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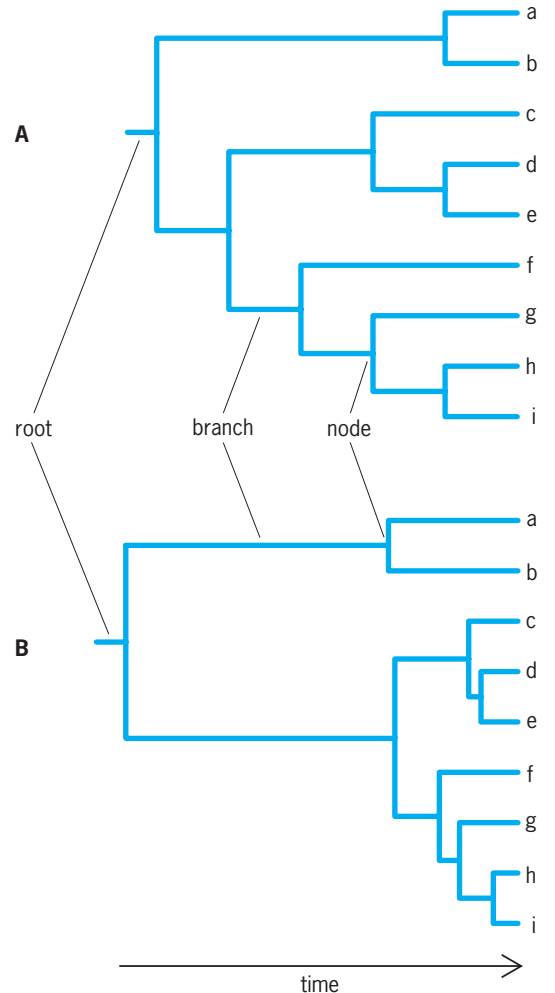
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 894 **Inferring patterns of diversification**

895 Episodes of prolific cladogenesis (branching of new
 896 taxa from common ancestral lineages), adaptive radiation
 897 (divergence of a species or single ancestral type into
 898 several forms that are each adaptively specialized for
 899 a specific environmental niche), species selection (the
 900 process responsible for the proliferation of species that
 901 have lower extinction and higher speciation rates), key
 902 innovations, and mass extinctions are a few examples of
 903 evolutionary phenomena involving differential rates of
 904 diversification (*speciation* minus *extinction* rate). Although
 905 traditionally based on patterns of fossil diversity
 906 chronicled in the paleontological record, the study of
 907 diversification increasingly relies upon information from
 908 *phylogenetic analyses* of extant species (estimates of
 909 evolutionary relationships that collectively comprise the
 910 Tree of Life). Tremendous technical progress in the
 911 generation of molecular sequence data and parallel
 912 theoretical, methodological, and computational advances
 913 in the analysis of those data have wrought an
 914 exponential increase of ever more reliable phylogenetic
 915 trees. Depending on the nature of the data and methods
 916 of analysis, phylogenetic trees can provide two sources
 917 of information relevant to the inference of diversification
 918 rates (Fig. 1): *topological* distribution of species
 919 diversity across branches of the tree and *temporal*
 920 distribution of branching events through time. These
 921 phylogenetic observations can be compared to expectations
 922 generated under various null models to explore numerous
 923 evolutionary phenomena.

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 925 **Stochastic models.** Diversification is an inherently
 926 stochastic (random) process: over a given time interval,
 927 two lineages with the same underlying probability of
 928 diversification may nevertheless possess substantially
 929 different rates of diversification. It is therefore
 930 necessary to compare our phylogenetic observations
 931 (on the topological distribution of species diversity or
 932 temporal distribution of branching events) to expectations
 933 generated by an appropriate stochastic branching model.
 934 Several statistical models have been proposed (see
 935 table). Most are stochastic Markov processes that model
 936 lineage extinction, μ , and/or speciation, λ , as
 937 instantaneous events that occur in continuous time with
 938 equal and independent probability along any tip of the
 939 growing tree. (In general, a stochastic Markov process
 940 assumes that in a series of random events the probability
 941 of an occurrence of each event depends only on the
 942 immediately preceding outcome.) During a brief
 943 interval Δt , every tip of the tree will speciate

946 with probability $\lambda(t)\Delta t$ and go extinct with probability
 947 $\mu(t)\Delta t$, such that $\lambda(t)$ and $\mu(t)$ are lineage-specific
 948 rates of speciation and extinction. The Markov family
 949 of branching processes includes four common models
 950 of increasing complexity:

- 951 1. The *constant-rate pure-birth* model (or *Yule*
 952 *model*) assumes a constant speciation rate and a zero
 953 extinction rate.
- 954 2. The *generalized pure-birth* model (or *equal-*
 955 *rates Markov* model) allows the speciation rate to
 956 vary through time, but assumes a zero extinction
 957 rate.
- 958 3. The *constant-rate birth-death* model assumes
 959 constant and nonzero rates for both speciation and
 960 extinction, provided that the net diversification rate
 961 is positive.



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Fig. 1. Phylogenetic trees can provide two sources of information for the study of diversification rates. Both the upper and lower trees specify identical evolutionary relationships among species a through i. However, the lengths of branches may be arbitrary (as in A) or drawn to reflect the (absolute or relative) timing of branching events (as in B). Two corresponding classes of methods have been developed. *Topological* (also referred to as *tree-balance*) methods rely exclusively on the species diversity of lineages descended from a common node in the tree. By contrast, *temporal* (also referred to as *tree-shape*) methods exploit estimates of the waiting times between speciation events in the tree.

Common stochastic branching process models used in the study of diversification rates

Family	Model	Parameters	Comments
Markov	Generalized birth-death	$\lambda(t), \mu(t)$	All Markov models assume speciation and extinction events are instantaneous, and that, even when $\lambda(t)$ and/or $\mu(t)$ may vary through time, they are nevertheless constant across every tip of the tree at any instant.
	Constant-rate birth-death	$\lambda(t) = \lambda, \mu(t) = \mu, \lambda \geq \mu$	Behavior of this model is well characterized mathematically.
	Generalized pure-birth	$\lambda(t), \mu(t) = 0$	Also referred to as the equal-rates Markov model. Equivalent to the constant-rate pure-birth model when temporal information is ignored.
	Constant-rate pure-birth	$\lambda(t) = \lambda, \mu(t) = 0$	Also referred to as the Yule model. Equivalent to the generalized pure-birth model when temporal information is ignored.
Non-Markov	Peripatric* pure-birth	$\lambda(t), \tau$	Most commonly used model owing to its tractable mathematical properties and convenient simplifying assumptions. All non-Markov models relax the assumption that speciation and extinction events occur instantaneously. Consequently, expectations may differ substantially from Markov models. Explicitly models diversification by peripheral isolates speciation. More realistic, but seldom used owing to difficulty in reliable estimation of the refractory period parameter, τ .
	Allopatric* pure-birth	$\lambda(t), \tau$	Explicitly models diversification by allopatric/vicariant speciation. More realistic, but seldom used owing to difficulty in reliable estimation of the refractory period parameter, τ .

*Allopatric speciation = Differentiation of populations in geographical isolation to the point where they are recognized as separate species. Peripatric speciation = A special version of allopatric speciation that occurs when one of the isolated populations has few individuals.

4. The *generalized birth-death* model permits speciation and extinction rates to vary through time.

Although less commonly used, non-Markov models are perhaps more realistic, in that they allow the process of diversification to have memory, as might arise, for example, when speciation events are followed by a refractory period in which newly formed species reestablish their geographic range or effective population size.

Stochastic branching models are central to both hypothesis testing and parameter estimation. Although our current focus is on the use of these models for generating expected (null) distributions, numerous approaches have also been developed that allow various diversification-rate parameters to be estimated from phylogenetic trees with an absolute time scale. For example, maximum-likelihood approaches (statistical techniques for which the likelihood distribution is so maximized as to produce an estimate to the random variables involved) can be used to fit the observed distribution of branching times to a constant-rate birth-death model to estimate rates of speciation and extinction.

Fundamental questions. Although differential rates of diversification are associated with myriad evolutionary phenomena, the study of these diverse processes ultimately entails a limited number of fundamental inference problems for which phylogeny-based methods have been developed.

Detecting variation in diversification rates across lineages. This inference problem addresses the question, "Have lineages diversified under significantly different rates?"

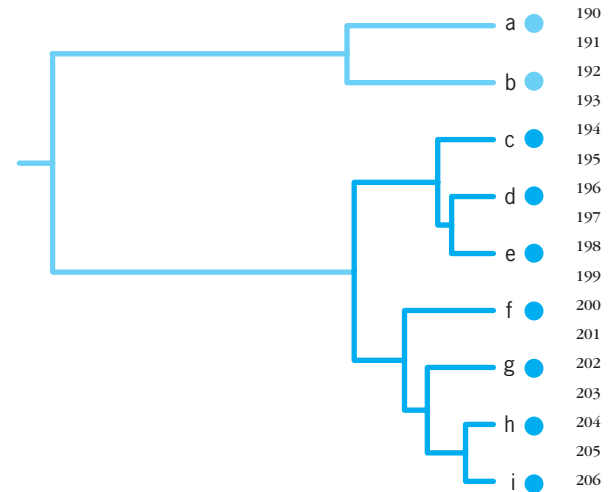
Detecting significant variation in rates of diversification has been used to investigate the prevalence of different modes of diversification (including adaptive radiation) in samples of estimated phylogenies, and also to evaluate whether a particular phylogenetic tree satisfies the assumptions of other inference methods (for example, for identifying diversification rate shifts through time; see below). In general, methods for detecting significant diversification rate variation involve statistics that variously summarize relevant aspects of the topological or temporal phylogenetic information. The value of the statistic is first calculated for the study tree. Monte Carlo simulation (a method that obtains a probabilistic approximation to the solution of a problem by using statistical sampling techniques) is then used to generate a null distribution of the statistic; this involves repeatedly simulating trees equal in size to the study tree under a stochastic model in which the probability of diversification is equal across all lineages (for example, the constant-rate pure-birth model). The statistic is calculated for each simulated tree, and resulting values collectively comprise a null distribution of the statistic against which the observed value can be compared to estimate the probability that all lineages in the study tree diversified under stochastically constant rates.

Locating shifts in diversification rate along branches. This second inference problem addresses the question, "Along which branches have significant changes in diversification rate occurred?" Locating significant shifts in diversification rate along branches of a tree has been used to investigate the influence of intrinsic

127 traits (key innovations, such as morphological, behav-
 128 129 of extrinsic events (key opportunities, such as the
 130 dispersal of continental lineages to oceanic islands).
 131 Relatively few methods have been developed to ad-
 132 dress this inference problem. One method, the rel-
 133 ative cladogenesis statistic, relies on temporal infor-
 134 mation to identify the set of k ancestral lineages that
 135 were contemporaneous at some arbitrary point in
 136 the past, t_k , that collectively gave rise to N extant
 137 species. The observed distribution of extant species
 138 diversity in each of the k ancestral lineages can be
 139 compared to the expected distribution generated
 140 under a stochastic branching model in which the un-
 141 derlying probability of diversification is equal among
 142 the set of lineages. Identification of an anomalously
 143 diverse lineage indicates that it diversified at a signifi-
 144 cantly higher rate than its contemporaries. The statis-
 145 tic can be evaluated over the entire duration of the
 146 tree (that is, by integrating t_k over the interval from
 147 the first to the last branching event) to assess the
 148 probability of a significant diversification rate shift
 149 along all internal branches.

150 *Exploring the association between traits and rates of diversi-*
 151 *fication.* This third inference problem addresses the
 152 question, “Are rates of diversification significantly
 153 correlated with a particular organismal trait?” Ident-
 154 ifying traits that are correlated with differential rates
 155 of diversification is critical to testing key innovation
 156 hypotheses, in which an evolutionary novelty is hy-
 157 pothesized to have promoted lineage diversification.
 158 Putative key innovations are typically morphological
 159 traits, but may also involve other biological attributes
 160 (associated with changes in ecology, physiology, behav-
 161 ior, etc.). Methods have been developed for both
 162 qualitative traits that occur in two or more discrete
 163 states and quantitative traits that exhibit a continuous
 164 number of states. These methods generally entail es-
 165 timating the evolutionary history of the putative trait
 166 (Fig. 2). A statistic is then calculated that reflects the
 167 association between the inferred trait history and di-
 168 versification rate. One such statistic, δ , provides a test
 169 of key innovations with two discrete states, i and j .
 170 The diversification rate is calculated for lineages in
 171 the study tree that possess alternate states of the trait,
 172 λ_i and λ_j , and the statistic is simply given by the dif-
 173 ference between the state-specific rates, $\delta = (\lambda_i - \lambda_j)$.
 174 A null distribution of this statistic is then generated
 175 by repeatedly simulating branching times for nodes
 176 in the study topology using a stochastic branching
 177 model in which the diversification rate is not corre-
 178 lated with the evolutionary history of the trait. The
 179 δ statistic is calculated for each simulated tree, and
 180 these values collectively comprise the null distribu-
 181 tion against which the observed value is compared to
 182 determine the probability that the trait is correlated
 183 with a significantly elevated diversification rate.

184 *Identifying shifts in diversification rate through time.* This
 185 fourth inference problem addresses the question,
 186 “Have rates of diversification significantly changed
 187 over time?” Detecting significant temporal shifts in
 188 diversification rate has been used to study the impact
 189 of extrinsic events that might simultaneously influ-



207
 208 **Fig. 2. Exploring association between organismal traits**
 209 **and rates of diversification. A hypothetical phylogenetic**
 210 **tree for species a through i includes estimates of the**
 211 **(absolute or relative) timing of branching events. The trait**
 212 **under consideration exhibits two discrete states, gray and**
 213 **black. Circles adjacent to the tips indicate the observed**
 214 **states in the extant species, and branches of the tree have**
 215 **been shaded to reflect the inferred evolutionary history of**
 216 **this trait. The key innovation hypothesis posits that the**
 217 **evolution of the black state promoted rates of**
 218 **diversification, which can be tested by means of a statistic**
 219 **that reflects the difference in state-specific rates of**
 220 **diversification.**

219 ence rates of diversification in all lineages of a study
 220 tree (for example, the onset of Pleistocene glacia-
 221 tions might uniformly have impacted rates of diver-
 222 sification in temperate groups). Establishing whether
 223 a particular tree has diversified under stochastically
 224 constant rates is also necessary to use other inference
 225 methods (for example, methods for estimating pa-
 226 rameters of constant-rate branching process models
 227 assume that rates have not changed over time). Sev-
 228 eral methods have been developed to identify tem-
 229 poral shifts in diversification rate. For example, the
 230 constant-rate test relies on a statistic, γ , that summa-
 231 rizes the relative distance of branching events from
 232 the root of a tree. The γ statistic is first calculated
 233 for the study tree: values of $\gamma < 0$ indicate that branching
 234 events are clustered near the root (that is, rates have
 235 decreased through time), whereas values of $\gamma > 0$
 236 indicate that branching events are concentrated to-
 237 ward the tips of the tree (that is, rates have increased
 238 through time). The observed value may then be com-
 239 pared to a null distribution of the γ statistic gen-
 240 erated by Monte Carlo simulation under a stochas-
 241 tic branching model in which diversification rates
 242 are constant through time. All methods for detecting
 243 shifts in diversification rate through time require that
 244 rates of diversification across lineages are stochas-
 245 tically constant, which can be ascertained with the
 246 methods described previously.

247 **Outlook.** Our ability to address these fundamental
 248 questions about diversification is currently unprece-
 249 dented. The profusion of phylogenetic research
 250 and the continuing development of phylogeny-based
 251 methods have profoundly transformed our capacity
 252 to discover the historical patterns and understand
 the processes of biological diversification.

For background information see BIODIVERSITY; EXTINCTION (BIOLOGY); MACROEVOLUTION; ORGANIC EVOLUTION; PHYLOGENY; SPECIATION; SPECIES CONCEPT; STOCHASTIC PROCESS in the McGraw-Hill Encyclopedia of Science & Technology. Brian R. Moore

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Integrated nanosensors

Integrated nanosensors are nanostructured systems in which several sensors of different types, including those sensitive to optical, magnetic, chemical, or biological stimuli, have been integrated on a single platform (Fig. 1). Integrated nanosensors are the subject of interdisciplinary research involving materials scientists, physicists, chemists, biologists, and engineers. The driving force behind the development of integrated nanosensors is the diverse range of applications (including the detection of explosives, gas-phase toxins, pathogens in food products, and so forth) and the development of sensitive biosensors (DNA, proteins, bacteria, neurons, and so forth).

Feynman's vision. It is generally accepted that a visionary discussion by Richard P. Feynman in 1959 of the problems and promise of miniaturization constituted the starting point for the new field that today is called nanotechnology. The spirit of this discussion was embodied in his statement: "I will not now discuss how we are going to do it, but only what is possible in principle—in other words, what is possible according to the laws of physics."

Nanoscale engineering is being applied to the miniaturization of the current generation of sensors and the creation of entirely new classes of sensors. The ability to manufacture a sensor's components—including power supply, sensing receptor, and transmitter—at a fraction of traditional sizes will allow sensors to be much smaller and thus much more easily incorporated into the environment for a broadening range of sensing applications. Nanoscale engineering could also improve the sensing element itself, which would be particularly important since shrinking the sensor size would also decrease the area of the sensor available for detection.

Use of nanoparticles. There are two kinds of nanosensors: nanoparticle sensors, which are intended to detect and study nanoparticles, and

nanoparticle-based detector systems, which rely on the formation of nanoparticles that have been developed as sensing species. Nanoparticles are unique tools as sensors for three reasons.

First, nanoparticles are similar in size to many proteins. This is part of the reason they can operate well inside cells. The sensors, which can detect a wide variety of proteins, could serve as a tool for diagnosing diseases like cancer by identifying the malformed proteins made by sickly cells. For instance, gold nanoparticles with attached fluorescent dyes have been developed by V. Rotello and his team to detect specific proteins. Depending on its shape, a particular protein molecule stimulates certain sensors to release their dye and glow. By analyzing the pattern of glowing, the researchers can identify the protein.

Second, nanoparticles possess unique physical characteristics with sensitivities orders of magnitude better than conventional devices and provide such performance advantages as fast response and portability. For example, N. J. Halas and her collaborators fabricated nanoshells and nanorice, which consist of nonconducting cores that are covered by metallic shells. (Nanorice consists of prolate spheroidal nanoparticles that resemble grains of rice and have dielectric cores and metallic shells.) Nanoshells are about 10,000 times more effective at surface-enhanced Raman scattering (SERS) than traditional systems. Nanoshells provide an opportunity to design all-optical nanoscale sensors—essentially new molecular-level diagnostic instruments—that could detect as little as a few molecules of a target substance.

Third, nanoparticles have unique physical properties that do not exist in bulk materials. For example, the optical response of gold colloidal nanoparticles (5–20 nm in size) is characterized by a localized

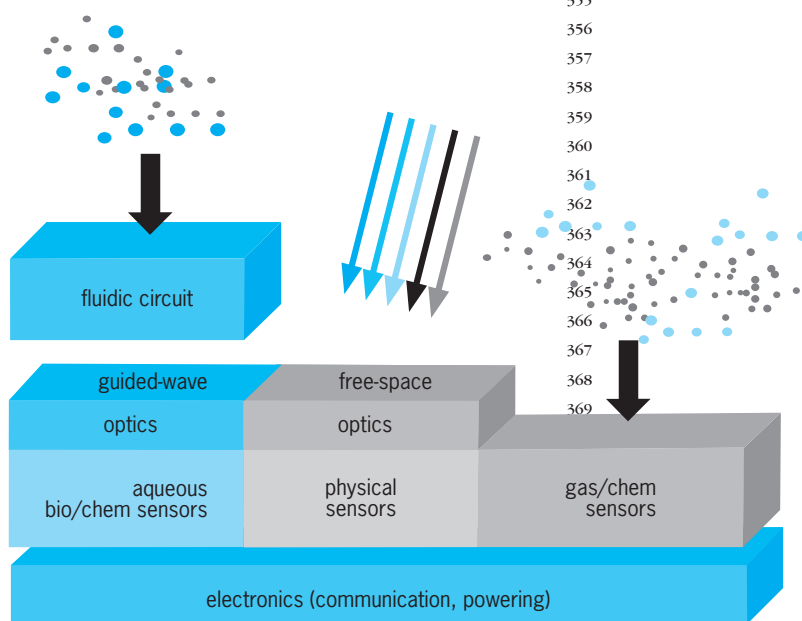


Fig. 1. Scheme of an integrated nanostructured supersensor. (From <http://nanosensors.ucsd.edu/Introduction.htm>, courtesy of I. K³Schuller)