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

$$
\begin{aligned}
R_{ij} &= \text{Rate of substitution } i \to j \\
C_{ij} &= E[\text{number of } i \to j \text{ substitutions}] \\
D_i &= E[\text{dwell time in state } i]
\end{aligned}
$$

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

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

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