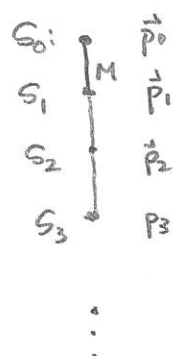


Question: How can you modify this for  $k=2,3,\dots$  time steps?



$\Delta t = 1$  time step

$$\vec{P}_1 = \vec{P}_0 M$$

$$\vec{P}_2 = \vec{P}_1 M = \vec{P}_0 M^2$$

$$\vec{P}_3 = \vec{P}_0 M^3$$

$$\vec{P}_K = \vec{P}_0 M^K$$

The formulation thus far is for "DISCRETE TIME" or modelling evolution from tail to tip of an edge.



Alternatively, there is the CONTINUOUS TIME formulation

$$\begin{aligned} S_0 &= S(t=0) \\ S_K &= S(t=t_K) \end{aligned}$$

In this setup, we introduce a rate matrix  $Q$

$$Q = \begin{pmatrix} q_{RR} & q_{RY} \\ q_{YR} & q_{YY} \end{pmatrix}$$

rates = derivatives!

the off-diagonal entries are non-negative  $q_{YR}, q_{RY} \geq 0$  and

row sums equal 0

$q_{RY}$  = rate at which  $R$ s are converted to  $Y$ s  $\geq 0$

$q_{YR}$  = " " "  $Y$ s are converted to  $R$ s  $\geq 0$

$q_{RR} \leq 0$  rate at which leaving  $R$  state

$q_{YY} \leq 0$

Importantly,  $q_{RR} + q_{RY} = 0$

rates balance

added to  $Y$

$\approx$  lost to  $R$  class

units  
substitution per site  
unit time

The root distribution is now a function of time

$$\vec{p}_0 = \vec{p}(t=0) = \begin{pmatrix} p_R(0), p_Y(0) \end{pmatrix} \quad \text{and at time } t$$

$$\vec{p}_t = \begin{pmatrix} p_R(t), p_Y(t) \end{pmatrix} \quad \text{distribution of purines, pyrimidines at time } t \geq 0.$$

The distribution of states satisfies the following system of differential equations:

$$(*) \quad \frac{d}{dt} p_R(t) = p_R(t) q_{RR} + p_Y(t) q_{YR}$$

$$\frac{d}{dt} p_Y(t) = p_R(t) q_{RY} + p_Y(t) q_{YY}$$

$$\underbrace{\left( \begin{array}{c} \text{current freq.} \\ \text{of R} \end{array} \right)}_{\downarrow} \underbrace{\left( \begin{array}{c} \text{rate of} \\ \text{conversion } R \rightarrow Y \end{array} \right)}_{\swarrow} + \underbrace{\left( \begin{array}{c} \text{current freq.} \\ \text{of Y} \end{array} \right)}_{\swarrow} \underbrace{\left( \begin{array}{c} \text{rate of} \\ \text{loss Y} \end{array} \right)}_{\searrow}$$

In matrix form, the right hand side is:

$$\vec{p}(t) Q$$

Check:

$$\begin{pmatrix} p_R(t) & p_Y(t) \end{pmatrix} \begin{pmatrix} q_{RR} & q_{RY} \\ q_{YR} & q_{YY} \end{pmatrix}$$

Thus, (\*) is the differential equation

$$\vec{p}'(t) = \vec{p}(t) Q \quad \text{with } \vec{p}(0) = (p_R(0), p_Y(0))$$

Using matrix exponentials, the solution is

$$\vec{p}(t) = \vec{p}(0) e^{Qt}$$

$$\text{with } e^{Qt} = 1 + (Qt) + \frac{(Qt)^2}{2!} + \frac{(Qt)^3}{3!} + \frac{(Qt)^4}{4!} + \dots$$

$$\vec{p}(t) = \vec{p}_0 e^{Qt} = \vec{p}_0 M(t)$$

↑  
distribution  
of  
states at time  $t$

↑     ↑  
initial     product  
state     Markov model at time  $t$   
substitution

$$M(t) = e^{Qt}$$

Demo:  $t=0$   $\vec{p}_0 = (.7, .3)$   $Q = \begin{pmatrix} -.1 & .1 \\ .2 & -.2 \end{pmatrix}$

$t$   $M(t) = e^{Qt}$

Note:

•  $e^{Qt}$  is a Markov matrix

• How should the diagonal entries of  $M(1)$  and  $M(2)$  compare?

$\uparrow$                        $\uparrow$   
 $t=1$                        $t=2$

• MATH: computing matrix exponentials:

a)  $Q$  is diagonalizable  $Q = S \begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{pmatrix} S^{-1}$

b)  $M = e^{Qt} = I + (Qt) + \frac{(Qt)^2}{2!} + \frac{(Qt)^3}{3!} + \dots$

$$= I + S \Lambda t S^{-1} + S \frac{(\Lambda t)^2}{2!} S^{-1} + S \frac{(\Lambda t)^3}{3!} S^{-1} + \dots$$

$$\Lambda t = \begin{pmatrix} \lambda_1 t & 0 \\ 0 & \lambda_2 t \end{pmatrix}$$

$$= S \left[ I + \Lambda t + \frac{(\Lambda t)^2}{2!} + \frac{(\Lambda t)^3}{3!} + \frac{(\Lambda t)^4}{4!} + \dots \right] S^{-1}$$

$$= S e^{\Lambda t} S^{-1} = S \begin{pmatrix} 1 & 0 \\ 0 & e^{-\lambda_2 t} \end{pmatrix} S^{-1}$$

i.e. diagonalize  $Q$ , exponentiate diagonal entries of  $\Lambda$ , ...

Summary: Continuous-time formulation

Initial base distribution  $\vec{p}_0 = (p_R(0), p_V(0))$   $t=0$ .

At any time  $t > 0$ , the Markov transition matrix is given by

$$M(t) = e^{Qt} \quad \text{for a fixed rate matrix } Q.$$