Muller's ratchet: model of accumulating delet. mutations in populations w/ no recombination

imagine a population w/ diff. genetic variants. The variant w/ k deleterious mutations has a growth rate:

$$f_k = f_0 (1 - k\sigma) \qquad k = 0, 1, 2, \ldots$$

f_0: growth rate w/o any mutations

σ: cost per mutation

additive model of fitness: additional mutations add linearly to cost

model of growth (ignore converrion b/t types):

$$\frac{dn_k(t)}{dt} = f_k n_k(t)$$

for now: populations assume large, ignore stochastic fluct.

$n_k(t)$ = # organisms of type k

$$n_k(t) = n_k(0)\, e^{f_k t}$$

derive an equ. for $X_k(t) \equiv \dfrac{n_k(t)}{\underbrace{\sum_{\ell=0}^{\infty} n_\ell(t)}_{N(t)\,=\,\text{total popul.}}}$

$X_k(t)$: frac. of k in total

$$\frac{dx_k}{dt} = \frac{d}{dt}\left(\frac{n_k}{N}\right) = \frac{1}{N}\frac{dn_k}{dt} - \frac{n_k}{N^2}\frac{d}{dt}N$$

$$= f_k \frac{n_k}{N} - \frac{n_k}{N^2}\frac{d}{dt}\sum_{l=0}^{\infty} n_l$$

$$= f_k x_k - \frac{n_k}{N^2}\sum_{l=0}^{\infty} f_l n_l$$

$$= f_k x_k - x_k \bar{f}$$

$$\bar{f} = \frac{1}{N}\sum_{l=0}^{\infty} f_l n_l$$

= mean fitness (growth rate) of entire popul.

$$\Rightarrow \quad \frac{dx_k}{dt} = (f_k - \bar{f})\, x_k$$

replicator equation

add conversion between types:

$$\frac{dx_k}{dt} = (f_k - \bar{f})\, x_k - \mu x_k + \mu x_{k-1}$$

loss to $k \to k+1$ mutations (w/ rate μ)

total mut. rate for deleterious mutations

gain from $k-1 \to k$ mutations

- no back mutations
- no adaptive mutations

(can't undo a mutation, $k+1 \to k$ is not allowed) in our case: $f_k = f_0(1 - k\sigma)$

$$\bar{f} = f_0(1 - \bar{k}\sigma)$$

avg. # of mutations $\quad \bar{k} = \frac{1}{N}\sum_{\ell=0}^{\infty} \ell n_\ell = \sum_{\ell=0}^{\infty} \ell x_\ell$

$$f_k - \bar{f} = (\bar{k} - k)\sigma$$

$$\frac{dx_k}{dt} = \left[(\bar{k} - k)\sigma - \mu\right] x_k + \mu x_{k-1} \qquad k = 0, 1, 2, \ldots$$

look for steady state sol'n $\frac{dx_k}{dt} = 0$

check: $x_k = \frac{e^{-\lambda}\lambda^k}{k!}$ Poisson distrib. $\lambda = \frac{\mu}{\sigma}$

$$\sum_{k=0}^{\infty} x_k = 1$$

$$\bar{k} = \sum_{k=0}^{\infty} k x_k = \lambda$$

plug in + check it works:

$$\left[(\lambda - k)\sigma - \mu\right]\frac{e^{-\lambda}\lambda^k}{k!} + \mu\frac{e^{-\lambda}\lambda^{k-1}}{(k-1)!}$$

$$= \frac{e^{-\lambda}\lambda^{k-1}}{(k-1)!}\left\{\underbrace{\left[(\lambda - k)\sigma - \mu\right]\frac{\lambda}{k}}_{\sigma\left[\cancel{\lambda} - k - \cancel{\lambda}\right]\cdot\frac{\lambda}{k}} + \mu\right\} = 0 \checkmark$$

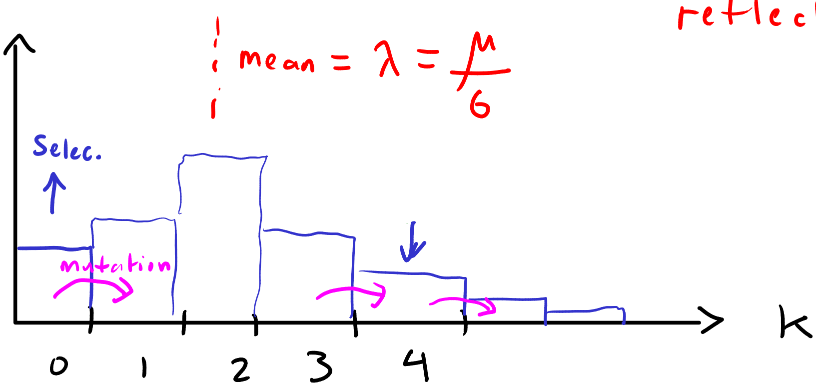
$-\mu \qquad\qquad + \mu$

Stationary distrib. is not unique.

Any shifted Poisson works:

$$x_k = \begin{cases} 0 & \text{for } k \le k_{min} \\ \dfrac{e^{-\lambda} \lambda^{k-k_{min}}}{(k-k_{min})!} & \end{cases} \qquad \text{for any integer } k_{min} \geq 0$$

$k_{min} = 0$ solution:



reflects mutation-selection balance

$k = k_{min}$ class has fraction $x_{k_{min}} = e^{-\lambda}$

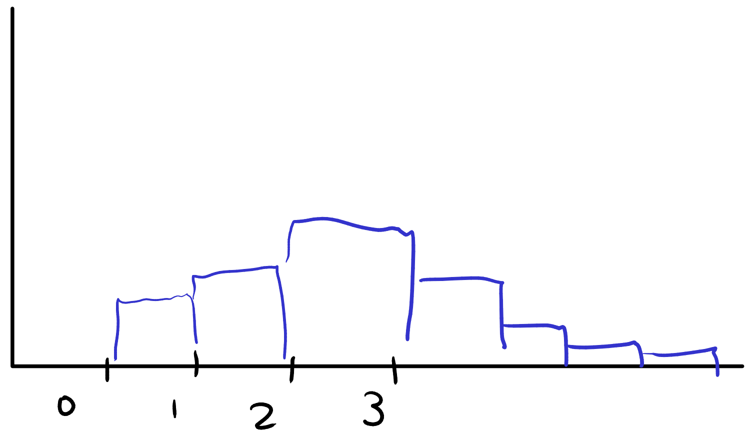
$$= e^{-\mu/6}$$

if $\mu >> 6$ we can have $x_{k_{min}}$ quite small

if $x_{k_{min}}$ is small enough + we add stochastic fluctuations, $n_{k_{min}}$ can fluctuate to zero

loss of k_{min} category $\Rightarrow$ "click" of ratchet

$k_{min} = 1$



loss of $k_{min} = 1$ $\Rightarrow$ another "click"

w/ enough clicks, all f_k become negative

$\Rightarrow$ whole population goes extinct

$\Rightarrow$ "mutational meltdown"

What about small rate of adaptive mutations going in other direction? } ad. rate ν

$$\frac{dx_k}{dt} = (f_k - \bar{f}) x_k - \mu x_k + \mu x_{k-1} - \nu x_k + \nu x_{k+1}$$