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A stochastic model of a cell population with quiescence

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A cell population in which cells are allowed to enter a quiescent (nonproliferating) phase is analyzed using a stochastic approach. A general branching process is used to model the population which, under very mild conditions, exhibits balanced exponential growth. A formula is given for the asymptotic fraction of quiescent cells, and a numerical example illustrates how convergence toward the asymptotic fraction exhibits a typical oscillatory pattern. The model is compared with deterministic models based on semigroup analysis of systems of differential equations.

Keywords: cell cycle dynamics; branching process; asynchronous exponential growth; quiescence

AMS 2000 Mathematics Subject Classification Codes: 60G99; 60K99; 62P10; 92D25

1. Introduction

The cell cycle of a eukaryotic cell consists of four phases: G_1 where the cell grows, S where its DNA synthesizes, G_2 where it prepares for division, and M where it divides. However, it may also happen that a cell in G_1 enters another phase called G_0 where the cell is said to be *quiescent*. The decision whether to enter G_0 is made at a particular time, the *restriction point*. A cell may remain quiescent indefinitely, as is for example often the case with neurons, but it may also leave G_0, re-enter G_1 a the point where it left, and proceed through the cell cycle, [6].

Cell populations with quiescence have attracted interest from the mathematical modelling community, primarily via deterministic models based on differential equations, [1,3,4]. In such models, a fundamental property of cell populations is that of *asynchronous* (or *balanced*) *exponential growth*, which means that the population grows exponentially at the same time as proportions of various individual characteristics converge to a stable limiting distribution, independently of initial conditions.

In [1] and [3], deterministic models of a population of proliferating and quiescent cells are introduced and analyzed. The models in the two papers differ only slightly from each other, and are based on stating a system of partial differential equations for the densities of quiescent and proliferating cells. The variables are time and cell age, and the main goal is to establish sufficient

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(and to some extent necessary) conditions for asynchronous exponential growth, using semigroup methods.

We propose a stochastic model that is intuitively clear and avoids some of the assumptions of the deterministic models, yet establishes similar results. The theoretical tools come from the theory of general branching processes, [5].

2. The branching process model

The fundamental mathematical object in a general branching process is the *reproduction process*, ξ. This is a point process on $[0, \infty]$ that describes how an individual reproduces, thus $\xi(a) = \int_0^a \xi(\mathrm{d}t)$ gives the number of children up to age a. Each newborn individual starts reproducing according to a copy of ξ, independently of other individuals. In cell populations where reproduction is by division, ξ is characterized by two random variables: the lifetime L and the number of offspring X. Specifically,

$$\xi(\mathrm{d}t) = X\delta_L(\mathrm{d}t)$$

where δ_L is the unit point mass at L.

To capture the growth rate of the process, we consider the *mean reproduction process*, $\mu(\mathrm{d}t) = E[\xi(\mathrm{d}t)]$, and, in particular, its Laplace transform

$$\widehat{\mu}(r) = \int_0^\infty \mathrm{e}^{-rt}\mu(\mathrm{d}t).$$

The growth rate is now determined by the *Malthusian parameter*, which is the number α that satisfies $\widehat{\mu}(\alpha) = 1$. If $\alpha > 0$, the process is said to be *supercritical*, which means that it grows as $\mathrm{e}^{\alpha t}$ and has a chance of avoiding extinction. In a cell population with no death, the equation defining α becomes

$$2\widehat{F}(\alpha) = 1$$

where F is the distribution function of L. For a comprehensive treatment of general branching processes, see [5].

Let us now turn to our model. Denote by T the time until the restriction point. At this point, with probability q, the cell enters the G_0 phase and becomes quiescent for a time denoted by G_0, after which it returns to G_1 and finishes the cell cycle in an additional amount of time U. With probability $1 - q$, the cell does not enter G_0 and finishes the cycle in an additional amount of time U. When the cell cycle is completed, the cell divides into two daughter cells. We assume that T, U, and G_0 are continuous random variables with finite expectations. Let Q denote the event that the cell becomes quiescent, let F_{T+U} denote the distribution function of $T + U$ and F_{T+G_0+U} the distribution function of $T + G_0 + U$. The reproduction process becomes

$$\xi(\mathrm{d}t) = 2I_{Q^c}\delta_{T+U}(\mathrm{d}t) + 2I_Q\delta_{T+G_0+U}(\mathrm{d}t)$$

where I denotes indicator function. Further

$$\mu(\mathrm{d}t) = 2(1-q)F_{T+U}(\mathrm{d}t) + 2qF_{T+G_0+U}(\mathrm{d}t) \tag{1}$$

and the Malthusian parameter is defined by the equation

$$\widehat{\mu}(\alpha) = 2(1-q)\widehat{F}_{T+U}(\alpha) + 2q\widehat{F}_{T+G_0+U}(\alpha) = 1.$$

To keep track of quiescent cells, we employ the use of *random characteristics*. In a general branching process, a random characteristic χ is a stochastic process that follows an individual

from its birth and at age a records the score $\chi(a)$. The notation Z_t^{χ} is introduced for the χ-*counted population*, that is, the sum of all χ-scores in a population at time t. To count the number of quiescent cells at time t, we introduce the characteristic χ_Q, defined by

$$\chi_Q(a) = I\{Q \cap \{T < a, T + G_0 > a\}\}, \quad a \geq 0$$

the indicator of the event that the cell is quiescent at age a, which means that $Z_t^{\chi_Q}$ is the number of quiescent cells at time t.

The characteristic counting the total number of cells present in the population is χ_T defined by

$$\chi_T(a) = I\{Q^c \cap \{T + U > a\}\} + I\{Q \cap \{T + G_0 + U > a\}\} \tag{2}$$

the indicator of the event that the cell is present in the population at age a, where we separate into the two cases that it is proliferating and that it is quiescent. Thus, the fraction of quiescent cells at time t is

$$Q(t) = \frac{Z_t^{\chi_Q}}{Z_t^{\chi_T}}$$

and we are interested in the limit of $Q(t)$ as $t \to \infty$ (bearing in mind that $Q(t)$ is a random quantity). To ease notation, introduce the two survival functions $G_{T+U} = 1 - F_{T+U}$ and $G_{T+G_0+U} = 1 - F_{T+G_0+U}$, and the function $H(t) = P(T < t < T + G_0)$. The Laplace transform $\widehat{f}$ of a function f is given by $\widehat{f}(\alpha) = \int_0^\infty \mathrm{e}^{-\alpha t} f(t)\mathrm{d}t$ and we can state the main result next. The proof is given in Appendix A.

PROPOSITION 1 *Let $Q(t)$ denote the proportion of quiescent cells in the population at time t. Then, with probability* 1,

$$Q(t) \longrightarrow \frac{q\widehat{H}(\alpha)}{(1-q)\widehat{G}_{T+U}(\alpha) + q\widehat{G}_{T+G_0+U}(\alpha)}$$

as $t \to \infty$.

Note that our formula for the asymptotic fraction is very similar to the one given in Theorem 2 in [3], with their parameter f, the probability that a cell is born into the proliferating phase, equal to one, and their w's playing the role of our G's (which, as is easily checked, satisfy the differential equation given for W in [3]).

3. An example

To illustrate how the convergence toward the limit in Proposition 1 occurs, let us consider an example where we suppose that T, U, and G_0 are independent random variables, each with a gamma distribution with parameters 3 and 1. Then $T + U$ and $T + G_0 + U$ also have gamma distributions: $T + U \sim \Gamma(6, 1)$ and $T + G_0 + U \sim \Gamma(9, 1)$, where we recall that the probability density function of $\Gamma(n, 1)$ is

$$f_n(t) = e^{-t}\frac{t^{n-1}}{(n-1)!}, \quad t \geq 0.$$

The gamma distribution is a flexible and useful distribution for quantities that are nonnegative and tend to have slightly skewed distributions as is typically the case for cell lifetimes. Our

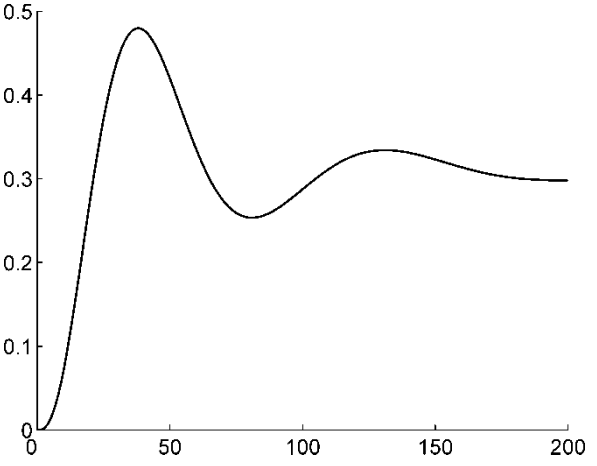

Figure 1. The fraction of quiescent cells as a function of time.

choice of parameters is arbitrary, but the parameter values do not qualitatively alter the pattern of convergence toward the limit.

The Laplace transform of the $\Gamma(n, 1)$ density is $1/(1+\alpha)^n$ and the Malthusian parameter is defined by the equation

$$\frac{2(1-q)}{(1+\alpha)^6} + \frac{2q}{(1+\alpha)^9} = 1.$$

For this example, we choose $q = 0.9$, which gives $\alpha \approx 0.08$ and the limit of $Q(t)$ becomes ≈ 0.30 (see Appendix B for details).

To illustrate the convergence of $Z_t^{\chi_Q}/Z_t^{\chi_T}$ toward its limit, we consider its expected value and make the following simplifying first-order approximation:

$$E\left[\frac{Z_t^{\chi_Q}}{Z_t^{\chi_T}}\right] \approx \frac{E[Z_t^{\chi_Q}]}{E[Z_t^{\chi_T}]} \tag{3}$$

where it is shown in Appendix B how to deal computationally with $E[Z_t^{\chi_Q}]$ and $E[Z_t^{\chi_T}]$. As a side note, let us point out that it is the latter ratio in Equation (3) that also the deterministic models deal with. In Figure 1, $E[Z_t^{\chi_Q}]/E[Z_t^{\chi_T}]$ is plotted as a function of time and we can notice an oscillatory behaviour which is typical for functions dealing with cell cycle properties, [2].

4. Discussion

We have established explicit expressions for the asymptotic fraction of quiescent cells in a population of quiescent and proliferating cells. The model is a general branching process whose conditions are mild and biologically reasonable. It is interesting to compare with the deterministic model in [3], where similar results are established but the assumptions are more restrictive.

One problem with the model in [3] is that the transition rates between states, as well as the division rate, all depend on the cell's age and nothing else. Thus, two proliferating cells of the same age are considered equally likely to divide even if one of them has spent most of its life as quiescent. Our way of modelling the stages of the cell cycle avoids this undesirable property.

The model in [3] allows a cell to transfer in and out of quiescence any number of times, which is not allowed in our model. However, it does not seem to be motivated by biological considerations [6], and we could adjust our model to allow for such back-and-forth transitions simply by adding more checkpoints. In such a model, it is important to keep track of the total amount of time spent in the proliferating state as it is this time, not the age of the cell, that determines the cell's position in the cell cycle and thus its readiness to divide.

Finally, in [3] there are assumptions about boundedness of lifetimes as well as other technical conditions that we avoid altogether.

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Appendix A

The proof of Proposition 1 follows from Theorem 5.10 in [5]. Suppose that the mean reproduction process $\mu(\mathrm{d}t)$ is nonlattice (cannot be supported by any lattice $\{a, 2a, 3a, \ldots\}$), let $\alpha > 0$ be the solution to the equation $\widehat{\mu}(\alpha) = 1$, define $\beta = \int_0^\infty t\mathrm{e}^{-\alpha t}\mu(\mathrm{d}t)$, and let χ_1 and χ_2 be two random characteristics. Then,

$$\frac{Z_t^{\chi_1}}{Z_t^{\chi_2}} \longrightarrow \frac{E[\widehat{\chi}_1(\alpha)]}{E[\widehat{\chi}_2(\alpha)]}$$

almost surely as $t \to \infty$ under the following conditions:

(i) $\beta < \infty$

(ii) $\widehat{\mu}(r) < \infty$ for some $r < \alpha$

(iii) $E\left[\sup_a \mathrm{e}^{-\alpha a}\chi(a)\right] < \infty$

(iv) $\sum_{k=0}^{\infty} \sup_{k\le a\le k+1} \mathrm{e}^{-\alpha a}E[\chi(a)] < \infty$

Recalling that, we have

$$\mu(\mathrm{d}t) = 2(1-q)F_1(\mathrm{d}t) + 2qF_2(\mathrm{d}t)$$

where F_1 and F_2 are distributions functions of finite-mean random variables, it is easily seen that (i) and (ii) hold. Moreover, the characteristic counting all cells is

$$\chi_T(a) = I\{Q^c \cap \{T + U > a\}\} + I\{Q \cap \{T + G_0 + U > a\}\}$$

which implies that $\chi_T(a) \le 1$, and (iii) and (iv) follow immediately. Similarly, (iii) and (iv) hold for the characteristic χ_Q, and as $E[\widehat{\chi}_Q(\alpha)] = q\widehat{H}(\alpha)$ and $E[\widehat{\chi}_T(\alpha)] = (1-q)\widehat{G}_1(\alpha) + q\widehat{G}_2(\alpha)$, the proof of Proposition 1 is complete.

Appendix B

In Section 3, we used the approximation

$$E\left[\frac{Z_t^{\chi_Q}}{Z_t^{\chi_T}}\right] \approx \frac{E[Z_t^{\chi_Q}]}{E[Z_t^{\chi_T}]}$$

where $E[Z_t^{\chi_Q}]$ and $E[Z_t^{\chi_T}]$ were computed numerically. To do so, standard results from renewal theory yield

$$E[Z_t^{\chi}] = E[\chi] * \nu(t) = \int_0^t E[\chi(t-u)]\nu(\mathrm{d}u)$$

where ν is the renewal measure

$$\nu(\mathrm{d}u) = \sum_{n=0}^{\infty} \mu^{*n}(\mathrm{d}u)$$

μ^{*n} being the n-fold convolution of μ where μ^{*0} by definition equals δ_0, the unit point mass at 0. For details, see [5].

In our cell population reproduction is by division. Denote the lifetime distribution function by F to get the relation

$$\mu^{*n}(t) = 2^n F^{*n}(t)$$

Here, 2^n is the number of individuals in the nth generation and $F^{*n}(t)$ is the distribution function of the sum of n independent lifetimes.

Recalling that the lifetime L equals $T + G_0 + U$ if quiescence occurs, and $T + U$ otherwise, we can obtain an expression for F^{*n}, the distribution of the sum of n independent copies of L. Such a sum contains n copies each of T and U and X copies of G_0 where X has a binomial distribution with parameters n and q. We get

$$F^{*n} = \sum_{k=0}^{n} \binom{n}{k} q^k (1-q)^{n-k} F_T^{*n} * F_U^{*n} * F_{G_0}^{*k}$$

In our example, we chose T, U, and G_0 to be independent $\Gamma(3, 1)$, in which case $F_T^{*n} * F_U^{*n} * F_{G_0}^{*k}$ is the gamma distribution with parameters $6n + 3k$ and 1, and the density becomes

$$\frac{d}{\mathrm{d}u} F^{*n}(u) = \mathrm{e}^{-u} \sum_{k=0}^{n} \binom{n}{k} q^k (1-q)^{n-k} \frac{u^{6n+3k-1}}{(6n+3k-1)!}$$

The functions that are to be integrated are $E[\chi_Q(t)]$ and $E[\chi_T(t)]$, which are easily computed. For example,

$$E[\chi_Q(t)] = P(\text{cell is quiescent at age } t) = q \int_0^t P(G_0 > t-u) f_T(u)\mathrm{d}u$$

For the example, we chose $q = 0.9$ which gave $\alpha \approx 0.08$, which makes the limit in Proposition 1 ≈ 0.30.