A Deterministic Cell Cycle Model with Transition Probability-Like Behaviour

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I. INTRODUCTION

The time between cell birth and cellular division is known as the cell generation, or cell cycle, time. In a steady state population of apparently identical cells, the distribution of generation times is broad, thus indicating considerable variability in the rate at which cells traverse the cell cycle. Perturbation of a steady state population of cells is followed by a rapid return of successive distributions of cell cycle times to the unperturbed distribution. The interpretation of the origin of this variability in cellular processes has been uniformly based on probabilistic considerations [1-5].

Here it is shown how a completely deterministic process may lead to a description of cellular variability indistinguishable from that having its origins in probabilistic considerations. The model is very similar to that of [6] with the important exception that an alternative deterministic hypothesis replaces the assumption made previously concerning the probability of mitosis.

II. MATHEMATICAL PRELIMINARIES

In this section, the notions of a smooth density and Rényi transformations are introduced before starting a theorem that is central to the development of the model.

A function $h:[0,1] \to R$ that is Lipschitzean and satisfies

$$\min h > 0 \quad \text{and} \quad \int_0^1 h\,d\mu = 1,$$

where μ denotes the Lebesgue measure on $[0,1]$, is called a **smooth density.**

A mapping $S:[0,1] \to [0,1]$ which satisfies:

i) There exists a partition $0 = a_0 < a_1 < \ldots < a_p = 1$ of $[0,1]$ such that for each integer i, $i = 1, \ldots, p$, the restriction of S_i of S to the open interval (a_{i-1}, a_i) can be extended as a C^2 function to $[a_{i-1}, a_i]$;

ii) $S_i([a_{i-1}, a_i]) = [0,1]$, $i = 1, \ldots, p$; and

iii) $\inf_{(a_{i-1}, a_i)} |S'(x)| > 1 \quad i = 1, \ldots, p$

is called a **Rényi transformation.**

Theorem (LASOTA and YORKE [7]). Let $S:[0,1] \to [0,1]$ be a Rényi transformation, $S_\varepsilon = (1+\varepsilon)S$ where $\varepsilon > 0$, and $N_\varepsilon(x)$ be the smallest integer n, $n = 0,1, \ldots$, such that $S_\varepsilon^{n+1}(x) > 1$ for a given initial $x \in [0,1]$, i.e.

$$N_\varepsilon(x) = \inf \{n : S_\varepsilon^{n+1}(x) > 1\}.$$

Then there exists a unique constant $\sigma > 0$ such that for every smooth density h of initial $x \in [0,1]$

$$\lim_{\varepsilon \to 0} \mu_h\{x : N_\varepsilon(x) > T/\varepsilon\} = \exp(-\sigma T), \quad T \geq 0, \quad \text{where}$$

$$\mu_h(x) = \int_0^x h \, d\mu.$$

What is the content of this theorem? For $\varepsilon > 0$ it is clear that eventually there must exist some "kick-out time" [8] n such that $S_\varepsilon^{n+1}(x) \notin [0,1]$. The theorem merely states that, for $\varepsilon \to 0$ the fraction of points from an initial density h with kickout times greater than $T \geq 0$ is exponentially distributed:

$$\mu_h\{x : N_\varepsilon(x) > T\} \cong \exp(-\sigma\varepsilon T).$$

III. THE MODEL

With the preliminaries of the previous section, we may proceed to a development of the model of the cell cycle. The model is mathematically identical to that developed in [6]. Only the interpretation of one hypothesis is different.

The model rests on three hypotheses.

H1. There exists some substance(s) (mitogen) necessary, but not sufficient, for mitosis to take place.

There is ample experimental support for this concept, as reviewed in [9].

Consider a cell in a large population that was born at time $t = 0$ with mitogen content r. The evolution of mitogen following birth is governed by

$$\frac{dm}{dt} = g(m), \quad m(0) = r. \tag{1}$$

The solution of (1) is denoted by $m(r,t)$. Mitogen levels are assumed to be bounded on the closed interval to $[0,2\ell]$, and the mitogen production-rate satisfies

$$g(m) > 0 \quad \text{for } 0 < m < 2\ell \quad \text{and} \tag{2a}$$

$$g(2\ell) = 0. \tag{2b}$$

H2. There exists an intracellular variable, sufficient to trigger mitosis once it exceeds a threshold, that oscillates in an extremely complicated "chaotic" fashion.

Let $x(t)$ denote the level of this variable at time t, and t_n, $n = 0,1, \ldots$, denote the times at which $x(t)$ attains a relative maximum. If $x_n = x(t_n)$ denotes the values of these relative maxima, then it is assumed that

$$x_{n+1} = \lfloor 1+m(t_n) \rfloor S(x_n) \tag{3}$$

where $S:\lfloor 0,1 \rfloor \to \lfloor 0,1 \rfloor$ is a Rényi transformation. Mitosis is assumed to take place whenever $x_n > 1$.

This hypothesis, in conjunction with the theorem of the previous section, tells us that for small mitogen levels the fraction of a large population of cells with mitotic times greater than some number $T \geq 0$ is given approximately by

$$\mu_h\{x_0 : N_m(x_0) > T\} = \exp(-\sigma m T)$$

regardless of the density of h of initial values x_0. Thus the mitotic rate is approximately (σm) for small m.

Remark. This second hypothesis gives a deterministic interpretation of the probabilistic assumption of [6] that the probability of a cell with mitogen level m dividing in a time $[t, t+\Delta t]$ is

$$\phi(m)\Delta t + o(\Delta t), \quad \phi(0) = 0, \quad \liminf_{x \to 2\ell} \phi(x) > 0.$$

With a mitotic rate of (σm), if we let $\alpha(r,t)$ denote the fraction of cells born with mitogen level r that have not divided by time t, then we have approximately

$$\frac{d\alpha(r,t)}{dt} = -\sigma m(r,t)\alpha(r,t), \qquad \text{so}$$

$$\alpha(r,t) = \exp\left\{-\sigma \int_0^t m(r,s)\,ds\right\}.$$

Note that $-\alpha_t(r,t) = \sigma m(r,t)\alpha(r,t)$ is the density function for the distribution of mitotic (generation) times in these cells with initial mitogen levels r.

Generally, the initial mitogen level r in a large population of cells will be distributed on $[0,\ell)$ with a density $f(r)$, so the alpha-curve for the entire population is given by

$$\alpha(t) = \int_0^{\ell} \alpha(r,t) f(r)\,dr. \tag{4}$$

Finally, the density function for the distribution of generation times for the

entire population is given by

$$\psi(t) = -\int_0^{\ell} \alpha_t(r,t)f(r)dr. \tag{5}$$

Another statistic, widely used by cell kineticists in characterizing populations of renewing cells, is the fraction of sibling cell pairs whose intermitotic times differ by at least a time t. This fraction is denoted by $\beta(t)$. The derivation of the beta-curve for this hypothetical cellular population requires a third assumption concerning the fate of the mitogen in a mother cell when mitosis takes place. Here, as in [6], it is assumed that:

H3. Each sister cell receives exactly one-half of the mitogen present in the mother cell at mitosis.

This leads directly to the result

$$\beta(t) = -2\int_0^{\infty}\int_0^{\ell} \alpha_t(r,s)\alpha(r,s+t)f(r)dsdr$$

which has been obtained before [6].

To complete the specification of this model requires the distribution $f(r)$ of initial mitogen levels in the population of cells. As shown in [6], the distribution of mitogen f_{i+1} in the (i+1)st generation of cells is determined by that in the ith generation, f_i, from the integral equation

$$f_{i+1}(y) = \int_0^{\ell} k(y,r)f_i(r)dr \tag{6}$$

where the kernel $k(y,r)$ is given by

$$k(y,r) = \begin{cases} 0 & 0 \leq y < \tfrac{1}{2}r \\ 2q(2y)\exp\left\{\int_r^{2y} q(z)dz\right\} & \tfrac{1}{2}r \leq y < \ell \end{cases}$$

and $q(y) = \sigma y/g(y)$. With the properties of $g(y)$ specified in (2a,b), (6) has a unique globally, asymptotically stable solution $f_*(y)$. This ensures that there is a unique density function $\psi_*(t)$ for the distribution of cell cycle times in the entire population of cells.

IV. DISCUSSION

Of the three hypotheses used in the development of this model, H1 and H3 have appeared in a number of other cell cycle models. Only H2 is unique, and I will confine my comments to H2.

With respect to H2, at least two questions arise. The first is mathematical in nature. Is there any dynamical or semi-dynamical system that is oscillatory and which has successive maxima determined by the map (3)? Clearly, any such continuous time system must, by necessity, be of dimensionality 3 or greater. Though there is no analytic proof of the existence of such systems at this time, there is good numerical evidence for their existence.

Consider the LORENTZ [10] equations

$$\begin{aligned} \frac{dx}{dt} &= yz - bx \\ \frac{dy}{dt} &= -xz + rz - y \\ \frac{dz}{dt} &= \sigma(y-z) \end{aligned} \tag{7}$$

with $\sigma = 10$ and $b = 8/3$. Lorentz numerically investigated this system for a variety of values of r. If successive maxima in $x(t)$ are labeled as x_n, then the points (x_n, x_{n+1}) are approximately located on the graph of the one-dimensional mapping

$$T_{\varepsilon(r)}(x) = [1+\varepsilon(r)][1-\tfrac{1}{2}u^{\frac{1}{4}}(1+u)], \quad u = |1-2x|, \quad x \in (0,1).$$

YORKE and YORKE [8] studied this system (7) and found that there is a critical range of the parameter r such that $\varepsilon(r) > 0$ and the results of the theorem of section II hold. They were also able to demonstrate the exponential dependence of the kickout times predicted by the theorem of Lasota and Yorke.

The second question raised by H2 is related to its biological justification. In this regard I can offer arguments for the hypothesis that are no more, nor less, convincing than those put foward to justify the usual probabilistic assumption that H2 replaces.

The assumption that there is an intracellular oscillator timing the cell cycle is certainly not new, as a variety of investigators have proposed such a scheme [11-15] or criticized it [16]. Indeed, considering the nature of the cell cycle, it would be surprising if the existence of an underlying oscillator had not been hypothesized. The nature of the oscillators considered ranges from 'limit cycle' to 'relaxation' types, though the distinction is more one of degree than of type. Others have assumed that this intracellular oscillator has superimposed 'noise' to mimic the distribution of cell cycle events [17-21] though this assumption begs the question addressed here.

However, the existence of an oscillator such as that considered here -- one with a strange attractor -- seems not to have been considered even though all of the ingredients are present for its occurrence. (The existence of such an oscillator was all but explicitly postulated in [22]). It is well known that the biochemical control loops within the cycling cell are numerous, richly interconnected, and nonlinear. Further, many display mixed positive/negative feedback with or without significant time delays in their feedback pathways [23-25]. As has been shown numerically [26,27] these are exactly the conditions under which one may encounter the presence of strange attractors and the attendant Rényi transformation-like connection between successive maxima [28].

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