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I
Structured Populations

1
Analysis of a Cell Population Model with Unequal Division and Random Transition

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I. INTRODUCTION

In recent years we have witnessed considerable progress in the development of the theoretical tools of population dynamics. One of the most important is the theory of semigroups of positive linear operators. The foundations and basic results of this theory can be found in the book edited by Nagel (1986) and, in a more application-oriented manner, in a volume edited by Metz and Diekmann (1986). The principal use of semigroup theory in such models is to characterize the long-term behavior of dynamical systems, including a description of the inner structure of the population.

In this paper we are interested in those aspects of the theory that concern models of dynamics of cell populations of the type introduced in Kimmel et al. (1984) and investigated in Arino and Kimmel (1987, 1989) and in Sanchez et al. (1989). The philosophy of constructing these models differs from the usual approach based on partial differential equations. [This difference is clear, for example, from Example 3 in Webb's (1987) basic paper on cell cycle models.]

The models that we are interested in describe the regulation mechanisms of the cell cycle, starting from the birth mass of cells, with unequal division of mass between daughter cells being an important factor. The first analysis of a model of this type, published in Arino and Kimmel (1987), was carried out by these authors in 1984, when this paper was submitted, independent of the collection of uniform-

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ized results edited by Nagel (1986). Accordingly, this analysis, although also based on semigroup theory, included many details not covered by the uniformized approach. This model has also been quoted in Nagel (1986) as Example C.IV.3.11, unfortunately with improper assumptions.

In the present paper we look at the analysis of the model of Kimmel et al. (1984) and Arino and Kimmel (1987), slightly generalized for this paper, from the viewpoint of the general theory of positive semigroups. After preliminaries, we prove that the model gives rise to a semigroup of positive linear bounded operators, and that this semigroup is strongly continuous, eventually compact, and in some sense irreducible. From these properties we prove the result on asymptotic exponential growth of solutions.

II. MODEL DERIVATION, ASSUMPTIONS, AND SUPPORT PROPERTY

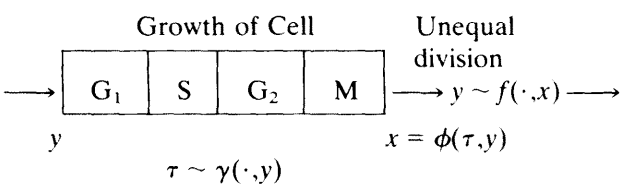
A. Derivation

We proceed as in Kimmel et al. (1984). The most important notion of the model is the distribution of cell mass flux at the beginning of the G_1 phase (the onset of the cell cycle). It is denoted by $n(t,y)$ and treated as an unnormed distribution density of the pair (t,y) (see the remark below).

The interpretation is that $n(t,y)\,dt\,dy$ is equal to the number of cells with mass between y and $y + dy$ that entered G_1 in the time inteval from t to $t + dt$. The following assumptions define the model.

1. Suppose that a mitotic cell just before division has mass x. The density of probability of the daughter cell's mass y, conditional on x, is denoted by $f(y,x)$. It is necessary that $f(y,x) = 0$, whenever $y > x$, and that $f(x - y, x) = f(y,x)$.
2. The fate of the daughter cell produced during division, which reenters the cycle with initial mass y, is described in probabilistic terms:
   a. The time τ it spends in the cycle is a random variable with conditional distribution density $\gamma(\tau,y)$, given y.
   b. The mass x of this cell when it reenters division is a function $\phi(\tau,y)$ of the time it spends in the cycle and of its birth mass y.

These hypotheses are depicted as follows:



The derivation of the model equation is carried out in several successive steps. Let us first suppose that cells spend in the cycle exactly τ time units and have birth mass equal to ξ. Then the distribution density of the flux at the beginning of the next G_1 phase is equal to

$$2f[y, \phi(\tau,\xi)] \tag{1}$$

But τ is distributed with density $\gamma(\cdot,\xi)$ conditional on ξ and ξ is distributed with density $n(s,\xi)$ at time s. Therefore, the distribution density of the pair (τ,ξ) is equal to

$$\gamma(\tau,\xi)n(s,\xi) \tag{2}$$

Consequently, the joint density $\tilde{n}(s + \tau, y; \tau, \xi)$ (contribution to the flux density through next G_1 of cells of size ξ at their birth which spend time τ in the cycle and which were born at time s with size y) is equal to the product of (1) and (2). After a change of variables $(s,y;\tau,\xi)$ into $(t,y;\tau,\xi)$, where $t = s + \tau$ (the Jacobian is equal to 1), we obtain

$$\tilde{n}(t,y;\tau,\xi) = 2f[y,\phi(\tau,\xi)]\gamma(\tau,\xi)n(t - \tau, \xi) \tag{3}$$

Continuity of the flow requires that $n(t,y) = \int\int \tilde{n}(t,y;\tau,\xi)\, d\tau\, d\xi$. Integrating (3) provides the equation of the model,

$$n(t,y) = 2\int_0^\infty \int_0^\infty f[y, \phi(\tau,\xi)]\gamma(\tau,\xi)n(t - \tau, \xi)\, d\xi\, d\tau \tag{4}$$

Remark. The derivation outlined above includes intuitive manipulations on informal unnormed densities. These manipulations can be formalized if $n(\cdot)$ and $\tilde{n}(\cdot)$ are treated as densities of the expectations of counting measures of a branching process describing our model [as in Kimmel (1983)].

The expression for the total number $N(t)$ of cells present at time t is derived in the following way. The density of cell flux through G_1, including cells born with size y at time s which spend time τ in the cycle, is equal to $n(s,y)\gamma(\tau,y)$. The population at time t includes cells born between $t - \tau$ and t:

$$\begin{aligned} N(t) &= \int_0^\infty \int_0^\infty \int_{t-\tau}^t n(s,y)\gamma(\tau,y)\, ds\, d\tau\, dy \\ &= \int_0^\infty \int_0^t n(s,y)\bar{\Gamma}(t - s, y)\, ds\, dy \end{aligned} \tag{5}$$

where $\bar{\Gamma}$ is the tail of the distribution of cell cycle length [i.e., $\bar{\Gamma}(u,y) = \int_u^\infty \gamma(\tau,y)d\tau$].

B. Assumptions

We proceed to specifying the basic hypotheses on functions f, γ, and ϕ, which formalize the requirements of cell cycle dynamics.

(H_f) $f \in L^1_{\text{loc}}(\mathbb{R}^2_+)$; $f \geq 0$; $\int_0^\infty f(y,x)\, dy = 1$; $f(x - y,x) = f(y,x)$; $f(y,x)$ is nonnegative and there exists $d_1 \in (0,\frac{1}{2})$ such that $f(y,x)$ is positive if and only if $y \in (d_1x, d_2x)$, where $d_2 = 1 - d_1$.

(H_γ) $\gamma \in L^1_{\text{loc}}(\mathbb{R}^2_+)$; $\int_0^\infty \gamma(\tau,x)\, d\tau = 1$; $\gamma(t,y)$ is nonnegative and there exist two continuous decreasing functions τ_1 and τ_2 such that $\lim_{\xi\to\infty} \tau_1(\xi) > 0$; $\tau_1 < \tau_2$, and $\gamma(\tau,\xi)$ is positive if and only if $\tau \in (\tau_1(\xi), \tau_2(\xi))$.

(H_ϕ) $\phi \in C_{\text{loc}}(\mathbb{R}^2_+)$; $\phi \geq 0$; $\phi(\cdot,\xi)$ *and* $\phi(\tau,\cdot)$ is increasing.

The assumptions on f express the fact that $f(\cdot,x)$ is the density of the con-

ditional distribution of the mass of daughter cell provided that the mass of the mother cell is x. The support property reflects the fact that the mass partition to daughter cells may not exceed a maximum degree of inequality.

The assumptions on γ express the fact that $\gamma(\cdot,\xi)$ is the density of the conditional distribution of the cell cycle duration given the birth mass of the cell ξ. The support property takes into account the following requirements; (1) cell cycle time varies only in certain limits; (2) it should be in inverse relationship to the birth mass; and (3) a minimum cell cycle time is required even for cells with large birth mass.

The assumptions on ϕ express the fact that the mass at division of the cell is larger for cells with higher birth mass and cells that stay longer in the cycle.

The assumptions that f and γ are positive on the entire corresponding intervals are technical. They are needed for the proof of Lemma 5. We see that, strictly speaking, f and γ are classes of functions. Due attention will be given to this point at the only place where it is needed, which is again the proof of Lemma 5.

C. Support Properties

It is reasonable from the biological viewpoint to require that the support with respect to the variable y of the solution $n(t,y)$, starting from any nonnegative initial data, be confined to a bounded interval I, separated from 0. The interpretation is that the regulation mechanisms of the cell cycle eliminate cells that are very small or very large.

Generally, to formally construct a solution of equation (4), after time t_0, it is necessary to know it on the set $\{(t,y) : t_0 - \tau_1(y) > t > t_0 - \tau_2(y),\ y > 0\}$. Along the solution n, the restriction of n to $\Delta_t = \{(s,y) : s \in (t - \tau_2(y),\ t - \tau_1(y)),\ y > 0\}$ comprises the data necessary and sufficient to continue the solution. We will adopt the standard notation (Hale, 1977)

$$\begin{aligned} &n_t(s,y) = n(t+s,y); \qquad t \geq 0, \quad (s,y) \in \Delta \\ &\Delta = \{(s,y) : y > 0,\ s \in (-\tau_2(y), 0)\} \end{aligned} \tag{6}$$

We prove the existence and some properties of the solution in the next section.

The fact that $n(t,\cdot)$ has a bounded support contained in $I = [A_1,A_2]$ implies that the system (4) has maximum and minimum delays θ_2 and θ_1,

$$\theta_1 = \tau_1(A_2), \qquad \theta_2 = \tau_2(A_1) \tag{7}$$

Therefore, the initial data can be restricted to Δ and the solution constructed in steps of length θ_1. Based on hypotheses (H_f), (H_γ), and (H_ϕ), the following implication is true:

$$\begin{aligned} &\operatorname{supp} n_0(s,\cdot) \subset I = [A_1,A_2]. \\ &\qquad \Rightarrow \forall t \in [0,\theta_1],\ \operatorname{supp} n(t,\cdot) \subset \overline{\{\eta \geq 0 : \eta \in [\phi_1(\xi), \phi_2(\xi)],\ \xi \in I\}} \end{aligned} \tag{8}$$

where

$$\phi_i(\xi) = d_i \phi[\tau_i(\xi), \xi], \qquad i = 1,2,\ \xi \in \mathbb{R}_+ \tag{9}$$

Functions ϕ_i are not, in general, monotone, which may complicate the analysis of the support properties. We will restrict ourselves to the case corresponding to one possible variant of cell cycle regulation (see Figure 1):

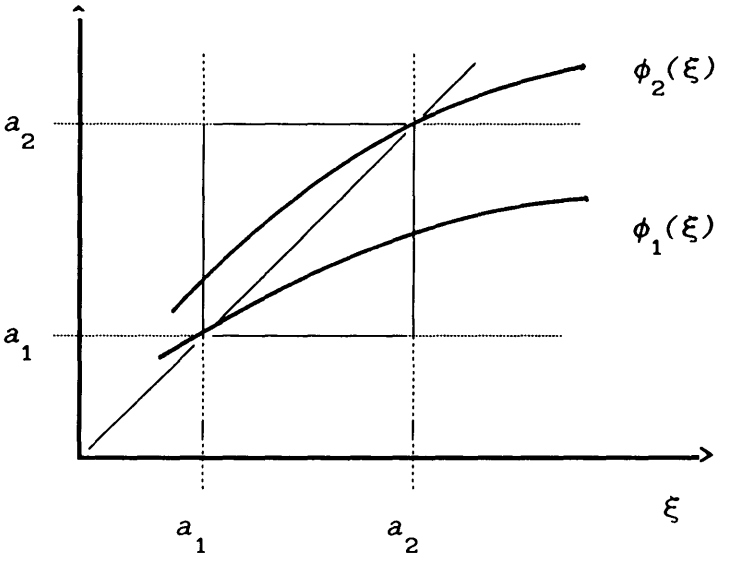


Figure 1 Support hypotheses for the model.

(H*) ϕ_i is increasing; $\phi_i(\xi) > \xi$, $\xi < a_i$; $\phi_i(a_i) = a_i$, $\phi_i(\xi) < \xi$, $\xi > a_i$; $i = 1,2$; where $0 < a_1 < a_2 < \infty$ are constants.

We will summarize certain properties of functions ϕ_i in the following lemma (stated without proof).

Lemma 1. Suppose that (H*) is satisfied. Let us define two sequences $\{\underline{\xi}_n\}$ and $\{\bar{\xi}_n\}$ such that $\underline{\xi}_0 = \bar{\xi}_0 = \xi \in \mathbb{R}_+$ and $\underline{\xi}_{n+1} = \phi_1(\underline{\xi}_n)$, $\bar{\xi}_{n+1} = \phi_2(\bar{\xi}_n)$. Then $\underline{\xi}_n \to a_1$, $\bar{\xi}_n \to a_2$, as $n \to \infty$. Moreover, $\xi < a_1 \Rightarrow \underline{\xi}_{n+1} > \underline{\xi}_n$, $\xi > a_1 \Rightarrow \underline{\xi}_{n+1} < \underline{\xi}_n$, $\xi < a_2 \Rightarrow \bar{\xi}_{n+1} > \bar{\xi}_n$, $\xi > a_2 \Rightarrow \bar{\xi}_{n+1} < \bar{\xi}_n$.

Application of Lemma 1 and implication (8) allow us to state the basic support property. The proof, which is elementary, is omitted.

Lemma 2. Let us choose $I = [A_1, A_2]$ such that $0 < A_1 \le a_1 \le a_2 < A_2 < \infty$. Then if

$$\operatorname{supp} n_0(s,\cdot) \subset I = [A_1, A_2], \qquad s \in [-\theta_2, 0]$$

then

$$\operatorname{supp} n(t,\cdot) \subset [\phi_1(A_1), \phi_2(A_2)] \subset I, \qquad t > 0$$

Therefore, $\operatorname{supp} n(t,\cdot)$ is asymptotically contained in $[a_1, a_2]$.

III. SEMIGROUP AND ASYMPTOTIC BEHAVIOR

As mentioned before, the solution $n(t,y)$ of equation (4) can be uniquely extended by steps of length θ_1 starting from initial data on $\Delta = \{(s,y) : , s \in (-\tau_2(y), 0), y \in I\}$. Lemma 2 assures that the support of solutions does not leave the strip $\mathbb{R}_+ \times I$. We will show that the solution exists in the L^1 sense.

Indeed, integrating (1), we obtain

$$\int_0^{\theta_1}\int_I |n(t,y)|\,dy\,dt \le 2\int_0^{\theta_1}\int_{\theta_1}^{\theta_2}\int_I \gamma(\tau,\xi)|n_0(t-\tau,\xi)|\,d\xi\,d\tau\,dt$$
$$\le 2\int_I\left[\int_{\theta_1}^{\theta_2}\gamma(\tau,\xi)\,d\tau\int_{-\theta_2}^{0}|n_0(s,\xi)|\,ds\right]d\xi$$
$$\le 2\int_I\int_{-\theta_2}^{0}|n_0(s,\xi)|\,ds\,d\xi$$

(In the integrations above, the initial data n_0 are treated as defined on the rectangle $[-\theta_2,0]\times I$, and equal to zero outside Δ.) The results can be restated as

$$\|n\|_{L^1((0,\theta_1)\times I)} \le 2\|n_0\|_{L^1(\Delta)} \tag{10}$$

We will accept $L^1(\Delta)$ as the basic space and call it X. Equation (10) yields

$$\|n_t\|_X \le 3\|n_0\|_X, \qquad t\in(0,\theta_1) \tag{11}$$

Lemma 3. Suppose that hypotheses (H_f), (H_γ), (H_ϕ), and (H^*) are satisfied. If $n_0 \ge 0$ belongs to $X = L^1(\Delta)$, then there exists a function $n\colon \Omega \to \mathbb{R}$, where $\Omega = \Delta \cup (\mathbb{R}_+ \times I)$, $n \ge 0$, $n \in L^1_{\mathrm{loc}}(\Omega)$; which verifies (11) almost everywhere in Ω; and $\lim_{t\to 0} n_t = n_0$ in X. The solution is unique in the sense of an equivalence class in $L^1_{\mathrm{loc}}(\Omega)$.

Proof. Existence of solutions is obtained by iteration of the a priori estimate (11). Uniqueness and nonnegativity are obvious. Continuity of n_t at $t = 0^+$ is implied by continuity of translations in L^1.

Corollary 1. The family of mappings $\{G(t), t \ge 0\}$,

$$G(t) : X \ni n_0 \to n_t \in X \tag{12}$$

is a strongly continuous semigroup of positive bounded linear operators on X.

The next result requires additional hypotheses regarding the conditional distributions f and γ.

(H'_f) $f \in L^\infty_{\mathrm{loc}}(\mathbb{R}^2_+)$.
(H'_γ) $\gamma \in L^\infty_{\mathrm{loc}}(\mathbb{R}^2_+)$.

Lemma 4. Under the hypotheses of Lemma 3 supplemented by (H'_f) and (H'_γ), $G(t)$ is compact from X into X for any $t > 2\theta_2$.

Proof. Under (H'_f) and (H'_γ), $n_{|(0,\infty)\times I} \in L^\infty_{\mathrm{loc}}((0,\infty)\times I)$. It is then enough to observe that the map $K\colon L^\infty((0,\theta_2)\times I) \to L^1((\theta_2,\theta_2+\theta_1)\times I)$, defined by

$$n(t,y) = (Kn)(t,y) = 2\int_{t-\theta_2}^{t-\theta_1}\int_I f[y,\phi(t-\tau,\xi)]\gamma(t-\tau,\xi)n(\tau,\xi)\,d\xi\,d\tau$$
$$= 2\int_0^{\theta_2}\int_I g(t,y;\tau,\xi)n(\tau,\xi)\,d\xi\,d\tau \tag{13}$$

is compact as being defined by the integrable kernel g. Indeed, g can be approximated in the norm of L^1 by continuous functions with compact support. The corresponding operators approximate K in the operator norm from L^∞ into L^1 and, by the Ascoli theorem, they are compact, even as operators from L^∞ into C. So K is compact as a norm limit of compact operators.

Remark. This lemma can also be proved with (H_f') and (H_γ') replaced by the weaker hypothesis that the operator K in the proof above is weakly compact. It is, however, difficult to find weaker assumptions on f and γ implying the weak compactness of K. We will denote A the generator of G, $\mathcal{D}(A)$ its domain.

We now define X_1 (respectively, X_2) as the set of functions in X that vanish when the y component of the variable is outside (respectively, inside) the interval $[a_1,a_2]$. X is the direct sum of X_1 and X_2, and X_1 (not X_2) is stable under G (Lemma 2). The definition of an irreducible semigroup can be found in Nagel (1986, Definition C-III.3.1).

Let us notice that $G_{|X_1}$ is a semigroup with generator $A_{|\mathcal{D}(A)\cap X_1}$.

Lemma 5. The restriction of G to X_1 is irreducible.

Remark. From Lemma 2 it follows that $\{G(t)\}$ is not irreducible if $I = [A_1,A_2]$ with $A_1 < a_1$ or $a_2 < A_2$. To see this, let us select n_0, $n \in X$, such that $\operatorname{supp} n(s,\cdot) \subset I \backslash [a_1,a_2]$, while $\operatorname{supp} n_0(s,\cdot) \subset [a_1,a_2]$.

Proof of Lemma 5. We want to check the equivalent form (iii) of the definition in Nagel (1986): namely, in our notation,

$$\forall\ (n_0,\ u \in X_1,\ n_0,\ u > 0)\ \exists (t_0 > 0),\ \text{such that } \inf[G(t_0)n_0,\ u] > 0 \tag{14}$$

n denotes the solution with initial data n_0 such that

$$G(t)n_0(\tau,\xi) = n_t(\tau,\xi) = n(t + \tau,\xi)$$

For any (τ,ξ) with $\xi \in (a_1,a_2)$ and $\tau > -\tau_2(\xi)$, we define the set

$$S_0(\tau,\xi) = \{(s,y) : s \in (\tau + \tau_1(\xi),\ \tau + \tau_2(\xi)),\ y \in (d_1\phi(s - \tau,\ \xi),\ d_2\phi(s - \tau,\ \xi)\}$$

and notice some of its properties. It is an open connected set. If (τ,ξ) is a point of density of the set $\{(s,x) : n(s,x) > 0\}$ (we will write, for brevity, a point of density of n), then n is positive on $S_0(\tau,\xi)$. The boundary of $S_0(\tau,\xi)$ contains the points $(\tau + \tau_1(\xi),\ \phi_1(\xi))$ and $(\tau + \tau_2(\xi),\ \phi_2(\xi))$, so $S_0(\tau,\xi)$ contains an arc joining these two points (endpoints excluded). As a consequence, for every y in $(\phi_1(\xi),\ \phi_2(\xi))$, there is a point (s,y) in $S_0(\tau,\xi)$. Finally, $S_0(\tau,\xi)$ contains points (s,y) with s positive.

Let (σ,η) and (τ_0,ξ_0) be points of density of u and n_0, respectively. We first take some point $(\tau_1,\xi_1) \in S_0(\tau_0,\xi_0)$ with τ_1 positive. We then define a sequence of sets and two sequences of numbers in the following way:

$$S_1 = \{(\tau_1,\xi_1)\}; \qquad S_{k+1} = \bigcup_{(\tau,\xi)\in S_k} S_0(\tau,\xi)$$

$$\alpha_1 = \xi_1, \qquad \alpha_{k+1} = \phi_1(\alpha_k)$$

$$\beta_1 = \xi_1, \qquad \beta_{k+1} = \phi_2(\beta_k)$$

n is positive on S_k, which is open for $k > 1$, and for every $y \in (\alpha_k,\beta_k)$ there is an s such that $(s,y) \in S_k$.

For k large enough, η belongs to (α_k,β_k) (Lemma 1), so that there is a number s such that n is positive on a neighborhood of (s,η). Let us set $t_0 = s - \sigma$, which implies that $G(t_0)n$ is positive on a neighborhood of (σ,η) as $\eta_{t_0}(\sigma,\eta) = n(s,\eta)$. It can be checked that t_0 is positive. As (σ,η) is a point of density of u, u is positive on a subset of positive measure of that neighborhood, which in turn implies (14).

We may now state the main result of this section.

Theorem 1. Suppose that hypotheses (H_f), (H_f'), (H_γ), (H_γ'), (H_ϕ), and (H^*) are satisfied. Then, for any initial data $n_0 > 0$, the semigroup exhibits asymptotic exponential growth, that is,

$$G(t)n_0 = C_{n_0}e^{\lambda^* t}\mu^* + o(e^{\lambda^* t}) \tag{15}$$

where $C_{ro} > 0$ is a constant depending on the initial data, $\lambda^* > 0$, $\mu^* \in L^1$ is nonnegative with support $[a_1,a_2]$, and (λ^*,μ^*) satisfy the equation

$$\mu(y) = 2\int_{\theta_1}^{\theta_2}\int_{a_1}^{a_2} f[y, \phi(\tau,\xi)]\gamma(\tau,\xi)e^{-\lambda\tau}\mu(\xi)\,d\xi\,d\tau, \qquad y \in (a_1,a_2) \tag{16}$$

with $\lambda^* > \operatorname{Re}\lambda$, for all other pairs (λ,μ) satisfying (16); and λ^*, $\mu^*(y)$ are the only solutions of (16) to within a constant multiple of μ^*.

Proof. We want to check the hypotheses of the following proposition, where $s(A)$ is the spectral bound of A:

$$s(A) = \sup\{\operatorname{Re}\lambda : \lambda \text{ in the spectrum of } A\}$$

Let T be an eventually compact semigroup and A its generator. Suppose that σ is the only eigenvalue of A with real part $s(A)$ and it is simple. Let us call v and v^* the associated eigenvectors of A and A' [where A' is the generator of the semigroup adjoint to T; see Nagel (1986, Chap. A.I.3.4)]. Then there is a number $\omega' < s(A)$ such that for all f,

$$T(t)f = \langle f,v^*\rangle e^{\sigma t}v + O(e^{\omega' t}), \qquad t \to \infty$$

(See, for example, Chapter 10, Proposition 4; other results in spectral theory and asymptotic behavior of semigroups used in this demonstration can be also found there.)

Since G is an eventually compact semigroup, its spectrum and the spectrum of its generator A consist of isolated eigenvalues of finite multiplicity. The restriction $G_{|X_1}$ of G to X_1, being both irreducible and eventually compact, satisfies the hypotheses of the proposition above.

In the direct sum decomposition $X = X_1 \oplus X_2$ the semigroup has a matrix of the form

$$\begin{pmatrix} G_{|X_1} & H \\ 0 & G_2 \end{pmatrix}$$

so that the eigenvalues are either eigenvalues of $G_{|X_1}$ or of G_2. But it is a consequence of Lemma 2 that G_2 can have no eigenvalue. Indeed, it is enough to look at the support of the associated eigenvector. This shows that there exists a unique eigenvalue with real part $s(A)$, it is the leading eigenvalue of $A_{|\mathcal{D}(A)\cap X_1}$, and it is known to be real [i.e., equal to $s(A)$ itself]. Let us call it λ^* and check that it is simple as an eigenvalue of A. We know that it has only one associated eigenvector, to within a coefficient. With λ^* is associated an eigenfunction u of $G_{|X_1}$. As it is of finite multiplicity, if it were not simple, it would have a generalized eigenvector

v, that is, a function satisfying

$$G(t)v = \exp(\lambda^* t)v + \alpha(t)u$$

But v cannot be in X_1 because λ^* is a simple eigenvalue of $A_{|\mathcal{D}(A)\cap X_1}$ and it cannot be outside it because of Lemma 2. Now the assumptions of the proposition above are verified.

Direct computation shows that the expression of u as the product of $\exp(\lambda^* t)$ by a function μ^* of y only that satisfies equation (16) just expresses the fact that it is an eigenfunction of the semigroup. μ^* is positive almost everywhere on (a_1,a_2) by the irreducibility of $G_{|X_1}$. We can take it of norm 1.

Let us show that λ^* is positive. Integrating (4) with respect to y and taking (H_f) into account yields

$$\int_0^\infty n(t,y)\,dy = 2\int_0^\infty \int_0^\infty \gamma(\tau,\xi)n(t-\tau,\xi)\,d\xi\,d\tau$$

Substituting the eigenfunction and dividing by $2\exp(\lambda^* t)$ provides

$$\int_0^\infty \int_0^\infty \gamma(\tau,\xi)\exp(-\lambda^*\tau)\mu^*(\xi)\,d\xi\,d\tau = \tfrac{1}{2}$$

In view of (H_γ), this is incompatible with $\lambda^* \leq 0$.

It remains to show that C_{n_0} is positive. It is given by $C_{n_0} = \int\int n_0(\tau,\xi)v(\tau,\xi)\,d\tau\,d\xi$, where v is an eigenvector of A'. It is an L^∞ function on Δ with support in $\{(s,y)\in\Delta : y\in[a_1,a_2]\}$ and positive almost everywhere on this set. On the other hand, we have $C_{G(t_0)n_0} = \exp(\lambda^* t_0)C_{n_0}$, which shows that it is enough to prove that $C_{G(t_0)n_0}$ is positive for some t_0. This will be true if the support of n (the solution with initial data n_0) contains a neighborhood of some point (s,y) with $y\in[a_1,a_2]$. A construction similar to the one used in the proof of Lemma 5 can be used to find such a point.

IV. CLOSING REMARKS

From the modeling viewpoint the present paper establishes asynchronous exponential growth in a situation more general than that considered previously (Arino and Kimmel, 1987). The model of cell cycle now includes intrinsic stochastic variability of cell generation time, in addition to that stemming from unequal division. As before, the results depend on very few general qualitative assumptions, and no particular parametric forms of functions defining the model are required. The dominating eigenvector λ^* can be interpreted as the Malthusian parameter of the population growth and the corresponding eigenvector μ^* as the asymptotic cell mass distribution in the population.

The established and now standard tools of the theory of semigroups of linear operators provide useful reference for analysis of asymptotic behavior of models of cell population dynamics. In the present model, it is enough to obtain strong continuity, eventual compactness, and irreducibility of the semigroup, and then the asymptotic exponential growth is a relatively straightforward consequence.

However, there is a price paid for this apparent simplicity. The approach cannot be extended in a straightforward manner to the case of the never compact

semigroup (Arino and Kimmel, 1987; Sanchez et al., 1989). Also, some of the arguments required for checking the assumptions of general properties employed are very similar to those originally used for a direct proof of asymptotic behavior in Arino and Kimmel (1989). A good example is the proof of irreducibility, as carried out in the present paper.

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2
Slow Oscillations in a Model of Cell Population Dynamics

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I. THE MODEL

The natural starting point for the study of cell population kinetics is the process described as the *cell cycle*. This terminology refers to the progression of cells that reproduce by binary fission through a series of distinct phases, the process being concluded by the fission of the mother cell to give two daughter cells. The same process repeats itself again and again, cyclically—hence the terminology. A cycle is usually divided into four distinct phases. One of these phases is the occurrence of DNA synthesis and is termed the S-phase. Another phase occurs when the cell actually divides and is known as mitosis or the M-phase. However, the newly born cells do not immediately begin the DNA synthesis, but go through a preparatory period that is referred to as the G_1-phase. Similarly, once DNA synthesis is completed, a cell does not immediately enter the M-phase but goes through another preparatory phase, referred to as G_2.

On the other hand, it was recognized that cells did not necessarily spend all their time traversing these four phases in a cyclical fashion but can be switched irreversibly out of the cycle into a *resting phase*. However, it is assumed that once a cell enters the cycle, it will go through it, that is, that there will be no loss of cells within the cycle. With regard to the cell cycle duration, it is recognized, based on experiments, that the size of the cell at birth determines its life length. More specifically, cells that are larger at the beginning of the cycle end it faster. Therefore, cell cycle duration is a decreasing function of cell size. As mentioned above, the size of the cell is determined by the quantity of its metabolic constituents, such as DNA, RNA, or any other species that may play a role. This quantity is referred to as *the cell mass*. It increases continuously as a cell traverses the cycle.

The model proposed by Arino and Kimmel (1989) includes unequal division of cells and nonlinear dependence of the fraction of cells reentering proliferation at time t on the total number of cells present in the cycle at that same time, while

here we assume that the dependence is on the total number of cells that were in the cycle at time $t-1$. The quantity we will be regarding in this model is the *instantaneous cell mass distribution* at the beginning of the G_1-phase. This is denoted by $n(t,x)$, where t is time and x is the cell mass. $n(t,x)\,dt\,dx$ represents the number of cells with mass in $(x, x+dx)$ that entered the cycle in the time interval $(t, t+dt)$.

A. Derivation of the Model

If a cell ends the cycle at time t with a cell mass y, it started the G_1-phase with a $\phi^{-1}(y)$ cell mass at time $t-\psi(\phi^{-1}(y))$. In view of the discussion above, ϕ is an increasing function while ψ is decreasing. After division, the daughter cells have x and $y-x$ cell mass, respectively. Let $f(x,y)$ be the density of probability distribution for a daughter cell to have x cell mass conditional on the mother having y. Therefore, $f(\cdot\,,\cdot)$ must satisfy the following natural conditions:

$$f(x,y)=0 \quad \text{for } x>y \qquad \text{and} \qquad f(x,y)=f(y-x,y).$$

If σ denotes the fraction of cells that enter proliferation (i.e., $1-\sigma$ is the fraction of cell switched out of the cycle irreversibly), σ is a decreasing function of the total number of cells present in the cycle at time $t-1$; also, $\sigma(0)=1$ and $\sigma(\infty)=0$. Finally, it is assumed that there is a probability of defective divisions. This will be denoted by $1-\lambda(0<\lambda<1)$.

Based on the assumptions and the discussion above, the following nonlinear functional integral equation was derived in Arino and Kimmel (1989):

$$n(t,x)=2\lambda\sigma(N(t))\int_I f(x,\phi(z))n(t-\psi(z),z)\,dz$$

$$N(t)=\int_0^{+\infty}\int_{t-\psi(u)}^{t} n(v,u)\,dv\,du$$

with the following assumptions:

- (H_f) f is a nonnegative measurable and bounded function on $[0,+\infty)^2$ with $f(x-y,x)=f(y,x)$, $f(y,x)=0$ for $x>y$, and $\int_0^y f(x,y)\,dx=1$. The support of $f(\cdot\,,y)$ is the interval $[yd, y(1-d)]$ for some given $d\in(0,\frac{1}{2})$.
- (H_ϕ) ϕ is a nonnegative function of class $C^1[0,+\infty)$ such that $\phi(0)=0$, $\phi'(z)>\phi_0'$, for all $z>0$, and for some positive constant ϕ_0'. Moreover, if we denote by $\phi_1(z)=d\phi(z)$, $\phi_2(z)=(1-d)\phi(z)$, there are two numbers a_1, a_2, $0<a_1<a_2<+\infty$, such that $\phi_i(z)>z$ (resp., $<z$) for $z<a_i$ (resp., $>a_i$), for $i=1,2$.
- (H_ψ) ψ is a positive function of class $C^1([0,+\infty))$ with $\psi(\infty)=0$ and $\psi'(z)<0$ for $z>0$.
- (H_σ) σ is a continuously differentiable function on $[0,+\infty)$ with $\sigma(0)=1$, $\sigma(\infty)=0$, and $\sigma'(z)<0$ for all $z\geq 0$.
- (H_λ) $\lambda\in(0,1]$.

It was shown in Arino and Kimmel (1989) that asymptotically the support in the structure variable of the solutions is contained in the interval $I=[a_1,a_2]$, and

also the property for a function to have its support $\subseteq [a_1, a_2]$ is invariant by the solution operator. These facts are still valid in the context of the present chapter. For simplicity, we restrict ourselves to such functions, and thus we will work in the following state space: $L^1[(-\psi(a_1), 0) \times I]$. As usual, we will denote by n_t the function defined by $n_t(\tau, x) = n(t + \tau, x)$. The asymptotic behavior of nonnegative solutions is as follows: $n_t \to N(\infty)v_0(x)$, as $t \to +\infty$, where $v_0(x)$ is the unique solution of the fixed-point problem $v_0(x) = \int_I v_0(z) f(x, \phi(z))\, dz$, normed by $\int_I v_0(z)\psi(z)\, dz = 1$, and $N(\infty) = 0$ for λ in $(0, \frac{1}{2})$ and $N(\infty) = N_\lambda^{*\,\text{def}} = \sigma^{-1}(1/2\lambda)$ for λ in $(\frac{1}{2}, 1]$. That is, asymptotic extinction of the cell population is expected if the probability of correct divisions is less than $\frac{1}{2}$, while a stabilized steady state is reached if λ is greater than $\frac{1}{2}$.

The modified model we consider here provides an example where slow oscillations are forced into existence by the introduction of a delay term. Let us write the equation and state the hypotheses needed throughout this paper.

The Equation

$$n(t, x) = 2\lambda\sigma[N(t-1)] \int_I f(x, \phi(z)) n(t - \psi(z), z)\, dz \tag{1}$$

$$N(t) = \int_I \int_{t-\psi(u)}^{t} n(v, u)\, dv\, du \tag{2}$$

Hypotheses. Essentially, they are the assumptions introduced above, some of them being reinforced. This will be indicated by a prime added to the old notation.

$(H_\phi)'$ In addition to (H_ϕ), it is assumed that $\Phi_1(a_2) < \Phi_2(a_1)$.

$(H_\psi)'$ In addition to (H_ψ), it is assumed that $\bar{r} = \psi(a_1)$ and $\underline{r} = \psi(a_2)$ are such that $0 < \bar{r} < 2\underline{r}$ and $4\bar{r} \leq 1$.

By differentiating both sides of (2), and using (1) and the fact that $\int_I f(x, \phi(z))\, dx = 1$, (1)–(2) yields

$$\dot{N}(t) = [2\lambda\, \sigma(N(t-1)) - 1]k(t) \tag{3}$$

where $k(t) = \int_I n(t - \psi(z), z)\, dz$. This equation suggests the analysis of $\dot{x}(t) = g(x(t-1))\, k(t)$ in the general setting of *nonautonomous functional differential equations* verifying conditions motivated directly by those of the model.

II. SLOWLY OSCILLATING SOLUTIONS FOR A NONAUTONOMOUS FUNCTIONAL DIFFERENTIAL EQUATION

The aim of this section is to study the oscillatory properties of the solutions of the equation

$$\dot{x}(t) = g(x(t-1))k(t) \tag{4}$$

The autonomous case

$$\dot{x}(t) = g(x(t-1)) \tag{5}$$

has been studied extensively for the last three decades. [See notably Hale (1977)

or Nussbaum (1978) as survey papers.] For instance, it is well known that if $|g'(0)| > \pi/2$, equation (5) has a nontrivial slowly periodic solution. The proof of this result uses an asymptotic fixed-point theorem due to Browder (1965). However, the nonautonomous case has not yet been studied. Even the existence of slowly oscillating solutions has not been investigated for equations of type (4). In this section it is our intention to show that under conditions on g similar to those in the autonomous case, there are slowly oscillating solutions with sustained oscillations. That is, sufficient conditions on g and k will be provided, ensuring the ejectivity of the trivial solution.

Hypotheses

(H_g) g is in $C^1(-\infty, +\infty)$, bounded, and such that $xg(x) < 0$, for $x \neq 0$.

(H_k) k is a positive continuous function on $(0, +\infty)$. There exist positive constants K_1 and K_2 such that $K_1 \leq \int_t^{t+r} k(s)\, ds \leq K_2$ for some r in $(0,1)$ with $[1/r] \geq 4$ ($[\cdot]$ denoting the integer part).

(H_g) and (H_k) will be assumed throughout this section. Let C be the Banach space of continuous functions on $[-1, 0]$. For each θ in C, there is a unique continuous function $x(t, \theta)$ on $[-1, +\infty)$ satisfying (4) and such that $x_{|[-1,0]} = \theta$. The solutions depend continuously upon the initial data in C. That is, the nonlinear evolution operator $U(t, v)\theta = x_t$, where $x_t(s) = x(t + s)$ for s in $[-1, 0]$, $x_v(s) = \theta(s)$ for s in $[-1, 0]$, and $t \geq v \geq 0$ [$T(t)\theta = U(t, 0)\theta = x_t$], is continuous from C into C.

Remark 1. If θ is in C and $T(t)\theta = 0$ for some $t > 0$, then $\theta = 0$. That is, the solution $x(t, \theta)$ may not take the value 0 and remain 0 for a time interval equal to 1, unless $\theta = 0$, which in turn implies that $x(t, \theta) = 0$ for all $t \geq -1$. This is not difficult to conclude from the conditions on g and k.

Let P be the subset of C consisting of all θ such that $\theta(-1) = 0$ and θ is nondecreasing on $[-1, 0]$.

Remark 2. For θ in $P\backslash\{0\}$, by (H_g) and (H_k), the corresponding solution $x(t, \theta)$ starts decreasing for $t > 0$ and keeps doing so unless it crosses the t-axis, say at t_1 (first cross-point), in which case it will attain its first local minimum at $t_1 + 1$ and starts increasing. It keeps doing so unless it crosses the t-axis, say at t_2 (second cross-point), in which case it will attain its local maximum at $t_2 + 1$ and starts decreasing; and so on.

Lemma 1. Suppose that (H_g) and (H_k) are satisfied. Let θ be given in P and $x(t, \theta)$ be the corresponding solution. If for some $T > 0$, we have $x(t, \theta) > 0$ [resp., $x(t, \theta) < 0$] for all $t \geq T$, then $x(t, \theta) \to 0$ as $t \to +\infty$.

Proof: When there is no risk of confusion, we will write $x(t)$ instead of $x(t, \theta)$. First, we note the fact that by virtue of (H_k), we have

$$\int_0^{+\infty} k(t)\, dt = +\infty \tag{6}$$

Second, if $x(t) > 0$ for all $t \geq T$, then, by Remark 2, $x(t)$ is decreasing on $(T + 1, +\infty)$. Therefore, $x(t) \to x(\infty) \geq 0$. On the other hand, integrating (4) on $(T + 1, \infty)$, we have

$$\int_{T+1}^{+\infty} |g(x(t-1))|\, k(t)\, dt = x(T+1) - x(\infty) < \infty$$