The asynchronous exponential growth property in a model for the kinetic heterogeneity of tumour cell populations

O. Arino [⚔], A. Bertuzzi [a], A. Gandolfi [a], E. Sánchez [b,*], C. Sinisgalli [a]

[a] *Istituto di Analisi dei Sistemi ed Informatica, "A. Ruberti" CNR, Viale Manzoni 30, 00185 Roma, Italy*
[b] *Departamento Matemática Aplicada, ETS Ingenieros Industriales, c. José Gutiérrez Abascal 2, 28006 Madrid, Spain*

Abstract

A continuous cell population model, which represents both the cell cycle phase structure and the kinetic heterogeneity of the population following Shackney's ideas [J. Theor. Biol. 38 (1973) 305–333], is studied. The asynchronous exponential growth property is proved in the framework of the theory of strongly continuous semigroups of bounded linear operators.
© 2004 Elsevier Inc. All rights reserved.

Keywords: Cell population dynamics; Cell kinetic heterogeneity; Asynchronous exponential growth

1. Introduction

Populations of proliferating cells are characterized by cell-to-cell variability of the cell cycle kinetic parameters. Even cell populations growing in vitro, that is in a homogeneous environment, exhibit different cell cycle times because of the intrinsic variabilities in the

---

machinery of cell cycle progression. Both experimental and clinical tumours, as demonstrated since the early studies using ^{3}H-thymidine labeling [14], show a larger extent of kinetic heterogeneity due to the possible presence of genetic heterogeneity, and to the different conditions of nutrition and oxygenation in the cell microenvironment, related to the tumour vascularization.

In the framework of deterministic models, the kinetic heterogeneity has been mainly represented by means of age-structured population models [1,2,4,15]. The age formalism, indeed, allows a simple representation of cell populations with variable (but uncorrelated) cell cycle times. Denoting by a ($a \geqslant 0$) the cell age and by $n(a, t)$ the cell density with respect to age, that is, $n(a, t)\, da$ is the number of cells with age between a and $a + da$ at time t, the basic model is given by

$$\frac{\partial n}{\partial t}(a, t) + \frac{\partial n}{\partial a}(a, t) = -\big[\beta(a) + \mu(a)\big]n(a, t),$$

$$n(0, t) = 2 \int\limits_0^{+\infty} \beta(a)n(a, t)\, da,$$

where $\beta(a)$ is the age-dependent division rate coefficient, which is related to the distribution of cell cycle duration, and $\mu(a)$ represents cell loss. More complex models, involving age-structured subpopulations, are required to take into account the different cell cycle phases [5].

Another approach to represent the kinetic heterogeneity was proposed by Lebowitz and Rubinow [9], considering the cell population as composed by a continuous spectrum of subpopulations each characterized by a given cell cycle transit time τ. The population is thus described by the cell density $n(a, \tau, t)$ ($a \in [0, \tau]$, $\tau > 0$), such that $n(a, \tau, t)\, da\, d\tau$ denotes the number of cells with age between a and $a + da$ and cell cycle time between τ and $\tau + d\tau$ at time t. The model is given by

$$\frac{\partial n}{\partial t}(a, \tau, t) + \frac{\partial n}{\partial a}(a, \tau, t) = -\mu(a, \tau)n(a, \tau, t),$$

$$n(0, \tau, t) = 2 \int\limits_0^{+\infty} \Theta(\tau, \tau')n(\tau', \tau', t)\, d\tau',$$

where $\Theta(\tau, \tau')$ is a transition kernel such that $\Theta(\tau, \tau')\, d\tau$ yields the probability that a cell originated from a cell with cycle time τ' will have cycle time between τ and $\tau + d\tau$. We note that the dependence of Θ on τ' introduces a partial heredity of the cell cycle transit time between mother and daughter cells. The model in [9], through the variable transformation $x = a/\tau$, can be written in terms of the cell maturity x and distributed cell maturation rates. Because the cell maturity, as defined by Rubinow [11], is a variable ranging from 0 to 1 which marks the progression through the cell cycle, the maturity formalism readily represents the cell cycle phases by assigned maturity intervals. It is easy to see that the preceding model implies a strict relationship among the transit times of the cell cycle phases. We remark that both the above models exhibit the asynchronous exponential growth property, that is, the population asymptotically shows an exponential growth