Bursting and division in a nonlinear cell population model
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1. The model: Pure-Jump Markov process

The building blocks of this model are two non-local operators that represent respectively the bursting and division.

- **Bursting:** at rate \( \lambda(x) \), a cell increases its molecular content, from \( x \) to \( y \), according to the bursting kernel distribution \( s(x,y) \).

- **Division:** at rate \( \mu(x) \), a cell gives rise to two cells of lower molecular content, \( y < x \), according to the (symmetric) division kernel distribution \( w(x,y) \).

Following a single cell line, this model gives a one-dimensional pure jump Markov \( \{X(t)\}_{t \geq 0} \) on \( \mathbb{R} \), whose typical trajectories are shown in figure 1.

![Figure 1: Single cell sample path trajectories.](image)

2. Single cell model

Following a single cell line, the generator of \( \{X(t)\}_{t \geq 0} \) is given by (for bounded functions \( f \))

\[
Af(x) = \lambda(x) \int (f(y) - f(x)w(x,y))dy + \mu(x) \int (f(y) - f(x)s(x,y))dy.
\]

The evolution equation (Master equation) on the probability density \( u(x,y,t) \) is given by

\[
\frac{du(x,y,t)}{dt} = -\lambda(x)u(x,y,t) + \int \lambda(y)u(x,y,z)w(x,z)dy - \mu(x)u(x,y,t) + \int \lambda(y)u(x,z,y)s(x,z)dz.
\]

This defines a semi-group \( P(t) \) on \( L^1 \). We will use the

**Lemma 1.** (taken from [4])

If \( P(t) \)

- is a stochastic semigroup: \( \|P(t)\| = \|\mu_{t}\| \),
- is partially integral: there exists \( \lambda_{0} > 0 \) and \( \mu_{0}, \mu_{1} \) s.t.
  \[
  \int \mu_{0}(x) \mu_{1}(y)dx\mu_{1}(y)dy > 0,
  \]
- and possesses a unique invariant measure, then \( P(t) \) is asymptotically stable.

2.1 Asymptotic stability of the density

The Master equation may be rewritten as

\[
\frac{du(x,t)}{dt} = -\lambda(x)u(x,t) + \int \lambda(y)u(x,y,t)w(x,y)dy - \mu(x)u(x,t) + \int \lambda(y)u(x,t)\mu_{1}(y)dy.
\]

where \( \lambda_{0} = \lambda(x) + \lambda(y) \) and

\[
\kappa(x,y) = \int \lambda(y)u(x,y,t)w(x,y)dy + \int \lambda(y)u(x,y,t)\mu_{1}(y)dy.
\]

If \( \kappa \) has a strictly positive fixed point in \( L^1 \), then \( P(t) \) is stochastic \([5, 1] \). We consider the separable kernel case

\[
\lambda_{0}(x,y) = \lambda(x), \quad x > y, \quad \lambda_{0}(x,y) = \lambda(y), \quad x < y.
\]

where \( \lambda_{0}(y) = \lambda_{0} \lambda_{y} = \lambda_{y}, \lambda_{y} \) and \( K(y) = \lambda_{y} \). We define

\[
\tilde{\lambda}(y) = \lambda_{0}(y) \frac{\lambda_{y}}{\lambda(y)}, \quad x > y, \quad \tilde{\lambda}(y) = \lambda_{0}(y) \frac{\lambda_{y}}{\lambda(y)}, \quad x < y.
\]

Theorem 1. Asymptotic stability

Suppose that

\[
\tilde{\lambda} = \int \lambda(y)K(y)^2 \mu_{1}(y)dy < \infty \quad \text{and} \quad \lim_{\mu_{1}(y)\rightarrow \infty} \int \lambda(y)K(y)^2 \mu_{1}(y)dy < \mu_{0}.
\]

Then the semigroup \( \{P(t)\}_{t \geq 0} \) is stochastically and asymptotically stable.

For any initial density \( u_{0}(x) \), \( u(x,t) \) converges to

\[
u_{0}(x) \kappa(x) \rightarrow \hat{u}(x).
\]

Remark 1 Lyapunov-function strategy (32) can be used to find sufficient conditions of ergodicity in more general cases.

Corollary 1 Bifurcation (see [2])

The number of modes of the stationary solution are linked to the number of solutions of

\[
0 = \frac{\lambda_{0}(x)}{\lambda_{y}(x)} K_{y}(x) K_{y}(x) + G_{y}(x) \lambda_{0}(x) \kappa(x).
\]

2.2 Mean waiting time

We can also solve (analytically) the backward equation, \( \frac{\partial}{\partial x} \hat{u}(x) = \hat{u}(x) \).

We found for instance that the mean waiting time is non-monotonic with respect to the bursting property.

![Figure 3: \( K_{y}(x) = e^{-\lambda_{y}(x)} \), \( \lambda_{y}(x) = \lambda_{0}(x) \lambda_{y}(x) \).](image)

3. Nonlinear population model

We wish to investigate the (macroscopic) population model with nonlinear feedback on the division rate

\[
\frac{dS(t)}{dt} = -\lambda(x)S(x,t) + \int \lambda(y)u(y,x,t)w(x,y)dy - \mu(x)S(x,t) + \int \lambda(y)u(y,x,t)\mu_{1}(y)dy.
\]

where the feedback strength is given by

\[
\int \left( \psi(x) \right) dx.
\]

We will restrict to the case of constant division and death rates, so that

\[
\int \left( \psi(x) \right) dx = \frac{\lambda_{0}(x)}{\lambda_{y}(x)} K_{y}(x) K_{y}(x) + G_{y}(x) \lambda_{0}(x) \kappa(x).
\]

3.1 All cells participate to the feedback

\[
x \geq 0, \quad S(t) = \int_{x=0}^{\infty} \psi(x) dx, \quad \lambda(y) = \text{constant}.
\]

We have immediately

\[
\frac{dS(t)}{dt} = -\lambda(x)S(x,t) + \int \lambda(y)u(y,x,t)w(x,y)dy - \mu(x)S(x,t) + \int \lambda(y)u(y,x,t)\mu_{1}(y)dy.
\]

2.3 A fraction on cells participate to the feedback

In the case \( x > 0 \), we can only prove a persistence result for the equation

\[
\frac{dS(t)}{dt} = -\lambda(x)S(x,t) + \int \lambda(y)u(y,x,t)w(x,y)dy - \mu(x)S(x,t) + \int \lambda(y)u(y,x,t)\mu_{1}(y)dy.
\]

Theorem 3 Persistence

With \( \psi \) smooth, bounded and bounded away from \( t \), starting with a positive \( S(0) \), we have

\[
0 < \int u(x,y,t)dy \leq \sup \{ \psi(x) \}, \quad \mu(x) \delta(t) < \infty
\]

3.3 Numerical results indicate Hopf bifurcation

![Figure 5: \( \lambda_{y}(x) = 0 \), \( \psi(x) = 0 \).](image)

![Figure 6: \( \lambda_{y}(x) = 0 \), \( \psi(x) = 0 \).](image)

We found that the bursting and the asymmetry of the division shift the Hopf bifurcation

\[
\frac{\lambda_{y}(x)}{\lambda_{y}(x)} K_{y}(x) K_{y}(x) + G_{y}(x) \lambda_{0}(x) \kappa(x)
\]

\[
\begin{array}{cccc}
\lambda_{y}(x) = 0.4 & 0.2 & 0.2 & 0.2 \\
\lambda_{y}(x) = 0.6 & 0.4 & 0.4 & 0.4 \\
\lambda_{y}(x) = 0.8 & 0.6 & 0.6 & 0.6 \\
\lambda_{y}(x) = 1.0 & 0.8 & 0.8 & 0.8
\end{array}
\]

Table 1: Effect of cell burst proportions. Right: with \( \lambda_{y}(x) = 0.4, \psi(x) = 1 \). \( \psi(x) \) is the asymmetry of the division prevents oscillations.

4. Conclusion and Perspectives

Upon an assumption of separable bursting and division kernel, we found a complete characterisation of the single cell model.

- Criteria for convergence towards steady-state, and analytical solution (and bifurcation)
- Mean waiting time to reach a given level
- Such study can be used to infer the burst rate and/or division rate in a dividing cell population.

While looking at the nonlinear population model, the bursting properties and division mechanism are shown to have a profound impact on homeostasis that will be further investigated.

References


