Chaos and evolution

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There is growing interest in applying nonlinear methods to evolutionary biology. With good reason: the living world is full of nonlinearities, responsible for steady states, regular oscillations, and chaos in biological systems. Evolutionists may find nonlinear dynamics important in studying short-term dynamics of changes in genotype frequency, and in understanding selection and its constraints. More speculatively, dynamical systems theory may be important because nonlinear fluctuations in some traits may sometimes be favored by selection, and because some long-run patterns of evolutionary change could be described using these methods.

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The idea that nonlinear dynamics (Box 1), and especially deterministic chaos, play an important role in biology has become more influential in recent years. Chaos has been suspected, and sometimes firmly documented, at the biochemical[1,2], organismal[3,4] and population[5,6] level. Nonlinear changes in phenotypes, gene frequencies or population sizes must affect the evolution of character traits (and clades), and the ways in which we study evolution.

In linear systems, only two kinds of long-term dynamics are possible: either the system stays constant, or it grows or declines at a constant rate. A familiar ecological example is the model for density-independent population growth:

$$N_{t+1} = rN_t$$

the population stays constant if $r=1$, and grows or declines at the constant rate r, if r is greater or less than 1, respectively.

Intuitively, this sort of model suggests that most biological systems are nonlinear: population size and other biological variables clearly vary over time without either disappearing or growing infinitely. Indeed, most biological models – whether describing physiology, changes in gene frequencies, population growth or interacting populations – are nonlinear. Such nonlinear systems can have several kinds of behavior not possible in linear systems, including cycles, quasicycles or chaos (see Box 1). 'Nonlinear dynamics' refers to these dynamical regimes that can occur only in nonlinear systems, and terms such as 'nonlinear methods' refer to special methods for analyzing them.

There are four areas where nonlinear dynamics may prove important to evolutionists. First, because the evolutionary process – as modeled in population genetic equations – is nonlinear, one can use nonlinear dynamics theory to analyze gene frequency change in response to deterministic forces like selection. Second, because many physiological and developmental mechanisms are nonlinear, the outcome of selection can be limited (or expanded) in ways that would not be anticipated without a nonlinear perspective. Third (and more speculatively), selection may sometimes promote nonlinear dynamics, including chaos, in some traits. Fourth (and still more speculatively), one can use nonlinear approaches to consider how adaptive peaks change as external conditions change.

Nonlinear dynamics and the genetics of populations

Even in simple models, gene and haplotype frequencies, and mean fitness, can change cyclically or chaotically. When such dynamics occur, Wrightian adaptive topographies no longer exist, because no fitness function[7] can be maximized. Perhaps more important, the traditional problem of explaining the maintenance of genetic diversity can disappear. We briefly review some results, and then consider their implications for evolutionary biology.

Simple genetic models

Complex dynamics can occur even under constant selection. Stable limit cycles – in gene and haplotype frequencies and mean fitness – can occur even in two-locus, two-allele models with constant selection and epistasis[8,9], and in one-locus, two-allele models with fertility selection[10].

Recombination may have varied effects in multilocus models, depending on selective regimes or genetic systems. For constant selection, complex dynamics are most likely to occur under intermediate recombination rates[11]. This is because Fisher's 'fundamental theorem of natural selection' applies when recombination rates are high (because the loci evolve almost independently) or low (because chromosomes behave like single genes). Populations therefore move up fitness gradients[12]. On the other hand, in a haploid frequency-dependent model, intermediate recombination rates tended to stabilize dynamics[13]. Clearly the problem of the dynamical consequences of recombination is still a wide-open field.

Models with more ecological realism

Cycles and chaos occur easily under frequency- and density-dependent selection. Gavrilets and Hastings[14] recently showed that chaos can occur over a wide range of parameters in a simple frequency-dependent model that generalizes a number of earlier models. Previous work[7,15] demonstrated complex dynamics in frequency-dependent models, but only for limited ranges of parameter values or when fitness was a complicated function of genotype frequencies. When parameters were near values where the dynamics change qualitatively (bifurcation points), Gavrilets and Hastings found intermittency – alterations between periods that appear to be chaotic and stable – as well as long chaotic transients in their model. Both cycles and chaos also can occur in models that allow gene frequencies and population size to vary[16–18].

Complex dynamics – and the coexistence of multiple genotypes – may thus be more likely in more ecologically realistic models. Quasicycles arise in a model of the evolution of gynodioecy[19]; because the parameter space was only partly explored, chaos may also occur in this model. A host–pathogen coevolutionary model by May and Anderson[20]

Box 1. Types of nonlinear dynamics

Three types of dynamics relevant to biology can only occur in nonlinear systems: limit cycles, quasicycles and chaos. A dynamical system may be 'attracting' – that is, the system resumes its dynamics after a perturbation – under these regimes as well as under equilibrial dynamics.

Systems on limit cycles repeat themselves regularly. Neighboring points on a limit cycle stay near one another; if one population is at the high point in this period-two cycle when another is at the low point, they will stay exactly out of phase.

Quasicycles resemble limit cycles, but the periods of the oscillations vary; the system never precisely repeats itself. Neighboring points remain near one another in quasicycles. Quasicycles often occur when periodic subsystems (e.g. physiological cycles) are coupled.

Chaotic oscillations do not have regular periods or amplitudes. Neighboring points tend to separate from one another at an exponential rate. This is why one cannot predict the system's behavior for more than a short time, even though the underlying mechanisms are deterministic.

shows a wider range of behavior. If population size is constant at carrying capacity, selection is frequency-dependent, and (for plausible parameter values) can lead to equilibria, cycles or chaos. If population size is regulated by the disease, both gene frequency and population size can fluctuate cyclically or chaotically. Finally, Holt[21] showed that when population dynamics are cyclic or chaotic, peripheral populations may maintain more genetic variation than they would under equilibrial dynamics.

Implications for population genetic studies

Adding population dynamics to population genetic models not only makes complex dynamics more likely; it also points to the danger of the traditional assumption that population size can be ignored. A recent phenotypic model of the evolution of conspecific brood parasitism[22] showed that the dynamics of phenotype frequencies and population size generally depend on one another, except in the special case of populations tending to stable equilibria.

These studies show that chaotic gene frequency changes are possible, but we do not know whether they actually occur. This issue can only be resolved empirically[23]. Unfortunately there are no extant data sets adequate to test such a hypothesis for even a single population. At present we can point only to the possibility of chaotic change in gene frequencies.

It should be possible in the coming years to change this situation through carefully designed studies. These would need to use short-lived organisms to obtain sufficiently long time series, and genotypes would need to be readily identifiable. Knowledge is growing rapidly of specific loci and their effects in organisms like *Caenorhabditis*, *Drosophila* and *Tribolium*. Methods for identifying genotypes are becoming faster and more affordable. Methods for testing hypotheses about dynamics are becoming more sophisticated[5,23]. For these reasons, we believe that well-designed laboratory studies of genetic dynamics may soon be within reach.

These results suggest caution in the application of optimality approaches. The central assumption of these models – that some quantity such as mean fitness is maximized – may often be violated. Evolutionary stable strategy (ESS) approaches have a similar difficulty because ESSs are defined as joint, constrained local optima. This does not negate the potential usefulness of optimality and ESS approaches in studying selection – only in predicting its outcome.

Nonlinear dynamics and gene substitutions

In the previous section, we discussed ways in which nonlinear dynamics can promote the coexistence of multiple genotypes. However, nonlinear genetic dynamics can also promote gene substitutions.

Complex spatial patterns – including spiral waves and chaos – can develop in nonlinear models of host–parasitoid systems[24]. Without a spatial component to the model, inefficient parasitoid genotypes fail to invade the population. Surprisingly, adding a spatial component creates new nonlinearities that allow mutants to invade, depending on where they are introduced. These invasions can lead to complete replacement[25]. Thus, the emergence of spatial patterns determines the outcome of natural selection. This result calls into question the definition of 'invasibility', which underlies much of population genetic theory.

Even without spatial dynamics, we speculate that there may be times when genotypes that are usually less fit can invade a chaotic resident population. This is because the complex shape of the chaotic attractor may include small regions where the net effect of the invader–resident interaction favors the 'less fit' mutants. Invasions may only succeed when the resident population is on such a vulnerable part of its attractor; they would not succeed otherwise. This speculation requires that the invaders appear in sufficiently large numbers such that their initial dynamics are nonlinear at first (they are approximately linear if initial numbers are very small).

Can the nonlinear dynamics underlying phenotypes sway selection?

The nonlinear dynamics of biochemical, cellular, physiological, neuronal and ecological systems can limit or enlarge the range of phenotypes reachable by selection. Small changes in parameters governing the system can cause it to qualitatively change its dynamics, that is, to 'bifurcate', say, from a steady state to a stable limit cycle (Box 2).

Bifurcations occur in physiologically plausible models of the cell cycle[26], ventilation rate and many other physiological processes[3]. In the cell cycle model, changing a rate parameter can cause the system to move between cycle periods that vary chaotically and periods that are constant[26]. In the ventilation model, changing a rate parameter can cause the system to move between normal and arrhythmic breathing[3]. There is some empirical evidence that these bifurcations also occur in real physiological systems[3]. Bifurcations also occur in models of population dynamics; an ongoing series of experiments with *Tribolium* beetles has shown that a biologically based model of population dynamics can predict bifurcations that can be induced in the laboratory[27]. Thus, bifurcations may be built-in to some basic physiological and demographic processes.

We suggest that bifurcations can sometimes correspond to abrupt changes in the range of phenotypes reachable by selection, regardless of whether they are bifurcations in physiological or population dynamics. We outline the sense

Box 2. What are bifurcations?

To understand what bifurcations are, consider one of the simplest nonlinear population models, the logistic map:

$$X_{t+1} = r X_t(1 - X_t)$$

For $r < 3$, the system reaches a steady state. At this 'bifurcation point', the stable equilibrium suddenly becomes unstable, and a stable limit cycle of period 2 simultaneously appears. Further increases in r cause a sequence of bifurcations in which the stable limit cycle of period n becomes unstable and simultaneously a new stable cycle of period $2n$ appears. As r passes the value 3.57, a chaotic attractor appears. Even within the chaotic region, there are bifurcation points; for example, there are values of $3.57 < r < 4$ for which there are stable limit cycles.

in which we believe that bifurcations may sometimes affect selective outcomes, and the sense in which this kind of effect may be similar regardless of whether the traits involved are physiological, developmental or demographic.

As a first example, consider a physiological trait with a stable cycle of period π, governed by a parameter μ. Selection might favor a slight increase in μ with the same period. Near a bifurcation of the underlying physiology, substitution of an 'increased-μ' allele would not have this effect: increasing μ causes a change to a cycle of different period (or to chaos). As a second example, consider a trait related to the intrinsic rate of population growth r, such as fecundity at some age i, b_i. Again, selection might favor a slight increase in b_i if the increase led to a larger steady-state population, but not if it led to the onset of population cycles. Near a bifurcation of the population dynamics, this favored phenotype cannot be achieved.

This purely verbal argument is supported by a theoretical study of the evolution of iteroparity versus semelparity[28,29]. Ferrière and Gato (Box 3) found that selection can favor one or the other life history, depending on whether bifurcations in population dynamics occur along a trade-off curve between adult survival and juvenile recruitment.

Bifurcations also restrict the applicability of some widely used models. Quantitative genetic approaches assume that fitness varies smoothly as a function of small allelic substitutions. This is not necessarily true near bifurcations of the physiological or population dynamics (and need not be true in nonlinear systems anyway). Optimality models are also likely to be misleading near such bifurcations, because fitness may not vary smoothly as a function of phenotypic value, and because some phenotypes may not be reachable.

Is chaos sometimes favored by selection?

If physiological or population dynamics are sometimes chaotic, it seems natural to ask whether this is because chaos is caused by selection. Two distinct cases are possible: chaos itself may be favored by selection, or it may be a by-product of selection on another trait[30]. We cannot presently distinguish between these hypotheses for any instance of biological chaos, but it is worth speculating about at least two kinds of mechanism suggested by Conrad[31] as candidates for adaptive chaos.

First, chaos may be adaptive in some cases of defense behavior. An example may occur in the behavior of foraging birds[32]. Bird vigilance can be characterized by the durations of scans (when the bird lifts its head and looks around) that alternate with feeding periods. Data from some species whose vigilance is likely to be anti-predatory (sandpipers, doves, finches) show typical features of chaos, such as high short-term predictability of scan and interscan durations, which decays exponentially over time. The long-term unpredictability may prevent waiting predators from timing their attack accurately, while the short-term predictability permits animals feeding in groups to improve their joint vigilance. This coordination also allows a whole flock to reduce the amount of time spent without surveillance by any of its members.

Second, chaos can provide maintenance and disturbance dissipation mechanisms: systems whose parts vary independently can be more efficient and persistent than tightly coupled systems. For example, chaos may help to prevent entrainment in neural networks. Physiologically plausible models of neurons can exhibit chaos[3]. It is conceivable that, without chaos, either very dull pacemaker activity, or highly

Box 3. Nonlinear dynamics and the evolution of itero- versus semelparity

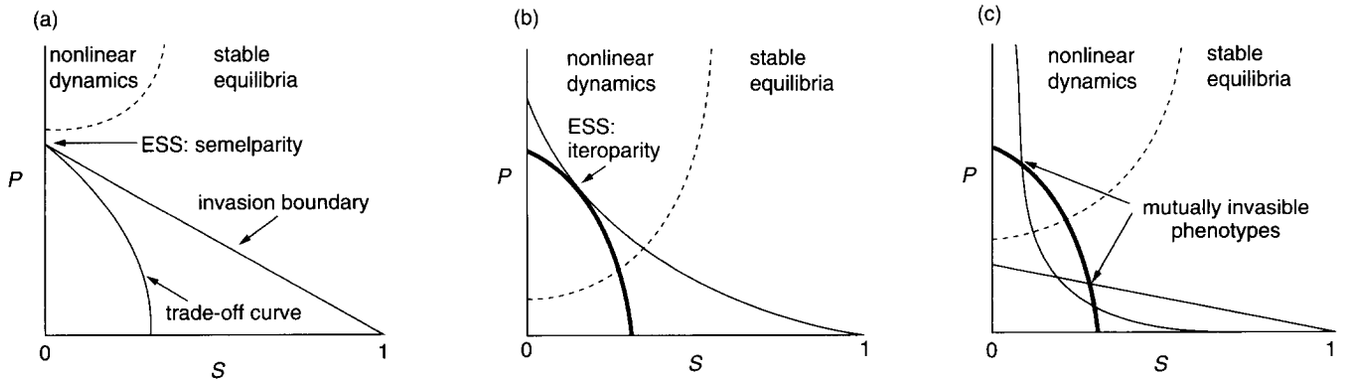
Ferrière and Gatto[28] studied the evolution of adult survival S and recruitment to adulthood P, when there is a trade-off between them (bold curves in figures below). What phenotype $\{S,P\}$ is the ESS? To each resident phenotype pair $\{S_{res},P_{res}\}$ we can attach an invasion boundary – a curve separating phenotypes able to outcompete the residents from those outcompeted by the residents. If the invasion boundary of a phenotype is just tangent to the trade-off curve, that phenotype is an ESS.

The dynamics of the resident population greatly affect the evolutionary outcome. Ferrière and Gatto used a delayed Ricker model that assumes overcompensatory density dependence (but other density-dependent functions would give similar results):

$$X_{t+1}^{res} = PX_{t-\alpha+1}^{res} e^{-\left(x_t^{res}+x_{t-1}^{res}+\ldots+x_{t-\alpha+1}^{res}\right)} + SX_t^{res}$$

where X_t^{res} denotes the adult resident population size at time t.

The shape of the invasion boundary is thus crucial, and it depends on the dynamics of the resident population[37]. It is a straight line if the dynamics are equilibrial, and a strictly convex curve if the dynamics are nonlinear. The invasion boundary of any resident phenotype passes through $\{S_{res},P_{res}\}$ itself, and through $(S=1,P=0)$.



If the trade-off curve is entirely contained in the region of stable equilibria (see figure a), the ESS is semelparous. If part of the trade-off curve is in the region of nonlinear dynamics [which may happen for a different value of age at maturity α (b)], the ESS is iteroparous. Finally, a polymorphism can be an ESS only if at least one of the phenotypes involved belongs to the region of complex dynamics (c).

explosive global neural firing patterns, would emerge. Neural chaos may maintain the functional independence of different parts of the nervous system; it could also provide a basis for adaptive chaos in behavior.

Another important example was recently provided by Schaffer and collaborators[33]. In challenging the view that group selection should make chaos rare in natural populations[34,35], they considered a spatially subdivided metapopulation whose local dynamics are governed by the Ricker or logistic map, plus local noise. This metapopulation was subject to stochastic global perturbations. Metapopulations with chaotic dynamics persisted longer than those with equilibrial or cyclic dynamics; cycles generally produced the least persistent metapopulation. These results are due to chaos' property of sensitive dependence on initial conditions, which promotes asynchrony and decoupling among local populations, increasing metapopulations' ability to withstand perturbations.

Adaptive chaos: could it really evolve?

If there are sometimes long-term group-level advantages to chaotic population dynamics, are there ever short-term, individual advantages? A life history study[28,29] (Box 3) showed that selection on several demographic parameters should often lead to chaos, especially in late-maturing species and when selection is constrained by steep trade-offs between traits.

Should we expect chaotic or stochastic mechanisms to be favored, where temporal variability is advantageous as a basis for defense behaviors or for maintenance and disturbance dissipation? Chaotic mechanisms may more often evolve for several reasons.

- Biological systems are often intrinsically nonlinear – the 'raw material' for generating chaos is already present. For example, population dynamics are generally nonlinear because of density dependence. Chaos may thus be an easy way to generate variability and uncertainty.
- By contrast, with random noise, chaos involves high short-term predictability that may also be selectively advantageous. It may be more difficult for organisms to achieve the same ends with autocorrelated stochastic processes.
- Even if stochasticity is intrinsically generated by a biological system, it may not produce sufficient levels of variability. Because chaotic systems have sensitive dependence on initial conditions, chaos can serve to magnify the internal randomness of the system.

Chaos may be selectively favorable in some circumstances, but cycles or equilibria are surely favored in others. It is time, however, to abandon the prejudice that selection always favors constancy at the biochemical, organismic and population levels.

Nonlinear dynamics in long-term evolution

The evolutionary walk along a limited-mutation pathway

In the discussion above, we considered evolution in the neighborhoods of evolutionary attractors – cycles, quasi-cycles and chaotic attractors – that did not change. But changes in selection and in the availability of mutant genotypes can affect both the location and the qualitative nature of these attractors. Recently there has been much interest in using nonlinear methods to study these long-term evolutionary changes.

Metz and his collaborators[36] have analyzed how ESSs come into being and disappear, and how they become (or cease to be) attracting, as the environment changes. An ESS is a combination of traits that, once established in a population, cannot be outcompeted by any other feasible phenotypes. Their theory assumes clonal reproduction or haploid genetics, and that mutations occur randomly but only one at a time (thus response to selection is strictly mutation-limited).

This theory also assumes that the sign of a simple function – the invader's long-term stochastic growth rate – decides the outcome of an attempt by phenotype Y to invade the set of resident phenotypes X. This growth rate is calculated as the dominant Lyapunov exponent of the resident community dynamics[37,38] (Box 4). Clearly a population growth rate like this is not a fixed quantity – it depends on the environment and on the composition and dynamics of the resident population. Therefore, it can change if the resident population evolves.

The central point of this theory is that the meanders of evolution reflect the randomness of mutation, but major trends in evolving traits are deterministic. These trends are determined by 'singular phenotypes' (Box 5), which move and change their nature (bifurcate) as the environment changes.

Bifurcations and long-term evolution

Metz *et al.* classified the ways that singular phenotypes can bifurcate in trait space. For example, an ESS (attracting or not) can be created or can disappear; a monomorphic ESS can become polymorphic, or vice versa. The analyses do not only concern ESSs: Lyapunov-unstable singular points can also occur. These points are like saddle-points: populations initially approach them, but are subsequently repelled from them. These points can bifurcate into attracting ESSs, or vice versa.

Such bifurcations are local: they occur when the local stability of a singular phenotype changes. Global bifurcations can occur as well, when a singular phenotype abruptly appears or disappears (Box 6). One way to interpret local bifurcations is as models for long-term changes in the genetic composition of a population, while global bifurcations could describe speciation and extinction. A study of a predator–prey–resource model, revealed a global bifurcation pattern that resembles a succession of stasis, punctuated equilibrium and gradualism[39].

This approach to evolutionary theory has important strengths. It provides an explicit (and explorable) connection between ecology and long-term evolution. Perhaps more

Box 4. Lyapunov exponents and their use for evolutionists

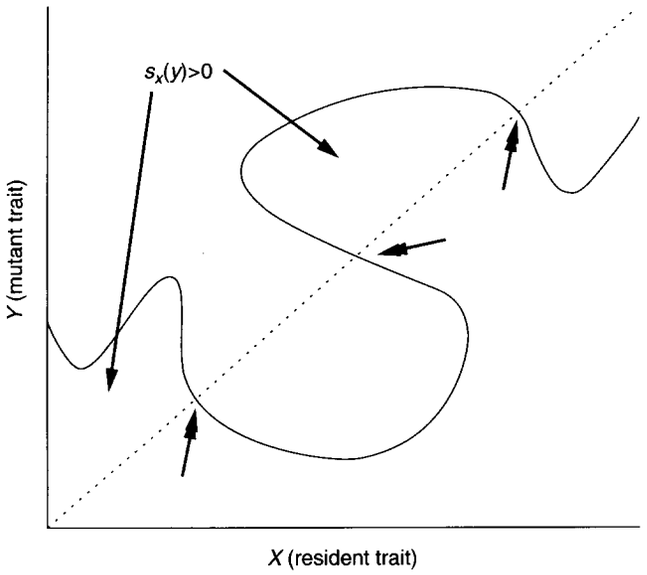
Lyapunov exponents provide a way to identify the qualitative dynamics of a system – for example, deciding whether it is chaotic. They can also be used to ask whether a system is invasible. This is because they describe the rate at which neighboring trajectories converge or diverge (if negative or positive, respectively) from one another in orthogonal directions. If the dynamics occur in an n-dimensional system, there are n exponents.

Ecologists may notice that Lyapunov exponents are similar to the eigenvalues used in local stability analysis. In fact, they are generalizations of these eigenvalues. Instead of describing what happens near a fixed point, Lyapunov exponents describe what happens near an entire trajectory.

To ask whether a system is chaotic, we find the Lyapunov exponents of the linearized system near a trajectory. Since chaos can be defined as divergence (on average) between neighboring trajectories, the presence of a positive exponent is diagnostic of chaos.

To ask whether a population is invasible, we study a new system: the resident population's dynamics embedded in an additional dimension (the number of invaders). Information on invasibility is given by the exponent corresponding to the new dimension. Positive values mean that the system diverges on average from the old attractor in this direction: the number of invaders will grow. Since Lyapunov exponents give the rates of divergence or convergence, this exponent is the long-term stochastic growth rate of the invader population.

Box 5. Singular phenotypes and adaptive dynamics



Here, we illustrate the Metz *et al.* theory of adaptive dynamics[36] for the case where the resident type can be described by one variable. The time unit of the dynamics is that taken to lose or fix a new mutation. Whether the mutant with trait Y can invade the resident with trait X is determined by the sign of the long-term stochastic growth rate of the invader – the dominant Lyapunov exponent (Box 4) of the X-type's dynamics[37,38].

$s_x(Y) > 0$: the mutant increases in frequency
$s_x(Y) < 0$: the mutant goes extinct

What happens where $s_x(Y)$ changes sign? Phenotypic singular points are the points where the line separating the negative from the positive values intersects the 45° line (see double-headed arrows in figure). An ESS is a special case of such a singular point. Using linear stability analysis of $s_x(Y)$ around a singular point $\hat{X}$, Metz *et al.* classified the properties of singular phenotypes. Defining:

$$c_{12} = \frac{1}{2}\frac{\partial^2 s_X(Y)}{\partial X \partial Y}\bigg|_{Y=X=\hat{X}}$$

and

$$c_{22} = \frac{1}{2}\frac{\partial^2 s_X(Y)}{\partial Y^2}\bigg|_{Y=X=\hat{X}}$$

they showed that:

- If $c_{22} < 0$, X is a local ESS; if $c_{22} > 0$, X is an 'Evolutionarily Unstable Strategy' (EUS).
- ESSs and EUSs can be either attracting ($c_{12} \leq c_{22}$) or repelling ($c_{12} \geq c_{22}$).
- Attracting EUSs are surrounded by mutually invasible phenotypes, and the same applies to approachable ESSs if $c_{12} < 0$.

Box 6. Local and global bifurcations in long-term evolution

Metz *et al.*[36] studied a simple case where two phenotypes compete, with Lotka–Volterra dynamics governed by the parameter ϵ. For small ϵ, the singular point is an attracting ESS. As ϵ increases, the resident population becomes invasible by nearby mutants, and then stable polymorphisms can develop. Further increases in ϵ change the shape of the mutant invasion rate still more, allowing additional phenotypes to invade, and others to go extinct. These local bifurcations occur when the local stability of a singular phenotypic point (Box 5) changes[36].

Global bifurcations occur when singular phenotypes appear or disappear. When global bifurcations occur, the property of singularity is passed on to quite a different phenotype. This can occur in response to gradual changes in parameters, and in the long-term stochastic growth rate. Thus, wild changes in these two quantities are not required to generate a pattern reminiscent of punctuated equilibrium.

important, it encourages the study of how evolutionary and ecological changes on different timescales are interrelated.

On the other hand, there are still important limitations to the theory. First, it is not yet explicitly genetic, so it can only be treated as heuristic. Second, the dominant Lyapunov exponent may not always be an appropriate invasibility criterion. Finally, continuous mutations (instead of one-step mutations) are known to influence the evolutionary walk[40]. Thus, there are important challenges ahead for this theory.

Conclusion

No simple dynamical system can be expected to capture the intricate nature of long-term evolution[41]. Attempts in this direction have nevertheless begun to appear in the literature. These mostly rely on verbal arguments, are not convincing and mainly show how one can misinterpret the ideas of nonlinear dynamics theory, by treating mathematical ideas as vague metaphors[42–44]. We think that the jargon of nonlinear dynamics can obfuscate, rather than clarify, when divorced from its mathematical roots.

On the other hand, ideas and methods from the theory of nonlinear dynamics may prove to be important to evolutionists. We have examined several distinct issues in the relationship between nonlinear dynamics and evolution. One issue is the effect of complex population and genetical dynamics on adaptation. When these nonlinearities operate, evolution cannot be assumed to be an adaptive process, and wrightian fitness landscapes are not defined. Standard evolutionary models may thus be more limited in their scope than is generally appreciated. The second issue is whether short-term nonlinear dynamics at the phenotypic level can be adaptive. Chaos is not necessarily an indicator of pathology; under some circumstances, natural selection may favor chaotic phenotypes. A final issue is whether large-scale evolutionary patterns can usefully be studied using methods from nonlinear dynamics. An initial theory attempting to do this is still in its early stages of development, but may prove important in organizing thinking about how ecology, population genetics and macroevolutionary patterns are interconnected.

Thus, chaos and other nonlinear phenomena can be important to evolutionists in several ways. Adding nonlinear analysis to the evolutionists' toolkit will require a grounding in the appropriate quantitative methods. We believe the potential benefits are well worth the effort.

Acknowledgements

We thank M. Gatto, B. Kendall and H. Metz for extensive discussions. R.F. was supported by US NIH grant HD-19949, awarded to R. Michod.

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Is mitochondrial DNA a strictly neutral marker?

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Variation and change in mitochondrial DNA (mtDNA) is often assumed to conform to a constant mutation rate equilibrium neutral model of molecular evolution. Recent evidence, however, indicates that the assumptions underlying this model are frequently violated. The mitochondrial genome may be subject to the same suite of forces known to be acting in the nuclear genome, including hitchhiking and selection, as well as forces that do not affect nuclear variation. Wherever possible, evolutionary studies involving mtDNA should incorporate statistical tests to investigate the forces shaping sequence variation and evolution.

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Mitochondrial genes have been employed extensively in evolutionary studies because of their uniparental mode of inheritance, high rate of evolution and relative simplicity of enzymatic amplification using 'universal' primers[1,2]. They have also been widely used in population studies owing to the general belief that gene frequencies are governed primarily by migration and genetic drift, and that most of the variation within a species is selectively neutral. However, factors other than genetic drift are expected to be important determinants governing the fate of mutations. The lack of normal recombination in mitochondria means that each genome has a single genealogical history and all genes will share that history. Any evolutionary force acting at one site will equally affect the history of the whole molecule. Thus, the fixation of an advantageous mutation by selection, for example, will cause the fixation of all other polymorphisms by a process known as genetic hitchhiking[3]. Even the quickly evolving noncoding origin of replication region cannot be assumed to have neutral allele frequencies because of its linkage to the rest of the genome. Selection need not even be acting on the mitochondrial genome itself: any maternally inherited factor could potentially influence haplotypic diversity. One such factor is the maternally inherited rickettsia *Wolbachia*, described below. The vast majority of studies employing mtDNA as an evolutionary marker have not attempted to test the basic assumptions of the neutral model: a constant mutation rate, a stationary allele frequency distribution, and a correlation between polymorphism levels and divergence. We will first review the evidence leading to the widespread belief that mtDNA conforms to the neutral model, and then discuss recent studies in humans, rodents and *Drosophila*, where the observed patterns of variation have been tested against these neutral theory predictions (Table 1).

Evidence for neutrality

A review of the literature leads us to conclude that the widespread acceptance of the selective neutrality of mtDNA follows from a series of plausibility arguments connecting