Evolution in the Everyday

Understanding of evolution is fostering powerful technologies for health care, law enforcement, ecology, and all manner of optimization and design problems

BY DAVID P. MINDELL

Charles Darwin surely had no clue of the technological advances that his studies of beetles and birds would unleash. Our progress in comprehending the history and mechanisms of evolution has led to powerful applications that shape a wide variety of fields today.

For instance—as the *CSI* franchise of television shows has popularized—law-enforcement agencies now commonly use evolutionary analyses in their investigations. Knowledge of how different genes evolve determines the kind of information they can extract from DNA evidence.

In health care, phylogenetic analysis (studies of DNA sequences to infer their evolutionary relatedness, or genealogy) of a pathogen such as bird flu or West Nile virus can lead to vaccines and to guidelines for minimizing the disease's transmission to and among people. A laboratory process called directed evolution that rapidly evolves proteins can improve vaccines and other useful proteins.

Among other examples, computer scientists have adapted the concepts and mechanisms of evolution to create a general system known as genetic programming that can solve complex optimization and design problems. And a recently developed approach known as metagenomics has revolutionized scientists' ability to survey the kinds of microbes living in a region, bringing about the most dramatic change in our understanding of microbial diversity since the advent of microscopes.

About 400 years ago English philosopher and statesman Francis Bacon commented that knowledge is power. The extremely useful techniques borne of our growing comprehension of evolution bear him out in spectacular fashion.

KEY CONCEPTS

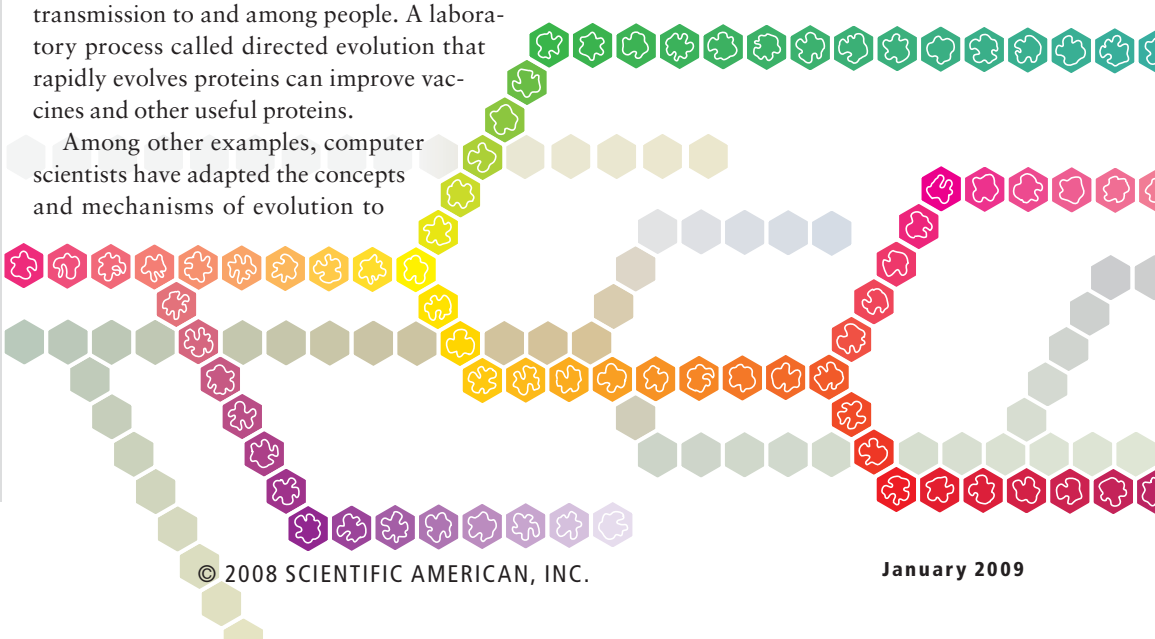
- The theory of evolution provides humankind with more than just a scientific narrative of life's origins and progression. It also yields invaluable technologies.
- For instance, the concept of molecular clocks—based on the accumulation of mutations in DNA over the eons—underlies applications such as the DNA analyses used in criminal investigations.
- DNA analysis of how pathogens evolve produces useful information for combating the outbreak and spread of disease. Accelerated evolution in laboratories has improved vaccines and other therapeutic proteins.
- Computer scientists have adapted evolution's mechanisms of mutation and selection to solve problems.

—The Editors

Beyond Reasonable Doubt

Evolutionary analyses and criminal investigations hold the same goal of revealing historical

JEN CHRISTIANSEN



events. Their fruitful combination awaited only the maturing of DNA-sequencing technology to provide large data sets, robust quantitative methods, and enlightened integration of science and the legal system.

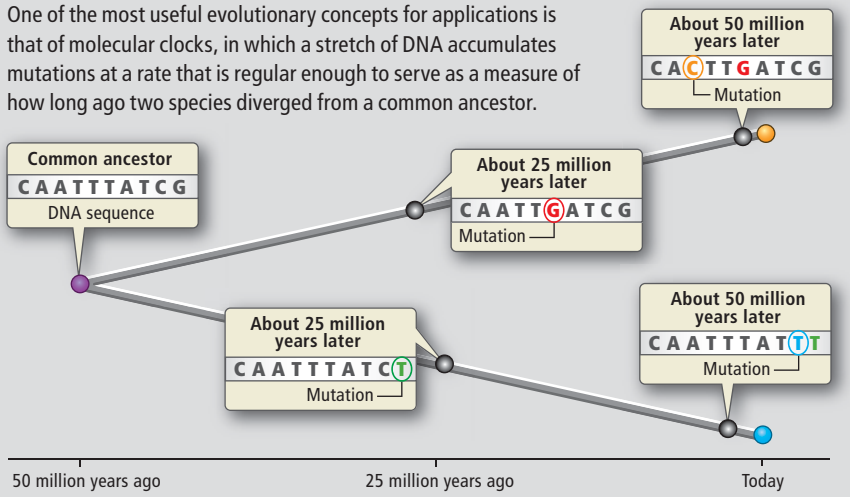
As with many applications of evolution, the concept of molecular clocks plays a vital role. Changes in many DNA sequences occur at roughly predictable rates over time, forming the basis for molecular clocks [*see box on next page*]. The clocks for two regions of DNA, however, can run at markedly different rates. In the early 1980s geneticists discovered regions of human DNA that evolve very rapidly, and scientists soon pressed these fast-evolving regions into service as genetic markers—unique identifiers of individuals, like fingerprints but with greater detail—in criminal cases and in paternity testing.

Forensic investigators assess specific genetic markers as indicators of links between suspects and crime scene evidence such as a single human hair, lip cells left on a beer can, saliva on envelope flaps and cigarette butts, as well as semen, blood, urine and feces. The most straightforward use is to demonstrate a suspect's innocence by the nonmatching of his or her markers compared with those of crime scene evidence. Indeed, the Innocence Project, a public policy organization promoting and tracking the use of genetic markers to overturn wrongful convictions, reports that since 1989, nonmatching of genetic markers has exonerated more than 220 people, many of them convicted for rape crimes and some of them on death row.

The standing of evolutionary science within the U.S. court system has completely reversed since its portrayal as an insidious scourge in the 1925 trial of Tennessee high school teacher John T. Scopes. In the 1998 criminal case of the *State of Louisiana v. Richard J. Schmidt*, the judge set precedent in ruling that phylogenetic analyses met judicial standards because they were subject to empirical testing, pub-

Molecular Clocks

One of the most useful evolutionary concepts for applications is that of molecular clocks, in which a stretch of DNA accumulates mutations at a rate that is regular enough to serve as a measure of how long ago two species diverged from a common ancestor.



A Ticktock of Mutations

In the example above, two species had a common ancestor 50 million years ago, and the DNA sequence from a particular gene they share acquires about one change every 25 million years. Thus, today the species' DNA differs at four locations. If we know the mutation rate (for instance, from genes and fossil evidence of closely related species), we can infer the 50-million-year time span from the four present-day DNA differences.

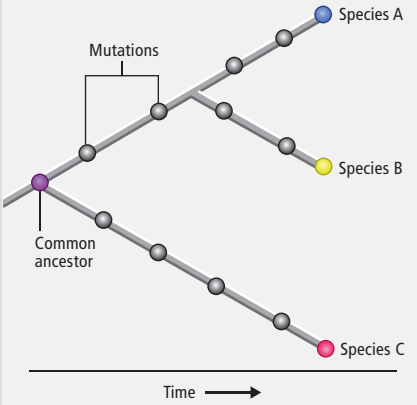
Common ancestor
C A A T T T A T C G

Modern species 1
C A C T T G A T C G

Modern species 2
C A A T T T A T T T

Evolutionary Trees

Scientists can apply the molecular clock technique to a group of related species to help infer their evolutionary tree, or phylogeny. Here, for example, the DNA from species A and B differ at four locations from each other, but each differs at eight locations from species C. Thus, the lineage of species C split from that of A and B's common ancestor twice as long ago as A and B's individual lineages diverged. A, B and C could also represent strains of a virus, mutating over a time span of a few years.



lished in peer-reviewed sources and accepted within the scientific community—some of the criteria commonly known as the Daubert standard for scientific evidence, after the name of a plaintiff in an earlier precedent-setting case.

I was fortunate to be invited to participate in *Louisiana v. Schmidt* as a scientist and expert witness by Michael L. Metzker of the Baylor College of Medicine and David M. Hillis of the University of Texas at Austin. The three of us worked together on the molecular analyses.

The uncontested facts in the case are that a gastroenterologist broke into the home of his former office nurse and mistress and gave her an injection. He claimed it was a vitamin B shot. She claimed it was HIV. She had begun feeling ill several months after the injection and a blood test revealed that she had become infected with HIV, at which point she went to the district attorney's office to file charges. The DA's detectives quickly obtained a search warrant for the physician's office, where they seized his record books and a vial of blood from a refrigerator. The physician said that the blood sample, drawn from one of his HIV-positive patients, was for his own research.

The next logical step in the investigation was to perform phylogenetic analyses of the HIV lineages from the nurse and the alleged source. My collaborators and I selected two HIV genes to sequence, one relatively fast-evolving, encoding part of the viral envelope (*env*), the other slow, encoding a vital enzyme called reverse transcriptase (RT). We also had blood samples from about 30 other infected individuals to serve as a reference point.

Our analyses of the *env* gene showed the HIV sequences from the victim and the doctor's sample formed two sister clades relative to the epidemiological sample. The likelihood of two random people from the infected population having such similar viruses is extremely small. This result is consistent with the accusation that the physician used the blood sample from one of his patients to infect the nurse, but it could also be that the patient was infected with HIV from the nurse. The phylogeny inferred from the more slowly evolving RT sequences showed that viruses from the victim were younger, arising from within the clade of viruses from the alleged source. This result clearly indicated that viruses from the alleged source had infected the nurse.

The jury found the doctor guilty of attempted murder, and he was sentenced to 50 years in prison. Of course, we cannot know how much weight the jurors placed on the evolutionary evidence and how much on other items such as the physician's notebooks and behavior. But we do know that phylogenetic analyses will continue to be used in U.S. courts, thanks to the Supreme Court upholding the *Louisiana v. Schmidt* precedent in 2002.

JEN CHRISTIANSEN; SOURCE: "MOLECULAR CLOCKS," FROM THE UNDERSTANDING EVOLUTION WEB SITE, UNIVERSITY OF CALIFORNIA MUSEUM OF PALEONTOLOGY, 2008 (*http://evolution.berkeley.edu/evolibrary/article/molecclocks_01*)

Microbial Arms Race

Like crime, infectious disease will always be a fact of life for us. Parasitic viruses, bacteria, fungi and animals have been co-evolving with people throughout *Homo sapiens*'s entire history, driving evolution of our wonderfully adaptable immune systems. Human populations provide ever larger breeding grounds for microbial pathogens, and even if we do hold some at bay and drive a few to extinction, others will evolve to invade successfully and spread. We are in this arms race for the long haul.

Understanding the evolutionary history of pathogens entails determining their genealogy, often based on phylogenetic analyses of DNA, which represent our best method for identifying unknown pathogens and their genes. Learning a pathogen's genealogy allows us to form valuable working hypotheses about its means of reproduction and transmission, as well as its preferred habitats, because close relatives are more likely to share heritable life history traits than distant relatives are. In turn, we can use this key information to make recommendations about how to minimize the pathogen's transmission opportunities and, potentially, how to enhance immunity.

Understanding evolutionary mechanisms requires identifying the causes of mutation and the roles of natural selection and chance events in the origin and persistence of particular heritable changes. We may track heritable changes across genotypes and morphology (physical form), as well as across life history traits such as virulence, transmissibility, host specificity and reproductive rate. For example, growing knowledge of distantly related bacteria exchanging drug-resistance genes, a process called horizontal transfer, has led biologists to seek new kinds of antibiotics that would block the ability of these mobile genetic elements to replicate and transfer themselves.

The deadly history of human influenza epidemics and our increasing grasp of flu virus evolution illustrates some of these points in action. Phylogenetic analyses of flu virus genes sampled broadly from host species have shown us that wild birds are a primary source and that domestic pigs are often, though not always, the intermediary hosts between birds and humans. Thus, health officials now recommend that people in certain regions keep their poultry and pigs in separate enclosed facilities to prevent contact with wild birds. They advise doing surveillance for a highly pathogenic variety known as influenza A strain H5N1 and other phylogenetically identified strains not just in poultry but also in select wild species, including waterfowl and shorebirds.

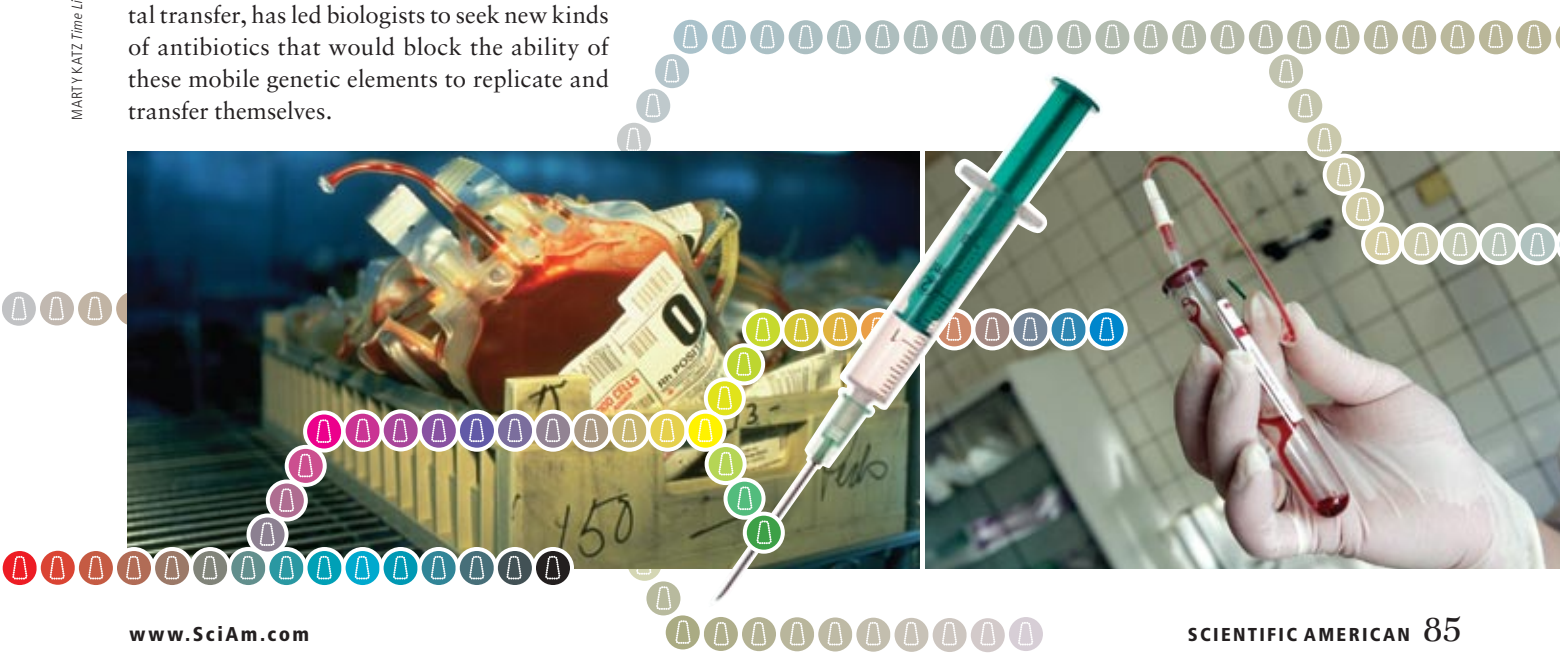
Phylogenies also demonstrate that influenza A genomes have eight unique segments that can be mixed and matched among strains from different host species. This form of recombination, known as shift, combined with mutation in DNA sequences, provides the near kaleidoscopic variation that allows reconfigured viruses to elude previously developed immune system antibodies, requiring us continually to develop new vaccines. Coupling geographic sampling with the phylogenetic history of specific segments and particular mutations known to be pathogenic helps in predicting the spread of the disease and in identifying candidates for use in vaccine development.

In 1997 scientists barely contained a potentially catastrophic outbreak in Hong Kong of H5N1, when they convinced authorities to slaughter all domestic fowl, the local virus source. Although future pandemics are a ques-

EVOLVING HIGH SPEED

Training a robot to walk as fast as possible while keeping its balance can require laborious fine-tuning of its gait for each new walking surface. Researchers at Carnegie Mellon University used an evolutionary algorithm for this task with four-legged Sony Aibos. Four of these robots tried out various gaits and shared the resulting performance data with one another. They then selected the best gaits and produced mutated "offspring" walks to evaluate next. After about 100 generations of this evolutionary process, the quadrupeds could walk 20 percent faster than they could with the scientists' best efforts at hand-tuning them.

FORENSIC SCIENCE can thank biologists' understanding of evolving DNA sequences for the powerful tool of genetic markers, which can indicate or rule out links between suspects and crime scene evidence. In a precedent-setting 1998 case, phylogenetic analysis of HIV samples strongly supported the accusation that a doctor had injected his victim with blood from an infected patient.



MARTY KATZ *Time Life Pictures/Getty Images (blood bags)*; DANIEL SAMBRAUS *(syringe)*; MAXIM MARMUR *AFP/Getty Images (test tube)*

THE AUTHOR

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HUMAN INFLUENZA virus strains often start out in wild birds, with domestic pigs serving as intermediary hosts between birds and humans. Understanding of this evolutionary history, revealed by analyses of virus DNA sampled from a wide variety of host species, helped scientists convince authorities in Hong Kong to slaughter all domestic fowl in 1997 to prevent a possible pandemic of the highly pathogenic H5N1 strain, also known as bird flu.

tion of when, not if, our knowledge about evolutionary sources, hybridization among genomes and the host-shifting capability of flu viruses helps us to minimize risk.

Evolutionary Medicine

Another way that evolution influences our health is through what might be called "unintelligent design features" of our bodies—legacies of our evolutionary past [see "This Old Body," by Neil H. Shubin, on page 64]. For instance, humans have a higher incidence of birthing problems as compared with other primates because female pelvis size in humans has not kept pace with selection for larger infant brain size. Some traits that may seem unintelligently designed, however, can actually be useful. Examples include fever, diarrhea and vomiting, which aid in purging microbial infections.

Applying an evolutionary perspective in understanding our susceptibilities and promoting health is known as evolutionary or Darwinian medicine. A vital step in this new endeavor is integration of basic evolutionary science into the curricula for medical and public health students.

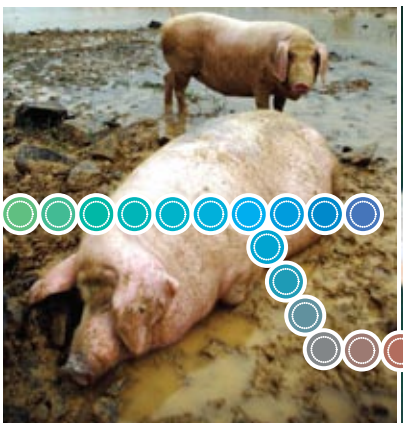
The matching of human genotypes with particular diseases has given rise to the possibility of personalized medicine, in which physicians can specify medications and dosages for individuals based on particular genetic traits. An example of this nascent approach involves the drug Herceptin (trastuzumab), which can reduce early-stage breast cancers in roughly 25 percent of cases but occasionally causes heart problems. Doctors can use information about an individual's genotype to identify the likelihood of positive response to Herceptin and whether the low probability of heart problems is a worthwhile risk [see "Gaining Ground on Breast Cancer," by Francisco J. Esteva and Gabriel N. Hortobagyi; Scientific American, June 2008].

Many people are reluctant to be genetically profiled, however, fearing unfair treatment by employers or insurance companies. In response, Congress passed the Genetic Information Nondiscrimination Act last May, outlawing such discrimination. Another concern is that race might be used as a proxy for genetic predisposition to particular diseases. Yet that kind of approach misunderstands the nature of human genetic variation, in which even closely related people may differ in their response to a drug. [For a cautionary tale on this topic, see "Race in a Bottle," by Jonathan Kahn; Scientific American, August 2007.]

In Vitro and In Silico

Evolution acting over billions of years has proved itself to be a versatile, if sometimes quirky, designer. Researchers are now borrowing from evolution's drawing board, using directed evolution to enhance useful functions of proteins. These molecular biologists intentionally mutate genes, produce the proteins the genes encode, measure the proteins' functional performance, and then select sets of top performers for subsequent bouts of mutation and testing. Repeating this cycle millions of times often yields impressive results.

Understanding of evolutionary history and mechanisms improves directed evolution in several ways. First, discovering the phylogenetic relationships of genes is an important step in determining their functions and, therefore, in selecting genes as targets for directed evolution. The relatedness of genes is our best proxy for estimating a gene's function prior to experiments.



DAVID BAY (*Mindell*); CHINA PHOTOS/GETTY IMAGES (*swan*); AP PHOTO (*pigs*); MIKE CLARKE *AFP/Getty Images* (*person in mask*)

If we have experimentally determined the functions for a gene in mice, say, it is reasonable to hypothesize that the most closely related gene in humans will have similar functions.

Second, knowledge of how particular genes evolve—understanding of the mechanisms of mutation and how natural selection operates on them—informs the choice of mutations to impose in directed evolution. A protein is a chain of amino acids whose sequence ultimately determines the protein's function. Directed evolutionists may choose to alter single amino acids at random locations anywhere within the sequence or only in certain regions or even at specific sequence positions known to be functionally important. Protein-coding genes are structured in segments, which we can shuffle to try to create arrangements with novel capabilities. We can also mix the structural segments of related genes from within a gene family (phylogenetically identified) or from sister species to construct so-called chimeric proteins. Recombination and shuffling of gene segments has produced rapid evolution of proteins in nature, and mimicking this approach has proved to be powerful in the lab. Researchers have further accelerated evolutionary change by shuffling whole genomes among populations of select microbes.

Among directed evolution's successes are a vaccine against human papillomavirus and better hepatitis C vaccines. Shuffling segments of 20 different human interferons (a family of immune system proteins) has led to chimeric proteins that are 250,000 times more effective at slowing viral replication. An improved human p53 protein, a tumor suppressor, has yielded better inhibition of tumor growth in lab experiments, and researchers are working on transferring this success to individuals who have compromised p53 proteins.

Another way that scientists and engineers emulate evolution in the lab is with computer programs called evolutionary or genetic algorithms. People have used this technique extensively to search for optimal solutions to complex problems, including scheduling air traffic, forecasting weather, balancing stock portfolios and optimizing combinations of medicines, as well as for designing bridges, electronic circuits and robot-control systems [see "Evolving Inventions," by John R. Koza, Martin A. Keane and Matthew J. Streeter; Scientific American, February 2003].

The general structure of an evolutionary algorithm includes five steps:

1. Generate a population of candidate solutions.
2. Evaluate the suitability, or fitness, of each candidate solution.
3. If any candidate solution meets all the target criteria, stop the process.
4. Otherwise, select groups of relatively fit individuals in the population to be parents.
5. Subject the parents to mutational changes and "sexual" recombination of their traits to produce a new population of candidate solutions. Then begin again with step 2.

Genetic programming sometimes finds solutions very unlike typical human designs. For instance, an evolutionary computation to find orbits for constellations of communications satellites minimizing signal loss by ground-based receivers identified orbit configurations that were unusually asymmetric, with variable gaps between the individual satellite paths. These evolved optimal constellations outperformed the more symmetrical arrangements usually considered by designers.

Critical Services

As humankind's numbers continue to grow and cause environmental changes at a rapid pace, concerns mount about conserving biological diversity and sustaining human populations over time. We rely on healthy ecosystems, made up of organisms and their environments, to provide us with usable water, arable land and clean air. These critical ecosystem services are essential for human well-being, yet we have little understanding of their regulation and the consequences of changes in ecosystems. What are the roles of particular species and communities within an ecosystem? How sensitive are these natural systems to loss of species and habitats? How do ecosystem changes influence local climates, pollination and seed dispersal in plants, decomposition of waste, and the emergence and spread of disease? These are difficult questions that evolutionary methods and knowledge help to answer.

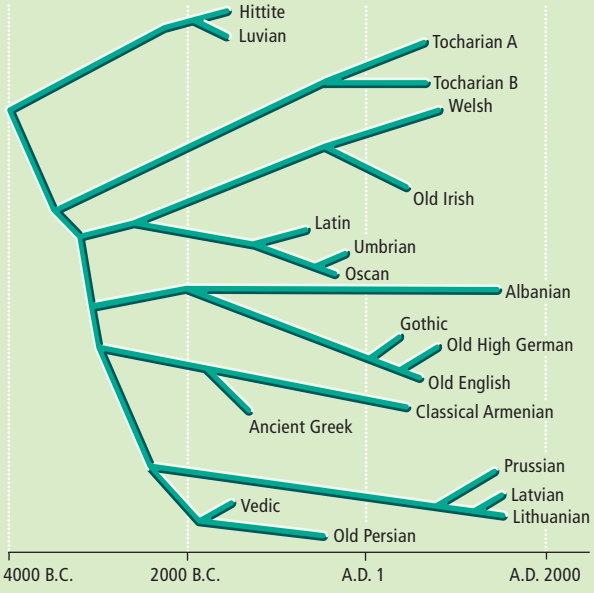
Taking inventory is critical for understanding and managing resources. Yet a great many lifeforms remain to be discovered and described, particularly the very small, including untold legions of viruses, bacteria and protists. The effort to determine the genealogical links among all life-forms includes extensive genetic sampling of biological diversity, within species as well as among them. With information from phylogenetic analyses of these samples, biologists can

Directed evolution of immune system proteins called interferons has produced variants that are 250,000 times more effective at slowing viral replication.

The Tree of Tongues

Charles Darwin himself noted the relation between human genealogy and language change: "If we possessed a perfect pedigree of mankind, a genealogical arrangement of the races of man would afford the best classification of the various languages now spoken throughout the world; and if all extinct languages, and all intermediate and slowly changing dialects, were to be included, such an arrangement would be the only possible one."

Languages do not evolve in a strict biological sense. Yet they do change over time in a manner analogous to biological evolution, with human innovation and borrowing playing an important role. Study of the evolution of languages began in the 1950s with compilation of cognate words, those sharing common origins, among language pairs. More recently, linguists and evolutionary scientists have applied the statistical methods of maximum likelihood and Bayesian analysis (used by biologists for phylogenetic analyses of evolution) in studies of language evolution. They apply the techniques to data sets of shared cognates and language structures such as grammar and the sounds used. Analyses using evolutionary models focusing on the most slowly changing features of language structure suggest that some historical relations can be traced back 20,000 years ago or more. —*D.P.M.*



INDO-EUROPEAN LANGUAGES form evolutionary trees (*right*) when scientists apply biologists' phylogenetic methods to sets of related words and other shared characteristics. Which of the many alternative trees best represents the history of the languages, however, remains unclear.

JEN CHRISTIANSEN; SOURCE: "RECONSTRUCTING THE EVOLUTIONARY HISTORY OF INDO-EUROPEAN LANGUAGES USING ANSWER SET PROGRAMMING," BY E. ERDEM, V. LIFSCHITZ, L. NAKHLEH AND D. RINGE, IN *PRACTICAL ASPECTS OF DECLARATIVE LANGUAGES (PADL): 5TH INTERNATIONAL SYMPOSIUM, 2003*; SPRINGER, 2003

assess the relative distinctiveness of groups of organisms and delineate the evolutionary units (such as particular species or groups of species) of concern for conservation.

Many phylogenetic analyses have revealed previously unrecognized species. DNA from African elephant populations supported recognition of two distinct species in Africa rather than one, as was long believed. *Loxodonta africana* is found primarily in forest habitats, whereas the newly named *L. cyclotis* lives in the savanna. DNA analyses have also found new species of Asian soft-shelled turtles, right whales and Old World vultures, among many others.

The development of unique genetic markers for vertebrate species increasingly aids the enforcement of conservation laws by identifying protected animals or their parts being smuggled or sold illegally. This approach has helped prosecution of cases of illicit whaling, use of tiger products in Asian medicines and harvesting of caviar from protected sturgeon species.

Metagenomics

The DNA from one organism makes up one genome. Collect the DNA from an entire community of microbes of various species in some location, and you have a metagenome. Biologists can now isolate DNA fragments from such a community, determine the fragments' sequences and reassemble them into contiguous sequences—all without first requiring the difficult and labor-intensive steps involved in growing the microbes in the lab.

Metagenomic analysis of microbes in the human intestinal tract has revealed more than 100 times as many different genes as are found in our own genomes (which contain about 25,000 protein-coding genes) and about 300 previously unknown and, so far, unculturable microbial lifeforms. The known microbes and their genes play important roles in development of our immune systems, in the production of fatty acids (which power healthy intestinal cell growth), and in detoxification of ingested substances that could otherwise lead to cancerous cell growth or alter our ability to metabolize medicines. Metagenomic analyses suggest that changes in the occurrence, abundance and interactions of both known and unknown microbes play a role in human diseases such as inflammatory bowel disease or in conditions such as obesity.

Similar metagenomic analyses of the reproductive tract in females have shown that bacterial vaginosis, a disease associated with premature labor and delivery, pelvic inflammatory disease and the acquisition of sexually transmitted pathogens such as HIV, is accompanied by dramatic changes in the species composition of vaginal bacteria communities. Researchers have found many newly discovered bacterial groups in both healthy and unhealthy vaginal ecosystems. Improved treatment of bacterial vaginosis requires better understanding of how these changes in vaginal ecosystems occur and how they affect ecosystem function and disease progression.

Turning to external ecosystems and sustainability, metagenomic analyses of water samples from the Pacific Ocean and from the Sargasso Sea in the North Atlantic have similarly indicated that a vast amount of oceanic biological diversity, including many viruses, remains to be discovered and understood. Scientists know relatively little about the metabolic abilities and ecological functions of these diverse microbial

lineages and have numerous projects under way. We need to learn about them because microbial communities are largely responsible for supporting life on earth. They conduct most of the world's photosynthesis, and they make the necessary elements of carbon, nitrogen, oxygen and sulfur accessible to other life-forms, including people.

Using the evolution-based analyses of metagenomics to learn the composition of communities in a variety of circumstances is only the first step in learning what the community members do, how they interact, and how they are changed and sustained over time. Are diverse microbial communities more resilient to environmental change than less diverse ones? Are some particular groups of species of great importance in maintaining an ecosystem? What drives formation and turnover in the composition of microbial communities? The concepts and methods needed for this next level of understanding are largely within the realm of evolutionary ecology, which entails study of all interactions within and among species and populations and their environments.

We have yet to see applications arising from microbial metagenomics and evolutionary ecology, but possibilities abound. Microbes both produce and consume carbon dioxide, methane and other greenhouse gases and may play a role in determining the success of efforts to curtail global warming. Metagenomics-based systems might monitor environmental health and watch for pathogens, whether naturally emergent or introduced by terrorists. Metagenomics could diagnose a broad selection of diseases in humans and livestock, which might be treated with probiotic therapies (the introduction of beneficial microbes). Newly discovered microbes could be exploited in the development of new antibiotics, in the discovery of enzymes to extract glucose from cellulose (which could then be fermented to ethanol as a fuel), and in the bioremediation of contaminated soil or water.

Nearly all our scientific understanding stems from observing and interrogating nature at some level. Nature as teacher does not lecture or provide study guides. Instead natural systems appeal to our innate curiosity, with the awesome and strangely beautiful compelling us to learn as best we can. Evolution is the unifying principle for comprehending all life on earth, and applying its lessons about the history and mechanisms of change can promote human well-being. What was once a curiosity is now a powerful tool. ■

Metagenomic analysis has revealed about 300 previously unknown microbes living in the human gut.

MORE TO EXPLORE

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