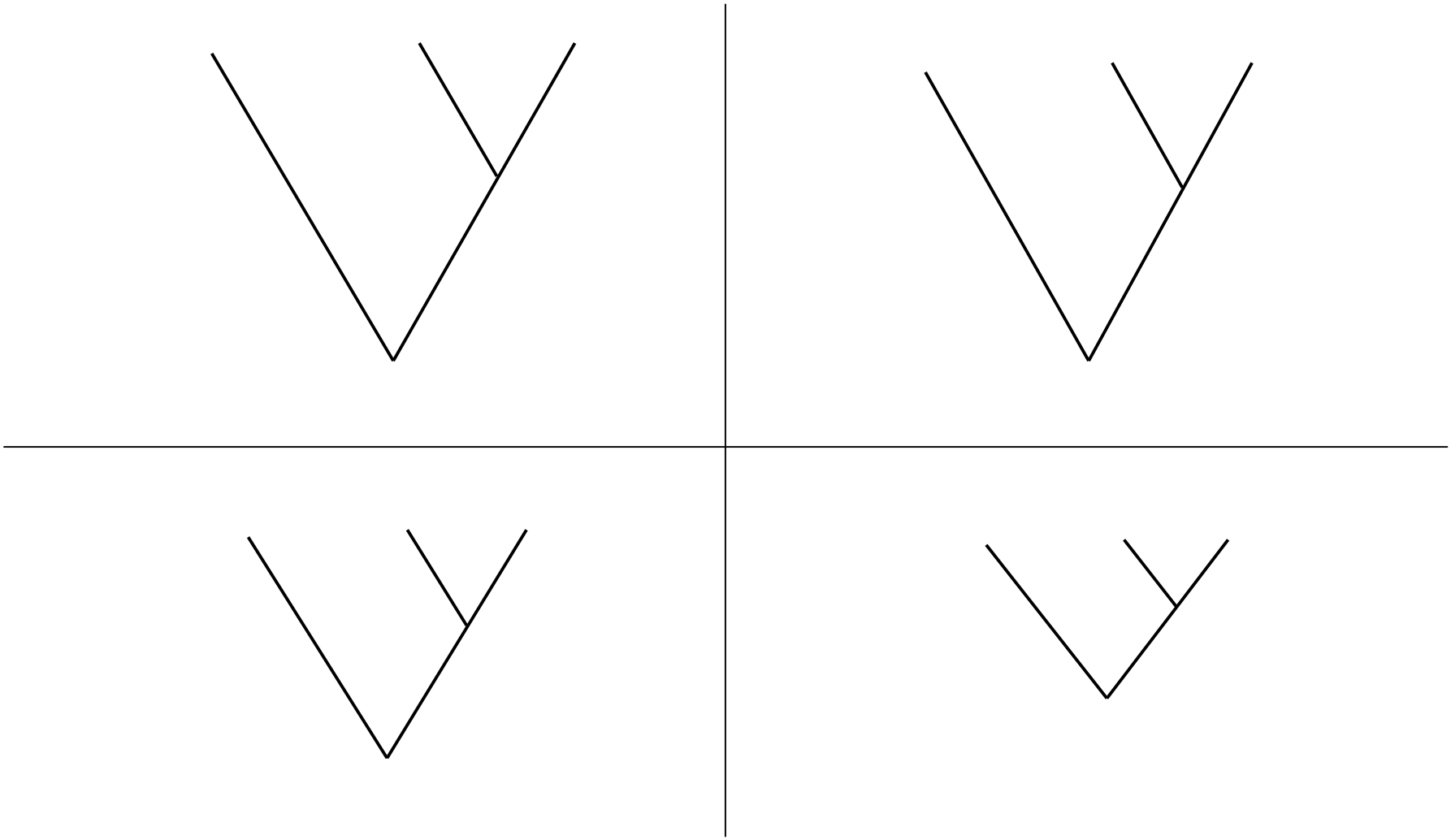
Estimating the contribution of sequence context to nucleotide substitution rate heterogeneity

Helen Lindsay and Gavin A. Huttley

The Gamma Model

- Yang (1993) used a gamma distribution to model rate variation in α- and β-globin genes
- The gamma distribution is often approximated by four equi-probable bins

Gamma rate variation



Improvements on the Gamma model

- Allow sites to change rates
- Allow clustering of rates
- Consider other/multiple rate distributions

What causes substitution rate variation?

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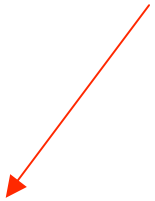
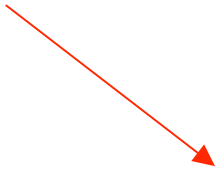


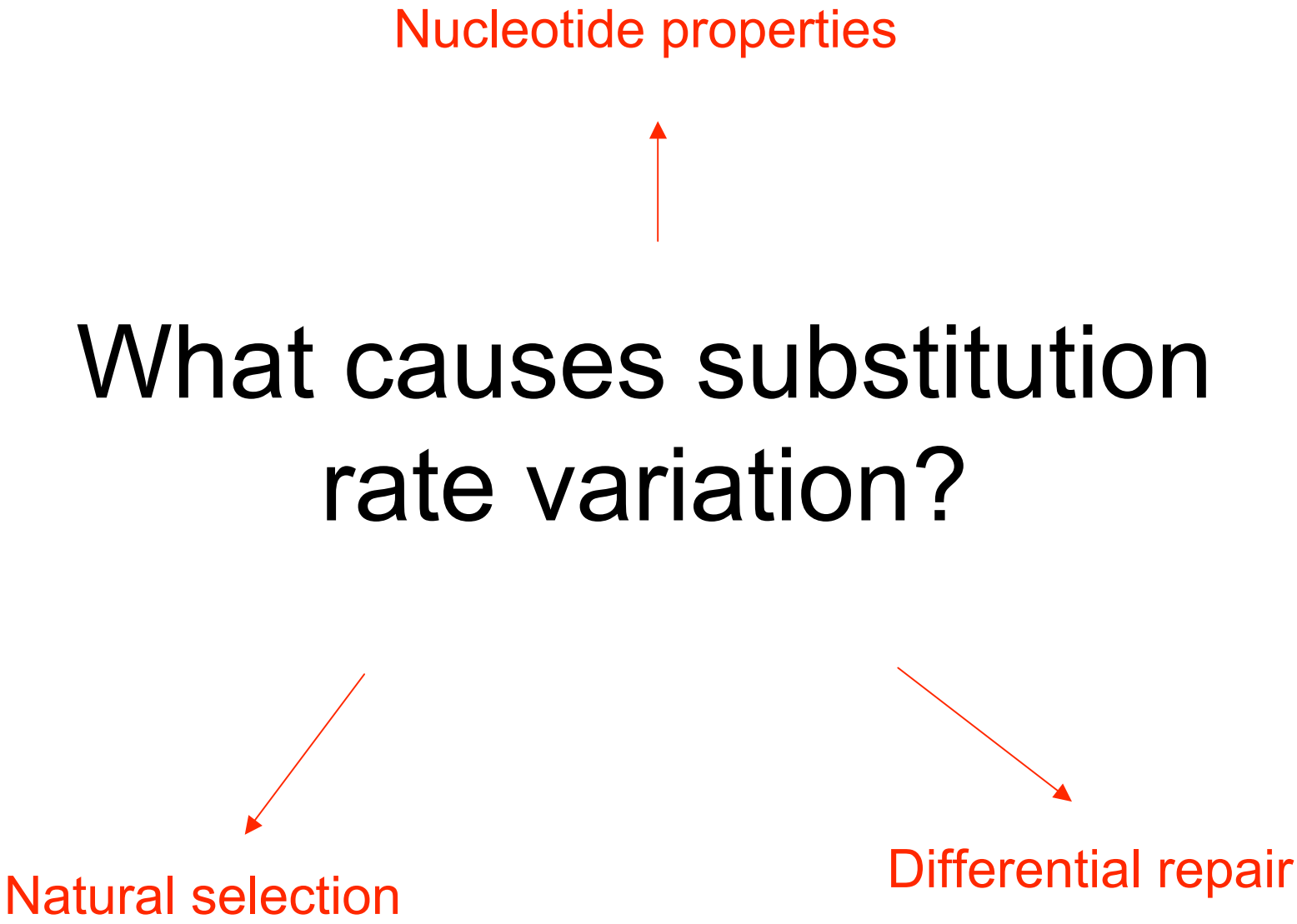
Natural selection

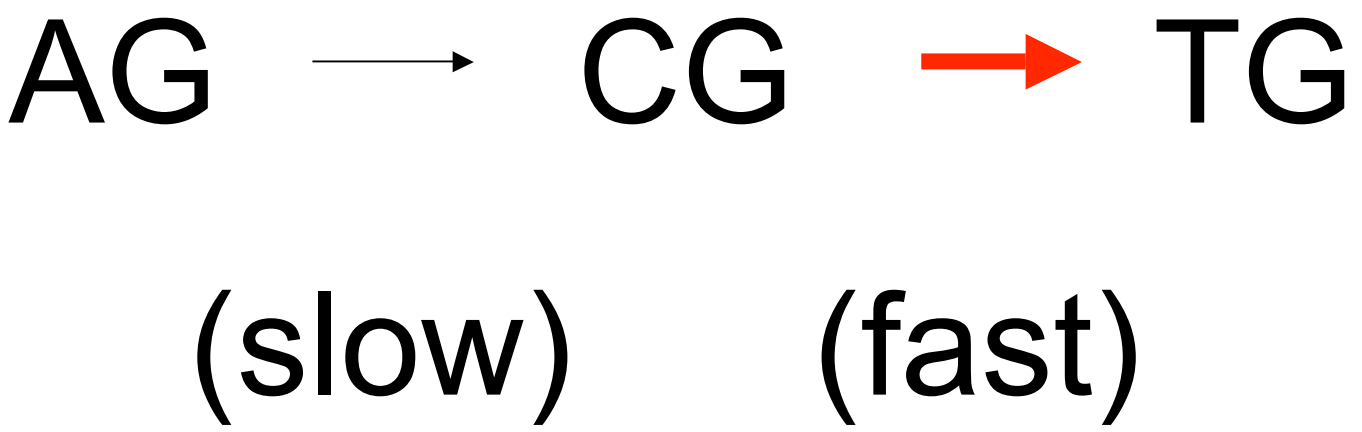
What causes substitution rate variation?

Natural selection



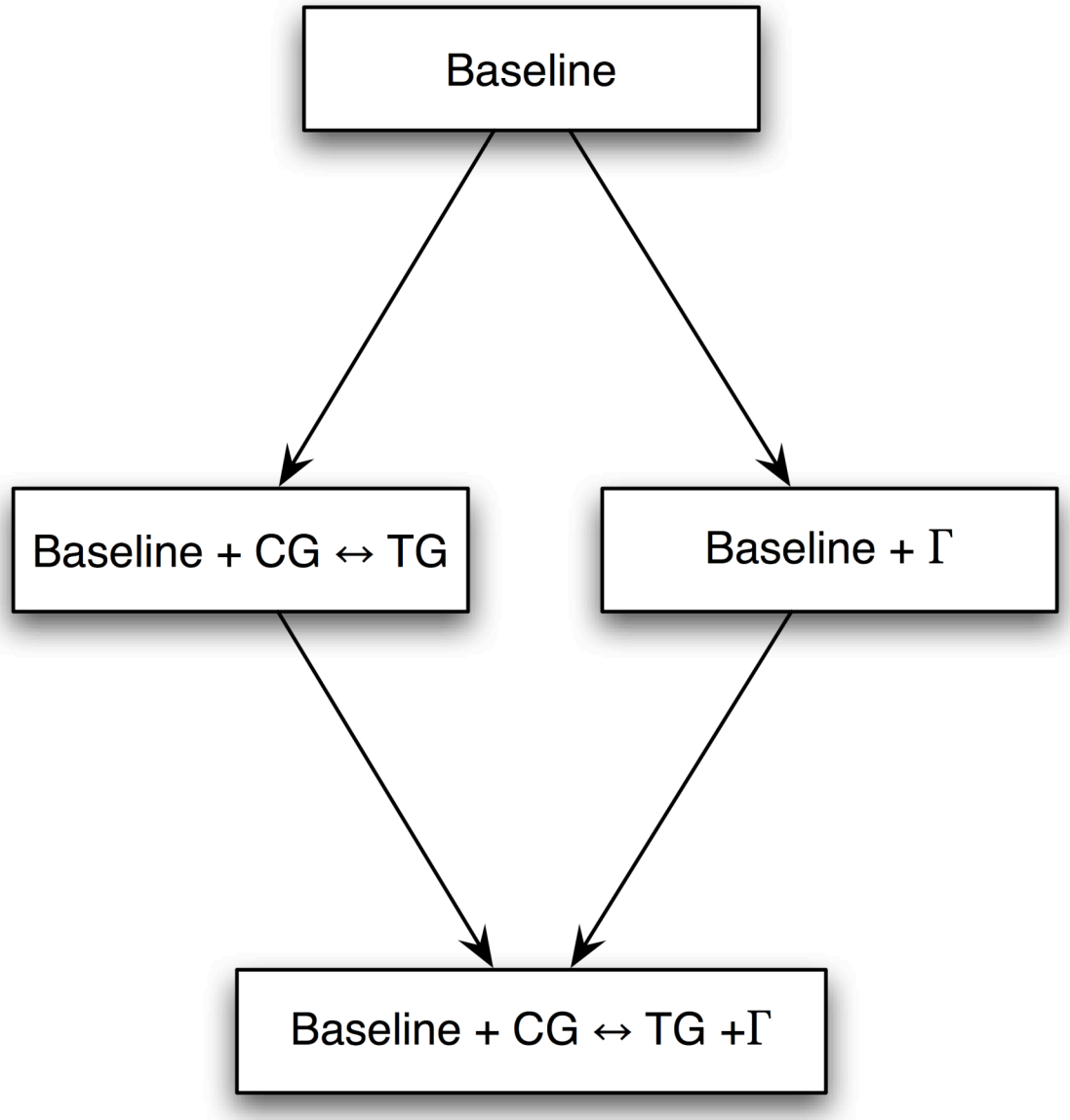
Differential repair


Nucleotide properties
What causes substitution rate variation?
Natural selection
Differential repair


AG
CG
TG
(slow)
(fast)

Data

- 470 alignments, each 50 000 nucleotides long, of introns from human, chimpanzee and macaque one-to-one orthologs.
- Sampled from Ensembl version 49.


Baseline
Baseline + CG ↔ TG
Baseline + Γ
Baseline + CG ↔ TG +Γ

The baseline model

$$q_{i_1 i_2, j_1 j_2} = \begin{cases} 0 & \text{more than one nucleotide difference} \\ \pi_{j_x} r_{A \leftrightarrow C} & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } A \leftrightarrow C \\ \pi_{j_x} r_{A \leftrightarrow G} & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } A \leftrightarrow G \\ \pi_{j_x} r_{A \leftrightarrow T} & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } A \leftrightarrow T \\ \pi_{j_x} r_{C \leftrightarrow G} & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } C \leftrightarrow G \\ \pi_{j_x} r_{C \leftrightarrow T} & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } C \leftrightarrow T \end{cases}$$

where x is the index at which $i_1 i_2$ and $j_1 j_2$ differ

The CpG model

$$q_{i_1 i_2, j_1 j_2} = \begin{cases} 0 & \text{more than one nucleotide difference} \\ \pi_{j_x} r_{A \leftrightarrow C} & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } A \leftrightarrow C \\ \pi_{j_x} r_{A \leftrightarrow G} & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } A \leftrightarrow G \\ \pi_{j_x} r_{A \leftrightarrow T} & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } A \leftrightarrow T \\ \pi_{j_x} r_{C \leftrightarrow G} & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } C \leftrightarrow G \\ \pi_{j_x} r_{C \leftrightarrow T} & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } C \leftrightarrow T, \{i, j\} \neq \{\text{CpG, TpG}\} \\ \pi_{j_x} r_{C \leftrightarrow T} r_{CG \leftrightarrow TG} & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } C \leftrightarrow T, \{i, j\} = \{\text{CpG, TpG}\} \end{cases}$$

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The Gamma Model

$$q_{i_1 i_2, j_1 j_2} = \begin{cases} 0 & \text{more than one nucleotide difference} \\ \pi_{j_x} r_{A \leftrightarrow C} \Gamma_n & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } A \leftrightarrow C \\ \pi_{j_x} r_{A \leftrightarrow G} \Gamma_n & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } A \leftrightarrow G \\ \pi_{j_x} r_{A \leftrightarrow T} \Gamma_n & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } A \leftrightarrow T \\ \pi_{j_x} r_{C \leftrightarrow G} \Gamma_n & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } C \leftrightarrow G \\ \pi_{j_x} r_{C \leftrightarrow T} \Gamma_n & i_1 i_2 \text{ and } j_1 j_2 \text{ differ by } C \leftrightarrow T \end{cases}$$

where x is the index at which $i_1 i_2$ and $j_1 j_2$ differ
and Γ_n is the rate category of site n.

Gamma vs Dinucleotide models

Parameter (P)	**LR** $(\frac{baseline+P}{baseline})$	**LR** $(\frac{baseline+P+\Gamma}{baseline+\Gamma})$	**LR** $(\frac{baseline+P+\Gamma}{baseline+P})$
baseline	-	-	51.07
$TG \leftrightarrow CG$ or $CA \leftrightarrow CG$	186.05	175.52	40.77
$TG \leftrightarrow CG$	89.53	84.79	46.07
$CA \leftrightarrow CG$	84.74	80.08	45.86
$AT \leftrightarrow GT$	28.83	28.01	50.09
$AA \leftrightarrow GA$	25.51	24.66	50.05
$TT \leftrightarrow CT$	23.24	22.48	50.23
$AA \leftrightarrow AG$	19.22	18.31	50.20
$TT \leftrightarrow TC$	15.41	14.63	50.22
$GA \leftrightarrow GG$	14.18	13.53	50.44
$TT \leftrightarrow CC$	10.80	10.43	50.78
$AT \leftrightarrow AC$	9.85	9.33	50.44

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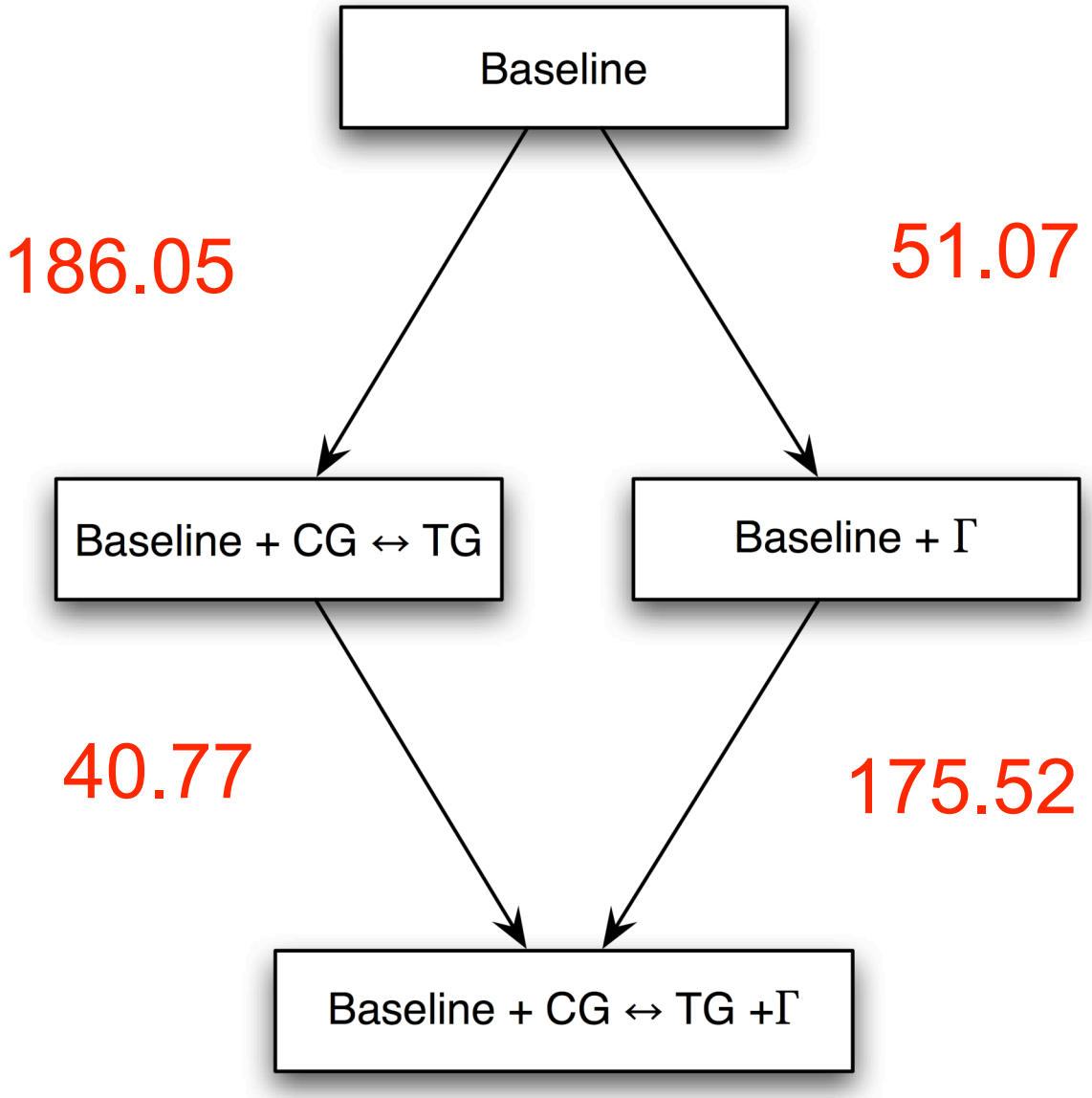
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Baseline + CG ↔ TG
Baseline + Γ
40.77
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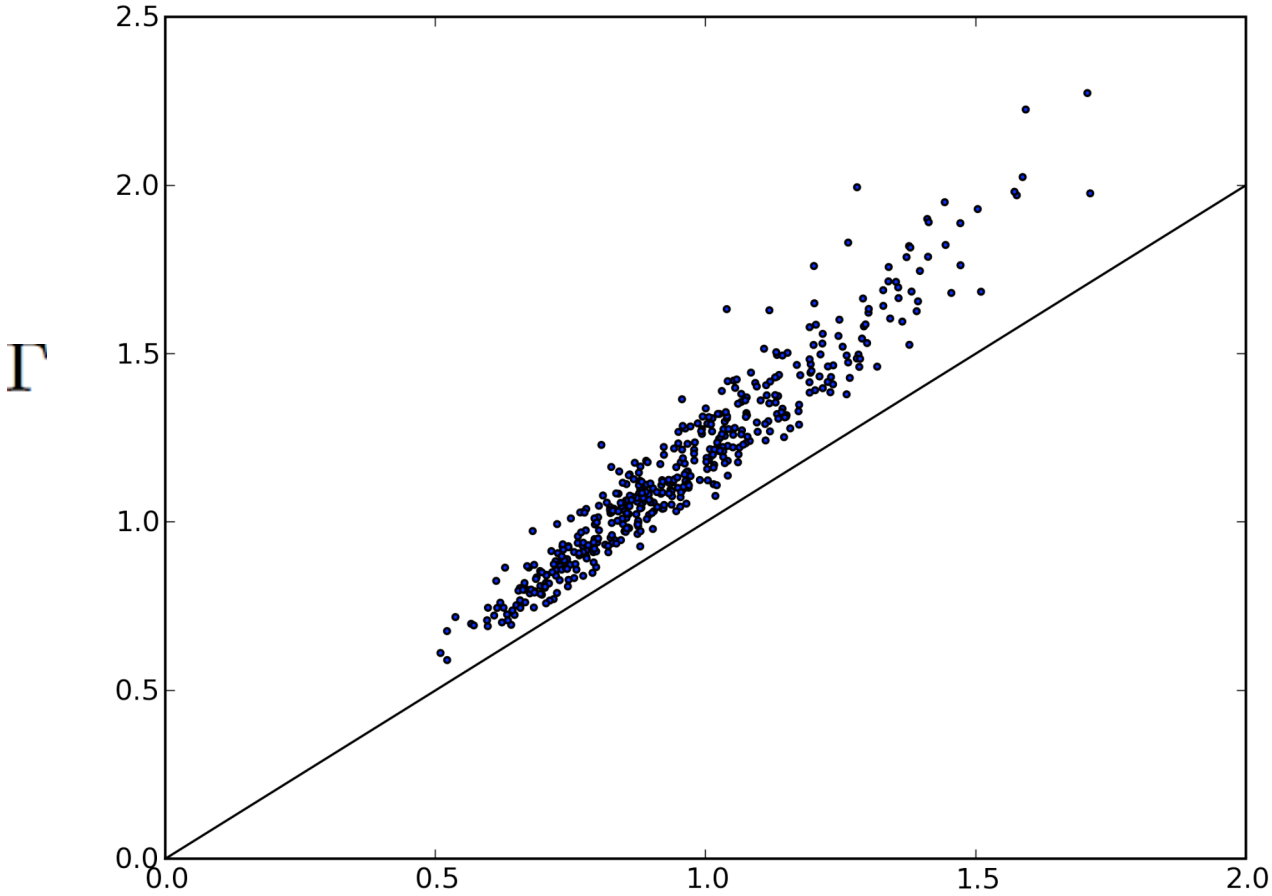
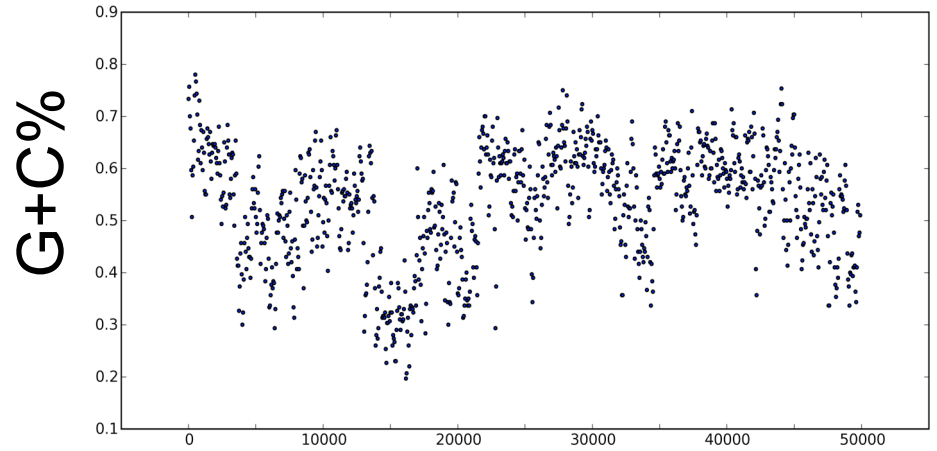
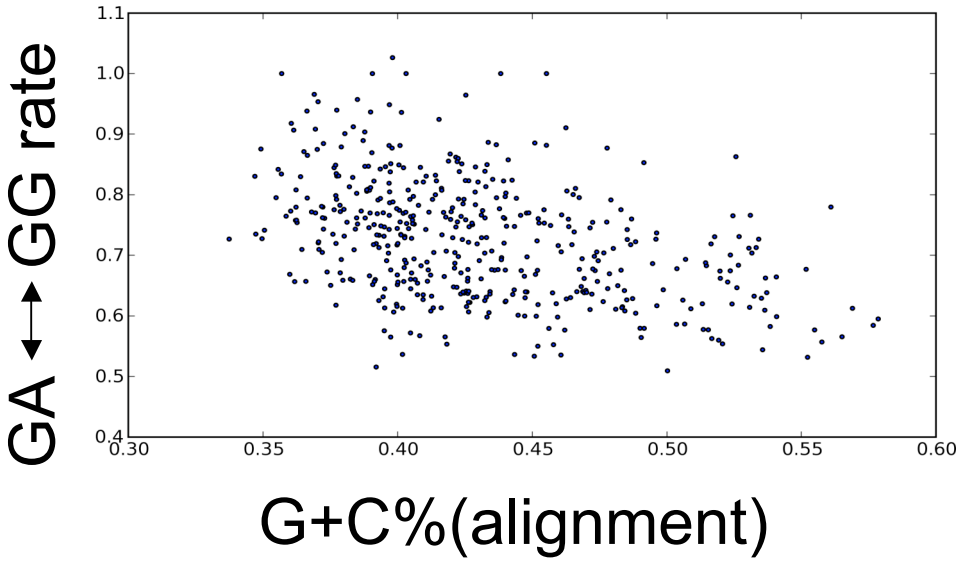
Accounting for CpG substitutions decreases rate variation



$\Gamma + CpG \leftrightarrow TpG$ symmetric

- Independent sites
- Reversible
- Compositional variance





Advantages of dinucleotide models

- Less likelihood computation
- Equivalently parameter-rich
- No assumed distribution of rate variation
- Can incorporate known mutation biases, for example deamination of methylated cytosine.
- Smaller alphabet than amino acids

Acknowledgements

Australian National University

- Gavin Huttley
- Hua Ying

University of Singapore

- Von Bing Yap