# Towards nonlinear cell population model structured by molecular content

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## Outline

Stochasticity in Molecular biology, links with cell fate

Single cell model : Bursting and Division as Jump Processes

Nonlinear (macroscopic) population model
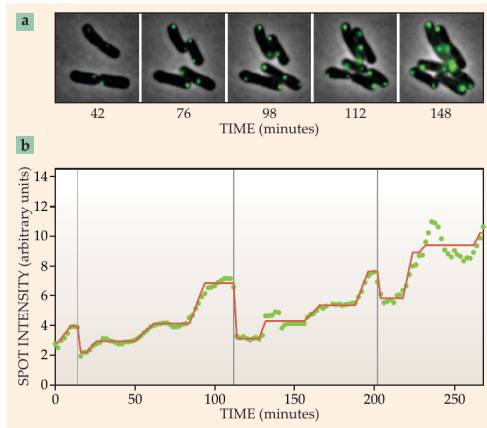   Theoretical results
   Numerical results

Stochasticity in Molecular biology, links with cell fate

Single cell model : Bursting and Division as Jump Processes

Nonlinear (macroscopic) population model

# Stochasticity in molecular biology

▶ Trajectories on single cells : bursting and repartition at division are major sources of randomness in gene expression.



[Golding et al. Cell 2005, Kondev Physics Today 2014]

# A typical example linking gene expression to cell fate

The antagonism between
regulatory proteins (Transcription
Factor) Gata-1/PU.1 in
heamatopoietic progenitor
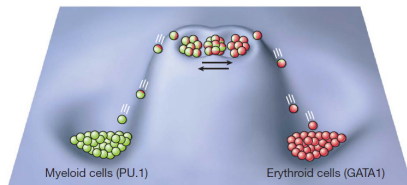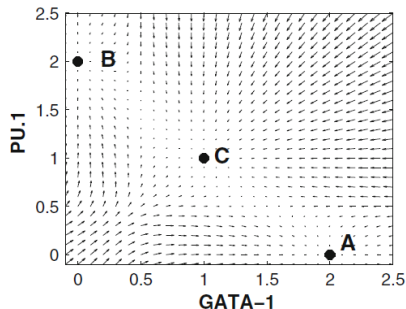


[Enver et al. Stem Cell 2009]

# Cell fate explained by a deterministic dynamical system

The antagonism Gata-1/PU1,
modeled by ODE

$$\frac{d[G]}{dt} = a_1 \frac{[G]^n}{\theta_{a1}^n + [G]^n} + b_1 \frac{\theta_{b1}^n}{\theta_{b1}^n + [P]^n} - k_1[G]$$
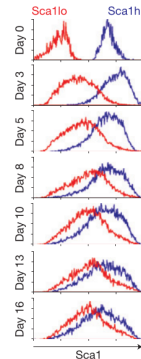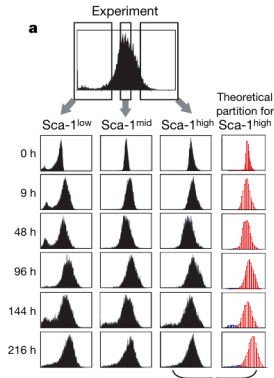
$$\frac{d[P]}{dt} = a_2 \frac{[P]^n}{\theta_{a2}^n + [P]^n} + b_2 \frac{\theta_{b2}^n}{\theta_{b2}^n + [G]^n} - k_2[P]$$

Cell fate "=" attractor of a
dynamical system.



[Duff et al. JMB 2012]

Reversibility of the gene expresion profile (and cell fate ?) in *in vitro* cell culture experiment



[Chang et al. Nature Letters 08]



[Pina et al. Nature cell bio. 2012]

# Outline

We define a pure-jump process $(X(t))_{t\geq 0}$ on $\mathbb{R}_+^*$ with two different transitions :

- ▶ **Bursting** at rate $\lambda_b(x)$ and jump distribution $\kappa_b(y,x)\mathbf{1}_{\{y>x\}}dy$
- ▶ **Division** at rate $\lambda_d(x)$ and jump distribution $\kappa_d(y,x)\mathbf{1}_{\{y<x\}}dy$

**Pathwise construction :** Let $(U_n, V_n)_{n\geq 1}$ be i.i.d $\propto \mathbb{U}(0,1)$,

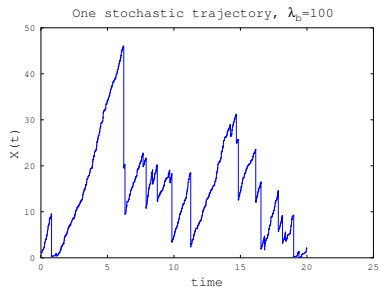- ▶ **Time step :** $T_n = T_{n-1} + (1/\lambda(X_{n-1}))\ln(1/U_{n-1})$, where

$$\lambda(x) = \lambda_b(x) + \lambda_d(x).$$

- ▶ **State step :** $X_n = F_\kappa^{-1}(V_n, X_{n-1})$, where $F_\kappa(y,x)$ is the cum. dist. fonct. associated to

$$\kappa(y,x) = \underbrace{\frac{\lambda_b(x)}{\lambda_b(x)+\lambda_d(x)}\kappa_b(y,x)\mathbf{1}_{\{y>x\}}}_{\text{Bursting (gain)}} + \underbrace{\frac{\lambda_d(x)}{\lambda_b(x)+\lambda_d(x)}\kappa_d(y,x)\mathbf{1}_{\{y<x\}}}_{\text{Division (loss)}}.$$

- ▶ $X(t) = X_{n-1}$ for all $T_{n-1} \leq t < T_n$.

# Example of sample paths
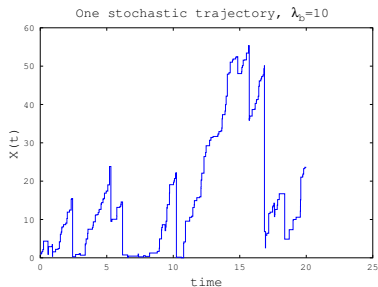
This model is well-defined up to the explosion time,

$$T_\infty = \lim_{n \to \infty} T_n$$

### Remark
*Non-explosion + irreducibility + Existence of a unique invariant measure ⇒ ergodicity.*

Lyapounov-fonction strategy (see [Meyn and Tweedie 93]) can provide sufficient criteria.

► An analogous study on the set of probability density ($\int u = 1$).

$$\frac{\partial u(t,x)}{\partial t} = \underbrace{-\lambda_b(x)u(t,x) + \int_0^x \lambda_b(y)u(t,y)\kappa_b(x,y)dy}_{\text{Bursting (gain)}}$$

$$\underbrace{-\lambda_d(x)u(t,x) + \int_x^\infty \lambda_d(y)u(t,y)\kappa_d(x,y)dy}_{\text{Division (loss)}}$$

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

Theorem (Pichor and Rudnicki JM2A 2000)

*If $P(t)$ is a stochastic semigroup : $\|P(t)u\|_1 = \|u\|_1$, is partially integral, e.g. there exists $t_0 > 0$ and $p$ s.t.*

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

*and if $P(t)$ possess a unique invariant density, then $P(t)$ is* **asymptotically stable.**

The Master equation may be rewritten as

$$\frac{du}{dt} = -\lambda u + K(\lambda u), \qquad (1)$$

where

$$Kv(x) = \underbrace{\int_0^x \frac{\lambda_b(y)}{\lambda_b(y) + \lambda_d(y)} u(t,y)\kappa_b(x,y)dy}_{\text{Bursting (gain)}}$$

$$+ \underbrace{\int_x^\infty \frac{\lambda_d(y)}{\lambda_b(y) + \lambda_d(y)} u(t,y)\kappa_d(x,y)dy}_{\text{Division (loss)}}$$

If $K$ has a strictly positive fixed point in $L^1$, then $P(t)$ is stochastic ([Mackey et al. SIAM 13]). Note also that any stationary solution $u^*$ of (1) must satisfy the flux condition

$$\underbrace{\int_0^x \Big( \int_x^\infty \kappa_b(z,y)dz \Big) \lambda_b(y)u^*(y)dy}_{\text{`` from } x^- \text{ to } x^+ \text{ ''}} = \underbrace{\int_x^\infty \Big( \int_0^x \kappa_d(z,y)dz \Big) \lambda_d(y)u^*(y)dy}_{\text{`` from } x^+ \text{ to } x^- \text{ ''}}$$

We consider the separable 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

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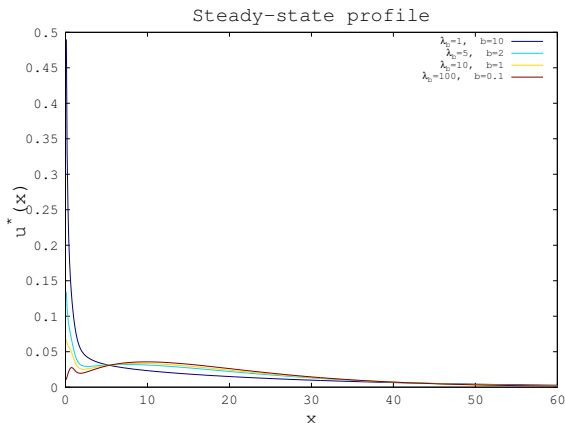
### Theorem
*Suppose that*

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

*Then the semigroup* $\{P(t)\}_{t \geq 0}$ *is stochastic and is asymptotically stable, with*

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

$$\frac{du^*}{dx} = \Big[ -\frac{\lambda'(x)}{\lambda(x)} + \frac{K_b'(x)}{K_b(x)} + \frac{G'(x)}{G(x)} + \frac{\lambda_b(x)}{\lambda(x)} G(x) \Big] u^*(x)$$



Steady-state profile

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

▶ This theorem can be used to show asymptotic convergence for "non-trivial" parameters function.

In particular, the growth-division model

$$\frac{\partial u(t,x)}{\partial t} + \underbrace{\frac{\partial g(x)u(t,x)}{\partial x}}_{\text{Continuous production}} = \underbrace{-\lambda_d(x)u(t,x) + \int_x^\infty \lambda_d(y)u(t,y)\frac{K_d'(x)}{K_d(y)}dy}_{\text{Division (loss)}},$$

converges for

$$\lambda_d(x) = \alpha x^{\beta-1} + x^{\beta+1}$$
$$g(x) = x^\beta$$
$$K_d(x) = x,$$

for $0 \le \beta \le 1$, $0 < \alpha < 1$, towards

$$u_*(x) = \frac{K_d(x)}{cg(x)}e^{-\int_{\bar{x}}^x \frac{\lambda_d(y)}{g(y)}dy},$$

but

$$\frac{\lambda_d}{g} \notin L_0^1$$

**Absorbing probabilities / Mean waiting time :** We can also
solve (analytically) the backward equation, $\mathcal{A}f(x) = A(x)$,

$$\mathcal{A}f(x) = \underbrace{\lambda_b(x)\Big( \int_x^\infty (f(y) - f(x))\kappa_b(y,x)dy \Big)}_{\text{Bursting (gain)}}$$

$$+ \underbrace{\lambda_d(x)\Big( \int_0^x (f(y) - f(x))\kappa_d(y,x)dy \Big)}_{\text{Division (loss)}}.$$
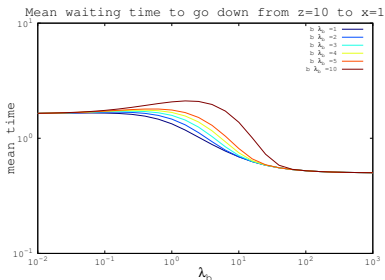
If

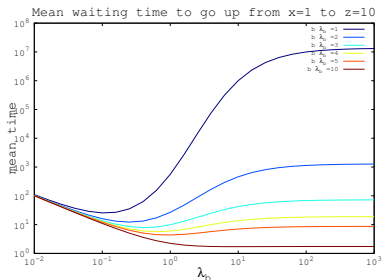$$\tau_z^+ := \inf\{t \geq 0, X_t \geq z\},$$

then

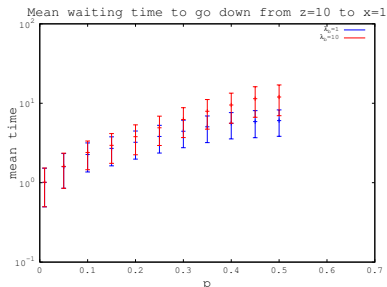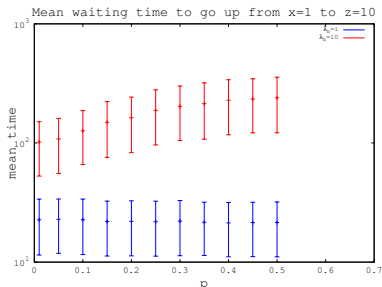$$V_z^+(y) = \mathbb{E}_y\big[\tau_z^+\big]$$

is solution of

$$\begin{cases} \mathcal{A}V_z^+(y) = -1, & y < z, \\ V_z^+(y) = 0, & y \geq z. \end{cases} \tag{2}$$

The mean waiting time is non-monotonic with respect to the bursting property.



$$\lambda_d \equiv 2, \ K_d(x) = x, \ \lambda_b(x) \equiv \lambda_b, \ K_b(x) = e^{-x/b}$$

The mean waiting time is also affected by the asymmetry of the division.



$$\lambda_d(x) \equiv 2,$$
$$\kappa_d(\cdot, x) = 0.5\mathcal{N}(xp, xp(1-p)) + 0.5\mathcal{N}(x(1-p), xp(1-p)),$$
$$K_b(x) = e^{-x/b}, \ b\lambda_b = 2$$

# Outline

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

$$\frac{\partial u(t,x)}{\partial t} = \underbrace{-\lambda_b(x)u(t,x) + \int_0^x \lambda_b(y)u(t,y)\kappa_b(x,y)dy}_{\text{Bursting}}$$

$$\underbrace{-\lambda_d(x,S)u(t,x) + 2\int_x^\infty \lambda_d(y,S)u(t,y)\kappa_d(x,y)dy}_{\text{Division}} - \underbrace{\mu(x)u(t,x)}_{\text{Cell death}}$$

with $\kappa_d$ symmetric (total molecular content preserved at division) 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

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

If all cells participate to the regulation of the division rate
($x_0 = 0$), we have immediately

Theorem

Let $\kappa_b(x, y) = -\frac{K_b'(x)}{K_b(y)}$, and $\kappa_d(x, y) = \frac{K_d'(x)}{K_d(y)}$. We assume

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

and that $S \mapsto \lambda_d(S)$ is continuous monotonically decreasing, with
$\lambda_d(0) > \mu$ and $\lim_{S\to\infty} \lambda_d(S) < \mu$, then, for any initial density $u_0$,
$u(t, x)$ converges as $t \to \infty$ in $L^1$ towards

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

In the case $x_0 > 0$, we can not prove convergence towards a steady-state, and numerical results indicate the presence of oscillation through a Hopf-bifurcation.
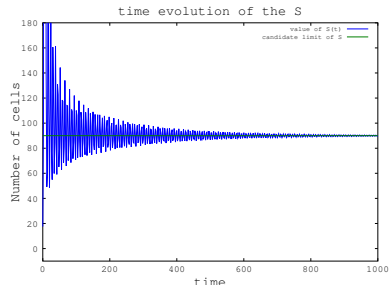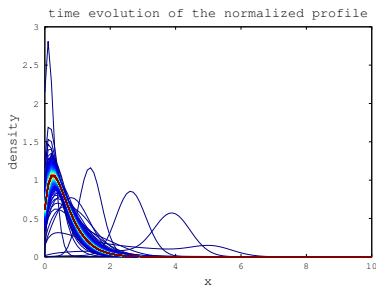
### Remark

*We can however prove persistance results in certain cases*

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

## Numerical results

$$\frac{\partial u(t,x)}{\partial t} + \underbrace{\frac{\partial g(x)u(t,x)}{\partial x}}_{\text{Continuous production}} = \underbrace{-\lambda_d(x,S)u(t,x) + 2\int_x^\infty \lambda_d(y,S)u(t,y)\kappa_d(x,y)dy}_{\text{Division}} - \underbrace{\mu(x)u(t,x)}_{\text{Cell death}}$$



time evolution of the normalized profile



time evolution of the S

$$\mu = 1,\ \lambda_d(x,S) \equiv \frac{10}{1+0.1*S},\ K_d(x) = x,\ x_0 = 1,\ g(x) \equiv 0.6$$
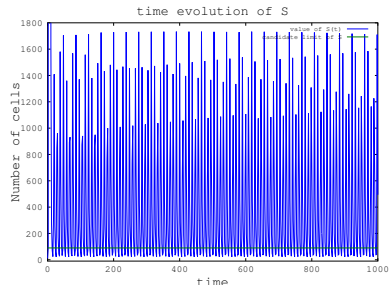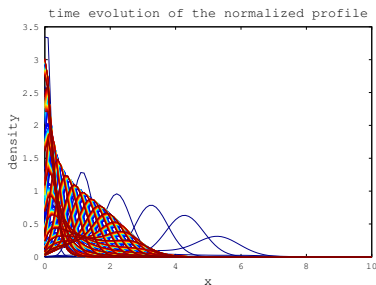
# Numerical results indicate a Hopf bifurcation

$$\underbrace{\frac{\partial u(t,x)}{\partial t}}_{} + \underbrace{\frac{\partial g(x)u(t,x)}{\partial x}}_{\text{Continuous production}} = \underbrace{-\lambda_d(x,S)u(t,x) + 2\int_x^\infty \lambda_d(y,S)u(t,y)\kappa_d(x,y)dy}_{\text{Division}} - \underbrace{\mu(x)u(t,x)}_{\text{Cell death}}$$



time evolution of the normalized profile



time evolution of S

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

# The bursting property shifts the Hopf bifurcation

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

with $\mu = 1$, $\lambda_d(x,S) \equiv \frac{10}{1+0.1*S}$, $K_d(x) = x$, $x_0 = 1$,
$K_b(x) = e^{-x/b}$, $\lambda_b(x) \equiv \lambda_b$

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

Table : +=Asymptotic convergence towards steady state - = oscillation

# The asymmetry at division also shifts the Hopf bifurcation

$$\frac{\partial u(t,x)}{\partial t} + \underbrace{\frac{\partial g(x)u(t,x)}{\partial x}}_{\text{Continuous production}} = \underbrace{-\lambda_d(x, S)u(t,x) + 2\int_x^\infty \lambda_d(y, S)u(t,y)\kappa_d(x,y)dy}_{\text{Division}} - \underbrace{\mu(x)u(t,x)}_{\text{Cell death}}$$

with $\mu = 1$, $\lambda_d(x, S) \equiv \frac{10}{1+0.1*S}$,
$\kappa_d(\cdot, x) = 0.5\mathcal{N}(xp, xp(1-p)) + 0.5\mathcal{N}(x(1-p), xp(1-p))$,
$x_0 = 1$, $g(x) \equiv g$

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

Table : +=Asymptotic convergence towards steady state - = oscillation

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.

**Thank you for your attention !**