Delay equation formulation of a cyclin-structured cell population model

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Abstract

The aim of this paper is to derive a system of two renewal equations from individual-level assumptions concerning a cyclin-structured cell population. Nonlinearity arises from the assumption that the rate at which quiescent cells become proliferating is determined by feedback. In fact we assume that this rate is a nonlinear function of a weighted population size. We characterize steady states and establish the validity of the principle of linearized stability.

Keywords: Delay equations, structured cell population, initial value problem, steady states, linearized stability principle.
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1 Introduction

Structured population models for cell populations were first introduced by Von Foerster [20] where age distribution was considered. Later on, Bell and Anderson [1] and Sinko and Streifer [19] proposed a model for the cell cycle where the cell size was taken into account. More recently [2], [3], [4] and [5] deal with structured cell

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populations where the structuring variable is the content of cyclin, which is a group of proteins that play a major role in the regulation of the cell cycle. These works and some previous ones ([14], [15]) distinguish between two groups of cells, proliferating and quiescent. All the mentioned models were formulated as functional partial differential equations or integro-partial differential equations. In this paper we use the delay equation formulation of structured population dynamics (see [8], [9] and [11]) to deal with a cell population model (see [10] where this formulation was used for a linear cell cycle model with equal division). Here we assume that proliferating cells can become quiescent only once, unlike other approaches (see [2], [3], [4] and [5]) where these transitions can occur infinitely many times. Moreover, we also assume that there is a particular value x_b of the cyclin content that separates cells which cannot yet divide from the others which are able to divide. Furthermore, here the state variables are not anymore densities, but they are the flux of the cells across the point x_b and the feedback variable. Finally, the model equation turns out to be a delay equation relating the current values of these variables with their history (their value in the past). We prove existence and uniqueness of solutions of the initial value problem, and the linear stability principle by means of a semi-linear formulation in the framework of dual semigroups (for the linear stability principle in the age dependent case see [17], [21] and [18]).

2 The model

2.1 Ingredients of the model

We consider a model based on the one introduced by Bekkal Brikci et al. (see [2] and [3]), but using a different approach and different techniques. Our model is similar to the one studied in [4] and [5] but with some different hypotheses on the biological system. Cells are structured by the content of cyclin x which is limited by some constant $x_M > 0$. We assume that only cells with a large content of cyclin can divide, i.e., there exists some positive constant $x_b < x_M$ such that cells with a cyclin level below this threshold do not divide. We also assume that when a cell divides, both daughter cells have cyclin content bigger than some positive constant x_m and smaller than x_b (notice that this requires that $x_b \geq \frac{x_M}{2}$ and $x_m \leq \frac{x_b}{2}$). When the cyclin content x of a cell is less than x_b, it can either be in the proliferating or in the quiescent stage. Division can only occur in the proliferating stage and only when $x > x_b$ and it happens with rate $F(x)$ which we assume is a bounded, positive and continuous function. Cells can also leave the proliferating stage by apoptosis (programmed cell death) which occurs with rate d_1 depending on cyclin content. Another way to leave the proliferating stage is to go to the quiescent one.

Cells in the proliferating stage can only go to the quiescent stage once and only when they have less cyclin content than x_b, i.e. when they are not yet able to reproduce. These are the main differences with respect to the model studied in [4] and [5]. This transition occurs according to a "leak" function $L(x)$ which we assume positive, bounded and continuous. In the quiescent stage cells do not change their cyclin content. They can leave this stage either by apoptosis, which is assumed to happen with a rate d_2 that depends on cyclin content, or by going back to the proliferating stage. This transition rate is given by a function $G(N)$ where N stands for a weighted population number. For shortness we will denote $I = G(N)$.

We will assume that both death rates $d_1(x)$ and $d_2(x)$ are bounded below by a positive constant.

Proliferating cells increase their cyclin content. The function $\Gamma(x)$ represents the growth rate (evolution speed) of the cyclin content of each individual cell. $\Gamma(x)$ is a smooth strictly positive function of $x \in [x_m, x_M)$ vanishing at x_M.

With this we can define the function $A(x, \xi)$ which is the time a cell needs to increase its cyclin content from ξ to x ignoring a possible quiescent phase, i.e.,

$$A(x, \xi) := \int_{\xi}^{x} \frac{d\sigma}{\Gamma(\sigma)}.$$

Let us denote by $\mathcal{F}_0(x, \xi)$ the probability that a cell does not die and does not go to the quiescent stage while it increases its cyclin content from ξ to $x < x_b$. This is given by

$$\mathcal{F}_0(x, \xi) := e^{-\int_{\xi}^{x} \frac{d_1(\sigma)+L(\sigma)}{\Gamma(\sigma)} d\sigma}.$$

In the same way, for cells that have already been in the quiescent stage and came back to the proliferating stage we define the function $\mathcal{F}_1(x, \xi)$ as the survival probability from ξ to x, i.e., the probability that a cell does not die while it increases its cyclin content from ξ to x , i.e.,

$$\mathcal{F}_1(x, \xi) := e^{-\int_{\xi}^{x} \frac{d_1(\sigma)}{\Gamma(\sigma)} d\sigma}$$

for $x_m \leq \xi \leq x \leq x_b$.

Finally, let $\mathcal{F}_2(x, \xi)$ be the survival probability from ξ to x, where $x_b \leq \xi < x \leq x_M$, that is, the probability that a (proliferating) cell does neither die nor divide while it increases its cyclin content from ξ to x. This is given by

$$\mathcal{F}_2(x, \xi) := e^{-\int_{\xi}^{x} \frac{d_1(\sigma)+F(\sigma)}{\Gamma(\sigma)} d\sigma}.$$

Defining $u(t)$ as the flux at the point x_b, we can express the density n at time t of cells with cyclin content $x \in (x_b, x_M)$ as

$$n(t, x) = \frac{1}{\Gamma(x)} u(t - A(x, x_b)) \mathcal{F}_2(x, x_b). \tag{1}$$

In terms of these quantities we compute the population birth rate at time t with cyclin content η as

$$b(t, \eta) = 2 \int_{x_b}^{x_M} \beta(\theta, \eta) F(\theta) n(t, \theta) d\theta$$

$$= 2\int_{x_b}^{x_M} \beta(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}_2(\theta,x_b)u(t-A(\theta,x_b))d\theta, \tag{2}$$

where $\beta(\theta,\cdot)$ is the probability density of the cyclin content of a daughter cell of a dividing cell with cyclin content $\theta > x_b$. For further use, we assume that β is a bounded function with upper bound β_∞. This is a slight generalization of the previous works ([4] and [5]) where we assumed a uniform distribution of the cyclin content of the newborn cells. Incidentally, note that the assumptions on β preclude that we consider a measure with respect to η concentrated in $\frac{1}{2}\theta$, i.e., splitting into two exactly equal daughters.

Notice that when $\theta < x_b + x_m$ then $supp\beta(\theta,\cdot) \subset [x_m, \theta - x_m]$ and that when $\theta > x_b + x_m$ (obviously only possible if $x_b + x_m < x_M$) then $supp\beta(\theta,\cdot) \subset [\theta - x_b, x_b]$. Moreover, consistency requires that $\beta(\theta,\theta-\eta) = \beta(\theta,\eta)$ which in turn guarantees that the expected cyclin content of the daughter cell is $\int \eta\beta(\theta,\eta)d\eta = \frac{\theta}{2}$.

Let us also define $p_0(t,x)$ as the density of cells at time t and cyclin content $x < x_b$ that are in the proliferating stage but never were in the quiescent stage, which is given by

$$p_0(t,x) = \frac{1}{\Gamma(x)}\int_{x_m}^{x} b(t-A(x,\eta),\eta)\mathcal{F}_0(x,\eta)d\eta. \tag{3}$$

The density of quiescent cells will be denoted by $q(t,\zeta)$. This is given by all the proliferating cells with cyclin content ζ that changed to quiescent in the past and are still alive and quiescent. That is

$$q(t,\zeta) = \int_0^{+\infty} L(\zeta)p_0(t-\tau,\zeta)e^{-d_2(\zeta)\tau - \int_{t-\tau}^{t} I(\sigma)d\sigma}d\tau. \tag{4}$$

Finally, let us denote by $p_1(t,x)$ the density of proliferating cells at time t and cyclin content $x < x_b$ that have been quiescent, which is given by

$$p_1(t,x) = \frac{1}{\Gamma(x)}\int_{x_m}^{x} q(t-A(x,\zeta),\zeta)I(t-A(x,\zeta))\mathcal{F}_1(x,\zeta)d\zeta. \tag{5}$$

By substitution of (2) into (3) and of (4) into (5), we can write p_0 and p_1 as follows

$$p_0(t,x) = \frac{2}{\Gamma(x)}\int_{x_m}^{x}\int_{x_b}^{x_M} \beta(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}_2(\theta,x_b)\mathcal{F}_0(x,\eta)$$
$$u(t-A(x,\eta)-A(\theta,x_b))d\theta d\eta, \tag{6}$$

$$p_1(t,x) = \frac{1}{\Gamma(x)}\int_{x_m}^{x}\int_0^{+\infty} L(\zeta)p_0(t-\tau-A(x,\zeta),\zeta)e^{-d_2(\zeta)\tau - \int_{t-\tau-A(x,\zeta)}^{t-A(x,\zeta)} I(\sigma)d\sigma}d\tau$$
$$I(t-A(x,\zeta))\mathcal{F}_1(x,\zeta)d\zeta. \tag{7}$$

2.2 Renewal equation

Let us now build up the concise formulation of the model by introducing parameterized families of linear functionals on the space of histories of u (the space of weight-integrable real valued functions defined on $(-\infty, 0]$).
Let us define $u_t(\tau) := u(t+\tau)$ for $-\infty < \tau \leq 0$.
We can then write (6) as

$$\Gamma(x)p_0(t,x) = \mathcal{L}_0(x)u_t \tag{8}$$

where $\mathcal{L}_0(x)$ is a linear map from $L_1((-\infty,0];\mathbb{R})$ into $\mathbb{R}$ given explicitly by

$$\mathcal{L}_0(x)\phi = 2\int_{x_m}^{x}\int_{x_b}^{x_M}\beta(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}_2(\theta,x_b)\mathcal{F}_0(x,\eta)\phi(-A(x,\eta)-A(\theta,x_b))d\theta d\eta.$$

Similarly we can write (7) as

$$\Gamma(x)p_1(t,x) = \mathcal{L}_1(x,I_t)u_t \tag{9}$$

where

$$\mathcal{L}_1(x,\psi)\phi := \int_{x_m}^{x}\int_0^{+\infty}\frac{L(\zeta)}{\Gamma(\zeta)}\mathcal{L}_0(\zeta)\phi_{-\tau-A(x,\zeta)}e^{-d_2(\zeta)\tau-\int_{-\tau-A(x,\zeta)}^{-A(x,\zeta)}\psi(\sigma)d\sigma}$$

$$\psi(-A(x,\zeta))\mathcal{F}_1(x,\zeta)d\tau d\zeta.$$

Now recall that $u(t)$ is the flux at x_b at time t. Hence

$$u(t) = \Gamma(x_b)p_0(t,x_b) + \Gamma(x_b)p_1(t,x_b).$$

Using (8) and (9) we rewrite this identity as a renewal equation

$$u(t) = \big(\mathcal{L}_0(x_b) + \mathcal{L}_1(x_b,I_t)\big)u_t, \tag{10}$$

which expresses the fact that the flux across the point x_b is given by the sum of the flux of proliferating cells that never were in the quiescent stage and the flux of proliferating cells that have been quiescent once, both types of cells being daughters of cells that crossed the point x_b in the past and divided afterwards.
The expression for $\mathcal{L}_0(x_b)$ and $\mathcal{L}_1(x_b,I_t)$ can be simplified somewhat as follows. Defining for $x_m \leq \eta \leq \theta \leq x_M$,

$$\mathcal{F}(\theta,\eta) := e^{-\int_\eta^\theta \frac{d_1(\sigma)+F(\sigma)}{\Gamma(\sigma)}d\sigma}$$

where we adopt the convention that $F(\sigma) = L(\sigma)$ for $\sigma < x_b$ (we can do this because these functions have disjoint support), we have for $\eta < x_b < \theta$

$$\mathcal{F}_2(\theta,x_b)\mathcal{F}_0(x_b,\eta) = \mathcal{F}(\theta,\eta).$$

Moreover, $A(\theta,x_b) + A(x_b,\eta) = A(\theta,\eta)$ for $\eta < x_b < \theta$ and then we obtain

$$\mathcal{L}_0(x_b)\phi = 2\int_{x_m}^{x_b}\int_{x_b}^{x_M}\beta(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)\phi(-A(\theta,\eta))d\theta d\eta.$$

In the case of $\mathcal{L}_1$, we multiply and divide by $e^{\int_\zeta^{x_b}\frac{L(\sigma)}{\Gamma(\sigma)}d\sigma}$ to compensate for the fact that from ζ to x_b we have survival described by $\mathcal{F}_1$ (and not by $\mathcal{F}_0$) and use the three step identities $\mathcal{F}_2(\theta,x_b)\mathcal{F}_0(x_b,\zeta)\mathcal{F}_0(\zeta,\eta)=\mathcal{F}(\theta,\eta)$, and $A(\theta,x_b)+A(x_b,\zeta)+A(\zeta,\eta)=A(\theta,\eta)$ in order to arrive at the completely explicit expression

$$\mathcal{L}_1(x_b,\psi)\phi := 2\int_{x_m}^{x_b}\int_0^{+\infty}\frac{L(\zeta)}{\Gamma(\zeta)}e^{\int_\zeta^{x_b}\frac{L(\sigma)}{\Gamma(\sigma)}d\sigma}\int_{x_m}^{\zeta}\int_{x_b}^{x_M}\beta(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)$$

$$\phi(-\tau-A(\theta,\eta))d\theta d\eta\ \psi(-A(x_b,\zeta))e^{-d_2(\zeta)\tau-\int_{-\tau-A(x_b,\zeta)}^{-A(x_b,\zeta)}\psi(\sigma)d\sigma}d\tau d\zeta.$$

2.3 Feedback

Up to now we have written a renewal equation for the flux of the cells across the point x_b. This equation contains another unknown function which is the transition rate I from the quiescent stage to the proliferating stage. As it was said at the beginning of the Section 2.1, the model assumes that the rate I is a decreasing function G of some weighted population number, in such a way that a nonlinear self limiting growth mechanism is provided.

Let N be the weighted total population size with weights $w(x)$ for proliferating and $\hat{w}(x)$ for quiescent cells. So, the weighted total population size is given by

$$\begin{aligned} N(t) &:= \int_{x_m}^{x_b}\left[w(x)\big(p_0(t,x)+p_1(t,x)\big)+\hat{w}(x)q(t,x)\right]dx+\int_{x_b}^{x_M}w(x)n(t,x)dx \\ &= \int_{x_b}^{x_M}\frac{w(x)}{\Gamma(x)}\mathcal{F}_2(x,x_b)u(t-A(x,x_b))dx \\ &+\int_{x_m}^{x_b}\left[\frac{w(x)}{\Gamma(x)}\Big(\mathcal{L}_0(x)u_t+\mathcal{L}_1(x,I_t)u_t\Big)+\widehat{w}(x)\mathcal{L}_2(x,I_t)u_t\right]dx \end{aligned}$$

where

$$\begin{aligned} \mathcal{L}_2(x,\psi)\phi &:= 2\frac{L(x)}{\Gamma(x)}\int_0^{+\infty}\int_{x_m}^{x}\int_{x_b}^{x_M}\beta(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}_2(\theta,x_b)\mathcal{F}(x,\eta) \\ &\quad \phi(-\tau-A(x,\eta)-A(\theta,x_b)\ d\theta d\eta e^{-d_2(x)\tau-\int_{-\tau}^{0}\psi(\sigma)d\sigma}d\tau, \end{aligned} \tag{11}$$

and we used (1), (8), (9), (4) and (5). Now defining

$$\begin{aligned} \mathcal{L}_N(\psi)\phi &= \int_{x_b}^{x_M}\frac{w(x)}{\Gamma(x)}\mathcal{F}_2(x,x_b)\phi(-A(x,x_b))dx \\ &+\int_{x_m}^{x_b}\left[\frac{w(x)}{\Gamma(x)}\Big(\mathcal{L}_0(x)+\mathcal{L}_1(x,\psi)\Big)+\widehat{w}(x)\mathcal{L}_2(x,\psi)\right]\phi dx \end{aligned} \tag{12}$$

we can write

$$N(t)=\mathcal{L}_N(I_t)u_t.$$

So, if we finally require

$$I(t)=G(N(t)),$$

then the complete model is captured by the system of nonlinear renewal equations

$$\left\{\begin{array}{rcl} u(t) &=& \big(\mathcal{L}_0(x_b)+\mathcal{L}_1(x_b,I_t)\big)u_t \\ I(t) &=& G(\mathcal{L}_N(I_t)u_t). \end{array}\right. \tag{13}$$

2.4 Constant I

When I is independent of time (and positive), the linear renewal equation (10) is time-translation invariant, with a positive kernel. In this section we will prove that exponential growth or decay is fully determined by the value of $R_0(I)$ relative to 1, where $R_0(I)$ is the integral of the kernel.

Indeed, let us first prove the following

Proposition 2.1. *For any $I \geq 0$, the operator*

$$\mathcal{L}_I := \mathcal{L}_0(x_b) + \mathcal{L}_1(x_b, I)$$

is a positive bounded linear form on the space $L^1_\rho(\mathbb{R}_-, \mathbb{R})$ of the locally integrable functions such that

$$\|u\|_{L^1_\rho} = \int_{-\infty}^0 e^{\rho\theta}|u(\theta)|d\theta < \infty$$

for any $\rho \in (0, d_0)$ where $d_0 := \min(\hat{d}_1, \hat{d}_2)$, $\hat{d}_1 := \inf d_1(x)$ and $\hat{d}_2 := \inf d_2(x)$.

Proof. This can be directly seen as follows:

$$|\mathcal{L}_0(x_b)\phi| \leq 2\beta_\infty F_\infty \int_{x_m}^{x_b}\int_{x_b}^{x_M} \frac{\mathcal{F}(\theta,\eta)}{\Gamma(\theta)}|\phi(-A(\theta,\eta))|d\theta d\eta$$

$$\leq 2\beta_\infty F_\infty \int_{x_m}^{x_b}\int_{x_b}^{x_M} \frac{e^{-\hat{d}_1 A(\theta,\eta)}}{\Gamma(\theta)}|\phi(-A(\theta,\eta))|d\theta d\eta$$

$$\leq 2\beta_\infty F_\infty \int_{x_m}^{x_b}\int_0^\infty e^{-\hat{d}_1 t}|\phi(-t)|dtd\eta = 2\beta_\infty F_\infty(x_b - x_m)\int_0^\infty e^{-\hat{d}_1 t}|\phi(-t)|dt$$

$$= 2\beta_\infty F_\infty(x_b - x_m)\int_{-\infty}^0 e^{\hat{d}_1 s}|\phi(s)|ds,$$

where we made (for any η) the change of variables $A(\theta,\eta) = t$ in the third inequality.

So, for $\rho \leq \hat{d}_1$ and $C = 2\beta_\infty F_\infty(x_b - x_m)$ we have that

$$|\mathcal{L}_0(x_b)\phi| \leq C\|\phi\|_{L^1_\rho}.$$

For $\mathcal{L}_1$ we have to make a similar but more complicated computation. Let us start by noting that, as above,

$$\left|\int_{x_m}^{\zeta}\int_{x_b}^{x_M} \beta(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)\phi(-\tau - A(\theta,\eta))d\theta d\eta\right|$$

$$\leq \int_{x_m}^{x_b}\int_{x_b}^{x_M} \beta(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)|\phi(-\tau - A(\theta,\eta))|d\theta d\eta$$

$$\leq \beta_\infty F_\infty(x_b - x_m) \int_0^\infty e^{-\hat{d}_1 t} |\phi(-\tau - t)| dt$$

$$= \beta_\infty F_\infty(x_b - x_m) e^{\hat{d}_1 \tau} \int_{-\infty}^{-\tau} e^{\hat{d}_1 s} |\phi(s)| ds.$$

Let us use the resulting inequality

$$\left| \int_{x_m}^{\zeta} \int_{x_b}^{x_M} \beta(\theta,\eta) \frac{F(\theta)}{\Gamma(\theta)} \mathcal{F}(\theta,\eta) \phi(-\tau - A(\theta,\eta)) d\theta d\eta \right|$$

$$\leq \beta_\infty F_\infty(x_b - x_m) e^{\hat{d}_1 \tau} \int_{-\infty}^{-\tau} e^{\hat{d}_1 s} |\phi(s)| ds \tag{14}$$

in the computation of a bound for $\mathcal{L}_1$:

$$|\mathcal{L}_1(x_b, I)\phi| \leq 2 \int_{x_m}^{x_b} \int_0^{+\infty} \frac{L(\zeta)}{\Gamma(\zeta)} e^{\int_\zeta^{x_b} \frac{L(\sigma)}{\Gamma(\sigma)} d\sigma} \Bigg[\int_{x_m}^{\zeta} \int_{x_b}^{x_M} \beta(\theta,\eta) \frac{F(\theta)}{\Gamma(\theta)} \mathcal{F}(\theta,\eta)$$

$$|\phi(-\tau - A(\theta,\eta))| d\theta d\eta \Bigg] I e^{-d_2(\zeta)\tau - I\tau} d\tau d\zeta$$

$$\leq 2\beta_\infty F_\infty(x_b - x_m) I \int_{x_m}^{x_b} \int_0^{+\infty} \frac{L(\zeta)}{\Gamma(\zeta)} e^{\int_\zeta^{x_b} \frac{L(\sigma)}{\Gamma(\sigma)} d\sigma} e^{\hat{d}_1 \tau} \int_{-\infty}^{-\tau} e^{\hat{d}_1 s} |\phi(s)| ds e^{-d_2(\zeta)\tau - I\tau} d\tau d\zeta$$

$$\leq 2\beta_\infty F_\infty(x_b - x_m) I \int_0^{A(x_b,x_m)} \int_0^{+\infty} L_\infty e^{L_\infty t} e^{(\hat{d}_1 - \hat{d}_2)\tau} \int_{-\infty}^{-\tau} e^{\hat{d}_1 s} |\phi(s)| ds d\tau dt$$

$$= 2\beta_\infty F_\infty(x_b - x_m) I \left(e^{L_\infty A(x_b,x_m)} - 1 \right) \int_0^{+\infty} \int_{-\infty}^{-\tau} e^{(\hat{d}_1 - \hat{d}_2)\tau} e^{\hat{d}_1 s} |\phi(s)| ds d\tau$$

$$= 2\beta_\infty F_\infty(x_b - x_m) I \left(e^{L_\infty A(x_b,x_m)} - 1 \right) \int_{-\infty}^{0} e^{\hat{d}_1 s} |\phi(s)| \int_0^{-s} e^{(\hat{d}_1 - \hat{d}_2)\tau} d\tau ds,$$

where in the third inequality we have made the change of variable $t = \int_\zeta^{x_b} \frac{1}{\Gamma(\sigma)} d\sigma$.

Now, taking $\rho < d_0 := \min(\hat{d}_1, \hat{d}_2)$ and using the Mean Value Theorem for the function e^z we have that

$$\int_{-\infty}^{0} e^{\hat{d}_1 s} |\phi(s)| \int_0^{-s} e^{(\hat{d}_1 - \hat{d}_2)\tau} d\tau ds = \int_{-\infty}^{0} \frac{e^{-(\hat{d}_1 - \hat{d}_2)s} - 1}{\hat{d}_1 - \hat{d}_2} e^{\hat{d}_1 s} |\phi(s)| ds$$

$$= \int_{-\infty}^{0} \frac{e^{\hat{d}_2 s} - e^{\hat{d}_1 s}}{\hat{d}_1 - \hat{d}_2} |\phi(s)| ds = \int_{-\infty}^{0} (-s) \frac{e^{(\hat{d}_2-\rho)s} - e^{(\hat{d}_1-\rho)s}}{(\hat{d}_2-\rho)s - (\hat{d}_1-\rho)s} e^{\rho s} |\phi(s)| ds$$

$$= \int_{-\infty}^{0} (-s) e^{z(s)} e^{\rho s} |\phi(s)| ds \le \int_{-\infty}^{0} (-s) e^{\max\{(\hat{d}_1-\rho)s, (\hat{d}_2-\rho)s\}} e^{\rho s} |\phi(s)| ds$$

$$\le \int_{-\infty}^{0} (-s) e^{-(d_0-\rho)(-s)} e^{\rho s} |\phi(s)| ds \le \frac{1}{(d_0-\rho)e} \int_{-\infty}^{0} e^{\rho s} |\phi(s)| ds,$$

where $\min\{(\hat{d}_1-\rho)s, (\hat{d}_2-\rho)s\} < z(s) < \max\{(\hat{d}_1-\rho)s, (\hat{d}_2-\rho)s\}$ and in the last inequality we used that $xe^{-\alpha x} \le \dfrac{1}{\alpha e}$ for any $\alpha > 0$. Note that we have assumed that $\hat{d}_1 \neq \hat{d}_2$. If $\hat{d}_1 = \hat{d}_2$, the first integral can be bounded by

$$\int_{-\infty}^{0} (-s) e^{-(\hat{d}_1-\rho)(-s)} e^{\rho s} |\phi(s)| ds$$

and the last part of the computation also applies.

Then, for $\rho \in (0, d_0)$ and $C = 2\beta_\infty F_\infty (x_b - x_m) I \left(e^{L_\infty A(x_b, x_m)} - 1 \right) \dfrac{1}{(d_0-\rho)e}$, we have the claim.

□

By the Riesz representation theorem, there exists a positive kernel $k \in L^\infty_\rho(\mathbb{R}_+, \mathbb{R})$ such that

$$\mathcal{L}_I u = \int_0^\infty k(s) u(-s) ds.$$

Note that k belongs to $L^1_\rho(\mathbb{R}_+, \mathbb{R})$, for any $\rho \in (0, d_0)$.
Indeed, let us take $\rho' < \rho$. Then

$$\|k\|_{L^1_{\rho'}} = \int_0^\infty e^{\rho' s} |k(s)| ds = \int_0^\infty e^{(\rho'-\rho)s} e^{\rho s} |k(s)| ds$$

$$\le \|k\|_{L^\infty_\rho} \int_0^\infty e^{(\rho'-\rho)s} ds = \frac{1}{\rho - \rho'} \|k\|_{L^\infty_\rho}.$$

So, in the case of constant I, equation (10) can be written as a linear renewal equation

$$u(t) = \int_0^\infty k(s) u(t-s) ds.$$

It is well known that the behaviour of the solutions of the last equation depends on the roots of the equation $1 - \hat{k}(\lambda) = 0$, where $\hat{k}$ is the Laplace transform of the kernel k, which has an abscissa of convergence not larger than $-d_0$ (see [13]).

In particular, all the solutions of (10) decay at an exponential rate ρ if there are no roots with real part larger than $-\rho$ (see Theorem 3.12 from [11]), whereas there are exponentially increasing solutions if and only if there is a positive root of $\hat{k}(\lambda) = 1$.

The "only if" claim follows from the fact that $\hat{k}$ is a strictly decreasing continuous function with limit 0 at infinity when restricted to real arguments. Hence, since a complex (non real) root satisfies

$$1 = Re\ \hat{k}(\lambda) < \hat{k}(Re\lambda),$$

this implies the existence of a real root larger than $Re\lambda$. (Incidentally, note that for other cell cycle models the inequality above need not be strict; see [10] and the references given there for a description of the asymptotic behaviour of the linear semigroup in the so-called lattice case characterized by equality.)
Finally, the mentioned properties of $\hat{k}$ as a function of real argument also imply that there is a positive root if and only if

$$1 < \hat{k}(0) = \int_0^\infty k(s)ds = \mathcal{L}_I \mathbf{1} =: R_0(I).$$

This allows us to state the following theorem

Theorem 2.2. *Let us consider a constant positive I in the linear renewal equation*

$$u(t) = \big(\mathcal{L}_0(x_b) + \mathcal{L}_1(x_b, I)\big)u_t = \mathcal{L}_I u_t.$$

Then
a) All the solutions of the equation tend exponentially to 0 if $R_0(I) = \mathcal{L}_I \mathbf{1} < 1$.
b) If $R_0(I) > 1$, there are solutions which grow exponentially.
c) If $R_0(I) = 1$, then any constant u is a stationary solution.

So, let us compute

$$\begin{aligned} R_0(I) &= \Big(\mathcal{L}_0(x_b) + \mathcal{L}_1(x_b, I)\Big)\mathbf{1} \\ &= 2\int_{x_m}^{x_b}\int_{x_b}^{x_M} \beta(\theta,\eta)\tfrac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)d\theta d\eta \\ &+ 2\int_{x_m}^{x_b} \tfrac{L(\zeta)}{\Gamma(\zeta)} e^{\int_\zeta^{x_b} \frac{L(\sigma)}{\Gamma(\sigma)}d\sigma} \tfrac{I}{I+d_2(\zeta)} \int_{x_m}^{\zeta}\int_{x_b}^{x_M} \beta(\theta,\eta)\tfrac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)d\theta d\eta d\zeta \end{aligned}$$

Since $I \to R_0(I)$ is a monotone increasing function, the equation

$$R_0(I) = 1$$

has a unique solution $I = \bar{I}$ in $(0, +\infty)$ if and only if $R_0(0) < 1$ and $R_0(\infty) > 1$. Moreover, note that

$$R_0(0) = 2\int_{x_m}^{x_b}\int_{x_b}^{x_M} \beta(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)d\theta d\eta$$

while, integrating by parts after computing the limit when I tends to ∞,

$$\begin{aligned} R_0(\infty) &= 2\int_{x_m}^{x_b} e^{\int_\zeta^{x_b}\frac{L(\sigma)}{\Gamma(\sigma)}d\sigma}\int_{x_b}^{x_M}\beta(\theta,\zeta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\zeta)d\theta d\zeta \\ &= 2\int_{x_m}^{x_b}\mathcal{F}_1(x_b,\zeta)\int_{x_b}^{x_M}\beta(\theta,\zeta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\zeta)d\theta d\zeta. \end{aligned}$$

Remark 2.1. In the case that d_2 does not depend on cyclin content, we can compute a little further using also integration-by-parts for the second integral. This leads to

$$R_0(I) = 2\frac{d_2}{I+d_2}\int_{x_m}^{x_b}\left(1+\frac{I}{d_2}e^{\int_\zeta^{x_b}\frac{L(\sigma)}{\Gamma(\sigma)}d\sigma}\right)\int_{x_b}^{x_M}\beta(\theta,\zeta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\zeta)d\theta d\zeta.$$

3 Existence and uniqueness of a solution

In order to show existence and uniqueness of a solution of the initial value problem for system (13) we use the theory developed in the works [8], [9] and [11] and references therein.

System (13) can be written as

$$x(t) = F(x_t), \quad t \geq 0 \tag{15}$$

where

$$x(t) = \begin{pmatrix} u(t) \\ I(t) \end{pmatrix},$$

$$F\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} \big(\mathcal{L}_0(x_b)+\mathcal{L}_1(x_b,y_2)\big)y_1 \\ \\ G(\mathcal{L}_N(y_2)y_1). \end{pmatrix},$$

and

$$x_t(\theta) = x(t+\theta), \ \forall\theta \leq 0.$$

We will prove existence and uniqueness of a solution of (15) provided with the initial condition

$$x(\theta) = \varphi(\theta), \text{for} \quad \theta \in (-\infty, 0]. \tag{16}$$

In order to do this we will follow [8] , [9] where the authors prove the equivalence between the renewal equation and the initial value problem for a certain abstract integral equation (AIE).

3.1 Abstract Integral Equation (AIE)

Let us consider as the history space X, the space $L^1_\rho(\mathbb{R}_-;\mathbb{R}^2)$ with the norm defined by

$$\|\psi\| = \int_{-\infty}^{0} e^{\rho\theta}|\psi(\theta)|d\theta, \quad \text{for} \quad \psi \in X,$$

for $\rho > 0$ in order that the space X contains the constant functions and hence the possible steady states of (15).

Let $T_0 := \{T_0(t)\}_{t\geq 0}$ be a strongly continuous semigroup of bounded linear operators on $X = L^1_\rho(\mathbb{R}_-;\mathbb{R}^2)$ with infinitesimal generator A_0.

The adjoint of T_0 is $T_0^* := \{T_0^*(t)\}_{t\geq 0}$ where $T_0^*(t) : X^* \to X^*$ is the adjoint operator of $T_0(t)$. T_0^* is a semigroup on the dual space X^*.

Now one defines the sun-subspace of the dual space X^* as the linear subspace where the adjoint operator T_0^* is strongly continuous, i.e.,

$$X^{\odot} := \{\phi^* \in X^* | \lim_{t\to 0} \|T_0^*(t)\phi^* - \phi^*\| = 0\}.$$

For $x \in X, \phi \in X^{\odot}, \phi^{\odot *} \in X^{\odot *}$ we will use the convention that

$$\phi(x) = < x, \phi > \quad \text{and} \quad \phi^{\odot *}(\phi) = < \phi^{\odot *}, \phi > .$$

With this we will define the "natural" linear mapping $j : X \to X^{\odot *}$ by

$$< jx, \phi > = < x, \phi > = \phi(x), \quad x \in X, \phi \in X^{\odot}.$$

If $x \neq y$, then there exists ϕ in $X^{\odot}$ such that $\phi(x) \neq \phi(y)$ since, as is well known, $X^{\odot}$ is *weak**-dense in X^*, which implies that j is an injection.

From now on, T_0 will be defined by translation to the left and extension by 0 on $\mathbb{R}_-$. Then it can be shown (see [6], [12], [16] for the case with $\rho = 0$ and [9] for the case with weight) that $L^1_\rho(\mathbb{R}_-;\mathbb{R}^2)^{\odot}$ can be identified with $BUC_\rho(\mathbb{R}_+;\mathbb{R}^2)$, the space of exponentially bounded and uniformly continuous functions on $[0, \infty)$ endowed with the norm

$$\|\phi^{\odot}\|_\rho^\infty = \sup_{\theta\in\mathbb{R}_+} e^{\rho\theta}|\phi^{\odot}(\theta)| < \infty.$$

Now, one can write a variation of constants formula for (15)-(16) in the form of the following Abstract Integral Equation (AIE) for continuous functions of t with values in X:

$$u(t) = T_0(t)\varphi + j^{-1}\int_0^t {T_0}^{\odot *}(t-s)(l \circ F)(u(s))ds \ , \tag{17}$$

where $F : X \to \mathbb{R}^2$ is a nonlinear map and $l : \mathbb{R}^2 \to X^{\odot *}$ is a bounded linear injection given by

$$< lx, \phi > = x \cdot \phi(0) \quad \text{for all} \quad x \in \mathbb{R}^2, \quad \phi \in X^{\odot},$$

where $\cdot$ is the scalar product in $\mathbb{R}^2$ and evaluation at 0 is well defined since ϕ is a continuous function.

In order that (17) makes sense one needs that the integral belongs to the range of j, which will be seen in the proof of the following theorem that gives the equivalence between the AIE formulation and the nonlinear renewal equation (15)-(16) (see [9] and [11]).

Theorem 3.1. *Let $\varphi \in X = L^1_\rho(\mathbb{R}_-;\mathbb{R}^2)$ be given.*

a) Suppose that $x \in L^1_{loc}((-\infty,\infty);\mathbb{R}^2)$ satisfies (15) with an initial condition $x(\theta) = \varphi(\theta)$, for $\theta \in (-\infty, 0]$. Then the function $u : [0,\infty) \to X$ defined by $u(t) := x_t$ is continuous and satisfies the abstract integral equation (AIE).

b) If $u : [0,\infty) \to X$ is continuous and satisfies the abstract integral equation, then the function x defined by

$$x(t) := \begin{cases} \varphi(t) & \textit{for} \quad -\infty < t < 0, \\ F(u(t)) & \textit{for} \quad t \geq 0, \end{cases}$$

specifies an element of $L^1_{loc}((-\infty,\infty);\mathbb{R}^2)$ and satisfies (15) with an initial condition $x(\theta) = \varphi(\theta)$, for $\theta \in (-\infty, 0]$.

Proof. For the sake of completeness we give the proof of this theorem. First notice that for any continuous function $u : [0,\infty) \to X$ and $\phi \in X^\odot$ we have

$$< \int_0^t {T_0}^{\odot *}(t-s)(l \circ F)(u(s))ds, \phi >= \int_0^t < {T_0}^{\odot *}(t-s)(l \circ F)(u(s)), \phi > ds$$

$$= \int_0^t < (l \circ F)(u(s)), {T_0}^{\odot}(t-s)\phi > ds = \int_0^t F(u(s)) \cdot ({T_0}^{\odot}(t-s)\phi)(0)ds$$

$$= \int_0^t F(u(s)) \cdot (\phi(\cdot + t - s))(0)ds = \int_0^t F(u(s)) \cdot \phi(t-s)ds$$

$$= \int_{-t}^0 F(u(t+\theta)) \cdot \phi(-\theta)d\theta = \int_{-\infty}^0 \chi_{[-t,0]}(\theta)F(u(t+\theta)) \cdot \phi(-\theta)d\theta$$

$$=< \chi_{[-t,0]}(\theta)F(u(t+\theta)), \phi >=< j(\chi_{[-t,0]}(\theta)F(u(t+\theta))), \phi >,$$

i.e.,

$$j(\chi_{[-t,0]}(\theta)F(u(t+\theta))) = \int_0^t {T_0}^{\odot *}(t-s)(l \circ F)(u(s))ds. \tag{18}$$

where, in the fourth equality we used that, with the representation of X^* we chose, $T_0^\odot$ is also translation to the left.

Let us assume a) and consider, on the one hand,

$$u(t)(\theta) - (T_0(t)\varphi)(\theta) = x(t+\theta) - (T_0(t)\varphi)(\theta)$$

$$= \begin{cases} \varphi(t+\theta) & \text{for} \quad t+\theta < 0 \\ F(x_{t+\theta}) & \text{for} \quad t+\theta \geq 0 \end{cases} - \begin{cases} \varphi(t+\theta) & \text{for} \quad t+\theta < 0, \\ 0 & \text{for} \quad t+\theta \geq 0, \end{cases}$$

$$= \begin{cases} 0 & \text{for } \theta < -t, \\ F(x_{t+\theta}) & \text{for } -t \le \theta \le 0, \end{cases}$$

whereas on the other hand, for any $\phi \in X^{\odot}$, we have, by (18),

$$(j^{-1}\int_0^t T_0{}^{\odot *}(t-s)(l \circ F)(u(s))ds)(\theta) = \chi_{[-t,0]}(\theta)F(u(t+\theta))$$

$$= \begin{cases} 0 & \text{for } \theta < -t, \\ F(x_{t+\theta}) & \text{for } -t \le \theta \le 0, \end{cases}$$

and the AIE holds.

Conversely, assuming b), we have by (18),

$$x_t(\theta) = x(t+\theta) = \begin{cases} \varphi(t+\theta) & \text{for } t+\theta < 0, \\ F(u(t+\theta)) & \text{for } t+\theta \ge 0, \end{cases}$$

$$= (T_0(t)\varphi)(\theta) + \chi_{[-t,0]}(\theta)F(u(t+\theta))$$

$$= (T_0(t)\varphi)(\theta) + (j^{-1}\int_0^t T_0{}^{\odot *}(t-s)(l \circ F)(u(s))ds)(\theta) = u(t)(\theta),$$

and so, $x(t) = F(u(t)) = F(x_t)$ for $t \ge 0$, i.e., (15) holds.

□

Theorem 3.2. *Let us assume that F is (locally) Lipschitz continuous. Then for all $\varphi \in X$, the Abstract Integral Equation has a unique solution $u(t)$ on $[0, T)$, for some $T > 0$.*

This theorem is stated and proved in [7] for the sun reflexive case. This hypothesis is only used to ensure that the AIE makes sense, i.e., that the integral belongs to $j(X)$, which here has already been proven.

Finally, since F maps the positive cone of X into the positive cone of $\mathbb{R}^2$, the solutions with positive initial conditions will remain positive.

4 Steady state and linearization

Obviously, $(0, G(0))$ is a trivial stationary solution of (15).

To find a nontrivial steady state of (15), we first need to solve

$$R_0(I) = 1. \tag{19}$$

Since R_0 is a monotone increasing function, $R_0(0) < 1 < R_0(\infty)$ are necessary and sufficient conditions in order that this equation has a (unique) solution $\bar{I}$. Then any constant u satisfies the first renewal equation in (15) if we take $I(t) \equiv \bar{I}$ (see Theorem 2.2). We find the right constant $\bar{u}$ from the second equation:

$$\bar{u} = \frac{1}{\mathcal{L}_N(\bar{I})\mathbf{1}} G^{-1}(\bar{I}) \tag{20}$$

provided that $\bar{I}$ belongs to the image of $[0, +\infty)$ under G. Since G is monotonously decreasing, this amounts to $G(\infty) < \bar{I} < G(0)$. Summarizing, we can state

Proposition 4.1. *Assuming that G is strictly monotone decreasing, (15) has a (unique) non-trivial stationary solution $(\bar{u}, \bar{I})$ where $\bar{I}$ is the solution of (19) and $\bar{u}$ is given by (20) if and only if*

$$R_0(G(\infty)) < 1 < R_0(G(0)).$$

In order to prove a linearized stability principle for (15)(see Theorem 3.15, [11]) we need that the function $F : L^{1,+}_\rho(\mathbb{R}_-, \mathbb{R}^2) \longrightarrow \mathbb{R}^2$ which we recall is defined by

$$\begin{pmatrix} u \\ I \end{pmatrix} \mapsto \begin{pmatrix} \mathcal{L}_0(x_b)u + \mathcal{L}_1(x_b, I)u \\ G(\mathcal{L}_N(I)u). \end{pmatrix} \tag{21}$$

is of class $\mathcal{C}^1$.
Here $L^{1,+}_\rho(\mathbb{R}_-, \mathbb{R}^2)$ stands for the positive cone of $L^1_\rho(\mathbb{R}_-, \mathbb{R}^2)$. We can decompose this function in this way:
Let $F_1 : \mathbb{R}^{2+} \longrightarrow \mathbb{R}^2$ be defined as

$$F_1 \begin{pmatrix} x \\ y \end{pmatrix} \mapsto \begin{pmatrix} x \\ G(y) \end{pmatrix}.$$

As G is a continuously differentiable function, F_1 is of class $\mathcal{C}^1$.
Let $F_2 : L^1_\rho(\mathbb{R}_-, \mathbb{R}^2) \times \left(L^1_\rho(\mathbb{R}_-, \mathbb{R}^2)^*\right)^3 \longrightarrow \mathbb{R}^2$ be defined by

$$\begin{pmatrix} u \\ \phi \\ \psi \\ \gamma \end{pmatrix} \mapsto \begin{pmatrix} < u, \phi > + < u, \psi > \\ < u, \gamma > \end{pmatrix}.$$

Note that F_2 is a smooth function.
Defining the map $F_3 : L^{1,+}_\rho(\mathbb{R}_-, \mathbb{R}^2) \longrightarrow L^1_\rho(\mathbb{R}_-, \mathbb{R}^2) \times \left(L^1_\rho(\mathbb{R}_-, \mathbb{R}^2)^*\right)^3$ by

$$\begin{pmatrix} u \\ I \end{pmatrix} \mapsto \begin{pmatrix} u \\ \mathcal{L}_0(x_b) \\ \mathcal{L}_1(x_b, I) \\ \mathcal{L}_N(I). \end{pmatrix},$$

we have that

$$F = F_1 \circ F_2 \circ F_3.$$

In order to show that F is continuously differentiable, it suffices to show that F_3 is continuously differentiable. Since the positive cone of L^1 has empty interior, as a definition of differentiability at a point ψ in the domain, we will use Definition 2.4 in [21] (see also [18]), where only perturbations φ such that $\psi+\varphi$ belongs to the domain are allowed.

Let us start by proving the differentiability of $\mathcal{L}_1(x_b,\cdot)$.
Let us recall that

$$\mathcal{L}_1(x_b,\psi)\phi := 2\int_{x_m}^{x_b}\int_0^{+\infty}\frac{L(\zeta)}{\Gamma(\zeta)}e^{\int_\zeta^{x_b}\frac{L(\sigma)}{\Gamma(\sigma)}d\sigma}\int_{x_m}^{\zeta}\int_{x_b}^{x_M}\beta(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)$$

$$\phi(-\tau-A(\theta,\eta))d\theta d\eta\ \psi(-A(x_b,\zeta))e^{-d_2(\zeta)\tau-\int_{-\tau-A(x_b,\zeta)}^{-A(x_b,\zeta)}\psi(\sigma)d\sigma}d\tau d\zeta.$$

In order to prove the differentiability of $\mathcal{L}_1(x_b,\psi)$ as a function of ψ, we start by proving the differentiability of the mapping $\tilde{H}: L^{1,+}_\rho(-\infty,0)\longrightarrow L^1_{2\rho}\Big((0,\infty)\times(x_m,x_b)\Big)$ defined by

$$\tilde{H}(\psi)(\tau,\zeta)=\psi(-A(x_b,\zeta))e^{-\int_{-\tau-A(x_b,\zeta)}^{-A(x_b,\zeta)}\psi(\sigma)d\sigma}, \tag{22}$$

or, equivalently, making a change of variables, by proving the differentiability of the mapping $H: L^{1,+}_\rho(-\infty,0)\longrightarrow L^1_{2\rho}\Big((0,\infty)\times(0,A(x_m,x_b))\Big)$ defined by

$$H(\psi)(\tau,a)=\psi(-a)e^{-\int_{-\tau-a}^{-a}\psi(\sigma)d\sigma}.$$

We use the weight function $e^{-2\rho\tau}e^{-2\rho a}$ in the norm of the spaces $L^1_{2\rho}\Big((0,\infty)\times(\alpha,\beta)\Big)$. The weight for the second variable is irrelevant because of compactness of the interval (α,β).

Lemma 4.2. *H is differentiable.*

Proof. Let us compute the finite difference for the function H.

$$H(\psi+\varphi)(\tau,a)-H(\psi)(\tau,a)$$

$$=(\psi(-a)+\varphi(-a))e^{-\int_{-\tau-a}^{-a}(\psi(\sigma)+\varphi(\sigma))d\sigma}-\psi(-a)e^{-\int_{-\tau-a}^{-a}\psi(\sigma)d\sigma}$$

$$=\left(\psi(-a)e^{-\int_{-\tau-a}^{-a}\psi(\sigma)d\sigma}\right)\left[e^{-\int_{-\tau-a}^{-a}\varphi(\sigma)d\sigma}-1\right]+\varphi(-a)e^{-\int_{-\tau-a}^{-a}(\psi(\sigma)+\varphi(\sigma))d\sigma}$$

$$=\left(\psi(-a)e^{-\int_{-\tau-a}^{-a}\psi(\sigma)d\sigma}\right)\left[-\int_{-\tau-a}^{-a}\varphi(\sigma)d\sigma+\frac{e^{\xi_1}}{2}\left(\int_{-\tau-a}^{-a}\varphi(\sigma)d\sigma\right)^2\right]+$$

$$+\varphi(-a)e^{-\int_{-\tau-a}^{-a}\psi(\sigma)d\sigma}\left[1-e^{\xi_2}\int_{-\tau-a}^{-a}\varphi(\sigma)d\sigma\right]$$

where $\xi_{1,2}\in\Big(-\int_{-\tau-a}^{-a}\psi(\sigma)d\sigma,0\Big)$. Note that $-\int_{-\tau-a}^{-a}\psi(\sigma)d\sigma+\xi_{1,2}\le 0$.

In order to show that the differential of H is given by

$$(DH(\psi)\varphi)(\tau,a)=-\psi(-a)\int_{-\tau-a}^{-a}\varphi(\sigma)d\sigma e^{-\int_{-\tau-a}^{-a}\psi(\sigma)d\sigma}+\varphi(-a)e^{-\int_{-\tau-a}^{-a}\psi(\sigma)d\sigma}, \tag{23}$$

we derive the following estimates:

$$|H(\psi+\varphi)(\tau,a)-H(\psi)(\tau,a)-(DH(\psi)\varphi)(\tau,a)|=$$

$$=\Big|\frac{\psi(-a)}{2}\Big(\int_{-\tau-a}^{-a}\varphi(\sigma)d\sigma\Big)^2 e^{-\int_{-\tau-a}^{-a}\psi(\sigma)d\sigma+\xi_1}$$

$$-\varphi(-a)\int_{-\tau-a}^{-a}\varphi(\sigma)d\sigma e^{-\int_{-\tau-a}^{-a}\psi(\sigma)d\sigma+\xi_2}\Big|.$$

So

$$\|H(\psi+\varphi)-H(\psi)-DH(\psi)\varphi\|_{L^1_{2\rho}}=$$

$$=\int_0^\infty\int_0^{A(x_m,x_b)}\Big|\frac{\psi(-a)}{2}\Big(\int_{-\tau-a}^{-a}\varphi(\sigma)d\sigma\Big)^2 e^{-\int_{-\tau-a}^{-a}\psi(\sigma)d\sigma+\xi_1}-$$

$$\varphi(-a)\int_{-\tau-a}^{-a}\varphi(\sigma)d\sigma e^{-\int_{-\tau-a}^{-a}\psi(\sigma)d\sigma+\xi_2}\Big|e^{-2\rho a}da e^{-2\rho\tau}d\tau$$

$$\le\int_0^\infty\int_0^{A(x_m,x_b)}\Big|\frac{\psi(-a)}{2}\Big|\Big(\int_{-\tau-a}^{-a}|\varphi(\sigma)|d\sigma\Big)\Big(\int_{-\tau-a}^{-a}|\varphi(s)|ds\Big)e^{-2\rho a}da e^{-2\rho\tau}d\tau+$$

$$+\int_0^\infty\int_0^{A(x_m,x_b)}|\varphi(-a)|\int_{-\tau-a}^{-a}|\varphi(\sigma)|d\sigma\Big|e^{-2\rho a}da e^{-2\rho\tau}d\tau$$

$$\le\int_0^{A(x_m,x_b)}\Big|\frac{\psi(-a)}{2}\Big|\int_0^\infty\Big(\int_{-\tau-a}^{-a}|\varphi(\sigma)|d\sigma\Big)\Big(\int_{-\tau-a}^{-a}|\varphi(s)|ds\Big)e^{-2\rho\tau}d\tau e^{-2\rho a}da+$$

$$+\int_0^{A(x_m,x_b)}\int_0^\infty|\varphi(-a)|\int_{-\tau-a}^{-a}|\varphi(\sigma)|d\sigma e^{-2\rho\tau}d\tau e^{-2\rho a}da$$

$$\leq \int_0^{A(x_m,x_b)} \Big|\frac{\psi(-a)}{2}\Big| \int_0^\infty \left(\int_{-\tau-a}^{-a} \left(\int_{-\tau-a}^{-a} |\varphi(s)|ds \right) |\varphi(\sigma)|d\sigma \right) e^{-2\rho\tau} d\tau e^{-2\rho a} da+$$

$$+ \int_0^{A(x_m,x_b)} |\varphi(-a)| \int_0^\infty \int_{-\tau-a}^{-a} |\varphi(\sigma)|d\sigma e^{-2\rho\tau} d\tau e^{-2\rho a} da$$

$$\leq \int_0^{A(x_m,x_b)} \Big|\frac{\psi(-a)}{2}\Big| \int_{-\infty}^{-a} \left[\int_{-\sigma-a}^{\infty} \left(\int_{-\tau-a}^{-a} |\varphi(s)|ds \right) e^{-2\rho\tau} \right] d\tau |\varphi(\sigma)|d\sigma e^{-2\rho a} da+$$

$$+ \int_0^{A(x_m,x_b)} |\varphi(-a)| \int_{-\infty}^{-a} \int_{-\sigma-a}^{\infty} e^{-2\rho\tau} d\tau |\varphi(\sigma)|d\sigma e^{-2\rho a} da$$

$$\leq \int_0^{A(x_m,x_b)} \Big|\frac{\psi(-a)}{2}\Big| \int_{-\infty}^{-a} \left[\int_{\sigma}^{-a} \int_{-\sigma-a}^{\infty} e^{-2\rho\tau} d\tau |\varphi(s)|ds \right.$$

$$\left. + \int_{-\infty}^{\sigma} \int_{-s-a}^{\infty} e^{-2\rho\tau} d\tau |\varphi(s)|ds \right] |\varphi(\sigma)|d\sigma e^{-2\rho a} da$$

$$+ \int_0^{A(x_m,x_b)} |\varphi(-a)| \int_{-\infty}^{-a} \frac{e^{2\rho(\sigma+a)}}{2\rho} |\varphi(\sigma)|d\sigma e^{-2\rho a} da$$

$$\leq \int_0^{A(x_m,x_b)} \Big|\frac{\psi(-a)}{2}\Big| \int_{-\infty}^{-a} \left[\int_{\sigma}^{-a} \frac{e^{2\rho(\sigma+a)}}{2\rho} |\varphi(s)|ds \right.$$

$$\left. + \int_{-\infty}^{\sigma} \frac{e^{2\rho(s+a)}}{2\rho} |\varphi(s)|ds \right] |\varphi(\sigma)|d\sigma e^{-2\rho a} da$$

$$+ \frac{1}{2\rho} \int_0^{A(x_m,x_b)} |\varphi(-a)| \int_{-\infty}^{-a} e^{2\rho\sigma} |\varphi(\sigma)|d\sigma da$$

$$\leq \int_0^{A(x_m,x_b)} \Big|\psi(-a)\Big| \int_{-\infty}^{-a} \left[\int_{-\infty}^{\sigma} \frac{e^{2\rho(s+a)}}{2\rho} |\varphi(s)|ds \right] |\varphi(\sigma)|d\sigma e^{-2\rho a} da+$$

$$+\frac{1}{2\rho}\|\varphi\|_{L^1_\rho}\int_0^{A(x_m,x_b)}|\varphi(-a)|e^{-\rho a}da$$

$$\leq \frac{1}{2\rho}\int_0^{A(x_m,x_b)}\Big|\psi(-a)\Big|e^{\rho a}\int_{-\infty}^{-a}e^{\rho\sigma}\int_{-\infty}^{\sigma}e^{\rho s}|\varphi(s)|ds|\varphi(\sigma)|d\sigma e^{-\rho a}da+\frac{1}{2\rho}\|\varphi\|^2_{L^1_\rho}$$

$$\leq \frac{e^{\rho A(x_m,x_b)}\|\varphi\|_{L^1_\rho}}{2\rho}\int_0^{A(x_m,x_b)}\Big|\psi(-a)\Big|\int_{-\infty}^{-a}e^{\rho\sigma}|\varphi(\sigma)|d\sigma e^{-\rho a}da+\frac{1}{2\rho}\|\varphi\|^2_{L^1_\rho}$$

$$\leq \frac{e^{\rho A(x_m,x_b)}\|\varphi\|^2_{L^1_\rho}}{2\rho}\int_0^{A(x_m,x_b)}\Big|\psi(-a)\Big|e^{-\rho a}da+\frac{1}{2\rho}\|\varphi\|^2_{L^1_\rho}$$

$$=\frac{e^{\rho A(x_m,x_b)}\|\varphi\|^2_{L^1_\rho}\|\psi\|_{L^1_\rho}}{2\rho}+\frac{1}{2\rho}\|\varphi\|^2_{L^1_\rho}$$

which implies

$$\frac{\|H(\psi+\varphi)-H(\psi)-DH(\psi)\varphi\|_{L^1_{2\rho}}}{\|\varphi\|_{L^1_\rho}}\leq\|\varphi\|_{L^1_\rho}\frac{1}{2\rho}\Big(\|\psi\|_{L^1_\rho}e^{\rho A(x_m,x_b)}+1\Big).$$

With this we have shown that $DH(\psi)\varphi$ defined in (23) is indeed the differential of H.

□

Lemma 4.3. $\mathcal{L}_1(x_b,\cdot)\cdot$ *is differentiable.*

Proof. $\mathcal{L}_1(x_b,\psi)\phi$ can be written as

$$\mathcal{L}_1(x_b,\psi)\phi:=2\int_{x_m}^{x_b}\int_0^{+\infty}K(\tau,\zeta)\tilde{H}(\psi)(\tau,\zeta)d\tau d\zeta,$$

where $\tilde{H}$ is given in (22) and

$$K(\tau,\zeta):=$$

$$\frac{L(\zeta)}{\Gamma(\zeta)}e^{\int_\zeta^{x_b}\frac{L(\sigma)}{\Gamma(\sigma)}d\sigma}\int_{x_m}^{\zeta}\int_{x_b}^{x_M}\beta(\theta,\eta)\frac{F(\theta)}{\Gamma(\theta)}\mathcal{F}(\theta,\eta)\phi(-\tau-A(\theta,\eta))d\theta d\eta e^{-d_2(\zeta)\tau}.$$

The differentiability follows from the fact that $\mathcal{L}_1$ is the composition of the differentiable mapping $\tilde{H}$ (which follows from the previous lemma) and a linear form that is bounded, since the kernel K belongs to $L^\infty_{-2\rho}\Big((0,\infty)\times(x_m,x_b)\Big)$.

Indeed, since $\frac{L(\zeta)}{\Gamma(\zeta)} e^{\int_\zeta^{x_b} \frac{L(\sigma)}{\Gamma(\sigma)} d\sigma} \leq C_1$, for some $C_1 > 0$, choosing $\rho < \min\{\hat{d}_1, \frac{\hat{d}_2}{3}\}$ (where recall, $\hat{d}_1 := \inf\{d_1(x)\}, \hat{d}_2 := \inf\{d_2(x)\}$) and using (14) we have

$$\left| e^{2\rho\tau} K(\tau, \zeta) \right| =$$

$$\left| e^{2\rho\tau} \left(\frac{L(\zeta)}{\Gamma(\zeta)} e^{\int_\zeta^{x_b} \frac{L(\sigma)}{\Gamma(\sigma)} d\sigma} \int_{x_m}^{\zeta} \int_{x_b}^{x_M} \beta(\theta, \eta) \frac{F(\theta)}{\Gamma(\theta)} \mathcal{F}(\theta, \eta) \phi(-\tau - A(\theta, \eta)) d\theta d\eta e^{-d_2(\zeta)\tau} \right) \right|$$

$$\leq C_1 e^{(2\rho - d_2(\zeta))\tau} \left| \int_{x_m}^{\zeta} \int_{x_b}^{x_M} \beta(\theta, \eta) \frac{F(\theta)}{\Gamma(\theta)} \mathcal{F}(\theta, \eta) \phi(-\tau - A(\theta, \eta)) d\theta d\eta \right|$$

$$\leq C_1 e^{(2\rho - d_2(\zeta))\tau} \beta_\infty F_\infty (x_b - x_m) e^{\hat{d}_1 \tau} \int_{-\infty}^{-\tau} e^{\hat{d}_1 s} |\phi(s)| ds$$

$$= C_1 e^{(2\rho - d_2(\zeta))\tau} \beta_\infty F_\infty (x_b - x_m) e^{\hat{d}_1 \tau} \int_{-\infty}^{-\tau} e^{(\hat{d}_1 - \rho)s} e^{\rho s} |\phi(s)| ds$$

$$\leq C_1 e^{(2\rho - d_2(\zeta))\tau} \beta_\infty F_\infty (x_b - x_m) e^{\hat{d}_1 \tau} \int_{-\infty}^{-\tau} e^{-(\hat{d}_1 - \rho)\tau} e^{\rho s} |\phi(s)| ds$$

$$\leq C_1 e^{(2\rho - d_2(\zeta))\tau} \beta_\infty F_\infty (x_b - x_m) e^{\rho \tau} \int_{-\infty}^{-\tau} e^{\rho s} |\phi(s)| ds$$

$$\leq C_1 e^{(3\rho - d_2(\zeta))\tau} \beta_\infty F_\infty (x_b - x_m) \|\varphi\|_{L^1_\rho}.$$

and we have the claim.

□

Remark 4.1. Notice that an analogous computation proves the differentiability of $\mathcal{L}_1(x, \cdot)$ and also notice that the differentiability of $\mathcal{L}_2(x, \cdot)$ given by (11) follows from a similar but somehow easier computation.

To prove that F_3 is differentiable, the only thing left to show is the differentiability of $\mathcal{L}_N$. This amounts to differentiating under the integral sign in (12) while using Remark 4.1. Since the differential of F_3 is continuous we obtain the following statement

Theorem 4.4. *The function F defined in (21) is of class $\mathcal{C}^1$.*

The results proved so far guarantee that the hypotheses of the principle of linearized stability stated in [11] (and for the sake of completeness repeated below) are satisfied.

Theorem 4.5. *Let $\rho > 0$ and assume that $F : L^1_\rho(\mathbb{R}_-, \mathbb{R}^2) \longrightarrow \mathbb{R}^2$ is continuously Fréchet differentiable. Let $\bar{x}$ be a steady state of (15). Let $K \in L^\infty_\rho(\mathbb{R}_+, \mathbb{R}^2)$ represent $DF(\bar{x})$:*

$$DF(\bar{x})\varphi = \int_0^\infty K(s)\varphi(-s)ds.$$

(a) If all the roots of the characteristic equation $\det(Id - \hat{K}(\lambda)) = 0$ *have negative real part, then the steady state $\bar{x}$ is exponentially stable.*

(b) If there exists at least one root of $\det(Id - \hat{K}(\lambda)) = 0$ *with positive real part, then the steady state $\bar{x}$ is unstable.*

The proof of this theorem is given in [11], Theorem 3.15.

Now we can state the following result on stability and instability of the trivial steady state and establish a relation of the instability of this one and the existence of the nontrivial steady state.

Theorem 4.6. *The trivial steady state of (15),* $(0, G(0))$, *is exponentially stable if* $R_0(G(0)) < 1$. *It is unstable if* $R_0(G(0)) > 1$.

Proof. The differential of F evaluated at the trivial steady state is given by

$$DF\begin{pmatrix} 0 \\ G(0) \end{pmatrix}\begin{pmatrix} \varphi \\ \psi \end{pmatrix} = \begin{pmatrix} \mathcal{L}_0 + \mathcal{L}_1(x_b, G(0)) & 0 \\ G'(0)\mathcal{L}_N(G(0)) & 0 \end{pmatrix}\begin{pmatrix} \varphi \\ \psi \end{pmatrix}. \tag{24}$$

Indeed, the second column of the matrix vanishes since it is the differential of the constant function $F(0, \psi) = \begin{pmatrix} 0 \\ G(0) \end{pmatrix}$, whereas the first column is the differential of $F(\varphi, 0) = \begin{pmatrix} (\mathcal{L}_0 + \mathcal{L}_1(x_b, G(0)))\varphi \\ G(\mathcal{L}_N(G(0))\varphi) \end{pmatrix}$.

Let $K \in L^\infty_\rho(\mathbb{R}_+, \mathbb{R}^{2\times 2})$ represent $DF\begin{pmatrix} 0 \\ G(0) \end{pmatrix}$ in the sense of Theorem 4.5.

The characteristic equation $\det(Id - \hat{K}(\lambda)) = 0$ reduces to $1 - \hat{K}_{11}(\lambda) = 0$, where $\hat{K}_{11}(\lambda)$ coincides with $\hat{k}(\lambda)$ defined in Section 2.4. There it is shown that this characteristic equation has a positive root if $R_0(G(0)) > 1$ and that all the roots have negative real part if $R_0(G(0)) < 1$. Theorem 4.5 gives the statement. □

Remark 4.2. Recall from Proposition 4.1 that the condition $R_0(G(0)) > 1$ is necessary (but not sufficient) for the existence of the nontrivial steady state.

The study of the stability of the nontrivial steady state involves the computation of the representation kernel which is technically very difficult and is beyond the scope of this paper.

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