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Evolutionary Dynamics

Assignment #04

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Thursday 15$^{\text{th}}$ November, 2012

1.1 Allometric scaling

We know (from lecture and an article 'Some Dynamic Aspects of HSC') that a number of active HSC follows negative allometry (power law) to mass of mammal with scaling exponent 0.75.

$$N_{sc} \approx M^{0.75}$$

That means that to get to know the number of Active HSC in any mammal we just need to calibrate that power law by experimentally getting to know N_{sc} and M of any mammal. It was done for cats and humans, so for humans $M = 70$ and $N_{SC} = 385$, so

$$N_{sc} = N_{sc_0} \times M^{0.75}$$
$$385 = N_{sc_0} \times 70^{0.75}$$
$$N_{sc_0} = 15.9088$$

Now, we can estimate the number of active HSC in hamster (average M=100gm = 0.1 kg), so

$$N_{sc} = 15.9088 \times 0.1^{0.75} \approx 2.3$$

Same for blue whale (M =100 000 kg, http://www.marinemammalcenter.org), so

$$N_{sc} = 15.9088 \times 100000^{0.75} \approx 89461$$

The range of total number of HSC is the same for all mammals and approximately equal to 11000...22000, so it is the same for hamster and blue whale.

2.1 Hematopoietic multicompartment model

K – number of compartments (successes, i.e. cell manages to move to k-th compartment)

E – probability of differentiation.

D – number of additional non-differentiating divisions which cell underwent before entering k-th compartment (failures, i.e cell failed to move to the next compartment).

So, $K + D$ is equal to the total number of cell divisions before k-compartment. D follows negative binomial distribution (in our case $P(D) = NBin$ is a probability of D failures (staying in the same compartment) before k successes (jumping into next compartment) occurred).

2.1.1 a

So, we know that expectation of *NBin* distribution (i.e expected number of staying in the same compartment before reaching k-th compartment) can be calculated as follows:

$$E[D] = \sum_{d=0}^{\inf} dP(D=d) = \sum_{d=0}^{\inf} d \binom{k+d-1}{d} (1-\varepsilon)^d \varepsilon^k$$

$$\sum_{d=1}^{\inf} d \frac{(k+d-1)!}{d!(k-1)!} (1-\varepsilon)^d \varepsilon^k = \sum_{d=1}^{\inf} \frac{(k+d-1)}{(d-1)!(k-1)!} (1-\varepsilon)^d \varepsilon^k$$

$$k \frac{1-\varepsilon}{\varepsilon} \sum_{d=1}^{\inf} \frac{(k+d-1)!}{(d-1)!(k)!} (1-\varepsilon)^{d-1} \varepsilon^{k+1}$$

by change of variable $z = d - 1$, we have:

$$E[D] = k\frac{1-\varepsilon}{\varepsilon} \sum_{z=0}^{\inf} \frac{k+z}{!} z! k! (1-\varepsilon)^z \varepsilon^{k+1} = k\frac{1-\varepsilon}{\varepsilon} \sum_{z=0}^{\inf} \binom{(k+1)+z-1}{z} (1-\varepsilon)^z \varepsilon^{k+1} = k\frac{1-\varepsilon}{\varepsilon}$$

So, for reaching $k = 30$ compartment (the last one, i.e to differentiate to a red blood cell) with e=0.85, we will expect the following number of identical divisions:

$$E[D] = k\frac{1-\varepsilon}{\varepsilon} = \frac{(30 \times (1-0.85))}{0.85} = 5.29$$

2.1.2 b

During the leukemia the self renewal probability $(1-e)$ increases by 15%, (so we can calculate a new $e = 0.827$) and in that case we will expect the following number of non-differentiated divisions till red blood cell formation:

$$E[D] = k\frac{1-\varepsilon}{\varepsilon} = \frac{(30 \times (1-0.827))}{0.827} = 6.25$$

To compute the number of leukemic cells, one should solve the following equation:

$$\frac{N_k}{N_{k-1}} = \frac{2\varepsilon}{2\varepsilon - 1} \times \frac{r_{k-1}}{r_k}$$

In the stationary condition, we assume $\frac{r_k}{r_{k-1}} = r$ and we can assume that r remains constant at $r = 1.27$ as claimed in (Dingli er al, *"Compartmental Architecture and Dynamics of Hematopoiesis"*, PlosOne, 2007, e345). Then:

$$\frac{N_k}{N_{k-1}} = \left(\frac{2\varepsilon}{2\varepsilon - 1} \times \frac{1}{r} \right)^k N_0 = N_k$$

$$\left(\frac{1.654}{0.654} * \frac{1}{1.27} \right)^{30} * 1 = N_{30} = 917,464,597$$

3.1 Treatment of chronic myeloid leukemia

$$x_0' = [\lambda x_0 - d_0]x_0 \rightarrow \text{quiescent stem cells}$$
$$x_1' = a_1 x_0 - d_1 x_1 \rightarrow \text{actively proliferating stem cells}$$
$$x_2' = a_1 x_1 - d_2 x_2 \rightarrow \text{early differentiated cells}$$
$$x_3' = a_3 x_2 - d_3 x_3 \rightarrow \text{fully differentiated blood cells}$$

$$0 < d_1 \ll d_2 \ll d_3 \qquad \frac{a_i}{d_i} > 1 \qquad \forall i$$

at steady state, all $(\vec{x_i'}) = \vec{0}$. In the trivial case: $x_0^* = 0 \leftrightarrow x_1^* = 0 \leftrightarrow x_2^* = 0 \leftrightarrow x_3^* = 0$ Other case from:

$$x_0^* = \frac{d_0}{\lambda}$$
$$x_1^* = \frac{a_1}{d_1}\frac{d_0}{\lambda}$$
$$x_2^* = \frac{a_2}{d_2}\frac{a_1}{d_1}\frac{d_0}{\lambda}$$
$$x_3^* = \frac{a_3}{d_3}\frac{a_2}{d_2}\frac{a_1}{d_1}\frac{d_0}{\lambda}$$

Thus, the most abundandt cell type at steady state is x_3 since $\frac{a_i}{d_i} > 1 \quad \forall i$

Proof exemplarily for:

$$x_3^* > x_2^* : \frac{a_3}{d_3} \underbrace{\frac{a_2}{d_2}\frac{a_1}{d_1}\frac{d_0}{\lambda}}_{\text{cancels out to 1}} > \underbrace{\frac{a_2}{d_2}\frac{a_1}{d_1}\frac{d_0}{\lambda}}_{\text{cancels out to 1}}$$

So,

$$\frac{a_3}{d_3} > 1$$

3.1.1 b

From the non trivial steady state above, if $x_1 = x_1^*$, then all other x_i are also in the steady state x_i^* at $t = 0$. Since imatinib treatment does not change x_0', and x_0 is in the steady state at $t = 0 : x_0' = 0 \leftrightarrows x_0 = \frac{d_0}{\lambda}$, it can be seen as constant. That leads to:

$$x_1' = a_1' x_0 - d_1 x_1 = a_1'\frac{d_0}{\lambda} - d_1 x_1$$

The solution for this is:

$$\frac{dx_1}{dt} = -d_1 x_1 \quad \text{general solution}$$

$$\frac{dx_1}{x_1} = -d_1 dt$$

$$\log x_1 = d_1 t + C$$

$$x_1(t) = e^{-d_1 t} \times C$$

In steady state conditions, when $x_1(0) = \frac{a_1 d_0}{d_1 \lambda}$, it is:

$$x_1(0) = e^{-d_1(0)} \cdot C = \frac{a_1 \cdot d_0}{d_1 \cdot \lambda}$$

$$C = \frac{a_1 d_0}{d_1 \lambda}$$

To retrieve solutions in nonhomogeneous differential equations, we have to take in account for partial solutions:

$$y'(x) + a(x)y(x) = s(x)$$

$$y(p) = \begin{cases} \dfrac{s}{a} & a \neq 0, a \wedge s = constant \\ \displaystyle\int s(x)e^{\int a(x)dx} & a(x) \wedge s(x) \neq constant \end{cases}$$

Hence,

$$\rightarrow \frac{s}{a} = \frac{a'_1 d_0}{\lambda d_1}$$

$$\rightarrow x_1(t) = e^{d_1 t}\frac{a_1 d_0}{\lambda d_1} + \frac{a'_1 d_0}{\lambda d_1}$$

This scales with $\frac{1}{d_1}$ (average life time of x_1-cells), since almost no x_1 cells differentiate from x_0 ($a'_1 \ll a_1$) and the death rate d_1 is constant:

$$x_1(t) = \frac{1}{d_1}\left(e^{d_1 t}\frac{a_1 d_0}{\lambda}\frac{a'_1 d_0}{\lambda}\right)$$

3.1.2   c

The bi-phasic decline of the number of leukemic blood cells $x3$ can be explained in the following way: the first slope describes the exponentially decline of the early differentiated leukemic cells until they reach the new steady state $x_2^* = \frac{a'_2}{d_2} \cdot x_1^*$ with the leukemic progenitors. Now, the decline of leukemic blood cells follows the decline of leukemic progenitors.

Thus, the death rates $d1$ and $d2$ can be directly determined from the graph:

- $d1 = 0.004$ death rate of leukemic progenitors during imatinib therapy
- $d2 = 0.03$ death rate of leukemic early differentiated cells during imatinib therapy

3.1.3 d

If the treatment with imatinib is stopped or the cells become resistant to imatinib after a certain time, the leukemic cells will exponentially appear again. Since imatinib does not affect the leukemic stem cells, x_0 but only the (in leukemia uncontrolled) differentiating blood cells x_1 and x_2 (and thus the number of leukemic blood cells x_3), a new population of leukemic cells will arise from the stem cell pool with exponential growth until the number of leukemic cells reaches the level of before treatment (or even above this level if the number of leukemic stem cells is not constant but increasing due to a higher proliferation rate). Same is true if the number of quiescent stem cells has not yet reached steady state at the onset of treatment: the leukemic blood cells will exceed the level from before by far, because, unchanged by the imatinib treatment, the quiescent stem cells will reach steady state and give exponentially rise to leukemic blood cells after the interruption of the treatment.

6.1 Absorption time in the diffusion approximation

The conditional expected waiting time for fixation, $\tau_1(p_0)$, in the neutral Wright-Fisher process can be computed as follows. Since we have a neutral process, there is not fitness advantage: $\omega_1 = \omega_2 = 1, M(p) = 0, V(p) = p(1-p)$ and $\rho(p) = p$ (due to the appropriate scale of time measurement, as below). Therefore,

$$A(p) = \int_0^p \frac{2M(p)}{V(p)} dp = \int_0^p 0 dp = 0$$

$$S(p) = \int_0^p e^{-A(p)} dp = \int_0^p 1 dp = p$$

Simplifying the equation:

$$\tau_1 = 2(1-0) \left(\int_{p_0}^1 \frac{p(1-p)}{1(p(1-p))} dp + \frac{a-p_0}{p_0} \int_0^{p_0} \frac{p^2}{1p(1-p)} \right)$$

$$= 2 \left(\int_{p_0}^1 1 dp + \frac{1-p_0}{p_0} \int_0^{p_0} \frac{p}{1-p} \right)$$

$$= 2 \left(1 - p_0 + \frac{1-p_0}{p_0} - p_0 - \log(1-p_0)) \right)$$

$$= 2 \left(\frac{p_0(1-p_0) - p_0 + p_0^2 - (\log(1-p_0) - p_0 \log(1-p_0)}{p_0} \right)$$

$$= 2 \left(\frac{\log(1-p_0)(p_0-1)}{p_0} \right) = -2 \frac{1-p_0}{p_0} \log(1-p_0)$$

The appropriate scale for the W-F process measured time in units of N generation [as in S.P. Otto and T. Day, *A biologist's guide to mathematical modelling in molecular evolution*, Number Bd. 13 in A biologist's guide to mathematical modeling in ecology and evolution. Princeton University Press, 2007, p.681], and we have to multiply this equation with N in order to get the fixation time in generations.

$$\tau_1(p_0) = -2N\frac{1-p_0}{p_0}\log(1-p_0)$$

In case of small p_0:

$$\lim_{p_0\to 0} -2N\frac{1-p_0}{p_0}\log(1-p_0) = \lim_{p_0\to 0} -2N\frac{\log(1-p_0)}{p_0} + \underbrace{\frac{p_0\log(1-p_0)}{p_0}}_{0}$$

$$= \lim_{p_0\to 0} -2N\frac{\log(1-p_0)}{p_0} = \frac{0}{0}$$

Use l'Hopital rule to solve undertermined forms

$$= \lim_{p_0\to 0} -2N\frac{\frac{-1}{1-p_0}}{1}$$

$$= \lim_{p_0\to 0} \frac{2N}{1-\underbrace{p_0}_{0}}$$

$$= 2N$$

Hence, for small p_0, the conditional expected waiting time for fixation is $\tau_1(p_0) = 2N$, two times the generation size.

6.1.1 c

The conditional expected waiting time until extinction τ_0 of type A is the same as the conditional expected waiting time for fixation of type B starting with p_0 in the same population (with two types).

$$\tau_0 = \tau_1$$

The unconditioned expected waiting time $\bar{\tau}$ until either fixation or extinction is the sum of the conditioned waiting times multiplied with their conditions probabilities

$$\bar{\tau} = \tau_1 \cdot \rho + \tau_0 \cdot (1-\rho)$$
$$= \tau_1 \cdot \rho + \tau_1 \cdot (1-\rho)$$
$$\bar{\tau} = \tau_1$$

Hence, the uncondition expected waiting time until either fixation or extinction equals the conditioned expected waiting times, because in populations with two types and a neutral Wright-Fisher process with two absorbing states at the boundaries, the fixation of one type corresponds to the extinction of the other type.