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ASYMPTOTIC ANALYSIS OF A CELL CYCLE MODEL BASED ON UNEQUAL DIVISION*

OVIDE ARINO† AND MAREK KIMMEL‡

Abstract. We provide an analysis of the asymptotic behavior of a novel cell cycle model offering a uniform description of the processes of RNA production and division and explaining the cell generation time variability, at least in certain cell lines. We prove that the distribution $m(t, x)$ of the RNA level (x) in the dividing cells at a given time (t) tends to $\exp(\lambda^* t)\mu^*(x)$, as t tends to infinity, i.e., that there exists the so-called exponential steady state for our model, and that perturbed cell populations reach this state in the limit.

The result is obtained by applying the semigroup theory to a functional integral equation describing the evolution of $m(t, x)$ in time. For a variety of reasons, the analysis requires explicit characterization of the semigroup spectrum. Our asymptotic result may be viewed as a generalization of similar results for the generalized branching processes with continuous time, under less restrictive assumptions. Also, we discuss related models and asymptotic results including the results obtained using the notion of essential spectrum of an operator. The present paper is a continuation of another work in which the biological background and discussions were provided.

Key words. cell kinetics, exponential growth, functional equation, operator semigroup, essential spectrum, general branching process

AMS(MOS) subject classifications. 92A15, 47D05

1. Introduction. The aim of this paper is to provide an analysis of the asymptotic behavior of a novel type of cell cycle kinetics model, based on the assumption of unequal RNA division during cytokinesis. This model, first described by Kimmel et al. [10] offers uniform description of some recently recognized phenomena related to RNA production and division in cycling cells. It also offers an explanation for the origin of a considerable part of the variability of cell generation times in certain cell populations.

1.1. Model assumptions and basic formulae. During their lifetime, between successive divisions, cells traverse the so-called cell cycle, composed of four phases: initial growth phase G_1, DNA synthesis phase S, preparatory phase G_2 and division phase M (mitosis). During this period, cells continuously synthetize RNA, one of the major metabolic constituents related to transcription of genetic information. Two rules of RNA production and division can be specified [10]:

(a) Cells which have more RNA in early G_1 phase (immediately after division) traverse the cell cycle faster than those which inherited less RNA.

(b) RNA is divided unequally, in an apparently random way, between the daughter cells.

Based on these assumptions, a mathematical model of the cell population kinetics was built by Kimmel et al. [10]. Unequal RNA division to daughter cells is the only source of randomness within the model. The model reproduces the experimental growth of the Chinese hamster ovary (CHO) cells, including the observed variability in RNA content. The model (as indicated by numerical simulations) has stabilizing properties which explain why a cell population with increased RNA content (i.e., in unbalanced

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† Département de Mathématiques, Université de Pau, Avenue de l'Université, 64000 Pau, France.

‡ Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York 10021.

growth) returns, after a few cell cycles, to the original RNA distribution pattern. Other cell cycle characteristics, like sister-to-sister and mother-to-daughter lifetime correlations implied by the model, are close to their experimental analogues. The conceptual basis of the model is general enough to include unequal division of factors other than RNA (cell mass, cell proteins, etc.) as sources of variability.

The most important notions of the model are "instantaneous" RNA distributions at the end of mitosis and at the beginning of the G_1 phase. They are denoted by $m(t, x)$ and $n(t, x)$, respectively, and understood in the following way: $m(t, x)\, dt\, dx$ is equal to the number of cells with an RNA content between x and $x+dx$ which divided in the time interval from t to $t+dt$, while $n(x, t)\, dt\, dx$ is equal to the corresponding number of cells which entered the early G_1 phase. Both $m(t, x)$ and $n(t, x)$ are distribution densities with respect to x (RNA content) and rates of cell flow with respect to time t.

As mentioned above, the only source of randomness in the model is the unequal division of RNA between two daughter cells. Suppose that the mitotic cell just before division has X units of RNA. The conditional probability density of a daughter size Y is denoted by $f(Y|X)$. Of course, $f(Y|X)=0$ for $Y>X$ since no daughter cell can have more RNA than the original mother cell. The other daughter cell with RNA content $X-Y$ must have the same conditional density, i.e., it must hold: $f(X-Y|X)= f(Y|X)$, $0 \leqq Y \leqq X$, which is equivalent to a symmetry requirement for $f(Y|X)$.

As a consequence of cell division, the number of cells doubles and the positions of the newly divided cells on the RNA scale change (due to unequal division). In our quasi-probabilistic model, the relation between $m(t, x)$ and $n(t, x)$ will be:

$$n(t, y) = 2\int_0^\infty f(y|x)m(t, x)\, dx,$$

which can be understood as implied by the conditional probability definition. Once the daugher cell has obtained her share (Y) of RNA, her fate is determined. Thus, she will spend $T=\psi(Y)$ units of time in the cycle. We will assume that $\psi(\cdot)$ is a monotonic nonincreasing function, i.e., that cells with more RNA traverse the cell cycle faster. The amount X' of RNA at the end of the cycle (at the next division) is a function $X'=\phi(Y)$. It seems reasonable (see [10] for discussion) to assume that $\phi(\cdot)$ is a monotonic increasing function, i.e. cells richer in RNA at the outset of the cell cycle, conclude this cycle with a higher RNA content. These assumptions imply [10]:

$$m(t, x) = n\{t-\psi[\phi^{-1}(x)], \phi^{-1}(x)\}[\phi^{-1}(x)]'$$

and then, by elimination of $n(\cdot, \cdot)$, we obtain the equation which will be the basis for the present analysis,

$$m(t, x) = 2[\phi^{-1}(x)]' \int_0^\infty f[\phi^{-1}(x)|u]m[t-\psi\circ\phi^{-1}(x), u]\, du. \tag{0}$$

Based on more detailed considerations related to the stochasticity of unequal division (see [10, Appendix A]), we are able to define a constant d, such that

$$f(x|y)=0, \quad y \notin [xd, x(1-d)], \quad d \in (0, \tfrac{1}{2}).$$

1.2. Generalized model: Mathematical questions. As it was noted before, simulation experiments described in [10] indicated that the model exhibits stabilizing properties, i.e., that following a fairly wide range of perturbations of the RNA distribution, the population returned to the same RNA distribution pattern. It will be the main purpose of this paper to present a rigorous proof of this basic property of the model.

We will begin with rewriting the basic equation (0) in a more compact and general way:

$$m(t,x)=\int_0^\infty g(x,u)m[t-\theta(x),u]\,du, \tag{1}$$

where

$$g(x,u)=2[\phi^{-1}(x)]'f[\phi^{-1}(x)|u], \qquad \theta(x)=\psi\circ\phi^{-1}(x).$$

We will make the following assumptions concerning g and θ, which are slightly more general than we need, but this generalization will, in fact, simplify our considerations:

Hypothesis (H_g). The function g is nonnegative and continuous and $\int_0^\infty g(x,u)\,dx>1$. There exist functions ϕ_1, ϕ_2, defined on R^+, increasing and such that $0\leqq\phi_1<\phi_2$. For each $u\geqq 0$, the support of $g(\cdot,u)$ is equal to $[\phi_1(u),\phi_2(u)]$. Moreover, $\phi_1(u)>u$ for u small; $\phi_i(u)=u$ for $u=0$ and $u=a_i$, and $\phi_i(u)<u$ for $u>a_i$ (where the constants a_1 and a_2 satisfy $a_1<a_2$).

Hypothesis (H_g) implies that the graphs of ϕ_1, ϕ_2 are situated as depicted in Fig. 1. In terms of the original equation, we have $\phi_1(u)=\phi(ud)$, $\phi_2(u)=\phi[u(1-d)]$.

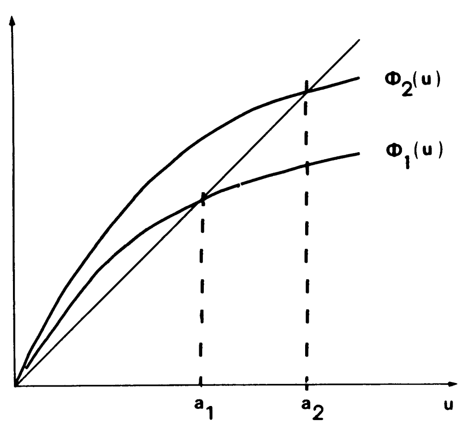

FIG. 1

The assumptions concerning θ will be of prime importance for the asymptotic behavior of the solutions of equation (1). The most "radical" assumption would be that θ is continuously differentiable and decreasing, with a derivative bounded away from zero. As we will see, an assumption of this type (see Hypothesis (H'_θ) below) simplifies the analysis of the solutions. However, it is reasonable to suspect, in the biological model, that the function $\psi(\cdot)$ (and thus also $\theta(\cdot)$) may have an interval of constancy (as it was in fact supposed in the original version of the model [10]). For instance, there probably exists a threshold content of RNA in the early G_1 cells such that a further increase of RNA content does not cause the cells to traverse the cycle faster. The reason for this is that the RNA production is not the only metabolic process in the cell; parallel processes (e.g., DNA synthesis) must also be completed. Thus there exists a minimum duration of the cell cycle, no matter how much RNA the cell inherited. Any assumption involving an interval of constancy for $\psi(\cdot)$ (see Hypothesis (H''_θ) below) poses a considerable challenge for the analysis of solutions. We accept this challenge, since in our opinion the case is of a considerable mathematical interest and the method developed is novel and can possibly be generalized to cover more complicated situations (e.g. several disjoint intervals of constancy for $\psi(\cdot)$).

The general hypothesis on $\theta(\cdot)$ will be:

Hypothesis (H_θ). θ is continuous, $0<\theta_1\leqq\theta(x)\leqq\theta_2<\infty$, $x\geqq 0$.

The next two hypotheses will be used alternatively.

Hypothesis (H'_θ). θ verifies (H_θ) and, for some A_1, A_2, $A_1<a_1<a_2<A_2$, θ has a derivative on $[A_1, A_2]$, with: $|\theta'(x)|\geqq\theta'_0$, $A_1\leqq x\leqq A_2$, for some $\theta'_0>0$.

Hypothesis (H''_θ). θ verifies (H_θ) and, for some A_1, A_2, $A_1<a_1<a_2<A_2$, there exists a partition $[A_1, A_2]=I_1\cup I_2$, where I_2 is a closed interval, such that $I_2\subset(a_1, a_2)$. Moreover, θ has a derivative on I_1 such that $|\theta'(u)|\geqq\theta'_0$, $x\in I_1$, for some $\theta'_0>0$, while $\theta(x)=\theta_0$, $x\in I_2$, for some θ_0, $\theta_1\leqq\theta_0\leqq\theta_2$.

Now, we are ready to formulate the mathematical problems for (1). In the model, no limitations of cell growth are considered. This corresponds to certain experimental cultures in which cells are replated so that the population never becomes overcrowded nor depleted of nutrients. Such cultures exhibit, for prolonged periods of time, a proportional exponential growth. The basic requirement for our model is to reproduce this phenomenon. Under the hypothesis of *equal* division we would find, asymptotically, a distribution of the form $\exp(\lambda^* t)\delta(x-x_\infty)$, where x_∞ is the asymptotically uniform RNA content in the newly divided cells, while λ^* is the Malthusian parameter of exponential growth (Mode [14]). The inequality of division spreads this distribution around x_∞ and so we expect asymptotically $m(t,x)\sim\exp(\lambda^* t)\mu^*(x)$.

Under both hypotheses ((H'_θ) and (H''_θ)), we will prove that the solutions of (1) indeed behave in this way. This is the main result stated as a theorem in § 2. The proof of this theorem requires a detailed analysis of the semigroup of operators generated by (1) (§ 3), analogous to the analyses in references [2], [3], [4], [13], [17], [21]. The resolvent of the generator of the semigroup is not compact, so it is necessary to more directly investigate the properties of the semigroup itself. Under Hypothesis (H'_θ), the semigroup is compact for t large. Under Hypothesis (H''_θ), it is necessary to analyse the spectrum of the semigroup. Assuming an additional, technical, hypothesis on g, it will be proved that the continuous spectrum of the semigroup is sufficiently "small." Finally (§ 4), we will briefly compare our method, to that employed in references [4], [17] and [21], which is based on the notion of the essential spectrum.

2. Main statement. Before stating precisely the main result, it is necessary to define the solution of (1). It is clear that to construct formally a solution after time t_0, it is necessary to know it on the product $[t_0-\theta_2, t_0]\times R^+$. Conversely, if data is given on this set and the integral in (1) exists, then a solution can be constructed, for $t>t_0$, by a step-by-step computation. Along the solution m, the restriction of m to $[t-\theta_2, t]\times R^+$ is the exact data necessary and sufficient to continue the solution from t to infinity. Therefore if, as is usual in the theory of functional differential equations [7], we translate the solution on a fixed time interval, say $[-\theta_2, 0]$, then we see that the equation (1) is associated with a dynamical system in a class of functions on $[-\theta_2, 0]\times R^+$ which will be specified later. We will adopt the standard Hale's notation [7]: $m_t(s,x)=m(t+s,x)$, $-\theta_2\leqq s\leqq 0$, $x\geqq 0$. We are able now to state the main result of this paper.

THEOREM. *Under Hypothesis* (H_g) *and either* (a) *Hypothesis* (H'_θ) *or* (b), *Hypothesis* (H''_θ) *and assumption*: $g(x,u)>0$, (x,u) *in* $I_2\times I_2$, *there exists a positive number* λ^* *and a continuous function* μ^* *such that*:

$$\mu^*(x)>0,\quad a_1<x<a_2,$$

$$\mu^*(x)=0,\quad x\leqq a_1 \text{ or } x\geqq a_2,$$

and, if m is a solution of (1) *for $t \geqq t_0$ with support $m_t(s, \cdot)$ in $[A_1, A_2]$ (where A_1 and A_2 are defined above) then there exists a constant C with the property that:*

$$m(t, x) - C \exp(\lambda^* t)\mu^*(x) = o[\exp(\lambda t)], \quad t \to \infty.$$

Moreover, if $m > 0$, then $C > 0$.

Remark 1 (concerning the support of solutions). In view of the biological context, it is natural to assume that the solutions have supports bounded both from zero and infinity. This explains why our statement restricts to such solutions. But, mathematically, the problems for other solutions are of interest and in fact, we are not able to provide a complete answer regarding exclusion of solutions that do not vanish outside a finite interval. In particular, we only know that for any exponential steady state $(\exp(\lambda^* t)\mu^*(x))$, the support of $\mu^*(x)$ is bounded away from zero. This incomplete result is proved in § 4 (Discussion).

On the other hand, for solutions with bounded support, the support changes with time. More precisely, the following can be readily proved.

PROPOSITION 1. *Suppose that m is a solution of* (1) *and that for t_0 and A_1, A_2, $0 < A_1 < A_2 < \infty$, we have*: $\operatorname{supp} m_t(s, \cdot) \subset [A_1, A_2]$, $-\theta_2 \leqq s \leqq 0$. *Then for $t \geqq t_0 + \theta_2$*, $\operatorname{supp} m(t, \cdot) \subset \{\min[a_1, \phi_1(A_1)], \max[a_2, \phi_2(A_2)]\}$. *Therefore*, $\operatorname{supp} m(t, \cdot)$ *is asymptotically contained in* $[a_1, a_2]$.

The last part of Proposition 1 is in accordance with the fact that $\operatorname{supp} \mu^* = [a_1, a_2]$. Now, if we substitute the expression $\exp(\lambda^* t)\mu^*(x) + o[\exp(\lambda^* t)]$, for m in (1), we see that the pair (λ^*, μ^*) is a solution of the following equation:

$$\mu(x) = \int_{a_1}^{a_2} g(x, u)\, e^{-\lambda\theta(x)}\mu(u)\, du = L_\lambda \mu. \tag{2}$$

The proof of the existence of such a pair (λ^*, μ^*) is independent of the rest of the paper and is given in an appendix. We state in the next proposition the main result concerning this problem. Note first that for each λ, L_λ is an integral operator with a nonnegative continuous kernel:

$$k_\lambda(x, u) = e^{-\lambda\theta(x)} g(x, u). \tag{3}$$

Therefore, L_λ is a positive compact operator on each class $L^p(a_1, a_2)$, $p \geqq 1$. We will use the adjoint L_λ^* of L_λ with respect to the scalar product in $L^2(a_1, a_2)$:

$$L_\lambda^* \nu(u) = \int_{a_1}^{a_2} k_\lambda(x, u)\nu(x)\, dx. \tag{4}$$

The problem posed here is to find a nontrivial fixed point of L_λ in the cone of the nonnegative functions. There are many results in this context in Gantmacher [6], Krasnoselskii [11], Bonsall [1] or Nussbaum [15]. Because neither k_λ nor any of its finite iterates are strictly positive, it is impossible to apply directly any of the results quoted in Gantmacher [6] or Mode [14]. We will use a theorem by Bonsall [1], the application of which yields the following result (cf. Appendix for the proof).

PROPOSITION 2. *Suppose that Hypotheses (H_g) and (H_θ) are verified. Then the set Λ of the (real and complex) numbers such that (λ, μ) is a solution of* (2) *for some μ, $\mu \neq 0$, in $L^2(a_1, a_2)$, is discrete. Set Λ has a unique element λ^* with the greatest real part: λ^* is real and the space of the functions μ such that (λ^*, μ) is a solution of* (2), *is one-dimensional, generated by a nonnegative function μ^*. Moreover, the one-dimensional space of the functions ν in $L^2(a_1, a_2)$ satisfying $L_{\lambda^*}^* \nu = \nu$ is generated by a strictly positive function ν^*.*

3. Proof of the theorem. First, we will define rigorously the semigroup of operators associated with (1). Then we will consider its infinitesimal generator and specifically its spectrum. Finally, to exploit this information for estimating the asymptotic growth of the semigroup, we will inspect it directly under Hypothesis (H'_θ) or (H''_θ).

3.1. The semigroup. It seems that a reasonable choice of the semigroup of operators associated with equation (1) is:

$$G(t)m_0 = m_t \tag{5}$$

provided a convenient space is chosen. Let us denote: $X = L^2((-\theta_2, 0)\times(A_1, A_2))$, endowed with the L^2 norm, $\|\cdot\|_X$, where $0 < A_1 < a_1 < a_2 < A_2 < \infty$.

LEMMA 1. *Suppose Hypothesis* (H_θ) *is verified. Let* m_0 *be in* X *and let* m *be defined on* $(-\theta_2, \theta_1)\times(A_1, A_2)$ *by:* $m = m_0$ *on* $(-\theta_2, 0)\times(A_1, A_2)$ *and*

$$m(t, x) = \int_{(A_1,A_2)} g(x, u) m_0[t - \theta(x), u]\, du \quad \text{on } (0, \theta_1)\times(A_1, A_2).$$

Then, for each t *in* $(0, \theta_1)$: m_t *is in* X *and* $\|m_t\|_X \leqq C\|m_0\|_X$, $0 < t < \theta_1$, *where* C *is independent of* m_0.

Proof.

$$\|m_t\|_X^2 = \int_{(-\theta_2,-t)\times(A_1,A_2)} [m(t+s, x)]^2\, ds\, dx + \int_{(-t,0)\times(A_1,A_2)} [m(t+s, x)]^2\, ds\, dx.$$

The first term is dominated by $\|m_0\|_X^2$. To estimate the second term, we will first observe that

$$m(t+s, x) = \int_{(A_1,A_2)} g(x, u) m_0[t+s-\theta(x), u]\, du,$$

$$|m(t+s, x)| \leqq \|g(x, \cdot)\|_{L^2(A_1,A_2)} \|m_0[t+s-\theta(x), \cdot]\|_{L^2(A_1,A_2)}.$$

This leads to:

$$\int_{(A_1,A_2)\times(-t,0)} [m(t+s, x)]^2\, ds\, dx$$

$$\leqq \int_{(A_1,A_2)} \|g(x, \cdot)\|^2_{L^2(A_1,A_2)} \left\{ \int_{(-t,0)} \|m_0[t+s-\theta(x), \cdot]\|^2_{L^2(A_1,A_2)}\, ds \right\} dx.$$

The term: $\int_{(-t,0)} \|m_0[t+s-\theta(x), \cdot]\|^2_{L^2(A_1,A_2)}\, ds$ is in fact the integral of m_0^2 over $(s-\theta(x), t+s-\theta(x))\times(A_1, A_2)$. So, it is dominated by $\|m_0\|_X^2$ and we obtain:

$$\int_{(-t,0)\times(A_1A_2)} [m(t+s, x)]^2\, ds\, dx \leqq \|m_0\|_X^2 \int_{(A_1,A_2)^2} [g(x, u)]^2\, dx\, du.$$

Summing up these two inequalities, we obtain the assertion of Lemma 1, with $C = (1 + \|g\|^2_{L^2((A_1,A_2)^2)})^{1/2}$.

As a consequence of Lemma 1, to each m_0 in X, we can associate a function m defined on $(-\theta_2, \infty)\times(A_1, A_2)$, which verifies (1) for $t > 0$ and is of class L^2_{loc}. Using the fact that the translations are continuous in L^2, we can assert that $t \to m_t$ is continuous from R^+ into X. The final conclusion of this section can then be stated.

PROPOSITION 3. *Under Hypothesis* (H_θ), *for each* A_1, A_2, $0 < A_1 \leqq a_1 < a_2 \leqq A_2 < \infty$, *the family of operators* $G(t)$ *defined by* (5) *sends* X *into itself and constitutes on* X *a strongly continuous semigroup of operators.*

3.2. The infinitesimal generator. Throughout this paragraph, we assume that Hypothesis (H_θ) is verified. From the classical theory of semigroups (Dunford and Schwartz [5]) we know that, by Proposition 3, the semigroup $G(t)$ has an infinitesimal generator that is a closed operator with a dense domain. First, we will describe this operator; then we will examine its spectral properties. These will be later related to the spectral properties of $G(t)$. The infinitesimal generator A is given by:

$$A\chi = \lim_{t\downarrow 0} [G(t)\chi - \chi]/t$$

for the χ's for which this limit exists in X. Formally, the generator is defined by $(A\chi)(s, x) = \partial\chi(s, x)/\partial s$, $-\theta_2 < s < 0$, $A_1 < x < A_2$, with $\partial\chi/\partial s$ in X. This means that χ is absolutely continuous from $[-\theta_2, 0]$ into $L^2(A_1, A_2)$ and so $\chi(s, \cdot)$ is well defined for each s in $[-\theta_2, 0]$. At $s = 0$, it coincides with $\lim_{t\downarrow 0} G(t)\chi$, yielding:

$$\chi(0, x) = \int_{(A_1, A_2)} g(x, u)\chi[-\theta(x), u]\, du. \tag{6}$$

Therefore, we see that $D(A) = \{\chi \in X: \partial\chi/\partial s \in X$ and χ verifies (6) and for χ in $D(A)$, we have $A\chi = \partial x/\partial s\}$. Now, consider the resolvent equation,

$$A\chi - \lambda\chi = \xi, \qquad \xi \in X; \tag{7}$$

(7) can be integrated into the form of

$$\chi(s, x) = \chi(0, x) \exp(\lambda s) + \int_0^s \exp[\lambda(s-u)]\xi(u, x)\, du. \tag{8}$$

From (7), we see that a solution of (8) is in $D(A)$ if and only if it is in X that is if it verifies (6). Substituting to $\chi(s, x)$ its expression in terms of $\chi(0, x)$ and ξ in (6), we obtain the following relation:

$$\chi(0, x) = \int_{(A_1, A_2)} g(x, u)\, e^{-\lambda\theta(x)}\chi(0, u)\, du + \int_{(A_1, A_2)} g(x, u)\left\{\int_0^{-\theta(x)} e^{-\lambda[\theta(x)+s]}\xi(s, u)\, ds\right\} du. \tag{9}$$

The first operator in (9) is similar to L_λ: it has the same fixed points with the same multiplicity. We will denote it by L_λ. We denote by S_λ the operator acting on ξ. The next lemma is only a rephrasing of what precedes.

LEMMA 2. *A necessary and sufficient condition for the existence of solution of* (7) *is that the equation*

$$\chi_0(x) = L_\lambda\chi_0 + S_\lambda\xi \tag{10}$$

has at least one solution. Moreover, if χ is a solution of (7), *then $\chi_0(x) = \chi(0, x)$ verifies* (10). *Conversely, if χ_0 verifies* (10), *then χ, defined by* (8) *with $\chi(0, x) = \chi_0(x)$, is a solution of* (7). *In particular, if $(I - L_\lambda)$ is invertible, then* (7) *has, for each ξ, one and only one solution given by the following*:

$$\chi(s, x) = e^{\lambda s}(I - L_\lambda)^{-1}S_\lambda\xi + \int_0^s e^{\lambda(s-u)}\xi(u, x)\, du. \tag{11}$$

So, the eigenvalue problem for A has been reduced, in a sense, to the fixed point problem for L_λ. We will make this more precise in the next statement.

Let us observe that S_λ is compact. Therefore, formula (11) defines a decomposition of the resolvent of A into a compact part which contains information about the spectrum and a noncompact part: $\int_0^s e^{\lambda(s-u)}\xi(u, x)\,du$ which seems to be neutral in this respect. To have a complete understanding of the spectral properties of A, it would be necessary to relate the iterates of $(A-\lambda I)$ to the corresponding iterates of $(L_\lambda - I)$. Attempts in this direction indicate that the relations are very complicated. Fortunately, for our present purposes, we are interested only in λ^*, which is a particular case.

PROPOSITION 4. (i) *The spectrum of* A, $\sigma(A)$ *is a pure point spectrum*; (ii) $\sigma(A)=\Lambda$ (*where* Λ *is as defined in Proposition* 2); (iii) *for each* λ, Range $(A-\lambda I)$ *is closed in* X *with* $\operatorname{Ker}(A-\lambda I)=e^{\lambda s}\otimes \operatorname{Ker}(I-L_\lambda)$; (iv) *for* $\lambda=\lambda^*$, $R=\operatorname{Range}(A-\lambda^* I)$ *has codimension* 1 *in* X *and so* $X=R\oplus N$.

Proof. For (i) and (ii), (10) shows that $\lambda\in\sigma(A)$ if and only if $(I-L_\lambda)$ is not invertible, which, by compactness of L_λ, is equivalent to the fact that $(I-L_\lambda)$ is noninjective. This proves (ii). But (8) and (10) show also that, if $(I-L_\lambda)$ is noninjective and if for some $\chi_0\neq 0$ we have $(I-L_\lambda)\chi_0=0$, then the function $\chi=e^{\lambda s}\chi_0$ verifies $(A-\lambda I)\chi=0$. So, $\lambda\in\sigma(A)$ if and only if $(A-\lambda I)$ is noninjective, which gives (i). For (iii) we only have to notice that from (10), Range $(A-\lambda I)=S_\lambda^{-1}[\operatorname{Range}(I-L_\lambda)]$ and to observe that the right-hand side is closed because S_λ is continuous and L_λ is compact which ensures that Range $(I-L_\lambda)$ is closed. To prove (iv), we observe first that from Proposition 2, the range of $(I-L_\lambda)$ can be characterized in terms of the adjoint equation: Range $(I-L_{\lambda^*})=\{\nu^*\}^\perp$. So, from (10), we deduce the following characterization of Range $(A-\lambda^* I)$:

$$\xi\in\operatorname{Range}(A-\lambda^* I)\quad\text{if and only if } \langle S_{\lambda^*}\xi, \nu^*\rangle=0. \tag{12}$$

This means that, besides its closedness, the range has a codimension less than or equal to one. On the other hand, $\xi\to\langle S_{\lambda^*}\xi, \nu^*\rangle$ is not identically null. In fact, S_{λ^*} is also a positive operator and we can observe that $\langle S_{\lambda^*}(e^{\lambda^* s}\mu^*), \nu^*\rangle>0$. This yields at once the two main results of (iv): codim $(R)=1$ and $\operatorname{Ker}(A-\lambda^* I)\cap R=\{0\}$, from which the rest of (iv) follows easily.

Now, on R, $(A-\lambda^* I)$ is a bijection from $R\cap D(A)$ onto R: $\sigma(A|_R)$ is contained in a set $\{\operatorname{Re}\lambda\leqq\lambda_1\}$ for some $\lambda<\lambda^*$. Using the Hille-Phillips theorem (Dunford and Schwartz [5]), we see that A generates a semigroup on R, $G_R(t)$, which in turn can be completed into a semigroup on X, $\tilde G_R$, such that

$$\tilde G_R(t)(e^{\lambda^* s}\mu^*)=e^{\lambda^*(t+s)}\mu^*.$$

Thus, the infinitesimal generator of $\tilde G_R$ is still A. So, $\tilde G_R=G$ and this implies that $G|_R=G_R$ which reads as an invariance property of R with respect to $G(t)$.

It may be surprising to prove, in a detailed way, such a naturally expected property. However, we are not able to see if, under the general assumption (H_θ), the semigroup enjoys standard properties that would permit us to extend the decomposition of the generator to a decomposition of the semigroup. Nor are we able to assert in general that $\sigma[G(t)|_R]$ is contained in a complex ball $\{z: |z|\leqq e^{\lambda_1 t}\}$ for some $\lambda_1<\lambda^*$, which would immediately imply the theorem. This will be discussed in the next paragraph.

3.3. More about $G(t)$. We note first that, in the extreme case of $\theta(x)=\theta_0$, $A_1\leqq x\leqq A_2$, $G(t)$ is never compact. Indeed, let us consider in more detail this situation and for the sake of simplicity let us assume, for this demonstration, that

$$g(x, u)=h(x)k(u). \tag{13}$$

We look for solutions of the form $m(t, x)=p(t)q(x)$. Substituting $p(t)q(x)$ for m in

(1), we get $p(t)q(x)=h(x)p(t-\theta_0)\int_{(A_1,A_2)} k(u)q(u)\,du$, which implies that $q(x)=Ch(x)$ and leads to

$$p(t)=p(t-\theta_0)\left[\int_{(A_1,A_2)} h(u)k(u)\,du\right].$$

So, $G(t)$ restricted to $L^2(-\theta_2,0)\otimes\{h\}$ is the semigroup associated with a difference equation on L^2 and so it is never compact.

We will now consider the two cases (H'_θ), (H''_θ). The first hypothesis will yield compactness of the semigroup, while under the other hypothesis, the semigroup is not compact (although the theorem is still true). Our method in that last case is similar to that introduced by Prüss [17] and employed successfully by Webb [21] and Diekmann et al. [4]. However, we will not use the notion of essential spectrum. Considering the classical classification of the operator spectrum into the point, residual and continuous parts [7], [9] is sufficient.

We will use the obvious notations σ_P, σ_R, and σ_C for the respective parts of the spectrum. It holds:

$$\sigma_P[G(t)]=\{\exp(\lambda t),\ \lambda\in\sigma_P(A)\},$$

$$\sigma_R[G(t)]\subset\{\exp(\lambda t),\ \lambda\in\sigma_R(A)\}.$$

Using the results of § 3.2, we can therefore state the following.

LEMMA 3. *$\sigma_P[G(t)|_R]\subset\{z\colon |z|\leqq\exp(\lambda_1 t)\}$, for some λ_1, $\lambda_1<\lambda^*$; $\sigma_R[G(t)]=\sigma_R[G(t)|_R]=\varnothing$.*

The uncertainty is about σ_C. It could happen that a point μ is in the continuous spectrum of $G(t)$ and all the λ's such that $e^{\lambda t}=\mu$ are in the resolvent set of A. Let us thus consider the case of $G(t)$ being compact for t large. Then the continuous spectrum of $G(t)$ would be void.

PROPOSITION 5. *Suppose that Hypothesis (H'_θ) is verified. Then $G(t)$ is compact, for $t\geqq 2\theta_2$.*

For $t\geqq 2\theta_2$, we can write $m(t,x)$ in the following way:

$$m(t,x)=\int_{(A_1,A_2)} g(x,u)\left\{\int_{(A_1,A_2)} g(u,v)m[t-\theta(x)-\theta(u),v]\,dv\right\}du. \tag{14}$$

The proof of Proposition 5 will be a direct consequence of this formula. At the same time, we have the following result (which is stated in such a form that it can be used without Hypothesis (H'_θ)).

LEMMA 4. *Suppose that on some interval I_1, $I_1\subset(A_1,A_2)$ and for some $\theta'_0>0$, we have $|\theta'(x)|\geqq\theta'_0$, $x\in I_1$. Let us define*

$$K_{I_1}m_0=\int_{I_1} g(x,u)\left\{\int_{(A_1,A_2)} g(u,v)m[t-\theta(x)-\theta(u),v]\,dv\right\}du. \tag{15}$$

Then for each $T\geqq 2\theta_2$, K_{I_1} is compact from X into $C([2\theta_2,T]\times[A_1,A_2])$.

Proof of Proposition 5. Let us observe that the right-hand side of formula (14) is equal to $K_{(A_1,A_2)}$ and the assumptions of Lemma 4 are equivalent to Hypothesis (H'_θ) if $I_1=(A_1,A_2)$.

Proof of Lemma 4. We will derive the lemma from the Ascoli theorem. First, we change the variable u into $w=\theta(u)$ so that

$$K_{I_1}m_0=\int_{(A_1,A_2)}\int_{\theta(I_1)} g[x,\theta^{-1}(w)]g[\theta^{-1}(w),v]m[t-\theta(x)-w,v]|(\theta^{-1})'(w)|\,dw\,dv.$$

Now, we note that in view of Lemma 1 and the boundedness of $(\theta^{-1})'$ and g, we have for each $T \geqq 2\theta_2$:

$$|K_{I_1} m_0(t, x)| \leqq C_T |m_0|_{L^2(A_1, A_2)} \tag{16}$$

where $t \leqq T$ and $C_T < \infty$. We can write $K_{I_1} m_0$ as:

$$K_{I_1} m_0(t, x) = \int_{(A_1, A_2)} \int_{\theta(I_1)} \tilde{g}(x, v, w) m[t - \theta(x) - w, v] \, dw \, dv, \tag{17}$$

where $\tilde{g}$ is continuous on $\overline{\theta(I_1) \times (A_1, A_2)}$ (in the second and third argument). Another change of variables: $z = t - \theta(x) - w$ leads to

$$K_{I_1} m_0(t, x) = \int_{(A_1, A_2)} \int_{\{t - \theta(x) - \theta(I_1)\}} \tilde{g}[x, v, t - \theta(x) - z] m(z, v) \, dz \, dv. \tag{18}$$

The right-hand side of (18) is equicontinuous as long as t stays in a bounded set and m_0 stays in a bounded set of X (this last fact is implied by Lemma 1). Using the Ascoli theorem, we conclude that K_{I_1} sends bounded subsets of X into relatively compact subsets of the space $C([2\theta_2, T] \times [A_1, A_2])$, for any $T \geqq 2\theta_2$, which is the desired conclusion of Lemma 4.

PROPOSITION 6. *Suppose that Hypothesis* (H''_θ) *is verified and* $g(x, u) > 0$ *at each point* (x, u) *in* $I_2 \times I_2$. *Then there exist* $\varepsilon > 0$, $C \geqq 0$ *such that for* t *large enough,* $G(t) = U(t) + V(t)$, *where* $U(t)$ *is compact and* $\|V(t)\| \leqq C \exp[(\lambda^* - \varepsilon)t]$.

We will present now the consequences of Propositions 5 and 6 for the asymptotic behavior of the semigroup $G(t)$. Then, at the end of this section, we will present the proof of Proposition 6.

The asymptotic growth of a semigroup can be best appreciated by considering its growth bound,

$$\omega_0 = \lim_{t \to \infty} \operatorname{Log} \|G(t)\| / t. \tag{19}$$

From the definition of ω_0, we get that for each $\eta > 0$, there exists $C \geqq 0$ such that

$$\|G(t)\| \leqq C \exp[(\omega_0 + \eta)t]. \tag{20}$$

On the other hand, it is well known that the spectral radius of $G(t)$ is given in terms of ω_0 by the following:

$$r[G(t)] \leqq \exp(\omega_0 t). \tag{21}$$

This inequality can be used, in fact, to estimate ω_0.

Suppose now that we assume that Hypothesis (H'_θ) is verified. From Proposition 5 we conclude that $\sigma_C[G(t)] = \varnothing$ for t large enough. So, $\sigma_C[G(t)|_R] = \varnothing$ for t large enough and then in view of Lemma 3, we get $\sigma[G(t)|_R] \subset \{z\colon |z| \leqq \exp(\lambda_1 t)\}$, for some $\lambda_1 < \lambda^*$ and t large. This implies that the spectral radius of $G(t)|_R$ is less than $e^{\lambda_1 t}$ and so, from (21), we conclude that $\omega_0[G(t)|_R] \leqq \lambda_1$. Using (20), we can then find $C \geqq 0$, $\varepsilon > 0$ such that

$$\|G(t)|_R\| \leqq C \exp[(\lambda^* - \varepsilon)t].$$

Suppose next that Hypothesis (H''_θ) is true. Then, we are able to use Proposition 6, provided we note the following basic lemma.

LEMMA 5. *Suppose that* $L = U + V$, *a linear operator, is a sum of a compact operator* U *and a bounded operator* V. *Then* $\sigma_C(L) \subset \{z\colon |z| \leqq \|V\|\}$.

Proof. Let us fix a λ in C, $|\lambda| > \|V\|$ and consider $L-\lambda I = (V-\lambda I)+U = (V-\lambda I)[I+(V-\lambda I)^{-1}U]$. $V-\lambda I$ is invertible. $K=(V-\lambda I)^{-1}U$ is compact, so it has a closed range and $R(L-\lambda I) = R(I+K)$. In view of the definition of the continuous spectrum, such λ's do not belong to it.

From Lemma 5, we conclude that $\sigma_C[G(t)] \subset \{z : |z| \leqq C \exp[(\lambda^* - \varepsilon)t]\}$, for t large. The same holds for $G(t)|_R$ which, in view of Lemma 3, yields $\sigma[G(t)|_R] \subset \{z : |z| \leqq C \exp(\lambda_1 t)\}$, for some $\lambda_1 < \lambda^*$ and C independent of t, for t large. The conclusion is the same as in the case of Hypothesis (H'_θ).

From this point on, the proof of the theorem can be continued as follows. Let m be a solution of (1), with m_0 as initial data, m_0 in X. Projecting m_0 on N and R, we can write it as $m_0 = C \exp(\lambda^* s)\mu^*(x) + \rho(s, x)$ so that $G(t)m_0 = C e^{\lambda^*(t+s)}\mu^*(x) + G(t)|_R \rho$. On the other hand, we have $\|G(t)|_R\| = o(e^{\lambda^* t})$, so the first part of the theorem is proved. Now, if we assume $C=0$, it means that m_0 and m_t stay in R, for $t \geqq 0$ and from (12), this is equivalent to $\langle S_{\lambda^*} m_t, \nu^* \rangle = 0$, which implies that m_t changes sign. Therefore, if $m_0 > 0$ then $C > 0$ and the theorem is proved.

Proof of Proposition 6. Using the result of Lemma 4, we will decompose iteratively the right-hand side of (14) into a sum of integrals over I_1 and I_2:

$$m(t,x) = \int_{I_1} g(x,u)\left\{\int_{(A_1,A_2)} g(u,v)m[t-\theta(x)-\theta(u), v]\,dv\right\}du$$
$$+\int_{I_2} g(x,u)\left\{\int_{(A_1,A_2)} g(u,v)m[t-\theta(x)-\theta_0, v]\,dv\right\}du.$$

From Lemma 4 we know that, for $t \geqq 2\theta_2$, the first term on the right-hand side is compact. For $t \geqq 2\theta_2 + \theta_0$, we can express $m[t-\theta(x)-\theta_0, v]$ inside the second term in terms of (14) and then decompose (A_1, A_2) into the disjoint union of I_1 and I_2:

$$\int_{I_2} g(x,u)\int_{I_1} g(u,v)\int_{(A_1,A_2)} g(v,w)m[t-\theta(x)-\theta_0-\theta(v), w]\,dw\,dv\,du$$
$$+\int_{I_2} g(x,u)\int_{I_2} g(u,v)\int_{(A_1,A_2)} g(v,w)m[t-\theta(x)-2\theta_0, w]\,dw\,dv\,du.$$

The first term is compact, due to Lemma 4. For $t \geqq 2\theta_2 + 2\theta_0$, we can express $m[t-\theta(x)-2\theta_0, w]$ inside the second term, using the integral form (14). This procedure can be repeated as long as $t \geqq 2\theta_2 + n\theta_0$. This ends with $m(t,x) = \bar{m}(t,x) + \tilde{m}(t,x)$, where $m_0 \to \bar{m}$ is compact from X into $C([t, t+T]\times[A_1, A_2])$, for $t \geqq 2\theta_2 + n\theta_0$ and any $T > 0$ and,

(22)
$$\tilde{m}(t,x) = \int_{I_2^n \times (A_1,A_2)} g(x,u)g(u,v_1)\cdots g(v_{n-1},v_n)m[t-\theta(x)-n\theta_0, v_n]\,dv_n\cdots dv_1\,du.$$

For $t \geqq 3\theta_2 + n\theta_0$, let us define:

(23) $$[U(t)m_0](s,x) = \bar{m}(t+s,x), \qquad [V(t)m_0](s,x) = \tilde{m}(t+s,x).$$

$U(t)$ is compact from X into itself. We will now estimate $\|V(t)\|$. Let us introduce a new function,

(24) $$\tilde{g}_n(x, v_n) = \int_{I_2^n} g(x,u)g(u,v_1)\cdots g(v_{n-1},v_n)\,dv_{n-1}\cdots dv_1\,du.$$

We have

$$\tilde{m}(t,x)=\int_{(A_1,A_2)}\tilde{g}_n(x,v_n)m[t-\theta(x)-n\theta_0,v_n)\,dv_n.$$

CLAIM 1. *There exists* $C \geqq 0$ *such that for* t *in* $[3\theta_2+n\theta_0, 4\theta_2+n\theta_0]$, *we have* $\|V(t)\|\leqq C\|\tilde{g}_n\|_{L^2((A_1,A_2)\times(A_1,A_2))}$.

Proof of Claim 1. First, we estimate $|\tilde{m}(t+s,x)|$:

$$(25)\qquad \begin{aligned}&|\tilde{m}(t+s,x)|\leqq|\tilde{g}_n(x,\cdot)|_{L^2(A_1,A_2)}|m[t+s-\theta(x)-n\theta_0,\cdot]|_{L^2(A_1,A_2)},\\ &\int_{(-\theta_2,0)}|\tilde{m}(t+s,x)|^2\,ds\leqq|\tilde{g}_n(x,\cdot)|^2_{L^2(A_1,A_2)}\|m_{t-\theta(x)-n\theta_0}\|^2_X.\end{aligned}$$

In view of the restrictions on t, we have $\theta_2\leqq t-\theta(x)-n\theta_0\leqq 3\theta_2$ and, from Lemma 1, this implies that for some $C\geqq 0$, independent of t, we have $\|m_{t-\theta(x)-n\theta_0}\|_X\leqq C\|m_0\|_X$. So, integrating both sides of (25) on (A_1,A_2), we obtain:

$$\|\tilde{m}_t\|_X^2\leqq\|\tilde{g}_n\|^2_{L^2((A_1,A_2)^2)}C^2\|m_0\|^2.$$

In view of the definition of $V(t)$, the above inequality yields the claimed result.

CLAIM 2. *There exist* $C'\geqq 0$ *and* $\lambda_1<\lambda^*$ *such that for* t *in the closed interval* $[3\theta_2+n\theta_0, 4\theta_2+n\theta_0]$, *we have* $\|\tilde{g}_n\|_{L^2((A_1,A_2)^2)}\leqq C'e^{\lambda_1 t}$.

Proof of Claim 2. Let us introduce the operator K_{I_2} defined on $L^2(I_2)$ by:

$$(26)\qquad (K_{I_2}\mu)(x)=\int_{I_2}g(x,u)\mu(u)\,du.$$

In terms of K_{I_2}, $\tilde{g}_n$ is the kernel of the $(n+1)$st iterates of K_{I_2} and $\|\tilde{g}_n\|_{L^2(I_2\times I_2)}=\|K_{I_2}^{n+1}\|$. In fact, what we should estimate is $\|\tilde{g}_n\|_{L^2((A_1,A_2)^2)}$. However, the following estimate:

$$\|\tilde{g}_n\|_{L^2((A_1,A_2)^2)}\leqq\|g\|_{L^2((A_1,A_2)\times I_2)}\|\tilde{g}_{n-2}\|_{L^2(I_2\times I_2)}\|g\|_{L^2(I_2\times(A_1,A_2))}$$

shows that it will be enough to estimate $\|\tilde{g}_n\|_{L^2(I_2\times I_2)}$.

With the restrictions on t, we have $t\sim n\theta_0$, for t large and so the claim will be a consequence of

$$\lim_{n\to\infty}\|K_{I_2}^{n+1}\|^{1/n}<\exp(\lambda^*\theta_0),$$

that is

$$(27)\qquad r(K_{I_2})<\exp(\lambda^*\theta_0).$$

To prove this inequality, we observe first that

$$(28)\qquad K_{I_2}\mu^*<\exp(\lambda^*\theta_0)\mu^*\quad\text{in } I_2.$$

Here, μ^* verifies (2) and we know that supp $\mu^*=[a_1,a_2]$. On the other hand, from the "technical" assumption made on g in Proposition 6 and from the fact that $I_2\subset(a_1,a_2)$, we have

$$\int_{(a_1,a_2)}g(x,u)\mu^*(u)\,du>\int_{I_2}g(x,u)\mu^*(u)\,du,$$

for each x in I_2. This is precisely (28). Now, supposing that $r(K_{I_2})>0$ (otherwise there is nothing to prove) we can invoke Bonsall's [1] theorem (see our Appendix, Lemma 6), to obtain a positive solution of the adjoint equation,

$$(29)\qquad K_{I_2}^*\nu=r(K_{I_2})\nu.$$

Using the L^2 scalar product of μ^* with both sides of (29) and the inequality (28), we get,

$$r(K_{I_2})\langle \nu, \mu^*\rangle = \langle K_{I_2}^* \nu, \mu^*\rangle = \langle \nu, K_{I_2}\mu^*\rangle < \exp(\lambda^*\theta_0)\langle \nu, \mu^*\rangle,$$

so that $r(K_{I_2}) < \exp(\lambda^*\theta_0)$ yielding Claim 2.

A direct consequence of Claims 1 and 2 is that there exist C'' and $\lambda_1 < \lambda^*$ such that $\| V(t)\| \leqq C'' \exp(\lambda_1 t)$, for $t \geqq 0$. This completes the proof of Proposition 6.

4. Discussion. The consequences of the unequal division of any metabolic constituent important for cell progression towards division, can be considered in two aspects. First, the statistical properties of individual cell lifetimes can be followed. It was demonstrated by Kimmel et al. [10] that our model reproduces at least part of such characteristics (sister-sister and mother-daughter lifetime correlations). Another aspect, which is important but more difficult to study and thus usually not considered rigorously in the metabolic models of the cell cycle (see the literature review in Kimmel et al. [10]), is the impact of the inequality of division and metabolic regulation (as represented by functions ϕ and ψ, in this model) on the transient processes of cell kinetics. This problem has been studied by numerical simulations and intuitive estimates in Kimmel et al. [10] and by rigorous methods in this paper. The result of our theorem, translated into the cell kinetics language, means simply that any perturbation of the population's RNA distribution (e.g. overloading with RNA, as considered by Kimmel et al. [10]) will be damped and the RNA distribution will return eventually to the exponential steady state pattern $\mu^*(x)$. It is worth noting that this basic result is obtained under very general assumptions, with no parametric form of functions f, ϕ and ψ postulated.

The process of cell proliferation with unequal division can be understood as a special case of a generalized continuous time branching process (see Mode [14, Chap. 7]). In Mode's terminology, cells with different RNA content occupy different states in the process state space. Thus, our equation (1) is, in fact, an equation for the expected values of the process, analogous to Mode's [14] equation (7.7.2). Also, our equation (2) is analogous to Mode's [14] equation (7.9.15). However, the results for the general case cannot be specialized for our problem. The reason is that the kernel k_λ, defined in equation (3) is not strictly positive on its domain (nor is any of its finite iterates). This forces us to look for different ways of investigating equation (1).

The following technical comments seem to be of some importance. The case of the semigroup not being compact is of considerable mathematical interest. Therefore it was included in our considerations. Proposition 6 concerns a special case of function θ being constant on a single interval. A more general result, under the assumption that θ is constant on a finite number of intervals, seems to be readily available. We chose not to consider it, for the sake of brevity, and to concentrate on the methods.

The proof of the theorem is based on the notion of continuous spectrum while several authors, after Prüss [17], considered instead the properties of the essential spectrum of an operator, and that of the essential spectrum radius computed using a formula developed by Nussbaum [16]. It may be worthwhile to observe that our method applies to the situations considered by Diekmann et al. [4] and Webb [21]. In fact, in these papers, the semigroup is represented as a sum $G(t) = U(t) + V(t)$, where U is compact and $\| V(t)\| \leqq M \exp[(\lambda^* - \varepsilon)t]$. This is precisely the form provided by Proposition 6, after which we estimate the continuous spectrum using the result of Lemma 5.

Another problem of mathematical interest is the possible existence of an exponential steady-state RNA distribution $\mu^*(x)$ with unbounded support. We are not able to exclude this possibility. What we know is only that supp μ^* is in $[\varepsilon, \infty)$, for some $\varepsilon > 0$, i.e. it is bounded away from zero. Indeed, from equation (2) it follows that

$$\int_0^{\varepsilon} \mu^*(x)\, dx \leqq 2\alpha \int_0^{\phi^{-1}(\varepsilon)/d} \mu^*(u)\left[\int_{ud}^{u(1-d)} f(v|u)\, dv\right] du = 2\alpha \int_0^{\phi^{-1}(\varepsilon)/d} \mu^*(u)\, du,$$

where $\alpha = \exp[-\lambda^* \psi \circ \phi^{-1}(\varepsilon)]$; if $\int \mu^* < \infty$, $\lambda^* > 0$. But $\phi'(0)d > 1$, so $\phi^{-1}(\varepsilon)/d < \varepsilon$. Also:

$$\int_0^{\infty} \mu(x)\{\exp[\lambda^* \psi \circ \phi^{-1}(x)] - 2\}\, dx = 0.$$

So, for ε small enough, $\alpha < \frac{1}{2}$. This means that $\int_0^{\varepsilon} \mu^* < \int_0^{\varepsilon} \mu^*$, which implies $\mu^*(x) = 0$, $x \leqq \varepsilon$. Of course, in view of Proposition 1, this means that supp $\mu^* \subset [a_1, \infty)$. It is likely that we could exclude the infinite supports by imposing different assumptions on functions ϕ and ψ. However, no biological properties seem to suggest such assumptions.

Recently, Lasota and Mackey [12] presented a metabolic model of the cell cycle, assuming *equal* division of the so-called "mitogen". They are also interested in proving the existence of an exponential steady state in their model. In order to do so, they are looking for a nontrivial solution of equation $Pf^* = f^*$, where f^* is a distribution density and P is an integral operator with stochastic kernel. However, there is a basic difference between their approach and that of the present paper. The f^* of Lasota and Mackey [12] corresponds to the distribution of the mitogen in a given *generation* of cells. Because the cell life lengths are not equal for all the cells (on the contrary, they differ depending on the "mitogen" content), then at a given time the population is composed of cells from various generations. Therefore, Lasota and Mackey's f^* [12] is not directly comparable to any experimentally measurable distribution (except if complete cell pedigrees are established using the time lapse cinematographical technique, though this is generally done on a relatively small cell sample, of the order of 10^2 cells, thus providing statistically ambiguous results). This disadvantage is not present in our model, where the RNA distribution μ^* corresponds to experimental frequency plots, based on cell samples of the order of $5\text{–}20 \times 10^3$ cells.

Appendix. We will prove, in a number of steps, Proposition 2. We will follow the lines of Appendix B of Kimmel et al. [10], where a particular case was considered. It means that we will first prove the existence of a pair (λ^*, μ^*); then that Λ is discrete, and finally we will look at the dimension of the space of μ^*'s. In proving the existence we will use the following result by Bonsall [1].

LEMMA 6. *Let X be a Banach space and K a closed convex cone in X. Further, let $L: X \to X$ be a bounded linear operator, such that $LK \subset K$ and $L|_K$ is compact. Define $\|L\|_K = \sup\{\|Lx\|, \|x\| \leqq 1, x \in K\}$, and suppose that $r_K(L) = \lim_{n\to\infty} \|L^n\|_K^{1/n}$ (which exists) is positive. Then, there exists $\mu \in K \backslash \{0\}$ such that: $L\mu = r_K(L)\mu$.*

Remark. In our application, L is L_λ defined by (2), K will be a class of nonnegative functions defined on (a_1, a_2). Here, it will be advantageous to use the space L^1 to exploit certain properties related to the order, but the fixed points of L are in fact in $L^\infty(a_1, a_2)$. To get μ^*, we only have to find a number λ^* so that $r_K(L_{\lambda^*}) = 1$. The next lemma determines the dependence of $r_K(L_\lambda)$ with respect to λ.

LEMMA 7. *The function $\lambda \to r_K(L_\lambda)$ is continuously decreasing in λ. Moreover, $r_K(L_\lambda) > 1$ for λ near to zero, $r_K(L_\lambda) < 1$ for λ large enough. Therefore, there exists exactly one real value λ^* such that: $r_K(L_{\lambda^*}) = 1$.*

Proof. We note that for μ in K, $L_\lambda \mu$ is nonincreasing with respect to λ, and, moreover: $\|L_\lambda\|_K$ is decreasing. The same is true with the iterates of L_λ. In fact, we have:

(A1) $$L_\lambda^j \mu \geqq e^{j(\lambda' - \lambda)\theta_1} L_{\lambda'}^j \mu,$$

for $\lambda < \lambda', j \geqq 1$. This implies $\|L_\lambda^j\|_K \geqq e^{j(\lambda'-\lambda)\theta_1}\|L_{\lambda'}^j\|_K$, and then from the definition of $r_K(L_\lambda)$:

(A2) $$r_K(L_\lambda) \geqq e^{(\lambda'-\lambda)\theta_2} r_K(L_{\lambda'}).$$

But, we also have

$$e^{j(\lambda'-\lambda)\theta_2} L_{\lambda'}^j \mu \geqq L_\lambda^j \mu$$

which gives

$$r_K(L_\lambda) \leqq e^{(\lambda'-\lambda)\theta_2} r_K(L_{\lambda'}).$$

This and (A2) yield the first part of Lemma 7, continuity and monotonicity. We look at $r_K(L_0)$: (H_g) implies that $\|L_0\mu\| \geqq \alpha\|\mu\|$, with $\alpha > 1$ and μ in K; from the inequality and the positivity of L_0, we get:

$$\|L^j\mu\| \geqq \alpha^j\|\mu\|, \qquad j \geqq 1, \quad m \in K,$$

and so: $r_K(L_0) > 1$. Now, it is easily seen from (2) that for λ large enough: $\|L_\lambda\| < 1$, and this automatically implies that: $r_K(L_\lambda) < 1$.

Proof of the existence of (λ^*, μ^*). From Lemma 7, we know that for exactly one value λ^*, we have: $r_K(L_{\lambda^*}) = 1$, and, from Lemma 6, we know that there exists μ in $K \backslash \{0\}$ such that for this value λ^*: $L_{\lambda^*}\mu = \mu$.

We now turn to the discreteness of Λ: for that, we will express locally Λ as the set of the roots of a "characteristic equation." To $\tilde{\lambda} \in \Lambda$ we can associate a decomposition of L^1: $L^1 = N \oplus E$ $(I = \pi_N + \pi_E)$ in which N is the finite dimensional generalized eigenspace corresponding to the eigenvalue 1 of $L_{\tilde{\lambda}}$ and E is the generalized range of $(I - L_{\tilde{\lambda}})$. We know that $(I - L_{\tilde{\lambda}})$ is an isomorphism from E onto itself.

The equation $(L_{\tilde{\lambda}} - I)\mu = 0$ can be split into two:

(A3) $$\pi_E(L_{\tilde{\lambda}} - I)\mu_E = -\pi_E(L_{\tilde{\lambda}} - I)\mu_N,$$

(A4) $$\pi_N(L_{\tilde{\lambda}} - I)\mu_N = -\pi_N(L_{\tilde{\lambda}} - I)\mu_E.$$

If λ is near to $\tilde{\lambda}$, $\pi_E(L_\lambda - I)|_E$ is invertible, and so (A3) leads to:

$$\mu_E = \mathcal{L}(\lambda)\mu_N,$$

in which $\mathcal{L}(\lambda)$ is analytical in λ, and then the equation $(L_\lambda - I)\mu = 0$ reduces to an equation in the space N:

$$\mathcal{R}_{\tilde{\lambda}}(\lambda)\mu_N = 0,$$

where

$$\mathcal{R}_{\tilde{\lambda}}(\lambda)\mu_N = \pi_N(L_\lambda - I)\mu_N + \pi_N(L_\lambda - I)\mathcal{L}(\lambda)\mu_N$$

is analytical in λ, for λ near to $\tilde{\lambda}$. Define now: $\Phi_{\tilde{\lambda}}(\lambda) = \det \mathcal{R}_{\tilde{\lambda}}(\lambda)$, and $M = \{\tilde{\lambda}: \Phi_{\tilde{\lambda}} = 0$ in a neighborhood of $\tilde{\lambda}\}$. Then M is an open set by definition. But, if $(\tilde{\lambda}_n)$ is a sequence in M, which converges to a point $\tilde{\lambda}$, there exists a sequence $(\tilde{\mu}_n)$, $\tilde{\mu}_n \in L^1$, such that $(\tilde{\lambda}_n, \tilde{\mu}_n)$ is solution of (2). From the compactness of L_λ (which holds independently of λ, as long as λ stays bounded) it follows that we can extract a subsequence from $(\tilde{\mu}_n)$ which converges to a point $\tilde{\mu}$. By continuity, $(\tilde{\lambda}, \tilde{\mu})$ is a solution of (2), so: $\tilde{\lambda} \in \Lambda$, $\Phi_{\tilde{\lambda}}$ is defined, analytic near to $\tilde{\lambda}$, and $\Phi_{\tilde{\lambda}}(\tilde{\lambda}_n) = 0$ for a large n. This implies that: $\Phi_{\tilde{\lambda}} = 0$ near to $\tilde{\lambda}$, and so: $\tilde{\lambda} \in M$. This proves M is closed. Then M is both open and closed in the complex field. So, $M = C$ or $M = \varnothing$. To prove that M is empty, we will verify that λ^* is not in M. We first note that, from $K - K = L^1$, $\|x\| = \|x_+\| + \|x_-\|$, it follows that for any positive operator L on L^1: $\|L\|_K = \|L\|$ and so: $r_K(L) = r(L)$. From Lemma

7, we can say that $r(L_\lambda)<1$ for $\lambda>\lambda^*$. This implies that the equation (2) has no nontrivial solution for $\lambda>\lambda^*$, and from the reduction around λ^* implied by (A3), (A4), it follows that:

$$\det \mathcal{R}_{\lambda^*}(\lambda)\neq 0, \quad \lambda>\lambda^*, \quad \text{near to } \lambda^*.$$

This completes the proof of the discreteness of Λ.

We will now prove that the space of solution corresponding to λ^* is one-dimensional . We introduce the adjoint equation (4), using the duality in $L^2(a_1, a_2)$. Since we work for the moment with a fixed λ, $\lambda=\lambda^*$, we can drop the index λ^*, and denote the operators by: L, L^*. We state in the next lemma the property mentioned in Proposition 2 that the nonnegative fixed points of L^* are positive on the closed interval $[a_1, a_2]$. On the other hand, we note that the dimensions of the space of fixed points of L and L^* are the same (cf. e.g. Hellinger and Toeplitz [8]). But, because of the mentioned property, it will be easier to estimate this dimension using the adjoint equation.

LEMMA 8. *If ν is a nonnegative fixed point of L^*, then*: $\nu(u)>0$, *for all* u, $a_1\leqq u\leqq a_2$.

Proof. We look at the kernels of the iterates of L^*. Let us call $k^{(i)}$ the ith kernel, so that we have:

$$k^{(i)}(x, u)=\int_{a_1}^{a_2} k^{(i-1)}(x, y)k(y, u)\, dy.$$

Consider the support of $k^{(i)}$ as a function of x for fixed u:

$$\begin{aligned}&\operatorname{Supp} k(\cdot, u)=[\phi_1(u), \phi_2(u)],\\&\operatorname{Supp} k^{(2)}(\cdot, u)=[\phi_1^{(2)}(u), \phi_2^{(2)}(u)],\\&\operatorname{Supp} k^{(i)}(\cdot, u)=[\phi_1^{(i)}(u), \phi_2^{(i)}(u)]\end{aligned}$$

where

$$\phi^{(i)}=\phi\circ\phi^{(i-1)}.$$

So, the support of the iterates fills asymptotically the interval $[a_1, a_2]$, uniformly in $u\in[a_1, a_2]$. Now, if ν is a nonnegative fixed point of L^*, we have: $\nu(u)=(L^{*i}\nu)(u)$, $i\geqq 1$, and so for i large enough and for all $a_1\leqq u\leqq a_2$, supp $\nu\cap$ supp $k^{(i)}(\cdot, u)$ contains some set F, with a nonzero measure, which means that $\nu(u)>0$, for all u, $a_1\leqq u\leqq a_2$. Another interesting consequence of the supports of the kernels is a strong comparison property.

LEMMA 9. *If ν_1 and ν_2 are two fixed points of L^* such that*: $\nu_1\geqq\nu_2$ *and at some point* u_0: $\nu_1(u_0)=\nu_2(u_0)$, *then*: $\nu_1(u)=\nu_2(u)$, $a_1\leqq u\leqq a_2$.

Proof. Note that this result contains, in fact, the preceding if we take: $\nu_1=\nu$, $\nu_2=0$. Lemma 9 will be proved by expressing $\nu_1-\nu_2$ in terms of large iterates of L^*.

$$\begin{aligned}&\nu_1(u_0)-\nu_2(u_0)=L^{*i}(\nu_1-\nu_2)(u_0),\\&0=\int_{a_1}^{a_2} k^{(i)}(x, u_0)(\nu_1(x)-\nu_2(x))\, dx.\end{aligned}$$

If $\nu_1-\nu_2\neq 0$, for i large enough the intersection of supports of $k^{(i)}(\cdot, u_0)$ and $\nu_1-\nu_2$ will be a nonnegligible set, and so the right-hand side above cannot be zero.

We can conclude on the dimension; consider a positive solution ν_1, and any other solution ν_2 of $L^*\nu=\nu$. Because $\nu_1>0$ at each point, we can find a scalar α such that:

$$\alpha\nu_1(u)\geqq\nu_2(u), \qquad a_1\leqq u\leqq a_2$$

and at some point u_0 the equality holds

$$\alpha\nu_1(u_0) = \nu_2(u_0).$$

Then Lemma 9 implies that: $\nu_2 = \alpha\nu_1$. So, the dimension is 1. Also, because the null spaces of $L-I$ and L^*-I are generated by nonnegative functions μ and ν, we can see that there is nothing more in the null spaces of the iterates $(L-I)^j$, so that the dimension of the generalized eigenspace of L is also equal to 1.

To end with the proof of Proposition 2, we must now look at the maximality of λ^* in Λ.

First, we see from Lemma 7, that for $\lambda > \lambda^*$, $r_k(L_\lambda) < 1$. Therefore, (2) has no nontrivial solution for $\lambda > \lambda^*$. If we assume λ to be a complex number:

$$\lambda = \alpha + i\beta,$$

we have once again

$$r_K(L_\lambda) \leqq r_K(L_\alpha) < 1 \quad \text{if } \alpha > \lambda^*.$$

So, we can restrict our consideration to $\lambda = \alpha + i\beta$, $\alpha = \lambda^*$. It will be easier to consider the adjoint equation. Suppose that ν is a (complex) fixed point of L_λ^*, $\lambda = \lambda^* + i\beta$ so we have

$$\text{(A5)} \qquad L_{\lambda^*}^*|\nu| \geqq |\nu|$$

and, denoting by ν^* a positive fixed point of L^*, for some $C \geqq 0$, we have also

$$\text{(A6)} \qquad L_{\lambda^*}^*|\nu| \leqq C\nu^*.$$

From (A5) and (A6), we can see that the sequence: $\nu_j = L_\lambda^{*j}|\nu|$ is nondecreasing and bounded, so it converges to some function which is a fixed point of $L_{\lambda^*}^*$, i.e. $\lim_{j\to\infty} \nu_j = \gamma\nu^*$. If we assume that for some u_0 in $[a_1, a_2]$, $|\nu(u_0)| = \gamma\nu^*(u_0)$, then the conclusion will be that the equality holds for all u, $a_1 \leqq u \leqq a_2$. On the other hand, if we do not assume this, it means that for all u, $|\nu(u)| < \gamma\nu^*(u)$, so for some $\delta > 1$ and j_0 large enough we would have $\delta|\nu| \leqq L^{*j_0}(|\nu|)$. But then if would iterate this inequality:

$$L^{*kj_0}(|\nu|) \geqq \delta^k|\nu|,$$

we would find the sequence $L^{*i}(|\nu|)$ would be unbounded, which contradicts (A6). So we have, in fact, $|\nu| = \gamma\nu^*$. Coming back to the equation verified by ν, we obtain

$$\text{(A7)} \qquad \left|\int_{a_1}^{a_2} k_\lambda(x, u)\nu(x)\, dx\right| = \int_{a_1}^{a_2} |k_\lambda(x, u)||\nu(x)|\, dx$$

which implies that

$$\text{(A8)} \qquad k_\lambda(x, u)\nu(x) = |k_\lambda(x, u)||\nu(x)|C,$$

C being a constant complex number. So $\nu(x) = C|\nu(x)|$, and from (A8) we get: $k_\lambda(x, u) = |k_\lambda(x, u)|$, which implies that λ is a real number. So λ^* is the unique point in Λ with $\operatorname{Re}\lambda \geqq \lambda^*$.

Remark. In fact, if we use specifically the expression of L_λ given in (2), we can obtain more properties of Λ: we can prove that when the real part is bounded, the imaginary part also stays bounded. This implies, in particular, that λ^* is isolated in the following sense: for some $\varepsilon > 0$, λ^* is the only element of Λ in the set of $\{z: \operatorname{Re} z \geqq \lambda^* - \varepsilon\}$. To prove the boundedness, consider a pair (λ, μ), solution of (2). We write that $\mu = L_\lambda^2\mu$:

$$\text{(A9)} \qquad \mu(x) = e^{-\lambda\theta(x)} \int_{a_1}^{a_2} \mu(y)\left(\int_{a_1}^{a_2} g(x, u)g(u, y)\, e^{-\lambda\theta(u)}\, du\right) dy.$$

It is now a well-known fact in the Fourier series theory that $\int e^{-i\alpha\theta}h(\theta)\,d\theta$ tends to zero as α tends to ∞. This result is uniform with respect to x, y in $[a_1, a_2]$ and Re λ in a fixed bounded set. So the norm of the right-hand side of (A9) will be small if the imaginary part of λ is large, and then $\|L_\lambda^2\| < 1$, making it impossible for L_λ to have a nontrivial fixed point.

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REFERENCES

[1] F. F. BONSALL, *Linear operators in complete positive cones*, Proc. London Math. Soc., 8 (1958), pp. 53–63.

[2] O. DIEKMANN, *Volterra integral equations and semigroups of operators*, Stichting Mathematisch Centrum, TW 197/80 (1980), Amsterdam.

[3] O. DIEKMANN, H. J. A. M. HEIJMANS AND H. R. THIEME, *On stability of the cell size distribution*, Stichting Mathematisch Centrum, TW 242/83 (1983), Amsterdam.

[4] ———, *On the stability of the cell size distributions*, J. Math. Biol., 19 (1984), pp. 227–268.

[5] N. DUNFORD AND J. T. SCHWARTZ, *Linear Operators, Part* I, John Wiley, New York, 1957.

[6] F. R. GANTMACHER, *Theory of Matrices*, Chelsea, New York, 1960.

[7] J. HALE, *Theory of Functional Differential Equations*, Springer, New York, 1977.

[8] E. HELLINGER AND O. TOEPLITZ, *Integralgleichungen und Gleichungen mit unendlichvielen Unbekannten*, Chelsea, New York, 1953.

[9] E. HILLE, *Functional Analysis and Semigroups*, Amer. Math. Soc. Colloq. Publ., Vol. 31, New York, 1948.

[10] M. KIMMEL, Z. DARZYNKIEWICZ, O. ARINO AND F. TRAGANOS, *Analysis of a model of cell cycle based on unequal division of mitotic constituents to daughter cells during cytokinesis*, J. Theoret. Biol., 101 (1984), pp. 637–664.

[11] M. A. KRASNOSELSKII, *Positive Solutions of Operator Equations*, Noordhoff, Groningen, 1964.

[12] A. LASOTA AND M. C. MACKEY, *Globally asymptotic properties of proliferating cell populations*, J. Math. Biol., 19 (1984), pp. 43–62.

[13] R. K. MILLER, *Linear Volterra integrodifferential equations as semigroups*. Funkcial. Ekvac., 17 (1974), pp. 39–55.

[14] CH. MODE, *Multitype Branching Processes*, American Elsevier, New York, 1971.

[15] R. NUSSBAUM, *Topological Methods in Nonlinear Analysis*, Unpublished Lecture Notes, Summer Course of the University of Montreal, 1983.

[16] ———, *The radius of the essential spectrum*, Duke. Math. J., 38 (1970), pp. 473–478.

[17] J. PRÜSS, *Equilibrium solutions of age specific population dynamics of several species*, J. Math. Biol., 11 (1981), pp. 65–84.

[18] C. C. TRAVIS AND G. F. WEBB, *Existence and stability for partial differential equations*, Trans. Amer. Math. Soc., 200 (1974), pp. 395–418.

[19] J. J. TYSON AND K. G. HANNSGEN, *The distributions of cell size and generation time in a model of the cell cycle incorporating size control and random transitions*, J. Theoret. Biol., 113 (1985), pp. 29–62.

[20] G. WEBB, *A semigroup proof of the Sharpe-Lotka Theorem*, in Infinite-Dimensional Systems, F. Kappel and W. Schappather, eds., Lecture Notes in Mathematics 1076, Springer-Verlag, Berlin, 1984.

[21] G. F. WEBB, *Theory of Nonlinear Age Dependent Population Dynamics*, Marcel Dekker, New York, 1985.