mension to 2D (*7*). However, spreading targets on a plane or a layer might not always be an option. This could be the case in the microscopic fly brain, which might not be able to accommodate the space required to spread its glomeruli in two dimensions. Moreover, there are many structures in the mammalian brain that have a 3D, not layered, structure during development, suggesting that the dimensional reduction approach identified by Lyu *et al.* might also apply there.

The study of Lyu *et al.* relied on the use of advanced genetic tools to label (and manipulate the gene expression of) individual types of ORN and projection neuron throughout development. Previous studies noted that ORNs only target the surface of the antennal lobe during development, but an inability to identify and manipulate specific cell types prevented these studies from reaching more definitive conclusions (*8*). Advances in single-cell technologies have since allowed the identification of specific marker genes that are expressed throughout development in many transcriptionally distinct neuronal types (*9*). The promoters of these marker genes can be harnessed to genetically manipulate individual cell types. However, not all cell types can be distinguished by the expression of a single gene. One solution to this problem is to identify pairs of genes that are only coexpressed in one neuronal type. Intersectional genetics approaches (e.g., split-Gal4) can then be used to restrict the expression of target genes only in cells that simultaneously express the gene pairs (*10*, *11*). This was the approach used by Lyu *et al.* However, finding a gene pair with expression that is specific to a single cell type is not always feasible. Another strategy is to use single-cell RNA sequencing and single-nucleus ATAC (assay for transposase-accessible chromatin) sequencing datasets to find regions of open chromatin, which often correspond to enhancers that drive cell type–specific gene expression during development. This allows the identification of more cell type–specific genetic tools that can be combined with intersectional genetics methods (*12*).

Over the past decades, powerful genetic tools in *Drosophila* and vertebrate model organisms have accelerated the understanding of the development and function of different cell types. As technological advances and knowledge of the nervous system deepen, genetic tools with single–cell type resolution will be essential for tackling fundamental biological and developmental questions, for example, how do neurons establish their identity? Further work is also required to establish how neurons form precise synaptic connections and how the resulting neuronal circuits contribute to the behaviors of the organism. □

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EVOLUTIONARY BIOLOGY

An uphill grind for wild plant populations

Genetic variation is inadequate for the adaptation of a montane plant to new climates

Sally N. Aitken

The range of temperature and precipitation across which populations remain viable forms the climatic niche for terrestrial life. Many plant (*1*) and animal (*2*) species consist of populations that are locally adapted to their preindustrial climates, with each subgroup tolerating a smaller range of climate conditions compared with the whole species (*3*). Will existing genetic variation be sufficient for the adaptation needed to reverse population decline as climates change (a process known as evolutionary rescue) (*4*)? Can migration from warmer to cooler regions provide the diversity required for climate adaptation (genetic rescue) (*5*)? On page 525 of this issue, Anderson *et al.* (*6*) report that even for the widely distributed species of the rock cress *Boechera stricta* in the United States Rocky Mountains, gene flow from warmer to cooler elevations—possibly facilitated by human intervention—is needed to support future survival of some plants in a warming climate.

Plants have three potential responses if fitness of local genotypes declines with climate warming: adaptation, migration, or extirpation. Predicting this fate requires understanding local adaptation. For this knowledge, transplant experiments in natural conditions are the gold standard. Although analyses of genomic data (*7*, *8*) or of variation in phenotypes in controlled environments can provide more rapid information on population variation, they do not quantify the effects of that variation on growth, mortality, or fitness in nature (*9*). Field-based transplant experiments move genotypes from different origins to experimental gardens in different locations, substituting spatial variation for anticipated temporal changes in climate. This type of experiment provides insights into the potential for, and limitations of, evolutionary and genetic rescue of natural populations under climate change. Such experiments are common with some plants, such as forest trees (*10*), but estimating lifetime fitness for long-lived species is difficult. *B. stricta* is a short-lived, widespread montane perennial plant, making it an ideal model for this type of ecoevolutionary experiment.

Anderson *et al.* planted more than 100,000 *B. stricta* plants in two large experiments. In a reciprocal transplant experiment, genotypes were sourced from, and transplanted to, five different elevations in the Colorado Rocky Mountains. In a provenance transplant experiment, *B. stricta* sampled from a wider geographic range were planted at the same five elevations, and snowpack levels were also manipulated. Populations showed strong local adaptation to both temperature and snowpack, factors that the authors identified as key climate variables. Genotypes originating from close to planting sites had the highest fitness under preindustrial climatic conditions at all five sites.

In current climatic conditions, Anderson *et al.* found that the transplanted populations with optimum performance at mid and high elevations were from source locations that were ~150 to 350 m lower in elevation. At the lowest elevation site, where the warmest, most stressful current conditions occur, phenotypic variation among genotypes was lowest, indicating a reduced capacity for adaptation through natural selection. Under both moderate and high greenhouse gas emissions (reflecting those projected for the period 2071–2100), the authors' modeling predicted that local genotypes would be maladapted at all sites

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and that genotypes from the lowest elevation would have the highest fitness, relative to all sources, at almost all sites. In the case of the highest elevation site examined, modeling indicated that for conditions at the end of this century, the optimal genotypes currently occur nearly 800 m lower in elevation.

Results on germination, survival, growth, and fecundity from the transplant experiments allowed Anderson *et al.* to develop evolutionary models that predict where populations would grow, remain stable, or contract under preindustrial, current, and future climates. The models predict that, under current conditions, the lowest elevation site is already demographically unsustainable and populations at the two lowest elevation sites will be extirpated with climate change regardless of genotype, thereby contracting the species range. Other studies have also predicted range contractions at lower elevations for many montane plant species.

The natural movement of pollen or seeds between populations can facilitate genetic adaptation to environments (*11*), but only if the source genotypes are better adapted to the new conditions of the recipient population than local genotypes. For *B. stricta* (and many other species), this would require gene flow upslope from warmer to cooler locations. Anderson *et al.* estimated long-term gene flow rates from genomic data and found that genetic exchange in this mostly self-pollinating species is very low. Furthermore, the authors detected no sign of recent upslope gene flow. They propose that human-assisted gene flow (*12*) would be needed for these populations to be genetically rescued under a changing climate. The capacity for such genetic rescue will be species specific, depending on life history factors such as outcrossing rate and dispersal dynamics, highlighting the need for additional comprehensive ecoevolutionary studies like that of Anderson *et al.*

The impact of climate change on the ranges of terrestrial plants and animals is often predicted using species distribution models that estimate the climatic niche from the current range and then project the future distribution of those conditions under various climate change scenarios (*13*). Anderson *et al.* compared estimates of future population viability, accounting for local adaptation and gene flow, with those from species-level climatic niche projections and found a poor fit between the two predictions. This illustrates the importance of knowledge on local adaptation and gene flow for evaluating both population- and species-level responses to climate change.

The lessons from Anderson *et al.* are sobering with respect to the ability of natural populations to adapt to, and persist under, rapid global warming. Although the capacity for persistence will vary among species and with life history traits, populations cannot persist simply because their locations remain within the overall range of climatic tolerances for that species as a whole. Adequate genetic variation for adaptation to new conditions may not be present or may not be expressed phenotypically under stressful conditions. Even if well-adapted genotypes exist elsewhere in the species range, gene flow may be insufficient to redistribute genetic variation quickly enough. Greenhouse gas emission reductions that slow climate change may provide enough time for adaptation to occur for some species. Human intervention in the form of assisted gene flow among populations could increase the probability of species persisting in a warming climate. □

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MICROBIOLOGY

A fungal ally wards off liver disease

A metabolite secreted by an intestinal fungus blunts metabolic disease

Lora V. Hooper[1,2,3] *and* **Andrew Y. Koh**[2,4,5]

The human gut is home to trillions of microorganisms, collectively known as the gut microbiota. Most microbiota constituents are bacteria, which produce a diverse array of metabolites that signal to human cells or interact with enzymatic pathways to shape host biology. The microbiota also includes a range of commensal, mutualistic, and pathogenic fungi that, like gut bacteria, produce an abundance of metabolites. However, outside of a few well-studied toxin-producing pathogenic fungi, very little is known about how these fungal compounds interact with host cells to affect health. On page 491 of this issue, Zhou *et al.* (*1*) report a fungal species that resides in the human gut and produces a compound that protects against metabolic disease in mice. The findings point to intestinal fungi as a potentially rich source of beneficial chemical compounds that could be harnessed for human health.

...the fungal microbiome may be a rich, untapped source of compounds with therapeutic potential.

Many intestinal fungi cause disease. For example, *Candida albicans* frequently colonizes the human intestine and causes life-threatening infections in people undergoing cancer therapy or immune suppression for organ and stem cell transplants (*2*, *3*). However, intestinal fungi can also establish symbiotic relationships with hosts, as indicated by the recent discovery that *Kazachstania pintolopesii* stably colonizes the mouse intestine and induces protective immunity against gut pathogens (*4*).

To identify other fungal symbionts in the human intestine, Zhou *et al.* cultured human fecal samples in medium containing nutrients derived from the human gut. The authors then identified fungi by sequencing their DNA. One species—*Fusarium foetens*—was almost universally present in people from different geographic locales and readily grew under culture conditions that mimic conditions of the human gut, such as low oxygen. When inoculated into mice, *F. foetens* stably colonized the gastrointestinal tract without causing injury or invading deeper tissues. These characteristics suggest that *F. foetens* is not merely passing through from the environment but instead is well adapted to the mammalian intestine and leads a symbiotic rather than pathogenic lifestyle. By contrast, other *Fusarium* species can cause opportunistic infections in humans with normal immune systems and life-threatening

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