

$$\theta^{(n+1)} = \operatorname{argmax}_{\theta} \mathcal{E}(\theta|\theta^{(n)})$$

$$\mathcal{E}(\theta|\theta^{(n)}) = \sum_x P(x|y, \theta^{(n)}) \log P(x, y|\theta)$$

$$y = \text{present-day sequences (observed)}$$

$$x = \text{ancestral sequences (unobserved)}$$

$$\mathcal{E}(\theta|\theta^{(n)}) = \sum_i \left(\hat{s}_i \log \pi_i + \hat{w}_i R_{ii} + \sum_{j \neq i} \hat{u}_{ij} \log R_{ij} \right)$$

$$\hat{s}_i = E [\# \text{ of ancestral residues in state } i]$$

$$\hat{w}_i = E [\# \text{ of residues} \times \text{time spent in state } i]$$

$$\hat{u}_{ij} = E [\# \text{ of mutations } i \rightarrow j]$$