Max. likelihood & Bayesian techniques are both likelihood-based.

Weaknesses of likelihood for phylogeny reconstruction:
1) Computational tractability
2) Based on overly simplistic evolutionary models.

But,

a) All phylogeny reconstruction methods are based on assumptions but some (e.g. parsimony) are not based on explicit ones. For methods based on unstated assumptions, we need to worry not just whether the assumptions are realistic but also we need to worry about what they are.

b) Likelihood methods allow assumptions to be rigorously tested. When an assumption is found to be particularly poor, it can be replaced with a better one (i.e., models will improve over time!)

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Strengths of likelihood methods:

1. Explicit Assumptions – we know what we're assuming.
2. Use **all** information in a data set. Distance methods, for example, do not. This is part of the explanation for success of likelihood methods in simulations – they tend to yield estimates that are closer to the truth than other methods.
3. Likelihood approaches are consistent. Estimates get better as amount of data increases. (Caveat: violation of model assumptions may cause loss of consistency property)
4. Because likelihood applied to so many statistical situations in addition to phylogenetics, powerful theory & tools for performing likelihood analyses have developed. This theory and these tools (e.g., tools for hypothesis testing) can be applied to phylogenetics.
5. Likelihood lets you know how good estimate is, in addition to what estimate is.

Mechanistic versus Phenomenological Models of Sequence Evolution

see Ph.D. thesis by Nicolas Rodrigue ("Phylogenetic structural modeling of molecular evolution", 2008, University of Montreal)

(see also Rodrigue & Philippe. 2010. Trends in Genetics 26:248-252)

Mutation-Selection Balance:

For change from i to j, evolutionary rate is R_{ij} where

R_{ij} = (Mutation Rate) x (Fixation Probability)

(see Halpern & Bruno. 1998. MBE 15:910-917)

With low mutation rates, this depends on effective pop'n size "N" and relative fitness of j minus i (call this difference "s")

Population Genetic formulae for fixation probability allows estimation of Ns

One good idea for more realistic models ...

TUFFLEY, C., and M. A. STEEL. 1998. Modeling the covarion hypothesis of nucleotide substitution. Math. Biosci. 147:63–91.

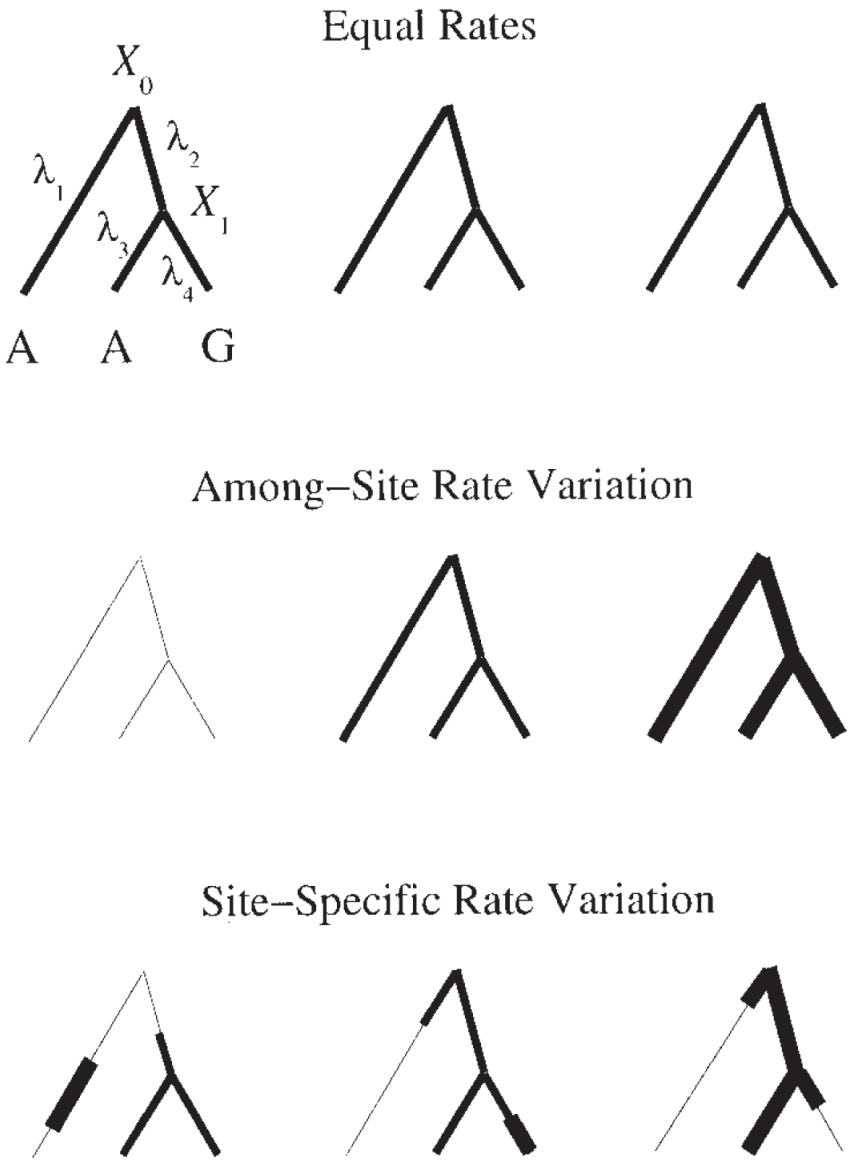


FIG. 1.—Distribution of rates across sites and lineages under three models of evolution. Each tree plot describes the distribution of rates across lineages for a particular site under the considered model. Three categories of rate are assumed, represented by different line thicknesses. Under the equal-rates (ER) model, all sites evolve at a constant, unique, moderate rate. Under the among-site rate variation (ASRV) model, each site has its own rate (low, moderate, or high), which is constant between lineages. Under the site-specific rate variation (SSRV) model, the rate of a site can switch between categories; a site has distinct rates in distinct lineages.

From Galtier. 2001. Mol. Biol. Evol. 18(5):866-873.

Tuffley/Steel -type model

		Slow				*Fast*			
		A	**C**	**G**	**T**	**A**	**C**	**G**	**T**
Slow	**A**	**-**	**r**	**r**	**r**	**f**	**0**	**0**	**0**
	C	**r**	**-**	**r**	**r**	**0**	**f**	**0**	**0**
	G	**r**	**r**	**-**	**r**	**0**	**0**	**f**	**0**
	T	**r**	**r**	**r**	**-**	**0**	**0**	**0**	**f**
Fast	**A**	**s**	**0**	**0**	**0**	**-**	**q**	**q**	**q**
	C	**0**	**s**	**0**	**0**	**q**	**-**	**q**	**q**
	G	**0**	**0**	**s**	**0**	**q**	**q**	**-**	**q**
	T	**0**	**0**	**0**	**s**	**q**	**q**	**q**	**-**

Substitution Rates: q>r

Switching rates: f (slow to fast), s (fast to slow)

Inspired by Lartillot and Philippe's CAT model of amino acid replacement that permits variation of preferred residues among sites, there is active development of sequence evolution models that allow variation of evolutionary processes among sites without prespecifying the number of categories, the nature of categories, or which sites are in which categories.

Key Ingredient: "Dirichlet Process" as a prior for the number of categories and for the probabilities of the categories.

Nicolas Lartillot and Hervé Philippe. 2004. A Bayesian Mixture Model for Across-Site Heterogeneities in the Amino-Acid Replacement Process. Mol. Biol. Evol. 21(6):1095-1109. 2004

Dirichlet Process Priors ("Chinese restaurant process", not same as Dirichlet distribution):

Useful to specify prior distribution for situations when number of categories is unknown and where prior probability of each possible category needs determination.

Additional applications in Evolution Include:

Characterization of population structure
Huelsenbeck and Andolfatto. 2007. Genetics. 175:1787-1802.

Variation in nonsyn. and synonymous rates among sites
Huelsenbeck et al. 2006. PNAS 103(16): 6263-6268.

Variation in evolutionary rate across a phylogeny
Heath et al. 2012. Mol. Biol. Evol. 29(3): 939-955.

Codon Models: Evolution occurs at the DNA level rather than at the amino acid level.

It makes sense to frame a model of protein evolution in terms of codons rather than amino acid types (Schoniger et al. 1990; Goldman and Yang 1994; Muse and Gaut 1994).

Codon-based models are typically framed in terms of 61 codon-states rather than 64 codon-states because the common genetic codes have three stop codons, and the possibility that a stop codon may appear or disappear from a sequence is not allowed.

One simplification that is often adopted holds that changes from one codon to another are only possible when the two codons differ at exactly one of the three codon positions.

The instantaneous rates of other changes between codons are set to 0.

Typical parameterization of a codon model when physicochemical differences between amino acids are ignored...

Instantaneous rate $\alpha_{i,j}$ from codon i to codon j is set to 0 if i and j differ at more than one nucleotide or if j encodes a premature stop codon. For cases where i and j differ by exactly one nucleotide, rate matrix entries are:

$$\alpha_{i,j} = \begin{cases} u\pi_j & \text{for a synonymous transversion} \\ u\pi_j\kappa & \text{for a synonymous transition} \\ u\pi_j\omega & \text{for a nonsynonymous transversion} \\ u\pi_j\kappa\omega & \text{for a nonsynonymous transition} \end{cases}$$

u, π_j, and κ reflect mutation rates

$\omega > 1$ means positive **diversifying** selection (i.e., nonsyn. rates higher than they would be if changes were synonymous)

Other kinds of positive selection exist (e.g., positive directional selection)

The previous rate matrix can be modified so that each codon k has its own parameter ω_k. The rates then become:

$$\alpha_{i,j} = \begin{cases} u\pi_h & \text{for a synonymous transversion} \\ u\pi_j\kappa & \text{for a synonymous transition} \\ u\pi_j\omega_k & \text{for a nonsynonymous transversion} \\ u\pi_j\kappa\omega_k & \text{for a nonsynonymous transition} \end{cases}$$

As with the rate heterogeneity among sites treatment, the distribution of ω_k values among codons can be modelled. Often, we want to know if certain codons have ω_k values that exceed 1.

Alternatively, we can assume all codons share the same value of ω but that ω values vary among branches on the tree. The rate matrix then becomes:

$$\alpha_{i,j} = \begin{cases} u\pi_j & \text{for a synonymous transversion} \\ u\pi_j\kappa & \text{for a synonymous transition} \\ u\pi_j\omega_B & \text{for a nonsynonymous transversion} \\ u\pi_j\kappa\omega_B & \text{for a nonsynonymous transition} \end{cases}$$

where ω_B is the parameter value for branch B. Many other possibilities for parameterizing codon models exist. and codon models can become very elaborate.

For example, Pedersen and colleagues (1998) carefully designed a codon model to reflect the fact that CpG dinucleotide levels are depressed in lentiviral genes.

Codon models have received attention for their potential ability to detect positive selection (Nielsen and Yang 1998).

Early methods for detecting positive selection from protein-coding DNA sequence data were designed to looked for an "excess" of nonsynonymous amino acid replacements throughout the sequence.

Codon methods offer the potential of detecting positive selection at individual sites and for detecting the existence of a small proportion of sites at which positive selection may operate.

Best statistical technique for detecting positive selection is a contentious issue at the moment...

Some future directions for codon-based models ...

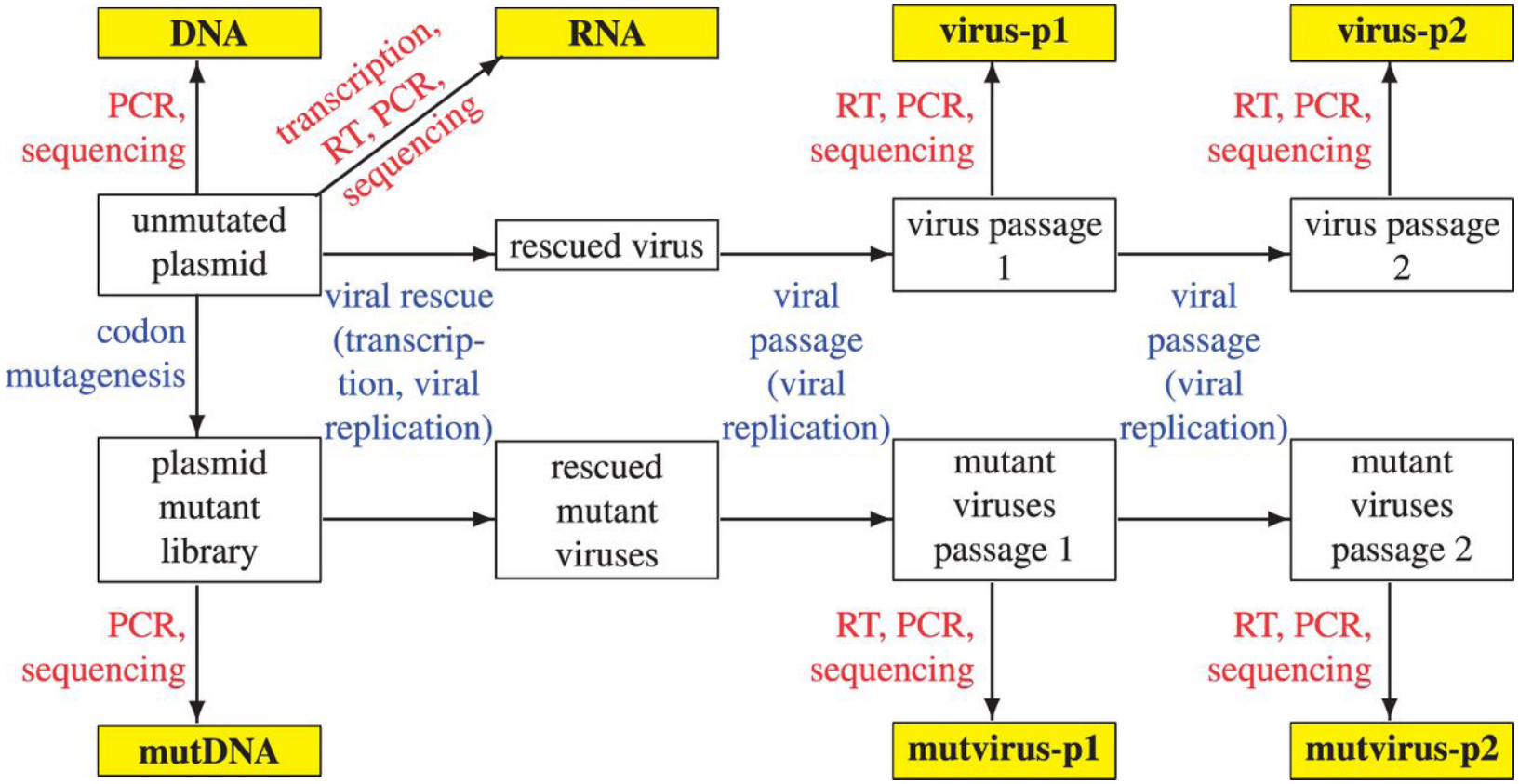
Evolutionary changes that simultaneously affect two consecutive positions could be allowed (Averof et al. 2000 have claimed empirical evidence for these kinds of changes).

Reconciliation of codon-based models with classical population genetic models – some progress has been made (see Halpern and Bruno 1998).

Improved treatment of effects of chemical similarity of amino acids on protein evolution

Experimental Evolution Can Inform Models

Fig. 2 from Bloom J.D. MolBiol Evol 2014;molbev.msu173



”**Design of the deep mutational scanning experiment.** The sequenced samples are in yellow. Blue text indicates sources of mutation and selection; red text indicates sources of errors. The comparison of interest is between the mutation frequencies in the mutDNA and mutvirus samples, because changes in frequencies between these samples represent the action of selection. However, because some of the experimental techniques have the potential to introduce errors, the other samples are also sequenced to quantify these unintended sources of error. “

Databases can inform models ...

Dayhoff model of protein evolution (see Dayhoff et al. 1972; Dayhoff et al. 1978) operates at the level of the 20 amino acid types.

π_i is the probability of amino acid type i

α_{ij} is the instantaneous rate of replacement from amino acid i to amino acid j

Dayhoff model is most general time-reversible 20-state model of amino acid replacement.

This means $\pi_i \alpha_{ij} = \pi_j \alpha_{ji}$ for all i and j.

It is important to separate the Dayhoff model of protein evolution from:

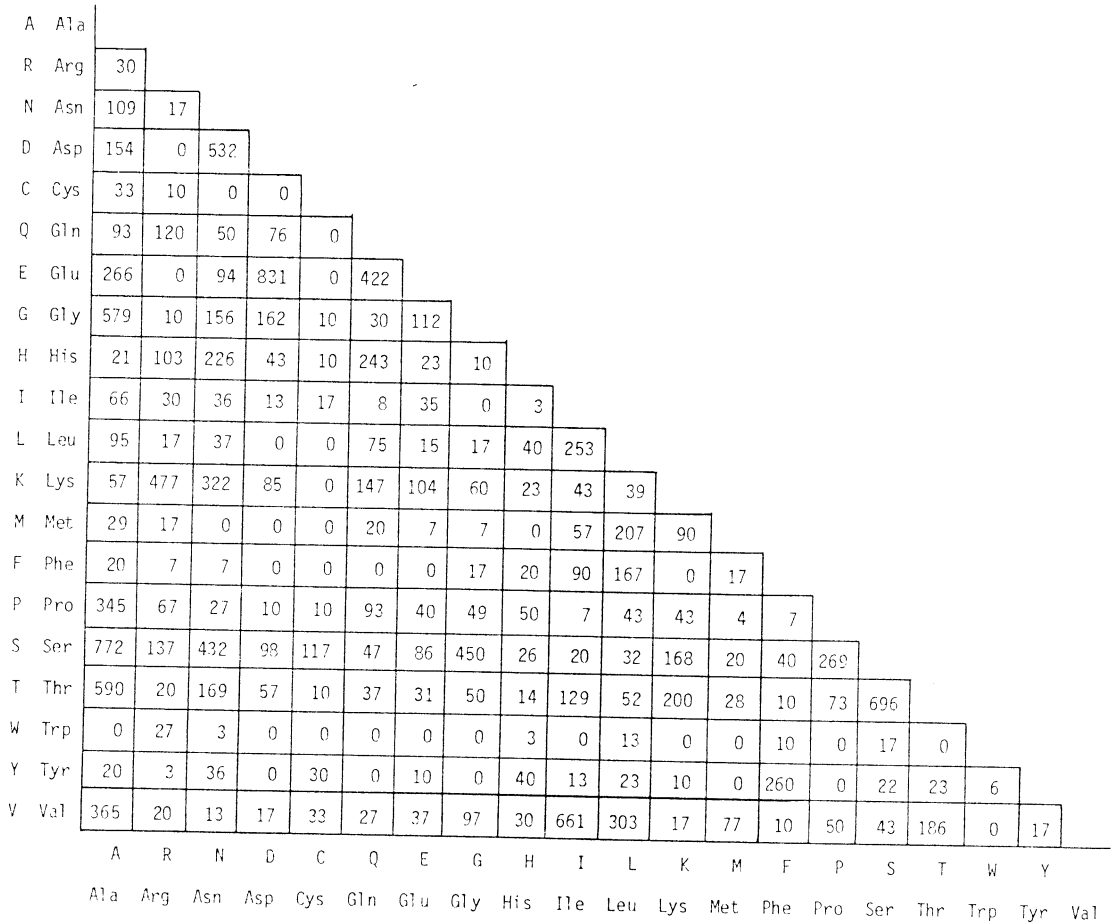
1. The procedure used by Dayhoff and collaborators to estimate the α_{ij} AND

2. The data set upon which the α_{ij} estimates were based.

Dayhoff and collaborators exploited the fact that the probability of replacements from amino acid type i to type j (i not equal to j) is approximately linear in time for small amounts of time.

In other words, the probability of a replacement from amino acid type i to a different type j is approximately $\alpha_{ij}t$ if t represents some small amount of time.

Subsequent studies (e.g., Jones et al. 1992) adopted the Dayhoff model but employed different data sets and parameter estimation procedures.



		A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y
A	Ala																			
R	Arg	30																		
N	Asn	109	17																	
D	Asp	154	0	532																
C	Cys	33	10	0	0															
Q	Gln	93	120	50	76	0														
E	Glu	266	0	94	831	0	422													
G	Gly	579	10	156	162	10	30	112												
H	His	21	103	226	43	10	243	23	10											
I	Ile	66	30	36	13	17	8	35	0	3										
L	Leu	95	17	37	0	0	75	15	17	40	253									
K	Lys	57	477	322	85	0	147	104	60	23	43	39								
M	Met	29	17	0	0	0	20	7	7	0	57	207	90							
F	Phe	20	7	7	0	0	0	0	17	20	90	167	0	17						
P	Pro	345	67	27	10	10	93	40	49	50	7	43	43	4	7					
S	Ser	772	137	432	98	117	47	86	450	26	20	32	168	20	40	269				
T	Thr	590	20	169	57	10	37	31	50	14	129	52	200	28	10	73	696			
W	Trp	0	27	3	0	0	0	0	0	3	0	13	0	0	10	0	17	0		
Y	Tyr	20	3	36	0	30	0	10	0	40	13	23	10	0	260	0	22	23	6	
V	Val	365	20	13	17	33	27	37	97	30	661	303	17	77	10	50	43	186	0	17

A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y
Ala	Arg	Asn	Asp	Cys	Gln	Glu	Gly	His	Ile	Leu	Lys	Met	Phe	Pro	Ser	Thr	Trp	Tyr	Val

Figure 80. Numbers of accepted point mutations (X 10) accumulated from closely related sequences. Fifteen hundred and seventy-two exchanges are shown. Fractional exchanges result when ancestral sequences are ambiguous.

ORIGINAL AMINO ACID

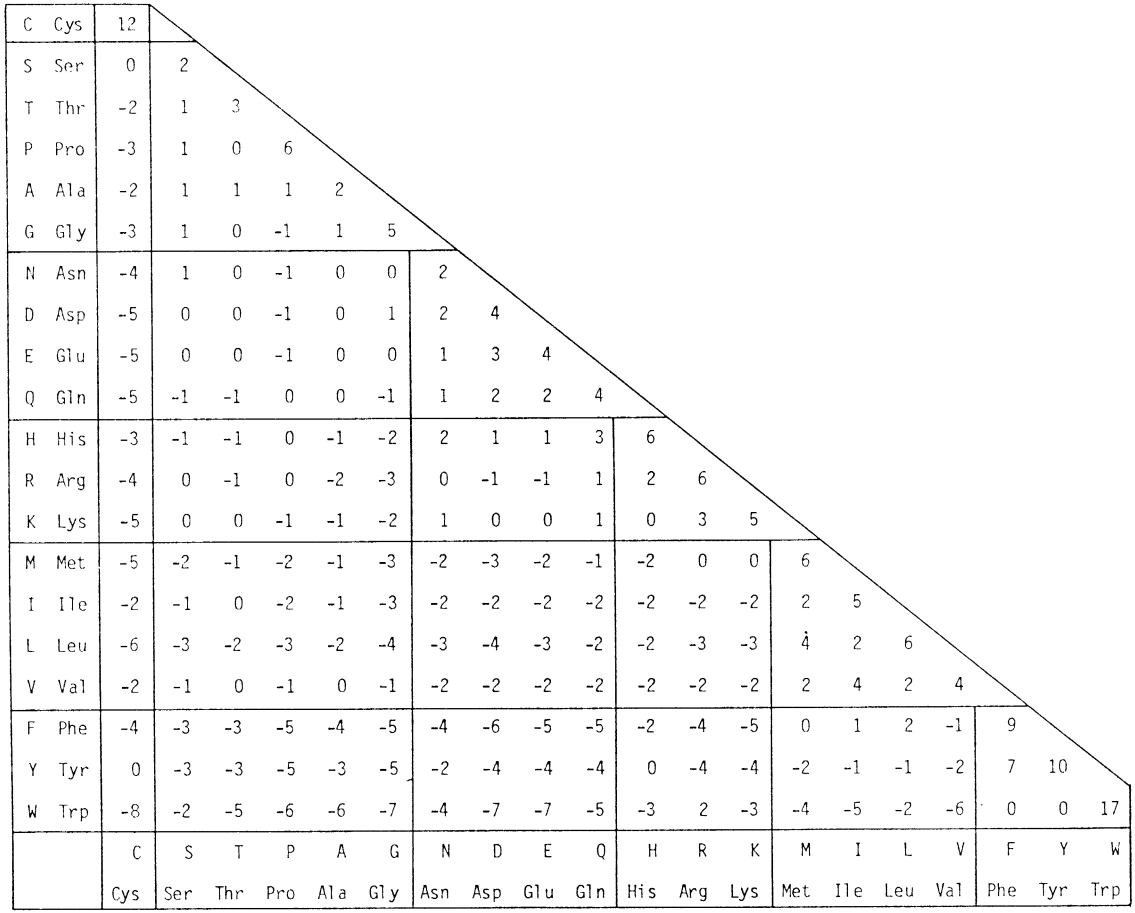
REPLACEMENT AMINO ACID	A Ala	R Arg	N Asn	D Asp	C Cys	Q Gln	E Glu	G Gly	H His	I Ile	L Leu	K Lys	M Met	F Phe	P Pro	S Ser	T Thr	W Trp	Y Tyr	V Val
A Ala	9867	2	9	10	3	8	17	21	2	6	4	2	6	2	22	35	32	0	2	18
R Arg	1	9913	1	0	1	10	0	0	10	3	1	19	4	1	4	6	1	8	0	1
N Asn	4	1	9822	36	0	4	6	6	21	3	1	13	0	1	2	20	9	1	4	1
D Asp	6	0	42	9859	0	6	53	6	4	1	0	3	0	0	1	5	3	0	0	1
C Cys	1	1	0	0	9973	0	0	0	1	1	0	0	0	0	1	5	1	0	3	2
Q Gln	3	9	4	5	0	9876	27	1	23	1	3	6	4	0	6	2	2	0	0	1
E Glu	10	0	7	56	0	35	9865	4	2	3	1	4	1	0	3	4	2	0	1	2
G Gly	21	1	12	11	1	3	7	9935	1	0	1	2	1	1	3	21	3	0	0	5
H His	1	8	18	3	1	20	1	0	9912	0	1	1	0	2	3	1	1	1	4	1
I Ile	2	2	3	1	2	1	2	0	0	9872	9	2	12	7	0	1	7	0	1	33
L Leu	3	1	3	0	0	6	1	1	4	22	9947	2	45	13	3	1	3	4	2	15
K Lys	2	37	25	6	0	12	7	2	2	4	1	9926	20	0	3	8	11	0	1	1
M Met	1	1	0	0	0	2	0	0	0	5	8	4	9874	1	0	1	2	0	0	4
F Phe	1	1	1	0	0	0	0	1	2	8	6	0	4	9946	0	2	1	3	28	0
P Pro	13	5	2	1	1	8	3	2	5	1	2	2	1	1	9926	12	4	0	0	2
S Ser	28	11	34	7	11	4	6	16	2	2	1	7	4	3	17	9840	38	5	2	2
T Thr	22	2	13	4	1	3	2	2	1	11	2	8	6	1	5	32	9871	0	2	9
W Trp	0	2	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	9976	1	0
Y Tyr	1	0	3	0	3	0	1	0	4	1	1	0	0	21	0	1	1	2	9945	1
V Val	13	2	1	1	3	2	2	3	3	57	11	1	17	1	3	2	10	0	2	9901

Figure 82. Mutation probability matrix for the evolutionary distance of 1 PAM. An element of this matrix, M_{ij}, gives the probability that the amino acid in column j will be replaced by the amino acid in row i after a given evolutionary interval, in this case 1 accepted point mutation per 100 amino acids. Thus, there is a 0.56% probability that Asp will be replaced by Glu. To simplify the appearance, the elements are shown multiplied by 10,000.

ORIGINAL AMINO ACID

REPLACEMENT AMINO ACID	A Ala	R Arg	N Asn	D Asp	C Cys	Q Gln	E Glu	G Gly	H His	I Ile	L Leu	K Lys	M Met	F Phe	P Pro	S Ser	T Thr	W Trp	Y Tyr	V Val
A Ala	13	6	9	9	5	8	9	12	6	8	6	7	7	4	11	11	11	2	4	9
R Arg	3	17	4	3	2	5	3	2	6	3	2	9	4	1	4	4	3	7	2	2
N Asn	4	4	6	7	2	5	6	4	6	3	2	5	3	2	4	5	4	2	3	3
D Asp	5	4	8	11	1	7	10	5	6	3	2	5	3	1	4	5	5	1	2	3
C Cys	2	1	1	1	52	1	1	2	2	2	1	1	1	1	2	3	2	1	4	2
Q Gln	3	5	5	6	1	10	7	3	7	2	3	5	3	1	4	3	3	1	2	3
E Glu	5	4	7	11	1	9	12	5	6	3	2	5	3	1	4	5	5	1	2	3
G Gly	12	5	10	10	4	7	9	27	5	5	4	6	5	3	8	11	9	2	3	7
H His	2	5	5	4	2	7	4	2	15	2	2	3	2	2	3	3	2	2	3	2
I Ile	3	2	2	2	2	2	2	2	2	10	6	2	6	5	2	3	4	1	3	9
L Leu	6	4	4	3	2	6	4	3	5	15	34	4	20	13	5	4	6	6	7	13
K Lys	6	18	10	8	2	10	8	5	8	5	4	24	9	2	6	8	8	4	3	5
M Met	1	1	1	1	0	1	1	1	1	2	3	2	6	2	1	1	1	1	1	2
F Phe	2	1	2	1	1	1	1	1	3	5	6	1	4	32	1	2	2	4	20	3
P Pro	7	5	5	4	3	5	4	5	5	3	3	4	3	2	20	6	5	1	2	4
S Ser	9	6	8	7	7	6	7	9	6	5	4	7	5	3	9	10	9	4	4	6
T Thr	8	5	6	6	4	5	5	6	4	6	4	6	5	3	6	8	11	2	3	6
W Trp	0	2	0	0	0	0	0	0	1	0	1	0	0	1	0	1	0	55	1	0
Y Tyr	1	1	2	1	3	1	1	1	3	2	2	1	2	15	1	2	2	3	31	2
V Val	7	4	4	4	4	4	4	5	4	15	10	4	10	5	5	5	7	2	4	17

Figure 83. Mutation probability matrix for the evolutionary distance of 250 PAMs. To simplify the appearance, the elements are shown multiplied by 100. In comparing two sequences of average amino acid frequency at this evolutionary distance, there is a 13% probability that a position containing Ala in the first sequence will contain Ala in the second. There is a 3% chance that it will contain Arg, and so forth. The relationship of two sequences at a distance of 250 PAMs can be demonstrated by statistical methods.



C Cys	12																					
S Ser	0	2																				
T Thr	-2	1	3																			
P Pro	-3	1	0	6																		
A Ala	-2	1	1	1	2																	
G Gly	-3	1	0	-1	1	5																
N Asn	-4	1	0	-1	0	0	2															
D Asp	-5	0	0	-1	0	1	2	4														
E Glu	-5	0	0	-1	0	0	1	3	4													
Q Gln	-5	-1	-1	0	0	-1	1	2	2	4												
H His	-3	-1	-1	0	-1	-2	2	1	1	3	6											
R Arg	-4	0	-1	0	-2	-3	0	-1	-1	1	2	6										
K Lys	-5	0	0	-1	-1	-2	1	0	0	1	0	3	5									
M Met	-5	-2	-1	-2	-1	-3	-2	-3	-2	-1	-2	0	0	6								
I Ile	-2	-1	0	-2	-1	-3	-2	-2	-2	-2	-2	-2	-2	2	5							
L Leu	-6	-3	-2	-3	-2	-4	-3	-4	-3	-2	-2	-3	-3	4	2	6						
V Val	-2	-1	0	-1	0	-1	-2	-2	-2	-2	-2	-2	-2	2	4	2	4					
F Phe	-4	-3	-3	-5	-4	-5	-4	-6	-5	-5	-2	-4	-5	0	1	2	-1	9				
Y Tyr	0	-3	-3	-5	-3	-5	-2	-4	-4	-4	0	-4	-4	-2	-1	-1	-2	7	10			
W Trp	-8	-2	-5	-6	-6	-7	-4	-7	-7	-5	-3	2	-3	-4	-5	-2	-6	0	0	17		
	C Cys	S Ser	T Thr	P Pro	A Ala	G Gly	N Asn	D Asp	E Glu	Q Gln	H His	R Arg	K Lys	M Met	I Ile	L Leu	V Val	F Phe	Y Tyr	W Trp		

Figure 84. Log odds matrix for 250 PAMs. Elements are shown multiplied by 10. The neutral score is zero. A score of -10 means that the pair would be expected to occur only one-tenth as frequently in related sequences as random chance would predict, and a score of +2 means that the pair would be expected to occur 1.6 times as frequently. The order of the amino acids has been arranged to illustrate the patterns in the mutation data.

Table 23

Correspondence between Observed Differences and the Evolutionary Distance

Observed Percent Difference	Evolutionary Distance in PAMs
1	1
5	5
10	11
15	17
20	23
25	30
30	38
35	47
40	56
45	67
50	80
55	94
60	112
65	133
70	159
75	195
80	246
85	328

Table 21

Relative Mutabilities of the Amino Acids[a]

Asn	134	His	66
Ser	120	Arg	65
Asp	106	Lys	56
Glu	102	Pro	56
Ala	100	Gly	49
Thr	97	Tyr	41
Ile	96	Phe	41
Met	94	Leu	40
Gln	93	Cys	20
Val	74	Trp	18

[a]The value for Ala has been arbitrarily set at 100.

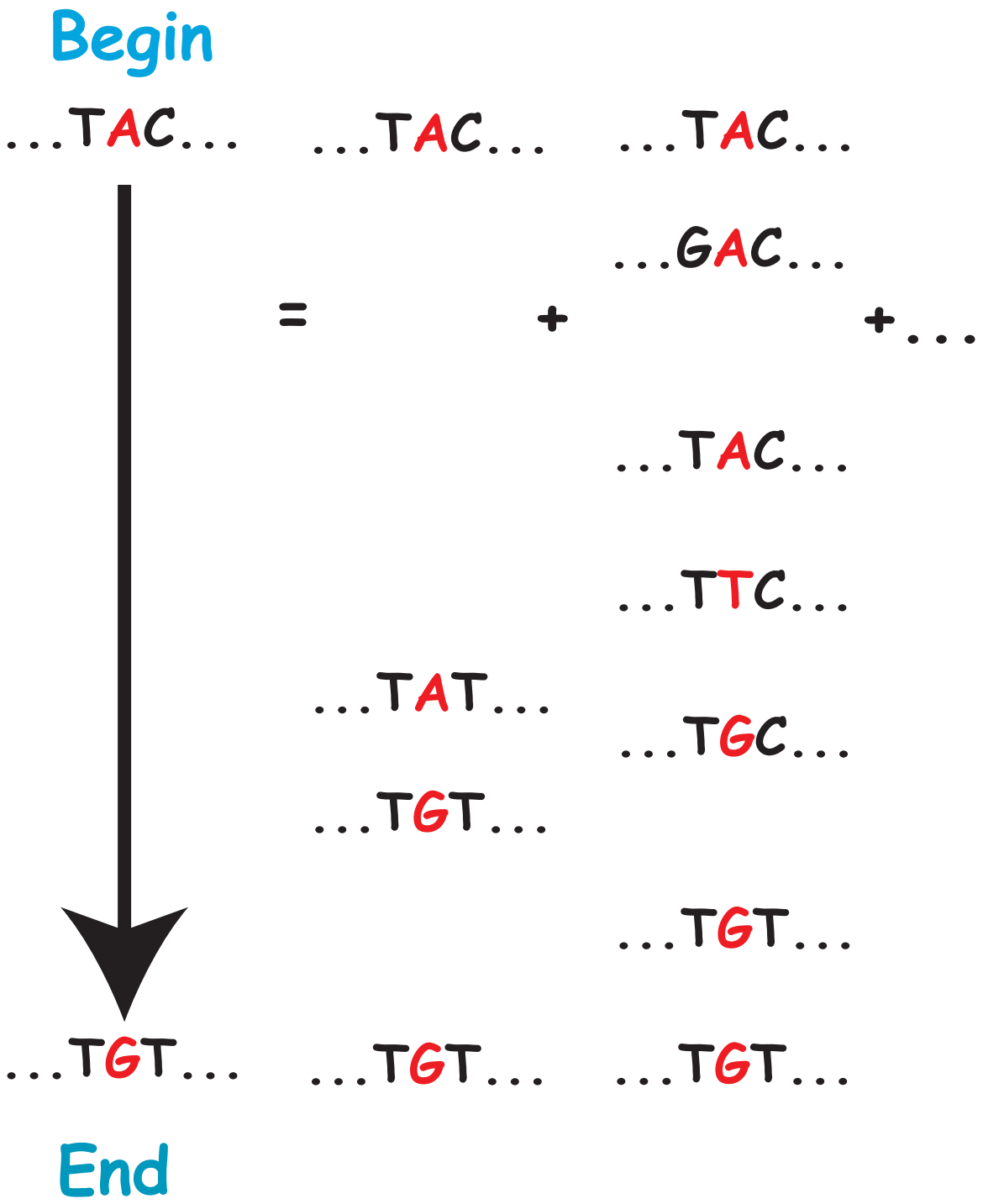
Table 22

Normalized Frequencies of the Amino Acids in the Accepted Point Mutation Data

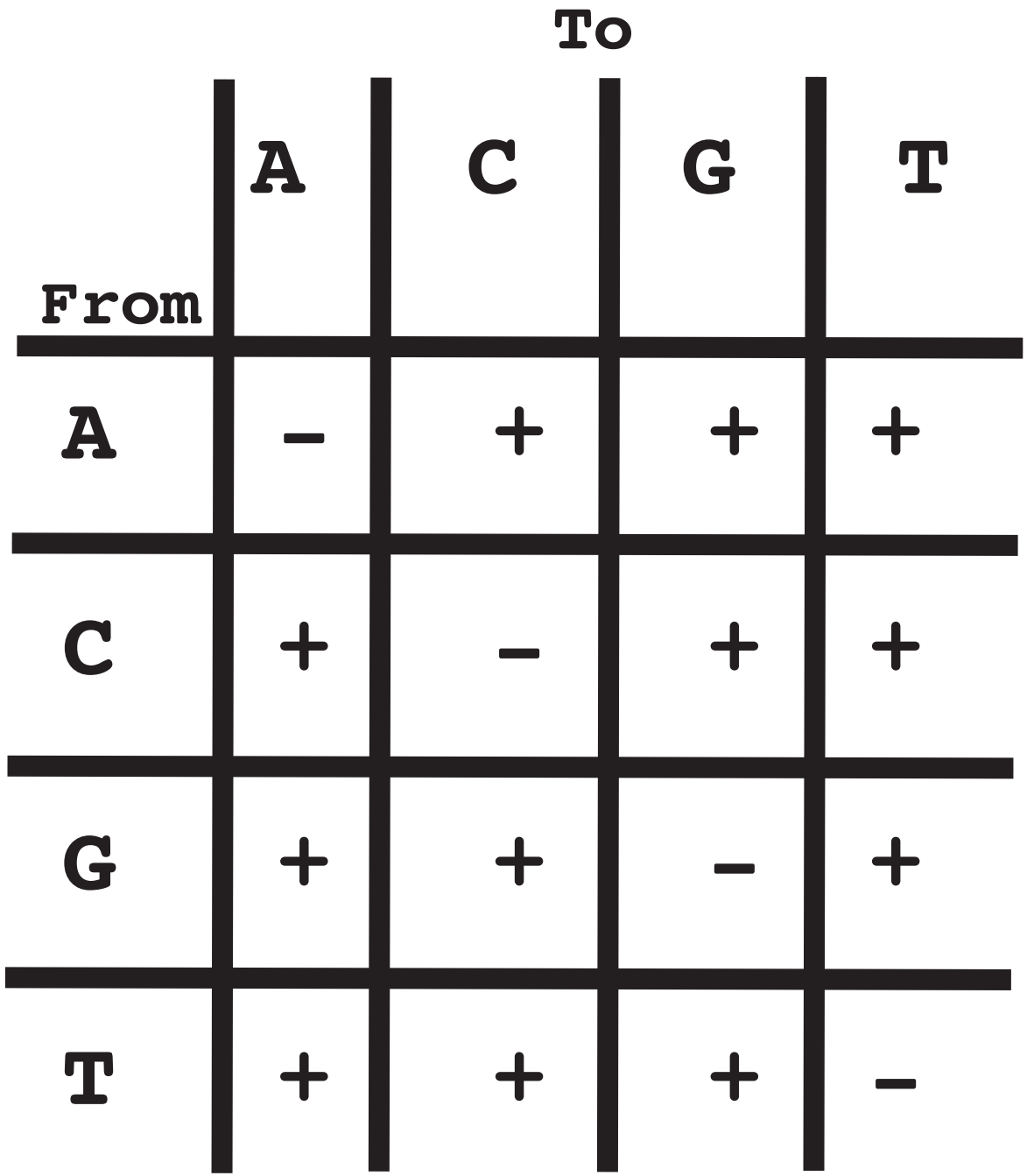
Gly	0.089	Arg	0.041
Ala	0.087	Asn	0.040
Leu	0.085	Phe	0.040
Lys	0.081	Gln	0.038
Ser	0.070	Ile	0.037
Val	0.065	His	0.034
Thr	0.058	Cys	0.033
Pro	0.051	Tyr	0.030
Glu	0.050	Met	0.015
Asp	0.047	Trp	0.010

An infinite number of possible evolutionary histories are consistent with sequences at the beginning and end of a branch on a tree.

transition probabilities add up all these possible histories...



4-state substitution model

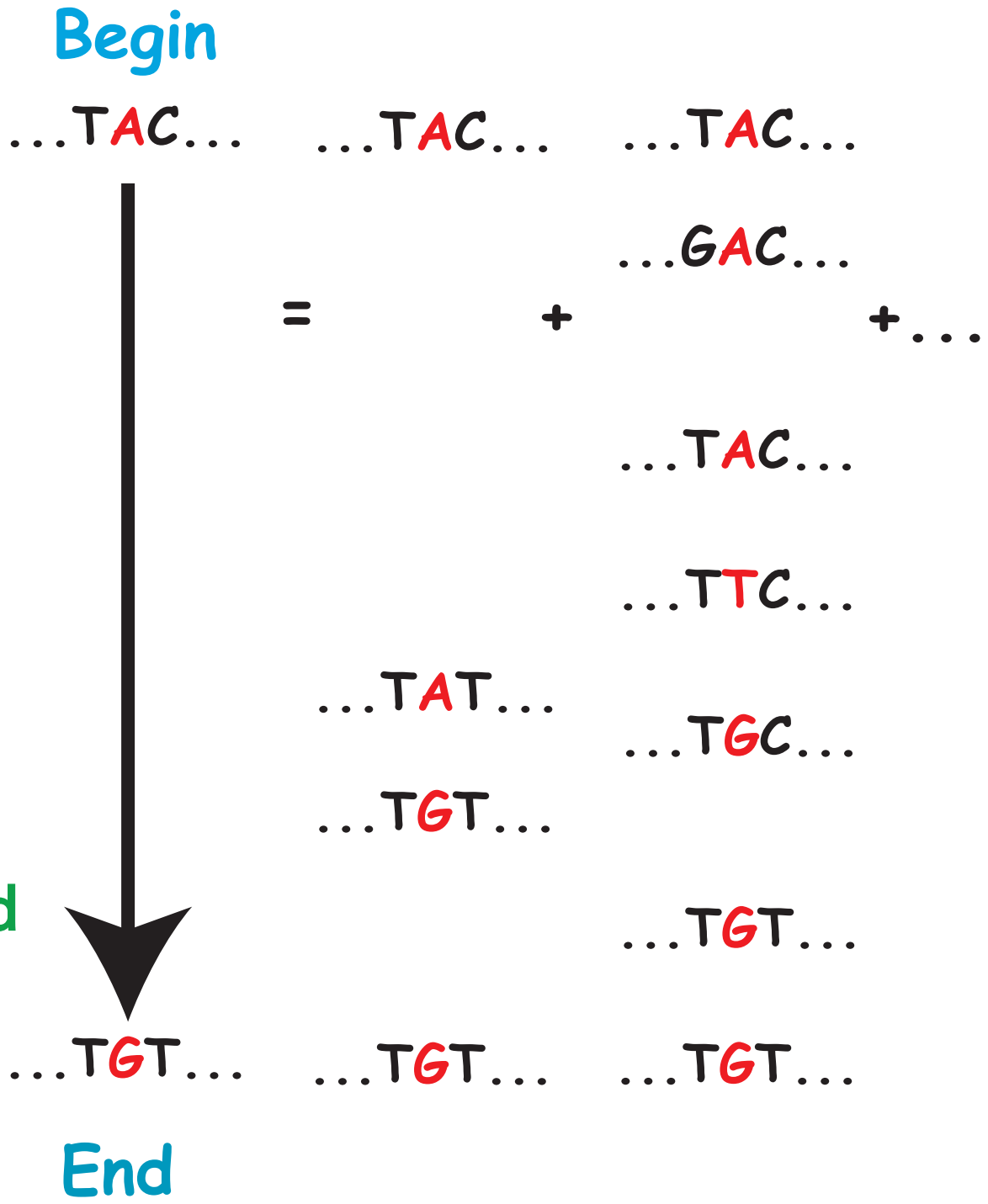


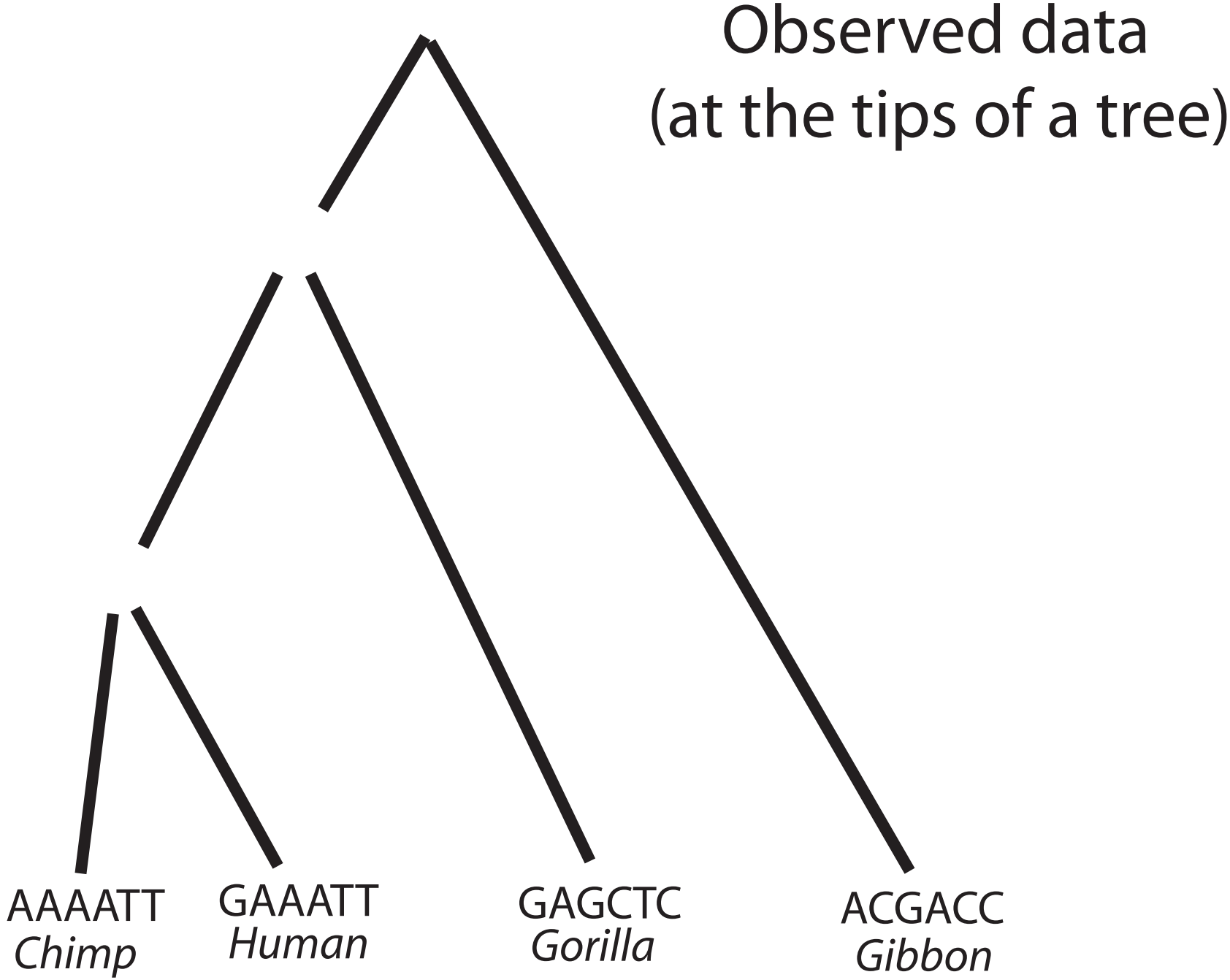
4^N by 4^N rate matrix

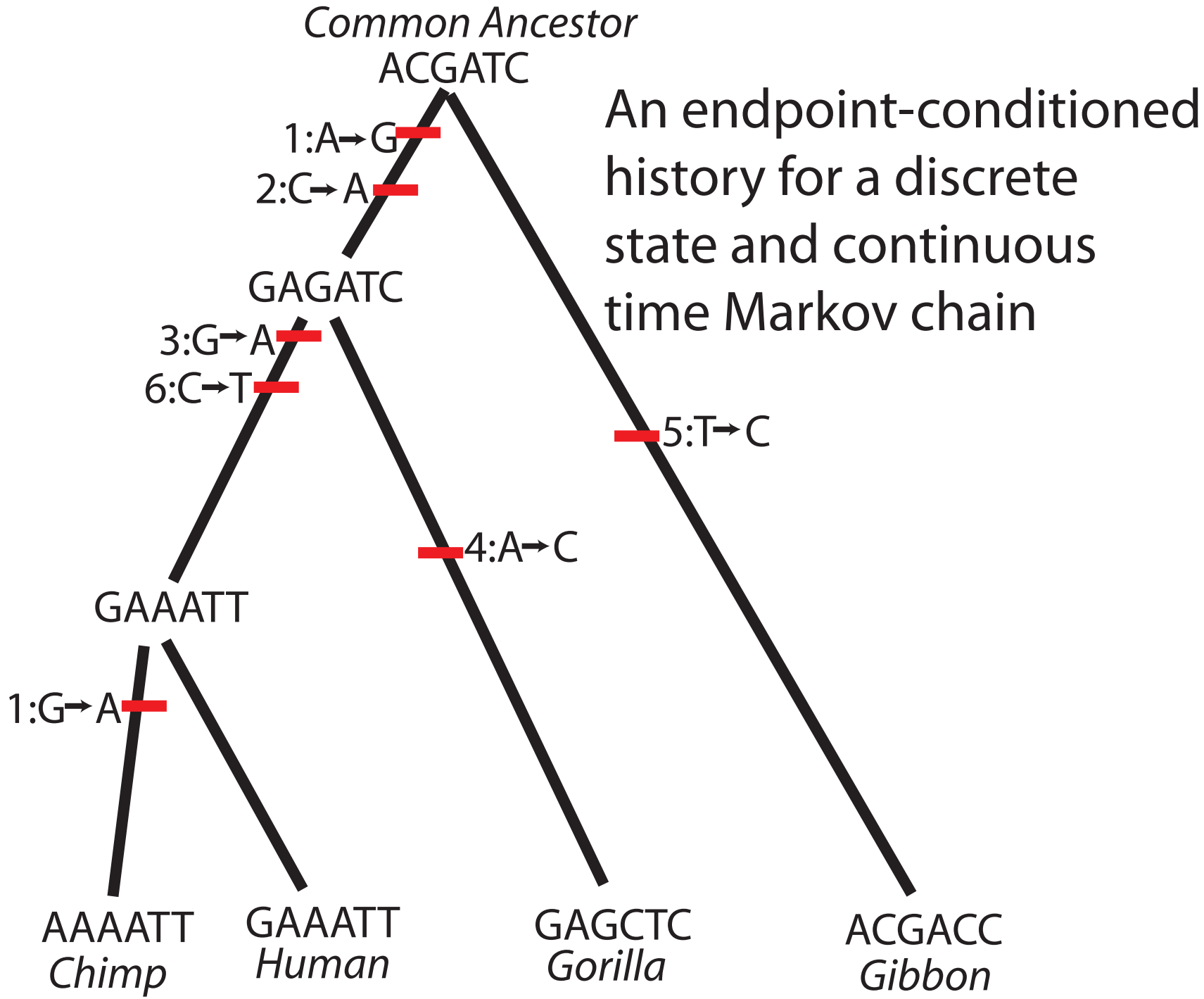
From \ *To*	*AA…AA*	*AA…AC*	*AA…AG*	*AA…AT*	*AA…CA*	…	*TT…GT*	*TT…TA*	*TT…TC*	*TT…TG*	*TT…TT*
AA…AA	-	+	+	+	+		0	0	0	0	0
AA…AC	+	-	+	+	0		0	0	0	0	0
AA…AG	+	+	-	+	0		0	0	0	0	0
AA…AT	+	+	+	-	0		0	0	0	0	0
AA…CA	+	0	0	0	-		0	0	0	0	0
…											
TT…GT	0	0	0	0	0		-	0	0	0	+
TT…TA	0	0	0	0	0		0	-	+	+	+
TT…TC	0	0	0	0	0		0	+	-	+	+
TT…TG	0	0	0	0	0		0	+	+	-	+
TT…TT	0	0	0	0	0		+	+	+	+	-

An infinite number of possible evolutionary histories are consistent with sequences at the beginning and end of a branch on a tree.

If we cannot add up all of these histories, then maybe we can still sample these histories according to their probabilities (this is called "endpoint-conditioned sampling")




Observed data
(at the tips of a tree)
AAAATT
Chimp
GAAATT
Human
GAGCTC
Gorilla
ACGACC
Gibbon



An endpoint-conditioned history for a discrete state and continuous time Markov chain

Example Rate Matrix (Continuous Time)

FROM \ To	A	C	G	T
A	−5	2	2	1
C	1	−2	0	1
G	3	3	−10	4
T	1	3	1	−5

Exponentially distributed waiting time for change ...

from A has mean 1/5
from C has mean 1/2
from G has mean 1/10
from T has mean 1/5

Respective change probabilities to (A,C,G,T) from ...

A are (0, 0.4, 0.4, 0.2)
C are (0.5, 0, 0, 0.5)
G are (0.3, 0.3, 0, 0.4)
T are (0.2, 0.6, 0.2, 0)

FROM \ To	A	C	G	T
A	−5	2	2	1
C	1	−2	0	1
G	3	3	−10	4
T	1	3	1	−5

Uniformization where waiting time to events are exponential with mean 10* (events that do not change state are known as virtual events)

Exponentially distrib. waiting time for change ...

from A has mean 1/5
from C has mean 1/2
from G has mean 1/10
from T has mean 1/5

Respective change probs to (A,C,G,T) from ...

A are (0, 0.4, 0.4, 0.2)
C are (0.5, 0, 0, 0.5)
G are (0.3, 0.3, 0, 0.4)
T are (0.2, 0.6, 0.2, 0)

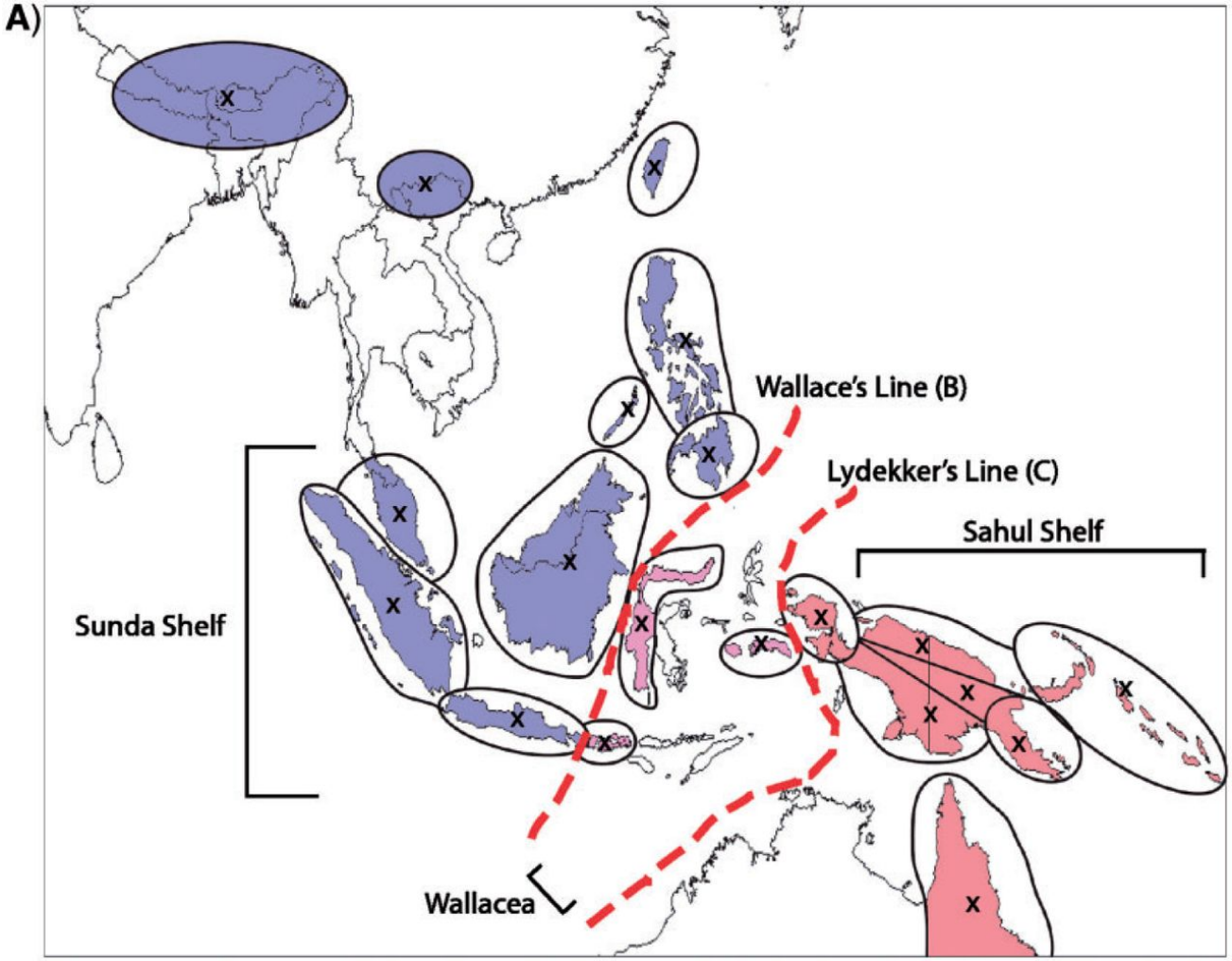
Uniformized change probs to (A,C,G,T) from ...

A are (0.5, 0.2, 0.2, 0.1)
C are (0.1, 0.8, 0, 0.1)
G are (0.3, 0.3, 0, 0.4)
T are (0.1, 0.3, 0.1, 0.5)

Uniformization Idea: Convert process to Poisson process by making waiting time distributions identical among states. Do this by adding "virtual events" that do not alter the state.

***Note: Any number >= 10 could have been chosen**

Biogeographic history of Malesian Rhododendron.



Landis et al. employ endpoint conditioned sampling to infer species ranges change on a phylogeny (total geographic area divided into 20 discrete ranges for this example)

Figure 8a from Landis M J et al. Syst Biol 2013;62:789-804

Data augmentation strategies employed to study protein evolution with dependence due to protein structure

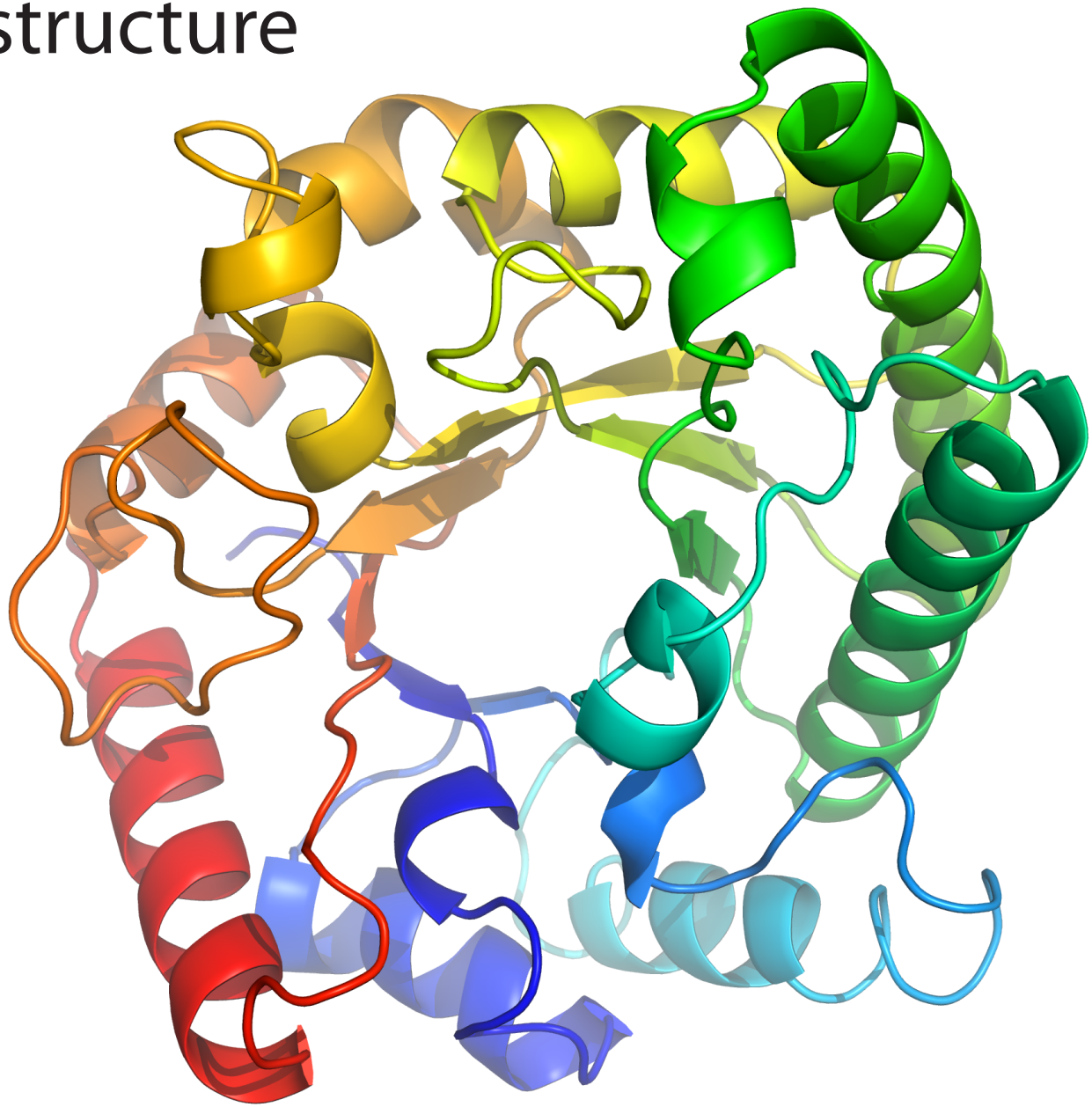
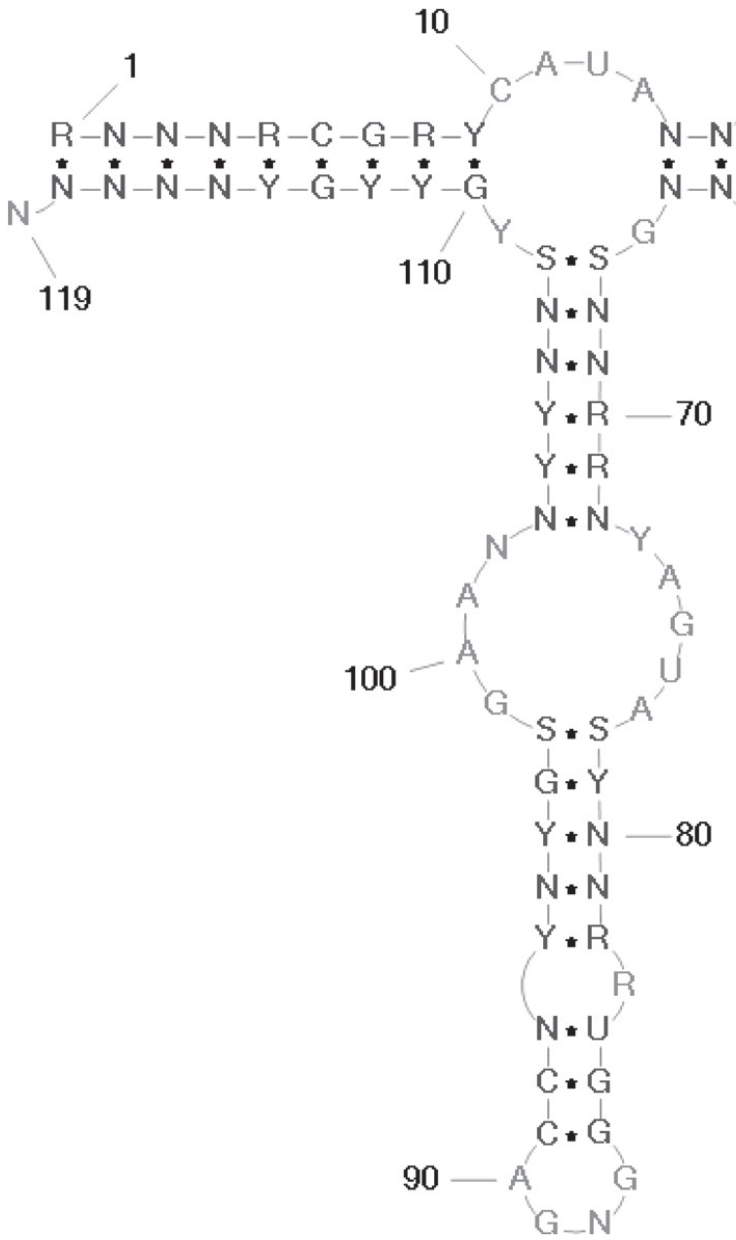


image from http://www.topsan.org/Proteins/JCSG/3qxb

see...

Robinson et al. 2003. MBE 18: 1692-1704

Rodrigue et al. MBE 2006 23:1762-1775 and Gene 2005 347:207-217.



Data augmentation strategies employed to study evolution with dependence due to RNA secondary structure

(e.g., Yu and Thorne 2006. MBE 23:1525-1537)

Data augmentation strategies employed to study context-dependent substitution in mammals

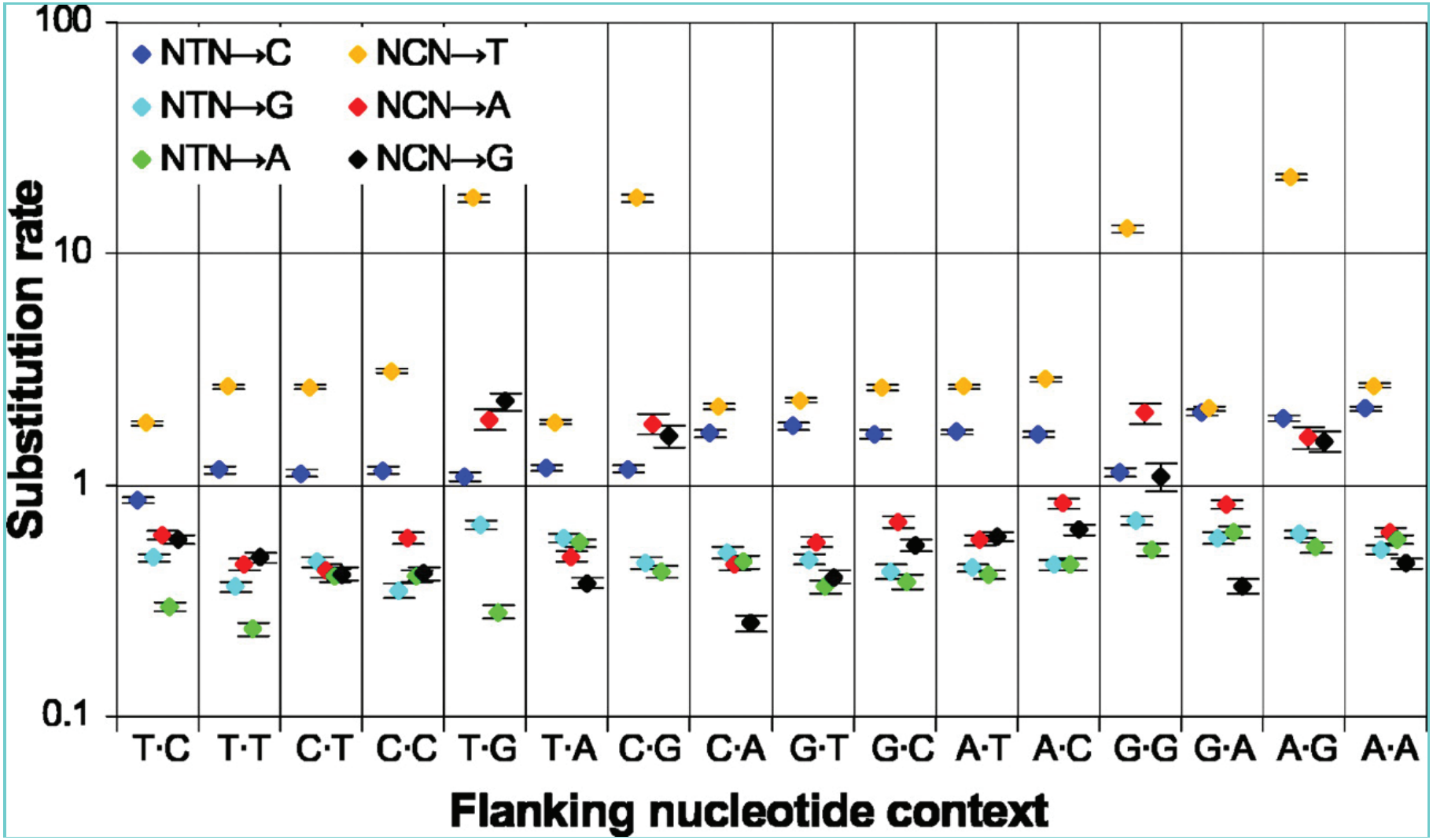


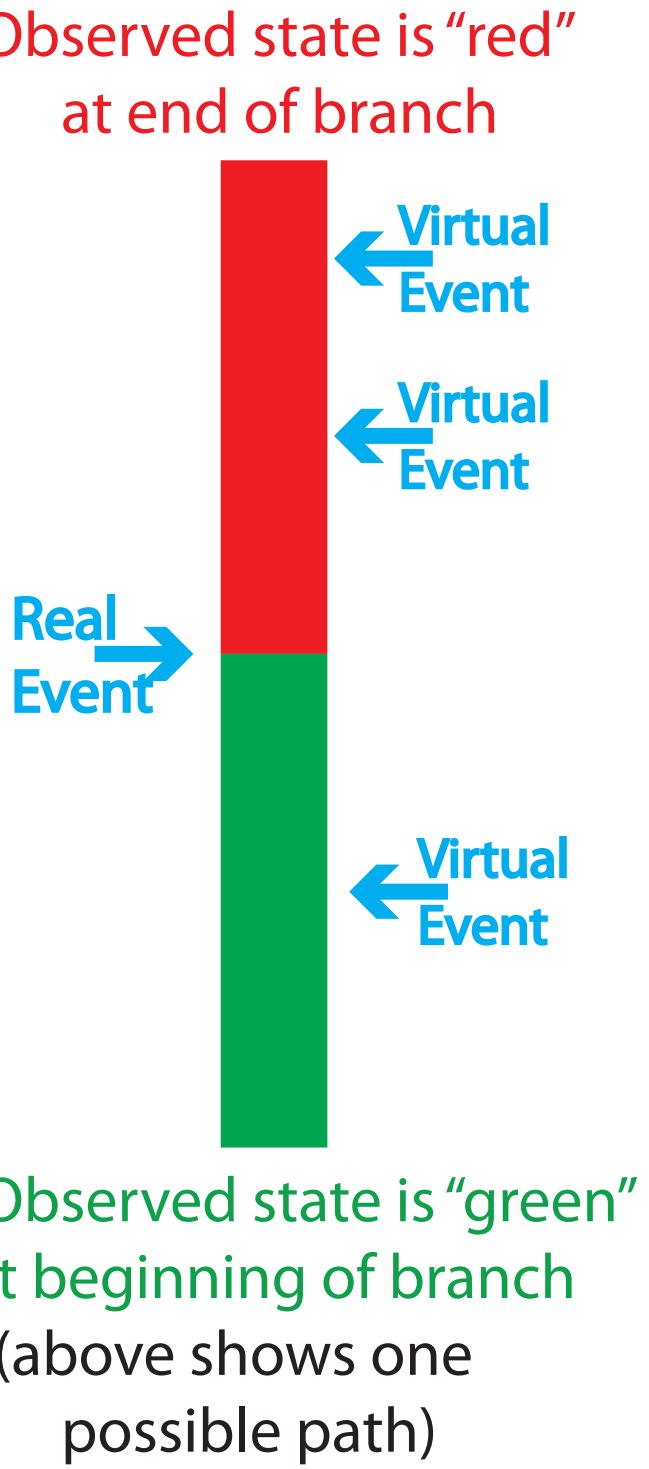
Figure 4 from Hwang and Green. 2004. PNAS 101:13994-14001.

Rao-Teh algorithm: Combines Gibbs Sampling and Uniformization to yield endpoint-conditioned samples.

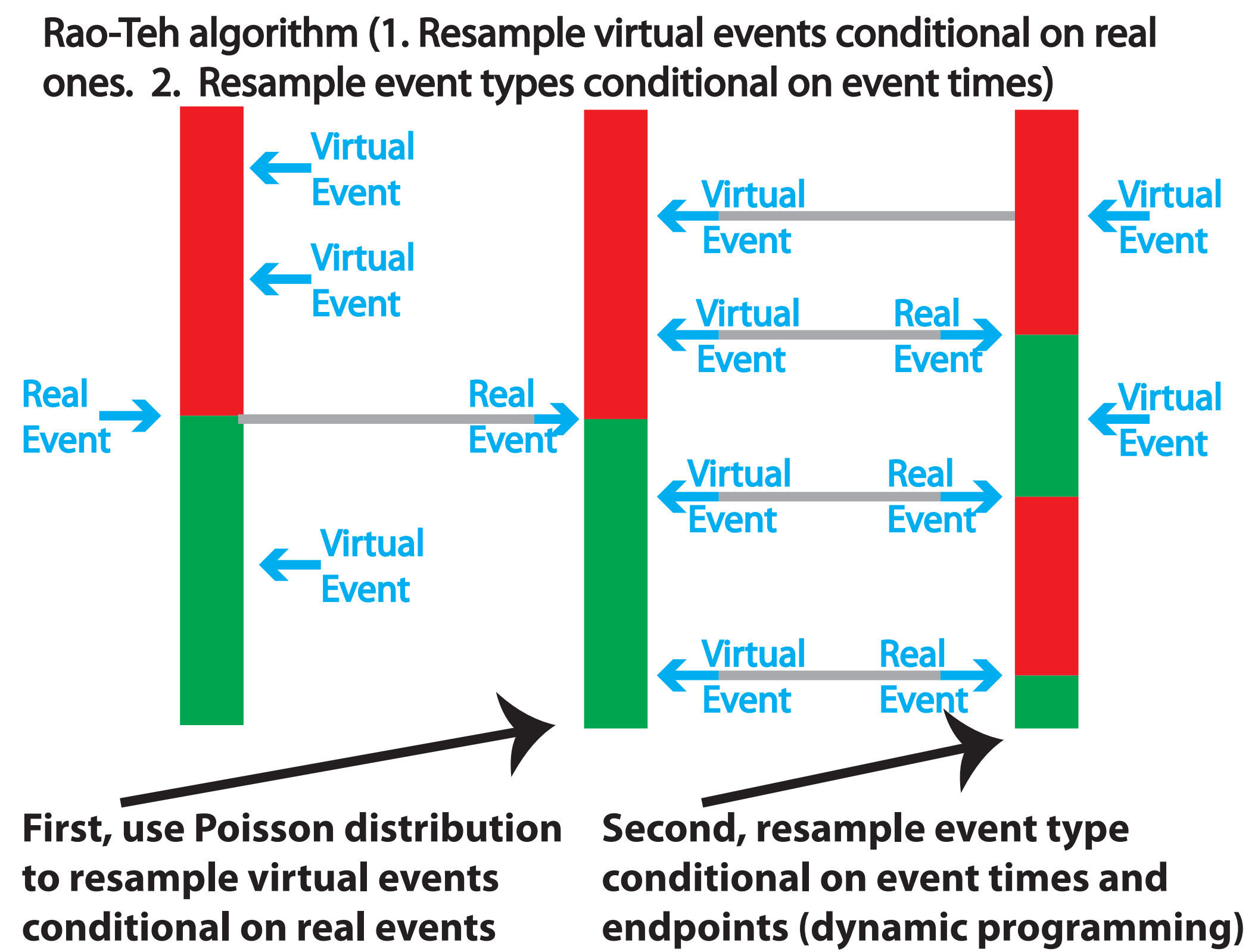
See Rao and Teh. 2013.
Journal of Machine Learning 14:3295-3320.

"Usual" uniformization may not scale well to large state space because requires calculation of transition probabilities.

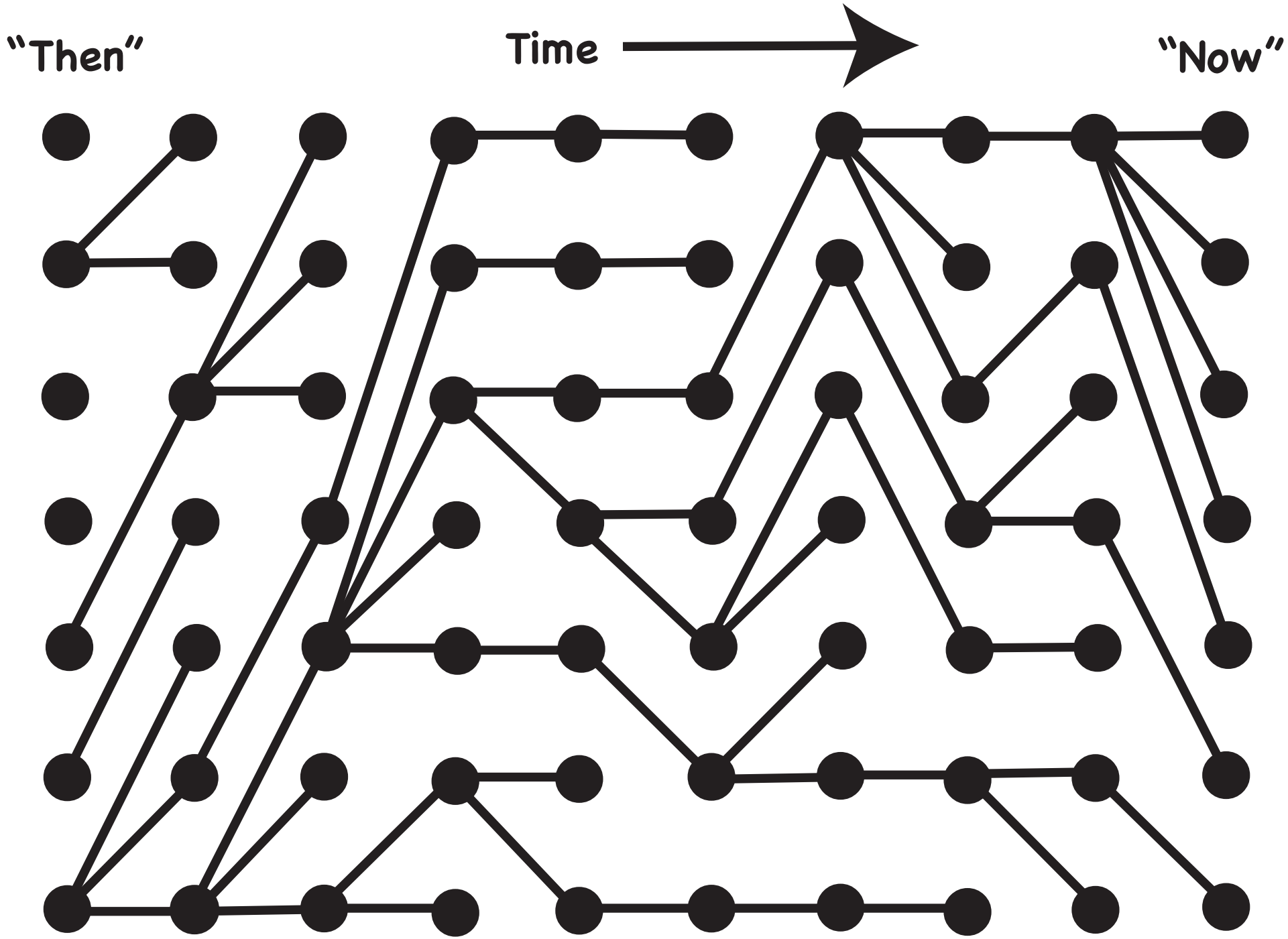
Rao-Teh uniformization is well-suited to evolutionary inference with large state space and sparse rate matrices (computation proportional to product of state space size and number of "neighbors" of typical state).

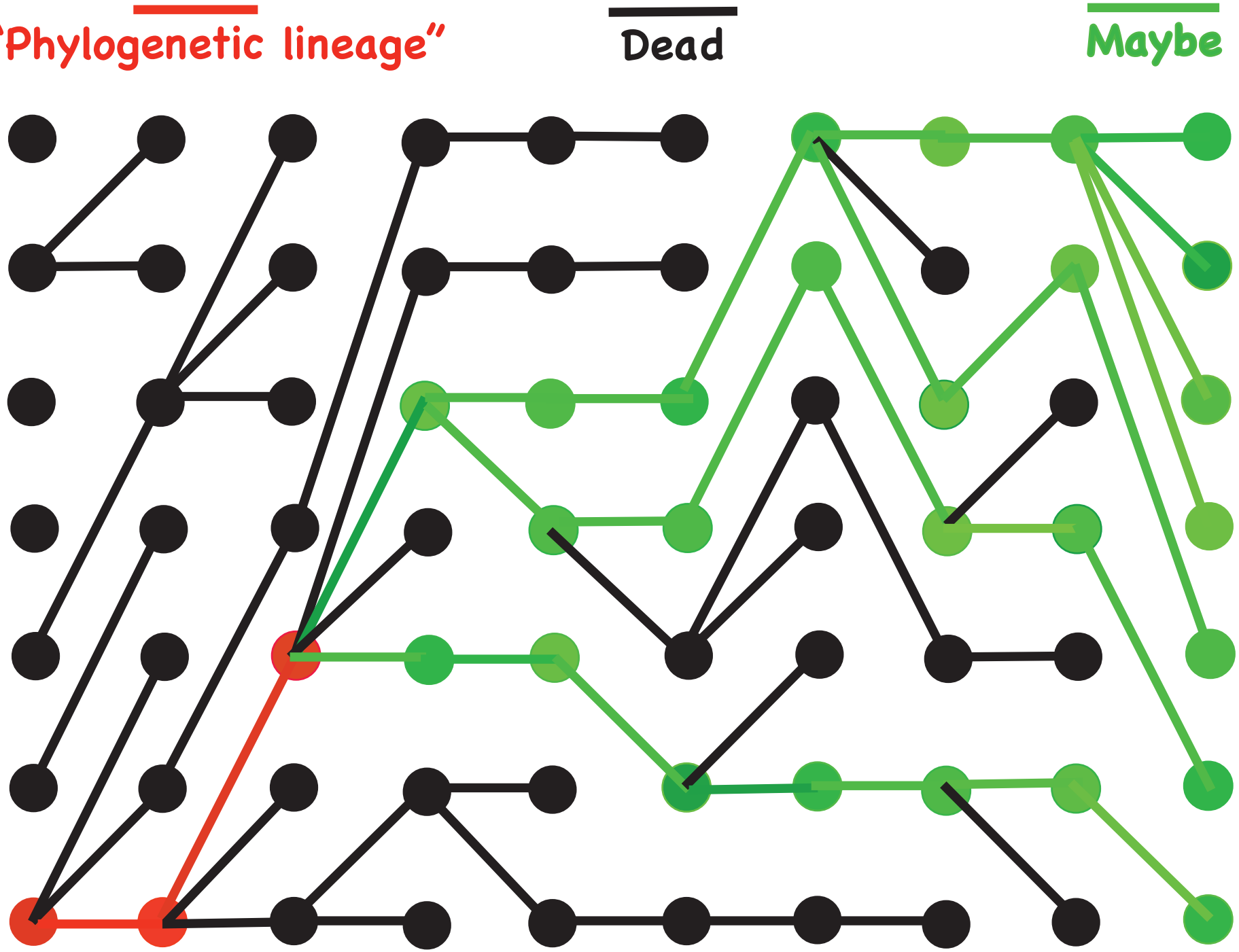


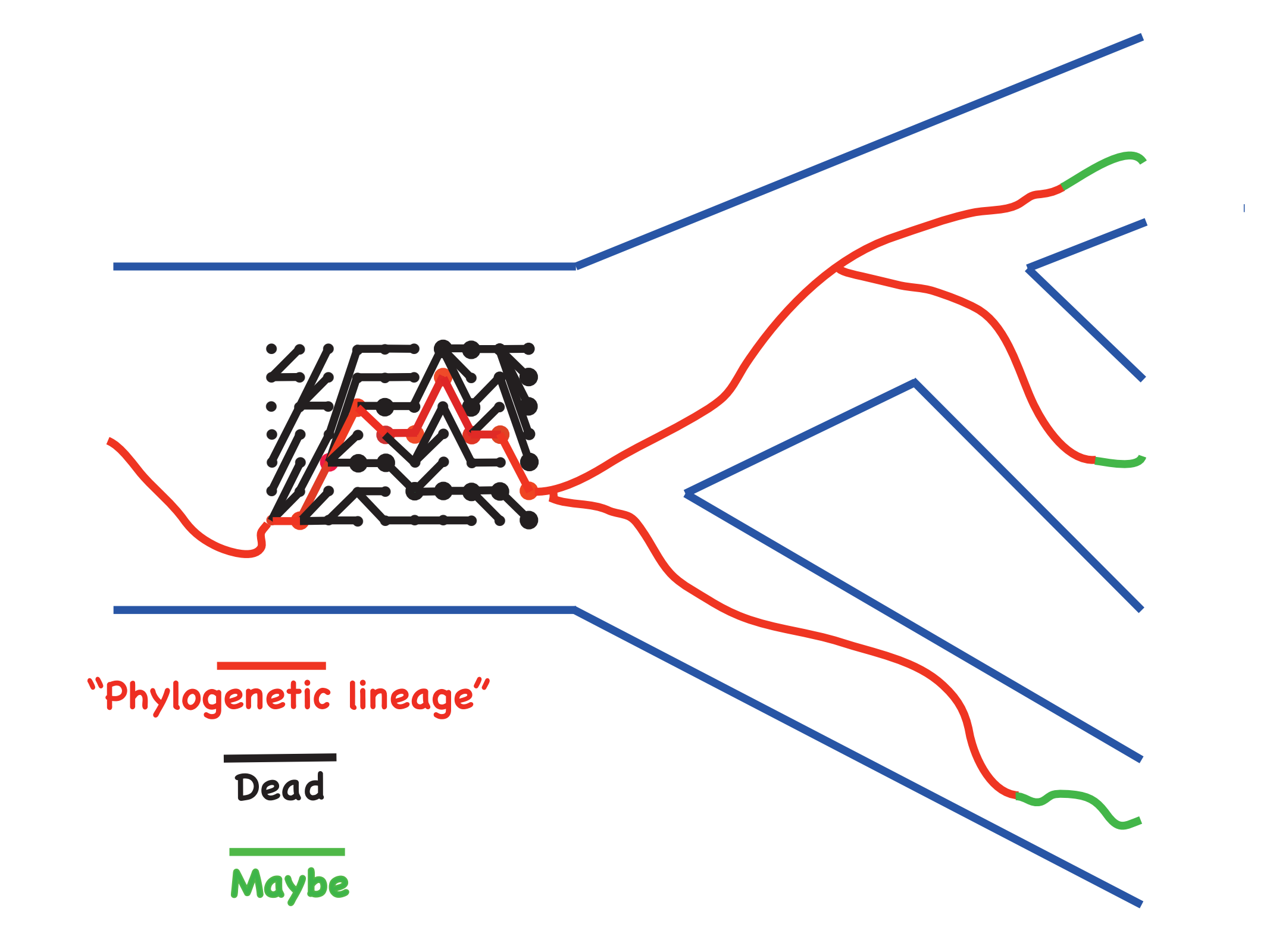
"Virtual" events do not actually change character state. Real events do change character state.


Rao-Teh algorithm (1. Resample virtual events conditional on real ones. 2. Resample event types conditional on event times)
Virtual Event
Virtual Event
Real Event
Real Event
Virtual Event
Virtual Event
Real Event
Virtual Event
Real Event
Virtual Event
Real Event
Virtual Event
Real Event
Virtual Event
Virtual Event
Virtual Event
First, use Poisson distribution to resample virtual events conditional on real events
Second, resample event type conditional on event times and endpoints (dynamic programming)

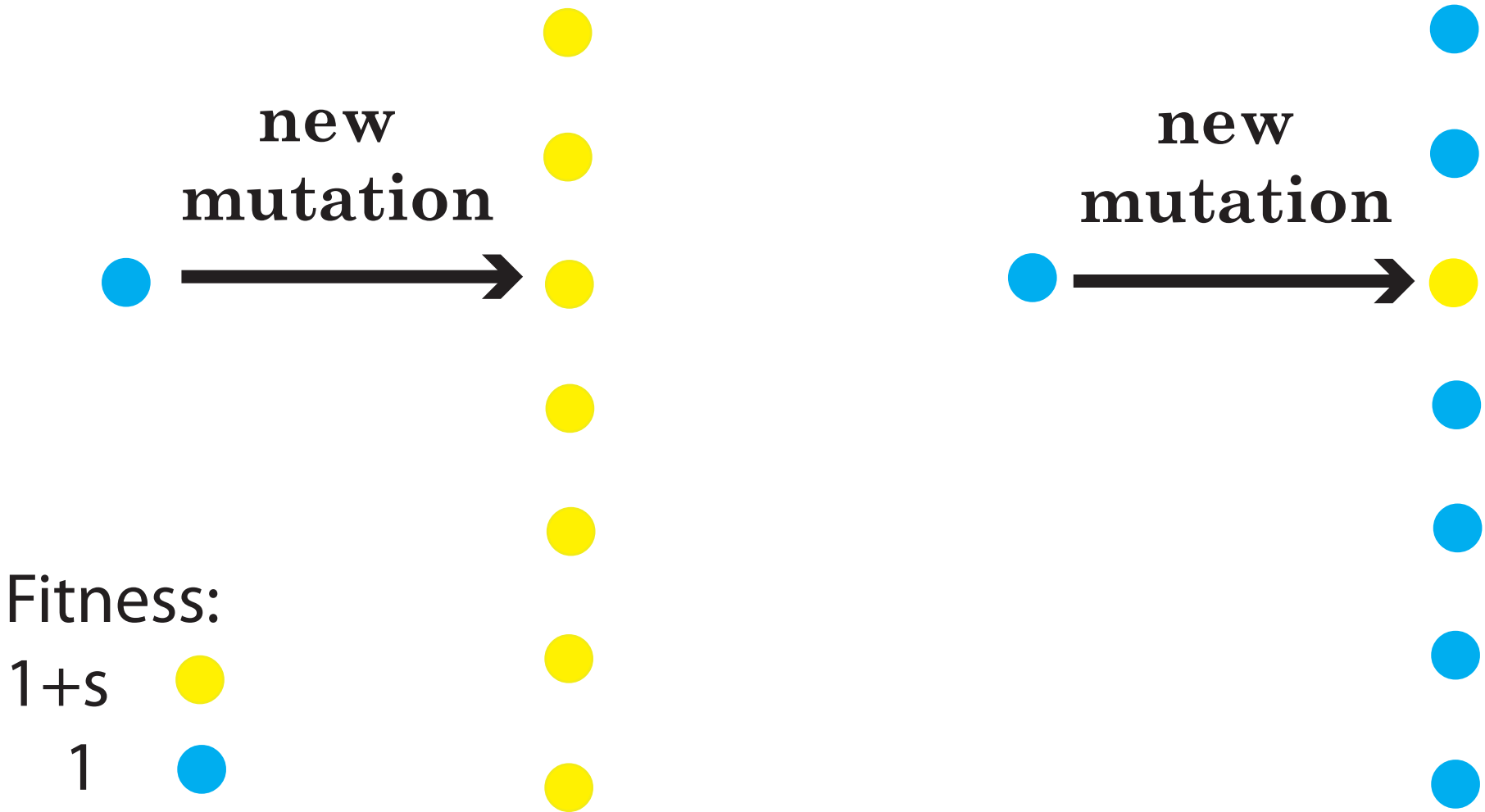
What justifies the assumption of phylogenetic models that sequences change over time according to a Markov process?


"Then"
Time
"Now"


"Phylogenetic lineage"
Dead
Maybe


"Phylogenetic lineage"
Dead
Maybe

Fixation probabilities depend on the other alleles in the population



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