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C. R. Acad. Sci. Paris, Ser. I 341 (2005) 731–736
COMPTES RENDUS MATHEMATIQUE
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Partial Differential Equations

Fitness optimization in a cell division model

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Received 19 September 2005; accepted 11 October 2005

Available online 11 November 2005

Presented by Carlo Cercignani

Abstract

We consider a size structured cell population model where a mother cell gives birth to two cells. We know that the asymptotic behavior of the density of cells is given by the solution to an eigenproblem. The eigenvector gives the asymptotic shape and the eigenvalue gives the exponential growth rate and so the Maltusian parameter. The Maltusian parameter depends on the division rule for the mother, i.e., symmetric (the two daughter cells have the same size) or asymmetric. We give some example where the symmetrical division is not the best fitted division, i.e., the Maltusian parameter is not optimal. ***To cite this article: P. Michel, C. R. Acad. Sci. Paris, Ser. I 341 (2005).***

Résumé

Optimisation du taux de croissance dans un modèle de division cellulaire. Nous considérons un modèle d'évolution d'une densité de cellules structurée en taille. Nous savons que la densité de cellules se comporte en temps long comme le produit d'une fonction indépendante du temps et d'une exponentielle dépendant du temps. Le taux de croissance exponentiel étant donné par un paramètre Maltusien dont nous allons montrer qu'il depend de la manière dont la cellule se divise, symétriquement ou non symétriquement. On donnera des exemples pour lesquels la division symétrique n'est pas la mieux adaptée, c'est-à-dire pour lesquels le taux de croissance exponentiel n'est pas maximal. ***Pour citer cet article : P. Michel, C. R. Acad. Sci. Paris, Ser. I 341 (2005).***

Version française abrégée

La division cellulaire asymétrique est observée pour les levures (par bourgeonement), pour certaines bactéries et d'autres cellules. Elle peut être expliquée par une meilleure capacité de développement (sélection naturelle). L'objectif de cette note est de montrer que certains modèles mathématiques peuvent représenter ce phénomène. On modélise l'évolution d'une densité de cellules $n(t,y)$ structurée en taille y, en un temps t, par l'équation,

$$\begin{cases} \dfrac{\partial n}{\partial t}(t,y) + \dfrac{\partial nV(y)}{\partial y}(t,y) + B(y)n(t,y) = \displaystyle\int_y^\infty b(y',y)n(t,y')\,\mathrm{d}y', \quad y \geqslant 0, \\ n(\cdot,0) = 0, \end{cases} \tag{1}$$

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1631-073X/$ – see front matter
doi:10.1016/j.crma.2005.10.012

où V est le taux de croissance, B le taux de naissance et b la manière dont une cellule de taille y' se divise. On sait (voir [8,9]) qu'en temps long $n(t,\cdot)$ se comporte comme $\mathrm{e}^{\lambda t}N(\cdot)$, où N et λ sont solutions d'un problème aux valeurs propres. Nous allons montrer à travers ce modèle simple de division cellulaire que le taux de croissance λ depends de la manière dont la cellule se divise. Par exemple on peut se restreindre à la paramétrisation par un paramètre $\sigma \in]0,1[$ qui exprime la division en deux cellules de taille σy et $(1-\sigma)y$. Nous nous intéressons donc au problème simplifié

$$\frac{\partial n}{\partial t}(t,y)+\frac{\partial nV(y)}{\partial y}(t,y)+B(y)n(t,y)=\frac{1}{\sigma}B\left(\frac{y}{\sigma}\right)n\left(t,\frac{y}{\sigma}\right)+\frac{1}{1-\sigma}B\left(\frac{y}{1-\sigma}\right)n\left(t,\frac{y}{1-\sigma}\right). \tag{2}$$

On sait (voir [9]) que $n(t,y)\sim_{t\to\infty}\rho N_\sigma(y)\,\mathrm{e}^{\lambda_\sigma t}$, où ρ est une constante dépendant de la condition initiale et $(\lambda_\sigma,N_\sigma,\phi_\sigma)$ est une solution d'un problème aux valeurs propres et de son dual, défini par

$$\begin{cases}\dfrac{\partial N_\sigma}{\partial y}+\big(B(y)+\lambda_\sigma\big)N_\sigma(y)=\dfrac{1}{\sigma}B\left(\dfrac{y}{\sigma}\right)N_\sigma\left(\dfrac{y}{\sigma}\right)+\dfrac{1}{1-\sigma}B\left(\dfrac{y}{1-\sigma}\right)N_\sigma\left(\dfrac{y}{1-\sigma}\right),\\ -\dfrac{\partial \phi_\sigma}{\partial y}+\big(B(y)+\lambda_\sigma\big)\phi_\sigma(y)=B(y)\big[\phi_\sigma(\sigma y)+\phi_\sigma\big((1-\sigma)y\big)\big],\\ N_\sigma(0)=0,\quad N_\sigma(y)\geqslant 0,\quad \phi_\sigma(y)\geqslant 0,\quad \forall y\geqslant 0,\quad \displaystyle\int_0^\infty N_\sigma(y')\phi_\sigma(y')\,\mathrm{d}y'=1.\end{cases} \tag{3}$$

On obtient alors

Théorème 0.1. *Soit $(\lambda_\sigma,N_\sigma,\phi_\sigma)$ solution de (3) alors*

$$\left(\frac{\partial}{\partial\sigma}\lambda_\sigma\right)_{\sigma=\sigma_0}=\int_0^\infty B(y)yN_{\sigma_0}(y)\left[\left(\frac{\partial}{\partial_y}\phi_{\sigma_0}\right)(y\sigma_0)-\left(\frac{\partial}{\partial_y}\phi_{\sigma_0}\right)\big(y(1-\sigma_0)\big)\right]\mathrm{d}y. \tag{4}$$

De plus si $((\frac{\partial}{\partial_y}\phi_{\sigma_0})(y\sigma_0)-(\frac{\partial}{\partial_y}\phi_{\sigma_0})(y(1-\sigma_0)))=0$ pour tout y alors

$$\left(\frac{\partial^2}{\partial\sigma\partial\sigma}\lambda_\sigma\right)_{\sigma=\sigma_0}=\int_0^\infty B(y)y^2\left[\left(\frac{\partial^2}{\partial y\partial y}\phi_{\sigma_0}\right)(y\sigma_0)+\left(\frac{\partial^2}{\partial y\partial y}\phi_{\sigma_0}\right)\big(y(1-\sigma_0)\big)\right]N_{\sigma_0}(y)\,\mathrm{d}y. \tag{5}$$

Par conséquent on a

Théorème 0.2. *Si $V=1$ et $K=\operatorname{Supp}B$ est un intervalle tel que $(\sigma_0K)\bigcap K=\emptyset$ avec $\sigma_0\in]1/2,1[$ alors $(\partial\sigma\lambda_\sigma)_{\sigma=\sigma_0}>0$. En particulier pour $K=\operatorname{Supp}B\subset[a,b]$ avec $a>b/2$, la division symétrique n'est pas la division la mieux adaptée, i.e., il existe $\sigma>1/2$ tel que $\lambda_\sigma>\lambda_{1/2}$.*

Si $V=1$ et $K=\operatorname{Supp}B=[0,\beta]$ tel que

$$\frac{\lambda_\sigma(\lambda_\sigma-B(0))}{B(0)}\leqslant\frac{B'(y)}{B(y)}\leqslant 0,\quad \forall y\in]0,\beta[,$$

alors la division symétrique est la mieux adaptée, i.e., pour tout $\sigma\in]0,1[$, $\lambda_\sigma\leqslant\lambda_{1/2}$. En particulier pour $B=1_{[0,\beta]}$ avec $\beta>0$ on a $\lambda_{1/2}\geqslant\lambda_\sigma$ pour tout σ dans $]0,1[$.

1. Introduction

General models of cell division have been known for a long time. Although the most classical case is division in two equal new cells, it is now well established that this is not always the case. In the large class of budding yeasts, E. Coli or for some bacteria or for instance Physcomitrella protoplast, division is not always symmetric and give birth to a bigger and a smaller cell. We can explain this by adaptive dynamic. In some cases, the symmetric division is not the best fitted way of division. Our aim is to exhibit a parameter that characterizes the fitness for a cell division and to optimize it under some constraints on the cell division parameter. The natural model to study it, is a cell division model (see [2,7]) in which the density of cells $n(t, y)$ is structured by their size y and evolution is describes by the master equation

$$\frac{\partial n}{\partial t}(t,y)+\frac{\partial nV(y)}{\partial y}(t,y)+B(y)n(t,y)=\frac{1}{\sigma}B\left(\frac{y}{\sigma}\right)n\left(t,\frac{y}{\sigma}\right)+\frac{1}{1-\sigma}B\left(\frac{y}{1-\sigma}\right)n\left(t,\frac{y}{1-\sigma}\right), \tag{6}$$

where a cell of size y gives birth to a cell of size $y\sigma$ and an another of size $(1-\sigma)y$, with $\sigma \in]0,1[$, i.e., $b(y,y') = B(y')[\delta_{y'=\sigma y} + \delta_{y'=(1-\sigma)y}]$. A Similar model also arises to describe fragmentation in physics [4,6] and the growth term $\partial_y n$ arises after rescaling [1,3]. The asymptotic behavior of $n(t, y)$ gives the invasive capacity of the population and thus a fitness measure of populations under different rates and probabilities in (6).

2. Asymptotic result and definition of a fitness parameter

We recall the result of asymptotic behavior of $n(t, y)$ solution to (6), given by the General Relative Entropy (see [9]) $n(t,y) \sim_{t\to\infty} \rho N_\sigma(y)\,\mathrm{e}^{\lambda_\sigma t}$, where λ_σ is the first eigenvalue associated to the following eigenproblem

$$\begin{cases} \dfrac{\partial V N_\sigma}{\partial y} + \big(B(y)+\lambda_\sigma\big)N_\sigma(y) = \dfrac{1}{\sigma}B\left(\dfrac{y}{\sigma}\right)N_\sigma\left(\dfrac{y}{\sigma}\right) + \dfrac{1}{1-\sigma}B\left(\dfrac{y}{1-\sigma}\right)N_\sigma\left(\dfrac{y}{1-\sigma}\right), \\ -V(y)\dfrac{\partial \phi_\sigma}{\partial y} + \big(B(y)+\lambda_\sigma\big)\phi_\sigma(y) = B(y)\big(\phi_\sigma(\sigma y) + \phi_\sigma\big((1-\sigma)y\big)\big), \\ N_\sigma(0)=0, \quad N_\sigma(y)\geqslant 0, \quad \phi_\sigma(y)\geqslant 0, \quad \forall y\geqslant 0, \quad \displaystyle\int_0^\infty N_\sigma(y')\phi_\sigma(y')\,\mathrm{d}y' = 1, \end{cases} \tag{7}$$

and ρ is a constant depending on the initial data. We notice that ϕ_σ is a solution to the dual eigenproblem of the eigenproblem in N_σ. This means that λ_σ is the Maltusian parameter that gives the exponential growth and N_σ is the asymptotic shape. Our point here is to focus on the Maltusian parameter that gives an invasive parameter and we choose λ_σ as the fitness parameter. Therefore we fix the birth rate B and the speed growth V, and we study the variation of λ_σ with respect to the parameter σ that describes all sizes after division.

3. Dependence of the fitness parameter with respect to σ

Here we show that the symmetric division is not necessarily the best fitted division. We study two cases, B has a compact support and $B(y) = y^p$. We notice that we only have to consider $\sigma \in [1/2, 1[$, indeed (7) does not change if we exchange σ and $1-\sigma$, therefore we have $\lambda_\sigma = \lambda_{1-\sigma}$. Then we have the following results.

3.1. Assume B has a compact support

In this case, symmetric division might or not be the best fitted division. More precisely, we have

Theorem 3.1. *Assume $V = 1$, $K = \operatorname{Supp} B = [a,b] \subset [0,\infty[$ s.t.*

$$(\sigma_0 K)\cap K = \emptyset,$$

with $\sigma_0 \in]1/2,1[$ then $(\frac{\partial}{\partial\sigma}\lambda_\sigma)_{\sigma=\sigma_0} > 0$. In particular, if $a > b/2$ then the symmetric division is not the best fitted division, i.e., there exists $\sigma > 1/2$ s.t. $\lambda_\sigma > \lambda_{1/2}$.

Assume $V = 1$ and $\operatorname{Supp} B = [0,\beta]$ s.t. $B \not\equiv 0$, decreases and satisfies

$$\frac{\lambda_\sigma(\lambda_\sigma - B(0))}{B(0)} \leqslant \frac{B'(y)}{B(y)} \leqslant 0, \quad \forall y \in]0,\beta[,$$

then the symmetric division is the best fitted division, i.e., for all $\sigma \in]0,1[$, we have $\lambda_\sigma \leqslant \lambda_{1/2}$. In particular for $B = 1_{[0,\beta]}$, with $\beta > 0$, we have $\lambda_{1/2} \geqslant \lambda_\sigma$ for all σ in $]0,1[$.

Numerically, we find, by setting $b = 1$ and $a = 0,\ 0.1,\ 0.5$ that λ_σ is increasing on $[1/2, 1[$ for $a = 0$, reaches a maximum at $\sigma_0 \in]1/2, 1[$ for $a = 0.1$ and is decreasing on $[1/2, 1[$ for $a = 0.5$ (see Fig. 1).

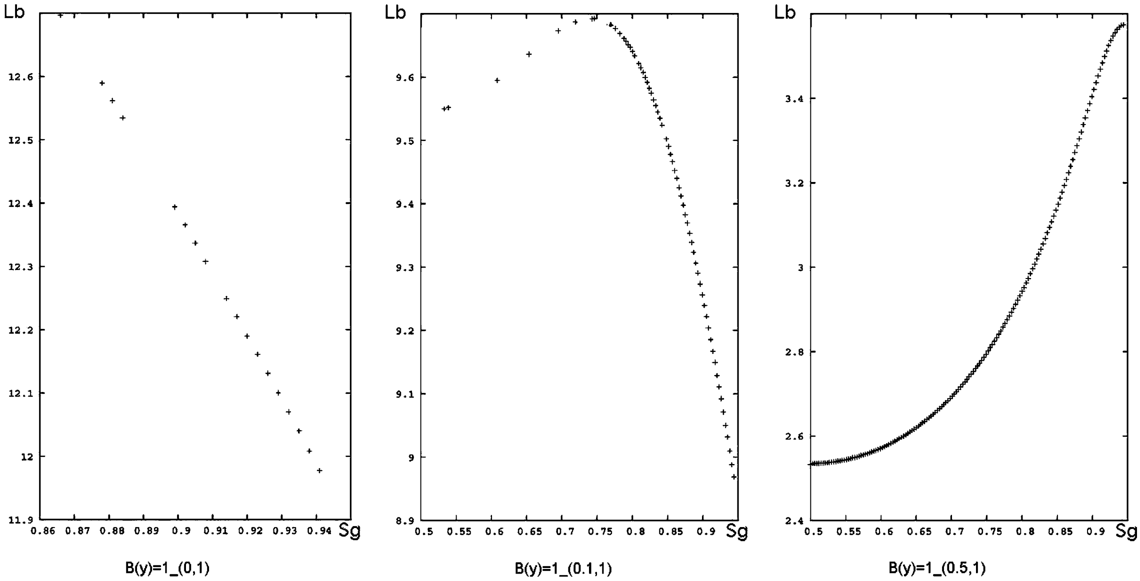

Fig. 1. $\sigma \mapsto \lambda(\sigma)$ for $a = 0$, $a = 0.1$ and $a = 0.5$ with $b = 1$ and $B(y) = 1_{[a,b]}$.

3.2. Assume $B(y) = y^p$

Using the moment of N_σ, $\mathcal{M}_k = \int_0^\infty N_\sigma(y) y^k \,\mathrm{d}y$, we have,

Proposition 3.2. *Assume $B(y) = C + Dy$ and $V(y) = \alpha + \beta y$ then*

$$\lambda_\sigma = \frac{\beta + C + \sqrt{(\beta - C)^2 + 4\alpha D}}{2},$$

and we have λ_σ is independent of σ.

Proposition 3.3. *Assume $V(y) = \beta y$ with $\beta > 0$ then for all B we have $\lambda_\sigma = \beta$ is independent of σ.*

From Proposition 3.2, we know that for $p = 1$ and $V = 1$, λ_σ is independent of σ, the following proposition gives the behavior of λ_σ in a neighborhood of $p = 1$.

Proposition 3.4. *Assume $V = 1$ and $B(y) = y^p$ then there exists $\epsilon > 0$ such that*

$$\forall p \in]1 - \epsilon, 1[, \quad \lambda_\sigma \text{ decreases on } [1/2, 1[,$$
$$\forall p \in]1, 1 + \epsilon[, \quad \lambda_\sigma \text{ increases on } [1/2, 1[.$$

Therefore the symmetrical division is not necessarily the best fitted division, it depends on the birth rate B and the speed growth V, an adaptive strategy would be to have a large spectrum of way to divide, i.e. σ, to be able to fit in the case of a change of the environment, i.e., B and V. In other words the full class of division rules $b(y, y')/B(y)$ might still give a better eigenvalue (see [7,9,3,6]).

4. Main theorem

In order to prove these propositions, we use the eigenproblem (7) that gives the asymptotic behavior of $n(t, \cdot)$ (see [7,11,9,10,8] for the existence of solution to (7) and long time asymptotic) and the following theorem,

Theorem 4.1. *Assume there exists λ_σ, N_σ, ϕ_σ solution to* (7) *for all $\sigma \in [1/2, 1[$ and for $\sigma_0 \in [1/2, 1[$ we have*

$$\left(\frac{\partial}{\partial\sigma}\lambda_\sigma\right)_{\sigma=\sigma_0} = \int_0^\infty B(y) y N_{\sigma_0}(y)\left[\left(\frac{\partial}{\partial_y}\phi_{\sigma_0}\right)(y\sigma_0) - \left(\frac{\partial}{\partial_y}\phi_{\sigma_0}\right)\big(y(1-\sigma_0)\big)\right] \mathrm{d}y. \tag{8}$$

Moreover if we have $(\frac{\partial}{\partial_y}\phi_{\sigma_0})(y\sigma_0) = (\frac{\partial}{\partial_y}\phi_{\sigma_0})(y(1-\sigma_0)) = 0$ for all $y \geqslant 0$, for instance when $\sigma_0 = 1/2$, $B = C^{st}$ or $B(y) = y$, then

$$\left(\frac{\partial^2}{\partial\sigma^2}\lambda_\sigma\right)_{\sigma=\sigma_0} = \int_0^\infty B(y) y^2\left[\left(\frac{\partial^2}{\partial y^2}\phi_{\sigma_0}\right)(y\sigma_0) + \left(\frac{\partial^2}{\partial y^2}\phi_{\sigma_0}\right)\big(y(1-\sigma_0)\big)\right] N_{\sigma_0}(y)\, \mathrm{d}y. \tag{9}$$

Proof of Theorem 4.1. Indeed, we have $\lambda_\sigma = \int_0^\infty \mathcal{L}_\sigma^*(\phi_\sigma)(y) N_\sigma(y)\,\mathrm{d}y$, where the operator $\mathcal{L}_\sigma$ and its dual $\mathcal{L}_\sigma^*$ are defined by

$$\mathcal{L}_\sigma(g) = -\frac{\partial}{\partial y}(Vg) - B(y)g + \frac{B(y/\sigma)g(y/\sigma)}{\sigma} + \frac{B(y/(1-\sigma))g(y/(1-\sigma))}{1-\sigma},$$
$$\mathcal{L}_\sigma^*(g) = V\frac{\partial}{\partial y}g - B(y)g + B(y)g(y\sigma) + B(y)g\big(y(1-\sigma)\big).$$

Thus we deduce

$$\frac{\partial}{\partial\sigma}\lambda_\sigma = \int_0^\infty \left(\frac{\partial}{\partial\sigma}\mathcal{L}_\sigma^*\right)(\phi_\sigma)(y)N_\sigma(y) + \mathcal{L}_\sigma^*\left(\frac{\partial}{\partial\sigma}\phi_\sigma\right)(y)N_\sigma(y) + \mathcal{L}_\sigma^*(\phi_\sigma)(y)\frac{\partial}{\partial\sigma}N_\sigma(y)\,\mathrm{d}y,$$

but $\mathcal{L}_\sigma^*(\phi_\sigma)(y) = \lambda_\sigma\phi_\sigma(y)$, $\mathcal{L}_\sigma(N_\sigma)(y) = \lambda_\sigma N_\sigma(y)$ and

$$\int_0^\infty \left(N_\sigma(y)\frac{\partial}{\partial\sigma}\phi_\sigma(y) + \phi_\sigma(y)\frac{\partial}{\partial\sigma}N_\sigma(y)\right)\mathrm{d}y = \frac{\partial}{\partial\sigma}\int_0^\infty N_\sigma(y)\phi_\sigma(y)\,\mathrm{d}y = 0,$$

and so, finally we have,

$$\frac{\partial}{\partial\sigma}\lambda_\sigma = \int_0^\infty \left(\frac{\partial}{\partial\sigma}\mathcal{L}_\sigma^*\right)(\phi_\sigma)(y)N_\sigma(y)\,\mathrm{d}y = \int_0^\infty B(y)yN_\sigma(y)\left[\left(\frac{\partial}{\partial y}\phi_\sigma\right)(y\sigma) - \left(\frac{\partial}{\partial y}\phi_\sigma\right)\big(y(1-\sigma)\big)\right]\mathrm{d}y. \qquad \square$$

The equality (9) covers the case where $(\frac{\partial}{\partial\sigma}\mathcal{L}_\sigma^*)_{\sigma=\sigma_0} = 0$ and thus $(\frac{\partial}{\partial\sigma}\lambda_\sigma)_{\sigma=\sigma_0} = 0$ which appears for $\sigma_0 = 1/2$, therefore we need $(\frac{\partial^2}{\partial\sigma^2}\lambda_\sigma)_{\sigma=\sigma_0}$ to find the local behavior of λ_σ in the neighborhood of σ_0. We refer to [5] for the proof of this result in the matrix case. We notice that Theorem 4.1 gives some simple conditions on the dual eigenfunction ϕ_σ to prove the decay or the growth of λ_σ.

Corollary 4.2. *Let σ_0 fixed in $[1/2, 1[$. Assume ϕ_{σ_0} is convex* (*resp. concave*) *then $(\frac{\partial}{\partial\sigma}\lambda_\sigma)_{\sigma=\sigma_0} \geqslant 0$* (*resp. $(\frac{\partial}{\partial\sigma}\lambda_\sigma)_{\sigma=\sigma_0} \leqslant 0$*).

As a consequence we can prove the second part of Theorem 3.1. Indeed, let $\sigma = 1/2$ then using the definition of ϕ_σ, we have $\phi_{1/2}(y) = C\,\mathrm{e}^{\lambda_{1/2}y}$ for all $y \in [0, b/2]$ with $C > 0$. Thus ϕ is convex on $(1/2K) = [a/2, b/2]$ and $(\frac{\partial^2}{\partial\sigma\partial\sigma}\lambda_\sigma)_{\sigma=1/2} > 0$ and $(\frac{\partial}{\partial\sigma}\lambda_\sigma)_{\sigma=1/2} = 0$, therefore λ_σ is locally increasing and $\lambda_{1/2} < \lambda_\sigma$ for some $\sigma > 1/2$.

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