A kinetic model of quorum sensing

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Motivation: bacterial communication

Bacterial communication poses many purely scientific and applied problems. For example, in the context of bacterial resistance to anti-microbials. An important component of social interaction of bacteria is *quorum sensing*. As explained in the classical review of Miller and Bassler [7], quorum sensing refers to the regulation of bacterial function, *e.g.* gene expression, in response to fluctuations in cell-population density. Such regulation operates via the production and release of signal micromolecules (autoinducers). Increase in bacterial cell density beyond a threshold triggers a substantial increase in the concentration of the autoinducer, function of cell density, which then leads to an alteration in bacterial gene expression and metabolism.

Individual model

The model, as introduced by D. Brown [1] describes the evolution of: y the intracellular and x the extracellular signal molecules' concentration.

$$\frac{dy}{dt} = \underbrace{a_0}_{\text{basal prod.}} + \underbrace{\frac{a_1 y^2}{K^2+y^2}}_{\text{autoinduce prod.}} - \underbrace{m_I y}_{\text{decay}} + \underbrace{D(x-y)}_{\text{membrane transport}}$$

and

$$\frac{dx}{dt} = \frac{\phi}{1-\phi} D(y-x) - m_E x$$

with ϕ a scaling factor, $\phi = V_{bact.}/V_{tot.} \in (0,1)$. Hence

$$\frac{d}{dt}\left[\frac{\phi}{1-\phi} y + x\right] = \text{production} - \text{decay}.$$

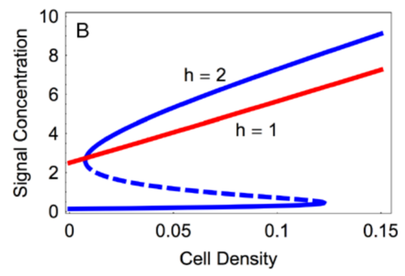

Figure 1. Bistability diagram from [1]. $\phi \to 1$ corresponds to high cell density while $\phi \to 0$ corresponds to low cell density.

Brown uses $\phi \in (0,1)$ as a bifurcation parameter and exhibits bistability in the equilibrium value of $y(t)$ as ϕ is increased from 0. The diagram from [1] is showed in Figure 1.

Population model in measure

Consider a fixed number N of cells having identical volume. Hence, the model becomes

$$\begin{cases} \dfrac{dy_i}{dt} = a_0 + \dfrac{a_1 y_i^2}{K^2+y_i^2} - m_I y_i + D(x-y_i), \ i = 1,\dots,N, \\ \dfrac{dx}{dt} = \dfrac{\phi}{1-\phi} D\left(\dfrac{1}{N}\displaystyle\sum_{i=1}^{N}(y_i - x)\right) - m_E x\,. \end{cases} \tag{1}$$

The population model can be interpreted through its empirical measure $\mu_t = \frac{1}{N}\sum_{i=1}^{N} \delta_{y_i(t)}$.

Straightforwardly, from (1), the system reads

$$\begin{cases} \partial_t \mu_t(dy) + \partial_y(v(x(t),y)\mu_t(dy)) = 0, \\ x'(t) = \dfrac{\phi}{1-\phi}\displaystyle\int_0^\infty D(y-x(t))\mu_t(dy) - m_E x(t). \end{cases} \tag{2}$$

with

$$v(x,y) = a_0 + \frac{a_1 y^2}{K^2+y^2} - m_I y + D(x-y).$$

Note μ_t is a probability measure and $\mu_t([y, y+dy))$ is the fraction of cells with contents comprised within $[y, y+dy)$.

We introduce the notion of solution we deal with and state a well-posedness result.

Definition: *Let $T > 0$. A measure-valued solution to (2) on $[0,T]$ is a pair $(\mu, x) \in \mathcal{C}^0([0,T],\mathcal{P}_1) \times \mathcal{C}^0([0,T],\mathbb{R}_+)$ such that for all $t \in [0,T]$,*

(i) *for all $\varphi \in \mathcal{C}^1(\mathbb{R}_+)$ with $\varphi' \in L^\infty(\mathbb{R}_+)$,*

$$\int_0^\infty \varphi(y)\mu_t(dy) = \int_0^\infty \varphi(y)\mu_0(dy) + \int_0^t \int_0^\infty v(x(s),y)\varphi'(y)\mu_s(dy)ds$$

(ii) and

$$x(t) = x(0) + \int_0^t \left(\frac{\phi}{1-\phi}\int_0^\infty D(y-x(t))\mu_t(dy) - m_E x(t)\right) ds\,.$$

Theorem: *Let $(\mu^{\text{in}}, x^{\text{in}}) \in \mathcal{P}_1 \times \mathbb{R}_+$. There exists a unique global solution (μ, x) to (2) satisfying $\mu_0 = \mu^{\text{in}}$ and $x(0) = x^{\text{in}}$.*

The proof relies on a fixed point argument once we have constructed characteristic for (2) with $x \in \mathcal{C}^0([0,T],\mathbb{R}_+)$ given, which we call the linear problem.

Corollary: *If μ^{in} has a density with respect to the Lebesgue measure on $\mathbb{R}_+$, then the solution μ has a density $f(t,\cdot)$ for all t, which belongs to $\mathcal{C}^0([0,\infty), w - \mathrm{L}^1(\mathbb{R}_+,(1+x)dx))$.*

We introduce some notation in order to describe stationary solutions. For $y > 0$, we define

$$g_1(y) = \left(1 + \frac{m_I}{D}\right) y - \frac{a_0}{D} - \frac{a_1 y^2}{D(K^2+y^2)} \text{ and } g_2(y) = \frac{y}{1 + \frac{m_E(1-\phi)}{D\phi}}.$$

A steady solution $(\mu, x) \in \mathcal{P}_1 \times \mathbb{R}_+$ hence satisfy for all $\psi \in \mathcal{C}_b^0(\mathbb{R}_+)$

$$\int_0^\infty (x - g_1(y))\psi(y)\mu(dy) = 0 \text{ and } \int_0^\infty (x - g_2(y))\mu(dy) = 0.$$

This entails that the support of μ belongs to $\{y \,|\, g_1(y) = x\}$ which consists in at most three points, thus the general form of μ is

$$\mu = \sum_{i=1}^{3} \rho_i \delta_{y_i(x)} \text{ and } \sum_{i=1}^{3} \rho_i g_2(y_i(x)) = x,$$

with $\rho_i \geq 0$ and $\sum_{i=1}^3 \rho_i = 1$; while $y_1(x) \leq y_2(x) \leq y_3(x)$ are the roots of $g_1(y) - x$ with possible repetition.

This equation is very intricated and does not provide a complete description unless separating a multitude of cases depending on the choice of parameters. Under suitable conditions on the coefficients, we can prove that the steady solution consists of one Dirac mass and in another case we prove that a "continuum" of steady solutions exist.
In the case where steady solution consist of one Dirac mass, we are able to construct a Lyapunov functional. Similar Lyapunov arose e.g. in the Lifshitz-Slyozov equation [4, 2, 3].

Theorem: *Let $(\mu^{\text{in}}, x^{\text{in}}) \in \mathcal{P}_1 \times \mathbb{R}_+$. If*

$$\exists! y^* \geq 0, g_1(y^*) = g_2(y^*) \text{ and } \int_0^\infty y^2 \mu^{\text{in}} < \infty,$$

then the solution starting at $(\mu^{\text{in}}, x^{\text{in}})$ satisfies

$$\lim_{t\to\infty} W_1(\mu_t, \delta_{y^*}) = 0 \text{ and } \lim_{t\to\infty} x(t) = x^* := g_2(y^*).$$

Population model with fluctuations

Originating from jump processes, the second order approximation system (*e.g.* [5]) is given by fluctuation with variance proportional to the rates. We choose to only keep fluctuation through membrane transport, the density follows

$$\partial_t u(t,x) + \partial_y\left\{v(x(t),y)u(t,y) - \frac{\varepsilon D}{2}\partial_y((x(t)+y)u(t,y))\right\} = 0, \ t > 0, y > 0, \tag{3}$$

and the balance of molecules yields

$$x'(t) = \frac{\phi}{1-\phi}\int_0^\infty D(y-x(t))u(t,y)dy - m_E x(t) - \varepsilon D x(t) u(t,0), \ t > 0. \tag{4}$$

Conservation of cells imply a Robin type boundary condition, similar assumptions have been used e.g. in [6], and conservations of total number of molecules imply the modification in (4).

The notion of solution we deal with is a couple $(u,x) \in \mathrm{L}^\infty((0,T)\times\mathbb{R}_+) \cap \mathrm{L}^\infty(0,T;\mathrm{L}^1(\mathbb{R}_+,(1+x)dx)) \times \mathcal{C}^0([0,T],\mathbb{R}_+)$ such that u satisfy the weak form of (3) in the L^2 sense and the classical integral weak form for x. We state the following well-posedness result:

Theorem: *Let $x^{\text{in}} > 0$ and $u^{\text{in}} \in \mathrm{L}^\infty(\mathbb{R}_+) \cap \mathrm{L}^1(\mathbb{R}_+,(1+y)^2 dy)$ a non-negative function. Then there exists a unique global weak solution (x,u) to (3)-(4) satisfying $u_0 = u^{\text{in}}$ and $x(0) = x^{\text{in}}$. Moreover, for all $T > 0$,*

$$u \in \mathcal{C}^0([0,T],\mathrm{L}^1(\mathbb{R}_+,(1+y)dy)) \text{ and } \int_0^\infty u(t,y)dy = \int_0^\infty u^{\text{in}}(y)dy = 1, \text{ for all } t \in [0,T].$$

For a given x, a steady state profile M should have constant flux j with $j(0) = 0$. Thus, the steady solution M has the form

$$M_x(y) = \frac{x}{x+y}\exp\left(\frac{1}{\eta}\int_0^y \frac{v(x,z)}{x+z}dz\right) \times \left(\int_0^\infty \frac{x}{x+y'}\exp\left(\frac{1}{\eta}\int_0^{y'}\frac{v(x,z)}{x+z}dz\right)dy'\right)^{-1},$$

normalized to satisfy $\int_0^\infty M(y)dy = 1$. On the other hand, at equilibrium

$$\Psi(x) := D\frac{\phi}{1-\phi}\int_0^\infty y M_x(y)dy - D\frac{\phi}{1-\phi}x - m_E x - \frac{\phi}{1-\phi}\eta x M_x(0) = 0.$$

The zeros of Ψ completely determine steady state solutions. A numerical illustration is given in Figures 2 and 3. Numerical simulations show that the blue equilibrium is unstable (as in Brown) in Figure 4, and we retrieve a bifurcation diagram in Figure 5. One question arise, is the second order model able to choose, at vanishing viscosity, Dirac masses in the first order model ? A numerical prospection is given in Figure 6.

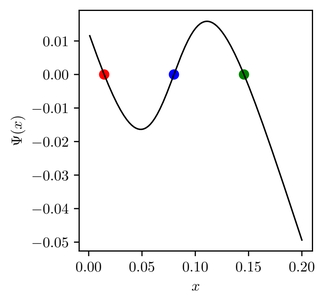

Figure 2. Three zeros of Ψ: three different steady states.

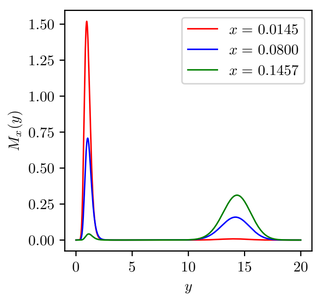

Figure 3. Different steady states.

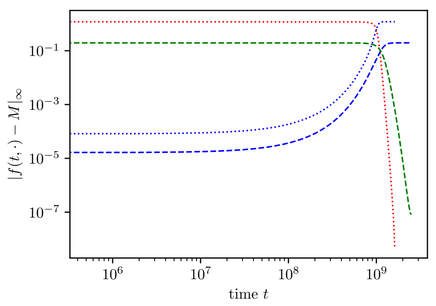

Figure 4. The blue steady state is unstable.

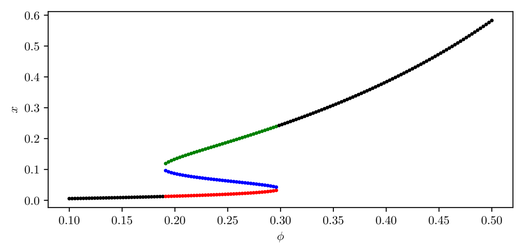

Figure 5. Bifurcation diagram.

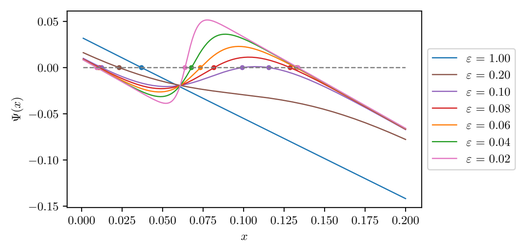

Figure 6. Dirac selection at vanishing viscosity?

Let $(M, \bar{x})$ a steady state. In some regime of parameters, ϕ small, we expect that the steady state is linearly stable.

Conjecture: *Let $(M,\bar{x})$ a steady state, and (m,z) the solution of the linearized equations around that steady state. Then, there exists a constant $\Theta > 0$ such that for all $t \geq 0$,*

$$\frac{1}{2}\frac{d}{dt}\left[\int_0^\infty \frac{m^2(t,y)}{M(y)}dy + z^2\right] \leq -\Theta\left[\int_0^\infty \frac{m^2(t,y)}{M(y)}dy + z^2\right].$$

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