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G1/S TRANSITION AND CELL POPULATION DYNAMICS

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Abstract. In this paper we present a model connecting the state of molecular components during the cell cycle at the individual level to the population dynamic. The complexes *Cyclin E/CDK2* are good markers of the cell state in its cycle. In this paper we focus on the first transition phase of the cell cycle ($S-G_2-M$) where the complexe *Cyclin E/CDK2* has a key role in this transition. We give a simple system of differential equations to represent the dynamic of the *Cyclin E/CDK2* amount during the cell cycle, and couple it with a cell population dynamic in such way our cell population model is structured by cell age and the amount of *Cyclin E/CDK2* with two compartments: cells in the G1 phase and cells in the remainder of the cell cycle ($S-G_2-M$). A cell transits from the G1 phase to the S phase when *Cyclin E/CDK2* reaches a threshold, which allow us to take into account the variability in the timing of G1/S transition. Then the cell passes through $S-G_2-M$ phases and divides with the assumption of unequal division among daughter cells of the final *Cyclin E/CDK2* amount. The existence and the asymptotic behavior of the solution of the model is analyzed.

1. Introduction.

Since the 80's, cell population dynamics has received much attention from the mathematical modeling community. The first models were related to the proliferation of cell populations. The interest focused not only on the evolution in time of the cell population densities, but also on some other structure variable characterizing individual cells (age, size, *DNA* or *RNA* content, cell maturation). Many differential equations models were built according to the balance between proliferation and cell loss and structured by these variables which influence growth, stabilization, oscillation or other behavior of the population [27] [20] [24] and [51].

Moreover, cells with the same size may have very different age and vice versa, so variability in the cell size and in the cell cycle duration implies that both size and age

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structure variables do not give exact information on the state of the cell in its cell cycle. The cell cycle can be split into four phases: G_1, S, G_2 and M. In mammalian cells, the duration of the G_1 phase is variable whereas the length of S, G_2 and M phases is relatively constant. The origin of the variability of the G_1 phase duration lies in the amounts and the interactions of the proteins driving the cell from birth to the S phase. Experiments in [12] showed that the S phase cannot be started if the concentration of some proteins which are expressed at the G_1 phase is not high enough. The G_1 phase has been the object of several investigations, especially in relation to the S phase entry (called the G_1/S transition). The G_1/S transition is a critical event in the cell cycle progression, and the molecular interactions involved in this transition have a great complexity and require many different families of proteins [23]. Hartwell [16] indicated that cyclins are the most determinant control proteins for phase transitions. These cyclins make complexes with *CDK kinases*, enzymes which are needed for the cyclin activation, and these complexes are able to phosphorylate other proteins which are important for the cell cycle progression. The more important ones for the G_1/S transition are the complex formed by *Cyclin E* and *CDK2* kinase (called *Cyclin E/CDK2*), the retinoblastoma protein (*pRb*), the growth factor *E2F* and the cdk inhibitor $p27^{KIP1}$ [38, 21]. Under a specific assumptions, several authors [33, 32, 34, 17, 42, 30, 35, 41, 31] have described and simulated part of these complicated reactions regulating the timing of the S phase entry. They have modeled the cell cycle as limit cycles [15, 17, 30, 33], bistable systems [31, 47, 42, 41] and transient processes [1, 23]. The simulations give some insight into the proteins behavior and help us in the choice of the most relevant components influencing the variability of G_1 phase duration [9]. Moreover, even if the cell cycle control is central for cell progression and cell division most of the previous works focus on the simulation of the cell cycle from a molecular standpoint. The connection between the cell population and the cell cycle progression was hardly considered. Our goal in this paper is to present a model taking into account the interdependence between the cell number regulation and the cell cycle progression [7]. Among the few previous works, we cite the paper of Val and Tyson [48]: In their paper, they assumed that molecular mechanisms required in the cell cycle are cell size dependent and then they coupled this cell cycle model with a structured population of budding yeast cells. Actually, they considered three cell cycle components with the cell mass obeying a system of differential equations describing the cell cycle at the molecular level of individual cell and used these four variables as structures of a cell population model. However in this paper, we propose on one hand to connect the cell age with an event implicating a cell component such as a *cyclin E/CDK2* complex which is a key entity for the cell cycle control and use this component together with the age as structure variables for the cell population. On the other hand, we take into account the variability of cell cycle duration giving an hypothesis on the amount of cyclins and we also consider an unequal division.

We focus on the critical event: the G_1/S transition. In section 2, we give a simplified description of the molecular interactions for the G_1/S transition using the results given in [9, 45, 23]. Afterwards in section 3.1, we present a simple model describing the evolution of only two cell components regulating the G_1/S transition. In section 3.2 we discuss the variability of the G1 phase duration. Then, in section 3.3 we introduce a linear formulation of these two components in the remain of the cell cycle (S, G2 and M phases). Finally, in section 4 we connect the G_1/S model with a cell population model with two compartments, which the first one corresponds to the G_1 phase, with variable duration, and the second to the remainder part of the cell cycle, with constant duration. Then we analyze the behavior of the solution of the cell population model.

2. **A quick description of molecular interactions.** In this paper, we focus on the G_1/S transition. The *Cyclin E/CDK2* complex is the cyclin/CDK complex which has a key role at late G_1 phase for beginning the S phase. Koff et al. [21] observed that the *Cyclin E/CDK2* increases during G_1 and is maximal in G_1 cells. Afterwards, it decays as cells progress through the remainder of the the cell cycle [37]. The experiments in [45, 9] showed the existence of a threshold value of *Cyclin E* just before the S phase. Indeed, only cells with *Cyclin E* amount above the threshold are found in early S phase, while G_1 cells had a very variable content, mostly below the threshold [45].

Hence, we are interested in the molecular interactions that are related to the activity of *Cyclin E/CDK2* and the fundamental assumption we take into account is that the S phase begins when the level of *Cyclin E/CDK2* complex reaches a threshold.

Using Kohn's model, Chiorino and Lupi [9], have discussed the molecular network model for the G_1 phase proposed in [23]. They choose this approach because it considers single molecular species and it possible to include all the possible interactions among them. But, of course, the more reactions we add to the system, the more complex it becomes and harder to manage, especially if we want to connect it with a cell population model. Their simulations give the duration of the G_1 phase and its variability as a function of G_1-related molecular components which have a significative influence on this duration and thus they showed that the higher the pRb level, the longer the G_1 phase, while high initial values of *Cyclin E/CDK2* correlate with short G_1 phase. They also remark that the presence of the inhibitor *p27* can slow down the G_1 phase, but, after an initial delay, the activity of *Cyclin E/CDK2* complex is stronger for a small initial amount of *p27*. Based on these results, we select the complex *Cyclin E/CDK2* and the *pRb* as the determinant variable of our G_1/S transition model. Here we don't consider the *p27* since we assume that it has a low level at the G1 phase in normal cells.

At the beginning of the cell cycle, pRb is bound to the transcription factor *E2F* then the complex *Cyclin D/CDK4,6* phosphorylates partially the *pRb* but remains bound to the *E2F* before the so called the restriction point *R*. Afterwards the activated *Cyclin E/CDK2* complex achieves the *pRb* phosphorylation and release *E2F*. The newly released *E2F* activates some genes which are important to initiate the *S* phase (see Figure 1). One of the targets of *E2F* is to promote the synthesis of *Cyclin E* [13], [14] (see Figure 1). Then pRb binding to *E2F* prevent *Cyclin E* synthesis, which suggests that *pRb* is responsible for the low expression of *Cyclin E* gene in early and mid G_1. Moreover, as well as *Cyclin E* is synthetisized it binds to the *CDK2* kinase and forms the complexe *Cyclin E/CDK2*. At the G_1/S transition *pRb* is completely hyperphosphorylated (inactive) and cannot bind *E2F* again. It persists in this state through the remainder of the cell cycle and is converted into hypophosphorylated (active) form in the mitotic phase [29]. Then, we assume that the activity of *Cyclin E/CDK2* is strongly related to the *pRb* phosphoryaltion.

3. **Mathematical model.** Our aim is not to give an elaborate model of the molecular mechanisms of the G_1 phase but to give a simple system representing the

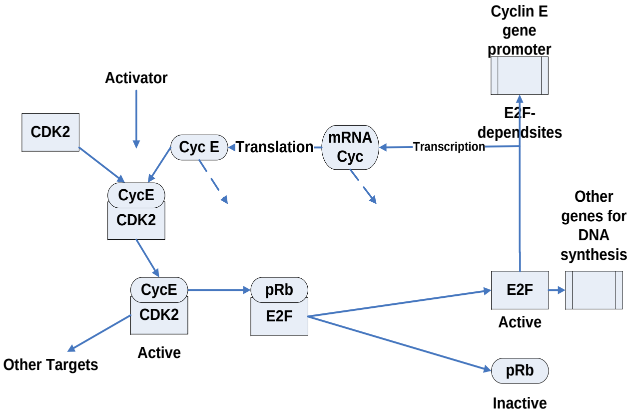


FIGURE 1. : simple scheme of the molecular interactions in the late G_1 phase

progression of the *Cyclin E/CDK2* which is a key component for the G_1/S transition and the G_1 phase duration in order to use the *Cyclin E/CDK2* as a structure variable of the cell population evolving during the cell cycle.

3.1. **The G_1/S transition model: pRb - CycE/CDK2.** Based on the molecular mechanisms given in section 2, we give a simple model to describe the activity of *Cyclin E/CDK2* and *pRb* phosphorylation in the G_1 phase. We consider that the transition G_1/S occurs when the level of *Cyclin E/CDK2* reaches a threshold (denoted x_{thr}).

Let x be the amount of *Cyclin E/CDK2* and y the concentration of hypophosphorylated *pRb* . Then, we consider x and y as regulating variables in a simple nonlinear system of differential equations with respect to age a.

The *Cyclin E/CDK2* is regulated by *pRb/E2F* pathway inducing the *pRb* phosphorylation. The synthesis of x occurs at the rate k and depends on the concentration $(R-y)$ of the hyper phosphorylated pRb and its degradation occurs at a rate d_1. Moreover, the total concentration of *pRb* (hypo as well as hyper phosphorylated *pRb*), denoted R, remains constant throughout the cell cycle and we assume that y is chiefly phosphorylated during the G_1 phase by the action of the complex *Cyclin E/CDK2*, at a rate d_2. Thus, we give the following system with only two variables (*Cyclin E/CDK2*, *pRb*) with respect to age a:

$$\begin{cases} \dfrac{dx}{da} = k(R-y) - d_1(x - x_{\min}), \\ \dfrac{dy}{da} = -d_2 x y, \\ x(0) = x_i, \quad 0 < x_{\min} \leq x_i \leq x_{thr}, \\ y(0) = R. \end{cases} \tag{1}$$

Where all the parameters are positive $(k > 0,\ d_i > 0\ i = 1, 2,\ R > 0)$. We assume that at the beginning of the cell cycle, *pRb* is totally hypo phosphorylated. Thus the initial concentration of *pRb* is at its maximum R; whereas the amount of *Cyclin E/CDK2* is variable for different cells; bigger than the minimal value $x_{\min}$ and smaller than a threshold value denoted x_{thr}. Now, we investigate the behavior of the solutions of the model described in (1) and we state some results which are useful for further purposes.

Proposition 1. *System* (1) *has two steady states* $\left(x_{\min} + \dfrac{k}{d_1} R, 0\right)$ *which is a sink, and* $\left(0, \frac{d_1}{k} x_{\min} + R\right)$ *which is a saddle point.*

For the global behavior of the solutions of system (1), we state the following proposition.

Proposition 2. *For any initial conditions* (x_i, R), *such that* $x_i \in \left(x_{min}, x_{min} + \frac{k}{d_1} R\right)$, *$y$ always decreases, whereas x can decrease initially, never reaching the minimal value* $x_{\min}$ *(unless when* $x_i = x_{\min}$*), and then increases towards the asymptotic value* $x_{\min} + \frac{k}{d_1} R$.

proof. We assume that there exists an $\hat{a} > 0$ such that $x(\hat{a}) = x_{min}$ then the left derivative of x calculated at $\hat{a}$ would be less than or equal to zero but from system (1) we remark that whenever $x = x_{\min}$ ($\hat{a}$ is the smallest one), the derivative of x is strictly positive, which gives a contradiction. After this initial decrease (if it occurs), x increases towards the asymptotic value: $x_{\min} + \frac{k}{d_1} R$. Indeed, x is bounded and if we look at the expression giving the second derivative (x' is the derivative of x and x'' is the second derivative):

$$x'' = -ky' - d_1 x',$$

we see that whenever $\exists \tilde{a} > 0$ such that $x'(\tilde{a}) = 0$, $x(a)$ is increasing $\forall a \geq \tilde{a}$ (the second derivative $x''(\tilde{a})$ is strictly positive). Moreover, we have

$$y(a) = R\, e^{-d_2 \int_0^a x(\alpha) d\alpha} \tag{2}$$

then $0 \leq y(a) \leq R \quad \forall a \geq 0$ and y decreases exponentially to 0. Indeed, assuming that

$$\lim_{a \to +\infty} y(a) > 0,$$

yields $\int_0^{+\infty} x(\alpha)\, d\alpha < +\infty$ then $\lim\limits_{a \to +\infty} x(\alpha) = 0$, which provides a contradiction with

$$x(a) > x_{\min} \quad \forall a > 0\ .$$

Moreover when the initial value $x(0)$ is equal to $x_{\min}$, then x always increases. □

Remark 1. As observed experimentally [16, 21, 45], we consider that the *Cyclin E/CDK2* increases at least in the late G_1 phase until it reaches its maximum at the G_1/S transition. Moreover, *pRb* represented by the variable y goes to zero at the end of the G_1 phase which coincides with the fact that the *pRb* becomes totally hyper phosphorylated at the end of the G_1 phase.

3.2. **The G1 phase duration.** The main assumption we consider here is that the transition G_1/S occurs when *Cyclin E/CDK2* reaches the threshold x_{thr} provided a minimum time $T_{\min}$ passed from the beginning of the cell cycle (see [11] for an experimental support of this matter). Therefore we have a variable G_1 phase duration which depends on the initial state of *Cyclin E/CDK2* [39]. To ensure that x reaches the threshold x_{thr} we consider the following condition: $x_{min} < x_{thr} \leq x_{\min} + \frac{k}{d_1} R$. Then, we can state some hypotheses and results on the system (1) which give us some properties on the G_1 phase duration and the cell age at the transition G_1/S.

Proposition 3. *For any two initial conditions* $(x_1(0), R)$, $(x_2(0), R)$ *of (1) with* $x_1(0) < x_2(0)$ *then* $x_1(a) < x_2(a)$, $\forall a > 0$.

proof. Indeed, if there exists an $a^* > 0$ (a^* is the smallest one), such that $x_1(a^*) = x_2(a^*)$ then we have:

$$\left.\begin{array}{r} x_1(a) < x_2(a), \ 0 < a < a^* \\ x_1(a^*) = x_2(a^*) \end{array}\right\} \Longrightarrow x_1'(a^*) \geq x_2'(a^*),$$

but from (1) we have $y_1(a) = Re^{-d_2 \int_0^a x_1(s)ds}$ and $y_2(a) = Re^{-d_2 \int_0^a x_2(s)ds}$. Which implies that $y_2(a^*) < y_1(a^*)$ and $x_1'(a^*) < x_2'(a^*)$, which gives a contradiction. □

Remark 2. This proposition can ensure that the higher the initial *Cyclin E/CDK2* level, the faster *Cyclin E/CDK2* reaches the threshold and thus the cell passes.

Lemma 3.1. *if* $x_{thr} < \frac{kR}{d_1}(1 - e^{-d_2 T_{min} x_{min}}) + x_{min}$ *then there exists* $\bar{a} \geq T_{\min}$ *such that* $x(\bar{a}) = x_{thr}$

proof. Since $y(T_{\min}) \leq R \cdot e^{-d_2 T_{min} x_{min}}$ and since we have $x(a) \leq x_{thr}$ (else the lemma is proved) then

$$\begin{aligned} \frac{dx}{da} &\geq k(R - y) - d_1(x_{thr} - x_{min}) \\ &\geq kR\left(1 - e^{-d_2 T_{\min} x_{\min}}\right) - d_1(x_{thr} - x_{\min}) \end{aligned}$$

which gives the following necssary condition:

$$\text{if} \quad \frac{kR}{d_1}\left(1 - e^{-d_2 T_{\min} x_{\min}}\right) > x_{thr} - x_{\min} \ \text{ then } \ \frac{dx}{da} > 0 \quad \text{for } a \geq T_{\min}.$$

□

Remark 3. We assume that the degradation rate of the *Cyclin E/CDK2* in the G_1 phase is low ($d_1 << 1$) whereas the degradation of the pRb is high (d_2) which ensure that the condition in Lemma 3.1 is not a strong constraint.

Then from theses results we can give some conclusions on the G_1 phase duration. So, let $\varphi_1(a, x_i)$ be the first component of the flow associated to the solution of x in (1) with initial condition x_i (the *Cyclin E/CDK2* amount at age a of a cell beginning the cell cycle with the amount x_i) and let x^* be the *Cyclin E/CDK2* amount such that $\varphi_1(T_{\min}, x^*) = x_{thr}$. That means an initial amount smaller than x^* leads to a transition age bigger than T_{min} while an initial condition larger than x^* leads the cell to remain in the G_1 phase until it reaches the minimal age T_{min} (see Figure 2). Thus in the first case,the duration of G_1 phase changes and the amount of the *Cyclin E/CDK2* at the end of G_1 is equal to the threshold value:

$$\varphi_1(T_1(x_i), x_i) = x_{thr}. \tag{3}$$

In the second case, the duration of G_1 is the same T_{min}, but the amount of the *Cyclin E/CDK2* at the transition is an increasing function of x_i.

Remark 4. The longest duration (denoted $\bar{T}$) that the cell can spend in the G_1 phase is associated to the initial value equal to x_{min}:

$$T_1(x_{min}) = \bar{T} \geq T_1(x_i) \qquad \forall x_i \in [x_{min}, x_{thr}], \tag{4}$$

$\varphi_1(\bar{T}, x_{\min}) = x_{thr}$, and the largest *Cyclin E/CDK2* amount (denoted $\bar{x}$) reached at the end of the G_1 phase is associated to the initial value x_{thr}:

$$T_1(x_{thr}) = T_{min}, \qquad \varphi_1(T_{\min}, x_{thr}) = \bar{x}. \tag{5}$$

From above, we summarize that at the G_1/S transition we have the cell age $T_1\left(x_i\right)$, the amount x of *Cyclin E/CDK2* and the concentration y of *pRb* are such that:

$$T_1(x_i) = \begin{cases} a \ \text{ with } \varphi_1(a, x_i) = x_{thr}, & \text{if } x_{min} \le x_i \le x^* \\ T_{\min}, & \text{if } x^* \le x_i \le x_{thr}, \end{cases}$$

$$x = x_{G_1}(x_i) = \begin{cases} x_{thr} & \text{if } x_{min} \le x_i \le x^* \\ \varphi_1(T_{min}, x_i) & \text{if } x^* \le x_i \le x_{thr} \end{cases} \tag{6}$$

$$y = y_{G_1}(x_i) = \begin{cases} R\ e^{-d_2 \int_0^{T_1(x_i)} \varphi_1(\alpha, x_i) d\alpha} & \text{if } x_{\min} \le x_i \le x^* \\ R\ e^{-d_2 \int_0^{T_{\min}} \varphi_1(\alpha, x_i) d\alpha} & \text{if } x^* \le x_i \le x_{thr} \end{cases}$$

Lemma 3.2. *The function $T_1\left(x_i\right)$ defined in (6) is a decreasing function.*

proof. From Proposition 3 and Lemma 3.1, φ_1 is increasing in x_i and increasing in a close to $T_1\left(x_i\right)$. Then, differentiating the function given in (3) with respect to x_i we obtain:

$$\frac{\partial \varphi_1}{\partial a}_{|a=T_1(x_i)} T_1'\left(x_i\right) + \frac{\partial \varphi_1}{\partial x_i} = 0, \tag{7}$$

then

$$T_1'\left(x_i\right) < 0, \quad \forall x_i \in \left[x_{\min}, x_{thr}\right].$$

$\square$

That means the required cell age $T_1\left(x_i\right)$ to pass to the S phase is a decreasing function of the initial value of the *Cyclin E/CDK2* (see Figure 2 and Figure 3).

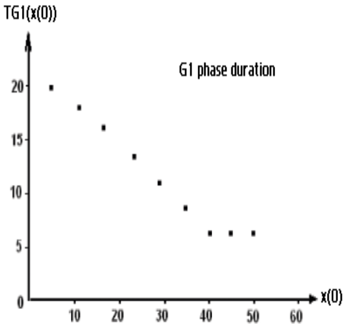


FIGURE 2. This graphic represents the simulation of the G_1 phase duration (TG_1) as a function of the initial value associated to the variable x and under the assumption that the S phase begins as soon as x reaches a threshold value x_{thr}, provided a minimum age T_{min}. The resulting empirical function (TG_1) has an interval of constancy corresponding to the initial values (x^*, x_{thr}).

3.3. **The *S*-G_2-*M* phase formulation.** The unequal distribution of some chemicals as cyclins during cell division certainly affects subsequent cell cycles. Therefore, a way to connect cell cycle and proliferation could be that of describing the evolution

of the cyclins until the end of the cell cycle with the assumption of unequal subdivision among daughter cells of the final cyclin content. Then, we have to describe the *Cyclin E/CDK2* evolution in this remainder of the cell cycle (S-G_2-M). In the previous section, the G_1 duration function $T_1(x_i)$ depends on the initial amount of *Cyclin E/CDK2* whereas we assume that S, G_2 and M phases altogether have fixed duration equal to T_2, with $T_2 + T_{min} > \bar{T}$. We assume that the variable x follows (1) until $\bar{T}$ then decreases linearly with velocity $\frac{\varphi_1(\bar{T},x_i)-dx_{min}}{T_2}$ whereas y increases linearly to the final value R. That means we describe the evolution of the *Cyclin E/CDK2* complex and the *pRb* during the S, G_2 and M as follows:
for $T_1(x_i) < a < \bar{T}$

$$\begin{aligned} x(a) &= \varphi_1(a, x_i) \\ y(a) &= Re^{-d_2 \int_0^a \varphi_1(\alpha,x_i)d\alpha} \end{aligned} \tag{8}$$

and for $\bar{T} < a < T_1(x_i) + T_2$

$$\begin{aligned} x(a) &= \varphi_1(\bar{T}, x_i) - \tfrac{\varphi_1(\bar{T},x_i)-dx_{\min}}{T_2}(a-\bar{T}) \\ y(a) &= \tfrac{R-\varphi_2(\bar{T},x_i)}{T_1(x_i)+T_2-\bar{T}}(a-\bar{T}) + \varphi_2(\bar{T}, x_i) \end{aligned} \tag{9}$$

where $\varphi_2(\bar{T}, x_i) = R\ e^{-d_2 \int_0^{\bar{T}} \varphi_1(\alpha,x_i)d\alpha}$.

Remark 5. Since $x(a)$ decreases at worst to $dx_{\min}$ at the end of the cell cycle and have to divide at least with a value bigger than x_min for each cell daughter then we assume that $d > 2$.

Moreover, the system (9) agree with the fact that the *Cyclin E/CDK2* complex is degraded as cells progress through S phase [40] and that pRb is completely hypophosphorylated at the end of the cell cycle [18], although we do not know whether the dephosphorylation process is gradual or if it occurs only at mitosis. The system (9) can be written under the form of an ODE's system, in the following way:

$$\begin{cases} \frac{dx}{da} = -\frac{\varphi_1(\bar{T},x_i)-dx_{min}}{T_2} \\ \frac{dy}{da} = \frac{R-\varphi_2(\bar{T},x_i)}{T_1(x_i)+T_2-\bar{T}} \\ x(0) = \varphi_1(\bar{T}, x_i) \\ y(0) = R\ e^{-d_2 \int_0^{\bar{T}} \varphi_1(\alpha,x_i)d\alpha} \end{cases} \tag{10}$$

Remark 6. The following condition on the parameters allows us to ensure that, at $T_1(x_i) + T_2$, $x(a)$ belongs to the interval $(dx_{\min}, 2x_{thr})$:

$$\bar{x} - \frac{\bar{x} - dx_{\min}}{T_2}\left(T_2 + T_{\min} - \bar{T}\right) < 2x_{thr}. \tag{11}$$

The conditions given in (5) and (6) ensure that the amount of *Cyclin E/CDK2* shared between the two daughters cell belongs to (x_{min}, x_{thr}) in each one.

Proposition 4. *Let X_f be the function such that:*

$$\begin{array}{rccc} X_f: & (x_{min}, x_{thr}) & \longrightarrow & (dx_{min}, \widehat{x}) \\ & x_i & \longrightarrow & X_f(x_i) = x_f \end{array}$$

where

$$x_f = \varphi_1\left(\bar{T}, x_i\right) - \frac{\varphi_1\left(\bar{T}, x_i\right) - dx_{\min}}{T_2}\left[T_1\left(x_i\right) + T_2 - \bar{T}\right].$$

Then X_f is invertible.

proof. We will prove the above proposition in the case corresponding to a variable duration of the G_1 phase, the other situation being easier to treat (i.e. when $T_1\left(x_i\right) = T_{\min}$).

From the definition of X_f we have:

$$\begin{aligned} X_f(x_i) =& \varphi_1\left(\bar{T}, x_i\right) - \\ & \frac{\varphi_1\left(\bar{T}, x_i\right) - dx_{\min}}{T_2}\left[T_1\left(x_i\right) + T_2 - \bar{T}\right]. \end{aligned}$$

That means the final value x_f depends on the initial value x_i. The derivative of this function is:

$$\begin{aligned} X_f'\left(x_i\right) =& \frac{\partial\varphi_1}{\partial x_i}\left(\bar{T}, x_i\right)\left[\frac{\bar{T} - T_1\left(x_i\right)}{T_2}\right] - \\ & \frac{\varphi_1\left(\bar{T}, x_i\right) - dx_{\min}}{T_2} T_1'\left(x_i\right). \end{aligned}$$

Then we are interested in its sign. We have $T_1(x_i) < 0$ and $T_1(x_i) \leq \bar{T}$. Moreover $\varphi_1\left(\bar{T}, x_i\right) \geq dx_{min}$. Then $X_f^{'}(x_i) \geq 0$ which implies that X_f is invertible in (x_{min}, x_{thr}) and thus x_i is a function of x_f. □

Remark 7. This proposition means that from any final value $x_f = X_f\left(x_i\right)$ of *Cyclin E/CDK2* associated to mother cell at mitosis it is possible to go back to the initial content x_i which has generated the final state x_f.

4. Connection with the population level.

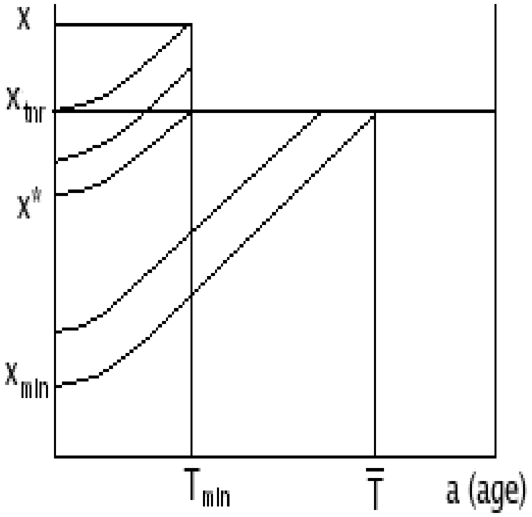
In a population of normal cells there is a balance between proliferation, quiescence and cell death [44]. This balance is maintained by a system of closely interconnected inhibitory and stimulatory signals and ensure tissue homeostasis, but embryonic cells or cancer cell lines growing under optimal conditions present different features avoiding cell quiescence, cell loss and the strong dependence on growth factor stimulation. Our attention was focused on cancer cell lines growing in suspension. Obviously, immortal cell lines growing in vitro do not give a correct idea of the complexity of the environment where either normal or tumor cells grow. Nevertheless, cell lines are a very important tool for the study of cell cycle regulation and cell proliferation, and of cell kinetic parameters, such as cell cycle duration and phase transition times.

4.1. Formulation of the evolution problem.

In the previous section, we considered the evolution of *Cyclin E/CDK2* inside a single cell and the way to regulates the timing of cell cycle. We now aim to take into account a cell population structured by the time spent inside the cell cycle since birth (variable a) and the amount of *Cyclin E/CDK2* complex (variable x). The evolution of x is described by the following equations:

$$\begin{cases} \frac{dx}{da} = \Gamma(a, x) \\ x(0) = x_i \end{cases}$$

where



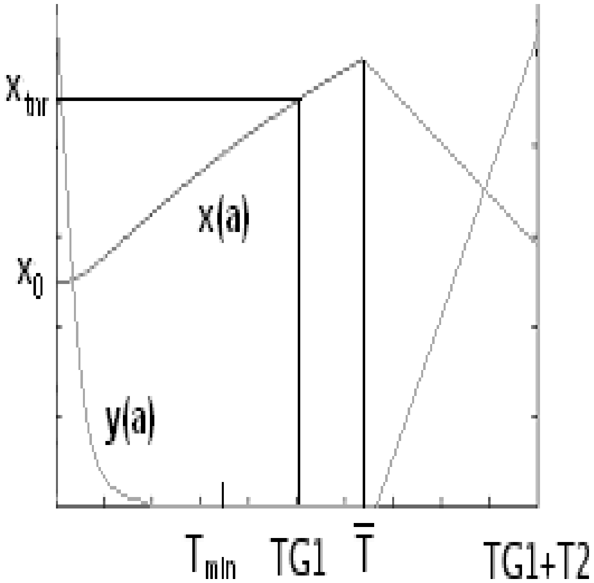


FIGURE 3. The first graphic shows the evolution of the complex CyclinE/CDK2 (x) during the G_1 phase. For the initial conditions bigger than x^* we have $x(TG_1) = x(T_{min})$ whereas for the initial conditions smaller than x^* we have $x(TG_1) = x_{thr}$ where $TG_1 > T_{min}$. The second graphic shows the evolution of the complex CyclinE/CDK2 (x) and the pRb (y) during the cell cycle.

$$\Gamma(a,x) = \begin{cases} \Gamma_1(a,x) & for\ 0 < a < T_1(x_i), \\ \Gamma_2(a,x) & for\ T_1(x_i) < a < T_1(x_i) + T_2, \end{cases}$$

$$\Gamma_1\left(a,x\right)=kR\left(1-e^{-d_1\int_0^a\varphi_1(\alpha,x_i)d\alpha}\right)-c\left(x-x_{\min}\right),$$

and

$$\Gamma_2(a,x)=\begin{cases} k\ R(1-e^{-d_1\int_0^a\varphi_1(\alpha,x_i)d\alpha})- \\ c(x-x_{\min}) \quad \text{if } T_1(x_i)<a<\bar{T} \\ -\frac{\varphi_1(\bar{T},x_i)-dx_{\min}}{T_2} \quad \text{if } \bar{T}<a<T_1(x_i)+T_2 \end{cases}$$

where $\varphi_1\left(a,x_i\right)$ is the solution of the first equation associated to the initial condition x_i at the age a. We denote $P_1\left(t,a,x\right)$ and $P_2\left(t,a,x\right)$ the densities, with respect to a and x, of cells that, at time t, are in the G_1 phase or in the remainder part of the cell cycle, respectively. Then, we can write the following partial differential equations associated to P_i, $i=1,2$:

$$\begin{cases} \frac{\partial P_1}{\partial t}+\frac{\partial P_1}{\partial a}+\frac{\partial}{\partial x}[\Gamma(a,x)P_1(t,a,x)]=0 \\ \\ \frac{\partial P_2}{\partial t}+\frac{\partial P_2}{\partial a}+\frac{\partial}{\partial x}[\Gamma(a,x)P_2(t,a,x)]=-F(x)P_2(t,a,x) \end{cases} \tag{12}$$

The left sides of the equations represent the variation of the subpopulation P_1 and P_2 with respect to time, age and *Cyclin E/CDK2* amount where γ represents the speed of x with respect to the physiological age a. Moreover, we assume that no mortality occurs during cell cycle progression (as we have discussed before this assumption is true as far as we deal with cell cultures growing under optimal conditions) and finally the term $F(x)P_2(t,a,x)$ is the cell subpopulation density which have the *Cyclin E/CDK2* amount equal to x when they leave the cell cycle.

The boundary conditions describing the flow of cells from one compartment (G_1) to the other $(S,\ G2,\ M)$ are the following:

- (a) $P_2(t,a,x_{thr})=P_1(t,a,x_{thr}),\qquad T_{\min}<a<\bar{T};$
- (b) $P_2(t,T_{\min},x)=P_1(t,T_{\min},x),\qquad x_{thr}<x<\overline{x}.$

Now, we have to consider the boundary condition that determines the cell division event at the end of the second compartment and the birth of two new cells which enter the cell cycle at the beginning of the G_1 phase $(a=0)$ but no such condition is needed at $x=0$, since cyclin level $x=0$ is never reached (2).

4.2. **Unequal division.** The distribution of the molecular materials between daughter cells such as cyclins is assumed to be unequal. That means the amount x of the *Cyclin E/CDK2* inherited by a newborn cell from its mother follows a conditional density $f(x,x')$, x' being the mother state at the end of its cell cycle [20]. In [2, 3, 4, 5] such condition is given for a model describing the evolution of cells classified according to a constituent which, after division (by mitosis), is divided in a certain stochastic way amongst the two daughter cells. Then the fraction $F(x)$ of cells which have x *Cyclin E/CDK2* content leave the cell cycle to undergo cell division - disappearing and being replaced by two daughter cells - is defined by:

$$F(x)=\int_{x_{min}}^{x_{thr}}f(x^{'},x)dx^{'} \tag{13}$$

Therefore, we have the following condition at the boundary $a=0$ which corresponds to the new borns density:

$$P_1(t,0,x)=2\int_0^{+\infty}f(x,x')P_2[t,T_2+T_1(X_f^{-1}(x')),x']dx' \tag{14}$$

where X_f^{-1} is the inverse of the function X_f that supplies the value of x at mitosis, given x_i at the beginning of the cell cycle. From the above definition of the function f, we can state the following properties:

1. The daughter amount of cyclins cannot be bigger than the mother one: $f(x, x^{'}) = 0$ if $x > x^{'}$.
2. The amount x' of the *Cyclin E/CDK2* of the mother cell is exactly conserved and shared by the two daughters: $f(x, x') = f(x' - x, x')$.
3. The amount x of the *Cyclin E/CDK2* of the daughter cells entering the G_1 phase belongs to the interval $[x_{\min}, x_{thr}]$: $f(x, x') = 0$ if $x \notin [x_{\min}, x_{thr}]$, which yields
$$\int_{x_{\min}}^{x_{thr}} f(x, x')dx = 1. \tag{15}$$
4. There exists a positive value x_1 such that $x_{\min} < x_1 < x^* < x_{thr}$ ans a, b such that $0 < a < b$, with $aX_f(x_1) = x_1$ and $bX_f(x_{thr}) = x_{thr}$, $aX_f(x) > x$ for $x > x_1$, $bX_f(x) > x$ for $x > x_{thr}$, $aX_f(x) < x$ for $x < x_1$, and $bX_f(x) < x$ for $x < x_{thr}$, such that:
$$Supp\ 2f(x, X_f(y)) = [aX_f(y), bX_f(y)].$$
This property allows us to show that if P is a solution of (27), whose support is initially contained in the interval $(x_{\min}, x_{thr})$, then $P(t, x) = 0$ for $t > 0$, and $x < x_{\min}$ or $x > x_{thr}$. Moreover, the x-support shrinks asymptotically to the interval $[x_1, x_{thr}]$.
5. $f(x, X_f(y))$ is bounded with respect to both variables x and y.
6. $2f(x, X_f(y))$ is nonnegative, continuous and $2\int_0^\infty f(x, X_f(y))dx > 1$.

4.3. **The cell cycle duration T_c.**

Here, we take into account the variability of the cell cycle duration. We denote T_c the function of the total cell cycle duration defined as follows:
$$T_c(y) = T_1(y) + T_2, \quad \forall y \in [x_{\min}, x_{thr}]. \tag{16}$$
where $T_1(y)$ corresponds to the G1 phase duration and T_2 to the duration of the remainder of the cell cycle. Using (6) and Lemma 3.2 we obtain the following results:

1. T_c is continuous, nondecreasing such that
$$0 < T_{\min} + T_2 < T_c(y) < \bar{T} + T_2 < +\infty. \tag{17}$$
and
$$T_c(y) = T_{\min} + T_2 \quad \forall y \in [x^*, x_{thr}]. \tag{18}$$
2. There exists a constant $\theta' > 0$, such that
$$|T_c'(y)| \geq \theta' \quad \forall y \in [x_{\min}, x^*] \tag{19}$$
Inequality (19) can be assured by proposition 3 (see also the graphic representation of T_1 shown in Figure 2).

4.4. **Analysis and qualitative behavior.** We now perform the analysis of the model developed above. We use for this purpose the method based on the theory of semigroups following the approach in [2].

Using the characteristic lines corresponding to (12) we obtain:

$$\begin{cases} P_1(t(s),a(s),x(s)) = P_1(t_0,a_0,x_0)e^{-\int_0^s \frac{\partial\Gamma_1}{\partial x}(\tau,\varphi_1(\tau,x_i))d\tau}, \\ \\ P_2(t(s),a(s),x(s)) = \\ P_2(t_0,a_0,x_0)e^{-\int_0^s \left(\frac{\partial\Gamma_2}{\partial x}(\tau,\varphi_1(\tau,x_i))+F(\varphi_1(\tau,x_i))\right)d\tau}. \end{cases}$$

Therefore at the G_1/S transition we have:

$$\begin{cases} P_1(t,T_1(X_f^{-1}(x)),x_{thr}) = \\ P_1(t-T_1(X_f^{-1}(x)),0,X_f^{-1}(x))e^{-r_1(x)} \quad for\ x \in [x_{min},x^*] \\ \\ P_1(t,T_{min},\varphi_1(T_{min},X_f^{-1}(x))) = \\ P_1(t-T_{\min},0,X_f^{-1}(x))e^{-r_2(x)} \quad for\ x \in [x^*,x_{thr}] \end{cases} \tag{20}$$

where

$$r_1(x) = \int_0^{T_1(X_f^{-1}(x))} \frac{\partial\Gamma_1}{\partial x}(s,\varphi_1(s,X_f^{-1}(x)))ds \tag{21}$$

and

$$r_2(x) = \int_0^{T_{min}} \frac{\partial\Gamma_1}{\partial x}(s,\varphi_1(s,X_f^{-1}(x)))ds \tag{22}$$

and at the age of the division, we have:

$$\begin{cases} P_2(t,T_1(X_f^{-1}(x))+T_2,x) = \\ P_2(t-T_2,T_1(X_f^{-1}(x)),x_{thr})e^{-r_3(x)} \quad for\ x \in [x_{min},x^*] \\ \\ P_2(t,T_{min}+T_2,x) = \\ P_2(t-T_2,T_{min},\varphi_1(T_{min},X_f^{-1}(x)))e^{-r_4(x)} \quad for\ x \in [x^*,x_{thr}] \end{cases} \tag{23}$$

where

$$\begin{aligned} r_3(x) = &\int_{T_1(X_f^{-1}(x))}^{\bar{T}} \frac{\partial\Gamma_2}{\partial x}(s,\varphi_1(s,X_f^{-1}(x)))ds + \\ &\int_{T_1(X_f^{-1}(x))}^{T_1(X_f^{-1}(x))+T_2} F(\varphi_1(s,X_f^{-1}(x)))ds \end{aligned} \tag{24}$$

and

$$\begin{aligned} r_4(x) = &\int_{T_{min}}^{\bar{T}} \frac{\partial\Gamma_2}{\partial x}(s,\varphi_1(s,X_f^{-1}(x)))ds + \\ &\int_{T_{min}}^{T_{min}+T_2} F(\varphi_1(s,X_f^{-1}(x)))ds. \end{aligned} \tag{25}$$

Using the boundary condition (14) and the system (23), we obtain:

$$\begin{aligned} & P_1(t,0,x) = 2\int_0^{+\infty} f(x,x')P_2(t,T_1(X_f^{-1}(x'))+T_2,x')dx' \\ & = 2\int_{X_f(x_{\min},x^*)} \\ & f(x,x')P_2(t-T_2,T_1(X_f^{-1}(x')),x_{thr})e^{-r_3(x')}dx' + \\ & 2\int_{X_f(x^*,x_{thr})} \\ & f(x,x')P_2(t-T_2,T_{min},\varphi_1(T_{min},X_f^{-1}(x)))e^{-r_4(x')}dx'. \end{aligned} \tag{26}$$

Moreover, from the system (20) and the conditions (a) and (b), we obtain:

$$\begin{aligned} & P_1(t,0,x) = \\ & 2\int_{X_f(x_{\min},x^*)} \\ & f(x,x')P_1(t-T_1(X_f^{-1}(x'))-T_2,0,X_f^{-1}(x'))e^{-(r_1(x')+r_3(x'))}dx' + \\ & 2\int_{X_f(x^*,x_{thr})} \\ & f(x,x')P_1(t-T_{min}-T_2,0,X_f^{-1}(x'))e^{-\left(r_2(x')+r_4(x')\right)}dx', \end{aligned}$$

Now, let $P(t,x)$ be such that $P(t,x) = P_1(t,0,x)$ and $y = (X_f)^{-1}(x')$. Then the integral equation (26) becomes:

$$\begin{aligned} P(t,x) \quad = \quad & 2\int_{x_{min}}^{x^*} f(x,X_f(y))P(t-T_1(y)-T_2,y)e^{-R_1(y)}dy \\ & +2\int_{x^*}^{x_{thr}} f(x,X_f(y))P(t-T_{min}-T_2,y)e^{-R_2(y)}dy \end{aligned} \tag{27}$$

where

$$\begin{aligned} R_1(y) = \quad & \int_0^{T_1(y)} \frac{\partial\Gamma_1}{\partial x}(s,\varphi_1(s,y))ds + \\ & \int_{T_1(y)}^{\bar{T}} \frac{\partial\Gamma_2}{\partial x}(s,\varphi_1(s,y))ds + \int_{T_1(y)}^{T_1(y)+T_2} F(\varphi_1(s,y))ds \end{aligned} \tag{28}$$

and

$$\begin{aligned} R_2(y) = \quad & \int_0^{T_{min}} \frac{\partial\Gamma_1}{\partial x}(s,\varphi_1(s,y))ds + \\ & \int_{T_{min}}^{\bar{T}} \frac{\partial\Gamma_2}{\partial x}(s,\varphi_1(s,y))ds + \int_{T_{min}}^{T_{min}+T_2} F(\varphi_1(s,y))ds. \end{aligned} \tag{29}$$

The equation (27) is a delay integral equation involving only the population of G_1 phase cells which are about to start a new cell cycle. The delay term corresponds to the duration of the cell cycle which from (6) it is constant and equal to $(T_{\ \min} + T_2)$ if the initial value associated to y belongs to the interval (x^*, x_{thr}) otherwise it is bigger than $T_{\min} + T_2$. The maximal cell cycle duration corresponds to $\bar{T} + T_2$. We denote $\rho = \bar{T} + T_2$ the maximal delay.

If we consider the time interval $[-\rho, 0]$, we will see that the equation (27) is associated to a dynamical system in a class of functions on $(-\rho, 0) \times (x_{min}, x_{thr})$.

We choose the positive cone of the Lebesgue space

$$L^1_+\left((-\rho,0)\times(x_{min},x_{thr})\right) = X,$$

as the space of the initial data. Let P_t be the trajectory defined as follows:

$$P_t\left(\theta,x\right)=P\left(t+\theta,x\right). \tag{30}$$

Proposition 5. *Let* P_0 *be in* X *(or in* X^∞*), and let* P *be defined on* $(-\rho,T_2+T_{\min})\times(x_{\min},x_{thr})$ *by* $P=P_0$ *on* $(-\rho,0)\times(x_{\min},x_{thr})$ *and by*

$$\begin{aligned}&P(t,x)=\\&2\int_{x_{min}}^{x^*}f(x,X_f(y))e^{-R_1(y)}P_0[t-T_2-T_1(y),y]dy+\\&2\int_{x^*}^{x_{thr}}f(x,X_f(y))e^{-R_2(y)}P_0(t-T_2-T_{min},y)dy,\end{aligned}$$

on $(0,T_2+T_{min})\times(x_{min},x_{thr})$*. Then for each* t *in* $(0,T_2+T_{min})$*,* P_t *is in* X *(or in* X^∞*) and* $\|P_t\|_X\le C\|P_0\|_X$ *,* $0<t<T_2+T_{\min}$*, where* C *is independent of* P_0*.*

proof. Since the minimum delay is $T_{\min}+T_2$, then the solution is automatically known on the interval $[0,T_{\min}+T_2]$ by means of simple integration, and therefore we have just to check that this first portion of the solution is in X (or in X^∞), given P_0 in X (or in X^∞). To do that, we consider

$$\int_0^{T_2+T_{\min}}\int_{x_{\min}}^{x_{thr}}\left|P\left(t,x\right)\right|dxdt$$

and we integrate it first in the variable x (using the probability property (15)) and then in t. This gives:

$$\begin{aligned}&\int_0^{T_2+T_{\min}}\int_{x_{\min}}^{x_{thr}}\left|P\left(t,x\right)\right|dxdt\\&\le 2\int_0^{T_2+T_{\min}}\left\{\int_{x_{\min}}^{x^*}\left|P\left(t-T_2-T_1\left(y\right),y\right)\right|dy\right\}dt+\\&2\int_0^{T_2+T_{\min}}\left\{\int_{x^*}^{x_{thr}}\left|P\left(t-T_2-T_{\min},y\right)\right|dy\right\}dt\\&\le 2\int_{-\rho}^{0}\left\{\int_{x_{\min}}^{x^*}\left|P\left(\theta,y\right)\right|dy\right\}d\theta\\&+2\int_{-\rho}^{0}\left\{\int_{x^*}^{x_{thr}}\left|P\left(\theta,y\right)\right|dy\right\}d\theta\\&\le C\int_{-\rho}^{0}\int_{x_{\min}}^{x_{thr}}\left|P\left(\theta,y\right)\right|dyd\theta.\end{aligned}$$

We have therefore come back to the interval $(-\rho,0)\times(x_{\min},x_{thr})$. So, this shows that, starting from any element in X, the solution remains in X, at least for all $t\in[0,T_{\min}+T_2]$. For initial values in X^∞, we just have to notice that f being a distribution probability in the x, the right hand side of equation (27) is uniformly bounded on the domain $[0,T_{\min}+T_2]\times(x_{min},x_{thr})$. □

Characterization of the solution Using the approach developed in [2], we can prove the following theorem which gives the asymptotic behavior of the solution of 27.

Theorem 4.1. *Let us assume that all the properties defined above for the functions* T_c *and* f *are verified. Then, there exist a positive number* λ^* *and a continuous function* μ^* *such that:*

$$\begin{array}{rcl} \mu^*(x) & > & 0, \quad x_1 < x < x_{thr}, \\ \mu^*(x) & = & 0, \quad x \leq x_1 \quad \text{or} \quad x \geq x_{thr}, \end{array}$$

and, if P *is a solution of* (27) *for* $t \geq t_0$ *with support* $P_t(\theta, \cdot)$ *in* $[x_{\min}, x_{thr}]$, *then there exists a constant* C' *with the property that:*

$$P(t,x) - C' \exp(\lambda^* t)\mu^*(x) = o\left[\exp(\lambda^* t)\right], \qquad t \to \infty.$$

If $P > 0$, *then* $C' > 0$.

First of all, we have to establish the existence of the stationary solution. If we substitute the expression $\exp(\lambda^* t)\mu^*(x) + o\left[\exp(\lambda^* t)\right]$, for P in (27), we see that the pair (λ^*, μ^*) is a solution of the following equation:

$$\mu(x) = 2\int_{x_{\min}}^{x_{thr}} f(x, X_f(y)) e^{-\lambda T_2 - \lambda T_1(y)} \mu(y)\, dy = L_\lambda(\mu)(x), \tag{31}$$

where $T_1(y) = T_{\min}$, $\forall y \in (x^*, x_{thr})$.

For each λ, L_λ is an integral operator with a nonnegative continuous kernel:

$$k_\lambda(x,y) = 2e^{-\lambda T_2 - \lambda T_1(y)} f(x, X_f(y)).$$

Therefore, L_λ is a positive compact operator on each class $L^p(x^*, x_{thr}), p \geq 1$. We will use the adjoint $L_\lambda^* \nu$ of L_λ with respect to the scalar product in $L^2(x_{\min}, x_{thr})$:

$$L_\lambda^* \nu = \int_{x_{\min}}^{x_{thr}} k_\lambda(x,y)\, \nu(x)\, dx.$$

We have to find a nontrivial fixed point of L_λ in the cone of the nonnegative functions.

Theorem 4.2. *Suppose that property 4 for the function* f *be verified. Then the set* Λ *of the (real and complex) numbers such that* (λ, μ) *is a solution of (31) for some* $\mu \neq 0$ *in* $L^2(x_{\min}, x_{thr})$ *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 (31), is one-dimensional, generated by a nonnegative function* μ^*. *Moreover, the one-dimensional space of the functions* ν *in* $L^2(x_{\min}, x_{thr})$ *satisfying* $L_{\lambda^*}^* \nu = \nu$ *is generated by a strictly positive function* ν^*.

Theorem 4.2 has been proved in [2] under analogous hypotheses. To prove the existence of a pair (λ^*, μ^*) the authors used a result by Bonsall. Then they proved the discreteness of Λ. An important role in the demonstration of the last part of theorem 4.2 is played by the above mentioned property 4 of the function f, since it allows to show that the support of the iterates of $L_{\lambda^*}^*$ fills asymptotically the interval $[x_1, x_{thr}]$.

Semigroup of the operator associated to (27) and its infinitesimal generator. Now, we associate to (27) the family of operators defined by:

$$T(t)\, P_0 = P_t. \tag{32}$$

As a consequence, using the fact that the translations are continuous in L^1, we can assert that $t \longrightarrow P_t$ is continuous from $\mathbb{R}^+$ into X.

Proposition 6. *The family of operators* $T(t)$ *defined by (32) sends* X *into itself and constitutes on* X *a strongly continuous semigroup of operators.*

Now, we will describe the infinitesimal generator of the semigroup $T(t)$ and examine its spectral properties. We know that it is a closed operator with a dense domain and it is given by:

$$A\chi = \lim_{t\to 0^+} \frac{[T(t)\chi - \chi]}{t}$$

for all the χ's for which the limit above exists in X. Formally, the generator is defined by

$$(A\chi)(s,x) = \frac{\partial \chi(s,x)}{\partial s}, \quad -\rho < s < 0, \quad x_{\min} < x < x_{thr},$$

with $\frac{\partial\chi}{\partial s}$ in X. This means that χ is absolutely continuous from $[-\rho, 0]$ into $L^1\left(]x_{\min}, x_{thr}[\right)$ and so $\chi(s,\cdot)$ is well defined for each s in $[-\rho,0]$ and continuous. At $s = 0$, it coincides with $\lim\limits_{t\to 0^+} T(t)\chi$, yielding:

$$\chi(0,x) = 2\int_{x_{\min}}^{x_{thr}} \tilde{f}(x,y)\chi(-T_1(y) - T_2, y)dy, \tag{33}$$

where

$$\tilde{f}(x,y) = \begin{cases} f(x, X_f(y))e^{-R_1(y)} & if \quad y \in (x_{min}, x^*) \\ f(x, X_f(y))e^{-R_1(y)} & if \quad y \in (x^*, x_{thr}) \end{cases}$$

Conversely, one can check (we skip this) that any χ in X such that χ is absolutely continuous as a function from $[-\rho, 0]$ into $L^1\left(]x_{\min}, x_{thr}[\right)$ and χ satisfies the boundary condition (33) is in the domain of A. Therefore, we have established that the set $D(A)$ of all the $\chi \in X$ such that χ is absolutely continuous from $[-\rho, 0]$ into $L^1\left(]x_{\min}, x_{thr}[\right)$ satisfies (33) and, for χ in $D(A)$, we have $A\chi = \frac{\partial\chi}{\partial s}$. Now, we consider the resolvent equation,

$$A\chi - \lambda\chi = \xi, \quad \xi \in X; \tag{34}$$

The equation (34) can be integrated in the form of

$$\chi(s,x) = \chi(0,x)\exp(\lambda s) + \int_0^s \exp[\lambda(s-u)]\,\xi(u,x)\,du. \tag{35}$$

Assuming that $\chi(0,x)$ is well defined and belongs to $L^1\left(]x_{\min}, x_{thr}[\right)$, it is straightforward to see that the right hand side of formula (35) is indeed absolutely continuous as a function of s into L^1. Substituting this term for $\chi(s,x)$ in (33), we obtain the following equation:

$$\begin{aligned} \chi(0,x) = 2\int\limits_{x_{\min}}^{x_{thr}} \tilde{f}(x,y)\chi(0,y)\exp(-\lambda(T_1(y)+T_2))dy + \\ 2\int\limits_{x_{\min}}^{x_{thr}} \tilde{f}(x,y) \\ \left(\int\limits_{0}^{-T_1(y)-T_2} \exp\left[-\lambda(T_1(y)+T_2) - u\right]\xi(u,y)du\right) dy. \end{aligned} \tag{36}$$

where

$$T_1(y) = T_{\min} \text{ if } y \in (x^*, x_{thr}),$$

The linear operator in equation (36) is similar to the operator L_λ defined in equation (31). It has the same fixed points with the same multiplicity. We denote by S_λ the operator acting on ξ.

Compactness of L_λ yields that existence of a solution to equation (36) for all ξ is equivalent to $(I - L_\lambda)$ being invertible, which itself is equivalent to $(I - L_\lambda)$ being one-to-one. So the spectrum of the generator is precisely the set of $\lambda' s$ for which the null set of $(I - L_\lambda)$ is $\neq 0$. Now, for λ in the resolvent set, the solution associated to each ξ reads in terms of ξ as

$$\chi(s,x) = \exp(\lambda s)\left(I - L_\lambda\right)^{-1} S_\lambda \xi + \int_0^s \exp\left[\lambda(s-u)\right]\xi(u,x)\,du. \tag{37}$$

Now, it is easy to see that S_λ is compact, as it is essentially an integral operator in both variables and on bounded domains. So, formula (37) defines a decomposition of the resolvent of $(\lambda - A)^{-1}$ into the sum of a compact part which contains information about the spectrum and a noncompact part which seems to be neutral in this respect.

It can be proved (see [2]) that the infinitesimal generator A enjoys then the following properties:

1. The spectrum of A, $\sigma(A)$, is a pure point spectrum;
2. $\sigma(A) = \Lambda$;
3. for each λ, $Im\,(A - \lambda I)$ is closed in X with $Ker\,(A - \lambda I) = e^{\lambda s} \otimes Ker\,(I - L_\lambda)$;
4. for $\lambda = \lambda^*$, $S = Im\,(A - \lambda^* I)$ has codimension 1 in X and so $X = N \oplus S$.

On S, $(A - \lambda^* I)$ is a bijection from $S \cap D(A)$ onto S: $\left(\sigma\left(A_{|S}\right)\right) \subseteq \{Re\lambda \leq \lambda_1\}$ for some $\lambda_1 \leq \lambda^*$. A generates a semigroup on S, $T_S(t)$, which can be completed into a semigroup on X, $\widetilde{T}_S$, such that

$$\widetilde{T}_S(t)\left(e^{\lambda^*}\mu^*\right) = e^{\lambda^*(t+s)}\mu^*.$$

The infinitesimal generator of $\widetilde{T}_S$ is A, so $\widetilde{T}_S = T$ and $T_{|S} = T_S$. Therefore S is invariant with respect to $T(t)$.

However, since the semigroup $T(t)$ is not compact, we are not allowed to extend the decomposition of the generator to a decomposition of the semigroup. Nor we are able to assert in general that the spectrum of the semigroup restricted to S, $\sigma\left[T(t)_{|S}\right]$ is contained in a complex ball $\left\{z : |z| \leq e^{\lambda_1 t}\right\}$ for some $\lambda_1 < \lambda^*$, which would immediately prove theorem 4.1.

Properties of the semigroup $T(t)$. Our aim is to show that, for t large enough, the semigroup $T(t)$ is "quasi compact", that is, it can be decomposed into the sum of two operators, one of which is compact, while the other is "small", in the sense that its growth rate is dominated by the growth rate of the compact part. This way, we will be able to prove that the solution asymptotically reaches asynchronous exponential growth.

Let us introduce the following notations:

$$(KP)(t,x) = 2\int_{x_{\min}}^{x^*} \widetilde{f}(x,y)\,P\left[t - T_2 - T_1(y), y\right]dy, \quad P \in X. \tag{38}$$

where $K : X \longrightarrow X$.

Iterating the operator K yields:

$$\begin{aligned}
&\left(K^2P\right)(t,x) = 2\int_{x_{\min}}^{x^*} \widetilde{f}(x,y)\,(KP)\left[t-T_2-T_1(y),y\right]dy \\
&= 4\int_{x_{\min}}^{x^*} \widetilde{f}(x,y) \\
&\int_{x_{\min}}^{x^*} \widetilde{f}(y,z)\left\{P\left[t-2T_2-T_1(y)-T_1(z),z\right]dz\right\}dy.
\end{aligned}$$

Proposition 7. *Under the assumptions that property 5. for function $\widetilde{f}$ be verified and that*

$$\left|T_1'\right|_\infty + \left|\left(T_1^{-1}\right)'\right|_\infty < +\infty,$$

then the operator K^2 sends functions of L^1 into bounded functions:

$$K^2 : L^1 \longrightarrow L^\infty.$$

proof. We have:

$$\begin{aligned}
&\left|\left(K^2P\right)(t,x)\right| \leq \\
&4\left|\widetilde{f}\right|_\infty^2 \int_{x_{\min}}^{x^*}\int_{x_{\min}}^{x^*} \left|P\left[t-2T_2-T_1(y)-T_1(z),z\right]\right| dzdy.
\end{aligned}$$

Now, the following change of variable $\tau = T_1(y)$, gives:

$$\begin{aligned}
&\left|\left(K^2P\right)(t,x)\right| \\
&\leq 4\left|\widetilde{f}\right|_\infty^2 \\
&\int_{x_{\min}}^{x^*}\left\{\int_{T_1(x^*)}^{T_1(x_{\min})} \left|P\left[t-2T_2-\tau-T_1(z),z\right]\right| \left|\left(T_1^{-1}\right)'(\tau)\right| d\tau\right\}dz \\
&\leq \gamma(t)\left|P_0\right|_{L^1} \Longrightarrow \forall t>0 : K^2P \in L^\infty.
\end{aligned}$$

□

Proposition 8. *The operator K^2 is compact from L^∞ to L^1.*

proof. We now introduce another change of variables:

$$\left\{\begin{array}{l} \tau = t-2T_2-T_1(y)-T_1(z) \\ z = z \end{array}\right.$$

and write the operator K^2 as follows:

$$\begin{aligned}
&\left(K^2P\right)(t,x) = 4\int_{x_{\min}}^{x^*}\int_{t-2T_2-T_1(z)-T_1(x_{\min})}^{t-2T_2-T_1(z)-T_1(x^*)} \\
&g\left(x, T_1^{-1}\left[t-2T_2-T_1(z)-\tau\right], z\right) \\
&P(\tau,z)\left|\left(T_1^{-1}\right)'\left[t-2T_2-T_1(z)-\tau\right]\right| d\tau dz.
\end{aligned}$$

Since the function $g\left(x, T_1^{-1}\left[t-2T_2-T_1(z)-\tau\right], z\right)$ is in L^1 of the four variables (t,x,y,z), it can be approximated by a sequence $\left\{g_n(t,x,y,z)\right\}_{n\in N}$ of functions, continuous in those variables. Now, we denote G_n the operator associated to one of such continuous functions:

$$\begin{aligned}
&\left(G_nP\right)(t,x) = 4\int_{x_{\min}}^{x^*}\int_{t-2T_2-T_1(z)-T_1(x_{\min})}^{t-2T_2-T_1(z)-T_1(x^*)}\\
&g_n\left(x, T_1^{-1}\left[t-2T_2-T_1(z)-\tau\right], z\right)\\
&P(\tau,z)\left|\left(T_1^{-1}\right)'\left[t-2T_2-T_1(z)-\tau\right]\right| d\tau dz.
\end{aligned}$$

The following lemma can then be proved:

Lemma 4.3. *The operator G_n is compact from L^∞ to $\mathcal{C}\left([2\rho,T]\times[x_{\min},x^*]\right)$, $T\geq 2\rho$.*

proof. Since g_n is continuous, bounded sets of L^∞ are mapped by G_n into uniformly bounded and equicontinuous sets of the space $\mathcal{C}\left([A,B]\times[x_{\min},x^*]\right)$. Therefore, by applying the Arzelà-Ascoli theorem, we conclude that bounded sets of L^∞ are mapped by G_n into relatively compact sets of $\mathcal{C}\left([A,B]\times[x_{\min},x^*]\right)$, which proves that G_n is compact. The interval $[A,B]$ has to be chosen in a way such that t is big enough to bypass any delay, that is:

$$\begin{aligned}
A &= 2\rho\\
B &\geq 2\rho.
\end{aligned}$$

□

Corollary 1. *The operator G_n is compact from L^∞ to L^1.*

Now, if we let n go to infinity, we conclude that the sequence $\{G_n\}_{n\in N}$ of operators converges to K^2 in the operator norm:

$$\left\|K^2 - G_n\right\|_{\mathcal{L}(L^1,L^\infty)} \leq \|g-g_n\|_{L^1} \underset{n\longrightarrow\infty}{\longrightarrow} 0.$$

Therefore, K^2 is compact from L^∞ to L^1. □

Let us now consider K^4, which acts on L^1. We know that K^2 maps L^1 into L^∞ and another application of K^2 maps L^∞ into L^1 compactly. Then we can state the following result:

Proposition 9. *the operator K^4, defined as:*

$$\begin{aligned}
&\left(K^4P\right)(t,x) = 4\int_{x_{\min}}^{x^*}\widetilde{f}(x,y)\\
&\int_{x_{\min}}^{x^*}\widetilde{f}(y,z)\left\{K^2P\left[t-2T_2-T_1(y)-T_1(z), z\right]dz\right\}dy
\end{aligned}$$

is compact from L^1 to L^1.

Now, for $t \geq 2\rho$, we can write $P(t,x)$ in the following way:

$$P(t,x) = 4\int_{x_{\min}}^{x^*} \widetilde{f}(x,y)$$
$$\int_{x_{\min}}^{x_{thr}} \widetilde{f}(y,z)\left\{P\left[t-2T_2-T_1(y)-T_1(z),z\right]dz\right\}dy+$$
$$4\int_{x^*}^{x_{thr}} \widetilde{f}(x,y)$$
$$\int_{x_{\min}}^{x_{thr}} \widetilde{f}(y,z)\left\{P\left[t-2T_2-T_{\min}-T_1(z),z\right]dz\right\}dy.$$

Let us decompose $(x_{\min},x_{thr})$ into the union of $(x_{\min},x^*)$ and (x^*,x_{thr}) in the second integral of the second term on the right hand side. We will obtain again a compact part, the one corresponding to the integration interval $(x_{\min},x^*)$, and a noncompact part.

Now, for $t \geq 5\rho + n(T_2+T_{\min})$, we obtain:

$$P(t,x) = \overline{P}(t,x) + \widetilde{P}(t,x),$$

where the operator $P_0 \longrightarrow \overline{P}$ is compact and $\widetilde{P}(t,x)$ is given by:

$$\widetilde{P}(t,x) = 2^n \int_{(x^*,x_{thr})^n \times (x_{\min},x_{thr})}$$
$$\widetilde{f}(x,y)\,\widetilde{f}(y,z_1)\ldots\widetilde{f}(z_{n-1},z_n)$$
$$P\left(t-2nT_2-2(n-1)T_{\min}-T_1(z_n),z_n\right)dz_n\ldots dz_1 dy.$$

If we define:

$$\begin{aligned}(G(t)P_0)(s,x) &= \overline{P}(t+s,x)\\ (L(t)P_0)(s,x) &= \widetilde{P}(t+s,x)\end{aligned}$$

then we can prove that $G(t): X \longrightarrow X$ is compact and that $\exists C,\varepsilon>0 : \|L(t)\| \leq C\exp\left[(\lambda^*-\varepsilon)t\right]$. This results in the following

Proposition 10. *Assume that properties 2. for the function T_c and 7. for the function f are verified. Then, there exist $\varepsilon>0$, $C\geq 0$ such that, for t large enough, $T(t) = G(t)+L(t)$ where $G(t)$ is compact and $\|L(t)\| \leq C\exp\left[(\lambda^*-\varepsilon)t\right]$.*

proof. The proof is obtained by comparing operators L_λ (defined in (31)) and $L(t)$. We introduce the operator $\mathcal{L}$ defined by

$$\mathcal{L}\mu(x) = 2\int_{(x^*,x_{thr})} \widetilde{f}(x,y)\,\mu(y)\,dy,$$

on the space $L^1\left(]x^*,x_{thr}[\right)$.

In terms of $\mathcal{L}$ formula (39) reads:

$$\widetilde{P}(t,x) =$$
$$\mathcal{L}^n \int_{x_{\min}}^{x_{thr}} \widetilde{f}(x,z)\,P\left(t-2nT_2-2(n-1)T_{\min}-T_1(z),z\right)dz,$$

from which we deduce that

$$\|L(t)\varphi\|_X \leq C\,\|\mathcal{L}^n\|_{L^1(]x^*,x_{thr}[)}\,\|\varphi\|_X \tag{39}$$

for $4\rho + n(T_{\min}+T_2) \leq t \leq 5\rho + n(T_{\min}+T_2)$.

To estimate the quantity $\|\mathcal{L}^n\|_{L^1(]x^*,x_{thr}[)}$ amounts to estimating the spectral radius r of the operator $\mathcal{L}$. It can be shown (see [6]) that, under the hypothesis that $\widetilde{f}(x,y)$ is positive at each point (x,y) in $[x^*,x_{thr}]\times[x^*,x_{thr}]$, the following inequality holds:

$$r < \exp\left(\left(T_{\min}+T_2\right)\lambda^*\right). \tag{40}$$

Now, inequality (39) holds when t is of the order of $n(T_{\min}+T_2)$, for t large. Therefore, $\|L(t)\|^{\frac{1}{t}}$ is equivalent to $\|L(t)\|^{\frac{1}{n(T_{\min}+T_2)}}$. If we apply the same reasoning to $\|\mathcal{L}^n\|_{L^1(]x^*,x_{thr}[)}$, we obtain, when n goes to infinity, a term which is bounded by $r^{\frac{1}{(T_{\min}+T_2)}}$. From (40), it follows that the latter is less than $\exp\lambda^*$ and, going back to (39), we can conclude that there exists $\varepsilon>0$, such that $\|L(t)\|\le C\exp\left[(\lambda^*-\varepsilon)\,t\right]$.
□

5. **Conclusion.** A way to connect cell cycle and proliferation could be that of describing the evolution of the content of some selected proteins until the end of the cell cycle, with the assumption of unequal subdivision among daughter cells of the final protein contents. We have considered a linear model connecting the behavior at individual cell level to the behavior at population level. The model describe a cell population structured by the cell age and the amount of *Cyclin E/CDK2* with two compartments: cells in the G_1 phase and cells in the remainder of the cell cycle (S-G_2-M). We have also taken into account the variability in the timing of G_1/S transition which dependent on the initial amount of *Cyclin E/CDK2*. The analysis we have carried out for the model allowed us to make simplifying assumptions, such as the homogeneity of the extra-cellular milieu, and the absence of mortality or quiescence since we have considered cell lines growing in vitro under optimal conditions. We have proved that the population $P(t,x)$ of cells which start a new cell cycle is such that $P(t,x)-C'\exp(\lambda^*t)\mu^*(x)=o\left[\exp(\lambda^*t)\right]$ when $t\to\infty$. In this first step, we have used only one cyclin/CDK complex but one can hope to give a model more realistic and take into account the other cyclin/CDK complexes which are important for cell cycle progression. We will keep the G_1 phase and separate the remainder of the cell cycle into the S, G_2 and M phases. We hope also to add drug effects since cell lines are used to test many anti-tumor treatments. The comparison between data related to treated cell populations and the kinetic data of unperturbed cell lines are an important source of information about cytostatic and cytotoxic activity of a drug against cancers and are used for the first tests of new drugs. However, maintaining the proper number of cells in any tissue requires a delicate balance between quiescence, differentiation, cell cycle length, cellular production by division and cell loss by necrosis or apoptosis ([19], [49]) and an imbalance between these processes can result in tumoral tissue. The representation of these effects on the cell cycle using modeling approach with linear or nonlinear parameters can be helpful to understand cell cycle regulation and cell proliferation.

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