prising feedbacks are likely to emerge. For example, long-term oscillations in ocean chemistry (for example, the Mg/Ca ratio), driven by changes in spreading rates at midocean ridges, may have favored or undermined skeletal construction of different reef-building organisms through the Phanerozoic (*20*).

Paleontology sits squarely at the interface between the earth and life sciences. The most powerful contributions will emerge from analysis of evolutionary dynamics at different scales and hierarchical levels over deep time and of the diverse ways life has driven, and been driven by, changes in the Earth's atmosphere, oceans, and lithosphere.

References and Notes

1. S. M. Stanley *et al.*, *Geobiology of Critical Intervals* (Paleontological Society, Lawrence, KS, 1997); H. R. Lane *et al.*, Eds., *Paleontology in the 21st Century*, Kleine Senckenbergreihe **25**, 1 (1997); K. W. Flesse *et al.*, *Geobiology and the Earth Sciences in the Next Decade:* National Science Foundation, Geology and Paleontology Program Workshop (Paleontological Society, Lawrence, KS, 1999).
2. C. R. Marshall and P. D. Ward, *Science* **274**, 1360 (1996); M. Foote and J. J. Sepkoski Jr., *Nature* **398**, 415 (1999); S. M. Holland and M. E. Patzkowsky, *Geology* **27**, 491 (1999).
3. J. J. Sepkoski Jr., *Paleobiology* **19**, 43 (1993).
4. ——— and D. C. Kendrick, *ibid.*, p. 168; C. Maley, H. Robeck, M. Donoghue, *Geol. Soc. Am. Abstr. Progr.* **29(6)**, A-31 (1997).
5. K. Roy, *Paleobiology* **22**, 436 (1996); A. I. Miller, *Science* **281**, 1157 (1998).
6. M. L. McKinney, *Annu. Rev. Ecol. Syst.* **28**, 495 (1997).
7. J. J. Sepkoski Jr., in *Evolutionary Paleobiology*, D. Jablonski, D. H. Erwin, J. H. Lipps, Eds. (Univ. of Chicago Press, Chicago, 1996), pp. 211–255; M. J. Benton, *ibid.*, pp. 185–210.
8. M. Foote, *Annu. Rev. Ecol. Syst.* **28**, 129 (1997); G. R. McGhee Jr., *Theoretical Morphology* (Columbia Univ. Press, New York, 1999); R. Lupia, *Paleobiology* **25**, 1 (1999).
9. S. Conway Morris, *Philos. Trans. R. Soc. London Ser. B* **353**, 327(1998); J. W. Valentine *et al.*, *Development* **126**, 851 (1999).
10. J. L. Kirschvink *et al.*, *Science* **277**, 541 (1997); A. H. Knoll, *Nature* **382**, 111 (1996).
11. L. Van Valen, *Science* **180**, 488 (1973).
12. N. Shubin, C. Tabin, S. Carroll, *Nature* **388**, 639 (1997); M. I. Coates and M. J. Cohn, *Bioessays* **20**, 371 (1998); M. J. Cohn and C. Tickle, *Nature* **399**, 474 (1999).
13. J. B. C. Jackson and A. H. Cheetham, *Trends Ecol. Evol.* **14**, 72 (1999).
14. S. J. Gould, *Philos. Trans. R. Soc. London Ser. B* **353**, 307 (1998).
15. M. L. Droser, D. J. Bottjer, P. M. Sheehan, *Geology* **25**, 167 (1997).
16. S. A. Bowring *et al.*, *Science* **280**, 1039 (1998).
17. D. Jablonski, *ibid.* **279**, 1327 (1998).
18. S. M. Kidwell and P. J. Brenchley, in *Evolutionary Paleobiology*, D. Jablonski, D. H. Erwin, J. H. Lipps, Eds. (Univ. of Chicago Press, Chicago, 1996), pp. 290–336.
19. G. A. Logan *et al.*, *Nature* **376**, 53 (1995).
20. S. M. Stanley and L. A. Hardie, *Palaeogeogr. Palaeoclimatol. Palaeoecol.* **144**, 3 (1998).
21. *I* thank D. H. Erwin, K. W. Flessa, M. Foote, and especially S. M. Kidwell for valuable comments.

VIEWPOINT

The Evolution of Species Interactions

John N. Thompson

Interactions between species are as evolutionarily malleable as the species themselves and have played a central role in the diversification and organization of life. This malleability creates complex geographic mosaics in interspecific interactions that can evolve rapidly over decades, blurring the distinction between evolutionary time and ecological time and making the study of coevolution crucial for human health and welfare.

The history of evolution and biodiversity is fundamentally a history of the evolution of species interactions. Species in pure isolation simply do not make sense. Most living organisms have evolved in ways that absolutely require them to use a combination of their own genetic machinery and that of one or more other species if they are to survive and reproduce. Indeed, most described species take this to an extreme, living symbiotically on other species as parasites, commensals, or mutualists. In turn, most organisms must devote a large share of their resources to defense. Even now, among human populations one-third of deaths are caused by infectious disease. The more we learn about the diversity of life and the structure of genomes, the more it appears that much of the evolution of biodiversity is about the manipulation of other species—to gain resources and, in turn, to avoid being manipulated.

Many of the major events in the diversification of life can be traced back to the appearance of novel species interactions (*1, 2*). The consequences of these events are so pervasive—and, in some cases, the genomes of the species so completely anastomosed—that it is easy to forget how central they have been to life on Earth: mitochondria and the origin of the eukaryotic cell; chloroplasts and the origin of plants; dinoflagellates and the origin of coral reefs; lichens, mycorrhizae, and rhizobia and the process of terrestrial plant succession; gut symbionts and animal digestion. Other interactions between free-living species are equally pervasive. A majority of plants would quickly become extinct without their animal pollinators (*3*). Even in a gene-centered view of evolution, it is the armies of gene packages we call species that wage the genetic wars and create the genetic alliances.

The Coevolutionary Framework

Despite the central importance of species interactions to the diversification of life, we still know little about how the genomes of separate species become intermeshed. The organizing framework for attacking the problem is the theory of coevolution, the process by which species undergo reciprocal evolutionary change through natural selection. Not all interactions are highly coevolved, but the potential for coevolution to drive rapid and far-reaching change is always there. Unlike adaptation to the physical environment, adaptation to another species can produce reciprocal evolutionary responses that either thwart these adaptive changes or, in mutualistic interactions, magnify their effects. We now have convincing examples of coevolution forging obligate mutualisms among free-living species such as yuccas and yucca moths (*4*); creating divergence in traits among competing fish, lizards, mammals, and other taxa [for example, (*5*)]; producing locally matched chemical defenses in plants and counterdefenses in insects (*6*); and maintaining genetic diversity among populations of interacting parasites and hosts (*7, 8*). It is this interactive and iterative process that makes coevolution such a potentially powerful evolutionary process in shaping biodiversity. It may be the most important process organizing the diversity of life.

Nevertheless, understanding precisely how coevolution molds the evolution of species interactions remains one of the most difficult challenges in evolutionary biology, because most species interact with multiple species. It is evident that species can coevolve with more than one other species. Legumes have simultaneously evolved sophisticated coevolutionary relationships with their rhizobia and with their pollinators. Many parasites evolve adaptations to multiple hosts by partitioning their interactions into different life history stages. But specific hypotheses on multispecific coevolution are only now developing, including that of coevolutionary alternation, whereby parasites may alternate among a group of host species over thousands of years, constantly evolving to prefer the host species with the currently lowest level of defense (*9*).

Departments of Botany and Zoology, Washington State University, Pullman, WA 99164, USA. E-mail: jnt@wsu.edu

Further collaboration between molecular biologists and population biologists may lead to an understanding of how genomes are structured and continually restructured through multispecific interactions.

Fluctuating Selection and Ecological Dynamics

The dynamics of coevolution may sometimes proceed even faster than we previously expected, changing interactions over decades. Even though phylogenetic analyses have shown that species are often evolutionarily conservative in the taxa with which they interact, research on natural selection within biological communities indicates much continuing evolutionary dynamics within the boundaries of that conservatism. Dozens of species interactions are known to have evolved during the past 100 years (*10*). Gene-for-gene coevolution in wild flax and flax rust in Australia has produced large changes in allele frequencies within and among populations over just the past decade alone (*7*). The frequency of clones in *Potamopyrgus antipodarum* snails within a single lake in New Zealand has changed within the past decade through time-lagged selection imposed by a major trematode parasite (*8*). The introduction of myxoma virus into Australia as a biological control agent against rabbits resulted in rapid evolution toward decreased virulence within only a few years (*11*). Examples like these have become increasingly common as evolutionary ecologists and evolutionary geneticists have carefully evaluated how natural selection acts on species interactions within natural communities.

The rapid evolution we observe over decades may often be driven by fluctuating selection, where the selective value of genotypes rises and falls rapidly and repeatedly over time. The stability of communities may even rely directly on the potential of populations to constantly make these short-term evolutionary changes in a constantly fluctuating world. But we simply do not know, because much of community ecology remains a nonevolutionary science. Few studies on community dynamics include rapid evolution of species interactions as one of the working hypotheses for observed patterns of change over time, even though its potential importance is clear. Eliminating this disconnect between the study of rapid evolution of species interactions and the ecological analysis of overall community dynamics is becoming increasingly important as we fragment the diversity of life into smaller communities with less local genetic diversity.

The Geographic Mosaic of Evolving Interactions

The same need applies to linking the ecology and evolution of species interactions over broader geographic scales (Fig. 1). The most fundamental result from the past 30 years of study of the evolutionary structure of species is that many, possibly most, species are collections of genetically differentiated populations. Concomitantly, the most fundamental result from the study of species interactions within natural communities is that an interaction between a pair or group of species can differ greatly in outcome across landscapes. Hence, any theory of the evolution of species interactions must take into account three fundamental properties of interactions that act at scales above the level of local communities (*12*). Interactions may show selection mosaics, such that different traits and outcomes are favored by natural selection in different communities. Landscapes may produce coevolutionary hotspots (regions where true reciprocal selection acts on an interaction) embedded in a matrix (or along a gradient) of coevolutionary coldspots. In addition, the genetic landscape on which an interaction occurs may be constantly changing through gene flow, random genetic drift, and local extinction of populations. These three biological properties of interactions constitute a geographic mosaic view of coevolution that links evolutionary and ecological time across broad landscapes. It suggests that species interactions are likely to be in continual flux as they evolve in different ways in different populations, that local maladaptation may be an occasional and important outcome of continuing coevolution between species, and that few coevolved traits will spread across the entire geographic range of interacting species.

Recent mathematical models have begun to explore these components of the geographic mosaic. They have so far indicated three results, all of which require further analysis but collectively emphasize the importance of spatial structure in coevolutionary dynamics. First, metapopulation structure can sometimes allow for longer persistence of coevolving antagonistic interactions than is possible in interactions lacking such structure (*13*). Second, geographic gradients in the productivity of species (for example, prey birth rates) can create regions where reciprocal selection is strong (coevolutionary hotspots) or weak (*14*). Third, selection mosaics and gene flow can create novel dynamics, pro-

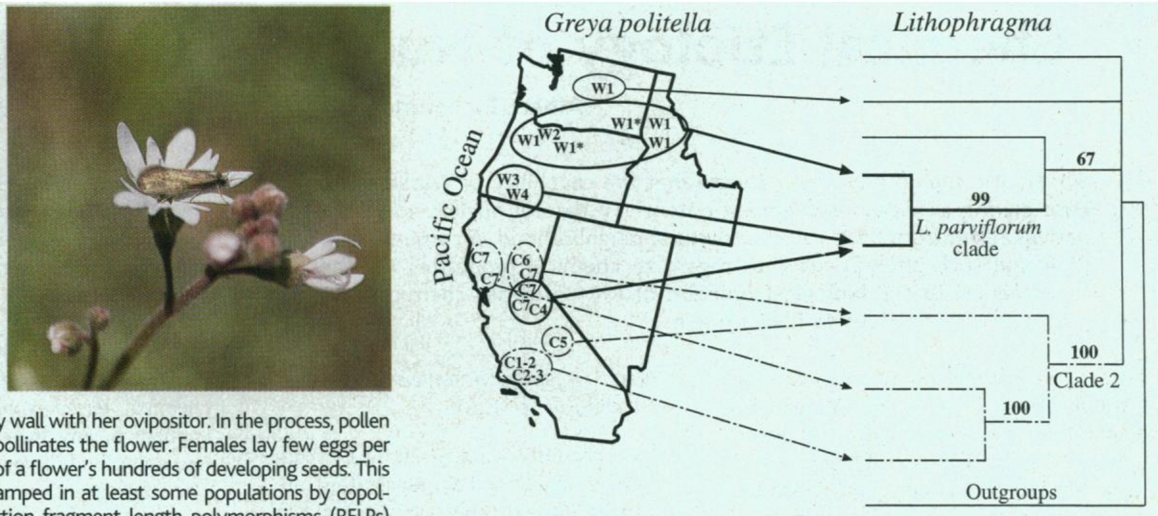

Fig. 1. Geographic structure of interacting populations of *Greya politella* (Prodoxidae) and its herbaceous host plants in the genus *Lithophragma* (Saxifragaceae) in western North America. The moths, which are close relatives of yucca moths, mate on host flowers. Once mated, a female lays her eggs in floral ovaries by sliding her abdomen down the corolla of each flower she visits, piercing the ovary wall with her ovipositor. In the process, pollen adhering to her abdomen pollinates the flower. Females lay few eggs per flower, and larvae eat few of a flower's hundreds of developing seeds. This potential mutualism is swamped in at least some populations by copollinators. Analysis of restriction fragment length polymorphisms (RFLPs) and mitochondrial DNA sequence of cytochrome oxidase I suggests a northern group of moth populations (W haplotypes; asterisks indicate multiple populations) and a southern group (C haplotypes). RFLP analysis of the plants indicates a monophyletic lineage with two well-resolved clades used by the moths. (Bootstrap values are shown on the cladogram.) These two clades differ in floral traits. Relationships to other *Lithophragma* populations and species limits are unresolved by this analysis, possibly as a result of cases of hybridization and polyploidization. Most W-clade moths use plants within the *L. parviflorum* clade (solid ovals, arrows, and branches on cladogram); most C-clade moths use plants within plant clade 2 (dashed ovals, arrows, and branches). Divergence among populations and use of the *L. parviflorum* clade by some C-clade moths creates a complex geographic mosaic in the genetic structure of the interaction. Data are from (*20*–*22*).

ducing overall coevolutionary trajectories quite different from those predicted by study of the component local interactions (*15*).

Some recent empirical studies have shown strong evidence for selection mosaics and coevolutionary hotspots (*16, 17*). For example, lodgepole pines differ geographically across northwestern North America in the sizes and shapes of their cones, which have been molded through a combination of adaptation to fire and two major seed predators, pine squirrels and red crossbills. In some regions the pines and crossbills show evidence of coevolution—large cones shaped in ways difficult for crossbills to handle, and crossbill morphology indicating local counteradaptation to these cones. In other parts of the Rockies, coevolution between the pines and crossbills is swamped by other selective forces, including predation on cones by abundant pine squirrels. Recent evidence suggests that the coevolutionary hotspots between crossbills and pines resulted from post-Pleistocene events, creating regions where pine squirrels were absent and crossbills were abundant and relatively sedentary. Similar selection mosaics are likely to be even more common in interactions involving parasitic species, which often have restricted potential for gene flow over large distances.

Coevolution and Human Welfare

As we learn more about the ongoing evolution of species interactions across Earth's complex landscapes, the effects seem to permeate every aspect of the health and welfare of human societies. A major spur to the development of the current ecological theory of evolving interactions came from models of the evolution of virulence in parasites (*18*). Those models suggested that differences among populations in the transmission dynamics of parasites could shape differences in the evolution of virulence. Continuing refinement of the theory of the evolution of virulence will be crucial to understanding how we can minimize the evolution of new virulent strains of pathogens that attack us, our domesticated animals, our crop plants, and conserved species within reserves.

For human pathogens, we can confront the problem partially through surrogate coevolution by developing procedural methods that mimic the evolution of new defenses. Antibiotics are the equivalent of mutant resistant hosts, but rapid evolution of resistance to antibiotics has shown how difficult it is for species to develop durable defenses against enemies. The same problems apply to the development of resistant crop varieties and the management of biological control agents. To deploy surrogate coevolution effectively, we require successful case studies to use as models. Those case studies are the interactions that have been shaped over millennia within natural biological communities. No amount of research funding could ever replace these valuable natural experiments.

We live at a time when we are increasingly manipulating much of Earth's biodiversity for our own ends. Indeed, Janzen (*19*) has referred to us as "the most coevolutionary animal of them all." As we continue to manipulate biodiversity, our experience so far with the evolution of virulence in diseases, short-term effectiveness of resistant crop varieties, and rapid evolution of interactions within natural communities suggests that the health and welfare of human societies will demand an increased understanding of the ongoing evolutionary dynamics of species interactions.

References and Notes

1. L. Margulis and R. Fester, Eds., *Symbiosis as a Source of Evolutionary Innovation: Speciation and Morphogenesis* (MIT Press, Cambridge, MA, 1991).
2. J. Maynard Smith and E. Szathmáry, *The Major Transitions in Evolution* (Freeman, San Francisco, 1995).
3. C. A. Kearns, D. W. Inouye, N. M. Waser, *Annu. Rev. Ecol. Syst.* **29**, 83 (1998).
4. O. Pellmyr *et al., Am Nat.* **148**, 827 (1996).
5. D. Schluter, *Science* **266**, 798 (1994).
6. M. Berenbaum and A. Zangerl, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 13743 (1998).
7. J. J. Burdon and P. H. Thrall, *Am. Nat.*, in press.
8. C. M. Lively, *ibid.*, in press.
9. N. B. Davies and M. de L. Brooke, *J. Anim. Ecol.* **58**, 225 (1989).
10. J. N. Thompson, *Trends Ecol. Evol.* **13**, 329 (1998).
11. G. Dwyer, S. A. Levin, L. Buttel, *Ecol. Monogr.* **60**, 423 (1990).
12. J. N. Thompson, *The Coevolutionary Process* (Univ. of Chicago Press, Chicago, 1994).
13. S. Gandon *et al., Proc. R. Soc. London Ser. B* **263**, 1003 (1996).
14. M. E. Hochberg and M. van Baalen, *Am. Nat.* **152**, 620 (1998).
15. S. L. Nuismer, J. N. Thompson, R. Gomulkiewicz, *Proc. R. Soc. London Ser. B* **266**, 605 (1999).
16. C. W. Benkman, *Am. Nat.*, in press.
17. M. A. Parker, *ibid.*, in press.
18. R. M. May and R. M. Anderson, *Proc. R. Soc. London Ser. B* **219**, 281 (1983).
19. D. H. Janzen, *Crawford Lectures R. Swed. Acad. Sci.* **3**, 1 (1984).
20. D. E. Soltis *et al., Syst. Bot.* **17**, 607 (1992).
21. J. M. Brown *et al., Mol. Ecol.* **6**, 215 (1997).
22. J. N. Thompson, unpublished data.
23. I thank C. Benkman, B. Cunningham, K. Merg, S. Nuismer, and T. Steury for helpful comments. Supported by NSF grant DEB-9707781 and by the National Center for Ecological Analysis and Synthesis (Coevolution Working Group), NSF grant DEB-9421535.

REVIEW

Chemical Etiology of Nucleic Acid Structure

Albert Eschenmoser

Systematic chemical studies indicate that the capability of Watson-Crick base-pairing is widespread among potentially natural nucleic acid alternatives taken from RNA's close structural neighborhood. A comparison of RNA and such alternatives with regard to chemical properties that are fundamental to the biological function of RNA provides chemical facts that may contain clues to RNA's origin.

> Wir wollen nicht nur wissen *wie* die Natur ist (und *wie* ihre Vorgänge ablaufen), sondern wir wollen auch nach Möglichkeit das vielleicht utopisch und anmassend erscheinende Ziel erreichen, zu wissen, warum die Natur *so und nicht anders ist.* [Albert Einstein (*1*, p. 126)]
>
> [We not only want to know *how* nature is (and *how* her transactions are carried through), but we also want to reach, if possible, a goal which may seem utopian and presumptuous, namely, to know why nature *is such and not otherwise*.]

Chemical etiology (*2*) of nucleic acid structure refers to systematic experimental studies aimed at narrowing the diversity of possible answers to the question of why nature chose the structure type of ribofuranosyl nucleic acids, rather than some other family of molecular structures, as the molecular basis of life's genetic system. The quest is to uncover the criteria by which nature arrived at this choice; comprehending these criteria in chemical terms would constitute a central element of any theory on the origin of the particular kind of chemical life known today. The strategy is to conceive (through chemical reasoning) potentially natural alternatives to the nucleic acid structure, to synthesize such alternatives by chemical methods, and to compare them with the natural nucleic acids with respect to those chemical properties that are fundamental to the biological function of RNA and DNA. Basic to this research is the

---

The Skaggs Institute for Chemical Biology at The Scripps Research Institute (TSRI), 10550 North Torrey Pines Road, La Jolla, CA 92037, USA, and Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule (ETH), Universitätstrasse 16, CH-8092 Zürich, Switzerland.