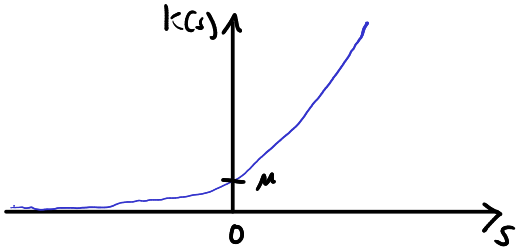
substitution rate $k(s) = 2N\mu \dfrac{1-e^{-s}}{1-e^{-2Ns}}$



$s = \dfrac{f}{g} - 1 \quad |s| \ll 1$

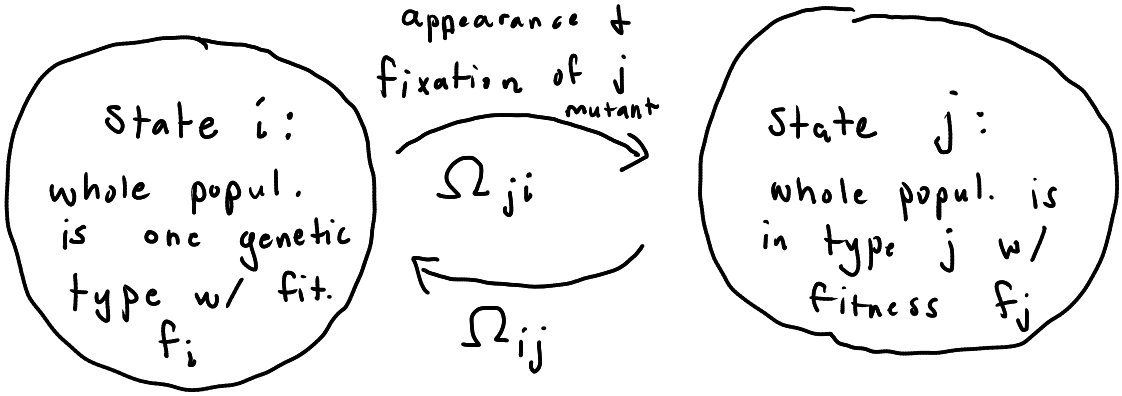
$k(0) = \mu$

- single mutant w/ fitness f competing against WT w/ fit. g

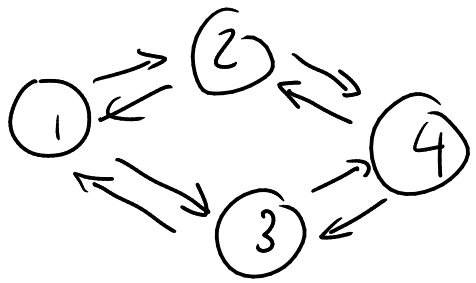
Look at rare mutation limit, but many possible mutant takeovers over time:

Sella & Hirsh PNAS (2005)

Zoom out & think about really long timescales



Create an entire network representing possible mutant fixation events:



type i
fitness f_i
$s_{ij} \equiv \dfrac{f_i}{f_j} - 1$

Ω_{ij} = prob. to start in j & trans. to i $= 2N\mu\left(\frac{1-e^{-s_{ij}}}{1-e^{-2Ns_{ij}}}\right)$

$|s_{ij}| \ll 1 \quad e^{-s_{ij}} = \frac{1}{e^{s_{ij}}} \approx \frac{1}{1+s_{ij}} = \frac{f_j}{f_i}$

$$\Rightarrow \Omega_{ij} = 2N\mu\left[\frac{1-\frac{f_j}{f_i}}{1-\left(\frac{f_j}{f_i}\right)^{2N}}\right]$$

$$\frac{\Omega_{ji}}{\Omega_{ij}} = \left(\frac{f_j}{f_i}\right)^{2N-1} = e^{-\left[(2N-1)\left(-\ln f_j - (-\ln f_i)\right)\right]}$$

$$\Rightarrow \beta = 2N-1 = \frac{1}{k_B T} \qquad E_i = -\ln f_i$$

$$\frac{\Omega_{ji}}{\Omega_{ij}} = e^{-\beta(E_j - E_i)}$$

LDB for a sys. w/ no work connected to a "temperature"

eff. popul. size $N \propto$ "inverse temp."

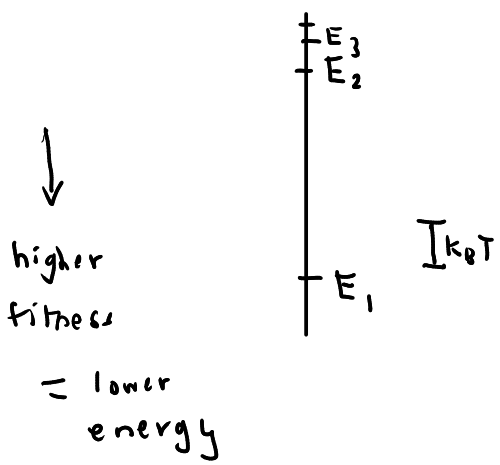
$T \propto \frac{1}{\beta} = \frac{1}{2N-1}$

$f_i \Rightarrow$ higher fitness $\rightarrow$ lower energy E_i

as $t \to \infty$, we can predict "equilibrium" distribution of states:

$$p_i^{eq} = \frac{e^{-\beta E_i}}{Z} \qquad Z = \sum_n e^{-\beta E_n}$$

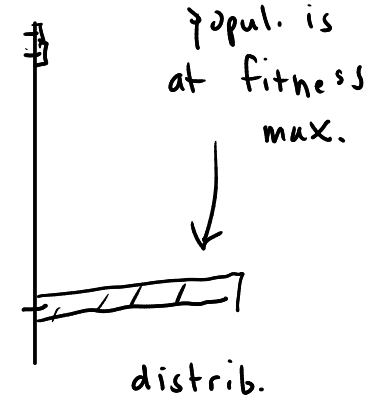
compare two possible mutation networks



natural scale of "energy" fluctuations due to "temp"

$$= k_BT = \frac{1}{\beta} = \frac{1}{2N-1}$$

$\Rightarrow$



if N is large & k_BT is small such that $k_BT \ll E_2 - E_1$ = the gap b/t ground & excited state energy

in order to have transitions from E_1 to E_2 likely:

we must have $k_BT \gg E_2 - E_1$

$$\frac{1}{2N-1} \gg -\ln f_2 - \ln f_1$$

$$= -\ln(1+s_{21})$$

$$\approx -s_{21} = |s_{21}|$$

$f_1 = 1$ reference fitness

$f_2 = 1 + s_{21}$

$$s_{21} = \frac{f_2}{f_1} - 1$$

f_1 = fitness maximum

$f_2 < f_1 \Rightarrow s_{21} < 0$

in order to transition away from high fit. state $|s_{21}| \ll \frac{1}{2N-1}$

humans $\frac{1}{2N-1} \approx 10^{-4}$

$\Rightarrow$ deleterious mutation w/ $|s_{21}| \ll 10^{-4}$ can take over in our population

for bacteria: $|s_{21}| \ll 10^{-9}$

$\frac{1}{2N-1}$ threshold $\Rightarrow$ "drift barrier" (Michael Lynch)