Bursting and division in a nonlinear cell population model

Romain Yvinec

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Romain YVINEC

Inra Nouzilly UMR85 (Tours, France)

MAThematics Center Heidelberg (University of Heidelberg, Germany)

romain.yvinec@tours.inra.fr

Summary

We use Pure-Jump Markov processes to describe the stochastic protein bursting production and molecular repartition at division. We find asymptotic convergence criteria and analytical solutions for the steady-state probability density of proteins in a single cell. We also find analytical solutions of mean waiting time to reach a given level. This findings are used to caracterise the behavior of the model as a function of parameters (bifurcation) and can be applied for inverse problems. Finally, we study a population model based on a non-linear extension of the single cell model. We find with numerical simulations situations where a Hopf bifurcation occurs, and where unfrequent but large burst prevents oscillations.

1. The model: Pure-Jump Markov process

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

- **Bursting**: at rate $\lambda_b(x)$, a cell **increases** its molecular content, from x to y according to the bursting kernel distribution $\kappa_b(y,x)\mathbf{1}_{\{y>x\}}dy$
- **Division**: at rate $\lambda_d(x)$, a cell gives rise to **two cells of lower molecular content**, y and $x-y$, according to the (symmetric) division kernel distribution $\kappa_d(y,x)\mathbf{1}_{\{y<x\}}dy$

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.

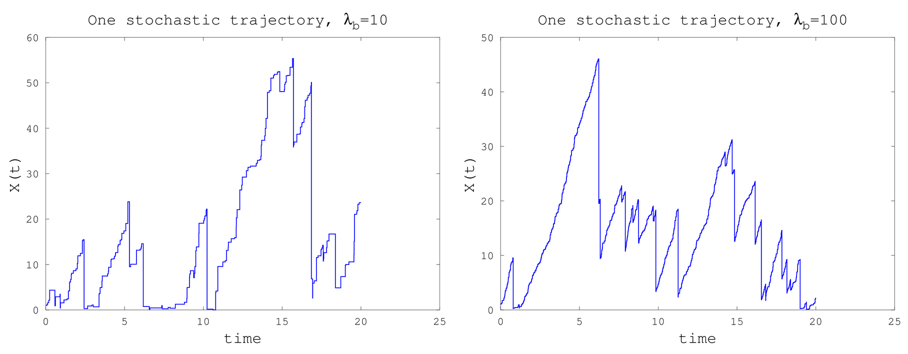

Figure 1: *Single cell sample path trajectories.*

Following the **whole population**, this model gives a measure-valued pure-jump Markov process, that can be represented as a tree (Figure 2)

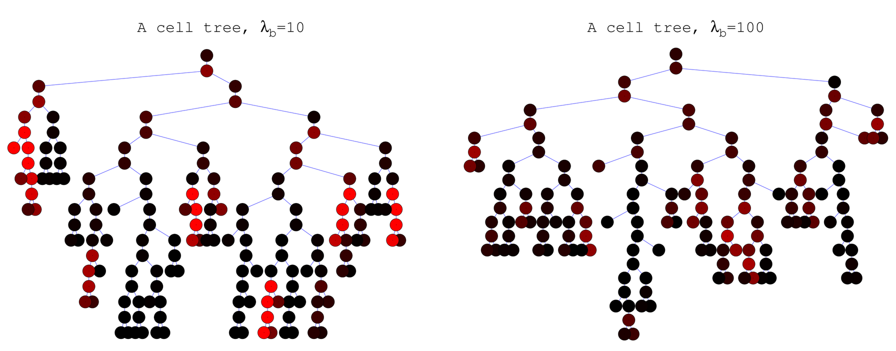

Figure 2: *Cell population evolution*

2. Single cell model

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

$$\mathcal{A}f(x) = \lambda_b(x)\Big(\int_x^\infty (f(y)-f(x))\kappa_b(y,x)dy\Big) + \lambda_d(x)\Big(\int_0^x (f(y)-f(x))\kappa_d(y,x)dy\Big).$$

The evolution equation (**Master equation**) on the probability density ($\int u(t,x)dx = 1$) is given by.

$$\frac{\partial u(t,x)}{\partial t} = -\lambda_b(x)u(t,x) + \int_0^x \lambda_b(y)u(t,y)\kappa_b(x,y)dy - \lambda_d(x)u(t,x) + \int_x^\infty \lambda_d(y)u(t,y)\kappa_d(x,y)dy$$

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: $\|P(t)u\|_1 = \|u\|_1$,
- is partially integral: there exists $t_0 > 0$ and p s.t.

$$\int_0^\infty\int_0^\infty p(x,y)\,dy\,dx > 0 \quad \text{and} \quad P(t_0)u(x) \geq \int_0^\infty p(x,y)u(y)\,dy$$

- and possess a unique invariant density,

then $P(t)$ is asymptotically stable.

2.1 Asymptotic stability of the density

The Master equation may be rewritten as

$$\frac{du}{dt} = -\lambda u + K(\lambda u),$$

where $\lambda(y) := \lambda_b(y) + \lambda_d(y)$ and

$$Kv(x) := \int_0^x \frac{\lambda_b(y)}{\lambda(y)}u(t,y)\kappa_b(x,y)dy + \int_x^\infty \frac{\lambda_d(y)}{\lambda(y)}u(t,y)\kappa_d(x,y)dy$$

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

$$\kappa_b(x,y) = -\frac{K_b'(x)}{K_b(y)}, \quad x>y, \quad \kappa_d(x,y) = \frac{K_d'(x)}{K_d(y)}, \quad x<y.$$

where $K_b(y) \to 0$ as $y\to\infty$ and $K(y)\to 0$ as $y \to 0$. We define

$$G(x) = \frac{K_d'(x)}{K_d(x)} - \frac{K_b'(x)}{K_b(x)}, \quad Q_b(x) = \int_x^{\overline{x}} \frac{\lambda_b(y)}{\lambda(y)}G(y)dy.$$

Theorem 1. Asymptotic stability

Suppose that

$$c_b := \int_0^\infty \frac{K_b(x)}{\lambda(x)}G(x)e^{-Q_b(x)}dx < \infty, \quad \int_0^\infty K_b(x)G(x)e^{-Q_b(x)}dx < \infty$$

Then the semigroup $\{P(t)\}_{t\geq 0}$ is stochastic and is asymptotically stable. For any initial density u_0, $u(t,x)$ converges to

$$u_*(x) = \frac{1}{c_b}\frac{K_b(x)}{\lambda(x)}G(x)e^{-Q_b(x)}$$

Remark 1 *Lyapounov-fonction strategy ([3]) 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

$$0 = -\frac{\lambda'(x)}{\lambda(x)} + \frac{K_b'(x)}{K_b(x)} + \frac{G'(x)}{G(x)} + \frac{\lambda_b(x)}{\lambda(x)}G(x)$$

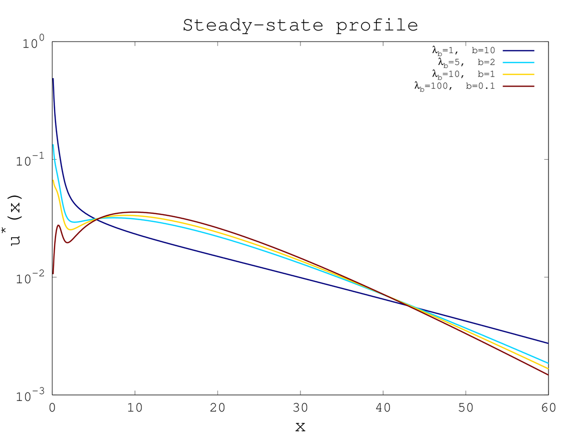

Figure 3: $K_b(x) = e^{-x/b}$, $\lambda_b(x) = \lambda_b\frac{1+x^n}{\Lambda+x^n}$, $K_d(x) = x$.

2.2 Mean waiting time

We can also solve (analytically) the backward equation, $\mathcal{A}f(x) = A(x)$. We found for instance that the mean waiting time is non-monotonic with respect to the bursting property.

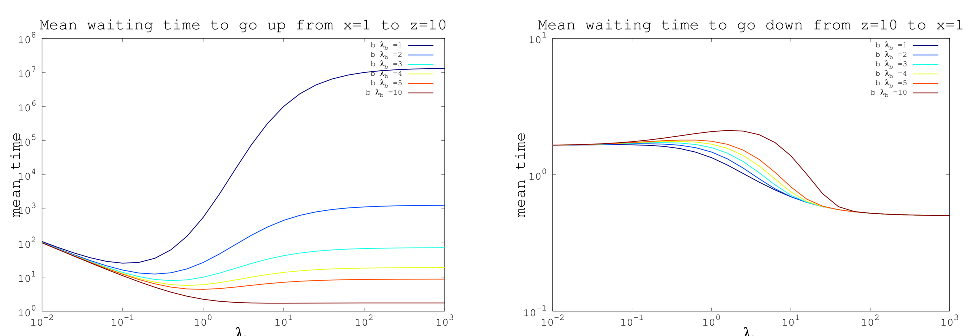

Figure 4: $K_b(x) = e^{-x/b}$, $\lambda_b(x) \equiv \lambda_b$, $K_d(x) = x$.

3. Nonlinear population model

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

$$\frac{\partial u(t,x)}{\partial t} = -\lambda_b(x)u(t,x) + \int_0^x \lambda_b(y)u(t,y)\kappa_b(x,y)dy - \lambda_d(x,S)u(t,x) + 2\int_x^\infty \lambda_d(y,S)u(t,y)\kappa_d(x,y)dy - \mu(x)u(t,x)$$

where the feeback strenght is given by

$$S(t) = \int_0^\infty \psi(x)u(t,x)dx, \quad \psi(x) = \mathbf{1}_{\{x\geq x_0\}}.$$

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

$$\frac{d}{dt}\Big(\int_0^\infty u(t,x)dx\Big) = (\lambda_d(S)-\mu)\int_0^\infty u(t,x)dx$$

3.1 All cells participate to the feedback

If $x_0 = 0$, $S(t) = \int_0^\infty u(t,x)dx$, and we have immediately

Theorem 2. Asymptotic stability
Under the hypothesis of Theorem 1, and if $S \mapsto \lambda_d(S)$ is continuous monotonically decreasing, with $\lambda_d(0) > \mu$ and $\lim_{S\to\infty}\lambda_d(S) < \mu$, then for any initial density u_0, the solution $u(t,x)$ converges as $t\to\infty$ in L^1 towards

$$\lambda_d^{-1}(\mu)u_*.$$

3.2 A fraction on cells participate to the feedback

In the case $x_0 > 0$, we can only prove a persistance result for the equation

$$\frac{\partial u(t,x)}{\partial t} + \frac{\partial g(x)u(t,x)}{\partial x} = - \lambda_d(S)u(t,x) + 2\int_x^\infty \lambda_d(S)u(t,y)\kappa_d(x,y)dy - \mu u(t,x)$$

Theorem 3. Persistance
With g smooth, bounded and bounded away from 0, starting with a positive $u_0 \in L^1$, we have

$$0 < \inf_{t\geq 0}\int_0^\infty u(t,x)dx \leq \sup_{t\geq 0}\int_0^\infty u(t,x)dx < \infty$$
$$0 < \inf_{t\geq 0} S(t) \leq \sup_{t\geq 0} S(t) < \infty$$

3.3 Numerical results indicate a Hopf bifurcation

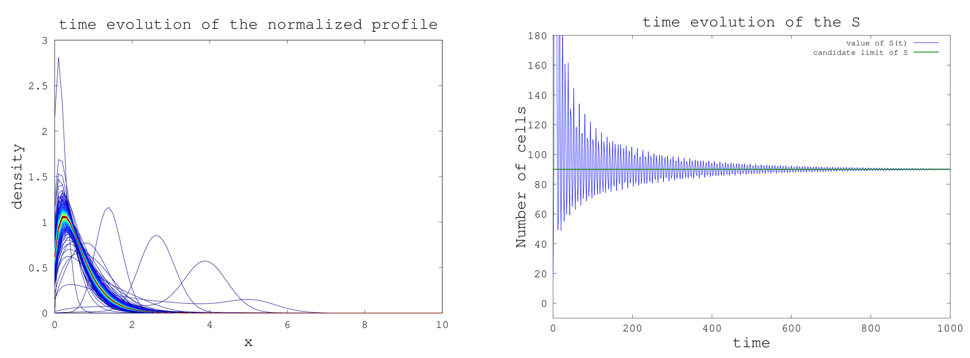

Figure 5: $\lambda_d(x,S) \equiv \frac{10}{1+0.1*S}$,$x_0 = 1$, $g(x) \equiv 0.6$

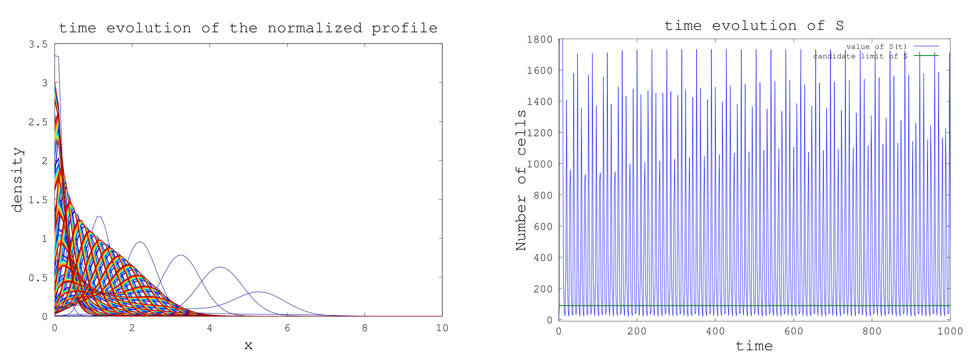

Figure 6: $\lambda_d(x,S) \equiv \frac{10}{1+0.1*S}$, $x_0 = 1$, $g(x) \equiv 0.5$

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

$b\lambda_b\backslash\lambda_b$	100	10	1	0.1
0.6	+	+	+	+
0.5	-	+	+	+
0.4	-	-	+	+
0.1	-	-	-	+

$g\backslash p$	0.5	0.4	0.2	0.1	0.01
0.7	-	+	+	+	+
0.6	-	-	+	+	+
0.5	-	-	-	-	+
0.4	-	-	-	-	-

Table 1: *Left: Unfrequent but large burst prevent oscillations. Right: with* $\kappa_d(\cdot,x) = 0.5\mathcal{N}(xp, xp(1-p)) + 0.5\mathcal{N}(x(1-p), xp(1-p))$*, 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.

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