

Supplementary material

Modelling resistance in leukaemia mediated by mutations and alternate mechanisms – their interactions and treatment-free periods (drug holidays)

Derivation of PDE solution

Assume that the expectation value of the noise is zero, i.e. $E[Y] = 0$, so that it does not induce any drift to the expression parameter x . Let N be large. If we think of the whole population, we can model the parameter x for the whole population at time t as a random variable, X_t , where $f_{X,t}$ is the probability density function for X_t at time t . It is a time-dependent distribution function so

$$\int_{-\infty}^{\infty} f_{X,t}(x) dx = 1 \quad (\text{S1})$$

for all t .

When a new cell is born, the probability density for the selected x_{parent} is proportional to $\lambda(x)f_{X,t}(x)$. More precisely

$$f_{X(\text{parent}),t}(x) = \frac{f_{X,t}(x)\lambda(x)}{\int \lambda(\xi)f_{X,t}(\xi)d\xi}. \quad (\text{S2})$$

Note that since deaths are independent of x , deaths do not change the distribution of X under the large N approximation. Births do however alter the distribution; after a birth event

$$f_{X,t+dt} = \frac{N}{N+1} f_{X,t} + \frac{1}{N+1} f_{X(\text{new}),t}. \quad (\text{S3})$$

The new distribution is a weighted average of the one before it (originating from N cells, and the new cell).

The time between birth events, dt , i.e. the average waiting time between events, is the inverse of the birthrate. Recall that

$$\lambda_n = \sum_{i=1}^N \lambda(x_i) \quad (\text{S4})$$

thus

$$\frac{1}{dt} = N \int \lambda(x) f_{X,t}(x) dx. \quad (\text{S5})$$

With noise (Y) included, the X_{new} probability density function for a new cell is

$$f_{X^{(\text{new})},t}(x) = (f_{X^{(\text{parent})},t} * f_Y)(x). \quad (\text{S6})$$

which, inserting the definition of $f_{X^{(\text{parent})}}$ from Equation S2, becomes

$$f_{X^{(\text{new})},t}(x) = \frac{1}{\int \lambda(\xi) f_{X,t}(\xi) d\xi} \int_{-\infty}^{\infty} f_{X,t}(\zeta) \lambda(\zeta) f_Y(x - \zeta) d\zeta. \quad (\text{S7})$$

We can rearrange Equation S3 to

$$f_{X,t+dt} - f_{X,t} = \frac{1}{N+1} [f_{X^{(\text{new})},t} - f_{X,t}] \quad (\text{S8})$$

i.e. (using Equation S5)

$$\frac{\partial f_{X,t}}{\partial t} = \frac{N}{N+1} [f_{X^{(\text{new})},t} - f_{X,t}] \int \lambda(\xi) f_{X,t}(\xi) d\xi. \quad (\text{S9})$$

Combined with Equation S7 and after rearranging we arrive at

$$\frac{\partial f_{X,t}(x)}{\partial t} = \frac{N}{N+1} \left[\int_{-\infty}^{\infty} f_{X,t}(\zeta) \lambda(\zeta) f_Y(x - \zeta) d\zeta - f_{X,t}(x) \int \lambda(\xi) f_{X,t}(\xi) d\xi \right] \quad (\text{S10})$$

which likely cannot be solved analytically for most cases. As $N \rightarrow \infty$, $\frac{N}{N+1} \rightarrow 1$ which removes the dependence on N and lets the time dependent probability density function be simulated in a straightforward manner.