3 Dimensional PDE to track cell age and Ki67 expression

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In order to track the dynamics of cells of age 'a' expressing the nuclear protein Ki67 with an intensity 'k' through time 't', we use the following PDE,

$$\frac{\partial u}{\partial t} + \frac{\partial u}{\partial a} - \beta\, k\, \frac{\partial u}{\partial k} = -\delta(a)\, u. \tag{1}$$

- β is constant and gives the rate of loss of Ki67 expression;
- δ varies with cell age and gives the rate with which cells are lost from the population, either by death or by differentiation.

Total size of the population at time t is derived by integrating the cell density u(t, a, k) over all allowable cell ages such that $u(t,k) = \int u(t,a,k)da$.
The intensity of Ki67 $\in$ (0, 1) such that it is maximum (k=1) upon entering division which then decays exponentially with rate constant β. By setting a threshold of Ki67 intensity for Ki67$^+$ cells (e.g. k $\geq$ 0.5 $\rightarrow$ Ki67$^+$) Ki67^{hi}and Ki67^{lo}subsets can be binned and tracked over time t.

To solve this linear first-order PDE (eq. 1), we need to transform it into an ODE such as,

$$\frac{d}{ds}u(t(s), a(s), k(s)) = F(u, t(s), a(s), k(s)), \tag{2}$$

along the (t(s), a(s), k(s)) ***characteristic curve***.

Using the ***chain rule*** we find,

$$\frac{d}{ds}u(t(s), a(s), k(s)) = \frac{\partial u}{\partial t}\frac{dt}{ds} + \frac{\partial u}{\partial a}\frac{da}{ds} + \frac{\partial u}{\partial k}\frac{dk}{ds}.$$

If we set $\dfrac{dt}{ds} = 1$, $\dfrac{da}{ds} = 1$ and $\dfrac{dk}{ds} = -\beta\, k$, we get

$$\frac{du}{ds} = \frac{\partial u}{\partial t} + \frac{\partial u}{\partial a} - \beta\, k\, \frac{\partial u}{\partial k},$$

which is the LHS of the PDE that we started with in eq. 1. This suggests that along the characteristic curve, the solution of the ODE (eq. 2) is given by,

$$
\begin{aligned}
&\frac{du}{ds} = -\delta(a)\, u, \\
&\text{which can be solved to give,} \\
&u(s) = u_0\, exp(-\int \delta(s) ds).
\end{aligned}
\tag{3}
$$

Therefore, if we know $u(t_0, a_0, k_0)(i.e. u_0)$ we can find $u(t(s), a(s), k(s)$ using eq. 3, since (t(s), a(s), k(s)) and (t(0), a(0), k(0)) both lie on the same characteristic curve. The general solution of PDE in eq. 1 thus can be determined by solving the system of characteristic ODEs.

Tracking cells coming from source

We assume that cells of age 0 constantly enter the target population from the source compartment which sets one of the boundary conditions for the PDE in eq. 1.

$$u_s(t, a = 0, k) = \phi(t, k)$$

where, ϕ is the function that gives the source influx. The system of characteristic ODEs for this population:

$$
\begin{aligned}
&\frac{da}{ds} = 1 \rightarrow a = s + a_0 \quad \text{since, } a_0 = 0 \rightarrow a = s \\
&\frac{dt}{ds} = 1 \rightarrow t = s + t_0 \quad \rightarrow t = a + t_0 \\
&\frac{dk}{ds} = -\beta\, k \rightarrow k = k_0\, e^{-\beta\, s} \quad \rightarrow k = k_0\, e^{-\beta\, a}
\end{aligned}
$$

Therefore, $\phi(t_0, k_0) = \phi(t - a, k\, e^{\beta\, a})$.

Following form eq. 3,

$$u_s(t, a, k) = \phi\Big(t - a, k\, e^{\beta\, a}\Big)\, exp\Big(-\int_0^a \delta(\tau) d\tau\Big). \tag{4}$$

Tracking cells that entered division

We assume that cells enter division with rate $\rho(a)$ depending on their age and will acquire the maximum Ki67 intensity *i.e.*k=1, forming the second boundary condition for our system.

$$u_d(t, a, k = 1) = 2\, \rho(a)\, u(t, a, k)$$

These cells can be tracked using the same system of characteristic ODEs:

$$
\begin{aligned}
&\frac{dk}{ds} = -\beta\, k \rightarrow k = k_0\, e^{-\beta\, s} \quad \text{since, } k_0 = 1 \rightarrow \frac{log(k)}{-\beta} = s\\
&\frac{da}{ds} = 1 \rightarrow a = s + a_0 \quad\;\; \rightarrow a = \frac{log(k)}{-\beta} + a_0\\
&\frac{dt}{ds} = 1 \rightarrow t = s + t_0 \quad\;\; \rightarrow t = \frac{log(k)}{-\beta} + t_0
\end{aligned}
$$

Therefore, $u_d(t_0, a_0, k_0) = 2\,\rho(a)\, u(t + \frac{log(k)}{\beta}, a + \frac{log(k)}{\beta}, k)$.

Following form eq. 3,

$$
u_d(t, a, k) = 2\,\rho(a)\, u(t + \frac{log(k)}{\beta}, a + \frac{log(k)}{\beta}, k)\, exp\Big(- \int_0^a \delta(\tau + \frac{log(k)}{\beta}) d\tau \Big). \tag{5}
$$

At any given time ‘t’ the density of cells with age ‘a’ and Ki67 intensity ‘k’ is the sum of the source influx and the dividing cells. We integrate over allowable ages to get the ki67 distribution of cells. The counts of $\text{Ki67}^{\text{hi}}$and Ki67^{lo}cells are then obtained by integrating from threshold k intensity ‘κ’ (derived form data) to 1 and from 0 to κ, respectively.

$$
\begin{aligned}
u(t, a, k) &= u_s(t, a, k) + u_d(t, a, k)\\
u(t, k) &= \int_0^a u(t, a, k)\\
u_{khi}(t) &= \int_\kappa^1 u(t, k)\\
u_{klo}(t) &= \int_0^\kappa u(t, k)
\end{aligned} \tag{6}
$$