Towards nonlinear cell population model structured by molecular content

Romain Yvinec, Michael C. Mackey, M. Tyran-Kamińska, A. Marciniak-Czochra

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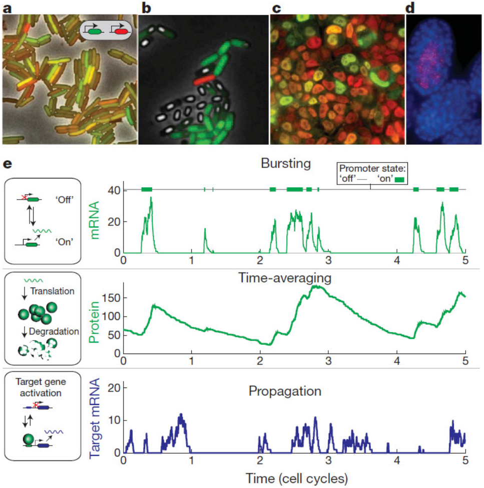
Joint work with M. Mackey, M. Tyran-Kaminska, A. Marciniak-Czochra

Outline

Outline

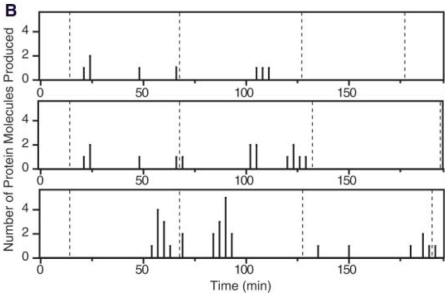
Stochasticity in molecular biology

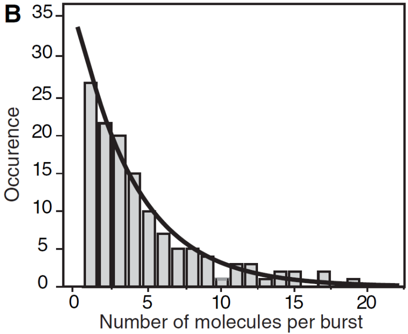


[Eldar and Elowitz Nature 2010]

Much more accurate measurements

- The bursting event are well characterized

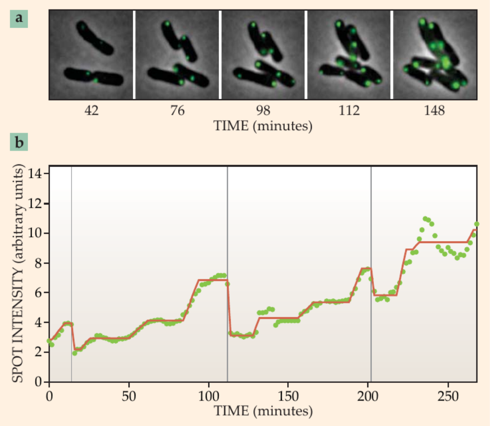




[Yu et al. Science 06]

Much more accurate measurements

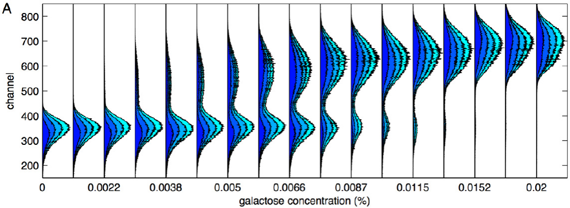
- Trajectories can be analyzed on single cells.

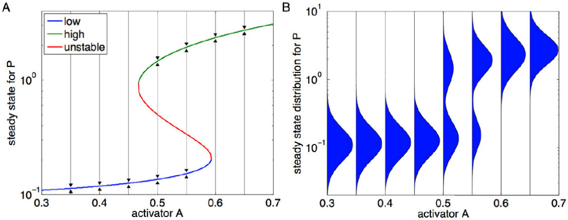


[Golding et al. Cell 2005, Kondev Physics Today 2014]

Much more accurate measurements

- Bifurcation can be studied on probability distributions.

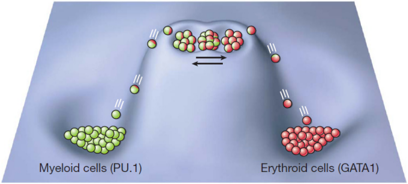




[Song et al. Plos CB 2010, Mackey et al. JTB 2011, SIAM 2013]

A typical example linking gene expression to cell fate

The antagonism Gata-1/PU.1 in heamatopoietic progenitor

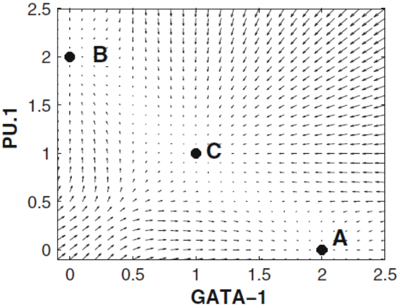


[Enver et al. Stem Cell 2009]

A typical example linking gene expression to cell fate

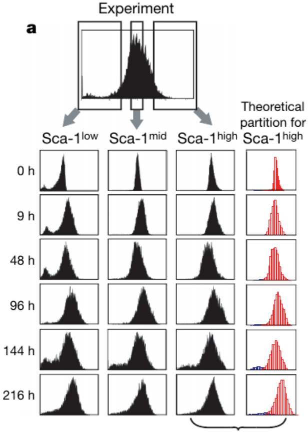
The antagonism Gata-1/PU1, modeled by ODE

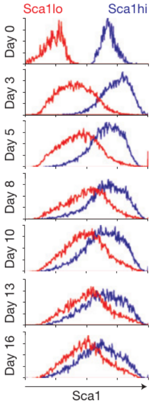
$$\frac{d[G]}{dt} = a_1 \frac{[G]^n}{\theta_{a1}^n + [G]^n} + b_1 \frac{\theta_{b1}^n}{\theta_{b1}^n + [P]^n} - k_1[G]$$
$$\frac{d[P]}{dt} = a_2 \frac{[P]^n}{\theta_{a2}^n + [P]^n} + b_2 \frac{\theta_{b2}^n}{\theta_{b2}^n + [G]^n} - k_2[P]$$



[Duff et al. JMB 2012]

A typical example linking gene expression to cell fate





[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 with the sequence $(U_n, V_n)_{n\geq 1}$, of i.i.d uniform random variable on $(0,1)$

- $T_n = T_{n-1} - (1/\lambda(X_{n-1}))\ln(U_{n-1})$, where
$$\lambda(x) = \lambda_b(x) + \lambda_d(x).$$
- $X_n = F_K^{-1}(V_n, X_{n-1})$, where $F_K(y,x)$ is the cum. dist. fonct. associated to
$$K(y,x) = \frac{\lambda_b(x)}{\lambda_b(x)+\lambda_d(x)}\kappa_b(y,x)\mathbf{1}_{\{y>x\}} + \frac{\lambda_d(x)}{\lambda_b(x)+\lambda_d(x)}\kappa_d(y,x)\mathbf{1}_{\{y<x\}}.$$
- $X(t) = X_{n-1}$ for all $T_{n-1} \leq t < T_n$.

This model is well-defined up to the explosion time,

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

A well-known sufficient condition for non-explosion ($T_\infty = \infty$) is given by

$$\sum_{n\geq 0} \frac{1}{\lambda_b(X_n) + \lambda_d(X_n)} = \infty.$$

In particular, this is the case for *bounded* jump rate.

Another criteria is provided by Lyapounov-fonction strategy (see [Meyn and Tweedie 93]). Let $\mathcal{A}$ be the generator of $(X(t))_{t\geq 0}$,

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

If there exists $c>0$, V a positive measurable function s.t $V(x)\to\infty$ when $x\to 0$ and $x\to\infty$, $V\in\mathcal{D}(\mathcal{A})$ and

$$\mathcal{A}V(x)\leq cV(x), \quad x>0,$$

then $(X(t))_{t\geq 0}$ is non-explosif.

The fonction $V(x) = x^{-\gamma}\mathbf{1}_{\{x\le 1\}} + x^{\alpha}\mathbf{1}_{\{x>1\}}$ is suitable if there exists A, B, β, δ,

- $\overline{\kappa}_b(y,x) = \int_y^\infty \kappa_b(z,x)dz \le c(x/y)^\beta$, $\beta > \alpha$
- $\overline{\kappa}_d(y,x) = \int_0^y \kappa_d(z,x)dz \le c(y/x)^\delta$, $\delta > \gamma$
- $\lambda_d(x) < A\lambda_b(x) + B$ as $x \to 0$ and

$$\lim_{x\to 0} \lambda_b(x)x^\delta \int_x^1 y^{-\delta}\kappa_b(y,x)dy < \infty$$

- $\lambda_b(x) < A\lambda_d(x) + B$ as $x \to \infty$ and

$$\lim_{x\to \infty} \lambda_d(x)x^{-\alpha} \int_1^x y^{\alpha}\kappa_d(y,x)dy < \infty$$

Remark

"Similar" condition holds for ergodicity.

Remark

Non-explosion + irreductibility + Existence of a unique invariant measure $\Rightarrow$ ergodicity.

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

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

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

Theorem (Pichor and Rudnicki JM2A 2000)

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.

The Master equation may be rewritten as

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

where

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

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

$$\int_0^x \overline{\kappa}_b(x,y)\lambda_b(y)u^*(y)dy = \int_x^\infty \overline{\kappa}_d(x,y)\lambda_d(y)u^*(y)dy$$

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

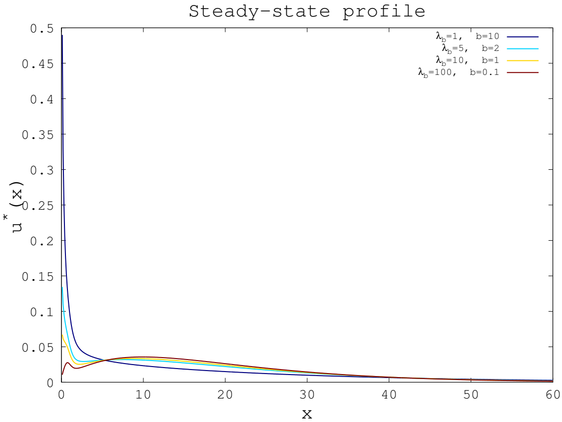
Suppose that

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

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

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

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



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

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

In particular, the growth-division model

$$\frac{\partial u(t,x)}{\partial t} + \frac{\partial g(x)u(t,x)}{\partial x} = -\lambda_d(x)u(t,x) + \int_x^\infty \lambda_d(y)u(t,y)\frac{K_d'(x)}{K_d(y)}dy,$$

converges for

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

for $0 \leq \beta \leq 1$, $0 < \alpha < 1$, 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, $\mathcal{A}f(x) = A(x)$.
If

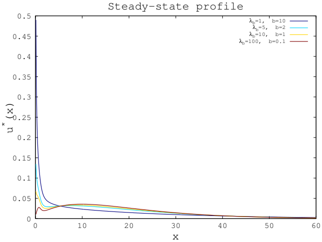
$$\tau_{u,z} := \inf\{t \geq 0, X_t \geq z\},$$

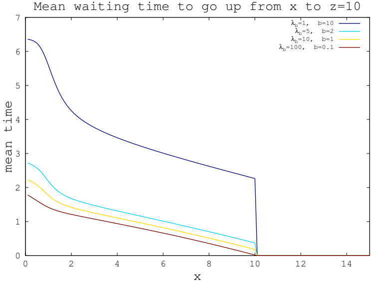
then

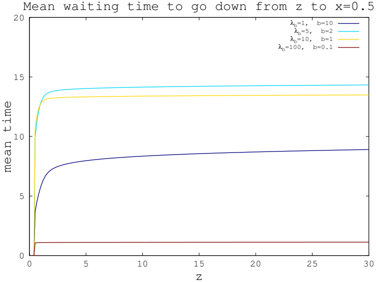
$$V_{u,z}(y) = \mathbb{E}_y\left[\tau_{u,z}\right]$$

is solution of

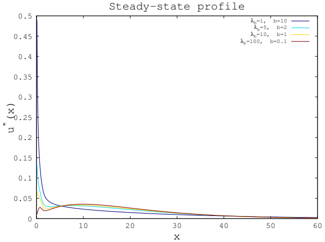
$$\begin{cases} \mathcal{A}V_{u,z}(y) = -1, & y < z, \\ V_{u,z}(y) = 0, & y \geq z. \end{cases} \tag{2}$$

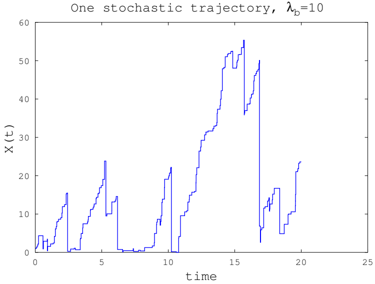


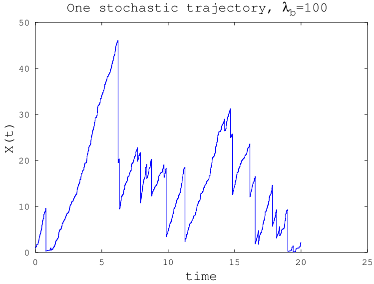




$$K_b(x) = e^{-x/b},\ \lambda_b(x) = \lambda_b \frac{1+x^n}{\Lambda + x^n},\ K_d(x) = x,\ \lambda_d(x) \equiv 1.$$

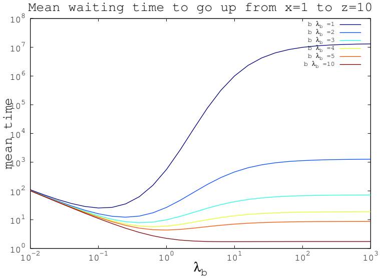


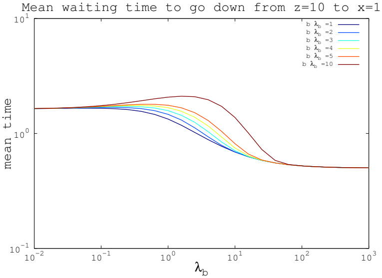




$$K_b(x) = e^{-x/b},\ \lambda_b(x) = \lambda_b \frac{1+x^n}{\Lambda+x^n},\ K_d(x) = x,\ \lambda_d(x) \equiv 1.$$

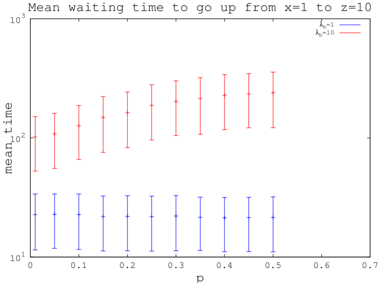
The mean waiting time is non-monotonic with respect to the bursting property.

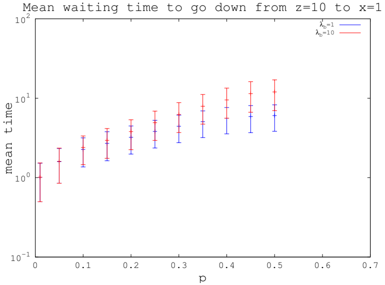




$$\lambda_d \equiv 2,\ K_d(x) = x,\ \lambda_b(x) \equiv \lambda_b,\ K_b(x) = e^{-x/b}$$

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





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

Outline

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

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

with κ_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 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

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

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

$$0 < \inf_{t\geq 0} S(t) \leq \sup_{t\geq 0} S(t) < \infty$$

Démonstration.

We define $v(t,x) := e^{\int_0^t (\mu - \lambda_d(S(s)))ds} u(t,x)$, so that

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

We use a coupling strategy to show that

$$\int_{x_0}^\infty v(t,x)dx \geq c(1+\varepsilon(t))$$

with $\varepsilon(t) \to 0$ (at exponential speed). For this, we use the coupling

$$\begin{aligned}\mathcal{A}f(x,y) &= g(x)f'(x) + g(y)f'(y) \\ &\quad + 2\lambda_d(S(t))\Big(\int_0^1 (f(xz,yz) - f(x,y))dz\Big) \\ &\quad + 2(\|\lambda_d\|_\infty - \lambda_d(S(t)))\Big(\int_0^1 (f(xz,y) - f(x,y))dz\Big).\end{aligned}$$

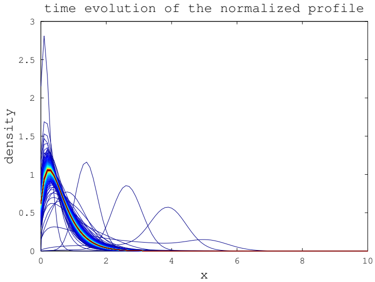
Then, $\int_{x_0}^{\infty} v(t,x)dx \geq \int_{x_0}^{\infty} w(t,x)dx$ where

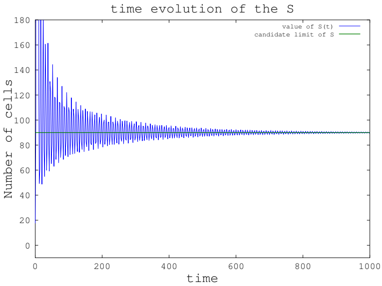
$$\frac{\partial w(t,x)}{\partial t}+\frac{\partial g(x)w(t,x)}{\partial x} = -2\|\lambda_d\|_\infty w(t,x)+2\|\lambda_d\|_\infty \int_x^\infty w(t,y)\kappa_d(x,y)dy$$

which converges as $t \to \infty$ due to hypotheses on g, κ_d.

Outline

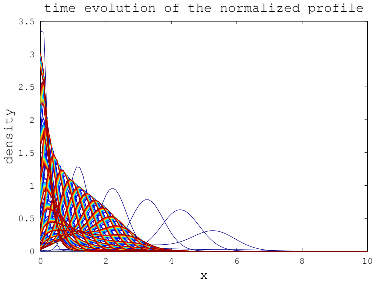
Numerical results

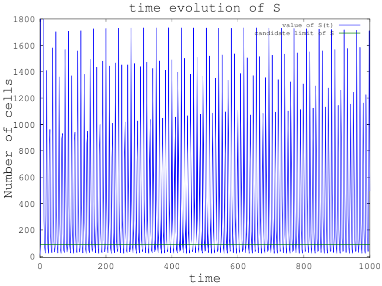




$$\mu = 1,\ \lambda_d(x, S) \equiv \frac{10}{1+0.1*S},\ K_d(x) = x,\ x_0 = 1,\ g(x) \equiv 0.6$$

Numerical results indicate a Hopf bifurcation





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

The bursting property shifts the Hopf bifurcation : 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 : 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

Vielen Dank !