0.1 VAF spectrum dynamics

To obtain the dynamics of the VAF spectrum we first consider the probabilistic dynamics of the size of a single variant in the population. In particular we wish to find a Fokker-Plank equation for the time evolution of the probability density of the variant's size. We first sketch the procedure for obtaining a well-known result for the Moran model, after which we show how to obtain the expression for a stochastically growing population.

0.1.1 Single variant Moran dynamics

In the Moran model the discrete probability distribution of the size of a variant is governed by the transition probabilities $\mathbb{P}\{l|k\}$ denoting the likelihood of the variant changing from size k to l after the occurrence of a symmetric division event. These take the tridiagonal form:

$$\begin{cases} \mathbb{P}\{k+1 \mid k\} = \dfrac{k}{N}\left(1-\dfrac{k}{N}\right) = T_{k+1,k} = T_k \\ \mathbb{P}\{k-1 \mid k\} = \dfrac{k}{N}\left(1-\dfrac{k}{N}\right) = T_{k-1,k} = T_k \\ \mathbb{P}\{k \mid k\} = 1-(T_{k+1,k}+T_{k-1,k}) \end{cases} \tag{1}$$

Assuming events occur with exponentially distributed waiting times at rate ν, the probability distribution of the variant's size P_k can be described through the master equation

$$\frac{1}{\nu}\frac{\mathrm{d}P_k}{\mathrm{d}t} = T_{k-1}P_{k-1} + -2T_kP_k + T_{k+1}P_{k+1} \tag{2}$$

For large population sizes this system of N differential equations can be computational taxing to solve. A diffusion approximation can be made on the assumption that N is large (i.e. there are many states $k = 0, 1, \dots, N$), which describes $p(\kappa)$ the probability density of the variant size on the continuous domain $\kappa \in [0, N]$. To this end a Fokker-Planck equation is constructed of the form

$$\partial_t p(\kappa,t) = -\partial_\kappa A(\kappa,t)p(\kappa,t) + \partial_\kappa^2 B(\kappa,t)p(\kappa,t)/2 \tag{3}$$

The coefficients are given through the infinitesimal propagator $t(\kappa+\Delta\kappa, t+\Delta t \,|\, \kappa, t)$:

$$\begin{aligned} A(\kappa,t) &= \lim_{\Delta t\to 0}\frac{1}{\Delta t}\int d(\Delta\kappa)\Delta\kappa\, t(\kappa+\Delta\kappa, t+\Delta t \,|\, \kappa, t) \\ B(\kappa,t) &= \lim_{\Delta t\to 0}\frac{1}{\Delta t}\int d(\Delta\kappa)(\Delta\kappa)^2\, t(\kappa+\Delta\kappa, t+\Delta t \,|\, \kappa, t) \end{aligned} \tag{4}$$

The integrals are the first and second moments of a displacement $\Delta\kappa$, and can be obtained using the heuristic:

$$\begin{aligned} \langle\Delta\kappa\rangle_{k,\Delta t} &\approx \langle\Delta\kappa\rangle_{k,1/\eta}\,\Delta t + \vartheta\big(\Delta t^2\big) = \sum_{\Delta k}\Delta k\, T_{k+\Delta k,k}\,\eta\,\Delta t + \vartheta\big(\Delta t^2\big) \\ \big\langle(\Delta\kappa^2)\big\rangle_{k,\Delta t} &\approx \big\langle(\Delta\kappa^2)\big\rangle_{k,1/\eta}\,\Delta t + \vartheta\big(\Delta t^2\big) = \sum_{\Delta k}(\Delta k)^2\, T_{k+\Delta k,k}\,\eta\,\Delta t + \vartheta\big(\Delta t^2\big) \end{aligned} \tag{5}$$

Typically a transformation to frequency space is performed – $f = \kappa/N$ – so that we obtain

$$A(f,t) = 0, \quad B(f,t) = \frac{2\nu}{N^2} f(1-f) \tag{6}$$

and thus

$$\partial_t p(f,t) = (\nu/N^2)\, \partial_f^2 f(1-f) p(f,t) \tag{7}$$

0.1.2 Moran dynamics with growth

We now consider a population in which there are Moran divisions – a self-renewal simultaneously accompanied by a loss or differentiation – occurring at rate $\rho N(t)$, as well as additional divisions which increase the population at rate $\gamma N(t)$. For simplicity we assume the population size $N(t)$ to grow deterministically according to the growth rate. The transition probabilities for a single clone are given by

$$\begin{cases} \mathbb{P}\{k+1, t+\Delta t \mid k, t\} = \dfrac{k}{N(t)}\left(1 - \dfrac{k}{N(t)}\right)\rho N(t)\Delta t + \dfrac{k}{N(t)}\gamma N(t)\Delta t \\ \mathbb{P}\{k-1, t+\Delta t \mid k, t\} = \dfrac{k}{N(t)}\left(1 - \dfrac{k}{N(t)}\right)\rho N(t)\Delta t \\ \mathbb{P}\{k, t+\Delta t \mid k, t\} = 1 - \mathbb{P}\{k+1, t+\Delta t \mid k, t\} - \mathbb{P}\{k-1, t+\Delta t \mid k, t\} \end{cases} \tag{8}$$

Using the previously described heuristic the coefficients of the Fokker-Planck equation become

$$\begin{aligned} A(\kappa,t) &= \kappa\gamma \\ B(\kappa,t) &= 2\kappa[1-\kappa/N]\rho + \kappa\gamma \end{aligned} \tag{9}$$

And the full equation becomes

$$\partial_t p(\kappa,t) = -\partial_\kappa \gamma\kappa\, p(\kappa,t) + \partial_\kappa^2[\kappa(1-\kappa/N)\rho + \kappa\gamma/2]\, p(\kappa,t). \tag{10}$$

Note that if there is no growth, i.e. $\gamma = 0$, this reduces to the standard Moran Fokker-Planck equation upon performing the transformation $f(\kappa) = \kappa/N$.

0.1.3 VAF spectrum dynamics

To obtain the dynamics of the spectrum of variants $v(\kappa,t)$ – i.e. the number of variants per size – we simply note that for independently evolving mutants the fluxes between states are identical to the above-derived transition probabilities. We however still require a flux of newly arising variants, which is limited to the state $k = 1$ and has amplitude

$$\mathcal{C} = 2\mu(\rho + \gamma + \phi/2) \tag{11}$$

where asymmetric divisions occurring at rate ϕ only introduce half as many varants into the population. In the continuous domain we introduce this flux as a Dirac delta function, so that the complete expression then takes the form

$$\begin{aligned} \partial_t v(\kappa,t) = -\partial_\kappa \gamma\kappa\, v(\kappa,t) + \partial_\kappa^2[\kappa(1-\kappa/N)\rho + \kappa\gamma/2]\, v(\kappa,t) \\ +2\mu(\rho + \gamma + \phi/2)\delta(\kappa - 1) \end{aligned} \tag{12}$$

While a solution to (7) is known, it is rather unwieldy, which does not bode well for the more complex expressions (10) and (12). We will here use numerical approximations of their solution, though to obtain these we must be cautious about the discontinuity at $\partial_t v(\kappa = 1, t)$ introduced by the incoming flux. We applied a method of lines approach with a finite difference discretization in the size coordinate κ. In order to optimize performance, we opted for a variable stepsize which is smallest near the singularity, with the distances in space given by

$$\Delta\kappa_i = 1 + (i - 1) \cdot \alpha_i \tag{13}$$

where $i \in 1, \ldots, n - 1$, with n the number of discretized points, and

$$\alpha_i = 2\frac{N - (n - 1)}{(n - 1)(n - 2)} \tag{14}$$

In this formalism the delta function in (12) is approximated as a step function with height $2/(\Delta\kappa_1 + \Delta\kappa_2)$.