

UNIDENTIFIABLE DIVERGENCE TIMES IN RATES–ACROSS–SITES MODELS

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ABSTRACT. The *rates–across–sites* assumption in phylogenetic inference posits that the rate matrix governing the Markovian evolution of a character on an edge of the putative phylogenetic tree is the product of a character-specific scale factor and a rate matrix that is particular to that edge. Thus, evolution follows basically the same process for all characters, except that it occurs faster for some characters than others. To allow estimation of tree topologies and edge lengths for such models, it is commonly assumed that the scale factors are not arbitrary unknown constants, but rather unobserved, independent, identically distributed draws from a member of some parametric family of distributions. A popular choice is the gamma family. We consider an example of a clock-like tree with three taxa, one unknown edge length, a known root state, and a parametric family of scale factor distributions that contain the gamma family. This model has the property that, for a generic choice of unknown edge length and scale factor distribution, there is another edge length and scale factor distribution which generates data with exactly the same distribution, so that even with infinitely many data it will be typically impossible to make correct inferences about the unknown edge length.

1. INTRODUCTION

Beginning with the germinal work [Fel78], statistically-based estimations of phylogenetic trees have become popular in molecular systematics, with Bayesian [HR01] and maximum likelihood methods [Swo96, GG03, PM00, Lew98, OMHO94] used with increasing frequency. Such statistically-based methods assume that the observed sequences are the result of a stochastic process that has operated on a tree, and they make assumptions about the stochastic process (that is, model) that has produced the data.

A fundamental question about any statistical model is whether it is identifiable: that is, whether different parameter values lead to different probability distributions for the data, so that, in particular, there is some hope of estimating the parameters with increasing accuracy as the amount of data increases. These questions have been investigated extensively for certain models used in phylogenetic inference (see, for example, [Ste94, Cha96]).

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Many models used in phylogenetic inference combine a (typically parameter rich) model of individual site evolution with the assumption that the different sites evolve under a *rates-across-sites* model, so that each site c has an associated rate of evolution r_c which is constant across the tree. Thus, sites evolve under essentially the same evolutionary process, and are just scaled up (or down) versions of each other. (Thus, the rates-across-sites assumption implies that if one site is expected to evolve twice as fast as another site on edge e , then it is expected to evolve twice as fast as the other site on every edge.)

Such rates-across-sites models in which each character has its own unknown scale factor are discussed in [SOWH96], but these models still pose difficult inferential problems. As remarked in Chapter 13 of [Fel04]:

As the number of sites increases, the number of parameters being estimated rises correspondingly. This is worrisome: in such “infinitely many parameters” cases maximum likelihood often misbehaves and fails to converge to the correct tree as the number of sites increases.

Indeed, our own example below shows that relative edge-lengths are, in general, unidentifiable for such models. (We discuss a situation in which the unknown scale parameters for the respective characters are unobserved, independent, identically distributed, realizations of some distribution belonging to a particular family of distributions. However, if edge-lengths are not identifiable in our set-up, then they certainly won't be identifiable in the analogous set-up where the scale parameters are arbitrary.)

A popular ‘fix’ that has been proposed for this problem is to adopt a *random effects* approach and suppose that the successive scale factors r_c are unobserved, independent random draws from a member of some parametric family of distributions. This reduces the dimensionality of the problem by replacing the deterministic sequence of r_c parameters with the small number of parameters that describe the generating distribution (see, for example, [UC71, NCF76, Ols87, HKY87, Yan96]).

A standard choice of distribution for the random scale factors is the two-parameter family of gamma distributions. This family has the mathematical advantage that likelihoods still have analytically tractable closed forms, and it was shown for a wide class of substitution models in [Rog01] that edge-lengths are identifiable in this setting. The choice of the gamma family is often supported by claims that it is sufficiently flexible to mimic the variation of

rates between characters that is likely to be seen ‘in practice’. There also appears to be a general sense among many practitioners that the choice of distributional family for the scale factors is primarily a matter of convenience and that, provided the family is rich enough, substantially correct inferences of relative edge-lengths will be possible with sufficient data. To our knowledge, there is no argument in any setting justifying why an assumption of an exact gamma distribution for the scale factors is biologically reasonable. As remarked in [Fel04]:

There is nothing about the gamma distribution that makes it more biologically realistic than any other distribution, such as the lognormal. It is used because of its mathematical tractability.

It was shown in [SSH94] that the use of random scale factors might not be completely without problems. In their paper they gave an example of a specific choice of edge-lengths for each tree topology and a specific choice of discrete distribution for the scale factors (rather than a continuous distribution such as a gamma) such that the resulting distribution for the data under the Neyman two-state model is the same for all tree topologies.

In this paper we go further, at least in some directions. We consider a rooted tree with three taxa and one unknown edge-length (with the remaining edge-lengths either known or fixed by the clock-like constraint that all lineages have the same total length), and a particular ten-parameter family \mathcal{F} of scale factor distributions with a certain nine-parameter sub-family \mathcal{G} of \mathcal{F} . We show that for a *generic* choice of unknown edge-length τ and model in $G \in \mathcal{G}$ there is a choice of edge-length $\sigma \neq \tau$ and model in $F \in \mathcal{F}$ with the property that data generated according to the Neyman 2-state model with known ancestral state, scale factor distributed according to G , and edge-length τ , has the same distribution as data generated according to a Neyman 2-state model with the same ancestral state, scale factor distributed according to F , and edge-length σ . Thus, even with infinitely many data, it would be impossible to decide whether the unknown edge-length is σ or τ – even if one somehow knew in advance that the distribution for the scale parameter was one of either F or G . Here the term *generic* means that the set of exceptional models G and edge-lengths τ for which no corresponding F and σ exist is a lower dimensional subset of $\mathcal{G} \times \mathbb{R}_+$. In particular, the set of G and τ that have corresponding F and σ is an everywhere dense open subset of $\mathcal{G} \times \mathbb{R}_+$.

Moreover, the family \mathcal{F} consists of distributions with smooth, unimodal, densities that possess moments of all orders. In this sense, each distribution in \mathcal{F} is as “nice” as a gamma distribution. Of course, the two-parameter family of gamma distributions is simpler than the ten-parameter family \mathcal{F} . However, the use of \mathcal{F} is essentially a technical device in our analysis. We could have described our results by simply saying that for a generic unknown edge-length τ there is a corresponding edge-length $\sigma \neq \tau$, and two scale parameter distributions G and F , such that data generated according to the Neyman 2-state model with known ancestral state, scale factor distributed according to G , and edge-length τ , has the same distribution as data generated according to a Neyman 2-state model with the same ancestral state, scale factor distributed according to F , and edge-length σ . In particular, unidentifiability is not inherently a case of “over-parametrization”: the effect can be produced when we have just a finite number of possible parameter values and is not produced by having a continuous space of possible parameter values with too high a dimension. We have included the mention of the families \mathcal{F} and \mathcal{G} in the description of our results to stress that the unidentifiability problem is, in some sense, generic.

The family \mathcal{G} (and hence \mathcal{F}) contains all the gamma distributions as a subfamily. Any gamma distribution and any edge-length t will have a distribution $G \in \mathcal{G}$ and τ arbitrarily close to them such that there is a corresponding $F \in \mathcal{F}$ and $\sigma \neq \tau$ as above.

Our example applies not only to the Neyman model but also to any model such as the binary General Time-Reversible model that contains the Neyman model as a sub-model. Furthermore, our example applies to the General Time-Reversible on an arbitrary finite state-space, because one can choose the substitution rate matrices for such a model to be sufficiently symmetric so that a suitable many-to-one binary encoding of the model is Markovian and evolves according to the Neyman model.

We should point out that we construct our example using a perturbative technique. Consequently, the edge-lengths τ and σ that arise will be “close” to each other. However, our analysis doesn’t rule out the possibility that a similar example could be produced with edge-lengths that are “far apart”. In order to fully assess the practical implications of the phenomenon we have observed, further research is necessary to quantify just how distant two edge-lengths can be and still have corresponding scale parameter distributions that lead to identical distributions for the data. Moreover, this is not a purely mathematical question,

because the notions of “close” and “far apart” are dependent on the scientific question being investigated with a particular data set.

Also, we note that if we actually knew the distribution of the scale parameter in our three taxa example, then the unknown edge-length could be recovered uniquely from the distribution of the data, and this is so for an arbitrary scale parameter distribution, not just the ones we consider in this paper. Moreover, the functional that recovers the unknown edge-length is continuous in the scale parameter distribution when one equips the space of distributions with the usual topology of weak convergence. This suggests that if we somehow knew the scale parameter distribution up to some small error, then this would constrain the errors we could make in determining the edge-length. However, it is not clear how well one can identify the relevant features of the scale parameter distribution: the functional that recovers the unknown edge-length depends on the functional inverse of the Laplace transform of the scale parameter distribution and hence, *a priori*, on the entirety of the distribution rather than some finite dimensional set of features such as the first few moments, and so there is an apparent need to estimate the whole distribution quite well. Once again, this is not solely a theoretical matter and the extent to which this continuity observation is relevant will depend partly on context.

The rest of the paper is organized as follows. We begin with an introduction of the mathematical terms in Section 2, and we present our example in Section 3. We conclude with a discussion of the ramifications of this result, and directions for future research in Section 4.

2. BASICS

In phylogenetic inference, the data are the respective states of an ensemble of characters exhibited by each of a collection of taxa. The most commonly used statistical models in the area are parameterized by a rooted tree with edge-lengths (which typically represent the expected number of times a site changes on the edge when the substitution mechanism is in equilibrium) and a set of Markovian stochastic mechanisms for the evolution of successive characters down the tree. It is usually assumed that the observed states for different characters are statistically independent. The goal of phylogenetic inference is to estimate

some or all of: the shape (topology) of the tree, the lengths of the edges, and any unknown parameters involved in the specification of the evolution mechanism.

We will restrict attention to the case where each character has the same finite set of possible states. For example, the characters could be nucleotides exhibited at different sites on the genome, and so each character is in one of the four states $\{A, G, C, T\}$. In the example we will give in this paper, we will work with (binary) characters having one of two possible states, 0 or 1. For each character c and each edge e in the tree, one then has a rate matrix $Q_{c,e}$ that describes the evolutionary process on edge e for character c (we refer the reader unfamiliar with continuous time Markov chains to a standard text such as [GS01]). Thus, given that the character is in state i at the beginning of the edge, the conditional probability of the (possibly unobserved) event that it is in state j at the end of the edge is the (i, j) entry of the matrix exponential $\exp(tQ_{c,e})$, where t is the length of e . The matrix $Q_{c,e}$ has row sums equal to 0 and non-negative off-diagonal entries: $-Q_{c,e}(i, i)$ is the rate at which the character leaves the state i and $-Q_{c,e}(i, j)/Q_{c,e}(i, i)$ is the probability that it jumps to state j when it leaves state i .

Single site substitution models can range from the very simple (e.g. the Jukes-Cantor and Kimura 2-parameter models) to the very complex (e.g. the General Markov Model), which, for a fixed character c , allow the $Q_{c,e}$ matrices to vary significantly from edge to edge, and to have many free parameters. However, the variation between the different matrices obtained by varying the character c is typically more proscribed. The most complex model is where there are no constraints placed on the $Q_{c,e}$; this is called the “no common mechanism model” [TS97]. Under this no common mechanism model, it will clearly be difficult to recover any information about edge-lengths. A simple class of models in which it is possible to extract information about edge-lengths is the class in which $Q_{c,e}$ is the same for all characters c and edges e . Even for this simple model, there is – as is well-known – a certain lack of identifiability, because the same probability distribution for the data would arise if the common rate matrix was multiplied by a common scale factor and all edge-lengths were divided by that same factor. Thus, even for this model one can only hope to make inferences about relative edge-lengths unless at least one edge-length is assumed to be known.

The more commonly used models assume that the different $Q_{c,e}$ matrices are themselves the product of a rate matrix specific to the edge e , and a scale factor that is specific to

the character c . Thus, the evolutionary process that governs one character is identical, up to a scalar multiple, to that governing another character. This is the *rates-across-sites* assumption in molecular phylogenetics, and it has the rather strong implication that if a character c is expected to evolve twice as fast on edge e as character c' , then c is expected to evolve twice as fast on *every* edge in the tree.

The assumption of a common rate matrix for all edges is the *molecular clock* assumption, which is known to be untenable in many situations [JN90, Ree92]. Perhaps the next simplest class of models is the family of *rates-across-sites* models in which $Q_{c,e}$ is the product of a character-specific scale factor and a rate matrix that is common to all characters and edges. That is, $Q_{c,e}$ is of the form $r_c \bar{Q}$. In other words, evolution follows basically the same pattern on all lineages for all characters, except that it occurs faster for some characters than others.

Because of the inferential difficulties of allowing the rates for the different sites to be arbitrary, these random scale factors are typically assumed to be drawn from a distribution. Of the many possible distributions, the most popular distributions are the two-parameter gamma distributions. In fact, in practice, almost all estimations of phylogenetic trees are based upon the assumption that the rates across sites are drawn from a gamma distribution, or a discretized gamma distribution. Also, it is sometimes assumed that certain characters are invariable (that is, that the scale parameter for such sites is 0).

3. THE EXAMPLE

We will present an example of a tree with three taxa, and with sites evolving under the Neyman two-state model (i.e., the two-state version of the Jukes-Cantor model of evolution) with a known state at the root.

Consider a tree with three taxa x , y , and z , a root v , and internal node w that is ancestral to x and y . The edges (w, x) and (w, y) have a known length, which we can take as 1. Suppose further that the edge (v, w) has unknown length σ and that the tree is clock-like, so that the edge (v, z) has length $\sigma + 1$.

Suppose there are $\{0, 1\}$ -valued characters labelled $1, 2, \dots$ that have evolved on this tree. The i^{th} character evolves according to the Neyman model with rate r_i . That is, the transition

matrix for an edge of length t is

$$\frac{1}{2} \begin{pmatrix} (1 + \exp(-2r_it)) & (1 - \exp(-2r_it)) \\ (1 - \exp(-2r_it)) & (1 + \exp(-2r_it)) \end{pmatrix} =: \begin{pmatrix} p_t^{(i)}(0,0) & p_t^{(i)}(0,1) \\ p_t^{(i)}(1,0) & p_t^{(i)}(1,1) \end{pmatrix},$$

say.

The probability distribution for the i^{th} character (that is, the marginal likelihood for this character) is given as follows. Suppose it is known that the state $s_v \in \{0, 1\}$ is exhibited by the root v . Then the probability that states s_x , s_y , and s_z are exhibited by the taxa x , y , and z is

$$\sum_{s_w \in \{0,1\}} p_\sigma^{(i)}(s_v, s_w) p_1^{(i)}(s_w, s_x) p_1^{(i)}(s_w, s_y) p_{\sigma+1}^{(i)}(s_v, s_z).$$

Assume that successive characters evolve independently.

The probability distribution for the i^{th} character is thus easily seen to be a linear combination of the terms

$$\begin{array}{ccc} 1 & & \\ \exp(-2r_i) & \exp(-4r_i) & \exp(-2r_i\sigma) \\ \exp(-2r_i(1 + \sigma)) & \exp(-2r_i(2 + \sigma)) & \exp(-2r_i(3 + \sigma)) \\ \exp(-2r_i(1 + 2\sigma)) & \exp(-2r_i(2 + 2\sigma)) & \exp(-2r_i(3 + 2\sigma)) \end{array}$$

As one of the referees of this paper remarked, by explicitly writing out the likelihood or using Corollary 8.6.6 of [SS03] one can show that only the terms 1 , $\exp(-4r_i)$, $\exp(-2r_i(1 + \sigma))$, $\exp(-2r_i(2 + 2\sigma))$, and $\exp(-2r_i(3 + \sigma))$ actually appear, but we do not need to use this fact.

As described in the Introduction, we will adopt the random effects approach and assume that the r_i are, in fact, realizations of a sequence of independent, identically distributed random variables that we will denote by (A_i) .

We are interested in finding such a sequence (A_i) and another independent, identically distributed sequence (B_i) such that the distribution for the data induced by the random choice of scale factors (A_i) is the same as that induced by the (B_i) for **another** choice of edge-length $\tau \neq \sigma$.

We thus have to find positive random variables A and B with distinct distributions and distinct positive constants σ and τ with the property that

$$\begin{aligned}\mathbb{E}[\exp(-2A)] &= \mathbb{E}[\exp(-2B)] \\ \mathbb{E}[\exp(-4A)] &= \mathbb{E}[\exp(-4B)] \\ \mathbb{E}[\exp(-2\sigma A)] &= \mathbb{E}[\exp(-2\tau B)] \\ &\dots\end{aligned}$$

$$\mathbb{E}[\exp(-2(3+2\sigma)A)] = \mathbb{E}[\exp(-2(3+2\tau)B)].$$

Take A to have the distribution which has Laplace transform

$$\mathbb{E}[\exp(-\zeta A)] = \left\{ \prod_{i=1}^9 (1 + d_i \zeta)^{-1} \right\} (1 + h\zeta)^{-1} (1 + k\zeta)^{-1}$$

for positive parameters d_1, \dots, d_7, h, k . Thus A has the distribution of the sum of 9 independent exponential random variables with respective means d_1, \dots, d_7, h, k . Take B to have the distribution which has Laplace transform

$$\mathbb{E}[\exp(-\zeta B)] = \left\{ \prod_{i=1}^7 (1 + g_i \zeta)^{-1} \right\} (1 + \ell \zeta)^{-2}$$

for positive parameters g_1, \dots, g_7, ℓ . Thus B has the distribution of the sum of 9 independent exponential random variables with respective means $g_1, \dots, g_7, \ell, \ell$.

Define maps $P : \mathbb{R}_+^{10} \rightarrow \mathbb{R}_+^9$ and $Q : \mathbb{R}_+^9 \rightarrow \mathbb{R}_+^9$ by

$$\begin{aligned}P_1(\sigma, d_1, \dots, d_7, h, k) &= \left\{ \prod_{i=1}^7 (1 + 2d_i) \right\} (1 + 2h)(1 + 2k) \\ P_2(\sigma, d_1, \dots, d_7, h, k) &= \left\{ \prod_{i=1}^7 (1 + 4d_i) \right\} (1 + 4h)(1 + 4k) \\ P_3(\sigma, d_1, \dots, d_7, h, k) &= \left\{ \prod_{i=1}^7 (1 + 2d_i \sigma) \right\} (1 + 2h\sigma)(1 + 2k\sigma) \\ &\dots \\ P_9(\sigma, d_1, \dots, d_7, h, k) &= \left\{ \prod_{i=1}^7 (1 + 2d_i(3 + 2\sigma)) \right\} (1 + 2h(3 + 2\sigma))(1 + 2k(3 + 2\sigma))\end{aligned}$$

and

$$\begin{aligned}
Q_1(\tau, g_1, \dots, g_7, \ell) &= \left\{ \prod_{i=1}^7 (1 + 2g_i) \right\} (1 + 2\ell)^2 \\
Q_2(\tau, g_1, \dots, g_7, \ell) &= \left\{ \prod_{i=1}^7 (1 + 4g_i) \right\} (1 + 4\ell)^2 \\
Q_3(\tau, g_1, \dots, g_7, \ell) &= \left\{ \prod_{i=1}^7 (1 + 2g_i\tau) \right\} (1 + 2\ell\tau)^2 \\
&\dots \\
Q_9(\tau, g_1, \dots, g_7, \ell) &= \left\{ \prod_{i=1}^7 (1 + 2g_i(3 + 2\tau)) \right\} (1 + 2\ell(3 + 2\tau))^2.
\end{aligned}$$

We want to show that $P(\sigma, d_1, \dots, d_7, h, k) = Q(\tau, g_1, \dots, g_7, \ell)$ for some choice of parameters with $\sigma \neq \tau$.

Write $J(\sigma, d_1, \dots, d_7, h, k)$ for the Jacobian matrix of the mapping $(d_1, \dots, d_7, h, k) \mapsto P(\sigma, d_1, \dots, d_7, h, k)$ (thus, J is a 9×9 matrix). Write $K(\tau, g_1, \dots, g_7, \ell)$ for the Jacobian matrix of Q . A straightforward check with a computer algebra package such as *Mathematica* shows that the polynomials $\det J$ and $\det K$ are not identically 0. (While the determinants could possibly be computed symbolically, it is easier to compute the matrices symbolically, substitute in appropriate integer values for the parameters, and use exact integer arithmetic to compute the determinant for those values: For example, $\det J(2, 3, 4, 5, 6, 7, 8, 9, 10, 11) \neq 0$ and $\det K(2, 3, 4, 5, 6, 7, 8, 9, 10) \neq 0$.) Because these determinants are polynomials, the set of values where J (resp. K) is non-singular is a relatively open subset of \mathbb{R}_+^{10} (resp. \mathbb{R}_+^9) with a closure that is all of \mathbb{R}_+^{10} (resp. \mathbb{R}_+^9) (that is, they are everywhere dense).

We can therefore find a point $(\bar{\tau}, \bar{g}_1, \dots, \bar{g}_7, \bar{\ell})$ in the interior of \mathbb{R}_+^9 such that

- (i) the matrix $K(\bar{\tau}, \bar{g}_1, \dots, \bar{g}_7, \bar{\ell})$ is non-singular and
- (ii) in any open neighborhood of $(\bar{g}_1, \dots, \bar{g}_7, \bar{\ell}, \bar{\ell}) \in \mathbb{R}_+^9$ there are points (d_1, \dots, d_7, h, k) such that the matrix $J(\bar{\tau}, d_1, \dots, d_7, h, k)$ is non-singular.

By assumption (i) and the implicit function theorem (see, for example, [KP02]), the range of Q contains an open neighborhood of $Q(\bar{\tau}, \bar{g}_1, \dots, \bar{g}_7, \bar{\ell})$. Note that $P(\bar{\tau}, \bar{g}_1, \dots, \bar{g}_7, \bar{\ell}, \bar{\ell}) = Q(\bar{\tau}, \bar{g}_1, \dots, \bar{g}_7, \bar{\ell})$, and so for all points $(\sigma, d_1, \dots, d_7, h, k)$ in some open neighborhood of $(\bar{\tau}, \bar{g}_1, \dots, \bar{g}_7, \bar{\ell}, \bar{\ell})$ we can find $(\tau, g_1, \dots, g_7, \ell)$ such that $P(\sigma, d_1, \dots, d_7, h, k) = Q(\tau, g_1, \dots, g_7, \ell)$.

We will be done if we can show that it is not always the case that $\sigma = \tau$ for such a solution. To see this, we will fix $\sigma = \bar{\tau}$ and let (d_1, \dots, d_7, h, k) vary. By assumption (ii) and the implicit function theorem, the image of any open neighborhood of $(\bar{g}_1, \dots, \bar{g}_7, \bar{\ell}, \bar{\ell})$ by the map $(d_1, \dots, d_7, h, k) \mapsto P(\bar{\tau}, d_1, \dots, d_7, h, k)$ has non-empty interior. However, the range of the map $(g_1, \dots, g_7, \ell) \mapsto Q(\bar{\tau}, g_1, \dots, g_7, \ell)$ is at most 8-dimensional, and, in particular, has empty interior. Therefore, there certainly exists (d_1, \dots, d_7, h, k) such that $P(\bar{\tau}, d_1, \dots, d_7, h, k) = Q(\tau, g_1, \dots, g_7, \ell)$ for some $(\tau, g_1, \dots, g_7, \ell)$ with $\tau \neq \bar{\tau}$.

Remark. Note that if we take $g_1 = \dots = g_7 = \ell$, then we have a gamma distribution with shape parameter 9. Also, we could still produce the unidentifiability phenomenon witnessed above if we raised all the Laplace transforms to the same power $c > 0$. In that case, setting $g_1 = \dots = g_7 = \ell$ would give a gamma distribution with shape parameter $9c$. Since the unidentifiability occurs on a dense set of parameters (g_1, \dots, g_7, ℓ) , any gamma distribution will have distributions arbitrarily close to it that exhibit the phenomenon.

4. CONCLUSIONS AND FUTURE RESEARCH

The example we have given shows that the attempt to achieve identifiability and reasonable inference of edge-lengths in the rates-across-sites model by using random scale factors that come from some common distribution can be problematic.

The gamma distributions ‘work’, but distributions arbitrarily close to any given gamma with smooth, unimodal densities and finite moments of all orders don’t. Using the gamma family is thus not just a matter of working with distributions that have enough flexibility to capture reasonable variation in rates. Rather, identifiability of edge-lengths for the gamma family relies on quite specific features of members of that family that are not shared by equally reasonable distributions.

The result has consequences for the estimation of times at internal nodes, since if edge-lengths cannot be estimated, then neither can the dates (since the edge-length is a product of the elapsed time on the edge, and the equilibrium expected rate of evolution for on that edge).

Finally, although our main result is theoretical, its consequences can be tested in simulation. To date, few (if any) such studies have been done that have not presumed that the rates are distributed by a gamma distribution, or a distribution consisting of some invariable

sites, and the remaining sites evolving under a gamma distribution. This also reflects the implicit belief that the assumption of a gamma distribution is acceptable. We hope this paper will help encourage researchers to reconsider this assumption.

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