

$$R_{ij} \leftarrow \frac{C_{ij}}{D_i}$$

$$R_{ij} = \text{Rate of substitution } i \rightarrow j$$

$$C_{ij} = E[\text{number of } i \rightarrow j \text{ substitutions}]$$

$$D_i = E[\text{dwell time in state } i]$$

$$\mathbf{R} = \mathbf{U}\mathbf{\Lambda}\mathbf{U}^{-1}$$

$$\exp(\mathbf{R}t) = \mathbf{U} \exp(\mathbf{\Lambda}t) \mathbf{U}^{-1}$$

$$\begin{aligned} C_{ij} &= \frac{1}{\exp(\mathbf{R}t)_{ab}} \int_0^T \exp(\mathbf{R}t)_{ai} \exp(\mathbf{R}t)_{jb} dt \\ &= \frac{R_{ij}}{\exp(\mathbf{R}t)_{ab}(T)} \sum_{k=1}^N U_{ak} U_{ki}^{-1} \sum_{l=1}^N U_{jl} U_{lb}^{-1} \mathcal{J}_{kl}(T) \end{aligned}$$

$$\mathcal{J}_{kl}(T) = \begin{cases} T \exp(\lambda_k T) & \text{if } \lambda_k = \lambda_l \\ (\exp(\lambda_k T) - \exp(\lambda_l T))/(\lambda_k - \lambda_l) & \text{if } \lambda_k \neq \lambda_l \end{cases}$$