Ordinary Differential Equation Model

A very useful feature of the pedigree model is that it can be readily described by a system of linear Ordinary Differential Equations (ODEs). The rate of change in cell numbers for each cell population is determined and when solved at steady state, gives an expression to estimate the stem cell division rate - an unknown quantity.

The ODE version of the pedigree model are given by the following equations:

\[
\begin{align*}
S(t) &= s \\
\dot{T}_1(t) &= \alpha_S S - \alpha_{T_1} T_1 \\
\dot{T}_2(t) &= 2\alpha_{T_1} T_1 - \alpha_{T_2} T_2 \\
\dot{T}_3(t) &= 2\alpha_{T_2} T_2 - \alpha_{T_3} T_2 \\
&
\vdots
\\n\dot{T}_n(t) &= 2\alpha_{T_{n-1}} T_{n-1} - \alpha_{T_n} T_n \\
\dot{Z}(t) &= 2\alpha_{T_n} T_n - \gamma Z,
\end{align*}
\] (S1)

where \(S(t) = s\) gives the constant number of stem cells, \(T_i(t)\) gives the number of \(i^{th}\) generation TA cells at time \(t\), and \(Z(t)\) gives the number of mature cells at time \(t\). Cell division rates (average rate of the whole cell cycle) for stem cells and TA cells are given by \(\alpha_S\) and \(\alpha_{T_i}\) respectively.

1Cell population here refers to either stem cells, different TA cell generations, or mature cells.
The steady state solution of the system in S1 are given by

\[ S^* = s \]

\[ T_1^* = \frac{\alpha_S}{\alpha_{T_1}} S^* \]

\[ T_2^* = \frac{2\alpha_{T_1}}{\alpha_{T_2}} T_1^* \]

\[ T_3^* = \frac{2\alpha_{T_2}}{\alpha_{T_3}} T_2^* \]

\[ \vdots \]

\[ T_n^* = \frac{2\alpha_{T_{n-1}}}{\alpha_{T_n}} T_{n-1}^* \]

\[ Z^* = \frac{2\alpha_{T_n}}{\gamma} T_n^*. \] (S2)

The expression for the steady state mature cell population can be simplified to \( Z^* = 2^n \frac{\alpha_S}{\gamma} s \). Interestingly this expression is independent of the transit amplifying cell division rates (even when they are different between TA cell generations) but strongly depends on \( n \) the number of amplifying generations.

We can also derive an expression for the total number of cells at steady state, by simply adding up the individual steady state populations:

\[ \text{Total} = S^* + T_1^* + \cdots + T_n^* + Z^* \]

\[ = s + \frac{\alpha_S}{\alpha_{T_1}} S^* + \frac{2\alpha_{T_1}}{\alpha_{T_2}} T_1^* + \cdots + \frac{2\alpha_{T_{n-1}}}{\alpha_{T_n}} T_{n-1}^* + \frac{2\alpha_{T_n}}{\gamma} T_n^* \]

\[ = s + 2^0 \frac{\alpha_S}{\alpha_{T_1}} s + 2^1 \frac{\alpha_S}{\alpha_{T_2}} s + \cdots + 2^{n-1} \frac{\alpha_S}{\alpha_{T_n}} s + 2^n \frac{\alpha_S}{\gamma} s \]

\[ = s \left( 1 + \alpha_S \left[ 2^0 \frac{1}{\alpha_{T_1}} + \cdots + 2^{n-1} \frac{1}{\alpha_{T_n}} + 2^n \frac{1}{\gamma} \right] \right). \] (S3)

It is often assumed that TA cell generations have a homogeneous division rate, that is \( \alpha_T \equiv \alpha_{T_1} = \alpha_{T_2} = \cdots = \alpha_{T_n} \). If this is the case the expression for the total cell population simplifies to

\[ \text{Total} = s \left( 1 + \frac{\alpha_S}{\alpha_T} \left[ 2^0 + 2^1 + \cdots + 2^{n-1} \right] + \frac{\alpha_S}{\gamma} 2^n \right) \]

\[ = s \left( 1 + \frac{\alpha_S}{\alpha_T} (2^n - 1) + \frac{\alpha_S}{\gamma} 2^n \right). \] (S4)

Reorganising gives us the expression for estimating \( \alpha_S \), the stem cell division rate:

\[ \alpha_S = \frac{\text{Total} \cdot \alpha_T \cdot \gamma - s \cdot \alpha_T \cdot \gamma}{s \cdot \gamma \cdot 2^n - s \cdot \gamma + s \cdot \alpha_T \cdot 2^n}. \] (S5)