

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 pesticide resistance in nearly 1,000 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 to either improve or undermine adaptation to modern environments by manipulating the relationships 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, but also manipulations that are often overlooked as evolutionary, specifically manipulations of development that modify traits independent of genetic change, and altering 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 makeup 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 ex-

plaining 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 evolutionary mismatch and the associated risks to populations experiencing strong selection. Those strategies can be classified as genotypic, developmental, or those related to environmental manipulations (Fig. 2). 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 bacteria is typically not sustainable for controlling highly adaptable microbe populations because they rapidly evolve resistance (28). Accordingly, the sustainability of antibiotics use can be increased by either reducing selection, e.g., 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 pre-adapted 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 percent 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 non-communicable 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 processed foods are increasingly implicated in the rapidly rising rates of obesity, diabetes and cardiovascular disorders (34). These mismatch 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 GDP (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 non-communicable diseases, including the 19% of global cancer incidents that the 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 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 approximately 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 ma-

nipulations (53).

An alternative to GE 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 GE has until now been less successful (55), is to improve abiotic tolerance due to 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 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 for genetic manipulations of mismatch to improve food security 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 currently 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 pre-clinical and clinical trials to reach final approval phase of 'post-marketing' surveillance trials (68, 69).

Using environmental heterogeneity to delay resistance evolution

One of the most costly and widespread outcomes of efforts to limit 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 herbicide glyphosate 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. EPA and regulatory agencies in many other countries 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 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 outcompete chemoresistant lines (85). Increasingly sophisticated models of tumor evolution may eventually support implementation of such non-eradication therapies (86).

While refuges delay resistance with genetic swamping of resistant lineages by 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 multi-toxin 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

While 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 non-local seeding sources for re-planting in environmental restoration and forestry, and 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 steer local 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 pre-adapted 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 performance 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 evolutionary 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 due to 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, while 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 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 US 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). Antibiotic-treated animals that are raised to feed 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 pollutants. 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' targets (148)] will require much greater integration of evolutionary principles into policy than has been widely acknowledged. Box 1 summarizes potential policy contributions of cases reviewed here. 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). Thus, 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 (157–159), but national and international guidelines are needed to avert potentially harmful outcomes (156, 160). Segments of medicine and agriculture include social scientists and economists in systematic risk assessment (76, 161). 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 (162–165). 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 (166). 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 U.S. 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 (167). 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 (167). Despite this benefit, farmer compliance with the refuge strategy for Bt corn in the U.S. has steadily declined and threatens the sustainability of resistance management (168). 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 (161). With pathogen resistance, both the relative fitness of resistant genotypes in untreated environments (171, 172) and the prevalence of resistance in natural environments (173) 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 (161, 174).

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 (175) (Fig. 3). Promoting greater adoption and consistency in the use of evolutionary

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.

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 pesticides/biocides.
- Apply reduced selection response techniques to maintain long-term efficacy of antimicrobials and avert the antibiotics crisis.
- Reconcile individual and group incentives in health systems to reduce virulence and resistance of emerging and re-emerging 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/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 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 pre-adapted or high diversity sources for increased habitat restoration success.
- Avoid collapse and protect genetic diversity of aquatic resources through non-selective 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 potential into green accounting for sustainable governance of the earth system.
- Coordinate strategies of SDG's 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, and additionally adoption of alternatives to strong selection agents such as toxins.

terminology, which is inconsistent across disciplines (176), 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 which share at their core the basic evolutionary principles governing life.

References and Notes

1. Millennium Ecosystem Assessment, *Ecosystems and Human Well-being: Synthesis*. (Island Press, Washington, DC, 2005).
2. E. C. Ellis, J. O. Kaplan, D. Q. Fuller, S. Vavrus, K. Klein Goldewijk, P. H. Verburg, Used planet: A global history. *Proc. Natl. Acad. Sci. U.S.A.* **110**, 7978–7985 (2013). [Medline doi:10.1073/pnas.1217241110](#)
3. R. G. Latta, Conservation genetics as applied evolution: From genetic pattern to evolutionary process. *Evol. Appl.* **1**, 84–94 (2008). [doi:10.1111/j.1752-4571.2007.00008.x](#)
4. S. R. Palumbi, Humans as the world's greatest evolutionary force. *Science* **293**, 1786–1790 (2001). [Medline doi:10.1126/science.293.5536.1786](#)
5. P. D. Gluckman, C. T. Bergstrom, Evolutionary biology within medicine: A perspective of growing value. *BMJ* **343** (dec19 1), d7671 (2011). [Medline doi:10.1136/bmj.d7671](#)
6. F. Gould, Broadening the application of evolutionarily based genetic pest management. *Evolution* **62**, 500–510 (2008). [Medline doi:10.1111/j.1558-5646.2007.00298.x](#)
7. P. H. Thrall, J. G. Oakeshott, G. Fitt, S. Southerton, J. J. Burdon, A. Sheppard, R. J. Russell, M. Zalucki, M. Heino, R. Ford Denison, Evolution in agriculture: The application of evolutionary approaches to the management of biotic interactions in agro-ecosystems. *Evol. Appl.* **4**, 200–215 (2011). [doi:10.1111/j.1752-4571.2010.00179.x](#)
8. R. F. Denison, *Darwinian Agriculture: How Understanding Evolution Can Improve Agriculture* (Princeton Univ. Press, Princeton, NJ, 2012).
9. D. W. Hollomon, Do we have the tools to manage resistance in the future? *Pest Manag. Sci.* **68**, 149–154 (2012). [Medline doi:10.1002/ps.2291](#)
10. C. A. Stockwell, A. P. Hendry, M. K. Kinnison, Contemporary evolution meets conservation biology. *Trends Ecol. Evol.* **18**, 94–101 (2003). [doi:10.1016/S0169-5347\(02\)00044-7](#)
11. A. P. Hendry, L. G. Lohmann, E. Conti, J. Cracraft, K. A. Crandall, D. P. Faith, C. Häuser, C. A. Joly, K. Kogure, A. Larigauderie, S. Magallón, C. Moritz, S. Tillier, R. Zardoya, A. H. Prieur-Richard, B. A. Walther, T. Yahara, M. J. Donoghue, Evolutionary biology in biodiversity science, conservation, and policy: A call to action. *Evolution* **64**, 1517–1528 (2010). [Medline](#)
12. A. P. Hendry, M. T. Kinnison, M. Heino, T. Day, T. B. Smith, G. Fitt, C. T. Bergstrom, J. Oakeshott, P. S. Jørgensen, M. P. Zalucki, G. Gilchrist, S. Southerton, A. Sih, S. Strauss, R. F. Denison, S. P. Carroll, Evolutionary principles and their practical application. *Evol. Appl.* **4**, 159–183 (2011). [doi:10.1111/j.1752-4571.2010.00165.x](#)
13. WHO, Antimicrobial resistance: global report on surveillance (2014); [www.who.int/drugresistance/documents/surveillancereport/en/](#)
14. B. E. Tabashnik, D. Mota-Sanchez, M. E. Whalon, R. M. Hollingworth, Y. Carrière, Defining terms for proactive management of resistance to Bt crops and pesticides. *J. Econ. Entomol.* **107**, 496–507 (2014). [Medline doi:10.1603/EC13458](#)
15. P. D. Gluckman, M. A. Hanson, *Mismatch: Why Our World No Longer Fits Our Bodies* (Oxford Univ. Press, Oxford, 2006).
16. A. D. Barnosky, N. Matzke, S. Tomiya, G. O. Wogan, B. Swartz, T. B. Quental, C. Marshall, J. L. McGuire, E. L. Lindsey, K. C. Maguire, B. Mersey, E. A. Ferrer, Has the Earth's sixth mass extinction already arrived? *Nature* **471**, 51–57 (2011). [Medline doi:10.1038/nature09678](#)
17. J. J. Bull, H. A. Wichman, Applied evolution. *Annu. Rev. Ecol. Syst.* **32**, 183–217 (2001). [doi:10.1146/annurev.ecolsys.32.081501.114020](#)
18. S. P. Carroll, C. W. Fox, *Conservation Biology: Evolution in Action* (Oxford Univ. Press, Oxford, 2008).
19. P. D. Gluckman, M. A. Hanson, T. Buklijas, F. M. Low, A. S. Beedle, Epigenetic mechanisms that underpin metabolic and cardiovascular diseases. *Nat. Rev. Endocrinol.* **5**, 401–408 (2009). [Medline doi:10.1038/nrendo.2009.102](#)
20. D. Hartl, *A Primer of Population Genetics* (Sinauer Associates, Inc., Sunderland, MA, 1988).
21. P. A. Abrams, Modelling the adaptive dynamics of traits involved in inter- and intraspecific interactions: An assessment of three methods. *Ecol. Lett.* **4**, 166–175 (2001). [doi:10.1046/j.1461-0248.2001.00199.x](#)
22. C. K. Ghalambor, J. K. McKay, S. P. Carroll, D. N. Reznick, Adaptive versus non-adaptive phenotypic plasticity and the potential for contemporary adaptation in new environments. *Funct. Ecol.* **21**, 394–407 (2007). [doi:10.1111/j.1365-2435.2007.01283.x](#)
23. M. T. Kinnison, N. G. Hairston, Eco-evolutionary conservation biology: Contemporary evolution and the dynamics of persistence. *Funct. Ecol.* **21**, 444–454 (2007). [doi:10.1111/j.1365-2435.2007.01278.x](#)
24. C. A. Aktipis, V. S. Kwan, K. A. Johnson, S. L. Neuberg, C. C. Maley, Overlooking evolution: A systematic analysis of cancer relapse and therapeutic resistance research. *PLOS ONE* **6**, e26100 (2011). [Medline doi:10.1371/journal.pone.0026100](#)
25. N. Mouquet, V. Devictor, C. N. Meynard, F. Munoz, L. F. Bersier, J. Chave, P. Couteron, A. Dalecky, C. Fontaine, D. Gravel, O. J. Hardy, F. Jabot, S. Laverigne, M. Leibold, D. Mouillot, T. Münkemüller, S. Pavoine, A. Prinzing, A. S. Rodrigues, R. P. Rohr, E. Thébaud, W. Thuiller, Ecophylogenetics: Advances and perspectives. *Biol. Rev. Camb. Philos. Soc.* **87**, 769–785 (2012). [Medline doi:10.1111/j.1469-185X.2012.00224.x](#)
26. G. M. Mace, A. Purvis, Evolutionary biology and practical conservation: Bridging a widening gap. *Mol. Ecol.* **17**, 9–19 (2008). [Medline doi:10.1111/j.1365-294X.2007.03455.x](#)
27. L.-M. Chevin, R. Gallet, R. Gomulkiewicz, R. D. Holt, S. Fellous, Phenotypic plasticity in evolutionary rescue experiments. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **368**, 20120089 (2013). [Medline doi:10.1098/rstb.2012.0089](#)
28. A. F. Read, S. Huijben, Evolutionary biology and the avoidance of antimicrobial resistance. *Evol. Appl.* **2**, 40–51 (2009). [doi:10.1111/j.1752-4571.2008.00066.x](#)
29. A. F. Read, T. Day, S. Huijben, The evolution of drug resistance and the curious orthodoxy of aggressive chemotherapy. *Proc. Natl. Acad. Sci. U.S.A.* **108** (suppl. 2), 10871–10877 (2011). [Medline doi:10.1073/pnas.1100299108](#)
30. M. V. Ashley, M. F. Willson, O. R. W. Pergams, D. J. O'Dowd, S. M. Gende, J. S. Brown, Evolutionarily enlightened management. *Biol. Conserv.* **111**, 115–123 (2003). [doi:10.1016/S0006-3207\(02\)00279-3](#)
31. S. E. Williams, E. A. Hoffman, Minimizing genetic adaptation in captive breeding programs: A review. *Biol. Conserv.* **142**, 2388–2400 (2009). [doi:10.1016/j.biocon.2009.05.034](#)
32. K. Leus, K. Traylor-Holzer, R. C. Lacy, Genetic and demographic population management in zoos and aquariums: Recent developments, future challenges and opportunities for scientific research. *Int. Zoo Yearb.* **45**, 213–225 (2011). [doi:10.1111/j.1748-1090.2011.00138.x](#)
33. P. D. Gluckman, F. M. Low, T. Buklijas, M. Hanson, A. S. Beedle, How evolutionary principles improve the understanding of human health and disease. *Evol. Appl.* **4**, 249–263 (2011). [doi:10.1111/j.1752-4571.2010.00164.x](#)
34. L. Cordain, S. B. Eaton, A. Sebastian, N. Mann, S. Lindeberg, B. A. Watkins, J. H. O'Keefe, J. Brand-Miller, Origins and evolution of the Western diet: Health implications for the 21st century. *Am. J. Clin. Nutr.* **81**, 341–354 (2005). [Medline](#)
35. R. C. Brownson, D. Haire-Joshu, D. A. Luke, Shaping the context of health: A review of environmental and policy approaches in the prevention of chronic diseases. *Annu. Rev. Public Health* **27**, 341–370 (2006). [Medline doi:10.1146/annurev.publhealth.27.021405.102137](#)
36. T. A. Gaziano, N. Pagidipati, Scaling up chronic disease prevention interventions in lower- and middle-income countries. *Annu. Rev. Public Health* **34**, 317–335 (2013). [Medline doi:10.1146/annurev-publhealth-](#)

- 031912-114402
37. C. D. Mathers, D. Loncar, Projections of global mortality and burden of disease from 2002 to 2030. *PLOS Med.* **3**, e442 (2006). [Medline doi:10.1371/journal.pmed.0030442](#)
 38. D. E. Bloom *et al.*, "The global economic burden of noncommunicable diseases" (Working paper no. 87, Program on the Global Demography of Aging, Harvard School of Public Health; World Economic Forum, Geneva, 2012).
 39. J. Woodcock, O. H. Franco, N. Orsini, I. Roberts, Non-vigorous physical activity and all-cause mortality: Systematic review and meta-analysis of cohort studies. *Int. J. Epidemiol.* **40**, 121–138 (2011). [Medline doi:10.1093/ije/dyq104](#)
 40. WHO, Environmental and occupational cancers. www.who.int/mediacentre/factsheets/fs350/en/.
 41. J. Lynch, G. D. Smith, A life course approach to chronic disease epidemiology. *Annu. Rev. Public Health* **26**, 1–35 (2005). [Medline doi:10.1146/annurev.publhealth.26.021304.144505](#)
 42. D. A. Chokshi, T. A. Farley, The cost-effectiveness of environmental approaches to disease prevention. *N. Engl. J. Med.* **367**, 295–297 (2012). [Medline doi:10.1056/NEJMp1206268](#)
 43. T. Rolph *et al.*, Loss-of-function mutations in SLC30A8 protect against type 2 diabetes. *Nat. Genet.* 2 March 2014.
 44. G. S. Omenn, Evolution in health and medicine Sackler colloquium: Evolution and public health. *Proc. Natl. Acad. Sci. U.S.A.* **107** (suppl. 1), 1702–1709 (2010). [Medline doi:10.1073/pnas.0906198106](#)
 45. J. C. Denny, L. Bastarache, M. D. Ritchie, R. J. Carroll, R. Zink, J. D. Mosley, J. R. Field, J. M. Pulley, A. H. Ramirez, E. Bowton, M. A. Basford, D. S. Carrell, P. L. Peissig, A. N. Kho, J. A. Pacheco, L. V. Rasmussen, D. R. Crosslin, P. K. Crane, J. Pathak, S. J. Bielinski, S. A. Pendergrass, H. Xu, L. A. Hindorf, R. Li, T. A. Manolio, C. G. Chute, R. L. Chisholm, E. B. Larson, G. P. Jarvik, M. H. Brilliant, C. A. McCarty, I. J. Kullo, J. L. Haines, D. C. Crawford, D. R. Masys, D. M. Roden, Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data. *Nat. Biotechnol.* **31**, 1102–1111 (2013). [Medline doi:10.1038/nbt.2749](#)
 46. M. Travisano, R. G. Shaw, Lost in the map. *Evolution* **67**, 305–314 (2013). [Medline doi:10.1111/j.1558-5646.2012.01802.x](#)
 47. S. M. Rappaport, Implications of the exposome for exposure science. *J. Expo. Sci. Environ. Epidemiol.* **21**, 5–9 (2011). [Medline doi:10.1038/jes.2010.50](#)
 48. H. C. J. Godfray, J. R. Beddington, I. R. Crute, L. Haddad, D. Lawrence, J. F. Muir, J. Pretty, S. Robinson, S. M. Thomas, C. Toulmin, Food security: The challenge of feeding 9 billion people. *Science* **327**, 812–818 (2010). [Medline doi:10.1126/science.1185383](#)
 49. C. James, "Executive summary. Global status of commercialized biotech/GM crops" (ISAAA Brief 46, International Service for the Acquisitions of Agri-Biotech Applications, New York, 2013).
 50. M. Ashraf, Inducing drought tolerance in plants: Recent advances. *Biotechnol. Adv.* **28**, 169–183 (2010). [Medline doi:10.1016/j.biotechadv.2009.11.005](#)
 51. E. Pauwels, Public understanding of synthetic biology. *BioScience* **63**, 79–89 (2013). [doi:10.1525/bio.2013.63.2.4](#)
 52. P. Aerni, Resistance to agricultural biotechnology: The importance of distinguishing between weak and strong public attitudes. *Biotechnol. J.* **8**, 1129–1132 (2013). [Medline doi:10.1007/s13593-013-0138-9](#)
 53. S.-E. Jacobsen, M. Sørensen, S. M. Pedersen, J. Weiner, Feeding the world: Genetically modified crops versus agricultural biodiversity. *Agron. Sustain. Dev.* **33**, 651–662 (2013). [doi:10.1007/s13593-013-0138-9](#)
 54. R. K. Varshney, K. C. Bansal, P. K. Aggarwal, S. K. Datta, P. Q. Craufurd, Agricultural biotechnology for crop improvement in a variable climate: Hope or hype? *Trends Plant Sci.* **16**, 363–371 (2011). [Medline doi:10.1016/j.tplants.2011.03.004](#)
 55. A. Marshall, Drought-tolerant varieties begin global march. *Nat. Biotechnol.* **32**, 308–308 (2014). [doi:10.1038/nbt.2875](#)
 56. R. K. Varshney, J. M. Ribaut, E. S. Buckler, R. Tuberosa, J. A. Rafalski, P. Langridge, Can genomics boost productivity of orphan crops? *Nat. Biotechnol.* **30**, 1172–1176 (2012). [Medline doi:10.1038/nbt.2440](#)
 57. S. Yang, B. Vanderbeld, J. Wan, Y. Huang, Narrowing down the targets: Towards successful genetic engineering of drought-tolerant crops. *Mol. Plant* **3**, 469–490 (2010). [Medline doi:10.1093/mp/ssq016](#)
 58. A. C. M. Gaudin, A. Henry, A. H. Sparks, I. H. Slamet-Loedin, Taking transgenic rice drought screening to the field. *J. Exp. Bot.* **64**, 109–117 (2013). [Medline doi:10.1093/jxb/ers313](#)
 59. International Service for the Acquisition of Agric. -Biotech Applications, Approval Database 2013, <http://www.isaaa.org/gmaprovaldatabase/default.asp> (2013).
 60. K. L. Mercer, H. R. Perales, J. D. Wainwright, Climate change and the transgenic adaptation strategy: Smallholder livelihoods, climate justice, and maize landraces in Mexico. *Glob. Environ. Change* **22**, 495–504 (2012). [doi:10.1016/j.gloenvcha.2012.01.003](#)
 61. M. Tachibana, P. Amato, M. Sparman, J. Woodward, D. M. Sanchis, H. Ma, N. M. Gutierrez, R. Tippner-Hedges, E. Kang, H. S. Lee, C. Ramsey, K. Masterson, D. Battaglia, D. Lee, D. Wu, J. Jensen, P. Patton, S. Gokhale, R. Stouffer, S. Mitalipov, Towards germline gene therapy of inherited mitochondrial diseases. *Nature* **493**, 627–631 (2013). [Medline doi:10.1038/nature11647](#)
 62. J. H. Kordower, D. Kirik, Introduction: Gene therapy has gone from a pipe dream to clinical reality. *Neurobiol. Dis.* **48**, 151–152 (2012). [Medline doi:10.1016/j.nbd.2012.07.014](#)
 63. I.-K. Choi, C.-O. Yun, Recent developments in oncolytic adenovirus-based immunotherapeutic agents for use against metastatic cancers. *Cancer Gene Ther.* **20**, 70–76 (2013). [Medline doi:10.1038/cgt.2012.95](#)
 64. D. M. Lipinski, M. Thake, R. E. MacLaren, Clinical applications of retinal gene therapy. *Prog. Retin. Eye Res.* **32**, 22–47 (2013). [Medline doi:10.1016/j.preteyeres.2012.09.001](#)
 65. K. J. Wert, R. J. Davis, J. Sancho-Pellus, P. M. Nishina, S. H. Tsang, Gene therapy provides long-term visual function in a pre-clinical model of retinitis pigmentosa. *Hum. Mol. Genet.* **22**, 558–567 (2013). [Medline doi:10.1093/hmg/ddt466](#)
 66. K. Suzuki, H. Matsubara, Recent advances in p53 research and cancer treatment. *J. Biomed. Biotechnol.* **2011**, 1 (2011). [Medline doi:10.1155/2011/978312](#)
 67. O. Kilpivaara, L. A. Aaltonen, Diagnostic cancer genome sequencing and the contribution of germline variants. *Science* **339**, 1559–1562 (2013). [Medline doi:10.1126/science.1233899](#)
 68. P. R. Lowenstein, M. G. Castro, Why do Most Phase III Clinical Trials Fail, Uncertainty in the translation of preclinical experiments to clinical trials. Why do most phase III clinical trials fail? *Curr. Gene Ther.* **9**, 368–374 (2009). [Medline doi:10.2174/156652309789753392](#)
 69. M. Edelstein, M. Gene Therapy Clinical Trials Worldwide. *J. Gene Medicine* database at <http://www.abedia.com/wiley/index.html> (2014). (accessed April 13 2014)
 70. C. C. Vigueira, K. M. Olsen, A. L. Caicedo, The red queen in the corn: Agricultural weeds as models of rapid adaptive evolution. *Heredity* **110**, 303–311 (2013). [Medline doi:10.1038/hdy.2012.104](#)
 71. S. E. Greene, A. Reid, *Moving Targets: Fighting the Evolution of Resistance in Infections, Pests, and Cancer* (American Society of Microbiology, Washington, DC, 2013); <http://bit.ly/YeNhoS>.
 72. S. B. Powles, Q. Yu, Evolution in action: Plants resistant to herbicides. *Annu. Rev. Plant Biol.* **61**, 317–347 (2010). [Medline doi:10.1146/annurev-arplant-042809-112119](#)
 73. I. Heap, The International Survey of Herbicide Resistant Weeds (2013); www.weedscience.com/summary/home.aspx.
 74. B. E. Tabashnik, Evolution of resistance to *Bacillus thuringiensis*. *Annu. Rev. Entomol.* **39**, 47–79 (1994). [doi:10.1146/annurev.en.39.010194.000403](#)
 75. F. Gould, Sustainability of transgenic insecticidal cultivars: Integrating pest genetics and ecology. *Annu. Rev. Entomol.* **43**, 701–726 (1998). [Medline doi:10.1146/annurev.ento.43.1.701](#)
 76. US Environmental Protection Agency, The Environmental Protection Agency's White Paper on Bt Plant-pesticide Resistance Management (EPA, Washington, DC, 1998).
 77. B. E. Tabashnik, T. Brévault, Y. Carrière, Insect resistance to Bt crops: Lessons from the first billion acres. *Nat. Biotechnol.* **31**, 510–521 (2013). [Medline doi:10.1038/nbt.2597](#)
 78. B. E. Tabashnik, A. J. Gassmann, D. W. Crowder, Y. Carrière, Insect resistance to Bt crops: Evidence versus theory. *Nat. Biotechnol.* **26**, 199–202 (2008). [Medline doi:10.1038/nbt1382](#)
 79. E. S. Dunlop, M. L. Baskett, M. Heino, U. Dieckmann, The propensity of marine reserves to reduce the evolutionary effects of fishing in a migratory species. *Evol. Appl.* **2**, 371–393 (2009). [doi:10.1111/j.1752-](#)

- [4571.2009.00089.x](#)
80. R. A. Gatenby, J. Brown, T. Vincent, Lessons from applied ecology: Cancer control using an evolutionary double bind. *Cancer Res.* **69**, 7499–7502 (2009). [Medline doi:10.1158/0008-5472.CAN-09-1354](#)
 81. A. S. Silva, R. A. Gatenby, A theoretical quantitative model for evolution of cancer chemotherapy resistance. *Biol. Direct* **5**, 25 (2010). [Medline doi:10.1186/1745-6150-5-25](#)
 82. R. J. Gillies, D. Verduzco, R. A. Gatenby, Evolutionary dynamics of carcinogenesis and why targeted therapy does not work. *Nat. Rev. Cancer* **12**, 487–493 (2012). [Medline doi:10.1038/nrc3298](#)
 83. M. Greaves, C. C. Maley, Clonal evolution in cancer. *Nature* **481**, 306–313 (2012). [Medline doi:10.1038/nature10762](#)
 84. D. B. Longley, P. G. Johnston, Molecular mechanisms of drug resistance. *J. Pathol.* **205**, 275–292 (2005). [Medline doi:10.1002/path.1706](#)
 85. R. A. Gatenby, A change of strategy in the war on cancer. *Nature* **459**, 508–509 (2009). [Medline doi:10.1038/459508a](#)
 86. V. Almendro, Y. K. Cheng, A. Randles, S. Itzkovitz, A. Marusyk, E. Ametller, X. Gonzalez-Farre, M. Muñoz, H. G. Russnes, A. Helland, I. H. Rye, A. L. Borresen-Dale, R. Maruyama, A. van Oudenaarden, M. Dowsett, R. L. Jones, J. Reis-Filho, P. Gascon, M. Gönen, F. Michor, K. Polyak, Inference of tumor evolution during chemotherapy by computational modeling and in situ analysis of genetic and phenotypic cellular diversity. *Cell Reports* **6**, 514–527 (2014). [Medline doi:10.1016/j.celrep.2013.12.041](#)
 87. J.-B. Michel, P. J. Yeh, R. Chait, R. C. Moellerling Jr., R. Kishony, Drug interactions modulate the potential for evolution of resistance. *Proc. Natl. Acad. Sci. U.S.A.* **105**, 14918–14923 (2008). [Medline doi:10.1073/pnas.0800944105](#)
 88. REX Consortium, Heterogeneity of selection and the evolution of resistance. *Trends Ecol. Evol.* **28**, 110–118 (2013). [Medline doi:10.1016/j.tree.2012.09.001](#)
 89. J. J. Cunningham, R. A. Gatenby, J. S. Brown, Evolutionary dynamics in cancer therapy. *Mol. Pharm.* **8**, 2094–2100 (2011). [Medline doi:10.1021/mp2002279](#)
 90. R. M. Gulick, Antiretroviral treatment 2010: Progress and controversies. *J. Acquir. Immune Defic. Syndr.* **55** (suppl. 1), S43–S48 (2010). [Medline doi:10.1097/QAI.0b013e3181f9c09e](#)
 91. R. K. Gupta, D. A. Van de Vijver, S. Manicklal, M. A. Wainberg, Evolving uses of oral reverse transcriptase inhibitors in the HIV-1 epidemic: From treatment to prevention. *Retrovirology* **10**, 82 (2013). [Medline doi:10.1186/1742-4690-10-82](#)
 92. H. Brun, A. M. Chèvre, B. D. Fitt, S. Powers, A. L. Besnard, M. Ermel, V. Huteau, B. Marquer, F. Eber, M. Renard, D. Andrivon, Quantitative resistance increases the durability of qualitative resistance to *Leptosphaeria maculans* in *Brassica napus*. *New Phytol.* **185**, 285–299 (2010). [Medline doi:10.1111/j.1469-8137.2009.03049.x](#)
 93. B. E. Tabashnik, Managing resistance with multiple pesticide tactics: Theory, evidence, and recommendations. *J. Econ. Entomol.* **82**, 1263–1269 (1989). [Medline](#)
 94. C. T. Bergstrom, M. Lo, M. Lipsitch, Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals. *Proc. Natl. Acad. Sci. U.S.A.* **101**, 13285–13290 (2004). [Medline doi:10.1073/pnas.0402298101](#)
 95. J. P. Torella, R. Chait, R. Kishony, Optimal drug synergy in antimicrobial treatments. *PLOS Comput. Biol.* **6**, e1000796 (2010). [Medline doi:10.1371/journal.pcbi.1000796](#)
 96. B. Jacquemin, J. Gasquez, X. Reboud, Modelling binary mixtures of herbicides in populations resistant to one of the components: Evaluation for resistance management. *Pest Manag. Sci.* **65**, 113–121 (2009). [Medline doi:10.1002/ps.1647](#)
 97. R. T. Roush, Two-toxin strategies for management of insecticidal transgenic crops: Can pyramiding succeed where pesticide mixtures have not? *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **353**, 1777–1786 (1998). [doi:10.1098/rstb.1998.0330](#)
 98. J.-Z. Zhao, J. Cao, H. L. Collins, S. L. Bates, R. T. Roush, E. D. Earle, A. M. Shelton, Concurrent use of transgenic plants expressing a single and two *Bacillus thuringiensis* genes speeds insect adaptation to pyramided plants. *Proc. Natl. Acad. Sci. U.S.A.* **102**, 8426–8430 (2005). [Medline doi:10.1073/pnas.0409324102](#)
 99. A. M. Shelton *et al.*, Resistance to insect pathogens and strategies to manage resistance: an update. in *Field Manual of Techniques in Invertebrate Pathology* (Springer Amsterdam, 2007).
 100. J. H. Pedlar *et al.*, Placing forestry in the assisted migration debate. *Bioscience* **62**, 835–842 (2012). [doi:10.1525/bio.2012.62.9.10](#)
 101. L. K. Gray, T. Gylander, M. S. Mbogga, P.-Y. Chen, A. Hamann, Assisted migration to address climate change: Recommendations for aspen reforestation in western Canada. *Ecol. Appl.* **21**, 1591–1603 (2011). [Medline doi:10.1890/10-1054.1](#)
 102. K. M. Potter, W. W. Hargrove, Determining suitable locations for seed transfer under climate change: A global quantitative method. *New For.* **43**, 581–599 (2012). [doi:10.1007/s11056-012-9322-z](#)
 103. S. Godefroid, C. Piazza, G. Rossi, S. Buord, A.-D. Stevens, R. Aguraiuja, C. Cowell, C. W. Weekley, G. Vogt, J. M. Iriando, I. Johnson, B. Dixon, D. Gordon, S. Magnanon, B. Valentin, K. Bjureke, R. Koopman, M. Vicens, M. Virevaire, T. Vanderborght, How successful are plant species reintroductions? *Biol. Conserv.* **144**, 672–682 (2011). [doi:10.1016/j.biocon.2010.10.003](#)
 104. L. M. Broadhurst *et al.*, Seed supply for broadscale restoration: Maximizing evolutionary potential. *Evol. Appl.* **1**, 587–597 (2008).
 105. A. R. Weeks, C. M. Sgro, A. G. Young, R. Frankham, N. J. Mitchell, K. A. Miller, M. Byrne, D. J. Coates, M. D. Eldridge, P. Sunnucks, M. F. Breed, E. A. James, A. A. Hoffmann, Assessing the benefits and risks of translocations in changing environments: A genetic perspective. *Evol. Appl.* **4**, 709–725 (2011). [Medline doi:10.1111/j.1752-4571.2011.00192.x](#)
 106. M. Byrne, L. Stone, M. A. Millar, Assessing genetic risk in revegetation. *J. Appl. Ecol.* **48**, 1365–1373 (2011). [doi:10.1111/j.1365-2664.2011.02045.x](#)
 107. K. Vander Mijnsbrugge, A. Bischoff, B. Smith, A question of origin: Where and how to collect seed for ecological restoration. *Basic Appl. Ecol.* **11**, 300–311 (2010). [doi:10.1016/j.baec.2009.09.002](#)
 108. S. Godefroid, T. Vanderborght, Plant reintroductions: The need for a global database. *Biodivers. Conserv.* **20**, 3683–3688 (2011). [doi:10.1007/s10531-011-0120-2](#)
 109. D. J. Merritt, K. W. Dixon, Conservation. Restoration seed banks—a matter of scale. *Science* **332**, 424–425 (2011). [Medline doi:10.1126/science.1203083](#)
 110. AdapTree website: <http://adaptree.sites.olt.ubc.ca/>.
 111. J. A. Hicke, J. C. Jenkins, Mapping lodgepole pine stand structure susceptibility to mountain pine beetle attack across the western United States. *For. Ecol. Manage.* **255**, 1536–1547 (2008). [doi:10.1016/j.foreco.2007.11.027](#)
 112. C. Moritz, Conservation units and translocations: Strategies for conserving evolutionary processes. *Hereditas* **130**, 217–228 (1999). [doi:10.1111/j.1601-5223.1999.00217.x](#)
 113. C. M. Donald, The breeding of crop ideotypes. *Euphytica* **17**, 385–403 (1968). [doi:10.1007/BF00056241](#)
 114. A. Gardner, A. Grafen, Capturing the superorganism: A formal theory of group adaptation. *J. Evol. Biol.* **22**, 659–671 (2009). [Medline doi:10.1111/j.1420-9101.2008.01681.x](#)
 115. A. Kumar, N. C. Turner, D. P. Singh, P. Singh, M. Barr, Diurnal and seasonal patterns of water potential, photosynthesis, evapotranspiration and water use efficiency of clusterbean. *Photosynthetica* **37**, 601–607 (2000). [doi:10.1023/A:1007127726207](#)
 116. P. R. Jennings, Plant type as a rice breeding objective. *Crop Sci.* **4**, 13–15 (1964). [doi:10.2135/cropsci1964.0011183X000400010005x](#)
 117. W. G. Duncan, W. A. Williams, R. S. Loomis, Tassels and productivity of maize. *Crop Sci.* **7**, 37–39 (1967). [doi:10.2135/cropsci1967.0011183X000700010013x](#)
 118. D. N. Duveck, K. G. Cassman, Post-green-revolution trends in yield potential of temperate maize in the north-central United States. *Crop Sci.* **39**, 1622–1630 (1999). [doi:10.2135/cropsci1999.3961622x](#)
 119. J. Weiner, S. B. Andersen, W. K. M. Wille, H. W. Griepentrog, J. M. Olsen, Evolutionary Agroecology: The potential for cooperative, high density, weed-suppressing cereals. *Evol. Appl.* **3**, 473–479 (2010). [doi:10.1111/j.1752-4571.2010.00144.x](#)
 120. M. J. Wade, P. Bijma, E. D. Ellen, W. Muir, Group selection and social evolution in domesticated animals. *Evol. Appl.* **3**, 453–465 (2010). [doi:10.1111/j.1752-4571.2010.00147.x](#)
 121. J. Liu, T. Dietz, S. R. Carpenter, C. Folke, M. Alberti, C. L. Redman, S. H. Schneider, E. Ostrom, A. N. Pell, J. Lubchenco, W. W. Taylor, Z. Ouyang, P. Deadman, T. Kratz, W. Provencher, Coupled human and natural systems. *Ambio* **36**, 639–649 (2007). [Medline doi:10.1579/0044-7447\(2007\)36\[639:CHANS\]2.0.CO;2](#)

122. P. Rabinowitz, L. Conti, Links among human health, animal health, and ecosystem health. *Annu. Rev. Public Health* **34**, 189–204 (2013). [Medline doi:10.1146/annurev-publhealth-031912-114426](#)
123. M. E. J. Woolhouse, S. Gowtage-Sequeria, Host range and emerging and reemerging pathogens. *Emerg. Infect. Dis.* **11**, 1842–1847 (2005). [Medline doi:10.3201/eid1112.050997](#)
124. B. Olsen, V. J. Munster, A. Wallensten, J. Waldenström, A. D. Osterhaus, R. A. Fouchier, Global patterns of influenza A virus in wild birds. *Science* **312**, 384–388 (2006). [Medline doi:10.1126/science.1122438](#)
125. G. J. D. Smith, D. Vijaykrishna, J. Bahl, S. J. Lycett, M. Worobey, O. G. Pybus, S. K. Ma, C. L. Cheung, J. Raghvani, S. Bhatt, J. S. Peiris, Y. Guan, A. Rambaut, Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. *Nature* **459**, 1122–1125 (2009). [Medline doi:10.1038/nature08182](#)
126. K. E. Jones, N. G. Patel, M. A. Levy, A. Storeygard, D. Balk, J. L. Gittleman, P. Daszak, Global trends in emerging infectious diseases. *Nature* **451**, 990–993 (2008). [Medline doi:10.1038/nature06536](#)
127. W. Ma, R. E. Kahn, J. A. Richt, The pig as a mixing vessel for influenza viruses: Human and veterinary implications. *J. Molec. Genet. Med.* **3**, 158–166 (2008). [Medline](#)
128. H. M. Yassine, C. W. Lee, Y. M. Saif, Interspecies transmission of influenza A viruses between swine and poultry. *Curr. Top. Microbiol. Immunol.* **370**, 227–240 (2013). [Medline doi:10.1007/82_2011_180](#)
129. S. Altizer, R. Bartel, B. A. Han, Animal migration and infectious disease risk. *Science* **331**, 296–302 (2011). [Medline doi:10.1126/science.1194694](#)
130. K. R. Ríos-Soto, B. Song, C. Castillo-Chavez, Epidemic spread of influenza viruses: The impact of transient populations on disease dynamics. *Math. Biosci. Eng.* **8**, 199–222 (2011). [Medline doi:10.3934/mbe.2011.8.199](#)
131. K. M. Pepin, S. Lass, J. R. Pulliam, A. F. Read, J. O. Lloyd-Smith, Identifying genetic markers of adaptation for surveillance of viral host jumps. *Nat. Rev. Microbiol.* **8**, 802–813 (2010). [Medline doi:10.1038/nrmicro2440](#)
132. European Center for Disease Prevention and Control and European Medicines Agency, *The Bacterial Challenge: Time to React* (ECDC/EMA Joint Technical Report, EMEA/576176/2009, Stockholm, 2009).
133. Alliance for the Prudent Use of Antibiotics, *The Cost of Antibiotic Resistance to US Families and the Healthcare System* (APUA, Boston, MA, 2010).
134. M. A. Cooper, D. Shlaes, Fix the antibiotics pipeline. *Nature* **472**, 32–32 (2011). [Medline doi:10.1038/472032a](#)
135. M. S. Butler, M. A. Blaskovich, M. A. Cooper, Antibiotics in the clinical pipeline in 2013. *J. Antibiot. (Tokyo)* **66**, 571–591 (2013). [Medline doi:10.1038/ja.2013.86](#)
136. A. M. Bal, I. M. Gould, Antibiotic stewardship: Overcoming implementation barriers. *Curr. Opin. Infect. Dis.* **24**, 357–362 (2011). [Medline doi:10.1097/QCO.0b013e3283483262](#)
137. C. MacDougall, R. E. Polk, Antimicrobial stewardship programs in health care systems. *Clin. Microbiol. Rev.* **18**, 638–656 (2005). [Medline doi:10.1128/CMR.18.4.638-656.2005](#)
138. US Food and Drug Administration, 2009 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals (FDA, Washington, DC, 2010).
139. E. K. Silbergeld, J. Graham, L. B. Price, Industrial food animal production, antimicrobial resistance, and human health. *Annu. Rev. Public Health* **29**, 151–169 (2008). [Medline doi:10.1146/annurev.publhealth.29.020907.090904](#)
140. M. E. J. Woolhouse, M. J. W. Ward, Microbiology. Sources of antimicrobial resistance. *Science* **341**, 1460–1461 (2013). [doi:10.1126/science.1243444](#) [Medline doi:10.1126/science.1243444](#)
141. A. R. Manges, J. R. Johnson, Food-borne origins of *Escherichia coli* causing extraintestinal infections. *Clin. Infect. Dis.* **55**, 712–719 (2012). [Medline doi:10.1093/cid/cis502](#)
142. J. L. Martinez, J. Olivares, in *Antimicrobial Resistance in the Environment*, P. L. Keen, M. H. M. Montforts, (Wiley-Blackwell, 2011), chap. 9 pp. 157–172.
143. Transatlantic Taskforce on Antimicrobial Resistance, *Recommendations for future collaboration between the US and EU* (TATFAR Report, 2011); http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/TATFAR/Documents/210911_TATFAR_Report.pdf.
144. European Commission, Communication from the Commission to the European Parliament and the Council: Action plan against the rising threats from Antimicrobial Resistance, COM 748 (2011); http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf.
145. FDA, New animal drugs; cephalosporin drugs; extralabel animal drug use; order of prohibition. *Fed. Regist.* **77**, 735 (2012); <http://federalregister.gov/a/2012-35>.
146. S. P. Carroll, M. T. Kinnison, L. Bernatchez, In light of evolution: Interdisciplinary challenges in food, health, and the environment. *Evol. Appl.* **4**, 155–158 (2011). [doi:10.1111/j.1752-4571.2011.00182.x](#)
147. D. Griggs, M. Stafford-Smith, O. Gaffney, J. Rockström, M. C. Ohman, P. Shyamsundar, W. Steffen, G. Glaser, N. Kanie, I. Noble, Policy: Sustainable development goals for people and planet. *Nature* **495**, 305–307 (2013). [Medline doi:10.1038/495305a](#)
148. Convention of Biological Diversity, Aichi Biodiversity Targets, Strategic Plan for Biodiversity 2011–2020, (2010); www.cbd.int/sp/targets/.
149. C. Jørgensen, K. Enberg, E. S. Dunlop, R. Arlinghaus, D. S. Boukal, K. Brander, B. Ernande, A. Gardmark, F. Johnston, S. Matsumura, H. Pardoe, K. Raab, A. Silva, A. Vainikka, U. Dieckmann, M. Heino, A. D. Rijnsdorp, Ecology: Managing evolving fish stocks. *Science* **318**, 1247–1248 (2007). [Medline doi:10.1126/science.1148089](#)
150. A. T. Laugen *et al.*, Evolutionary impact assessment: Accounting for evolutionary consequences of fishing in an ecosystem approach to fisheries management. *Fish Fish.* **15**, 1–32 (2012).
151. M. L. Baskett, R. S. Waples, Evaluating alternative strategies for minimizing unintended fitness consequences of cultured individuals on wild populations. *Conserv. Biol.* **27**, 83–94 (2013). [Medline doi:10.1111/j.1523-1739.2012.01949.x](#)
152. Convention on Biological Diversity, The Nagoya Protocol on Access and Benefit-Sharing, (2013); www.cbd.int/abs/.
153. L. Santamaría, P. F. Méndez, Evolution in biodiversity policy - current gaps and future needs. *Evol. Appl.* **5**, 202–218 (2012). [doi:10.1111/j.1752-4571.2011.00229.x](#)
154. E. W. Welch, Potential implications of the Nagoya Protocol for the livestock sector. *J. Anim. Breed. Genet.* **129**, 423–424 (2012). [Medline](#)
155. J. A. Jackson, L. Laikre, C. S. Baker, K. C. Kendall, Guidelines for collecting and maintaining archives for genetic monitoring. *Conserv. Genet. Resour.* **4**, 527–536 (2011). [doi:10.1007/s12686-011-9545-x](#)
156. G. V. Dana, T. Kuiken, D. Rejeski, A. A. Snow, Synthetic biology: Four steps to avoid a synthetic-biology disaster. *Nature* **483**, 29–29 (2012). [Medline doi:10.1038/483029a](#)
157. A. A. Snow, V. H. Smith, Genetically engineered algae for biofuels: A key role for ecologists. *Bioscience* **62**, 765–768 (2012). [doi:10.1525/bio.2012.62.8.9](#)
158. P. Mali, L. Yang, K. M. Esvelt, J. Aach, M. Guell, J. E. DiCarlo, J. E. Norville, G. M. Church, RNA-guided human genome engineering via Cas9. *Science* **339**, 823–826 (2013). [Medline doi:10.1126/science.1232033](#)
159. M. A. Thomas, G. W. Roemer, C. J. Donlan, B. G. Dickson, M. Matocq, J. Malaney, Ecology: Gene tweaking for conservation. *Nature* **501**, 485–486 (2013). [Medline doi:10.1038/501485a](#)
160. K. H. Redford, W. Adams, G. M. Mace, Synthetic biology and conservation of nature: Wicked problems and wicked solutions. *PLOS Biol.* **11**, e1001530 (2013). [Medline doi:10.1371/journal.pbio.1001530](#)
161. B. M. Althouse, T. C. Bergstrom, C. T. Bergstrom, Evolution in health and medicine Sackler colloquium: A public choice framework for controlling transmissible and evolving diseases. *Proc. Natl. Acad. Sci. U.S.A.* **107** (suppl. 1), 1696–1701 (2010). [Medline doi:10.1073/pnas.0906078107](#)
162. J. Liu, T. Dietz, S. R. Carpenter, M. Alberti, C. Folke, E. Moran, A. N. Pell, P. Deadman, T. Kratz, J. Lubchenco, E. Ostrom, Z. Ouyang, W. Provencher, C. L. Redman, S. H. Schneider, W. W. Taylor, Complexity of coupled human and natural systems. *Science* **317**, 1513–1516 (2007). [Medline doi:10.1126/science.1144004](#)
163. E. Ostrom, A general framework for analyzing sustainability of social-ecological systems. *Science* **325**, 419–422 (2009). [Medline doi:10.1126/science.1172133](#)
164. E. Ostrom, A diagnostic approach for going beyond panaceas. *Proc. Natl. Acad. Sci. U.S.A.* **104**, 15181–15187 (2007). [Medline doi:10.1073/pnas.0702288104](#)
165. G. Hardin, The tragedy of the commons. The population problem has no technical solution; it requires a fundamental extension in morality. *Science*

- 162, 1243–1248 (1968). [Medline](#)
166. F. Baquero, J. Campos, The tragedy of the commons in antimicrobial chemotherapy. *Rev. Esp. Quimioter.* **16**, 11–13 (2003) [Editorial]. [Medline](#)
167. W. D. Hutchison, E. C. Burkness, P. D. Mitchell, R. D. Moon, T. W. Leslie, S. J. Fleischer, M. Abrahamson, K. L. Hamilton, K. L. Steffey, M. E. Gray, R. L. Hellmich, L. V. Kaster, T. E. Hunt, R. J. Wright, K. Pecinovsky, T. L. Rabaey, B. R. Flood, E. S. Raun, Areawide suppression of European corn borer with Bt maize reaps savings to non-Bt maize growers. *Science* **330**, 222–225 (2010). [Medline](#) [doi:10.1126/science.1190242](#)
168. G. Jaffe, Complacency on the farm: significant noncompliance with EPA's refuge requirements threatens the future effectiveness of genetically engineered pest-protected corn. (Center for Science in the Public Interest Washington, DC, 2009).
169. P. A. Samuelson, The pure theory of public expenditure. *Rev. Econ. Stat.* **36**, 387–389 (1954). [doi:10.2307/1925895](#)
170. D. J. Nokes, R. M. Anderson, Vaccine safety versus vaccine efficacy in mass immunisation programmes. *Lancet* **338**, 1309–1312 (1991). [Medline](#) [doi:10.1016/0140-6736\(91\)92601-W](#)
171. K. Kaier, U. Frank, Measuring the externality of antibacterial use from promoting antimicrobial resistance. *Pharmacoeconomics* **28**, 1123–1128 (2010). [Medline](#) [doi:10.2165/11535640-000000000-00000](#)
172. K. Kaier, Economic modeling of the persistence of antimicrobial resistance. *Nat. Resour. Model.* **25**, 388–402 (2012). [doi:10.1111/j.1939-7445.2011.00114.x](#)
173. G. D. Wright, Antibiotic resistance in the environment: A link to the clinic? *Curr. Opin. Microbiol.* **13**, 589–594 (2010). [Medline](#) [doi:10.1016/j.mib.2010.08.005](#)
174. M. Herrmann, R. Laxminarayan, Antibiotic Effectiveness: New Challenges in Natural Resource Management. *Annu. Rev. Resource Econom.* **2**, 125–138 (2010). [doi:10.1146/annurev.resource.050708.144125](#)
175. C. N. Cook, M. B. Mascia, M. W. Schwartz, H. P. Possingham, R. A. Fuller, Achieving conservation science that bridges the knowledge-action boundary. *Conserv. Biol.* **27**, 669–678 (2013). [Medline](#) [doi:10.1111/cobi.12050](#)
176. J. Antonovics, J. L. Abbate, C. H. Baker, D. Daley, M. E. Hood, C. E. Jenkins, L. J. Johnson, J. J. Murray, V. Panjeti, V. H. Rudolf, D. Sloan, J. Vondrasek, Evolution by any other name: Antibiotic resistance and avoidance of the E-word. *PLOS Biol.* **5**, e30 (2007). [Medline](#) [doi:10.1371/journal.pbio.0050030](#)
177. A. M. Messenger, A. N. Barnes, G. C. Gray, Reverse zoonotic disease transmission (zooanthroponosis): A systematic review of seldom-documented human biological threats to animals. *PLOS ONE* **9**, e89055 (2014). [Medline](#) [doi:10.1371/journal.pone.0089055](#)
178. R. Salguero-Gomez, CompADRe III demographic database; [www.demogr.mpg.de/en/laboratories/evolutionary_biodemography_1171/projects/compadre_plant_matrix_database_comadre_animal_matrix_database_18_67.htm](#).
179. K. Todar, The Growth of Bacterial Populations, Textbook of Bacteriology, [http://textbookofbacteriology.net/growth_3.html](#).
180. A. G. Rodrigo, E. G. Shpaer, E. L. Delwart, A. K. Iversen, M. V. Gallo, J. Brojatsch, M. S. Hirsch, B. D. Walker, J. I. Mullins, Coalescent estimates of HIV-1 generation time in vivo. *Proc. Natl. Acad. Sci. U.S.A.* **96**, 2187–2191 (1999). [Medline](#) [doi:10.1073/pnas.96.5.2187](#)
181. N. R. Boyle, J. A. Morgan, Flux balance analysis of primary metabolism in *Chlamydomonas reinhardtii*. *BMC Syst. Biol.* **3**, 4 (2009). [Medline](#) [doi:10.1186/1752-0509-3-4](#)
182. K. Goulding, M. Merrett, The photometabolism of acetate by *Chlorella pyrenoidosa*. *J. Exp. Bot.* **17**, 678–689 (1966). [doi:10.1093/jxb/17.4.678](#)
183. R. W. Truman, J. L. Krahenbuhl, Viable *M. leprae* as a research reagent. *Int. J. Lepr. Other Mycobact. Dis.* **69**, 1–12 (2001). [Medline](#)
184. M. P. Zwart, J. A. Daròs, S. F. Elena, One is enough: In vivo effective population size is dose-dependent for a plant RNA virus. *PLOS Pathog.* **7**, e1002122 (2011). [Medline](#) [doi:10.1371/journal.ppat.1002122](#)
185. S. Y. Lee, J. Bollinger, D. Bezdicek, A. Ogram, Estimation of the abundance of an uncultured soil bacterial strain by a competitive quantitative PCR method. *Appl. Environ. Microbiol.* **62**, 3787–3793 (1996). [Medline](#)
186. H. Danks, Short life cycles in insects and mites. *Can. Entomol.* **138**, 407–463 (2006). [doi:10.4039/n06-803](#)
187. G. E. Cartwright, J. W. Athens, M. M. Wintrobe, The kinetics of granulopoiesis in normal man. *Blood* **24**, 780–803 (1964). [Medline](#)
188. E. Marshman, C. Booth, C. S. Potten, The intestinal epithelial stem cell. *BioEssays* **24**, 91–98 (2002). [Medline](#) [doi:10.1002/bies.10028](#)
189. R. Flindt, *Biologie in Zahlen* (Elsevier, Spektrum Akademischer Verlag, Heidelberg, ed. 6, 2003).
190. K. L. Spalding, E. Arner, P. O. Westermark, S. Bernard, B. A. Buchholz, O. Bergmann, L. Blomqvist, J. Hoffstedt, E. Näslund, T. Britton, H. Concha, M. Hassan, M. Rydén, J. Frisén, P. Arner, Dynamics of fat cell turnover in humans. *Nature* **453**, 783–787 (2008). [Medline](#) [doi:10.1038/nature06902](#)
191. R. D. Bhardwaj, M. A. Curtis, K. L. Spalding, B. A. Buchholz, D. Fink, T. Björk-Eriksson, C. Nordborg, F. H. Gage, H. Druid, P. S. Eriksson, J. Frisén, Neocortical neurogenesis in humans is restricted to development. *Proc. Natl. Acad. Sci. U.S.A.* **103**, 12564–12568 (2006). [Medline](#) [doi:10.1073/pnas.0605177103](#)
192. F. A. C. Azevedo, L. R. B. Carvalho, L. T. Grinberg, J. M. Farfel, R. E. L. Ferretti, R. E. Leite, W. J. Filho, R. Lent, S. Herculanou-Houzel, Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. *J. Comp. Neurol.* **513**, 532–541 (2009). [Medline](#) [doi:10.1002/cne.21974](#)
193. J. N. Fenner, Cross-cultural estimation of the human generation interval for use in genetics-based population divergence studies. *Am. J. Phys. Anthropol.* **128**, 415–423 (2005). [Medline](#) [doi:10.1002/ajpa.20188](#)
194. Department of Economic and Social Affairs, Population Division, United Nations, World Population Prospects: The 2010 Revision (United Nations, New York, 2011); [http://esa.un.org/unpd/wpp/](#).
195. M. B. Usher, A matrix approach to the management of renewable resources, with special reference to selection forests. *J. Appl. Ecol.* **3**, 355–367 (1966). [doi:10.2307/2401258](#)
196. M. Usher, A matrix model for forest management. *Biometrics* **25**, 309–315 (1969). [doi:10.2307/2528791](#)
197. S. Southerton, personal communication, 29 April 2014.
198. R. G. Wear, S. J. Haslett, N. L. Alexander, Effects of temperature and salinity on the biology of *Artemia franciscana* Kellogg from Lake Grassmere, New Zealand. 2. Maturation, fecundity, and generation times. *J. Exp. Mar. Biol. Ecol.* **98**, 167–183 (1986). [doi:10.1016/0022-0981\(86\)90081-X](#)
199. M. L. Winston, *The Biology of the Honey Bee* (Harvard Univ. Press, Cambridge, MA, 1991).
200. A. P. Martin, S. R. Palumbi, Body size, metabolic rate, generation time, and the molecular clock. *Proc. Natl. Acad. Sci. U.S.A.* **90**, 4087–4091 (1993). [Medline](#) [doi:10.1073/pnas.90.9.4087](#)
201. P. J. Van Mantgem, N. L. Stephenson, The accuracy of matrix population model projections for coniferous trees in the Sierra Nevada, California. *J. Ecol.* **93**, 737–747 (2005). [doi:10.1111/j.1365-2745.2005.01007.x](#)
202. K. McPherson, K. Williams, Establishment growth of cabbage palm, *Sabal palmetto* (Arecaceae). *Am. J. Bot.* **83**, 1566–1570 (1996). [doi:10.2307/2445830](#)
203. Á. Ferrero-Serrano, A. L. Hild, B. A. Meador, Can invasive species enhance competitive ability and restoration potential in native grass populations? *Restor. Ecol.* **19**, 545–551 (2011). [doi:10.1111/j.1526-100X.2009.00611.x](#)
204. M. L. Baskett, S. A. Levin, S. D. Gaines, J. Dushoff, Marine reserve design and the evolution of size at maturation in harvested fish. *Ecol. Appl.* **15**, 882–901 (2005). [doi:10.1890/04-0723](#)
205. D. R. Shaw, M. D. Owen, P. M. Dixon, S. C. Weller, B. G. Young, R. G. Wilson, D. L. Jordan, Benchmark study on glyphosate-resistant cropping systems in the United States. Part 1: Introduction to 2006–2008. *Pest Manag. Sci.* **67**, 741–746 (2011). [Medline](#) [doi:10.1002/ps.2160](#)
206. A. L. Melander, Can insects become resistant to sprays? *J. Econ. Entomol.* **7**, 167–173 (1914).
207. M. S. Niederman, Is “crop rotation” of antibiotics the solution to a “resistant” problem in the ICU? *Am. J. Respir. Crit. Care Med.* **156**, 1029–1031 (1997). [Medline](#) [doi:10.1164/ajrcrm.156.4.ed-14](#)
208. R. E. Rapp, A. Datta, S. Irmak, T. J. Arkebauer, S. Z. Knezevic, Integrated management of common reed (*Phragmites australis*) along the Platte River in Nebraska. *Weed Technol.* **26**, 326–333 (2012). [doi:10.1614/WT-D-11-00119.1](#)
209. D. M. Bergstrom, A. Lucieer, K. Kiefer, J. Wasley, L. Belbin, T. K. Pedersen, S. L. Chown, Indirect effects of invasive species removal devastate World Heritage Island. *J. Appl. Ecol.* **46**, 73–81 (2009). [doi:10.1111/j.1365-2664.2008.01601.x](#)
210. R. Van Den Bosch, V. M. Stern, The integration of chemical and biological

- control of arthropod pests. *Annu. Rev. Entomol.* **7**, 367–386 (1962). [Medline doi:10.1146/annurev.en.07.010162.002055](#)
211. P. Csermely, V. Ágoston, S. Pongor, The efficiency of multi-target drugs: The network approach might help drug design. *Trends Pharmacol. Sci.* **26**, 178–182 (2005). [Medline doi:10.1016/j.tips.2005.02.007](#)
 212. M. J. Mackinnon, S. Gandon, A. F. Read, Virulence evolution in response to vaccination: The case of malaria. *Vaccine* **26** (suppl. 3), C42–C52 (2008). [Medline doi:10.1016/j.vaccine.2008.04.012](#)
 213. K. A. Hanley, L. R. Manluc, L. E. Gilmore, J. E. Blaney Jr., C. T. Hanson, B. R. Murphy, S. S. Whitehead, A trade-off in replication in mosquito versus mammalian systems conferred by a point mutation in the NS4B protein of dengue virus type 4. *Virology* **312**, 222–232 (2003). [Medline doi:10.1016/S0042-6822\(03\)00197-1](#)
 214. S. Laverigne, J. Molofsky, Control strategies for the invasive reed Canarygrass (*Phalaris arundinacea* L.) in North American Wetlands: The need for an Integrated Management Plan. *Nat. Areas J.* **26**, 208–214 (2006). [doi:10.3375/0885-8608\(2006\)26\[208:CSFTIR\]2.0.CO;2](#)
 215. C. A. Schoner, R. F. Norris, W. Chilcote, Yellow foxtail (*Setaria lutescens*) biotype studies: Growth and morphological characteristics. *Weed Sci.* **26**, 632–636 (1978).
 216. M. F. Schetelig, F. Scolari, A. M. Handler, S. Kittelmann, G. Gasperi, E. A. Wimmer, Site-specific recombination for the modification of transgenic strains of the Mediterranean fruit fly *Ceratitis capitata*. *Proc. Natl. Acad. Sci. U.S.A.* **106**, 18171–18176 (2009). [Medline doi:10.1073/pnas.0907264106](#)
 217. S. Crotty, D. Maag, J. J. Arnold, W. Zhong, J. Y. N. Lau, Z. Hong, R. Andino, C. E. Cameron, The broad-spectrum antiviral ribonucleoside ribavirin is an RNA virus mutagen. *Nat. Med.* **6**, 1375–1379 (2000). [Medline doi:10.1038/82191](#)
 218. M. Eigen, Error catastrophe and antiviral strategy. *Proc. Natl. Acad. Sci. U.S.A.* **99**, 13374–13376 (2002). [Medline doi:10.1073/pnas.212514799](#)
 219. M. R. Wise de Valdez, D. Nimmo, J. Betz, H. F. Gong, A. A. James, L. Alphey, W. C. Black 4th, Genetic elimination of dengue vector mosquitoes. *Proc. Natl. Acad. Sci. U.S.A.* **108**, 4772–4775 (2011). [Medline doi:10.1073/pnas.1019295108](#)
 220. D. Bardsley, G. Hugo, Migration and climate change: Examining thresholds of change to guide effective adaptation decision-making. *Popul. Environ.* **32**, 238–262 (2010). [doi:10.1007/s11111-010-0126-9](#)
 221. T. Jacobsen, R. M. Adams, Salt and Silt in Ancient Mesopotamian Agriculture: Progressive changes in soil salinity and sedimentation contributed to the breakup of past civilizations. *Science* **128**, 1251–1258 (1958). [Medline doi:10.1126/science.128.3334.1251](#)
 222. J. Berger, S. P. Milroy, N. C. Turner, K. H. M. Siddique, M. Imtiaz, R. Malhotra, Chickpea evolution has selected for contrasting phenological mechanisms among different habitats. *Euphytica* **180**, 1–15 (2011). [doi:10.1007/s10681-011-0391-4](#)
 223. P. Carrera-Bastos, The western diet and lifestyle and diseases of civilization. *Res. Rep. Clin. Cardiol.* **2**, 15–35 (2011).
 224. L. B. Turner, A meta-analysis of fat intake, reproduction, and breast cancer risk: An evolutionary perspective. *Am. J. Hum. Biol.* **23**, 601–608 (2011). [Medline doi:10.1002/ajhb.21176](#)
 225. P. D. Gluckman, M. A. Hanson, F. M. Low, The role of developmental plasticity and epigenetics in human health. *Birth Defects Res. C Embryo Today* **93**, 12–18 (2011). [Medline doi:10.1002/bdrc.20198](#)
 226. K. R. Rice, N. C. Emery, Managing microevolution: Restoration in the face of global change. *Front. Ecol. Environ.* **1**, 469–478 (2003). [doi:10.1890/1540-9295\(2003\)001\[0469:MMRTF\]2.0.CO;2](#)
 227. C. M. Sgrò, A. J. Lowe, A. Hoffmann, Building evolutionary resilience for conserving biodiversity under climate change. *Evol. Appl.* **4**, 326–337 (2011). [doi:10.1111/j.1752-4571.2010.00157.x](#)
 228. N. Redpath, L. M. Osgathorpe, K. Park, D. Goulson, Crofting and bumblebee conservation: The impact of land management practices on bumblebee populations in northwest Scotland. *Biol. Conserv.* **143**, 492–500 (2010). [doi:10.1016/j.biocon.2009.11.019](#)
 229. A. Jarvis, A. Lane, R. J. Hijmans, The effect of climate change on crop wild relatives. *Agric. Ecosyst. Environ.* **126**, 13–23 (2008). [doi:10.1016/j.agee.2008.01.013](#)
 230. R. M. Trethowan, M. A. Turner, T. M. Chattha, Breeding strategies to adapt crops to a changing climate. In *Climate Change and Food Security*, D. Lobell, M. Burke, Eds. (Springer Netherlands, 2010), pp. 155–174.
 231. L. C. Dupuy, C. P. Locher, M. Paidhungat, M. J. Richards, C. M. Lind, R. Bakken, M. D. Parker, R. G. Whalen, C. S. Schmaljohn, Directed molecular evolution improves the immunogenicity and protective efficacy of a Venezuelan equine encephalitis virus DNA vaccine. *Vaccine* **27**, 4152–4160 (2009). [Medline doi:10.1016/j.vaccine.2009.04.049](#)
 232. T. A. Yap, C. P. Carden, S. B. Kaye, Beyond chemotherapy: Targeted therapies in ovarian cancer. *Nat. Rev. Cancer* **9**, 167–181 (2009). [Medline doi:10.1038/nrc2583](#)
 233. H. Cho, T. Daniel, Y. J. Buechler, D. C. Litzinger, Z. Maio, A.-M. H. Putnam, V. S. Kraynov, B. C. Sim, S. Bussell, T. Javahishvili, S. Kaphle, G. Viramontes, M. Ong, S. Chu, G. C. Becky, R. Lieu, N. Knudsen, P. Castiglioni, T. C. Norman, D. W. Axelrod, A. R. Hoffman, P. G. Schultz, R. D. DiMarchi, B. E. Kimmel, Optimized clinical performance of growth hormone with an expanded genetic code. *Proc. Natl. Acad. Sci. U.S.A.* **108**, 9060–9065 (2011). [Medline doi:10.1073/pnas.1100387108](#)
 234. M. A. Bartel, J. R. Weinstein, D. V. Schaffer, Directed evolution of novel adeno-associated viruses for therapeutic gene delivery. *Gene Ther.* **19**, 694–700 (2012). [Medline doi:10.1038/gt.2012.20](#)
 235. M. D. Venesky, J. R. Mendelson III, B. F. Sears, P. Stiling, J. R. Rohr, Selecting for tolerance against pathogens and herbivores to enhance success of reintroduction and translocation. *Conserv. Biol.* **26**, 586–592 (2012). [Medline doi:10.1111/j.1523-1739.2012.01854.x](#)
 236. S. Lopez, F. Rousset, F. H. Shaw, R. G. Shaw, O. Ronce, Joint effects of inbreeding and local adaptation on the evolution of genetic load after fragmentation. *Conserv. Biol.* **23**, 1618–1627 (2009). [Medline doi:10.1111/j.1523-1739.2009.01326.x](#)
 237. E. B. Davis, M. S. Koo, C. Conroy, J. L. Patton, C. Moritz, The California Hotspots Project: Identifying regions of rapid diversification of mammals. *Mol. Ecol.* **17**, 120–138 (2008). [Medline doi:10.1111/j.1365-294X.2007.03469.x](#)
 238. L. Hannah, A global conservation system for climate-change adaptation. *Conserv. Biol.* **24**, 70–77 (2010). [Medline doi:10.1111/j.1523-1739.2009.01405.x](#)
 239. D. F. Jacobs, Toward development of silvical strategies for forest restoration of American chestnut (*Castanea dentata*) using blight-resistant hybrids. *Biol. Conserv.* **137**, 497–506 (2007). [doi:10.1016/j.biocon.2007.03.013](#)
 240. W. M. Muir, Group selection for adaptation to multiple-hen cages: Selection program and direct responses. *Poult. Sci.* **75**, 447–458 (1996). [Medline doi:10.3382/ps.0750447](#)
 241. R. F. Denison, E. T. Kiers, S. A. West, Darwinian agriculture: When can humans find solutions beyond the reach of natural selection? *Q. Rev. Biol.* **78**, 145–168 (2003). [Medline doi:10.1086/374951](#)
 242. A. G. Condon, R. A. Richards, G. J. Rebetzke, G. D. Farquhar, Breeding for high water-use efficiency. *J. Exp. Bot.* **55**, 2447–2460 (2004). [Medline doi:10.1093/jxb/erh277](#)
 243. S. P. Carroll, J. V. Watters, Managing phenotypic variability with genetic and environmental heterogeneity: adaptation as a first principle of conservation practice. In *Conservation Biology—Evolution in Action*, S. P. Carroll, C. W. Fox, Eds. (Oxford Univ. Press, Oxford, 2008), pp. 181–198.
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Supplementary Materials

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Materials and Methods

Supplementary Text

Tables S1 to S2

References (177–243)

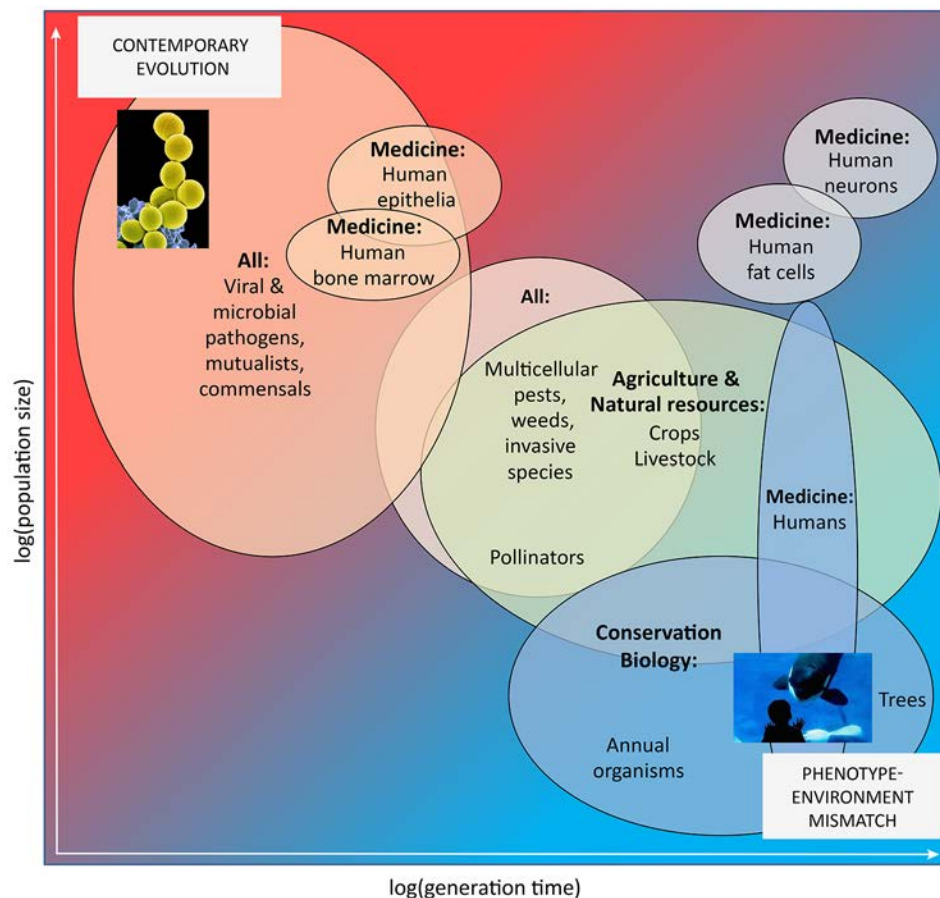


Fig. 1. The two central paradigms of applied evolution are managing contemporary evolution and phenotype-environment mismatch. Managing contemporary evolution is critical for rapidly reproducing organisms with large population sizes, such as the methicillin-resistant *Staphylococcus aureus* (MRSA) pictured in the upper 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 the 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.

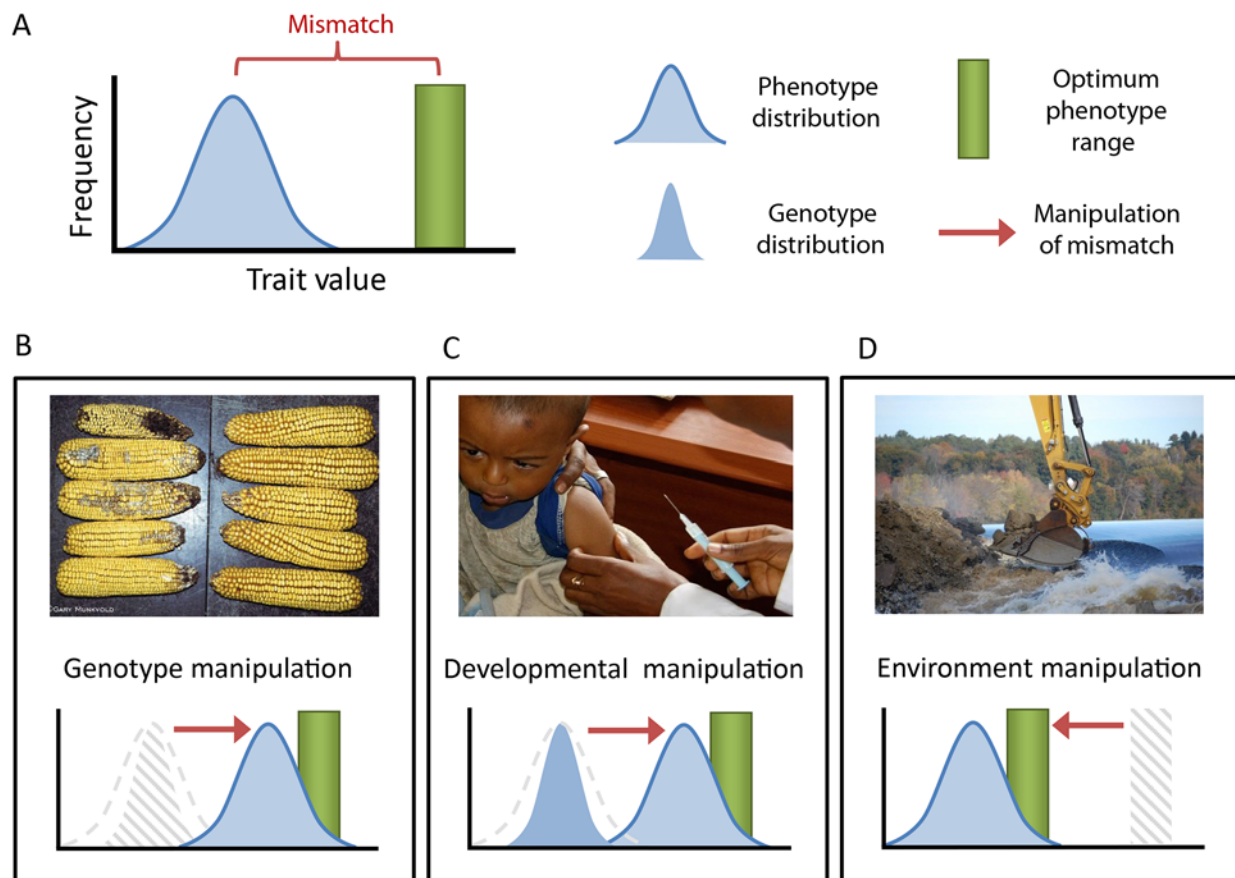


Fig. 2. Phenotype-environment mismatch. (A) Mismatch between phenotypes and an environment occurs when a population's phenotypic trait distribution differs from the optimum; greater mismatch increases selection for adaptation, but also implies greater costs through reduced survival and reproduction. (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 genetically engineered 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).




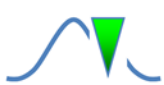

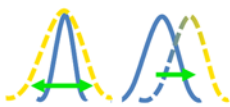
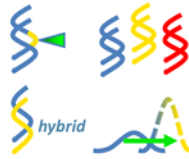

Strategy	Tactic	Food and fiber	Health	Environment	
1. Control pests, pathogens and invaders by ...					
... slowing unwanted evolution					
	Spatial variation in selection	Protect some susceptible forms	Nontoxic plantings save treatable pests	Favor susceptible pathogens, cell lines	Maintain genotypes 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
... reducing adversary fitness					
	Add mutational load	Transgenic mutation	Reduce pest fitness	Mutate viruses; eliminate vectors	Reduce invader fitness
2. Protect desirable populations by ...					
... reducing phenotype - environment mismatch					
	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
... increasing group performance					
	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: 1. Controlling adversaries and 2. Protecting valued populations. Together they are enabled by four strategies (boldface). A core set of eight evolutionary principles guides the execution of these strategies and underlies tactics (left hand columns) used to meet management objectives in the food and fiber production, health and environmental sectors (right hand 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 GE. 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.

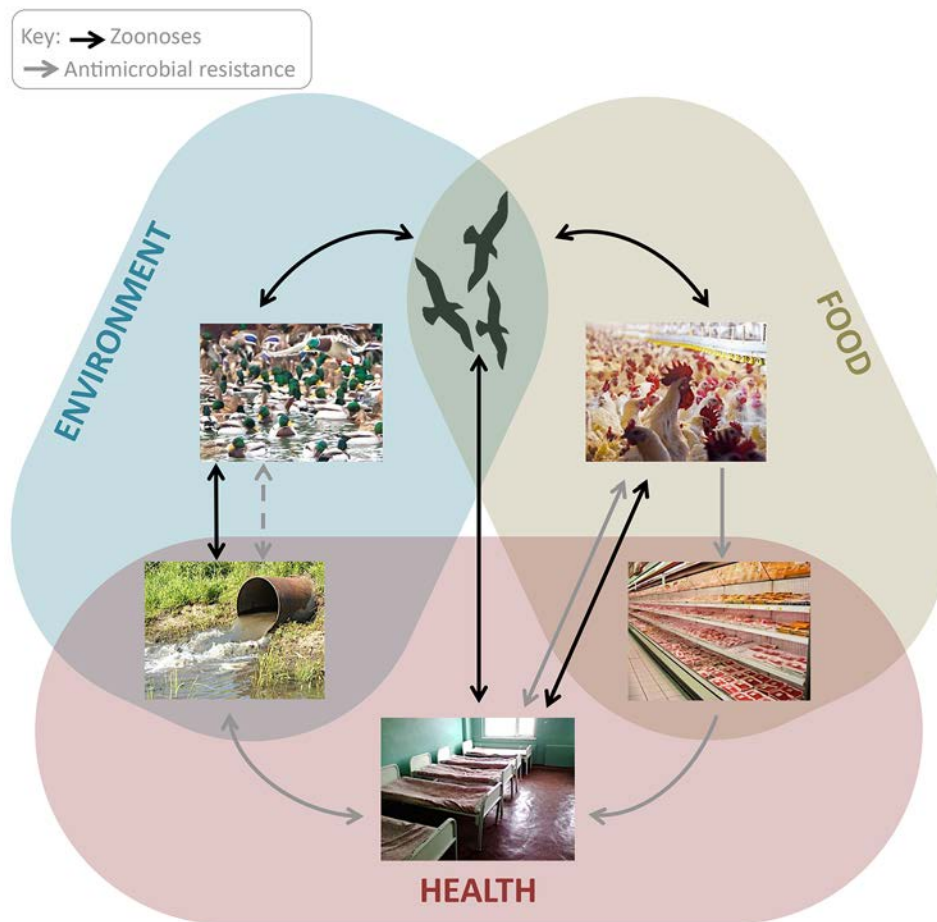


Fig. 4. Emerging pathogens such as zoonoses (black arrows) and resistant bacteria (gray arrows) illustrate interdependencies generated by gene flow among the economic sectors of food, health and the environment. In zoonoses, vertebrates such as birds act as reservoirs for pathogens that can infect humans. 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 strains associated with livestock evolves in response to widespread use of antibiotics in agriculture and to a lesser degree due to 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, e.g., in hospitals. Antibiotics in human effluent cause widespread resistance selection in natural and semi-natural 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.