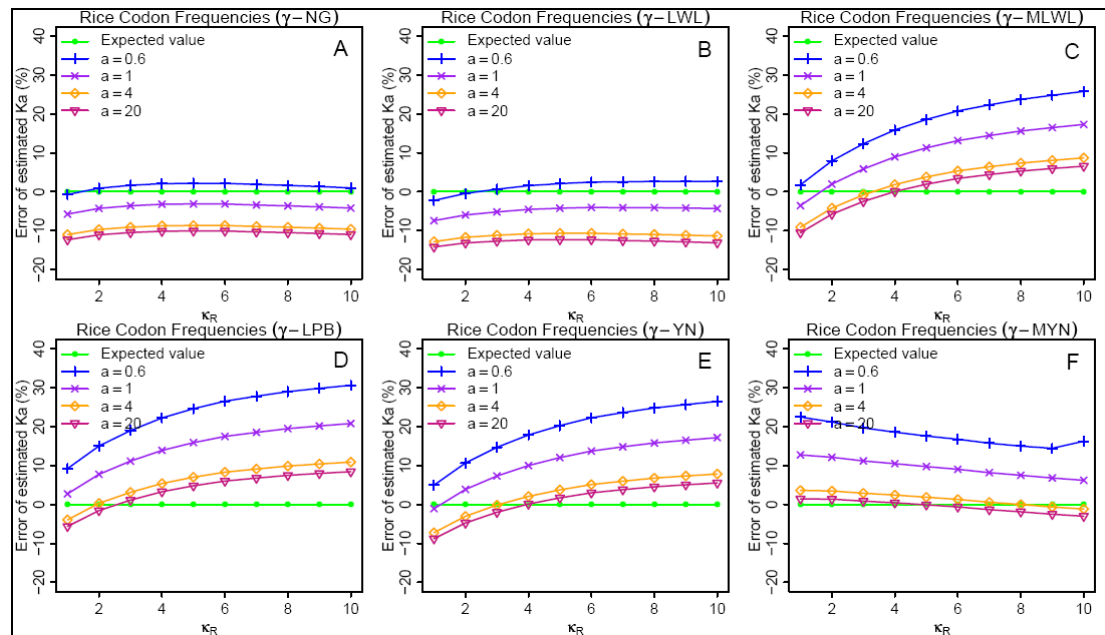


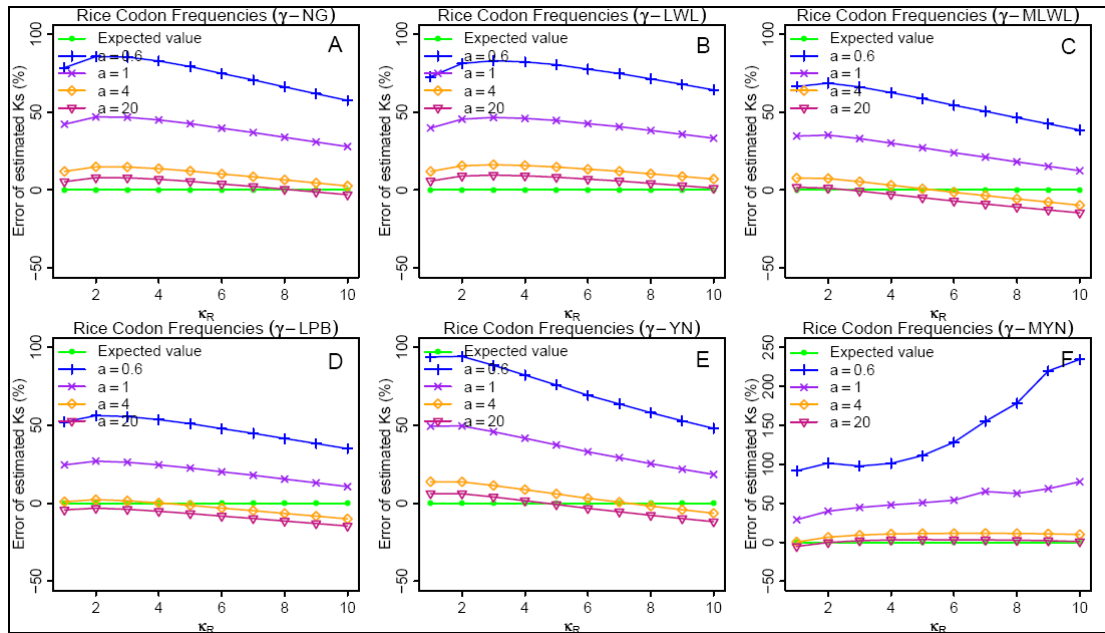
## Supporting Online Material

Wang, D., *et al.* 2009. How do variable substitution rates influence Ka and Ks calculations? *Genomics Proteomics Bioinformatics* 7: 116-127.

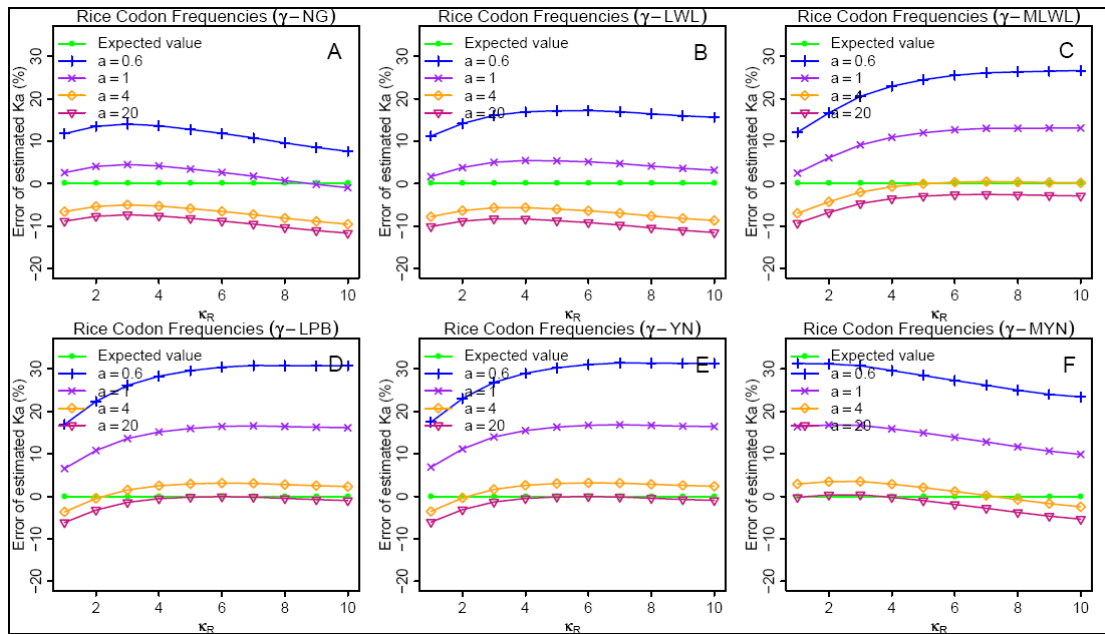
DOI: 10.1016/S1672-0229(08)60040-6



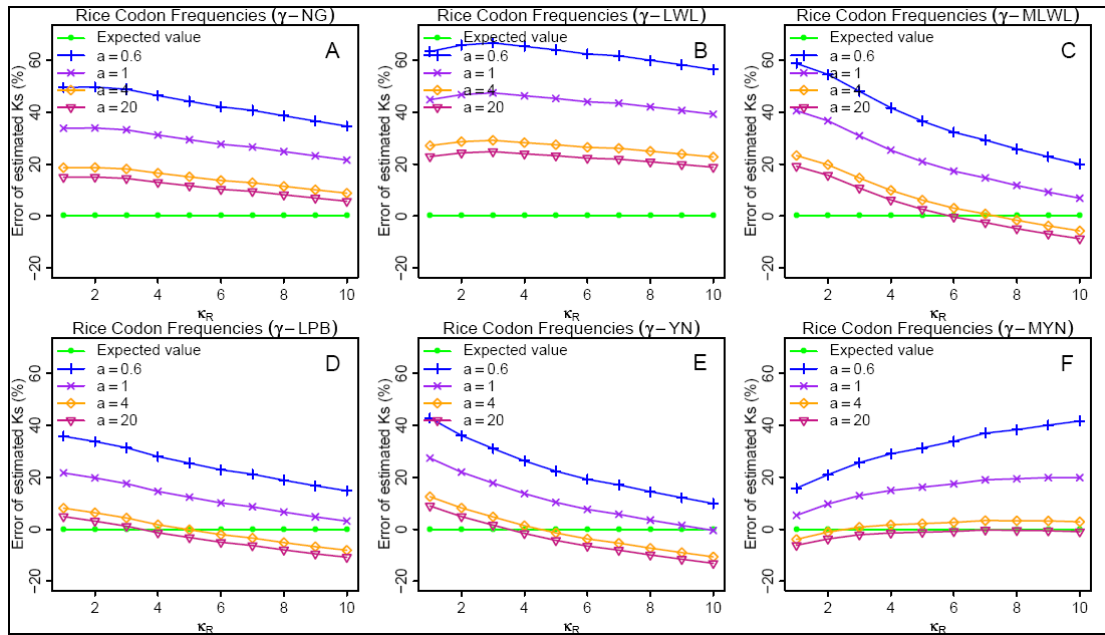
**Figure S1** Percentage errors of estimated Ka in the condition of expected  $\omega=0.3$ . We plotted percentage errors of Ka, averaging over 2,000 pairs of sequences by  $\gamma$ -NG,  $\gamma$ -LWL,  $\gamma$ -MLWL,  $\gamma$ -LPB,  $\gamma$ -YN, and  $\gamma$ -MYN, when  $\kappa_Y=3.75$  and  $\kappa_R$  varies from 1 to 10, in the condition of expected  $\omega=0.3$ . Sequences were simulated with the rice codon frequencies derived from rice protein-coding genes. The percentage error was calculated by the formula:  $100\% \times [(\text{estimated value}) - (\text{expected value})] / (\text{expected value})$ .



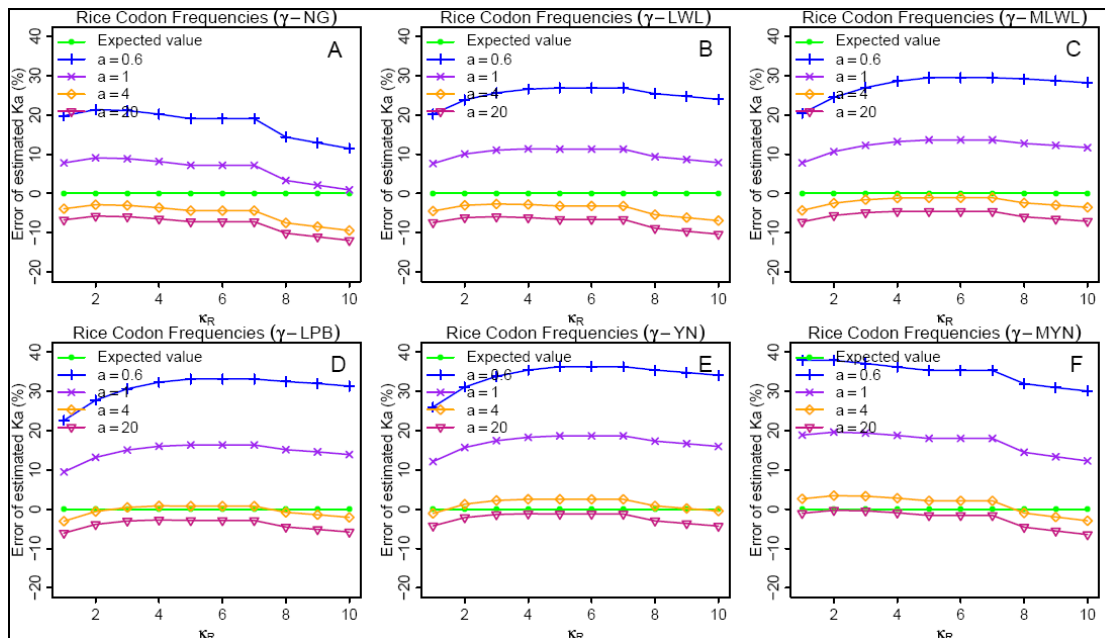
**Figure S2** Percentage errors of estimated  $K_s$  in the condition of expected  $\omega=0.3$ .



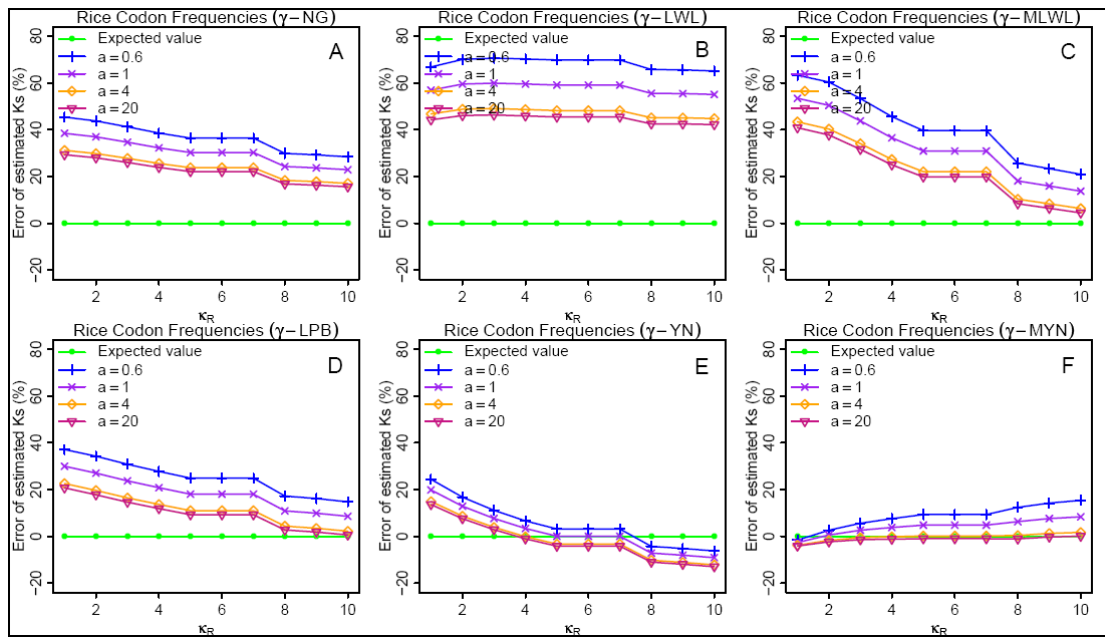
**Figure S3** Percentage errors of estimated  $K_a$  in the condition of expected  $\omega=1$ .



**Figure S4** Percentage errors of estimated  $K_s$  in the condition of expected  $\omega=1$ .



**Figure S5** Percentage errors of estimated  $K_a$  in the condition of expected  $\omega=3$ .



**Figure S6** Percentage errors of estimated Ks in the condition of expected  $\omega=3$ .

**Table S1 The optimal indexes of Ka, Ks and  $\omega$  based on a combination of six values of “a” and seven methods**

A. Optimal indexes of Ka estimates when  $\omega=0.3$

<i>a</i>	$\gamma$ -NG	$\gamma$ -LWL	$\gamma$ -MLWL	$\gamma$ -LPB	$\gamma$ -MLPB	$\gamma$ -YN	$\gamma$ -MYN
0.2	11547.54	19270.02	45690.11	68170.24	65472.78	59409.25	1615916
0.6	<b>26.762</b>	<b>46.5106</b>	3583.898	5906.709	5509.021	4103.508	3214.378
1	151.3296	241.4875	1452.381	2500.191	2288.53	1536.083	926.1002
4	865.4107	1259.782	384.0482	577.932	518.8555	302.3096	46.34939
20	1141.536	1643.657	291.8221	340.7176	314.1287	206.6636	<b>26.0993</b>
$\infty$	1215.59	1745.952	<b>279.856</b>	<b>297.192</b>	<b>278.252</b>	<b>195.967</b>	33.0314

B. Optimal indexes of Ks estimates when  $\omega=0.3$

<i>a</i>	$\gamma$ -NG	$\gamma$ -LWL	$\gamma$ -MLWL	$\gamma$ -LPB	$\gamma$ -MLPB	$\gamma$ -YN	$\gamma$ -MYN
0.2	3082012	2981870	2258079	1735173	1787809	3610240	34605799
0.6	55902.95	57327.73	31747.3	23120.76	24272.01	55233.91	226132.5
1	15783.32	17221.99	6899.777	4379.574	4774.601	13507.57	30977.05
4	1168.573	1673.119	<b>353.971</b>	<b>255.337</b>	<b>257.101</b>	686.887	962.5671
20	263.1357	468.3207	660.1346	791.9355	734.2831	<b>432.199</b>	82.79042
$\infty$	<b>168.859</b>	<b>298.789</b>	825.3646	997.0964	926.6511	501.2602	<b>57.3466</b>

C. Optimal indexes of  $\omega$  estimates when  $\omega=0.3$

<i>a</i>	$\gamma$ -NG	$\gamma$ -LWL	$\gamma$ -MLWL	$\gamma$ -LPB	$\gamma$ -MLPB	$\gamma$ -YN	$\gamma$ -MYN
0.2	0.520786	0.49793	0.400133	0.324493	0.333247	0.429116	0.308941
0.6	0.140898	0.14589	0.050369	0.022864	0.026797	0.074154	0.128693
1	0.076312	0.086779	0.018305	<b>0.0075</b>	<b>0.00907</b>	0.028887	0.047647
4	0.023863	0.035786	<b>0.01493</b>	0.019197	0.017591	<b>0.01104</b>	0.003026
20	0.014569	0.025608	0.020829	0.027804	0.025273	0.013745	<b>0.00104</b>
$\infty$	<b>0.0126</b>	<b>0.02331</b>	0.022782	0.030323	0.027555	0.014966	0.001218

D. Optimal indexes of Ka estimates when  $\omega=1$

<i>a</i>	$\gamma$ -NG	$\gamma$ -LWL	$\gamma$ -MLWL	$\gamma$ -LPB	$\gamma$ -MLPB	$\gamma$ -YN	$\gamma$ -MYN
0.2	58907.95	122534.3	152935.5	190618.5	186805	209668.6	1767742
0.6	1346.055	2518.576	5405.957	7853.904	7672.49	8201.335	7759.976
1	<b>84.5399</b>	<b>190.445</b>	1231.588	2171.984	2107.548	2257.878	2009.991
4	490.2283	488.9044	<b>71.9116</b>	69.31302	69.25104	71.45276	<b>56.4888</b>
20	846.2706	931.8537	211.2094	<b>52.528</b>	<b>61.723</b>	<b>50.4726</b>	77.65364
$\infty$	948.914	1061.436	269.6196	76.96815	88.08028	74.54203	110.9996

E. Optimal indexes of Ks estimates when  $\omega=1$

$a$	$\gamma$ -NG	$\gamma$ -LWL	$\gamma$ -MLWL	$\gamma$ -LPB	$\gamma$ -MLPB	$\gamma$ -YN	$\gamma$ -MYN
0.2	254219.3	476868.4	292138.5	178142.5	179026.7	141584.2	6071823
0.6	18824.58	38940.68	15259.76	6646.666	6760.638	6390.708	10466.78
1	8305.24	19374.12	5804.733	1780.699	1863.829	1943.952	2602.04
4	2183.109	7035.53	1340.185	<b>280.365</b>	<b>342.608</b>	<b>538.866</b>	71.47309
20	1305.79	4997.238	927.8209	380.2644	438.6278	636.4287	<b>62.364</b>
$\infty$	<b>1127.42</b>	<b>4554.74</b>	<b>865.451</b>	431.4219	488.9049	686.2089	93.00846

F. Optimal indexes of  $\omega$  estimates when  $\omega=1$

$a$	$\gamma$ -NG	$\gamma$ -LWL	$\gamma$ -MLWL	$\gamma$ -LPB	$\gamma$ -MLPB	$\gamma$ -YN	$\gamma$ -MYN
0.2	0.680797	0.84767	0.345015	0.323869	0.341138	1.127662	1.372097
0.6	0.3752	0.694656	0.175829	0.117227	0.129481	0.234247	0.077914
1	0.326145	0.656782	0.149473	0.094841	0.106057	0.172474	0.043912
4	0.276189	0.612876	0.123537	0.074518	0.084615	0.123632	0.022785
20	0.263804	0.601034	0.117321	0.069847	0.079656	0.113416	0.019249
$\infty$	<b>0.26077</b>	<b>0.59807</b>	<b>0.1158</b>	<b>0.06872</b>	<b>0.07846</b>	<b>0.11102</b>	<b>0.01847</b>

G. Optimal indexes of Ka estimates when  $\omega=3$

$a$	$\gamma$ -NG	$\gamma$ -LWL	$\gamma$ -MLWL	$\gamma$ -LPB	$\gamma$ -MLPB	$\gamma$ -YN	$\gamma$ -MYN
0.2	117427.5	268509.4	283279.6	326755.9	321937.9	389226.3	2517063
0.6	3290.478	6330.325	7626.924	9599.631	9529.177	11594.53	12160.55
1	459.1958	1017.903	1504.38	2180.039	2171.417	2906.486	2975.361
4	<b>318.135</b>	<b>188.506</b>	<b>58.6364</b>	<b>19.4999</b>	<b>20.0034</b>	<b>34.0555</b>	<b>64.5459</b>
20	673.8138	570.9903	316.4082	174.011	171.1972	71.22115	103.1384
$\infty$	783.6474	696.6727	413.0874	249.2517	245.3681	120.4233	152.7502

H. Optimal indexes of Ks estimates when  $\omega=3$

$a$	$\gamma$ -NG	$\gamma$ -LWL	$\gamma$ -MLWL	$\gamma$ -LPB	$\gamma$ -MLPB	$\gamma$ -YN	$\gamma$ -MYN
0.2	55840.05	191942.6	102904.4	50192.05	47548.5	7604.48	428626.3
0.6	13680.85	46729.61	18906.76	6913.527	6467.506	1159.572	955.1489
1	9492.459	33548.46	12275.49	3896.237	3639.276	829.01	266.5879
4	5916.31	22341.78	7075.586	1756.811	1659.059	<b>719.589</b>	<b>22.1801</b>
20	5140.708	19895.41	6023.675	1372.149	1309.021	733.6384	29.34963
$\infty$	<b>4957.59</b>	<b>19315.7</b>	<b>5779.83</b>	<b>1286.85</b>	<b>1231.92</b>	739.8674	35.28303

I. Optimal indexes of  $\omega$  estimates when  $\omega=3$

$a$	$\gamma$ -NG	$\gamma$ -LWL	$\gamma$ -MLWL	$\gamma$ -LPB	$\gamma$ -MLPB	$\gamma$ -YN	$\gamma$ -MYN
0.2	7.395717	<b>3.81038</b>	25.56014	57.74035	61.63727	250.1332	742.1982
0.6	<b>0.80107</b>	4.44375	<b>1.24481</b>	1.42028	1.838754	13.50247	10.38286
1	1.96461	6.751934	1.858692	<b>0.40606</b>	<b>0.58259</b>	5.513446	3.636866
4	3.668106	9.447704	3.212627	0.692306	0.6752	1.42975	0.535923
20	4.171876	10.16467	3.649382	0.94639	0.888573	0.939573	0.22437
$\infty$	4.300364	10.34319	3.761977	1.019101	0.951723	<b>0.84778</b>	<b>0.17253</b>

**Table S2 Substitution rate matrices for Markov models of nucleotide substitution used in this study (I)**

Model	From	To			
		T	C	A	G
JC69 (Jukes and Cantor 1969) (2)	T	–	$\alpha$	$\alpha$	$\alpha$
	C	$\alpha$	–	$\alpha$	$\alpha$
	A	$\alpha$	$\alpha$	–	$\alpha$
	G	$\alpha$	$\alpha$	$\alpha$	–
K80 (Kimura 1980) (3)	T	–	$\alpha$	$\beta$	$\beta$
	C	$\alpha$	–	$\beta$	$\beta$
	A	$\beta$	$\beta$	–	$\alpha$
	G	$\beta$	$\beta$	$\alpha$	–
F84 (Felsenstein 1984) (4)	T	–	$(1+\kappa/g_Y) \beta g_C$	$\beta g_A$	$\beta g_G$
	C	$(1+\kappa/g_Y) \beta g_T$	–	$\beta g_A$	$\beta g_G$
	A	$\beta g_T$	$\beta g_C$	–	$(1+\kappa/g_R) \beta g_G$
	G	$\beta g_T$	$\beta g_C$	$(1+\kappa/g_R) \beta g_A$	–
HKY85 (Hasegawa <i>et al.</i> 1984, 1985) (5)	T	–	$\alpha g_C$	$\beta g_A$	$\beta g_G$
	C	$\alpha g_T$	–	$\beta g_A$	$\beta g_G$
	A	$\beta g_T$	$\beta g_C$	–	$\alpha g_G$
	G	$\beta g_T$	$\beta g_C$	$\alpha g_A$	–
TN93 (Tamura and Nei 1993) (6)	T	–	$\alpha_2 g_C$	$\beta g_A$	$\beta g_G$
	C	$\alpha_2 g_T$	–	$\beta g_A$	$\beta g_G$
	A	$\beta g_T$	$\beta g_C$	–	$\alpha_1 g_G$
	G	$\beta g_T$	$\beta g_C$	$\alpha_1 g_A$	–

Note: The diagonals of the matrix are determined by the requirement that each row sums to 0. The equilibrium distribution is  $\pi = (1/4, 1/4, 1/4, 1/4)$  under JC69 and K80, and  $\pi = (g_T, g_C, g_A, g_G)$  under F84, HKY85, and TN93.  $\alpha$ , transitional rate;  $\beta$ , transversional rate;  $\alpha_1$ , transitional rate between purines;  $\alpha_2$ , transitional rate between pyrimidines;  $g_N$ , frequencies of nucleotide N, where  $N \in \{T, C, A, G\}$ ;  $g_R = g_A + g_G$ ;  $g_Y = g_T + g_C$ .



## A survey of gamma distribution

We assume that the rate of nucleotide substitution  $\lambda$  approximately follows the gamma distribution ( $I$ ):

$$f(\lambda) = \frac{b^a}{\tau(a)} e^{-b\lambda} \lambda^{a-1} \quad (S1)$$

where  $a = \bar{\lambda}^2 / V(\lambda)$  and  $b = a / \bar{\lambda}$ ,  $\bar{\lambda}$  and  $V(\lambda)$  is the mean and variance of  $\lambda$ , respectively, and  $\tau(a)$  is the gamma function. Here note that  $a$  is the square of the inverse of the coefficient of variation. To avoid using too many parameters, we set  $b = a$  so that the mean of the distribution is 1, with variance  $1/a$ . The shape parameter  $a$  is then inversely related to the extent of rate variation at sites.

## Deductions of related parameters based on gamma distribution

### (1) JC69 model

We directly describe the proportion of nucleotide sites showing differences ( $P$ ) between two sequences that diverged  $t$  evolutionary time units ago:

$$P = \frac{3}{4} - \frac{3}{4} \exp(-4\alpha t) \quad (S2)$$

Then, we can get the transformation:

$$\alpha t = -\frac{1}{4} \log_e \left( 1 - \frac{4}{3} P \right) \quad (S3)$$

Hence, the formula for estimating  $d$  is as follows:

$$d = 3\alpha t = -\frac{3}{4} \log_e \left( 1 - \frac{4}{3} P \right) \quad (S4)$$

Therefore, if  $\lambda$  or  $\alpha$  follows the gamma distribution, the mean of  $P$  is given by (7):

$$\bar{P} = \int_0^\infty P f(\lambda) d\lambda = \frac{3}{4} - \frac{3}{4} \left[ \frac{a}{a + 4\alpha t} \right]^a \quad (S5)$$

Then, we can get the transformation:

$$\frac{a}{\alpha t} = \frac{a}{4} \left[ \left( 1 - \frac{4}{3} \bar{P} \right)^{-\frac{1}{a}} - 1 \right] \quad (S6)$$

Hence, the formula for estimating  $\bar{d}$  is as follows:

$$\bar{d} = 3\bar{\alpha}t = \frac{3a}{4} \left[ \left( 1 - \frac{4}{3}\bar{P} \right)^{-1/a} - 1 \right] \quad (S7)$$

## (2) K80 (K2P) model

We directly describe the proportion of nucleotide sites showing transitional differences ( $P$ ) and of those showing transversional differences ( $Q$ ) between two sequences that diverged  $t$  evolutionary time units ago:

$$P = \frac{1}{4} + \frac{1}{4} \exp(-4\beta t) - \frac{1}{2} \exp[-2(\alpha + \beta)t] \quad (S8)$$

$$Q = \frac{1}{2} - \frac{1}{2} \exp(-4\beta t) \quad (S9)$$

Then, we can get the transformations:

$$\alpha t = -\frac{1}{2} \log_e(1 - 2P - Q) + \frac{1}{4} \log_e(1 - 2Q) \quad (S10)$$

$$\beta t = -\frac{1}{4} \log_e(1 - 2Q) \quad (S11)$$

Hence, the formulae for estimating  $d$  and  $\kappa$  are as follows:

$$d = (\alpha + 2\beta)t = -\frac{1}{2} \log_e(1 - 2P - Q) - \frac{1}{4} \log_e(1 - 2Q) \quad (S12)$$

$$\kappa = \frac{\alpha}{\beta} = \frac{2 \log_e(1 - 2P - Q)}{\log_e(1 - 2Q)} - 1 \quad (S13)$$

Therefore, if  $\lambda$  or  $\alpha, \beta$  follows the gamma distribution, the means of  $P$  and  $Q$  are given by (8):

$$\bar{P} = \int_0^\infty P f(\lambda) d\lambda = \frac{1}{4} + \frac{1}{4} \left[ \frac{a}{a + 4\beta t} \right]^a - \frac{1}{2} \left[ \frac{a}{a + 2(\alpha + \beta)t} \right]^a \quad (S14)$$

$$\bar{Q} = \int_0^\infty Q f(\lambda) d\lambda = \frac{1}{2} - \frac{1}{2} \left[ \frac{a}{a + 4\beta t} \right]^a \quad (S15)$$

Then, we can get the transformations:

$$\bar{\alpha}t = \frac{a}{2} \left[ \left( 1 - 2\bar{P} - \bar{Q} \right)^{-1/a} - 1 \right] - \frac{a}{4} \left[ \left( 1 - 2\bar{Q} \right)^{-1/a} - 1 \right] \quad (S16)$$

$$\bar{\beta}t = \frac{a}{4} \left[ \left( 1 - 2\bar{Q} \right)^{-1/a} - 1 \right] \quad (S17)$$

Hence, the formulae for estimating  $\bar{d}$  and  $\bar{\kappa}$  are as follows:

$$\bar{d} = \overline{(\alpha + 2\beta)t} = \frac{a}{2} \left[ (1 - 2\bar{P} - \bar{Q})^{-1/a} + \frac{1}{2} (1 - 2\bar{Q})^{-1/a} - \frac{3}{2} \right] \quad (\text{S18})$$

$$\bar{\kappa} = \frac{\bar{\alpha}}{\bar{\beta}} = \frac{2 \left[ (1 - 2\bar{P} - \bar{Q})^{-1/a} - 1 \right]}{(1 - 2\bar{Q})^{-1/a} - 1} - 1 \quad (\text{S19})$$

### (3) F84 model

We directly describe the proportion of nucleotide sites showing transitional differences ( $P$ ) and of those showing transversional differences ( $Q$ ) between two sequences that diverged  $t$  evolutionary time units ago:

$$P = 2(g_T g_C + g_A g_G) + 2 \left( \frac{g_T g_C g_R}{g_Y} + \frac{g_A g_G g_Y}{g_R} \right) \exp(-\beta t) - 2 \left( \frac{g_T g_C}{g_Y} + \frac{g_A g_G}{g_R} \right) \exp[-(\kappa + 1)\beta t] \quad (\text{S20})$$

$$Q = 2g_Y g_R [1 - \exp(-\beta t)] \quad (\text{S21})$$

Let

$$h = (\kappa + 1)\beta t = -\log_e \left( 1 - \frac{1}{2 \left[ (g_T g_C / g_Y) + (g_A g_G / g_R) \right]} P - \frac{[(g_T g_C g_R / g_Y) + (g_A g_G g_Y / g_R)] Q}{2(g_T g_C g_R + g_A g_G g_Y)} \right) \quad (\text{S22})$$

$$i = \beta t = -\log_e \left( 1 - \frac{1}{2g_Y g_R} Q \right) \quad (\text{S23})$$

Then we get

$$\begin{aligned} d &= 2(g_T g_C + g_A g_G + g_Y g_R)\beta t + 2(g_T g_C / g_Y + g_A g_G / g_R)\kappa\beta t \\ &= 2 \left( \frac{g_T g_C}{g_Y} + \frac{g_A g_G}{g_R} \right) h - 2 \left( \frac{g_T g_C g_R}{g_Y} + \frac{g_A g_G g_Y}{g_R} - g_Y g_R \right) i \end{aligned} \quad (\text{S24})$$

$$\kappa = \frac{(\kappa + 1)\beta t - \beta t}{\beta t} = \frac{(\kappa + 1)\beta t}{\beta t} - 1 = \frac{h}{i} - 1 \quad (\text{S25})$$

Therefore, if  $\lambda$  or  $\beta$  follows the gamma distribution, the means of  $P$  and  $Q$  are given by (1):

$$\begin{aligned} \bar{P} &= \int_0^\infty P f(\lambda) d\lambda \\ &= 2(g_T g_C + g_A g_G) + 2 \left( \frac{g_T g_C g_R}{g_Y} + \frac{g_A g_G g_Y}{g_R} \right) \left( \frac{a}{a + \beta t} \right)^a - 2 \left( \frac{g_T g_C}{g_Y} + \frac{g_A g_G}{g_R} \right) \left[ \frac{a}{a + (\kappa + 1)\beta t} \right]^a \end{aligned} \quad (\text{S26})$$

$$\bar{Q} = \int_0^\infty Qf(\lambda)d\lambda = 2g_Y g_R \left[ 1 - \left( \frac{a}{a + \beta t} \right)^a \right] \quad (S27)$$

Let

$$\bar{h} = \overline{(\kappa + 1)\beta t} = a \left\{ \left[ 1 - \frac{1}{2(g_T g_C / g_Y + g_A g_G / g_R)} \bar{P} - \frac{g_T g_C g_R / g_Y + g_A g_G g_Y / g_R}{2(g_T g_C g_R + g_A g_G g_Y)} \bar{Q} \right]^{-1/a} - 1 \right\} \quad (S28)$$

$$\bar{i} = \bar{\beta t} = a \left[ \left( 1 - \frac{1}{2g_Y g_R} \bar{Q} \right)^{-1/a} - 1 \right] \quad (S29)$$

Then we get

$$\begin{aligned} \bar{d} &= 2(g_T g_C + g_A g_G + g_Y g_R) \bar{\beta t} + 2(g_T g_C / g_Y + g_A g_G / g_R) \bar{\kappa} \beta t \\ &= 2 \left( \frac{g_T g_C}{g_Y} + \frac{g_A g_G}{g_R} \right) \bar{h} - 2 \left( \frac{g_T g_C g_R}{g_Y} + \frac{g_A g_G g_Y}{g_R} - g_Y g_R \right) \bar{i} \end{aligned} \quad (S30)$$

$$\bar{\kappa} = \frac{\overline{(\kappa + 1)\beta t} - \bar{\beta t}}{\bar{\beta t}} = \frac{\overline{(\kappa + 1)\beta t}}{\bar{\beta t}} - 1 = \frac{\bar{h}}{\bar{i}} - 1 \quad (S31)$$

#### (4) HKY85 model

We can get estimated  $\kappa_{HKY85}$  and  $\bar{\kappa}_{HKY85}$  using the following formulae (9, 10):

$$\kappa_{HKY85} = 1 + \frac{g_T g_C / g_Y + g_A g_G / g_R}{g_T g_C + g_A g_G} \kappa_{F84} \quad (S32)$$

$$\bar{\kappa}_{HKY85} = 1 + \frac{g_T g_C / g_Y + g_A g_G / g_R}{g_T g_C + g_A g_G} \bar{\kappa}_{F84} \quad (S33)$$

#### (5) TN93 model

We directly describe the proportion of nucleotide sites showing transitional differences between purines ( $P_1$ ) and between pyrimidines ( $P_2$ ) and of those showing transversional differences ( $Q$ ) between two sequences that diverged  $t$  evolutionary time units ago:

$$P_1 = \frac{2g_A g_G}{g_R} \{g_R + g_Y \exp(-\beta t) - \exp[-(g_R \alpha_1 + g_Y \beta)t]\} \quad (S34)$$

$$P_2 = \frac{2g_T g_C}{g_Y} \{g_Y + g_R \exp(-\beta t) - \exp[-(g_Y \alpha_2 + g_R \beta)t]\} \quad (S35)$$

$$Q = 2g_R g_Y [1 - \exp(-\beta t)] \quad (\text{S36})$$

Then, we can get the transformations:

$$\alpha_1 t = \frac{1}{g_R} \left[ g_Y \log_e \left( 1 - \frac{1}{2g_R g_Y} Q \right) - \log_e \left( 1 - \frac{g_R}{2g_A g_G} P_1 - \frac{1}{2g_R} Q \right) \right] \quad (\text{S37})$$

$$\alpha_2 t = \frac{1}{g_Y} \left[ g_R \log_e \left( 1 - \frac{1}{2g_R g_Y} Q \right) - \log_e \left( 1 - \frac{g_Y}{2g_T g_C} P_2 - \frac{1}{2g_Y} Q \right) \right] \quad (\text{S38})$$

$$\beta t = -\log_e \left( 1 - \frac{1}{2g_R g_Y} Q \right) \quad (\text{S39})$$

Let

$$h = \log_e \left( 1 - \frac{g_R}{2g_A g_G} P_1 - \frac{1}{2g_R} Q \right) \quad (\text{S40})$$

$$i = \log_e \left( 1 - \frac{g_Y}{2g_T g_C} P_2 - \frac{1}{2g_Y} Q \right) \quad (\text{S41})$$

$$j = \log_e \left( 1 - \frac{1}{2g_R g_Y} Q \right) \quad (\text{S42})$$

We can get

$$\begin{aligned} d &= 2g_A g_G \alpha_1 t + 2g_T g_C \alpha_2 t + 2g_R g_Y \beta t \\ &= -\frac{2g_A g_G}{g_R} h - \frac{2g_T g_C}{g_Y} i + \left( \frac{2g_A g_G g_Y}{g_R} + \frac{2g_T g_C g_R}{g_Y} - 2g_R g_Y \right) j \end{aligned} \quad (\text{S43})$$

$$\kappa_R = \frac{\alpha_1}{\beta} = \frac{h - g_Y \times j}{g_R \times j} \quad (\text{S44})$$

$$\kappa_Y = \frac{\alpha_2}{\beta} = \frac{i - g_R \times j}{g_Y \times j} \quad (\text{S45})$$

Therefore, if  $\lambda$  or  $\alpha_1$ ,  $\alpha_2$  and  $\beta$  follows the gamma distribution, the means of  $P_1$ ,  $P_2$ , and  $Q$  are given by (6):

$$\overline{P_1} = \int_0^\infty P_1 f(\lambda) d\lambda = \frac{2g_A g_G}{g_R} \left\{ g_R - \left[ \frac{a}{a + (g_R \alpha_1 + g_Y \beta)t} \right]^a + g_Y \left( \frac{a}{a + \beta t} \right)^a \right\} \quad (\text{S46})$$

$$\overline{P_2} = \int_0^\infty P_2 f(\lambda) d\lambda = \frac{2g_T g_C}{g_Y} \left\{ g_Y - \left[ \frac{a}{a + (g_Y \alpha_2 + g_R \beta)t} \right]^a + g_R \left( \frac{a}{a + \beta t} \right)^a \right\} \quad (\text{S47})$$

$$\bar{Q} = \int_0^\infty Qf(\lambda)d\lambda = 2g_R g_Y \left[ 1 - \left( \frac{a}{a + \beta t} \right)^a \right] \quad (S48)$$

Then, we can get the transformations:

$$\bar{\alpha}_1 t = \frac{a}{g_R} \left[ \left( 1 - \frac{1}{2g_R} \bar{Q} - \frac{g_R}{2g_A g_G} \bar{P}_1 \right)^{-1/a} - g_Y \left( 1 - \frac{1}{2g_R g_Y} \bar{Q} \right)^{-1/a} - g_R \right] \quad (S49)$$

$$\bar{\alpha}_2 t = \frac{a}{g_Y} \left[ \left( 1 - \frac{1}{2g_Y} \bar{Q} - \frac{g_Y}{2g_T g_C} \bar{P}_2 \right)^{-1/a} - g_R \left( 1 - \frac{1}{2g_R g_Y} \bar{Q} \right)^{-1/a} - g_Y \right] \quad (S50)$$

$$\bar{\beta} t = a \left[ \left( 1 - \frac{1}{2g_R g_Y} \bar{Q} \right)^{-1/a} - 1 \right] \quad (S51)$$

Let

$$\bar{h} = \left( 1 - \frac{g_R}{2g_A g_G} \bar{P}_1 - \frac{1}{2g_R} \bar{Q} \right)^{-1/a} \quad (S52)$$

$$\bar{i} = \left( 1 - \frac{g_Y}{2g_T g_C} \bar{P}_2 - \frac{1}{2g_Y} \bar{Q} \right)^{-1/a} \quad (S53)$$

$$\bar{j} = \left( 1 - \frac{1}{2g_R g_Y} \bar{Q} \right)^{-1/a} \quad (S54)$$

We can get

$$\begin{aligned} \bar{d} &= 2g_A g_G \bar{\alpha}_1 t + 2g_T g_C \bar{\alpha}_2 t + 2g_R g_Y \bar{\beta} t \\ &= 2a \left[ \frac{g_A g_G}{g_R} \bar{h} + \frac{g_T g_C}{g_Y} \bar{i} + \left( g_R g_Y - \frac{g_A g_G g_Y}{g_R} - \frac{g_T g_C g_R}{g_Y} \right) \bar{j} - g_A g_G - g_T g_C - g_R g_Y \right] \end{aligned} \quad (S55)$$

$$\bar{\kappa}_R = \bar{\alpha}_1 / \bar{\beta} = \frac{\bar{h} - g_Y \times \bar{j} - g_R}{g_R \times \bar{j} - g_R} \quad (S56)$$

$$\bar{\kappa}_Y = \bar{\alpha}_2 / \bar{\beta} = \frac{\bar{i} - g_R \times \bar{j} - g_Y}{g_Y \times \bar{j} - g_Y} \quad (S57)$$

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