J. Math. Biol. (1999) 38: 241–261

Journal of Mathematical Biology

Cell division and the stability of cellular populations

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Received: 15 January 1996 / Revised version: 31 July 1998

Abstract. This paper couples a general d-dimensional (d arbitrary) model for the intracellular biochemistry of a generic cell with a probabilistic division hypothesis and examines the consequence of division for stability of cell function and structure. We show rather surprisingly that cell division is capable of giving rise to a stable population of cells with respect to function and structure even if, in the absence of cell division, the underlying biochemical dynamics are unstable. In the context of a simple example, our stability condition suggests that rapid cell proliferation plays a stabilizing role for cellular populations.

Key words: Cell division – Stability – Gamma distribution – Measure

1 Introduction

Living organisms are composed of cells, and depending on the complexity of the organism the number of these cells may range from the tens to well over a billion. Each of these cells contains hundreds of intracellular molecular constituents that are constantly being synthesized and degraded, and estimates of the number of concomitant biochemical reactions occurring in a single cells range into the thousands.

In addition to this myriad of biochemical reactions taking place, cells are capable of cell division and most cells go through this process rather frequently. Due, perhaps, to the ubiquitous nature of the cell

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division process the literature is replete with studies related to *how* cells divide [cf. Murray and Hunt (1993) for an especially lucid overview of the state of knowledge at the time of publication]. Indeed, some recent advances in our understanding of a small portion of the dynamics of intracellular biochemistry have been combined with elegant modeling to provide a more comprehensive insight into the connection between intracellular dynamics and the dynamics of the cell division cycle [Goldbeter (1993) and Novak and Tyson (1993a,b)].

However, in spite of the rapid expansion of our knowledge concerning the way in which cells divide, it seems safe to say that there is little insight into the benefit of cell division, i.e. *why* cells divide. Here we examine a heretofore unmentioned potential role for the cell division process. Namely, we show that cell division may serve to confer stability on intracellular biochemical mechanisms that might be unstable in the absence of cell division.

In keeping with the inferred complexity of the biochemistry of the cell division process, this paper presents an analysis of a very general model for the intracellular biochemistry in which it is assumed that every cell contains d substances whose dynamic evolution governs the life history of the cell and its progeny. This general setting is coupled to a probabilistic cell division process. The model is neither one dimensional, nor is it necessarily autonomous and these two aspects of the model exclude the use of more traditional mathematical techniques for analysis employed in previous models of the cell cycle [cf. Lasota and Mackey (1984), Tyson and Hannsgen (1986), Tyrcha (1988), Lasota et al. (1992)].

This paper is organized as follows. Section 2 presents the biological background and derivation of the model that we analyze. This model is shown to be a type of iterated function system. In Sect. 3 we define a Markov operator P on measures which describes the statistical properties of our system and we formulate a criterion for the temporal convergence of the iterates P^n of P. These iterates correspond to consecutive generations of cells. (The proof of our convergence criterion is quite complicated and is postponed to the Appendix.) In Sect. 4 we develop the biological consequences of the convergence properties of the model that we have presented. We believe that these consequences may give some insight into the ubiquitous character of cells and cell division in all living creatures.

2 Biological background and development of the model

We consider a population of cells that proliferate and mature in an environment that may be constant or may vary with time. In keeping

with the very general point of view that we are taking in this work, we assume that each cell contains d substances whose masses (not concentrations) are denoted by the vector

$$y(t) = (y^1(t), \ldots, y^d(t)),$$

wherein t denotes the age of the cells which is the time that has elapsed since the birth of the cell. We assume further that the evolution of the vector $y(t)$ is given by the formula $y(t) = \Pi(x, t)$ where $\Pi(x, 0) = x$. Here $\Pi : X \times [0, T) \to X$ is a given function and X is a closed subset of R^d. A simple example fulfilling these criteria is given by assuming that $y(t)$ satisfies a system of ordinary differential equations

$$\frac{dy}{dt} = g(t, y) \tag{2.1}$$

with the initial condition

$$y(0) = x \tag{2.2}$$

and the solution of (2.1) is given by

$$y(t) = \Pi(x, t).$$

Note that the function g on the right hand side of (2.1) should be sufficiently regular to ensure the existence and uniqueness of the solution of (2.1)–(2.2) in a time interval $[0, T)$, where $T \leqq \infty$.

Having specified the internal dynamics of the cell in a very general way, we must now say something about the mitotic process.

We assume that the distribution of mitotic times $t_{\max}$, at which every cell divides to produce two daughter cells, has the form

$$\text{Prob}(t_{\max} < t) = \int_0^t p(x, s)\, ds \quad \text{for } 0 < t < T, \tag{2.3}$$

where p is a given density depending on the initial vector $y(0) = x$. Clearly since, for every given x, the function p is a density we have

$$\int_0^T p(x, t)\, dt = 1.$$

Remark 2.1. The fact that p depends on x is crucial. For example, in a one dimensional situation, it allows one to prove that the correlation coefficient between the mitotic times of mother and daughter cells is negative [Lasota and Mackey (1984)], as observed experimentally [Powell (1955)].

Let the initial value of substances $x = y(0)$ in the nth generation be denoted by x_n, and the mitotic time $t_{\max}$ in the nth generation by t_n. We

assume that in every generation the distribution of mitotic times is given by (2.3). More explicitly we have

$$\text{Prob}(t_n < t \,|\, x_n = x) = \int_0^t p(x, s)\, ds, \quad \text{for } 0 < t < T, \tag{2.4}$$

Then the vector

$$y(t_n) = \Pi(x_n, t_n)$$

represents the amount of intracellular substance just before mitosis in the nth generation. At division, we assume that each daughter cell receives exactly half of the component constituents of the mother cell, so

$$x_{n+1} = \tfrac{1}{2}\Pi(x_n, t_n) \quad \text{for } n = 0, 1, 2, \ldots . \tag{2.5}$$

Equations (2.4) and (2.5) constitute the analytical description of the mitotic process in our cell cycle model.

From a mathematical point of view, equations (2.4), (2.5) define a discrete time dynamical system with stochastic perturbations in which the times t_n play the role of the perturbations. These times have an interesting property. Namely, the distribution of the time t_n appearing in the formula for x_{n+1} depends on x_n. This makes the system more realistic but also much more difficult to study analytically.

How are we to consider the evolution of the system (2.4), (2.5)? We have, at successive mitoses, a time since the last mitosis with a corresponding density, and a value for the amount of intracellular substance just before the last mitosis. Since it is a basic tenant of cell biology that both cell structure and function are determined by the constellation of substances present in a given cell along with the the actual amounts, it is reasonable to think that the behaviour of (2.4), (2.5) can be described by the sequence of distributions

$$\mu_n(A) = \text{Prob}(x_n \in A) \quad \text{for } n = 0, 1, 2, \ldots ,$$

where A denotes an arbitrary Borel subset of R^d. In the next section, we will discuss the problem of asymptotic behaviour of the sequence $\{\mu_n\}$. In particular we will give sufficient conditions that ensure the convergence of $\{\mu_n\}$ to a *unique* μ_* that is independent of the initial measure μ_0.

From a biological point of view:

1. the initial measure μ_0 just represents the way in which a collection of cells is prepared at the start of, say, an experiment; while
2. the existence of a unique μ_* implies that the evolution of this population from every μ_0 with time ultimately produces a unique population of cells with respect to cell function and structure.

3 Criteria for asymptotic stability

In this section, we study the stochastically perturbed dynamical system (2.4)–(2.5) from a somewhat abstract point of view. We set $S = \frac{1}{2}\Pi$, so the equation (2.5) takes the form

$$x_{n+1} = S(x_n, t_n) \quad \text{for } n = 0, 1, 2, \ldots . \tag{3.1}$$

We make the following assumptions which we assume to hold throughout this section.

1. The function $S: X \times [0, T) \to X$ is continuous.
2. The $\{t_n\}$ are random variables with values in $[0, T)$ and the distribution of t_n conditional on $x_n = x$ is given by

$$\text{Prob}(t_n < t \,|\, x_n = x) = \int_0^t p(x, u)\, du \quad \text{for } 0 < t < T, \tag{3.2}$$

where $p: X \times [0, T) \to [0, T)$ is a lower semi-continuous, non-negative normalized function, i.e.,

$$\int_0^T p(x, t)\, dt = 1 \quad \text{for } x \in X.$$

We use the lower semi-continuity assumption, rather than the (apparently) more natural assumption of continuity, since this ensures that our results are applicable to models in which the density p is not continuous [Tyson and Hannsgen (1986)].

With this preliminary material, we now turn to a derivation of a recurrence relation between μ_{n+1} and μ_n, where μ_n is the distribution of x_n. Let $h: X \to R$ be an arbitrary bounded Borel measurable function. Using our previously developed notation, the mathematical expectation of $h(x_{n+1})$ is given by

$$E(h(x_{n+1})) = \int_X h(x)\mu_{n+1}(dx). \tag{3.3}$$

However, using (3.1) we also have

$$\begin{aligned} E(h(x_{n+1})) &= E(h(S(x_n, t_n))) \\ &= \int_X \left[\int_0^T h(S(x, t))p(x, t)\, dt \right] \mu_n(dx). \end{aligned} \tag{3.4}$$

If we pick $h = 1_A$, where 1_A denotes the indicator function for the set A, and equate (3.3) and (3.4), we obtain

$$\mu_{n+1}(A) = \int_X \left[\int_0^T 1_A(S(x, t))p(x, t)\, dt \right] \mu_n(dx), \tag{3.5}$$

which is the desired recurrence relation between μ_{n+1} and μ_n. Defining an operator P by

$$P\mu(A) = \int_X \left[\int_0^T 1_A(S(x,t))p(x,t)\,dt \right] \mu(dx), \tag{3.6}$$

equation (3.5) may be rewritten as

$$\mu_{n+1} = P\mu_n.$$

The operator P is called the *transition operator* for the system (3.1), (3.2). P is a linear operator in the space $\mathcal{M}_{fin}(X)$ of finite Borel measures on X. In particular, it maps every probability measure into a probability measure, and is thus called a Markov operator [Lasota and Mackey (1994)].

With the customary scalar product notation

$$\langle f, \mu \rangle = \int_X f(x)\mu(dx),$$

the operator U that is adjoint to P is defined by

$$\langle Uf, \mu \rangle = \langle f, P\mu \rangle \quad \text{for } f \in C(X),\ \mu \in \mathcal{M}_{fin}, \tag{3.7}$$

where $C(X)$ denotes the space of all continuous bounded functions $f: X \to R$ with the supremum norm. A straightforward calculation shows that

$$Uf(x) = \int_0^T f(S(x,t))p(x,t)\,dt. \tag{3.8}$$

The space of all probability measures will be denoted by $\mathcal{M}_1$. Clearly P maps $\mathcal{M}_1$ into $\mathcal{M}_1$ and therefore it is natural to take $\mathcal{M}_1$ as the phase space of our dynamical system describing the evolution of μ_n. The operator P describes the dynamics on $\mathcal{M}_1$. We say that the system (3.1), (3.2), or equivalently the transition operator P given in (3.6), satisfies the Prohorov property [Prohorov (1956)] if, for every $\varepsilon > 0$, there is a compact set $Y \subset X$ such that

$$\liminf_{n \to \infty} P^n\mu(Y) \geqq 1 - \varepsilon \quad \text{for } \mu \in \mathcal{M}_1. \tag{3.9}$$

Our goal is to find conditions which ensure the Prohorov property for P. Thus we assume that the continuous function $S: X \times [0, T) \to X$ satisfies the growth condition

$$\|S(x,t)\| \leqq \lambda_0(x,t)\|x\| + \lambda_1(x,t) \quad \text{for } x \in X,\ t \in [0, T) \tag{3.10}$$

where $\|\cdot\|$ is a norm in R^d and $\lambda_i : X \times [0, T) \to R_+$ are Borel measurable nonnegative functions of (x, t) such that

$$\int_0^T p(x, t)\lambda_i(x, t)\, dt \leqq r_i \quad \text{for } i = 0, 1;\ x \in X. \tag{3.11}$$

Inequalities (3.10), (3.11) allow the evaluation of the moments of the measures $P^n\mu$ for $n = 1, 2, \ldots$. Using these evaluations we have the following theorem, proved in the Appendix.

Theorem 3.1. *If conditions* (3.10), (3.11) *are satisfied and if* $r_0 < 1$, $r_1 < \infty$ *then the system* (3.1), (3.2) *has the Prohorov property.*

The Prohorov property can be easily interpreted dynamically. Namely, this condition says that for every $\varepsilon > 0$ there is a set $Y = Y(\varepsilon) \subset X$ such that the set of measures $\{\mu \in \mathscr{M}_1 : \mu(Y(\varepsilon)) \geqq 1 - \varepsilon\}$ is a global attractor. To obtain a more precise description of the behaviour of the sequence $\{P^n\mu_0\}$ we must introduce a topology in $\mathscr{M}_1$.

We say that a sequence of probabilistic measures $\{\mu_n\}$ *converges weakly* to a probabilistic measure μ_* if

$$\lim_{n\to\infty} \langle f, \mu_n \rangle = \langle f, \mu_* \rangle \quad \text{for } f \in C(X).$$

Furthermore, we will say that the system (3.1), (3.2), or equivalently the transition operator P, is *asymptotically stable* if

1. There is a unique measure $\mu_* \in \mathscr{M}_1$ such that

$$P\mu_* = \mu_*,$$

and

2. For every $\mu \in \mathscr{M}_1$, the sequence $\{P^n\mu\}$ converges weakly to μ_*.

To prove the asymptotic stability of system (3.1), (3.2) we must strengthen the properties assumed for the transformation S and the density p. Thus, instead of the growth conditions (3.10), (3.11) we will assume the Lipschitz type inequality

$$\|S(x, t) - S(y, t)\| \leqq \lambda_0(x, t)\|x - y\| \quad \text{for } x, y \in X;\ t \in [0, T) \tag{3.12}$$

where λ_0 and S are related to p by the conditions

$$\int_0^T \lambda_0(x, t)p(x, t)\, dt \leqq r_0 \quad \text{for } x \in X \tag{3.13}$$

and

$$\int_0^T \|S(0, t)\|\, p(x, t)\, dt \leqq r_1 \quad \text{for } x \in X. \tag{3.14}$$

We assume moreover that $p(x, t)$ satisfies an integral Lipschitz condition

$$\int_0^T \| p(x, t) - p(y, t) \| \, dt \leqq r_2 \| x - y \| \quad \text{for } x, y \in X. \tag{3.15}$$

Finally we assume that for every $x \in X$ there exists a minimal division time $\tau_x \in [0, T)$ such that

$$p(x, t) = 0 \quad \text{for } 0 \leqq t \leqq \tau_x \quad \text{and} \quad p(x, t) > 0 \quad \text{for } \tau_x < t < T. \tag{3.16}$$

The suggestive notation τ_x is used to highlight the fact that, biologically, the minimal division time is thought to depend on the initial supply of x.

With this background and these assumptions, we may formulate our criterion for asymptotic stability. The proof will be given in the Appendix.

Theorem 3.2. *If* $S: X \times [0, T) \to X$ *and* $p: X \times [0, T) \to R_+$ *satisfy conditions* (3.12) *through* (3.16) *with* $r_0 < 1$ *and* $r_1, r_2 < \infty$, *then the system* (3.1), (3.2) *is asymptotically stable.*

Observe that in the case when $T < \infty$ and S is defined and continuous in the closed set $X \times [0, T]$ condition (3.14) is automatically satisfied with

$$r_1 = \max_{0 \leqq t \leqq T} \| S(0, t) \|.$$

Analogously, (3.15) is satisfied with a finite r_2, if $T < \infty$, X is the closure of a convex domain and the derivatives p_{x_i} are bounded.

We close this section with a remark which concerns the localization of the support of the invariant measure μ_*. We say that $\mu \in \mathcal{M}_1$ is supported on a measurable set $Y \subset X$ if $\mu(Y) = 1$. A set $Y \subset X$ is called invariant with respect to dynamical system (3.1) if

$$S(x, t) \in Y \quad \text{for } x \in Y, \, t \in [0, T). \tag{3.17}$$

Remark 3.1. If the system (3.1), (3.2) is asymptotically stable and the set $Y \subset X$ is nonempty, closed, and invariant then the stationary measure μ_* is supported on Y. To prove this it is sufficient to start with a point $x_0 \in Y$. From condition (3.17) we have $x_n \in Y$ with probability one and consequently $\mu_n(Y) = 1$. Since Y is closed, this implies $\mu_*(Y) = 1$.

4 Biological consequences

We now return to the biological system (2.4), (2.5) which was derived in Sect. 2. Thus we have

$$S(x_n, t_n) = \tfrac{1}{2}\Pi(x_n, t_n), \tag{4.1}$$

We may also specifically interpret $\Pi(x, t)$ as the solution of the differential equation (2.1) with the initial condition (2.2). Since the solution Π describes the evolution of amounts of real chemicals, it must be the case that Π is non-negative for non-negative x. More precisely, setting

$$X = R_+ \times \cdots \times R_+, \qquad R_+ = [0, \infty),$$

we assume that $\Pi(x, t) \in X$ for $t \in [0, T)$, $x \in X$. Further, we assume that

$$\| \Pi(x_1, t) - \Pi(x_2, t) \| \leqq e^{\alpha(x_1)t} \| x_1 - x_2 \| \quad \text{for } x_1, x_2 \in X,\ t \in [0, T). \tag{4.2}$$

Note that if $\Pi(x, t)$ is the solution of (2.1)–(2.2) and g satisfies a Lipschitz condition with respect to y with Lipschitz constant α, then (4.2) is satisfied with $\alpha(x_1) = \alpha$. Substituting $\lambda_0(x, t) = \frac{1}{2}\exp[\alpha(x)t]$ into (3.13) gives

$$\int_0^T p(x, t) e^{\alpha(x)t}\, dt \leqq 2r_0.$$

As before we assume that $p: X \times [0, T) \to R$ is positive for $\tau_x < t < T$ and vanishes for $0 \leqq t \leqq \tau_x$. Further p is lower semicontinuous, satisfies (3.15) and $\Pi: X \times [0, T) \to X$ is continuous.

Applying Theorem 3.2 to the dynamical system (4.1) we have

Corollary 4.1. *If inequality* (4.2) *is satisfied and if*

$$\sup_x \int_0^T p(x, t) e^{\alpha(x)t}\, dt < 2, \tag{4.3}$$

and

$$\sup_x \int_{\tau_x}^T \| \Pi(0, t) \|\, p(x, t)\, dt < \infty \tag{4.4}$$

then the dynamical system (2.4), (2.5) *is asymptotically stable.*

The factor of 2 that appears on the right hand side of (4.3) is a consequence of the fact that the process of cell division produces two daughter cells, and it is quite important for the eventual stability of the system.

In a general setting, note that for $\alpha(x) \leqq 0$, inequality (4.3) is always satisfied since the left hand side is not larger than 1. To see this, note that for $\alpha(x) \leqq 0$

$$\int_0^T p(x,t)\mathrm{e}^{\alpha(x)t}\,dt \leqq \int_0^T p(x,t)\,dt = 1.$$

If T is finite we may say even more, since if $\max \alpha(x) > 0$, then

$$\int_0^T p(x,t)\mathrm{e}^{\alpha(x)t}\,dt \leqq \mathrm{e}^{T\max\alpha(x)}\int_0^T p(x,t)\,dt = \mathrm{e}^{T\max\alpha(x)},$$

and inequality (4.3) reduces to

$$T\max\alpha(x) < \ln 2.$$

We interpret this to imply that if the cell proliferation process is relatively rapid (T is small), then the system is asymptotically stable even if the underlying dynamics are unstable ($\max \alpha(x) > 0$).

When T is not finite, it is more difficult to make comprehensive statements about stability, but the flavor of the power of our result is given by the following two examples for which all calculations can be carried out completely. Of course, the most important condition is inequality (4.3). All other conditions are relatively easy to verify.

Example 4.1. Let the right hand side g of (2.1) be linear. More precisely we assume that (2.1) reduces to

$$\frac{dy}{dt} = Gy + b(t) \tag{4.5}$$

where G is a $d \times d$ constant matrix and $b:[0,T) \to X$ $(X = (R_+)^d)$ a continuous bounded vector. We denote the eigenvalues of G by $\lambda_1, \ldots, \lambda_d$. Choose a real number α_0 such that

$$\alpha_0 > \max_k \mathrm{Re}\,\lambda_k.$$

Then according to the classical results of Liapunov stability theory, there is a norm in R^d such that (4.2) holds with $\alpha(x) = \alpha_0$. We further assume that for some constant $\tau > 0$

$$p(x,t) = \begin{cases} 0 & \text{for } t \leqq \tau \\ \beta\mathrm{e}^{-\beta(t-\tau)} & \text{for } t > \tau, \end{cases} \tag{4.6}$$

where $\beta > 0$. This means that for $t > \tau$, the number of cells that have not yet divided decays exponentially with time, and the probability

that a single cell divides in the interval $[t, t + \Delta t]$, if it had not yet divided by time t, is constant. More precisely,

$$\text{Prob}(t_{\max} \in [t, t + \Delta t] \,|\, t_{\max} > t) = \beta \Delta t + o(\Delta t) \quad \text{for } t > \tau.$$

This last assumption is identical with the division assumption in the cell cycle model of Smith and Martin (1973).

Substituting (4.6) into (4.3) with $\alpha(x) = \alpha_0$ and $T = \infty$ we obtain, under the assumption that $\beta > \alpha_0$,

$$\beta \int_{\tau}^{\infty} e^{-\beta(t-\tau)+\alpha_0 t}\, dt < 2,$$

or

$$\frac{\beta}{\beta - \alpha_0} e^{\alpha_0 \tau} < 2. \tag{4.7}$$

Further observe that

$$\| \Pi(0, t) \| \leqq \int_0^t \| e^{G(t-u)} b(u) \|\, du \leqq c \int_0^t e^{\alpha_0 (t-u)}\, du \leqq \frac{c}{\alpha_0} e^{\alpha_0 t},$$

where $c = \sup_t \| b(t) \|$. For $\beta > \alpha_0$ we may verify inequality (4.4). Namely

$$\int_0^{\infty} \| \Pi(0, t) \| p(x, t)\, dt \leqq \frac{\beta c}{\alpha_0} \int_{\tau}^{\infty} e^{\alpha_0 t - \beta(t-\tau)}\, dt = \frac{\beta c e^{\alpha_0 \tau}}{\alpha_0 (\beta - \alpha_0)}.$$

Thus, the system under consideration is asymptotically stable if $\beta > \alpha_0$ and (4.7) is satisfied. This happens even for $\alpha_0 > 0$ [which means that the original dynamics leading to the production of y are unstable], when β is sufficiently large and τ is sufficiently small. A small τ and large β are indicative of relatively rapid cell proliferation.

If β is large, then p is concentrated in the vicinity of τ and condition (4.7) has the approximate form

$$\alpha_0 \tau < \ln 2$$

in analogy with the condition derived above for finite T.

Example 4.2. It is well known that the simple exponential distribution of mitotic times of the previous example never adequately describes the actual situation [cf. Powell (1955, 1958) for an especially complete treatment of this subject], and that one can often fit the intermitotic data using the density of the gamma distribution:

$$p(x, t) = \begin{cases} 0 & \text{for } t \leqq \tau \\ \frac{\beta^{k+1}}{\Gamma(k+1)} (t - \tau)^k e^{-\beta(t-\tau)} & \text{for } \tau < t, \end{cases} \tag{4.8}$$

where $\Gamma(\cdot)$ is the gamma function. In this case, in a manner entirely analogous to that of the previous example, it is easy to show that the system is asymptotically stable if $\beta > \alpha_0$ and

$$\left(\frac{\beta}{\beta - \alpha_0}\right)^{k+1} e^{\alpha_0 \tau} < 2, \tag{4.9}$$

a condition that clearly reduces to (4.7) when $k = 0$.

With the density (4.8) it is easy to show that the average intermitotic time is given by

$$\langle t \rangle = \tau + \frac{k+1}{\beta} \tag{4.10}$$

while the variance is

$$\sigma^2 = \frac{k+1}{\beta^2}. \tag{4.11}$$

Thus, writing the parameters k and β of the density (4.8) in terms of the average and variance we have

$$k + 1 = \left(\frac{\langle t \rangle - \tau}{\sigma}\right)^2 \quad \text{and} \quad \beta = \frac{\langle t \rangle - \tau}{\sigma^2} = \frac{k+1}{\langle t \rangle - \tau} \quad \text{with } \langle t \rangle > \tau.$$

These relations, coupled with the stability condition (4.9), imply that at constant k or constant β, stability is associated with smaller values of the average intermitotic time $\langle t \rangle$. Once again, this is in accord with our earlier conclusions concerning the stabilizing effects of relatively rapid proliferation.

The asymptotic stability criterion stated in Corollary 4.1 is formulated in terms of the weak convergence of measures. Thus if the system (2.4)–(2.5) is asymptotically stable the distributions μ_n defined by

$$\mu_n(A) = \text{Prob}(x_n \in A)$$

converge weakly to a unique distribution μ_*. This fact allows one to obtain some information concerning the behaviour of x_n (for example by using some ergodic theorems). However here we are going to show some consequences of the convergence of μ_n to μ_* using the Alexandrov theorem for weak convergence [Billingsley (1968)]. Let $A \subset X$ be a measurable set such that $\mu_*(A) = 1$. Denote by m the Lebesgue measure on X. Since m is regular, for evey $\varepsilon > 0$ there exists an open set $B \supset A$ such that

$$m(B \setminus A) \leqq \varepsilon. \tag{4.12}$$

The set B can also be chosen in such a way that the Hausdorff distance between A and B does not exceed ε, i.e. for every $x \in B$ there is a $y \in A$

such that $\|x - y\| \leqq \varepsilon$. On the other hand, since B is open and μ_n converges weakly to μ_* by the Alexandrov theorem there exists an integer n_0 such that

$$\mu_n(B) \geqq \mu_*(B) - \varepsilon \quad \text{for } n \geqq n_0,$$

and consequently

$$\text{Prob}(x_n \in B) \geqq 1 - \varepsilon \quad \text{for } n \geqq n_0. \tag{4.13}$$

Thus for large n the point x_n is close to A with probability near 1.

This last fact is especially interesting when the measure μ_* is singular. Recall that a measure $\mu_* \in \mathscr{M}_1$ is said to be singular if there is a measurable set $A \subset R^d$ such that

$$m(A) = 0 \quad \text{and} \quad \mu_*(A) = 1. \tag{4.14}$$

In order to show how a singular measure μ_* may appear let us return to equation (4.5) and assume that for every $t \geqq 0$ the vector $b(t)$ belongs to the set

$$\Gamma = \{\lambda b_0 : \lambda \in R_+\},$$

where b_0 is an eigenvector of the matrix G and has nonnegative coordinates. Then b_0 is also an eigenvector for the matrix e^{Gt} and from the formula

$$\Pi(t, x) = \int_0^t e^{G(t-u)} b(u)\, du + e^{Gt} x$$

it follows that Γ is invariant with respect to $S(x, t) = \frac{1}{2}\Pi(x, t)$. Therefore, according to Remark 3.1 the invariant measure μ_* is supported on the one dimensional set Γ. Of course, this is a very special example and in general the measure μ_* is more complicated.

We conjecture, however, that in the space of dynamical systems (3.1), (3.2) (or equivalently (2.4), (2.5)) satisfying conditions (3.12)–(3.16) most of the systems have a singular stationary measure μ_*. This fact may have an important biological consequence. To highlight the biological consequences consider a given system (2.4), (2.5) with a singular μ_*. Then for some $A \subset X$ we have (4.14). In this case, conditions (4.12) and (4.13) imply that

$$m(B) \leqq \varepsilon. \tag{4.15}$$

and

$$\text{Prob}(x_n \in B) = \mu_n(B) \geqq \mu_*(B) - \varepsilon = 1 - \varepsilon \quad \text{for } n \geqq n_0. \tag{4.16}$$

Recall that

$$x_n = (y_n^1(0), \ldots, y_n^d(0))$$

is the composition of substances (at birth) in the nth generation. Conditions (4.15), (4.16) imply, therefore, that with high probability the vector x_n belongs to a small set. This, in turn, means that the composition of substances is not arbitrary and the cell is highly structured. Summarizing, if our conjecture is true the structure of the cell is also to some extent the result of the cell cycle dynamics. For dynamical systems described by a finite number of transformations an analogous conjecture has been proved [Lasota and Myjak (1994)].

Acknowledgements. This research was supported by the State Committee for Scientific Research (Poland) Grant No. 2 PO3A 042 09 to AL, and by the Natural Sciences and Engineering Research Council (Canada) Grant No. A-0091, NATO, the Alexander von Humboldt Stiftung, and the Royal Society of London for MCM.

Appendix: proofs

Here we present the proofs of Theorems 3.1 and 3.2, using the notation of Sect. 3. The proof of Theorem 3.1 is rather elementary, but the proof of Theorem 3.2 is more complicated and based on techniques from the theory of iterated function systems.

Proof of Theorem 3.1. Fix an $\varepsilon > 0$. Define $m_n = \langle h, \mu_n \rangle$, $n = 0, 1, \ldots$, where $h(x) = \|x\|$. Consider first the case $m_0 < \infty$. Using the recurrence formula $\mu_{n+1} = P\mu_n$ and the expression (3.8) for the adjoint operator U we have

$$m_{n+1} = \langle h, P\mu_n \rangle = \langle Uh, \mu_n \rangle = \int_X \left\{ \int_0^T \|S(x,t)\| \, p(x,t)\, dt \right\} \mu_n(dx).$$

From this and inequalities (3.10), (3.11) it follows that

$$\begin{aligned} m_{n+1} &\leqq \int_X \left\{ \|x\| \int_0^T \lambda_0(x,t) p(x,t)\, dt + \int_0^T \lambda_1(x,t) p(x,t)\, dt \right\} \mu_n(dx) \\ &\leqq r_0 \int_X \|x\| \, \mu_n(dx) + r_1 \int_X \mu_n(dx) = r_0 m_n + r_1 . \end{aligned}$$

By an induction argument this gives

$$m_n \leqq r_0^n m_0 + \frac{r_1}{1 - r_0} \quad \text{for } n = 1, 2, \ldots$$

Since $m_0 < \infty$, there exists an integer n_0 such that $m_n \leqq c$ for $n \geqq n_0$ where $c = 1 + r_1/(1 - r_0)$. Using the Chebyshev inequality this implies

$$\mu_n(Y_L) \geqq 1 - \frac{c}{L} \quad \text{for } n \geqq n_0,\ L > 0,$$

where $Y_L = \{x \in X : \|x\| \leqq L\}$. Thus, in the case $m_0 < \infty$ the proof is finished. The general case $m_0 \leqq \infty$ can be reduced to the previous one as follows. For given $\delta > 0$ we choose a compact set $K \subset X$ such that $\mu_0(K) \geqq 1 - \delta$. Setting

$$\bar{\mu}_0(A) = \frac{\mu_0(A \cap K)}{\mu_0(K)}$$

we define a probabilistic measure $\bar{\mu}_0$ supported on K for which the initial moment $\bar{m}_0 = \langle h, \bar{\mu}_0 \rangle$ is finite. Thus, according to the first part of the proof there is a number $n_0 = n_0(\delta)$ such that

$$P^n \bar{\mu}_0(Y_L) \geqq 1 - \frac{c}{L} \quad \text{for } n \geqq n_0,\ L > 0.$$

Since $\mu_0(A) \geqq \mu_0(A \cap K)$, we have

$$P^n \mu_0(Y_L) \geqq \mu_0(K) P^n \bar{\mu}_0(Y_L) \geqq (1 - \delta)\left(1 - \frac{c}{L}\right).$$

Choosing δ sufficiently small and L sufficiently large we obtain

$$P^n \mu_0(Y_L) \geqq 1 - \varepsilon \quad \text{for } n \geqq n_0$$

which completes the proof. □

Proof of Theorem 3.2. The proof is based on the lower bound technique for Markov operators developed in Lasota and Yorke (1994). To apply this method we are going to verify the following three properties of the transition operator P.

1. P has the Prohorov property.
2. For some $L > 0$ the operator is nonexpansive with respect to the Fortet–Mourièr norm [Fortet and Mourièr (1953)] in $\mathcal{M}_1$ given by

$$\|\mu_1 - \mu_2\|_L = \sup\{|\langle f, \mu_1 \rangle - \langle f, \mu_2 \rangle| : f \in F_L\}$$

where F_L is the set of functions $f : X \to R$ satisfying

$$|f(x)| \leqq 1, \quad |f(x) - f(y)| \leqq L\|x - y\| =: \varrho_L(x, y). \tag{A.1}$$

The nonexpansiveness means that

$$\|P\mu_1 - P\mu_2\|_L \leqq \|\mu_1 - \mu_2\|_L \quad \text{for } \mu_1, \mu_2 \in \mathcal{M}_1.$$

3. P satisfies a lower bound condition: For every $\varepsilon > 0$ there is an $\alpha > 0$ such that for every two measures $\mu_1, \mu_2 \in \mathcal{M}_1$ there exists a Borel measurable set A, diam $A < \varepsilon$, and an integer n_0 for which

$$P^{n_0} \mu_k(A) \geqq \alpha \quad \text{for } k = 1, 2.$$

It was shown in Lasota and Yorke (1994) (Theorems 3.1 and 3.9) that if X is a locally compact metric space, then conditions (1)–(3) imply the asymptotic stability of P. In our case X may be considered with the metric ϱ_L. Thus the verification of (1)–(3) will complete the proof.

To prove (1) observe that conditions (3.13) and (3.14) imply (3.10) with $\lambda_1(x, t) = \| S(0, t) \|$. Thus, by Theorem 3.1 the Prohorov property follows.

In order to verify (2) we will use the adjoint operator. We have

$$\begin{aligned} \| P\mu_1 - P\mu_2 \|_L &= \sup \{ | \langle f, P\mu_1 - P\mu_2 \rangle | : f \in \mathscr{F}_L \} \\ &= \sup \{ | \langle Uf, \mu_1 - \mu_2 \rangle | : f \in \mathscr{F}_L \}. \end{aligned}$$

To prove the nonexpansiveness it is sufficient to show that $U(\mathscr{F}_L) \subset \mathscr{F}_L$ for some $L > 0$. Fix an $f \in \mathscr{F}_L$. We have $|f| \leqq 1$ and consequently

$$|Uf(x)| \leqq \int_X |f(S(x, t))| p(x, t)\, dt \leqq \int_X p(x, t)\, dt = 1,$$

so the first condition of (A.1) is satisfied by Uf. Further

$$\begin{aligned} |Uf(x) - Uf(y)| &\leqq \int_0^T |f(S(x, t))p(x, t) - f(S(y, t))p(y, t)|\, dt \\ &\leqq \int_0^T |f(S(x, t))|\, |p(x, t) - p(y, t)|\, dt \\ &\quad + \int_0^T |f(S(x, t)) - f(S(y, t))| p(y, t)\, dt. \end{aligned}$$

Using conditions (A.1) for f this gives

$$\begin{aligned} |Uf(x) - Uf(y)| &\leqq \int_0^T |p(x, t) - p(y, t)|\, dt \\ &\quad + L \int_0^T \| S(x, t) - S(y, t) \| p(y, t)\, dt. \end{aligned}$$

According to (3.15), (3.12) and (3.13) we finally obtain

$$|Uf(x) - Uf(y)| \leqq (r_2 + r_0 L) \| x - y \|$$

which for $L = r_2/(1 - r_0)$ reduces to

$$|Uf(x) - Uf(y)| \leqq L \| x - y \|.$$

Therefore the second condition of (A.1) is satisfied by Uf and $Uf \in \mathscr{F}_L$. The nonexpansiveness of P is verified.

Now we are going to show condition (3) holds, which is the most difficult part of the proof. By the Prohorov property there exists a compact set $Y \subset X$ such that for every $\mu \in \mathscr{M}_1$ we may find an integer $n_* = n_*(\mu)$ for which

$$P^n\mu(Y) \geqq \tfrac{1}{2} \quad \text{if } n \geqq n_*(\mu).$$

Now let an $\varepsilon > 0$ be given. We can find an integer m such that

$$4r_0^m \operatorname{diam} Y \leqq \varepsilon.$$

Consider a pair $(x, y) \in X^2$. Suppose first that $\tau_x \geqq \tau_y$. From inequality (3.13) it follows that there exists a value $\bar{t}_1 \in (\tau_x, T)$ such that $\lambda_0(x, \bar{t}_1) \leqq r_0$. Thus, according to (3.12) we have

$$\| S(x, \bar{t}_1) - S(y, \bar{t}_1) \| \leqq r_0 \| x - y \|.$$

Moreover, since $\bar{t}_1 \in (\tau_x, T) \subset (\tau_y, T)$ we have

$$p(x, \bar{t}_1) > 0, \quad p(y, \bar{t}_1) > 0.$$

If $\tau_y \geqq \tau_x$ we may obtain the same result by first choosing an appropriate number $\bar{t}_1 \in (\tau_y, T)$. Thus by an induction argument for every pair $(x, y) \in X^2$ we may construct a sequence $(\bar{t}_1, \dots, \bar{t}_m)$, $\bar{t}_i = \bar{t}_i(x, y)$ such that

$$|S_m(x, \bar{t}_1, \dots, \bar{t}_m) - S_m(y, \bar{t}_1, \dots, \bar{t}_m)| \leqq r_0^m \| x - y \| \tag{A.2}$$

$$p_m(x, \bar{t}_1, \dots, \bar{t}_m) > 0, \qquad p_m(y, \bar{t}_1, \dots, \bar{t}_m) > 0, \tag{A.3}$$

where the functions S_k $(k = 1, 2, \dots)$ are defined by the recurrence relations

$$S_1(x, t_1) = S(x, t_1), \quad S_{k+1}(x, t_1, \dots, t_{k+1}) = S(S_k(x, t_1, \dots, t_k), t_{k+1}),$$
$$k = 1, 2, \dots$$

and

$$p_k(x, t_1, \dots, t_k) = p(x, t_1) \cdots p(S_{k-1}(x, t_1, \dots t_{k-1}), t_k).$$

By the continuity of S and lower semi-continuity of p, for every $(x, y) \in Y^2$ there exist neighborhoods N_x of x, N_y of y and positive numbers $\delta = \delta(x, y)$, $\sigma = \sigma(x, y)$ such that

$$\| S_m(u, t_1^1, \dots, t_m^1) - S_m(v, t_1^2, \dots, t_m^2) \| \leqq r_0^m \| x - y \| + \frac{\varepsilon}{4}$$

$$\leqq r_0^m \operatorname{diam} Y + \frac{\varepsilon}{4} \leqq \frac{\varepsilon}{2} \tag{A.4}$$

and

$$p_m(u, t_1^1, \dots, t_m^1) \geqq \sigma(x, y), \qquad p_m(v, t_1^2, \dots, t_m^2) \geqq \sigma(x, y) \tag{A.5}$$

for $u \in N_x$, $v \in N_y$ and $|t_i^k - \bar{t}_i(x, y)| \leqq \delta(x, y)$ $(i = 1, \dots, m;\ k = 1, 2)$. Since Y^2 is a compact set, there is a finite covering

$$(N_{x_1} \times N_{y_1}) \cup \cdots \cup (N_{x_q} \times N_{y_q}) \supset Y^2. \tag{A.6}$$

Define

$$\delta = \min_{1 \leqq i \leqq q} \delta(x_i, y_i), \qquad \sigma = \min_{1 \leqq i \leqq q} \sigma(x_i, y_i).$$

We are going to show that P satisfies condition (3) with $\alpha = \sigma\delta^m/4q$. Let $\mu_1, \mu_2 \in \mathscr{M}_1$ be given. By the Prohorov property there is an integer $\bar{n} = \bar{n}(\mu_1, \mu_2)$ such that

$$P^n\mu_k(Y) \geqq \tfrac{1}{2} \quad \text{for } n \geqq \bar{n},\ k = 1, 2.$$

Let $\bar{\mu}_k = P^{\bar{n}}\mu_k$. Then $(\bar{\mu}_1 \times \bar{\mu}_2)(Y^2) \geqq \frac{1}{4}$ and according to (A.6)

$$(\bar{\mu}_1 \times \bar{\mu}_2)(N_{x_j} \times N_{y_j}) \geqq \frac{1}{4q} \tag{A.7}$$

for some integer j, $1 \leqq j \leqq q$. Fix this integer and set $N_1 = N_{x_j}$ and $N_2 = N_{y_j}$ for simplicity. Since the $\bar{\mu}_i$ are probabilistic, (A.7) implies

$$\bar{\mu}_k(N_k) \geqq \frac{1}{4q} \quad \text{for } k = 1, 2. \tag{A.8}$$

Now define $\tilde{t}_i = \bar{t}_i(\bar{x}_j, \bar{y}_j)$, $i = 1, \dots, m$, and

$$A = A_1 \cup A_2,$$

where

$$A_k = \{S_m(u, t_1, \dots, t_m) : u \in N_k, \quad |t_i - \tilde{t}_i| \leqq \delta\ (i = 1, \dots, m)\} \quad \text{for } k = 1, 2.$$

From inequalities (A.4) it follows that diam $A \leqq \varepsilon$ and from (A.5) that

$$p_m(u, t_1, \dots, t_m) \geqq \sigma \quad \text{for } u \in A, \qquad |t_i - \tilde{t}_i| \leqq \delta. \tag{A.9}$$

Let $n_0 = \bar{n} + m$. We have

$$P^{n_0}\mu_k(A) = P^m\bar{\mu}_k(A) = \langle U^m 1_A, \bar{\mu}_k \rangle \geqq \langle U^m 1_{A_k}, \bar{\mu}_k \rangle.$$

Using equation (3.8) m times, this inequality may be rewritten in the form

$$P^{n_0}\mu_k(A) \geqq \int_X \left\{ \int_0^T \cdots \int_0^T 1_{A_k}(S_m(x, t_1, \dots, t_m)) p_m(x, t_1, \dots, t_m)\, dt_1 \dots dt_m \right\} \bar{\mu}_k(dx).$$

For $x \in N_k$ and $|\tilde{t}_i - t_i| \leqq \delta$ we have $S_m(x, t_1, \ldots t_m) \in A_k$. This and inequality (A.9) allow us to evaluate the multiple integral from below. Namely

$$P^{n_0}\mu_k(A) \geqq \sigma\delta^m \bar{\mu}_k(N_k)$$

which, according to (A.8), finally gives

$$P^{n_0}\mu_k(A) \geqq \sigma\delta^m/4q = \alpha.$$

Condition (3) is thus verified and the proof of Theorem 3.2 is completed.

The proof presented above for Theorem 3.2 was quite long and complicated. However, until now this seems to be the state of the art and known proofs of the asymptotic stability for dynamical systems described by a finite number of transformations and state dependent distributions are also difficult [Barnsley et al. (1988), Lasota and Yorke (1994)]. Since we deal with an infinite family $S(x, t)$ parametrized by a continuous parameter $t \in [0, T)$, the situation is even more delicate. The density distribution function $p(x, t)$ of variables t_n depends on x. For some values of x it can be small or even equal to zero. This property of p, important from the biological point of view, does not allow us to easily exploit the contracting assumption (3.12) and in particular to use the Banach fixed point theorem. The asymptotic stability we have proved results not only from contracting properties of transformation S but also from positivity conditions (3.16) concerning p. We illustrate the importance of those conditions by the following example.

Example A.1. Consider the dynamical system (3.1) acting on the interval $X = [0, 3]$ with $t_n \in [0, 3)$. We assume that the transformation S is defined by

$$S(x, t) = t \quad \text{for } 0 \leqq x \leqq 3,\ 0 \leqq t < 3.$$

Thus, in fact S does not depend on x and the system (3.1) reduces to $x_{n+1} = t_n$. We assume that the conditional density distribution function $p(x, t)$ of random variables t_n is given by the formula

$$p(x, t) = \begin{cases} p_1(t) & \text{for } 0 \leqq x \leqq 1 \\ (2 - x)p_1(t) + (x - 1)p_2(t) & \text{for } 1 < x < 2 \\ p_2(t) & \text{for } 2 \leqq x \leqq 3, \end{cases}$$

where

$$p_1(t) = \max(2 - 2t, 0), \qquad p_2(t) = \max(2t - 4, 0) \quad \text{for } 0 \leqq t < 3.$$

Evidently all the assumptions of Theorem 3.2 are satisfied except (3.16). We have instead

$$p(x, t) = 0 \qquad \text{for } 0 \leqq x \leqq 1,\ 1 \leqq t < 3$$

and

$$p(x, t) = 0 \qquad \text{for } 2 \leqq x \leqq 3,\ 0 \leqq t \leqq 2.$$

These properties imply that for $x_0 \in [0, 1]$ the random variable

$$x_1 = S(x_0, t_0) = t_0$$

belongs to $[0, 1]$ with probability one and further by induction $x_n \in [0, 1]$ with probability one for every $n \geqq 0$. Analogously, if $x_0 \in [2, 3]$ then also $x_n \in [2, 3]$ with probability one for $n \geqq 0$. Thus, in the first case $\mu_n([0, 1]) = 1$ and in the second $\mu_n([2, 3]) = 1$. This shows that the system under consideration in not asymptotically stable. □

In the proof of Theorem 3.2 not all assumptions were fully exploited. We have not used the homogeneity of the norm $\|\cdot\|$ but only the triangle inequality. This fact is summarized in the following remark.

Remark A.1. Theorem 3.2 remains true if $S: X \times [0, T) \to X$ is continuous, $p: X \times [0, T) \to R_+$ lower semi-continuous and the conditions (3.12) through (3.16) are satisfied with $r_0 < 1$; $r_1, r_2 < \infty$. Under these conditions the distance $\|x - y\|$ may be replaced by an arbitrary metric $\varrho(x, y)$ generating the same standard topology in R^d and in particular the norm $\|x\|$ by $\varrho(x, 0)$.

The above remark can be quite useful when we look for possible sharp estimations which ensure the asymptotic stability. For example using Remark A.1 it is possible to find precise description of the region of asymptotic stability for the well known Tyson–Hannsgen (1986) model of the cell cycle. We omit, however the details here, since this model has been examined elsewhere [see Tyrcha (1988) and Lasota et al. (1992)].

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