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AN APPLICATION OF GENERAL BRANCHING PROCESSES TO A CELL CYCLE MODEL WITH TWO UNCOUPLED SUBCYCLES AND UNEQUAL CELL DIVISION

MARINA ALEXANDERSSON*

A cell population model is constructed and analysed in the framework of general branching process theory. The model uses the idea that the DNA division cycle and the cell growth cycle are loosely coupled. The cell division is assumed to be unequal and the structure variables of the model are size and growth, where the growth is regulated by supramitotic growth control. An explicit expression for the stable birth type distribution is given and asymptotics, such as the α- and β_1-curve and various size distributions, are derived. We also prove that the microheterogeneity in growth causes the mother-daughter life length correlation to be non-negative.

Keywords: branching process, cell cycle model, unequal cell division, stable type distribution, α-curve, β-curve, mother-daughter correlation

1. Introduction

Mathematical modelling of cell populations is of great importance e.g. in bacteriology and cell biology, since it enables us to compare theories in cell kinetics and cell growth with real observations. Cell kinetics provide mathematicians with interesting applications and solving the difficulties that arise stimulates not only the development of mathematical tools, but also the search for new biological interpretations and questions to be handed back to biologists. This may lead to new insights not only about the cell cycle control system, but also about the treatment of cell-related human diseases, e.g. diseases caused by too much cell division (cancer) or too little (non-regenerative tissues).

Modern mathematical population modelling has its roots in the beginning of the century when Sharpe and Lotka (1911) introduced the first structured model in demography. The first deterministic models were *age*-structured, meaning that every individual in the population is characterised by its age. Other structures, as we will see later, can be size, weight, growth etc. and will be referred to as the *types* of the individuals. Sharpe and Lotka conjectured the existence of a *stable age distribution*

* Department of Mathematical Statistics, Chalmers University of Technology and Gothenburg University, S-412 96 Göteborg, Sweden, e-mail: malex@math.chalmers.se

introducing a renewal equation treatment. An *age distribution* gives the proportions of individuals in various age intervals at a certain time, and *stable* indicates that the composition of the population has stabilised with respect to age. The importance of the existence of such a distribution is due to the fact that no matter what the initial age distribution is, the composition of age will tend to the stable one. In cell populations this would mean that it is possible to generate a large population from one single cell.

Since population dynamics originates from the study of human populations, where the fertility is clearly age dependent, the age-structure is a natural choice. But when considering cell populations, it seems more appropriate to take the *size* (e.g. mass, volume, DNA-content etc.) of the individuals into account. One of the most influential papers on size structured *cell* populations seems to be (Bell and Anderson, 1967), which gave rise to the so-called Bell-Anderson model. One approach to study such size structured cell populations was initiated in (Lasota and Mackey, 1984), where mitosis was thought to depend on some substance they chose to call mitogen. That is to say, the size structure is the mitogen level in the cells and each daughter cell receives exactly one half of the mitogen level of the mother, and the asymptotic distribution of mitogen was shown to be the solution to an integral equation that under mild assumptions becomes asymptotically stable. In (Heijmans, 1984) reproduction occurred by fission into two *unequal* parts introducing a variable p which is the ratio of the birth size of a daughter cell and the division size of the mother. We will use the same idea for unequal cell division in this paper. In (Webb, 1987) a deterministic *transition probability model* with inheritance was constructed using both age and size as structure variables. Transition probability models use the idea that the cell cycle consists of a completely deterministic B-phase and an indeterminate or stochastic A-phase. During its life length the cell is thought to progress through four, sometimes five, different stages: $G_1 + S + G_2 + M$, where S is the DNA synthesis period, M the mitosis or cell division, and G_1 and G_2 are preparation periods or 'gaps'. The cell cycle is sometimes expanded with a fifth stage G_0, which is a resting period between mitosis and G_1, and from which cells are recruited randomly into G_1. In the transition probability models the A-phase contains G_0, when introduced, and the first part of G_1, and the B-phase consists of the remainder of G_1, S, G_2 and M. The inheritance in (Webb, 1987) was introduced in the model by letting the growth of the cell, the transition between phases and the cell division depend on the birth size of the cell, since the birth size can be considered as an inheritance of the mother.

A more relevant reference to the present paper is the branching process version of the Bell-Anderson model that was presented in (Taib, 1996) and also treated in (Jagers, 1992), where the relationship between deterministic modelling and the *expected* evolution of a branching process was discussed. These two main approaches, deterministic modelling using partial differential equations and stochastic modelling using branching processes, were compared in detail in (Arino and Kimmel, 1993) considering a size-structured cell cycle model. It turns out that without the additional structure of cell age in the PDE approach there is no obvious counterpart in branching processes, while introducing the age variable gives equivalence between the PDE model and a forward equation in the branching process model. This made the authors

question the use of PDE models without the age variable, which, as we have seen, is a rather frequent approach. On the other hand, using size as structure variable is not completely indisputable either. Size-structured models are sometimes criticised because they render negative mother-daughter life length correlation. Especially for mammalian cells this correlation is observed zero or positive (cf. (Webb, 1987) and references therein). We come back to this later.

A recent, extensive list of references, and a fine collection of articles on different kinds of cell population models can be found in (Arino *et al.*, 1995).

In this paper, we use the theory of branching processes described in (Jagers and Nerman, 1996) to model a cell population, called the Two-Subcycle cell cycle model, based on experiments on multipotent embryonal carcinoma cells (PCC3) described and analysed in (Sennerstam and Strömberg, 1995). As we shall see later, the theory of general multi-type branching processes is unusually well suited for modelling and analysing the development of cell populations. The rules of cell proliferation are clearly individual based and branching processes are concentrated on the life career and reproduction pattern on the individual level. With some informal law of large numbers argument we then relate individual properties to the development on the population level.

In the Two-Subcycle model the cell cycle consists of two simultaneously running subcycles: the DNA division cycle (DDC) and the cell growth cycle (CGC). The cell is thought to enter mitosis as soon as the DDC is finished, regardless of the CGC. In the main case, which is the case treated here, the CGC extends past cell division. The cell divides unequally and the daughter cells continue to grow to complete their mother's CGC before they enter their own DDC. In the Two-Subcycle model the structure variables are, to begin with, both size and growth. Introducing the growth as a structure variable simply means that we let the growth vary somewhat between cells. Moreover, we assume supramitotic growth control, meaning that instead of choosing growth rate at the beginning of the cell cycle, the decision is made at a rate regulation point, sometimes called the restricition point, within the G_1-phase, and its influence extends past mitosis to the next decision point. We prove that in this model we avoid the problem of a negative mother-daughter life length correlation. We study the asymptotic composition of the model as a transition probability model, such as the α- and β-curves and various size distributions. We give an explicit expression of the stable birth type distribution, and we compare our model to the simulation results in (Sennerstam and Strömberg, 1995).

2. The Biological Model

The cell line in focus in (Sennerstam and Strömberg, 1995) consists of multipotent embryonal carcinoma cells (PCC3). The cell cycle is defined as the time period between two consecutive mitotic events (i.e. between two cell divisions) and is divided into four phases, $G_1 + S + G_2 + M$, where S is the period where the DNA synthesis takes place, M is mitosis and G_1 and G_2 are preparation periods ('gaps') or presynthetic phases of S and M, respectively. The idea here is that the cell cycle consists of

two mutually dissociated, simultaneously running subcycles: the DNA division cycle (DDC) causing a doubling of the genome, and the cell growth cycle (CGC) where the cell doubles its size.

The DDC is assumed to have a fairly constant duration and covers the $S+G_2+M$ phases and a pre-S phase. The pre-S phase is postulated to be a temporally constant (cf. Sennerstam and Strömberg, 1995) late G_1-period (G_1pS) when a cell is committed to enter S phase. In the simplest case the CGC spans over the same time interval as the DDC, beginning at some cell size m_0. However, this is usually not the case. The CGC is assumed to vary considerably in growth rate, as found experimentally (Fraser and Nurse, 1978), and the most common situation is that the cell grows rather slowly and the CGC extends past mitosis (Sennerstam and Strömberg, 1995). The cell divides unequally and each daughter cell continues to grow to complete its mother's CGC in what is called the post-M phase (G_1pM). When the cell reaches the critical size m_0, whenever that may occur in that G_1-period, a 'start' event is triggered, and the cell is committed to enter its own DDC and the pre-S phase begins.

In the Two-Subcycle model a microheterogeneity in growth is introduced: the growth control is supramitotic in the sense that a newborn cell continues to grow with the same growth rate as its mother until it reaches the critical size, where it chooses a new growth function. Two sister cells are assumed to get similar, but not identical, growth functions due to some inheritance from the mother. Here this inheritance is represented by a latent growth factor handed over by the mother to the daughters when they reach the critical size. If we assume that the individual cells grow exponentially two sister cells choose new growth rates according to

$$g_1' = g_L + \eta_1,$$

$$g_2' = g_L + \eta_2,$$

where g_L is a latent growth factor and η_1 and η_2 are individual contributions to the growth rates. This behaviour is depicted in Fig. 1.

3. General Multi-Type Branching Processes

A general branching population starts from one ancestor labelled 0. She (we use the convention to think of individuals in a one-sex population as female) gets a number of children which can be labelled according to the elements in $N = \{1, 2, 3, \ldots\}$. Her grandchildren are elements in N^2 and so forth, so that the set of all possible individuals in the population, the *Ulam-Harris space*, is

$$I = \bigcup_{n=0}^{\infty} N^n, \quad N^0 = \{0\}.$$

A newborn individual inherits a type from a *type space* $(S, \mathcal{S})$, where S can be any abstract space with a countably generated σ-algebra, $\mathcal{S}$. Based on its type the individual chooses a life from the *life space* $(\Omega, \mathcal{A})$ where Ω is the set of all possible life careers and $\mathcal{A}$ the corresponding σ-algebra. To do this we equip the *population*

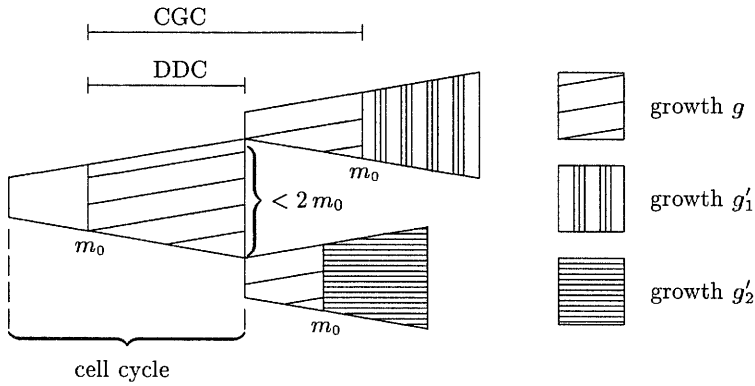

Fig. 1. The cell growth in two generations. Different patterns indicate different growth functions. A daughter cell continues her mother's CGC, with the same growth as the mother, until she reaches the critical size m_0. Then she chooses a new growth function.

space $(S \times \Omega^I, \mathcal{S} \times \mathcal{A}^I)$ with a set of probability kernels $P(s, A)$, $s \in S$, $A \in \mathcal{A}$, where

$$(\Omega^I, \mathcal{A}^I) = \prod_{x \in I} (\Omega, \mathcal{A}).$$

$P(s, \cdot)$ is called the *life law* for an s-type individual, which means that the individual chooses a life from $(\Omega, \mathcal{A})$ according to $P(s, \cdot)$. Now the reproduction point process ξ on $S \times \mathbb{R}_+$ is defined by

$$\xi(A \times B) = \#\{i \in N : \sigma(i) \in A, \tau(i) \in B\},$$

where $\sigma(i) : \Omega \to S$ and $\tau(i) : \Omega \to \mathbb{R}_+$ are measurable functions giving the type of the i-th child and the age at childbearing number i, respectively. The development of the population is then described in terms of the reproduction kernel

$$\mu(r, A \times B) = E_r[\xi(A \times B)]$$

giving the expected number of children with types in A to an r-type individual with age in B. E_r is the expectation corresponding to $P(r, \cdot)$.

We assume the population to be supercritical and Malthusian, meaning that there exists a number $\alpha > 0$, the Malthusian parameter, such that the kernel

$$\hat{\mu}_\alpha(r, A) = \int_0^\infty e^{-\alpha t}\, \mu(r, A \times \mathrm{d}t)$$

has Perron root one and is conservative (Shurenkov, 1992). Then by an abstract version of the Perron-Frobenius theorem (Shurenkov, 1992) there exists a σ-finite

measure π and a π-measurable function h on $(S, \mathcal{S})$ such that

$$h(r) = \int_S h(s)\hat{\mu}_\alpha(r, \mathrm{d}s),$$

$$\pi(A) = \int_S \hat{\mu}_\alpha(r, A)\pi(\mathrm{d}r).$$

The measure π and the function h are unique up to multiplicative constants and can be interpreted as a *stable birth type distribution* and the *reproductive value* respectively. By requiring strong or positive α-recurrence (Jagers and Nerman, 1996) and homogeneity in the sense that $\inf h > 0$ we can norm to

$$\int_S h(s)\,\pi(\mathrm{d}s) = 1 \quad \text{and} \quad \int_S \pi(\mathrm{d}s) = 1.$$

To be able to count the population with respect to various properties (e.g. being alive, being a mother, etc.) we introduce *random characteristics*. These are real-valued processes χ such that $\chi(a)$ is simply the score of a cell at age a and χ_x is the score of the cell x. Now the *branching process counted by* χ is defined to be

$$z_t^\chi = \sum_{x \in I} \chi_x(t - \tau_x),$$

where τ_x is x's birth time such that $t - \tau_x$ stands for x's age at time t, and χ_x is x's contribution to the population count at the current age. This means that z_t^χ is simply the sum of all scores evaluated at the individual's actual age at time t. When $\chi(a) = \mathbf{1}_{\mathbb{R}_+}(a)$, z_t^χ is just the total number of individuals born up to time t, and will be denoted y_t. Under certain conditions (cf. (Jagers and Nerman, 1996) and references therein) it holds that

$$\lim_{t\to\infty} e^{-\alpha t} E_s[z_t^\chi] = \frac{E_\pi[\hat{\chi}(\alpha)]}{\alpha\beta} h(s),$$

where $E_\pi[X] = \int_S E_s[X]\,\pi(\mathrm{d}s)$, $\hat{\chi}(\alpha) = \int_{\mathbb{R}_+} e^{-\alpha t}\chi(t)\,\mathrm{d}t$ and

$$0 < \beta = \int_{S\times S\times\mathbb{R}_+} t e^{-\alpha t} h(s)\,\mu(r, \mathrm{d}s \times \mathrm{d}t)\,\pi(\mathrm{d}r) < \infty.$$

For a more comprehensive description of the multi-type branching process theory, see (Jagers, 1989; Jagers and Nerman, 1996).

4. The Two-Subcycle Branching Process Model

The assumption that all cells proliferate our population is clearly supercritical. If $m_g(r, t)$ denotes the size of a cell with initial size r, age t and with exponential growth rate g this yields

$$m_g(r, t) = re^{gt}.$$

Let λ denote the life length or the cell cycle time of a cell and let its distribution be given by the hazard rate function $b(s)$, where s is the size of the cell. The division is assumed to be unequal and we let δ and $1-\delta$ denote the division fractions, where the density function of $\delta \in (0,1)$ is denoted by $f_\delta(m,p)$, $0 < p < 1$, and m is the size at division. We assume further that f_δ is unimodal and symmetric around $1/2$, i.e. $E[\delta] = 1/2$ and $f_\delta(m,p) = f_\delta(m,1-p)$.

We interpret

$$T(x_2,g) - T(x_1,g) = \int_{x_1}^{x_2} \frac{\mathrm{d}y}{g(y)}$$

as the time it takes for a cell to grow from size x_1 to size x_2 with growth function g. With exponential growth rate g we get

$$T(x_2,g) - T(x_1,g) = \frac{1}{g}\int_{x_1}^{x_2} \frac{\mathrm{d}y}{y} = \frac{1}{g}\ln\frac{x_2}{x_1}.$$

Finally, we let

$$C(x,g) = \int_0^x \frac{b(y)}{g(y)}\mathrm{d}y.$$

In this setting the type of a cell would consist of both birth size and growth rate. To avoid problems with a two-dimensional type space, we use the following trick. We assume that the intervals of possible birth sizes and possible division sizes are non-overlapping so that every newborn cell is smaller than the critical size m_0 and then it passes m_0 before division. Hence we can shift the cell cycle to begin at the critical size and to end when both daughter cells have reached m_0. The life span is now divided into two parts $\lambda = \lambda' + \lambda''$ where $\lambda'' = T(m_0,g) - T(\delta\, m_g(m_0,\lambda'),g)$ (cf. Fig. 2).

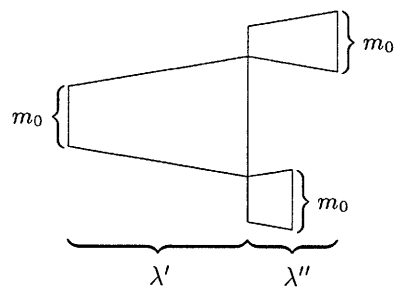

Fig. 2. The life starts when the cell reaches size m_0 and ends when both daughters have reached size m_0.

With this shift we get a population of *pseudo-cells*, all with the same birth size and also without change of growth rate during the life time. We let the growth rate

be the type and recall that the growth rates of two sister cells are given by

$$g_1' = g_L + \eta_1,$$
$$g_2' = g_L + \eta_2,$$

where g_L is the latent growth factor inherited from the mother and η_1 and η_2 the individual contributions. To avoid sister dependencies we let the type consist of the own growth rate g of the cell and the contribution g_L handed over to the daughters such that $\mathbf{g} = (g, g_L)$ is a typical element of the type space. With $\mathrm{d}\mathbf{g}' = \mathrm{d}g' \times \mathrm{d}g_L'$ the reproduction kernel takes the form

$$\begin{aligned}\mu(\mathbf{g}, \mathrm{d}\mathbf{g}' \times \mathrm{d}t) &= 2\,E_{\mathbf{g}}\big[\mathbf{1}(\lambda \in \mathrm{d}t)\mathbf{1}(g_L + \eta \in \mathrm{d}g')\mathbf{1}(\mathcal{L} \in \mathrm{d}g_L')\big] \\ &= 2\,E_{\mathbf{g}}\Big[\mathbf{1}(\lambda' + T(m_0, g) - T\big(\delta\, m_g(m_0, \lambda'), g\big) \in \mathrm{d}t)\mathbf{1}(g_L + \eta \in \mathrm{d}g')\mathbf{1}(\mathcal{L} \in \mathrm{d}g_L')\Big] \\ &= \int_{\mathbb{R}_+}\int_0^1 \mathbf{1}\Big(u + T(m_0, g) - T\big(p\, m_g(m_0, u), g\big) \in \mathrm{d}t\Big) f_\delta\big(m_g(m_0, u), p\big)\mathrm{d}p \\ &\qquad \times b\big(m_g(m_0, u)\big) e^{-\int_0^u b(m_g(m_0, v))\mathrm{d}v}\mathrm{d}u\, f_\eta(g' - g_L) f_{\mathcal{L}}(g_L')\mathrm{d}g'\,\mathrm{d}g_L'\end{aligned}$$

where $\mathcal{L}$ is a random variable for the latent growth factor to be handed over in the next generation and f_η and $f_{\mathcal{L}}$ are the density functions of η and $\mathcal{L}$, respectively. Making a change of variable $x = m_g(m_0, u)$ yields

$$\begin{aligned}&\mu(\mathbf{g}, \mathrm{d}\mathbf{g}' \times \mathrm{d}t) \\ &= 2\int_{m_0}^{2m_0}\int_0^1 \Big\{\big(T(x, g) - T(px, g)\big) \in \mathrm{d}t\Big\}\frac{b(x)}{g(x)} e^{-\int_{m_0}^x \frac{\mathrm{d}y}{g(y)}} f_\delta(x, p)\mathrm{d}p\,\mathrm{d}x \\ &\qquad \times f_\eta(g' - g_L) f_{\mathcal{L}}(g_L')\mathrm{d}g'\,\mathrm{d}g_L'.\end{aligned}$$

The basis of the kernel becomes

$$\begin{aligned}\hat{\mu}_\alpha(\mathbf{g}, \mathrm{d}\mathbf{g}') &= \int_{\mathbb{R}_+} e^{-\alpha t}\mu(\mathbf{g}, \mathrm{d}\mathbf{g}' \times \mathrm{d}t) \\ &= 2\int_{m_0}^{2m_0}\int_0^1 e^{-\alpha(T(x,g) - T(px,g)) - (C(x,g) - C(m_0,g))}\frac{b(x)}{g(x)} f_\delta(x, p)\mathrm{d}p\,\mathrm{d}x \\ &\qquad \times f_\eta(g' - g_L) f_{\mathcal{L}}(g_L')\mathrm{d}g'\,\mathrm{d}g_L' \\ &= \hat{\mu}(\alpha, g) f_\eta(g' - g_L) f_{\mathcal{L}}(g_L')\mathrm{d}g'\,\mathrm{d}g_L'\end{aligned}$$

where

$$\hat{\mu}(\alpha, g) = 2\int_{m_0}^{2m_0}\int_0^1 e^{-\alpha(T(x,g) - T(px,g)) - (C(x,g) - C(m_0,g))}\frac{b(x)}{g(x)} f_\delta(x, p)\mathrm{d}p\,\mathrm{d}x$$

Now we want to find the stable birth type distribution π and the eigenfunction h of our kernel, which are given by the integral equations

$$h(r) = \int_S h(s)\,\hat{\mu}_\alpha(r, \mathrm{d}s),$$

$$\pi(A) = \int_S \hat{\mu}_\alpha(\mathbf{g}, A)\,\pi(\mathrm{d}g),$$

subject to the conditions $\int_S h(s)\,\pi(\mathrm{d}s) = 1$ and $\int_S \pi(\mathrm{d}g) = 1$. With $\mathbf{g} = (g, g_L)$ as before it turns out that, asymptotically, g and g_L are independent such that π becomes a product measure $\pi = \psi_1 \times \psi_2$ over the product space $(S, \mathcal{S}) = (S_1 \times S_2, \mathcal{S}_1 \times \mathcal{S}_2)$. With $\mathrm{d}\mathbf{g}' = \mathrm{d}g' \times \mathrm{d}g'_L$ we get

$$\begin{aligned} h_1(g)h_2(g_L) &= \int_{S_1}\int_{S_2} h_1(g')h_2(g'_L)\hat{\mu}_\alpha(\mathbf{g}, \mathrm{d}\mathbf{g}') \\ &= \hat{\mu}(\alpha, g)\int_{S_1} h_1(g')f_\eta(g' - g_L)\mathrm{d}g' \int_{S_2} h_2(g'_L)f_\mathcal{L}(g'_L)\mathrm{d}g'_L \end{aligned}$$

$$\begin{aligned} \psi_1(\mathrm{d}g')\psi_2(\mathrm{d}g'_L) &= \int_{S_1}\int_{S_2} \hat{\mu}(\alpha, g)f_\eta(g' - g_L)f_\mathcal{L}(g'_L)\,\psi_2(\mathrm{d}g_L)\psi_1(\mathrm{d}g)\mathrm{d}g'\mathrm{d}g'_L \\ &= \int_{S_1} \hat{\mu}(\alpha, g)\,\psi_1(\mathrm{d}g) \int_{S_2} f_\eta(g' - g_L)\,\psi_2(\mathrm{d}g_L)\mathrm{d}g' f_\mathcal{L}(g'_L)\mathrm{d}g'_L \end{aligned}$$

which gives $h_1(g) = \hat{\mu}(\alpha, g)$ and $h_2(g_L) = 1$. Thus $\int_{S_1} \hat{\mu}(\alpha, g)\,\psi_1(\mathrm{d}g) = 1$ which yields

$$\psi_1(\mathrm{d}g) = f_{\eta+\mathcal{L}}(g)\mathrm{d}g,$$

$$\psi_2(\mathrm{d}g_L) = f_\mathcal{L}(g_L)\mathrm{d}g_L.$$

Hence $\pi(\mathrm{d}\mathbf{g}) = f_{\eta+\mathcal{L}}(g)f_\mathcal{L}(g_L)\mathrm{d}g\,\mathrm{d}g_L$ and this is used in the next section.

5. Asymptotics of the Two-Subcycle Model

In the previous section we shifted the cell cycle to begin at the critical size and considered a population of pseudo-cells. But when calculating the asymptotics we still want the results for the *real* cells, so we have to translate our model back to the real population. To do this we construct random characteristics that count each real cell with the desired properties. We also add the assumption here that the DDC is mainly constant in duration such that $\lambda' \equiv d$ in Fig. 2 for some constant $d > 0$.

The α-curve gives the probabilities $\alpha(a)$ that a cell, sampled at random among all cells born from a stabilised population, is still undivided at some age a. The

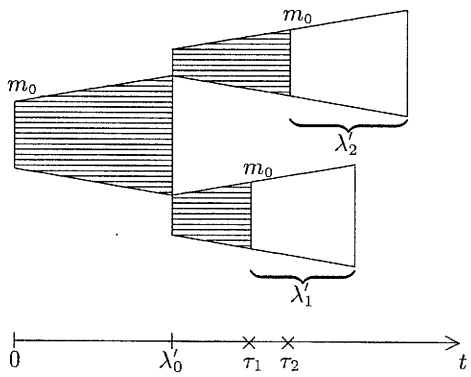

Fig. 3. The pseudo-cell mother is the patterned part. Its life starts at time 0 and τ_1 and τ_2 are the times of birth of the two pseudo-children.

characteristic that gives score one to each real daughter born and with life length $> a$ at time u is

$$\begin{aligned}\chi(u) &= \mathbf{1}(\lambda_0' < u)\big(\mathbf{1}(a + \lambda_0' < \tau_1 + \lambda_1') + \mathbf{1}(a + \lambda_0' < \tau_2 + \lambda_2')\big) \\ &= \mathbf{1}(d < u)\big(\mathbf{1}(a < \tau_1) + \mathbf{1}(a < \tau_2)\big)\end{aligned}$$

and the characteristic counting all real cells born is

$$\chi'(u) = 2\,\mathbf{1}(\lambda_0' < u) = 2\,\mathbf{1}(d < u).$$

From Section 3 we get that asymptotically

$$\alpha(a) = \frac{E_\pi[\hat{\chi}(\alpha)]}{E_\pi[\hat{\chi}'(\alpha)]}$$

where

$$\begin{aligned}E_\pi\big[\hat{\chi}(\alpha)\big] &= e^{-\alpha d}\int_S E_{\mathbf{g}}\big[\mathbf{1}(a < \tau_1) + \mathbf{1}(a < \tau_2)\big]\,\pi(\mathrm{d}\mathbf{g}) \\ E_\pi\big[\hat{\chi}'(\alpha)\big] &= 2e^{-\alpha d}.\end{aligned}$$

Since

$$\begin{aligned}\tau_1 &= T(m_0, g) - T\big(\max(\delta, 1-\delta)m_g(m_0, d), g\big) + d \\ \tau_2 &= T(m_0, g) - T\big(\min(\delta, 1-\delta)m_g(m_0, d), g\big) + d\end{aligned}$$

this yields

$$\alpha(a) = \int_{S_1}\int_0^1 \mathbf{1}(a < -\ln p^{1/g}) f_\delta(m_0 e^{gd}, p)\mathrm{d}p\,\psi_1(\mathrm{d}g).$$

Similarly, the β_1-curve among all born is given by

$$\beta_1(a) = \int_{S_1} \int_0^1 \mathbf{1}\left(\left|\frac{1}{g} \ln \frac{p}{1-p}\right| > a\right) f_\delta(m_0 e^{gd}, p) \mathrm{d}p \, \psi_1(\mathrm{d}g).$$

We use the parameter values defined in (Sennerstam and Strömberg, 1995):

Critical cell size (m_0)	7 (rel. size units)
DDC (d)	8 (hr)
Latent growth factor ($\mathcal{L}$)	$\sim N(0.06, 0.005^2)$
Individual growth contribution (η)	$\sim N(0, 0.015^2)$
$\mathcal{L} + \eta$	$\sim N(0.06, 0.005^2 + 0.015^2)$
$S_1 = S_2$	$(0, 0.12)$

and we let f_δ be the density function of a triangular distribution (cf. Fig. 4).

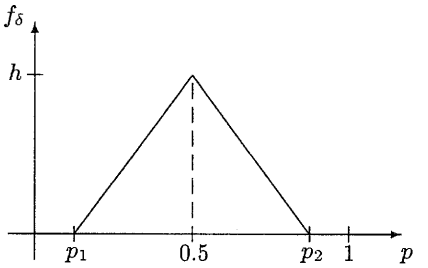

Fig. 4. The density function of δ.

Since a newborn cell has size less than m_0, the mother cell has to divide so that $p_1 \leq \delta \leq p_2$, where $p_2 = 1 - p_1$, and the condition

$$m_0 \, e^{gd} - m_0 \leq \delta \, m_0 \, e^{gd} \leq m_0$$

gives that $p_2 = e^{-gd}$. Now

$$f_\delta(m_0 \, e^{gd}, p) = \begin{cases} h^2\big(p - (1 - p_2)\big) & \text{if } p_1 \leq p \leq \dfrac{1}{2} \\ h^2(p_2 - p) & \text{if } \dfrac{1}{2} \leq p \leq p_2 \end{cases}$$

where $h = 1/(p_2 - 1/2)$. The Malthusian parameter is the value α such that

$$\int_{S_1} \hat{\mu}(\alpha, g) \, \psi_1(\mathrm{d}g) = 2 \int_{S_1} \int_0^1 p^{\alpha/g} f_\delta(m_0 \, e^{gd}, p) f_{\eta+\mathcal{L}}(g) \mathrm{d}p \, \mathrm{d}g = 1$$

yielding $\alpha \approx 0.0574$. Plots of the α- and the β_1-curve, the densities of the stable birth size distribution and the stable division size distributions are depicted in Figs. 5–8.

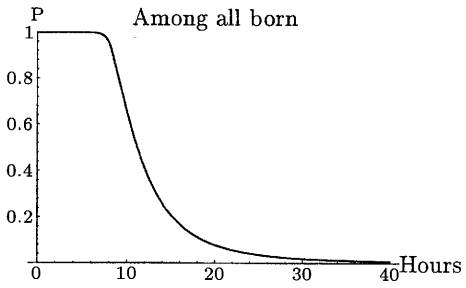

Fig. 5. The α-curve.

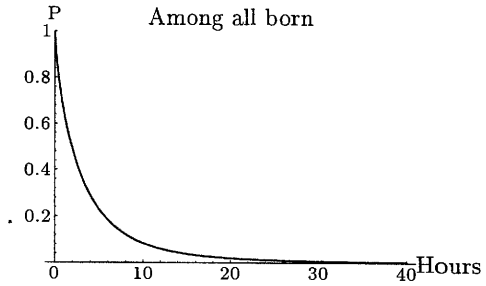

Fig. 6. The β_1-curve.

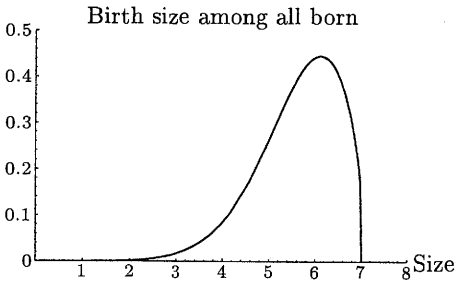

Fig. 7. The density of the stable birth size.

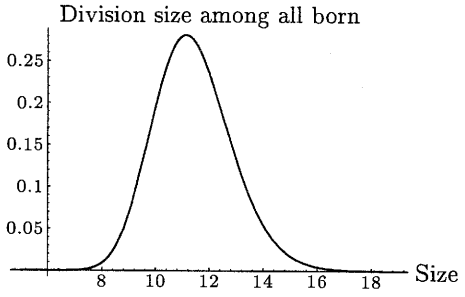

Fig. 8. The density of the stable division size.

6. Mother-Daughter Cell Cycle Time Correlation

As mentioned in the introduction, size control models are sometimes criticised because they predict a negative mother-daughter life length correlation. This is easy to see since for a cell population, where all cells have the same growth rate, a long cell cycle leads to a larger division size, and therefore bigger daughters. Since life length depends on size, the daughter's life lengths become shorter. Hence a negative correlation. In mammalian cells, however, this correlation is observed to be zero or positive. In the Two-Subcycle model, the cells change growth rate as pointed out at the critical size, and the new growth rate is chosen independently of the old one. This means that the length of the G_1-phase of the mother is independent of the length of the G_2-phase of the daughter.

We want to find the sign of the covariance $\mathrm{Cov}(\lambda_1, \lambda_{11})$. By writing the life lengths as

$$\begin{aligned} \lambda_1 &= \lambda_0'' + \lambda_1', \\ \lambda_{11} &= \lambda_1'' + \lambda_{11}' \end{aligned}$$

we see that λ_1 and λ_{11} are only dependent through λ_1' and λ_1'', and these two are

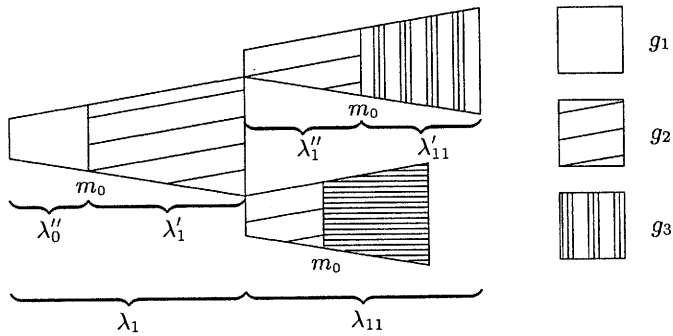

Fig. 9. λ_1' and λ_1'' are dependent through the growth rate g_2.

only dependent through the growth rate g_2 (see Fig. 9). This yields

$$\mathrm{Cov}(\lambda_1, \lambda_{11}) = \mathrm{Cov}(\lambda_0'' + \lambda_1', \lambda_1'' + \lambda_{11}') = \mathrm{Cov}(\lambda_1', \lambda_1'').$$

This must be nonnegative since fast growth leads to a shorter λ'-period as well as a shorter λ''-period. To see this, we use the trick

$$\begin{aligned}\mathrm{Cov}(\lambda_1', \lambda_1'') &= \mathrm{Cov}\Big(E[\lambda_1'|\mathcal{G}_2], E[\lambda_1''|\mathcal{G}_2]\Big) + E\Big[\mathrm{Cov}\big(\lambda_1', \lambda_1''|\mathcal{G}_2\big)\Big] \\ &= \mathrm{Cov}(E[\lambda_1'|\mathcal{G}_2], E[\lambda_1''|\mathcal{G}_2]).\end{aligned}$$

where $\mathcal{G}_2$ is a random variable for the growth rate denoted by g_2 in Fig. 9. The distributions of $\lambda_1'|\mathcal{G}_2$ and $\lambda_1''|\mathcal{G}_2$ are both decreasing in $\mathcal{G}_2$ since for $g_2 < g_2'$ we get

$$\begin{aligned}P\big(\lambda_1' > x|\mathcal{G}_2 = g_2\big) &\geq P\big(\lambda_1' > x|\mathcal{G}_2 = g_2'\big), \\ P\big(\lambda_1'' > x|\mathcal{G}_2 = g_2\big) &\geq P\big(\lambda_1'' > x|\mathcal{G}_2 = g_2'\big).\end{aligned}$$

Now it holds that for every random variable X and decreasing functions f and g, the random variables $f(X)$ and $g(X)$ are positively correlated. For a simple coupling proof of this, see (Thorisson, 1995, p. 161). In the special case when the DDC is considered to be constant, we get that λ_1 and λ_{11} are independent. Thus, the mother-daughter correlation is zero as a consequence of constant DDC, rather than due to the microheterogeneity in growth. Note that in this case the correlation is zero even if all cells have the same growth rate.

7. Conclusions

The main objective of the Two-Subcycle model is that the cell cycle consists of two simultaneously running, mutually dissociated subcycles, resembling large umbrellas covering a complex system of cyclic processes. The dissociation between these two subcycles, the DDC and the CGC, might enable the cell to alter gene expression from one cell to the next.

None of the various components of the Two-Subcycle model is new, except for the latent growth factor reflecting genetic similarities in a pair of daughter cells generating a similar answer to the growth factors at the reflection point, represented as a critical size in the model.

The model offers an alternative interpretation of cell cycle progression. The first part of the G_1 phase prior to the restriction point is considered more as a completion of the previous cell growth cycle than the first part of the current cycle.

Furthermore, the branching process approach serves well as an example of applications of the general branching process theory to various situations in population dynamics. The branching process theory turns out to be a machinery well suited for this type of modelling. We construct the branching process model corresponding to a rather detailed biological description of the cell population, and still get an analytical expression of the stable birth type distribution. From this distribution we then can derive all the asymptotic results of interest on the population level. A few of these results are viewed in Figs. 5–8, and they agree satisfactorily with the simulation results in (Sennerstam and Strömberg, 1995).

Another important feature of the model is that, unlike most size structured cell cycle models, the mother-daughter cell cycle time correlation becomes non-negative. This is due to the supramitotic growth regulation and the microheterogeneity in growth.

References

Arino O., Axelrod D. and Kimmel M. (Eds.) (1995): *Advances in Mathematical Population Dynamics — Molecules, Cells and Man.* — Proc. 4th Int. Conf. *Mathematical Population Dynamics*, May 23–27, Houston, Mathematical Biology and Medicine, Vol.6, Singapore: World Scientific.

Arino O. and Kimmel M. (1993): *Comparison of approaches to modelling of cell population dynamics.* — SIAM J. Appl. Math., Vol.53, pp.1480–1504.

Bell G.I. and Anderson E.C. (1967): *Cell growth and division I: A mathematical model with applications to cell volume distributions in mammalian suspension cultures.* — Bioph. J., Vol.7, pp.329–351.

Fraser R.S. and Nurse P. (1978): *Novel cell cycle control of RNA synthesis in yeast.* — Nature, Vol.271, pp.726–730.

Heijmans H.J.A.M. (1984): *On the stable size distribution of populations reproducing by fission into two unequal parts.* — Math. Biosci., Vol.72, pp.19–50.

Jagers P. (1989): *General branching processes as Markov fields.* — Stoch. Proc. Appl., Vol.32, pp.183–242.

Jagers P. (1992): *The deterministic evolution of general branching populations.* — Preprint 1992–25, Dept. Mathematics, Chalmers Univ. Tech. and Gothenburg Univ.

Jagers P. and Nerman O. (1996): *The asymptotic composition of multitype branching populations*, In: Séminaire de Probabilités (Mar Yor, Ed.). — Lecture Notes in Mathematics, Springer Verlag.

Lasota A. and Mackey M.C. (1984): *Globally asymptotic properties of proliferating cell populations.* — J. Math. Biol., Vol.19, pp.43–62.

Sharpe F.R. and Lotka A. (1911): *A problem in age-distribution.* — Philos. Mag, Vol.21, pp.435–438.

Sennerstam R. and Strömberg J-O. (1995): *Cell cycle progression: Computer simulation of uncoupled subcycles of DNA replication and cell growth.* — J. Th. Biol., Vol.175, pp.177–189.

Shurenkov V. (1992): *Markov renewal theory and its applications to Markov ergodic processes.* — Preprint 1992–24, Dept. Mathematics, Chalmers Univ. Tech. and Gothenburg Univ.

Taib Z. (1996): *A branching process version of the Bell-Anderson cell population model.* — Preprint 1996–14, Dept. Mathematics, Chalmers Univ. Tech. and Gothenburg Univ.

Thorisson H. (1995): *Coupling methods in probability theory.* — Scand. J. Stat., Vol.22, pp.159–182.

Webb G.F. (1987): *Random transitions, size control, and inheritance in cell population dynamics.* — Math. Biosci., Vol.85, pp.71–91.