slowing unwanted evolution</i>					
	Spatial variation in selection	Protect some susceptible forms	Nontoxic plantings save treatable pests	Favor susceptible pathogens, cell lines	Maintain genotypes vulnerable to control
	Temporal variation in selection	Switch treatments to slow adaptation	Rotate crops, pesticides	Cycle treatments of pathogens, cancers	Stress invader's weak points sequentially
	Diversified selection	Apply stressors together	Integrate multiple tactics, pyramiding	Multitarget vaccines; reduce transmission	Integrated control of invasive species
	Trait-based selection	Favor benign genotypes	Mow to select weeds to shade less	Favor survival of benign strains	Target mobile forms to reduce dispersal
<i>. . . reducing adversary fitness</i>					
	Add mutational load	Transgenic mutation	Reduce pest fitness	Mutate viruses; eliminate vectors	Reduce invader fitness
B Protect desirable populations by . . .					
<i>. . . reducing phenotype environment mismatch</i>					
	Reduce selection	Modify environment, or move	Adopt crops suited to current environment	Alter lifestyle for health, offspring	Alter local conditions or assist migration
	Improve fit to environment	Modify genotypes	Wild crop relatives; molecular breeding	Recombinant drugs; gene therapy	Selected, hybridized or GE genotypes
<i>. . . increasing group performance</i>					
	Group selection, cooperation	Select emergent group traits	Favor efficiency, weed suppression	Internalize public costs and benefits	Limit competition, protect in reserves

Fig. 3. Two management intervention categories of applied evolutionary biology: (A) Controlling adversaries and (B) Protecting valued populations. Together they are enabled by four strategies (headings). A core set of eight evolutionary principles guides the execution of these strategies and underlies tactics (left columns) used to meet management objectives in the food and fiber production, health, and environmental sectors (right columns). Colored squares

show different treatments; curves show frequency distributions of phenotypes; double helices are genomes; green arrows show change through space or time; green wedges show point interventions using selection or genetic engineering. Semicolons separate multiple management examples. Hypothetical applications are given in two cases that lack empirical examples. Expanded treatments for each cell and references are provided in table S2.

have mandated refuges since Bt crops were first commercialized (76, 77). Retrospective analysis, after more than a decade of monitoring, indicates that refuges do indeed delay resistance, particularly when resistance is a recessive trait (77, 78).

The success of refuge tactics in agriculture is now drawing attention in other management sectors, including fisheries, where refuges may impede costly life-history evolution and body-size evolution resulting from harvest selection (79). Likewise, in cancer management, portions of tumors with low vascularization and, consequently, low delivery of chemotoxins may serve as refuges that sustain chemosensitive tumor genotypes (80, 81) and slow the evolution of resistance to chemotherapy in metastatic cancer (82, 83). Such resistance accounts for a large proportion of current treatment failures (84). Compared with typical failures when oncologists try to eradicate a patient's cancer with high drug doses, lower doses could be more successful if they favor survival of chemosensitive cell lines that can out-compete chemoresistant lines (85). Increasingly sophisticated models of tumor evolution may eventually support implementation of such non-eradication therapies (86).

Whereas refuges delay resistance by swamping resistant lineages with susceptible lineages, another strategy attempts to curb resistance through selection that combines multiple modes of action (also known as “stacking” or “pyramiding”). In many human diseases—including HIV, tuberculosis, malaria, and cancer—resistance frequently evolves under selection from individual drugs (87). Combination therapies are based on the evolutionary principle that, if genes conferring resistance to each selection pressure are rare and inherited independently, individuals with all of the genes required for full resistance will be rare or even absent in target populations (4, 14, 88, 89). For example, resistance evolved rapidly to potent antiretroviral drugs administered singly in patients with HIV, but combinations of three such drugs have provided long-term efficacy and have become the standard of care (90, 91). The potential tradeoffs associated with combining two or more drugs or pesticides to delay resistance include short-term increases in costs (92) and negative side effects (93), as well as the concern that such combinations will also ultimately favor the evolution of multiple resistance (87, 94, 95). For example, incorporating two or more toxins together in GE varieties slows resistance evolution (96, 97), but this advantage may diminish when less-resistant single-toxin varieties are planted in the same area as multitoxin varieties and provide stepping stones for multiple-resistance evolution (98). Combined selection pressures are most likely to be durable when implemented as a facet of more broadly integrated systems, such as integrated pest management (IPM). IPM combines selection pressures from a diverse suite of tactics for pest suppression, including various forms of biological control and optimized spatiotemporal cropping schemes (99). By increasing treatment

durability, combinatorial strategies are among the most important instruments for the control of highly adaptable pests, pathogens, and cancers (Fig. 3).

Choosing population sources to anticipate climate change

Although some strategies of applied evolutionary biology are established or rapidly increasing, other rarely used strategies are of interest because of their underexplored potential to replace or complement longstanding management practices. These include using nonlocal seeding sources for replanting in environmental restoration and forestry, as well as the exploitation of group selection-based designs in crop and livestock breeding.

The mismatch of valued plants to new climates is an overarching challenge in forestry, agriculture, and conservation biology. A widespread debate concerns whether to use local versus external sources of genetic material for replanting to best anticipate climate change in forestry, agriculture, wildlife, and environmental restoration. The massive scale of many replanting efforts—400,000 ha of production forest is planted each year in Canada alone (100)—plus the long intervals between plantings for many perennial species and restoration projects, means that these choices may have broad economic and ecological consequences. Traditionally, resident stocks have been favored to capture locally valuable adaptations. In forestry this approach is exemplified by established bioclimatic “seed-transfer zones” that guide seed sourcing for planting of some of the world's largest production systems (101, 102). Evidence from wild-plant restoration programs indicates, however, that local sources are not always best, particularly in altered environments (103–108). This may arise when nearby sources share some of the vulnerabilities responsible for the declines of the original populations (102). In these situations, climate mismatches may be better relieved by translocating genotypes that are preadapted to expected conditions (109, 110), for example, more tolerant to heat, drought, or pest stresses (111). When single sources do not show the range of adaptations required at a given site, reintroduction may be improved with propagules pooled from a diversity of sources to increase overall genetic variation and, thus, the odds that some individuals will be suited for changing conditions (103, 104, 112). A recent meta-analysis in restoration ecology underscores shortcomings of the “local-is-best” dictum (108), and comparable analyses of sourcing successes and failures in forestry and perennial agriculture are needed to find ways to sustain productivity under climate change.

Exploiting group versus individual performance in crops and livestock

In most agriculture and aquaculture, productivity is measured at the level of groups (e.g., field or herd) rather than in individual performance. More attention to traits that improve group per-

formance may thus offer a broader suite of tactics to increase production while demanding fewer resources, including pesticides, to meet basic human needs (113) (Fig. 3). In the majority of natural systems, group selection is considered weak relative to selection among individuals (114). Consequently, past natural selection in the ancestors of domesticated species may have favored traits that promote individual performance but are costly to group productivity. One important consequence may be greater current opportunities for artificial selection of individual traits that improve group performance while avoiding inadvertent evolution of “uncooperative” individuals (8), such as those with competitive root structures in dryland field crops (115). Artificial selection for group yield in maize has produced lines with reduced male function and that bear more-vertical leaves, which reduce the shading of neighbors. Both of these traits decrease individual plant performance while enhancing group productivity (116, 117), but in the absence of strategic breeding to favor these changes directly, they have evolved only slowly, requiring 60 years to appear as unplanned responses to selection on group yield alone (118). Weiner and colleagues (119) have proposed a proactive design for wheat production that selects for traits that increase collective shading of weeds within specific planting configurations, in order to increase overall crop yield while reducing herbicide use. Similar group-based perspectives apply in animal husbandry, where traits like reduced aggressiveness favor group productivity under domestication, but might have been selected against in the wild (120). By combining agronomy and environmental physiology with evolutionary modeling, group-based agricultural systems may offer new and more sustainable paths to meet global production goals.

Addressing evolution across management sectors

One of the most significant outcomes of the scale of human activity is that evolutionary concerns in one management sector often spill over into, or depend on, others (Fig. 4). These connections result from novel biotic interactions because of natural, intentional, or inadvertent transport of organisms and their genes by trade, infrastructure, and waste streams (121, 122). Further coordination of prevention, control, and monitoring will be required to address growing interdependencies among management sectors. Increased exchange of emerging pathogens between health, agricultural, and natural systems is a key case in point (123–126). For example, although domestic pigs are the principal reservoir of “swine influenza” (H1N1), they simultaneously host other influenza strains, including those associated with human hosts and domestic and migratory avian hosts (127). The intensive communal raising of pigs and poultry for food therefore encourages virus strains to exchange genes and adapt to more host species (128). One overarching concern is that pigs hosting highly pathogenic wild avian strains (H5N1) could contribute to selection for

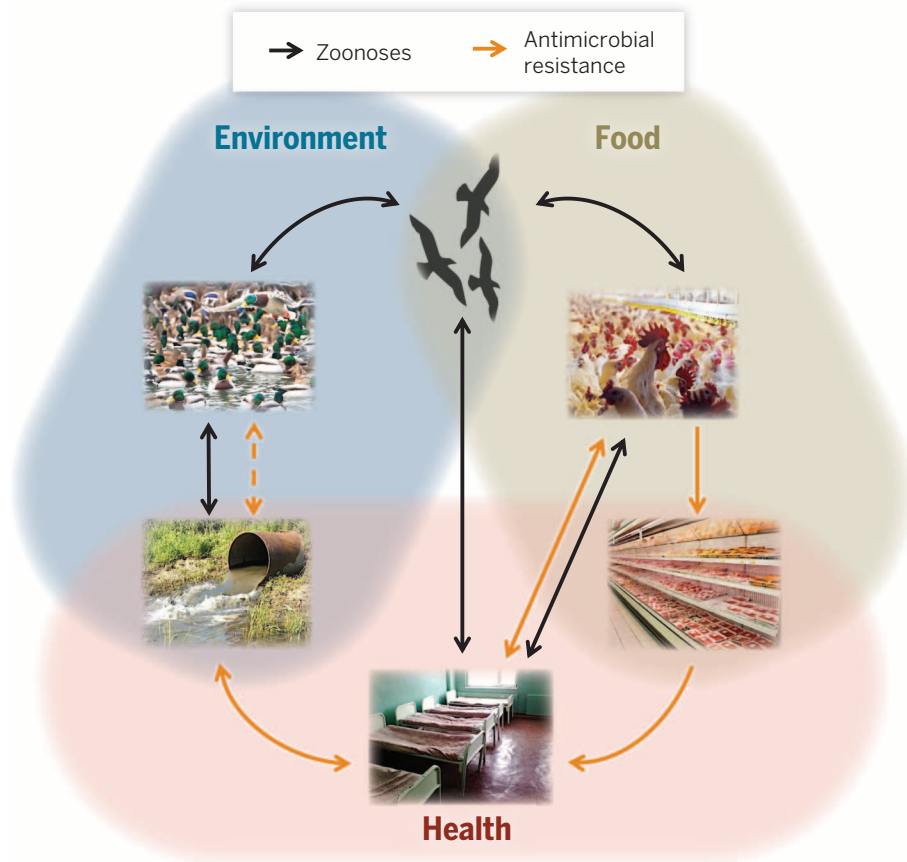


Fig. 4. Emerging pathogens such as zoonoses (black arrows) and resistant bacteria (orange arrows) illustrate interdependencies generated by gene flow among the economic sectors of food, health, and the environment. In zoonoses, vertebrates, such as birds, act as reservoirs for pathogens that can infect humans. Through direct transmission or via domesticated animals, zoonoses are passed to humans and cause regular local and rare global epidemics (such as the flu outbreaks of H5N1-2004 and H1N1-2009). “Reverse zoonoses” are transmitted from infected humans to wildlife (177). Antimicrobial resistance in bacterial stains associated with livestock evolves in response to widespread use of antibiotics in agriculture and to a lesser degree because of treatment in humans. Via food items, industry workers, and waste disposal, resistant strains enter other human contexts. In a public health context, resistant strains constitute a growing extra risk during treatment of illnesses, for example, in hospitals. Antibiotics in human effluent cause widespread resistance selection in natural and seminatural environments, which, together with resistance reservoirs in natural environments, further increase the risks of resistant pathogens in humans. In the figure, the dashed line indicates a variety of poorly known interactions among wild species.

the direct mammal-to-mammal transmission that underlies human epidemics. The consequences of such evolution (129) are foreshadowed by the recent global outbreaks of H5N1 in 2004 and H1N1 in 2009 (130). These events underscore the need for initiatives in prevention and control that cross traditional disciplinary boundaries, including coordinated surveillance of viral evolution and the monitoring of pathogen reservoir species across the food, health, and environment spectrum (125, 131).

The unresolved problem of rapidly evolving antimicrobial resistance is another pressing example of interdependence among management sectors, particularly between systems managed for food production and human health. Annual estimated costs of combatting multidrug-resistant microbes in the United States alone total \$35

billion (132, 133), and the failure to produce new antimicrobials as quickly as their predecessors lose efficacy (134, 135) places a premium on stewardship of the few drugs that remain broadly effective (136, 137). Although overprescribing of antibiotics for human treatment is a very real concern, the major use of antimicrobial drugs in many parts of the world is to promote the health and growth of livestock (138, 139). This use selects for antimicrobial-resistant microbes that may infect humans (Fig. 4) (139, 140). For example, antibiotic-treated animals that are raised as food for people are now implicated in the origins of the most extensively resistant *Escherichia coli* encountered in human sepsis (141). Particularly worrisome is that, once free in the environment, resistance genes do not dissipate with distance like many abiotic environmental pollu-

tants. Resistance genes can replicate, and thus, they can transfer horizontally among bacterial taxa, travel intact over great distances via hosts, and rise to new abundances in the presence of antimicrobials with similar modes of action. As pools of resistance genes become more prevalent and disseminated through human activities, they are likely to become increasingly important in new regions and management sectors (142). Because coupled evolutionary dynamics operate over such large spatial scales and multiple management sectors, their management requires political coordination, as exemplified by the Transatlantic Taskforce on Antimicrobial Resistance (143). Regulatory bodies have also taken the first steps to restrict use of some antibiotics to single management sectors (144, 145). Broader and more rigorous implementation of such restrictions will be needed to sustain the most critical public benefits of our modern antibiotic era.

Next steps Applied evolutionary biology in international policy

Applied evolutionary biology addresses both the rapidly evolving and the mismatched biological systems that underlie many global challenges (146). Meeting international objectives for sustainable development [Millennium Development Goals and the anticipated Sustainable Development Goals (147)] and biodiversity conservation [the Convention for Biological Diversity’s 2020 “Aichi” Biodiversity Targets (148)] will require much greater integration of evolutionary principles into policy than has been widely acknowledged. The potential policy contributions of cases reviewed here are summarized in Box 1. For example, we must implement resistance-management strategies for pesticides and antibiotics to meet newly proposed Sustainable Development Goals for human health, food, and water security (147). Likewise, choices of adaptable source populations will improve the resilience of restored habitats (Aichi Target 15: “restore 15 percent of degraded habitats before 2020”) and increase the reliability of crop supplies. Further, sustainable harvest strategies (149, 150) and early warning signs of unsustainable harvest (151) will help to achieve lasting stocks of fish and aquatic invertebrates (Aichi Target 6: all stocks should be harvested sustainably). The identification and protection of diverse genotypes is also critical to the future of crop improvement and for the discovery of chemical compounds such as new therapeutics. In this realm, the international Nagoya Protocol on Access and Benefit-Sharing of genetic resources (152) may assist in securing public access to resources for adaptation to local conditions, while coordinating with global research and development efforts (153–155).

The extensive and targeted genetic manipulations permitted through recent advances in biotechnology are setting the stage for novel biological functions for which we either lack an understanding of potential risks, or knowledge of how best to assess them (156). There is a need

Box 1: Recommended contributions of applied evolutionary biology to proposed themes of new international sustainable development goals (147), based on examples presented in this review. For the currently negotiated draft of the sustainable development goals, go to <http://sustainabledevelopment.un.org/focussdgs.html>.

Goal 1: Thriving lives and livelihoods

- Reduce chronic lifestyle disease through environmental alignment of human lifestyle.
- Reduce environmental levels of human toxicants through application of reduced selection response techniques* to biocides.
- Apply reduced selection response techniques to maintain long-term efficacy of antimicrobials and to avert the antibiotics crisis.
- Reconcile individual and group incentives in health systems to reduce virulence and resistance of emerging and reemerging pathogens.

Goal 2: Sustainable food security

- Increase crop yield through continued selection of varieties and improved access to these.
- Prolong efficacy of pesticides and artificially selected or GE crops through reduced selection–response techniques.
- Improve yields through integration of group selection in production of novel crop varieties.
- Reduce climate change impact by choosing crop varieties resilient to drought, flooding, and other extremes.

Goal 3: Secure sustainable water

- Increase water security through use of reduced selection–response techniques to water-polluting pesticides and/or biocides
- Use genetic manipulation to produce crop varieties with improved water economy.

Goal 4: Universal clean energy

- Improve biofuels through genetic manipulation with the aim to reduce CO₂ emissions and land area for energy production.
- Assess risks and benefits of synthetic organisms for biofuel production while taking gene flow, land use, and property rights issues into account.

Goal 5: Healthy and productive ecosystems

- Reduce biodiversity extinction rates through environmental alignment and genetic manipulation of fitness.
- Retain naturalness of captive biodiversity through environmental alignment.
- Choose preadapted or high-diversity sources for increased habitat restoration success.
- Avoid collapse and protect genetic diversity of aquatic resources through nonselective harvesting strategies informed by early warning signals.

Goal 6: Governance for sustainable societies

- Incorporate externalities from rapid evolution, as well as the loss of evolutionary history and evolutionary potential, into green accounting for sustainable governance of the Earth system.
- Coordinate strategies of sustainable development goals in a coupled-systems framework to reduce conflicts from inadvertent contemporary evolution and phenotype–environment mismatch.

*“Reduced selection–response techniques” refer to the four tactics in Fig. 3 that slow evolution by varying selection in space and time, diversifying selection, and targeting of specific traits, as well as adoption of alternatives to strong selection agents, such as toxins.

for an overarching international framework to regulate synthetic (156, 157), as well as conventional and advanced, GM organisms (158)—a framework that also would reduce conflict between existing frameworks (159). Perhaps the

area of applied evolutionary biology where development of international policy is most urgent is the area of synthetic biology. Synthesizing wholly or partially novel organisms offers tremendous opportunities in many areas such as biofuels,

medicine, environmental restoration, and conservation (160–162), but national and international guidelines are needed to avert potentially harmful outcomes (156, 163). Segments of medicine and agriculture include social scientists and economists in systematic risk assessment (76, 164). Similar practices would benefit conservation biology and natural resource management, as increasingly proactive and intensive manipulations appear on the horizon. These prospects include resurrected species and wild populations genetically engineered for resistance to lethal diseases such as chytrid fungus in frogs and white-nose syndrome in bats (161, 162).

Implementing applied evolutionary biology locally and globally

Reconciliation of individual and group stakeholder interests plays a central role in the effort to achieve sustainability through applied evolutionary biology (165–168). Anthropogenic evolutionary change often has consequences that extend beyond the immediate vicinity of the causal agents and pose dilemmas in achieving cooperation from local to global scales (169). Thus, in some applied evolutionary strategies, individuals must exchange their private short-term gains for the long-term public good. In managing pest resistance to transgenic Bt crops, farmers who plant refuges of conventional crops contribute to the long-term public good of sustained pest susceptibility to Bt toxin but may incur the short-term private cost of pest damage to their refuges. However, farmers in five midwestern states of the United States accrued nearly two-thirds of the estimated \$6.8 billion in Bt corn benefits between 1996 and 2009 from land planted with non-Bt corn refuges (170). This benefit arose because widespread adoption of Bt corn caused regional suppression of the major target pest and non-Bt corn seed was less expensive than Bt corn (170). Despite this benefit, farmer compliance with the refuge strategy for Bt corn in the United States has steadily declined and threatens the sustainability of resistance management (171). Farmers are increasingly planting Bt seeds alone, which may reflect their efforts to reduce the perceived risk of short-term losses from pest damage to refuges. Such conflicts between individual and public good may be the rule rather than the exception in the implementation of applied evolutionary biology.

The economic theories of public choice provide tools for reconciling individual and group conflicts (169) (Box 1). Governments can tax undesirable actions, subsidize desirable ones, regulate activities (144, 145), and create tradable property rights. For example, subsidies and regulated access to public schools can increase participation in vaccination programs that benefit public health but may increase risks to unvaccinated individuals (170). Theoretical modeling suggests that an unregulated vaccination market will yield too little advance vaccination and too much vaccination at the time of infection, which could select for increased virulence (164). With pathogen resistance, both the relative fitness of resistant genotypes in untreated environments

(174, 175) and the prevalence of resistance in natural environments (176) may increase the cost of lost susceptibility to a drug. Improved policies that reduce public costs may emerge from better accounting of the causes and consequences of such evolutionary externalities (154, 177).

Toward a unified discipline

As demonstrated by many of the examples above, applied evolutionary biology uses principles common to all areas of biology, and because of this, progress in one area may often enable solutions in others. New approaches in this developing field may best be generated and assessed through collaborations that span disciplinary boundaries (178) (Fig. 3). Promoting greater adoption and consistency in the use of evolutionary terminology, which is currently inconsistent across disciplines (179), will therefore be an important first step toward a more unified field of applied evolutionary biology.

The global scale of human impacts is now more widely appreciated than ever before. Successful governance of living systems requires understanding evolutionary history, as well as contemporary and future evolutionary dynamics. Our current scientific capacity for evolutionarily informed management does not match the need, but it can be increased through new and more widespread training and collaboration, monitored experimentation, and context-sensitive implementation. Like engineering, which is a multifaceted applied science with common core principles, shared vocabulary, and coordinated methods, applied evolutionary biology has the potential to serve society as a predictive and integrative framework for addressing practical concerns in applied biology that share at their core the basic evolutionary principles governing life.

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SUPPLEMENTARY MATERIALS

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