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A differential equation with state-dependent delay from cell population biology

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Abstract

We analyze a differential equation, describing the maturation of a stem cell population, with a state-dependent delay, which is implicitly defined via the solution of an ODE. We elaborate smoothness conditions for the model ingredients, in particular vital rates, that guarantee the existence of a local semiflow and allow to specify the linear variational equation. The proofs are based on theoretical results of Hartung et al. combined with implicit function arguments in infinite dimensions. Moreover we elaborate a criterion for global existence for differential equations with state-dependent delay. To prove the result we adapt a theorem by Hale and Lunel to the C^1-topology and use a result on metric spaces from Diekmann et al.

MSC: 34K05; 92C37; 37N25

Keywords: Delay differential equation; State-dependent delay; Semiflow; Global existence; Structured populations; Stem cell model

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0. Introduction

In this paper we analyze a class of differential equations of the form

$$w'(t) = q((v(t))w(t), \tag{0.1}$$

$$\begin{aligned} v'(t) = {} & \frac{\gamma(v(t-\tau(v_t)))g(x_2, v(t))w(t-\tau(v_t))}{g(x_1, v(t-\tau(v_t)))} e^{\int_0^{\tau(v_t)}(d-D_1 g)(y(s,v_t),v(t-s))ds} \\ & -\mu v(t). \end{aligned} \tag{0.2}$$

We use the standard notation

$$x_t(s) := x(t+s), \quad s < 0,$$

if a function x is defined in $t+s \in \mathbb{R}$. If t is fixed, then x_t is a function describing the history of x at time t. Both (0.1) and (0.2) are equations in $\mathbb{R}$ and all functions are real-valued. Next, τ is a nonlinear functional with domain in a space of functions. The functions q, γ, g and d have real arguments, μ is a parameter and γ, g, d, τ and μ take nonnegative values.

The functional τ describes the delay and is allowed to depend exactly on the second component v_t of the state. The delay is in general only implicitly given: For a function ψ defined on an interval $[-h, 0]$, we specify $\tau = \tau(\psi)$ as the solution of the equation

$$y(\tau, \psi) = x_1, \tag{0.3}$$

where $y(\cdot, \psi)$ is defined via the ordinary differential equation (ODE)

$$\begin{aligned} y'(s) &= -g(y(s), \psi(-s)), \quad s > 0, \\ y(0) &= x_2, \end{aligned} \tag{0.4}$$

and $x_1, x_2 \in \mathbb{R}$, $x_1 < x_2$ are given model parameters, see Fig. 1. We interpret s as the time to evolve from $y(s)$ to x_2, i.e., we define y going backward in time. This facilitates denoting time dependence in the second argument of g, given that ψ is defined on $[-h, 0]$. As a consequence $y(s, v_t)$ is the state at time $t-s$, given that x_2 is reached at time t. The notation allows to express this state, and hence also the delay τ, as a function of history v_t at time t. Equations (0.1)–(0.4) can be classified as a differential equation with implicitly defined delay with state dependence.

The system describes the maturation process of stem cells. The underlying model is formulated as a partial differential equation (PDE) of transport type in [12]. A special case of the PDE is derived via a limiting argument for related multi-compartment models. In our notation, the PDE formulation is (0.1) along with

$$\begin{aligned} g(x_1, v(t))u(t, x_1) &= \gamma(v(t))w(t), \\ \partial_t u(t,x) + \partial_x g(x, v(t))u(t,x) &= d(x, v(t))u(x, v(t)), \quad x \in (x_1, x_2), \\ v'(t) &= u(t, x_2)g(x_2, v(t)) - \mu v(t). \end{aligned}$$

An integration along the characteristics, similar to the one in Section II 4.1 in [24], yields that $u(t, x_2)$ is equal to the first summand on the right hand side of (0.2) divided by $g(x_2, v(t))$. Filling

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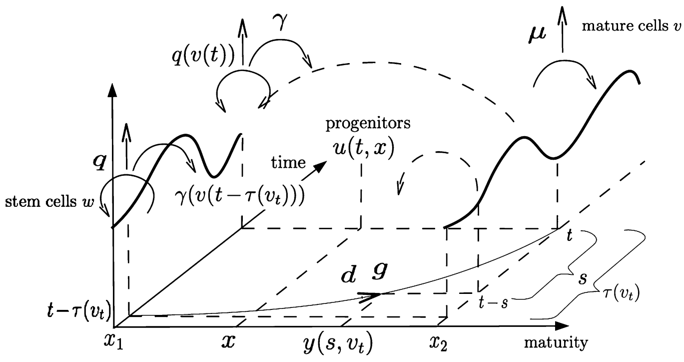

Fig. 1. Regulation of the maturation process of stem cells by the mature cells giving rise to state-dependent maturation delay: Dashed arrows refer to regulation by mature cells. Continuous arrows refer to mortality (vertical), self-renewal (circular, anti-clockwise) and transition to higher maturity (circular, clockwise).

this expression for $u(t, x_2)$ in the boundary condition at x_2 of the above PDE gives (0.2). Note that in transport equations the exponential of the integral over the derivative $-D_1 g$ is known as the dilation factor [24].

In the following we summarize the interpretation of the model ingredients, see also Fig. 1, referring to [2,12,13] for specifications and biological background. The dynamics of the whole cell population can be described in terms of the dynamics of the concentration of stem cells w and mature (by which we mean fully mature) cells v. The function q is the stem cell population net growth rate describing growth due to division as well as outflow due to maturation or decay. Stem cells commit themselves to maturation at a rate γ and the committed cells with density u that are not yet fully mature we call progenitors. The rates γ and q as well as the maturation velocity are regulated by the current size of the mature cell population. This regulation of the maturation velocity implies that the time spent for full maturation depends on the history of mature cells: $\tau(v_t)$ is the time for full maturation of progenitors given survival and that when reaching full maturity it is time t and history v_t has been experienced. Finally μ is the decay rate of mature cells.

We describe the maturity of a cell by a one-dimensional variable $x \in \mathbb{R}$ and assume that maturation occurs at a rate $g(x, y)$ that depends on maturity x and on the current size of the population of mature cells y. Stem cells w are then cells at initial maturity $x = x_1$, and fully mature cells v are cells of maturity $x = x_2 > x_1$. Net growth of the cell population during maturation, that includes reproduction and decay of cells, can be described by a per cell net rate $d(x, y)$ that, like g, depends on maturity and mature cell population.

In [19], Hartung et al. elaborated conditions that can be satisfied by differential equations with state-dependent delay and that guarantee the existence of a local (in time) semiflow for such equations. Additionally a linear variational equation is associated with the semiflow. A key point is to restrict initial histories to a submanifold of a space of C^1-functions. In [11, Proposition VII 2.2] the authors present a criterion for global existence for local semiflows on metric spaces. The idea is to show that if the maximal time interval of existence is finite, then an arbitrary compact set at some point in time is left for good. In applications it is useful to have a variant of this criterion in which the assumption of compact sets is relaxed to closed and bounded sets. For non-autonomous functional differential equations with functionals that satisfy smoothness conditions in a setting of continuous functions, such a criterion is [17, Theorem 2.3.2].

In this paper we apply the mentioned results of [19,11]. In this way we establish local and global existence for (0.1)–(0.2) and specify the linear variational equation associated to the semiflow. As our main result we consider the elaboration of biologically reasonable conditions on the rates γ, q, g and d that guarantee these results. As our aim is to preserve generality where possible, we do this stepwise in a top down approach.

At the top level we adapt the criterion for global existence of [11] to the setting for state dependent delay equations of [19] and obtain a new sufficient criterion for global existence, similar to the mentioned one in [17], but applicable to differential equations with state-dependent delay.

The next step is to elaborate conditions for a class of equations that contain (0.1)–(0.2) that allow to use the previously established theory. These are differentiability and Lipschitz conditions in finite and infinite dimensions. Finally we establish properties for the rates that guarantee that the differentiability and Lipschitz conditions hold. Part of this amounts to defining, sometimes implicitly, nonlinear operators and showing their differentiability with the implicit function theorem.

In Section 1 we present existing results from the literature and our main results (Theorems 1.7 and 1.13). Unless otherwise stated all results of Section 1 are proved in Section 2. In both sections each subsection refers to one step of the top down approach. Section 2.1 contains the proofs of Section 1.1, etc. Assumptions made in the running text are meant to hold until the end of the subsection except for in **Theorems**, where (to have them more self-contained) only the explicitly stated assumptions are assumed to hold. Section 3 contains a discussion of the results.

1. Existing results and main results of the paper

1.1. Differential equations with state dependent delay

Conditions for existence and uniqueness of a noncontinuable solution for differential equations with state dependent delay are given in [19]. We start by summarizing these results. For $n \in \mathbb{N}$ we will use the Banach spaces

$$(C([a,b],\mathbb{R}^n), \|\cdot\|), \ \|\phi\| := \max_{\theta\in[a,b]} |\phi(\theta)|,$$

$$(C^1([a,b],\mathbb{R}^n), \|\cdot\|^1), \ \|\phi\|^1 := \|\phi\| + \|\phi'\|.$$

We define solutions for delay differential equations (DDE) with N components. Let $h \in (0,\infty)$ and let $U \subset C^1([-h,0],\mathbb{R}^N)$ be open, $F : U \longrightarrow \mathbb{R}^N$.

Definition 1.1. For any $\phi \in U$, a *solution* on $[-h,t_*)$, for some $t_* \in (0,\infty]$, of the initial value problem (IVP)

$$x_0 = \phi, \ \ x'(t) = F(x_t), \ \ t > 0 \tag{1.1}$$

is a continuously differentiable function $x : [-h,t_*) \longrightarrow \mathbb{R}^N$, which satisfies $x_t \in U$ for all $t \in (0,t_*)$ as well as the IVP (1.1).

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Solutions on closed intervals $[-h, t_*]$, $t_* > 0$ are defined analogously. Suppose that F is at least continuous (the assumption will be sharpened below). Then a necessary condition for the solvability of IVP is that initial data are restricted to the set

$$X = X(F) := \{\phi \in U : \phi'(0) = F(\phi)\}. \tag{1.2}$$

We assume that F is such that $X = X(F)$ is nonempty. The following smoothness condition is appropriate and will be used for various model ingredients: Let $\mathcal{O} \subset C^1([-h, 0], \mathbb{R}^n)$ be open, $f : \mathcal{O} \longrightarrow \mathbb{R}^n$. We say that f fulfills (S) if

(S1) f is continuously differentiable,
(S2) each derivative $Df(\phi)$, $\phi \in \mathcal{O}$ extends to a linear map $D_e f(\phi) : C([-h, 0], \mathbb{R}^N) \longrightarrow \mathbb{R}^n$ and
(S3) the following map is continuous

$$\mathcal{O} \times C([-h, 0], \mathbb{R}^n) \longrightarrow \mathbb{R}^n; \;\; (\phi, \chi) \longmapsto (D_e f)(\phi)\chi.$$

For the remainder of this subsection we suppose that F satisfies (S) (with $n = N$ and $\mathcal{O} = U$).

In [19, Theorem 3.2.1] the existence of solutions of differential equations with state-dependent delays is discussed. These solutions induce a nonlinear semiflow as well as smoothness properties of the latter under the assumptions on F that we have made. The theorem also relates the nonlinear semiflow to a linear variational equation defined by the derivative of the functional F that defines the DDE. In the following theorem we rephrase these results. [19, Theorem 3.2.1] also contains a result on differentiability of the semiflow with respect to the time argument, which we do not use here. First note that the tangent space of X in an element ϕ can be computed as

$$\mathcal{T}_\phi X = \{\chi \in C^1([-h, 0], \mathbb{R}^N) : \; \chi'(0) = DF(\phi)\chi\}.$$

Theorem 1.2 *(Local semiflow). The set X is a continuously differentiable submanifold of U with codimension N. Moreover, for each $\phi \in X$ there exists some $t_\phi > 0$ and a unique noncontinuable solution $x^\phi : [-h, t_\phi) \longrightarrow \mathbb{R}^N$ of the IVP. All segments x_t^ϕ, $t \in [0, t_\phi)$, belong to X and for*

$$\Omega := \{(t, \phi) : \; t \in [0, t_\phi), \;\; \phi \in X\}$$

the map

$$S : \Omega \longrightarrow X; \;\; S(t, \phi) := x_t^\phi$$

defines a continuous semiflow. Each map

$$S(t, \cdot) : \{\phi \in X \;\; (t, \phi) \in \Omega\} \longrightarrow X$$

is continuously differentiable and for all $(t, \phi) \in \Omega$ and $\chi \in \mathcal{T}_\phi X$ we have

$$D_2 S(t, \phi) = v_t^{\phi, \chi}$$

with $v_t^{\phi,\chi} : [-h, t_\phi) \longrightarrow \mathbb{R}^N$ the solution of the linear IVP

$$v'(t) = DF(S(t, \phi))v_t, \;\; v_0 = \chi. \tag{1.3}$$

The set X is called the solution manifold. For $\phi \in X$, we denote by $I_\phi := [0, t_\phi)$ *maximal intervals* of existence of x_t^ϕ.

[11, Proposition VII 2.2 (iii)] states a property of semiflows on metric spaces in a context in which completeness of the metric space is assumed and we would like to use this property. See also the earlier [3, Section II 10] on flows. We do not know whether X is complete (we know that it is closed in the relative topology of the open set U) but for [11, Proposition VII 2.2 (iii)] completeness is not necessary and the proof needs not to be changed if one drops the completeness assumption. We rephrase the adapted result without proof as

Lemma 1.3. *Let E be a metric space and Σ be a local semiflow on E. Let $\phi \in E$, $[0, t_\phi)$ be the maximal interval and assume that $t_\phi < \infty$. Then, for any $W \subset E$ compact there exists some $t_W \in (0, t_\phi)$, such that $\Sigma(t, \phi) \notin W$ for all $t \in [t_W, t_\phi)$.*

In [17] non-autonomous functional differential equations with functionals that are defined on open subsets of $\mathbb{R} \times C([-h, 0], \mathbb{R}^N)$, where, in the second component, open refers to the C-topology, are analyzed. [17, Theorem 2.3.2] is a variant of the previous result adapted to DDE. Complete continuity, i.e., continuity and compactness of the closure of the image of a bounded set, again in the C-topology, of the functional inducing the DDE is assumed. The assumption of compact sets is relaxed to closed and bounded sets. Also in our setting we can elaborate such a result if we add more smoothness assumptions:

Definition 1.4. The functional $f : \mathcal{O} \longrightarrow \mathbb{R}^n$ is called (sLb) if for any bounded set $B \subset \mathcal{O}$ there exists some $L_B \geq 0$, such that

$$|f(\phi_1) - f(\phi_2)| \leq L_B \|\phi_1 - \phi_2\|, \text{ for all } \phi_1, \phi_2 \in B.$$

Remark 1.5. In (sLb) L refers to Lipschitz, b to bounded and s to strong, the latter because on the right hand side we require the C-norm and thus the property is stronger than usual (C^1-) Lipschitz (on bounded sets). The property (sLb) is stronger than the corresponding local property that would be implied by (S2)–(S3) and that is used in [27] and stronger than the property of being *almost locally Lipschitz* in [23]. In [19] (sLb) is used to show compactness of the maps $t \longrightarrow S(t, \cdot)$ for $t \geq h$.

We will use

Lemma 1.6. *If $f_1, f_2 : \mathcal{O} \longrightarrow \mathbb{R}$ are (sLb), then so are $f_1 + f_2$ and $f_1 \cdot f_2$.*

The first statement is obvious. To see the second statement, note that being (sLb) implies mapping bounded sets into bounded sets. We omit details of the proof. Let us denote by

$$T_\phi := \{x_t^\phi : t \in I_\phi\} \subset C^1([-h, 0], \mathbb{R}^N)$$

the orbit (or trace of the trajectory) of $\phi \in X$. We denote by $\overline{A}$ the closure of a set A. Our result for general differential equations with state dependent delay can then be formulated as

Theorem 1.7. *Suppose that F satisfies (S), (sLb) and that $X = X(F) \neq \emptyset$. Let $\phi \in X$ be such that $\overline{T}_\phi \subset U$. Then*

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(a) *if* $t_\phi < \infty$*, then for all closed and bounded* $L \subset U$ *there exists some* $t_L < t_\phi$*, such that* $x_t \notin L$ *for all* $t \in [t_L, t_\phi)$*,*
(b) *if* T_ϕ *is bounded, then* $t_\phi = \infty$*.*

For (a) see Section 2.1. (b) is then standard: If $t_\phi < \infty$ apply (a) to $L := \overline{T}_\phi$, which leads to the contradiction that $x_{t_L} \notin \overline{T}_\phi$ for some $t_L < t_\phi$.

1.2. A DDE describing stem cell maturation

In the following, we make a specification step for F and thus for the DDE (1.1) in the direction of the population equation of the stem cell model (0.1)–(0.2). We assume that F is $\mathbb{R}^2$-valued, i.e., that $N = 2$ such that the DDE has two components and that there is a delay τ that is allowed to depend on exactly the second of the two components. To specify U we introduce I as the range of the delay and assume that $I \subset \mathbb{R}$, $I \neq \emptyset$ is open. We agree that if the image space of a function space is $\mathbb{R}$ (rather than $\mathbb{R}^n$, for $n > 1$) we drop it in the notation, i.e., we define

$$C[a,b] := C([a,b],\mathbb{R}),\ C^1[a,b] := C^1([a,b],\mathbb{R}).$$

We introduce an open set M and specify U via

$$M := C^1([-h,0], I),\ \ U := C^1[-h,0] \times M.$$

Finally we denote the nonnegative cone of $\mathbb{R}^n$ by $\mathbb{R}^n_+$ (and similarly for $\mathbb{R}$):

$$\mathbb{R}^n_+ := \{x \in \mathbb{R}^n :\ x_i \geq 0,\ i = 1, \ldots, n\}.$$

Then we specify F via model ingredients

$$\beta : I \longrightarrow \mathbb{R}_+,\ \ q : I \longrightarrow \mathbb{R},\ \ \tau : M \longrightarrow [0,h],\ \ \mathcal{G} : M \longrightarrow \mathbb{R}_+,\ \ \mu \geq 0. \tag{1.4}$$

Note that since $\tau(M) \subset [0,h]$, for $\varphi \in C^1[-h,0]$ and $\psi \in M$ the evaluation $\varphi(-\tau(\psi))$ is well-defined and $\psi(-\tau(\psi)) \in I$ holds. Then we define

$$\begin{aligned} &F : U \to \mathbb{R}^2; \\ &F(\varphi,\psi) := \begin{pmatrix} q(\psi(0))\varphi(0) \\ \beta(\psi(-\tau(\psi)))\varphi(-\tau(\psi))\mathcal{G}(\psi) - \mu\psi(0) \end{pmatrix}. \end{aligned} \tag{1.5}$$

If we set $x = (w, v)$ the equation $x'(t) = F(x_t)$ yields (0.1)–(0.2) if we specify β and $\mathcal{G}$ appropriately, which will be done in Section 1.3. We first guarantee that $X \neq \emptyset$. We assume that $0 \in I$. The assumption is natural, since, it allows trivial equilibria to be in the domain of F: as $F(0) = 0$, we have that $0 \in X$, hence $X \neq \emptyset$. Similarly, if the DDE defined by F has a nontrivial equilibrium, the corresponding constant function also lies in X.

To guarantee global existence we would like to guarantee that the closure of the orbit lies in the domain $U = C^1[-h,0] \times M$. One way of doing this is to assume (in (b) of the following result) that $I = (R_-, \infty)$, for some $R_- < 0$.

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Theorem 1.8. *(a) Suppose that $I \subset \mathbb{R}$ open, $0 \in I$ and $M = C^1([-h,0], I)$. Let β, q, τ, $\mathcal{G}$ and μ be as in (1.4), suppose that β and q are continuously differentiable and τ and $\mathcal{G}$ satisfy* (S). *Let F be as in (1.5). Then F satisfies (S). For $(\varphi, \psi) \in U$ and $\chi, \xi \in C^1[-h,0]$, one has*

$$\begin{aligned} DF_1(\varphi,\psi)(\chi,\xi) &= q(\psi(0))\chi(0) + \varphi(0)q'(\psi(0))\xi(0),\\ DF_2(\varphi,\psi)(\chi,\xi) &= \mathcal{G}(\psi)\beta(\psi(-\tau(\psi)))[\chi(-\tau(\psi)) - \varphi'(-\tau(\psi))D\tau(\psi)\xi]\\ &\quad + \varphi(-\tau(\psi))\mathcal{G}(\psi)\beta'(\psi(-\tau(\psi)))\\ &\quad \cdot [\xi(-\tau(\psi)) - \psi'(-\tau(\psi))D\tau(\psi)\xi]\\ &\quad + \beta(\psi(-\tau(\psi)))\varphi(-\tau(\psi))D\mathcal{G}(\psi)\xi - \mu\xi(0). \end{aligned}$$

One obtains the extension D_eF if one replaces $D\tau$ and $D\mathcal{G}$ by the respective extensions. For the DDE induced by F there exists a local semiflow S on Ω in the sense of Theorem 1.2. Moreover for $(t,\phi) \in \Omega$ and $\phi \in C^1([-h,0], \mathbb{R}^2_+)$ one has $S(t,\phi) \in C^1([-h,0], \mathbb{R}^2_+)$.

(b) Suppose that, additionally to the assumptions of (a), τ and $\mathcal{G}$ are (sLb), $\mathcal{G}$ is bounded and β and q are Lipschitz on bounded sets and bounded. Then, if $\phi \in X$ and $\overline{T}_\phi \subset U$, one has $t_\phi = \infty$. If $I = (R_-, \infty)$, for some $R_- < 0$, then $\overline{T}_\phi \subset U$ and thus $t_\phi = \infty$ for any $\phi \in C^1([-h,0], \mathbb{R}^2_+)$.

We will sketch the proof of (a) and omit the details. A similar result was shown in [2] for the case where I is a bounded open interval. Part (b) will be shown in Section 2.2. Also for later use we define the evaluation operator

$$ev : C^1[a,b] \times [a,b] \to \mathbb{R}; (\psi, s) \mapsto \psi(s)$$

and recall that ev is C^1 with

$$D_1 ev(\phi, s)\chi = ev(\chi, s), \quad D_2 ev(\phi, s)1 = \phi'(s),$$

see also [19, p. 481]. To show that under the conditions stated in Theorem 1.8 the functional F fulfills (S1), one can set $[a,b] = [-h,0]$, use the decomposition

$$ev \circ (id, -\tau)(\varphi, \psi) = \varphi(-\tau(\psi))$$

and show continuous differentiability of F with sum, product and chain rules. To show (S2), extend the definition of ev to $C[-h,0] \times [-h,0]$ and to show (S3) use continuity of this extension. Then existence of a semiflow in (a) follows from Theorem 1.2. If we denote for some $\phi = (\varphi, \psi) \in X$ the solution by (w, v) the variation of constants formula yields

$$w(t) = \varphi(0)e^{\int_0^t q(v(s))ds}, \tag{1.6}$$

$$v(t) = e^{-\mu t}[\psi(0) + \int_0^t e^{\mu s}\beta(v(s-\tau(v_s)))\mathcal{G}(v_s)w(s-\tau(v_s))ds]. \tag{1.7}$$

With this formula it is easy to see that the semiflow maps nonnegative times and initial functions to nonnegative functions.

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1.3. Specification of τ, $\mathcal{G}$ and β

We denote open balls by $B(x_0, b) := \{x \in \mathbb{R} : |x - x_0| < b\}$ for some $x_0 \in \mathbb{R}$ and some $b > 0$. To specify the delay τ, we introduce the progenitor maturation rate g as a new modeling ingredient. We also become slightly more specific about the range I of the delay, introduced in the previous subsection. We assume that g satisfies property (G): There exist numbers $x_1, x_2, b, K, \varepsilon \in \mathbb{R}$ and open intervals I, J with

(G1) $\overline{B(x_2, b)} \subset J$ and $g : J \times I \longrightarrow \mathbb{R}$ is C^1,
(G2) $D_1 g(x, y)$ is bounded on $\overline{B(x_2, b)} \times I$,
(G3) $0 < \varepsilon \leq g(x, y) \leq K$ on $\overline{B(x_2, b)} \times I$ and $x_2 - x_1 \in (0, \frac{b}{K}\varepsilon)$.

Note that here, other than for the evaluation operator, $D_1 g(x, y)$ denotes a real number and not a linear map. Also below we will use symbols like D_1 with both meanings. Condition (G3) implies that $x_1 \in \overline{B(x_2, b)}$. To well-define τ via (0.3)–(0.4) and to show that $\psi \mapsto \tau(\psi)$ is smooth for appropriate ψ, we first establish existence and smoothness of y via (0.4). To save brackets, we will write $Ax(t)$ instead of $(Ax)(t)$ to denote evaluated functions in the image of an operator. In (c), however, the C-topology in the range space will turn out to be sufficient. See also the Discussion for references to related results in the literature. We now define

$$h := \frac{b}{K}, \quad M := C^1([-h, 0], I). \tag{1.8}$$

Proposition 1.9. *(a) For any $\psi \in M$ there exists a unique solution $y = y(\cdot, \psi) \in C^1[0, h]$ of (0.4) with $y([0, h], \psi) \subset \overline{B(x_2, b)}$ and a unique $\tau = \tau(\psi) \in (0, h)$, such that $y(\tau, \psi) = x_1$.*

(b) The map $Y : M \longrightarrow C^1[0, h]; Y(\psi)(t) := y(t, \psi)$ is C^1 with $DY(\psi) : C^1[-h, 0] \longrightarrow C^1[0, h]$

$$DY(\psi)\chi(t) = -\int_0^t e^{-\int_s^t D_1 g(Y(\psi)(\sigma), \psi(-\sigma))d\sigma} D_2 g(Y(\psi)(s), \psi(-s))\chi(-s)ds. \tag{1.9}$$

(c) The right hand side of (1.9) defines an extension $D_e Y(\psi) : C[-h, 0] \to C^1[0, h]$ and the map

$$\begin{array}{ccc} M \times C[-h, 0] & \longrightarrow & C[0, h] \\ (\psi, \chi) & \longmapsto & D_e Y(\psi)\chi \end{array}$$

is continuous.

Existence and uniqueness of $y(\cdot, \psi)$ on $[0, h]$ in (a) is straightforward if we first fix ψ and then apply the Picard–Lindelöf theorem (see e.g. Theorem II.1.1 in [18]) to a non-autonomous ODE defined by a function

$$f_\psi : [0, h] \times \overline{B(x_2, b)} \longrightarrow \mathbb{R}; \ f_\psi(s, y) := -g(y, \psi(-s)).$$

The remaining statements of (a) can be shown by integrating the ODE and using (G3). We omit further details of the proof of (a).

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In (b), the reason to choose the C^1-topology in the range space of Y will become clear in the context of Lemma 1.10. To prove (b) and for other use, we define an operator on an open domain via

$$\begin{aligned} &C^1([0,h],J)\times M \longrightarrow C^1[0,h] \\ &(z,\psi)\mapsto [t\mapsto G(z,\psi)(t) := \int_0^t k(z(s),\psi(-s))ds], \end{aligned} \tag{1.10}$$

where $k : J \times I \to \mathbb{R}$ is an arbitrary C^1-function, and I, J, h and M are as assumed. The function k will represent several model rates. To show (b), we set $k = g$. Then we consider for arbitrary $\psi \in M$ the equation

$$z + G(z,\psi) = x_2, \tag{1.11}$$

with x_2 denoting the constant function, in $C^1[0,h]$ and apply (in Section 2.3) the implicit function theorem to this equation. In (c) the extensibility is obvious. For the stated continuity property of the extension the C-topology in the range space will turn out to be sufficient. The next result will be used to show smoothness of τ (recall the convention on brackets).

Lemma 1.10. *The map $[0,h]\times M \to \mathbb{R}$; $(t,\psi)\mapsto y(t,\psi)$ is C^1. In particular $D_2y(t,\psi)\chi = DY(\psi)\chi(t)$.*

The proof is a straightforward application of the chain rule to the composition

$$\begin{array}{ccccc} [0,h]\times M & \to & [0,h]\times C^1[0,h] & \xrightarrow{ev} & \mathbb{R} \\ (t,\psi) & \mapsto & (t,Y(\psi)) & \mapsto & Y(\psi)(t). \end{array}$$

Note that the C-topology in the range space of Y would not do since ev is not partially differentiable with respect to the second argument on $[0,h]\times C[0,h]$.

Now note that

$$D_1y(s,\psi)|_{s=\tau(\psi)} = -g(x_1,\psi(-\tau(\psi))) \neq 0.$$

The implicit function theorem applied to (0.3) yields together with Lemma 1.10 directly the continuous differentiability statement in

Lemma 1.11. *The functional $M\to\mathbb{R}$; $\psi\mapsto\tau(\psi)$ is C^1 with*

$$D\tau(\psi)\chi = -\frac{DY(\psi)\chi(\tau(\psi))}{g(x_1,\psi(-\tau(\psi)))}.$$

For $\psi \in M$ the right hand side with DY replaced by D_eY defines an extension $D_e\tau(\psi) : C[-h,0]\to\mathbb{R}$ and

$$M\times C[-h,0]\to\mathbb{R};\ (\psi,\chi)\mapsto D_e\tau(\psi)\chi$$

is continuous. In particular, τ fulfills (S).

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The extension is clearly well-defined. The continuity statement follows directly from continuity of $(\psi, \chi) \mapsto D_eY(\psi)\chi$, τ, g and ev (used twice, recall the discussion below Theorem 1.8). We omit details of the proof. Next, we introduce the progenitor net production rate d. We assume that the functions $d, D_1g : J \times I \longrightarrow \mathbb{R}$ are C^1 and specify

$$\mathcal{G} : M \to \mathbb{R}_+;\;\; \mathcal{G}(\psi) := g(x_2, \psi(0))e^{\int_0^{\tau(\psi)}(d-D_1g)(Y(\psi)(s),\psi(-s))ds}. \tag{1.12}$$

For the proof of continuous differentiability we will use that

$$\mathcal{G}(\psi) = g(x_2, \psi(0))e^{G(\psi,Y(\psi))(\tau(\psi))} \tag{1.13}$$

if we set $k = d - D_1g$ in the definition of G. We then give an expression for the derivative in the notation of (1.12) (rather than in the notation of (1.13)). This makes the existence of the extension obvious and will allow to show continuity of the extension with the tools established for the proof of Proposition 1.9 (c).

Proposition 1.12. *The functional $\mathcal{G} : M \to \mathbb{R}$ is C^1 with*

$$\begin{aligned} D\mathcal{G}(\psi)\chi = \mathcal{G}(\psi)\{ &\int_0^{\tau(\psi)} [(D_1d - D_1^2g)(Y(\psi)(s), \psi(-s))DY(\psi)\chi(s) \\ &+ (D_2d - D_2D_1g)(Y(\psi)(s), \psi(-s))\chi(-s)]ds \\ &+ (d - D_1g)(x_1, \psi(-\tau(\psi)))D\tau(\psi)\chi + D_2g(x_2, \psi(0))\chi(0)\}. \end{aligned} \tag{1.14}$$

For $\psi \in M$ the right hand side with DY and $D\tau$ replaced by D_eY and $D_e\tau$ respectively defines an extension $D_e\mathcal{G}(\psi) : C[-h, 0] \to \mathbb{R}$ and $M \times C[-h, 0] \to \mathbb{R}$; $(\psi, \chi) \mapsto D_e\mathcal{G}(\psi)\chi$ is continuous. In particular, $\mathcal{G}$ fulfills (S).

The final specification of modeling ingredients used in (1.5) is

$$\beta(y) := \frac{\gamma(y)}{g(x_1, y)}, \tag{1.15}$$

where we introduce the progenitor inflow rate $\gamma : I \longrightarrow \mathbb{R}_+$ to describe the outflow of those stem cells that commit themselves to maturation. With the specifications of β, τ and $\mathcal{G}$ made in this subsection, the functional F that is defined in (1.5) and that defines the DDE (1.1) becomes

$$F(\varphi, \psi) = \begin{pmatrix} q(\psi(0))\varphi(0) \\ \frac{\gamma(\psi(-\tau(\psi)))\varphi(-\tau(\psi))}{g(x_1,\psi(-\tau(\psi)))} e^{\int_0^{\tau(\psi)}(d-D_1g)(Y(\psi)(s),\psi(-s))ds} - \mu\psi(0) \end{pmatrix} \tag{1.16}$$

with τ and Y defined in Proposition 1.9. The following theorem is the main result of this paper. Parts (a) and (b) are shown as Lemma 1.11 and Proposition 1.12 respectively. Part (c) follows by Theorem 1.8 (a) – note that under the assumptions β as defined in (1.15) is C^1. We omit further details of parts (a)–(c).

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Theorem 1.13. *Suppose that g satisfies (G). Define $h := \frac{b}{K}$ and $M := C^1([-h, 0], I)$. Then the following statements hold:*

(a) *The map $\tau : M \longrightarrow \mathbb{R}$ satisfies (S).*
(b) *Let additionally $d, D_1 g : J \times I \longrightarrow \mathbb{R}$ be C^1, then also $\mathcal{G} : M \longrightarrow \mathbb{R}$ satisfies (S).*
(c) *Suppose that moreover $0 \in I$, γ, q and μ are continuously differentiable and F is as in (1.16). Then F satisfies (S) with DF given as in Theorem 1.8 and $D\tau$, $D\mathcal{G}$ and DY as in Lemma 1.11, Proposition 1.12 and Proposition 1.9 respectively. Moreover F induces a local semiflow S on Ω in the sense of Theorem 1.2 and DF and S specify the linear variational equation (1.3). Finally, for $(t, \phi) \in \Omega$ and $\phi \in C^1([-h, 0], \mathbb{R}^2_+)$ one has $S(t, \phi) \in C^1([-h, 0], \mathbb{R}^2_+)$.*
(d) *Suppose that additionally*
   (i)
$$\sup_{(x,y)\in\overline{B(x_2,b)}\times I} |D_1 g(x, y)| < \frac{K}{b} \tag{1.17}$$
   (ii) *d is bounded on $\overline{B(x_2, b)} \times I$*
   (iii) *$D_2 g$, $D_i d$ and $D_i D_1 g$, $i = 1, 2$ are bounded on $\overline{B(x_2, b)} \times A$, whenever $A \subset I$ is bounded and that*
   (iv) *γ and q are Lipschitz on bounded sets and bounded.*
   Then, if $\phi \in X$ and $\overline{T}_\phi \subset U$ one has $t_\phi = \infty$. If $I = (R_-, \infty)$, for some $R_- < 0$, then $\overline{T}_\phi \subset U$ and thus $t_\phi = \infty$ for any $\phi \in C^1([-h, 0], \mathbb{R}^2_+)$.

2. Proofs of Section 1

2.1. Differential equations with state dependent delay – proofs of Section 1.1

We will apply the existing result that in case of a finite existence time compact sets are left for good (Lemma 1.3). A further useful tool is the following sufficient criterion for relative compactness in the C^1-topology that is a straightforward corollary (which we state without proof) of the Arzela–Ascoli theorem. For $A \subset C^1([a, b], \mathbb{R}^n)$, we denote by $A' := \{f' : f \in A\} \subset C([a, b], \mathbb{R}^n)$ the set of derivatives of A.

Lemma 2.1. *If $A \subset C^1([a, b], \mathbb{R}^n)$ is bounded and A and A' are equicontinuous, then A is relatively compact.*

Proof of Theorem 1.7 (a). Let $\phi \in X$, set $x = x^\phi$ and let $L \subset U$ be closed and bounded. Choose r, such that $\psi \notin L$, whenever $\|\psi\| \geq r$ or $\|\psi'\| \geq r$. We first consider the case that x is unbounded. By its continuity x is bounded on $[-h, t_\phi - h]$. From the unboundedness of x it then follows that there exists some $t_N \in [t_\phi - h, t_\phi)$, such that $|x(t_N)| \geq r$. Let $t \in [t_N, t_\phi)$. Then $\|x_t\| \geq r$ and thus $x_t \notin L$. Hence, the conclusion of the theorem holds. Now assume that x is bounded on $[-h, t_\phi)$. Choose $M_1 > 0$, such that $\|x_t\| \leq M_1$ for all $t \in I_\phi$. With similar arguments as above we can show that if x' is unbounded, the conclusion of the theorem holds. Hence, there is some $M_2 > 0$, such that $\|x_t'\| \leq M_2$ for all $t \in I_\phi$ and thus T_ϕ is bounded. Moreover, for $t_1 \geq t_2 \geq 0$ one has

$$|x(t_1) - x(t_2)| \leq \int_{t_2}^{t_1} |x'(t)|dt \leq M_2|t_1 - t_2|$$

and thus x is uniformly continuous on I_ϕ and thus also on $[-h, t_\phi)$. It follows that T_ϕ is equicontinuous. As F is (sLb) and T_ϕ is bounded there exists some $L_{T_\phi} \geq 0$, such that for $t \geq s > 0$

$$|F(x_t) - F(x_s)| \leq L_{T_\phi}\|x_t - x_s\|.$$

Then, as x' is bounded,

$$\begin{aligned}|F(x_t) - F(x_s)| &\leq L_{T_\phi} \sup_{\theta\in[-h,0]} |x(t+\theta) - x(s+\theta)| \\ &= L_{T_\phi} \sup_{\theta\in[-h,0]} \int_{s+\theta}^{t+\theta} |x'(\sigma)|d\sigma \leq L_{T_\phi}\kappa|t-s|\end{aligned}$$

for some constant κ. Thus x' is uniformly continuous on I_ϕ and thus also on $[-h, t_\phi)$. Hence, in the notation introduced above Lemma 2.1, T'_ϕ is equicontinuous. We have shown that T_ϕ satisfies the assumptions of Lemma 2.1. Thus, $\overline{T}_\phi$ is compact. The assumption $\overline{T}_\phi \subset U$ and the continuity of F imply that $\overline{T}_\phi \subset X$. Then Lemma 1.3 implies the existence of some $t_{\overline{T}_\phi}$, such that $x_t \notin \overline{T}_\phi$ for all $t \in [t_{\overline{T}_\phi}, t_\phi)$, which is a contradiction. □

2.2. A DDE describing stem cell maturation – proofs of Section 1.2

We would like to analyze global existence via Theorem 1.7. The boundedness and Lipschitz properties can be shown in a standard way if we suppose that the new model ingredients satisfy corresponding properties.

Lemma 2.2. *Let τ, $\mathcal{G}$, β and q be as defined in (1.4). Suppose that τ and $\mathcal{G}$ are (sLb) and β and q are Lipschitz on bounded sets, then F defined in (1.5) is (sLb).*

Proof. Let $B \subset U$ be bounded. First note that $\{\psi(0) : (\varphi, \psi) \in B\}$ is a bounded subset of $\mathbb{R}$. As q is Lipschitz on bounded sets, it follows that F_1 is (sLb). Next, note that $\{\varphi(-\tau(\psi)) : (\varphi, \psi) \in B\}$ and $\{\psi(-\tau(\psi)) : (\varphi, \psi) \in B\}$ are bounded subsets of $\mathbb{R}$. Then, one can show with the mean value theorem, using that φ and ψ are C^1 and that τ is (sLb), that the maps from U to $\mathbb{R}$ given by

$$(\varphi, \psi) \longmapsto \varphi(-\tau(\psi)) \text{ and } (\varphi, \psi) \longmapsto \psi(-\tau(\psi))$$

are (sLb). Finally, applying Lemma 1.6, it follows that F_2 is (sLb). □

Now suppose that the assumptions of Theorem 1.8 (a) hold. We have discussed that this implies the statements in Theorem 1.8 (a), in particular, that for every element $\phi = (\varphi, \psi)$ in the solution manifold X there exists a noncontinuable solution and thus an orbit T_ϕ on some interval $[0, t_\phi)$.

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Lemma 2.3. *Suppose that β, $\mathcal{G}$ and q are bounded. Then for any $\phi \in X$ if $t_\phi < \infty$ the orbit T_ϕ is bounded.*

Proof. Let $\phi \in X$ and denote by $x = x^\phi = (w, v)$ the noncontinuable solution. Then clearly $\{x(t) : t \in I_\phi\}$ is bounded by (1.6)–(1.7). Next, we can use the DDE induced by (1.5) and the boundedness of x to show that also x' is bounded on $[0, t_\phi)$. As $\phi \in U \subset C^1$, we also have boundedness of x and x' on $[-h, 0]$. It follows that T_ϕ is bounded. □

Proof of Theorem 1.8 (b). Global existence follows by Theorem 1.7 and the two previous results if $\overline{T}_\phi \subset U$. Now suppose that $I = (R_-, \infty)$ for some $R_- < 0$ and that $\phi \in C^1([-h, 0], \mathbb{R}^2_+)$. Then, as $C^1([-h, 0], \mathbb{R}^2_+)$ is C^1-closed and as, by our nonnegativity results we have $T_\phi \subset C^1([-h, 0], \mathbb{R}^2_+) \subset U$, we have $\overline{T}_\phi \subset U$. Hence again $t_\phi = \infty$. □

2.3. Specification of τ, $\mathcal{G}$ and β – proofs of Section 1.3

To show continuous differentiability of involved integral operators we first establish a technical result.

Lemma 2.4. *Let E be an open interval, $a, b, c \in \mathbb{R}$, $a < b$, $0 \le c \le 1$. For any $\overline{\psi} \in M_E := C^1([a, b], E)$ there exists some $\kappa = \kappa(\overline{\psi})$, such that for all $\delta \in (0, \kappa]$*

$$A_\delta := \{\overline{\psi}(s) + \theta(\psi(s) - \overline{\psi}(s)) : s \in [a, b], \theta \in [c, 1], \psi \in M_E, \|\psi - \overline{\psi}\|^1 \le \delta\}$$

is a compact subset of E.

Proof. Let $\overline{\psi} \in M_E$. By the openness of E and the compactness of $[a, b]$ with

$$\kappa(\overline{\psi}) := \begin{cases} \frac{1}{2}\operatorname{dist}(\overline{\psi}([a, b]), \mathbb{R}\backslash E), & \mathbb{R}\backslash E \neq \emptyset, \\ \frac{1}{2}, & \mathbb{R}\backslash E = \emptyset, \end{cases} \tag{2.1}$$

where dist denotes the distance function, we get $\kappa(\overline{\psi}) \in (0, \infty)$ and $A_\delta \subset E$ for all $\delta \in (0, \kappa(\overline{\psi})]$. Now fix some $\delta \in (0, \kappa(\overline{\psi})]$ and define

$$\Phi : [-\delta, \delta] \times [c, 1] \times [a, b] \longrightarrow \mathbb{R};\ \Phi(\alpha, \theta, s) := \overline{\psi}(s) + \theta\alpha.$$

As Φ is continuous its range is compact and the statement follows because the range equals A_δ. □

We use the previous result to show convergence properties that will in turn help to show differentiability and continuity properties of several operators. In the following we denote by l an arbitrary function for which we show properties that will be applied to functions of the model and their derivatives.

Lemma 2.5. *Suppose that I_1, I_2 are intervals, I_1 is open and that $l : I_1 \times I_2 \longrightarrow \mathbb{R}$ is partially differentiable in the first argument. Fix $\varphi \in C([a, b], I_2)$ and $\overline{y} \in C^1([a, b], I_1)$. Then for $y \in C^1([a, b], I_1)$*

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$$\sup_{s\in[a,b]} |l(y(s),\varphi(s)) - l(\overline{y}(s),\varphi(s)))$$
$$- D_1 l(\overline{y}(s),\varphi(s)))(y(s)-\overline{y}(s))|$$

is $o(\|y-\overline{y}\|^1)$ *as* $\|y-\overline{y}\|^1 \to 0$.

Proof. (a) By the mean value theorem for $s \in [a,b]$ there exists some $\theta_s \in [0,1]$, such that

$$|l(y(s),\varphi(s)) - l(\overline{y}(s),\varphi(s)) - D_1 l(\overline{y}(s),\varphi(s))(y(s)-\overline{y}(s))|$$
$$\le \|y-\overline{y}\|^1 |D_1 l(\overline{y}(s)+\theta_s(y(s)-\overline{y}(s)),\varphi(s)) - D_1 l(\overline{y}(s),\varphi(s))|.$$

Now we can use Lemma 2.4, with $\overline{\psi} := \overline{y}$, and uniform continuity of $D_1 l$ on the compact set $A_\delta \times \varphi([a,b])$ for some $\delta > 0$ to deduce the statement. □

The next lemma follows from uniform continuity of l on a set that by Lemma 2.4 is compact. We omit a formal proof.

Lemma 2.6. *Let* I_1, I_2 *be open intervals and let* $l : I_1 \times I_2 \longrightarrow \mathbb{R}$ *be continuous, then the following map is continuous*

$$C^1([a,b],I_1) \times C^1([a,b],I_2) \longrightarrow C[a,b]$$
$$(y,\varphi) \longmapsto [t \longmapsto l(y(t),\varphi(t))]. \tag{2.2}$$

The result can also be formulated as continuity of a Nemytskii operator. If a Nemytskii operator is generated by a function that is continuous on $\mathbb{R}$, its continuity is shown, e.g., as Theorem 9.1 in [4].

Lemma 2.7. *Let* I_1, I_2 *be open intervals,* $l : I_1 \times I_2 \longrightarrow \mathbb{R}$ *be* C^1. *Then the operator*

$$H : C^1([a,b],I_1) \times C^1([a,b],I_2) \longrightarrow C^1[a,b]$$
$$H(y,\varphi)(t) := \int_a^t l(y(s),\varphi(s))ds$$

is C^1 *with, for* $i = 1,2$, $D_i H(\psi,z) : C^1([a,b],I_i) \longrightarrow C^1[a,b]$;

$$D_i H(y,\varphi)\chi(t) := \int_a^t D_i l(y(s),\varphi(s))\chi(s)ds. \tag{2.3}$$

Proof. For reasons of symmetry it is sufficient to show that H is partially differentiable with respect to the first argument and that $(y,\varphi) \mapsto D_1 H(y,\varphi)$ is continuous. First, we define a bounded linear operator A by setting $A(y,\varphi)\chi(t)$ equal to the right hand side of (2.3). Then

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$$
\begin{aligned}
&|[H(y,\varphi)-H(\overline{y},\varphi)-A(\overline{y},\varphi)(y-\overline{y})](t)| \\
&\leq \int_a^b |l(y(s),\varphi(s))-l(\overline{y}(s),\varphi(s))-D_1 l(\overline{y}(s),\varphi(s))(y-\overline{y})(s)|ds.
\end{aligned}
$$

By Lemma 2.5 the integrand is $o(\|y-\overline{y}\|^1)$ as $\|y-\overline{y}\|^1 \to 0$, uniformly in s and thus also

$$\|H(y,\varphi)-H(\overline{y},\varphi)-A(\overline{y},\varphi)(y-\overline{y})\|$$

is $o(\|y-\overline{y}\|^1)$ as $\|y-\overline{y}\|^1 \to 0$. Next,

$$
\begin{aligned}
&|[H(y,\varphi)-H(\overline{y},\varphi)-A(\overline{y},\varphi)(y-\overline{y})]'(t)| \\
&= |l(y(t),\varphi(t))-l(\overline{y}(t),\varphi(t))-D_1 l(\overline{y}(t),\varphi(t))(y-\overline{y})(t)|.
\end{aligned}
$$

Again, this is $o(\|y-\overline{y}\|^1)$ as $\|y-\overline{y}\|^1 \to 0$ by Lemma 2.5. It follows that H is partially differentiable in the first argument and $D_1 H$ is as claimed. Next,

$$
\begin{aligned}
&|[D_1 H(y,\varphi)-D_1 H(\overline{y},\overline{\varphi})]\chi(t)| \\
&\leq \|\chi\|^1 \int_a^b |D_1 l(y(s),\varphi(s))-D_1 l(\overline{y}(s),\overline{\varphi}(s))|ds.
\end{aligned}
$$

The integral tends to zero by Lemma 2.6 if $\|y-\overline{y}\|^1$ and $\|\varphi-\overline{\varphi}\|^1$ tend to zero. Moreover

$$
\begin{aligned}
&|[(D_1 H(y,\varphi)-D_1 H(\overline{y},\overline{\varphi}))\chi]'(t)| \\
&\leq \|\chi\|^1 |D_1 l(y(t),\varphi(t))-D_1 l(\overline{y}(t),\overline{\varphi}(t))|.
\end{aligned}
$$

The last factor tends to zero in the desired limit by previously used arguments. □

We again assume that g satisfies (G), $h := b/K$ and $M := C^1([-h,0], I)$ and G is as in (1.10) with k an arbitrary C^1-function (below alternatively $k = g$ or $k = d - D_1 g$). The proof of the following result is a straightforward conclusion of the previous result.

Corollary 2.8. *The operator G is C^1. The derivative $DG = (D_1 G, D_2 G)$ for $(z,\psi) \in C^1([0,h], J) \times M$ is*

$$
\begin{aligned}
&D_1 G(z,\psi) : C^1[0,h] \longrightarrow C^1[0,h], \\
&D_1 G(z,\psi)\chi(t) = \int_0^t D_1 k(z(s),\psi(-s))\chi(s)ds, \\
&D_2 G(z,\psi) : C^1[-h,0] \longrightarrow C^1[0,h], \\
&D_2 G(z,\psi)\chi(t) = \int_0^t D_2 k(z(s),\psi(-s))\chi(-s)ds.
\end{aligned}
$$

Proof. In Lemma 2.7 set $a := 0$, $b := h$, $I_1 := J$, $I_2 := I$, $l := k$, then $C^1([a,b], I_1) = C^1([0,h], J)$ and $\psi \in M$ if and only if $\psi_- \in C^1([a,b], I)$. The proof of continuous differentiability becomes trivial if one uses that $G(z,\psi) = H(z,\psi_-)$, defining $\psi_-(s) := \psi(-s)$. □

Now we are ready for the

Proof of Proposition 1.9 (b). First, in the definition of G set $k = g$. The resulting operator is continuously differentiable by Corollary 2.8. Then it can be shown in a straightforward way that $\partial_z(z - G(z,\psi)) = id + D_1G(z,\psi)$ has the bounded linear inverse

$$(id + D_1G(z,\psi))^{-1} : C^1[0,h] \longrightarrow C^1[0,h]$$

$$(id + D_1G(z,\psi))^{-1}x(t)$$

$$= x(0)e^{-\int_0^t D_1g(z(s),\psi(-s))ds} + \int_0^t e^{-\int_s^t D_1g(z(\sigma),\psi(-\sigma))d\sigma} x'(s)ds$$

(recall the convention on brackets above Proposition 1.9). The implicit function theorem applied to (1.11) implies the conclusion. □

To show Proposition 1.9 (c) we prove

Lemma 2.9. *Let $k : J \times I \longrightarrow \mathbb{R}$, $p : \mathbb{R} \to \mathbb{R}$ and*

$$m : C^1([0,h], J) \times M \longrightarrow C[0,h]$$

be continuous maps. Then the following maps are continuous:

$$C^1([0,h], J) \times M \times C[-h,0] \longrightarrow C[0,h]$$

$$(z,\psi,\chi) \longmapsto [t \longmapsto \int_0^t m(z,\psi)(s)\chi(-s)ds] \tag{2.4}$$

$$C^1([0,h], J) \times M \longrightarrow C[0,h]$$

$$(z,\psi) \longmapsto [t \longmapsto p(\int_0^t k(z(s),\psi(-s))ds)]. \tag{2.5}$$

Proof. It is straightforward to show continuity of (2.4) and we omit the details. Next note that by continuity of (2.2), for $(\overline{z},\overline{\psi}) \in C^1([0,h], J) \times M$ there exist $\delta = \delta(\overline{z},\overline{\psi}) > 0$, $L = L(\overline{z},\overline{\psi}) > 0$ such that

$$|\int_0^t k(z(s),\psi(-s))ds| \le L, \text{ for all } t \in [0,h], (z,\psi) \in B((\overline{z},\overline{\psi}),\delta).$$

Now denote by f the operator defined in (2.5). Then

$$\begin{aligned}&|f(z,\psi)(t)-f(\overline{z},\overline{\psi})(t)|\\&=|p(\int_0^t k(z(s),\psi(-s))ds)-p(\int_0^t k(\overline{z}(s),\overline{\psi}(-s))ds)|.\end{aligned}$$

Note that $p|_{[-L,L]}$ is uniformly continuous. To show continuity of f for $(z,\psi)\to(\overline{z},\overline{\psi})$ it is thus sufficient to show that

$$\int_0^t k(z(s),\psi(-s))ds \to \int_0^t k(\overline{z}(s),\overline{\psi}(-s))ds$$

uniformly in t in this limit. The latter follows from continuity of (2.2). □

Continuity of (2.2) and (2.4)–(2.5) will be used in the

Proof of Proposition 1.9 (c). We first show that

$$\begin{aligned}&C^1([0,h],J)\times M\times C[-h,0]\longrightarrow C[0,h]\\&(z,\psi,\chi)\longmapsto[t\longmapsto-\int_0^t e^{-\int_s^t D_1g(z(\sigma),\psi(-\sigma))d\sigma}D_2g(z(s),\psi(-s))\chi(-s)ds]\end{aligned}\tag{2.6}$$

is continuous. Then $(\psi,\chi)\mapsto D_eY(\psi)\chi$ is continuous as a composition of the above map with the continuous map

$$\begin{aligned}M\times C[-h,0]&\longrightarrow C^1([0,h],J)\times M\times C[-h,0]\\(\psi,\chi)&\longmapsto (Y(\psi),\psi,\chi).\end{aligned}$$

The map in (2.6) is the product of -1 and the two maps

$$C^1([0,h],J)\times M\times C[-h,0]\longrightarrow C[0,h]$$

$$(z,\psi,\chi)\longmapsto[t\longmapsto e^{-\int_0^t D_1g(z(\sigma),\psi(-\sigma))d\sigma}]\tag{2.7}$$

$$(z,\psi,\chi)\longmapsto[t\longmapsto\int_0^t e^{\int_0^s D_1g(z(\sigma),\psi(-\sigma))d\sigma}D_2g(z(s),\psi(-s))\chi(-s)ds],\tag{2.8}$$

so it suffices to show continuity of these two maps. Continuity of (2.7) and continuity of

$$\begin{aligned}C^1([0,h],J)\times M&\longrightarrow C[0,h]\\(z,\psi)&\longmapsto[t\longmapsto e^{\int_0^t D_1g(z(\sigma),\psi(-\sigma))d\sigma}]\end{aligned}\tag{2.9}$$

follow from continuity of (2.5). Continuity of (2.9) together with continuity of (2.2) imply continuity of

$$
\begin{aligned}
&C^1([0,h],J)\times M \longrightarrow C[0,h]\\
&(z,\psi)\longmapsto [t\longmapsto e^{\int_0^t D_1 g(z(\sigma),\psi(-\sigma))d\sigma} D_2 g(z(t),\psi(-t))].
\end{aligned}
$$

This, together with continuity of (2.4), implies continuity of (2.8). □

Proof of Proposition 1.12. First, in the definition of G in (1.10), we now set $k = d - D_1 g$. By the chain rule the composition defined as follows is C^1:

$$
\begin{aligned}
&\psi \xmapsto{(id\times Y)\times\tau} ((\psi, Y(\psi)), \tau(\psi)) \mapsto (G(Y(\psi),\psi), \tau(\psi))\\
&\xmapsto{ev} G(Y(\psi),\psi)(\tau(\psi)) \xmapsto{e} e^{G(Y(\psi),\psi))(\tau(\psi))}.
\end{aligned}
$$

Next, note that $M\to\mathbb{R}$; $\psi\mapsto ev(\psi,0)$ is C^1, hence so is $\psi\mapsto g(x_2,\psi(0))$. Thus, by the product rule $\psi\mapsto\mathcal{G}(\psi)$ is C^1. The existence of $D_e\mathcal{G}$ is obvious. To see the continuity statement we apply sum and product rules. To see continuity of

$$
(\psi,\chi)\mapsto (d - D_1 g)(x_1, \psi(-\tau(\psi)))D_e\tau(\psi)\chi,
$$

use that $(\psi,\chi)\mapsto D_e\tau(\psi)\chi$ is continuous and so is $d - D_1 g$, τ and ev. Next, $\psi\mapsto\mathcal{G}(\psi)$ is C^1, so $(\psi,\chi)\mapsto\mathcal{G}(\psi)$ is continuous. Now, define $\mathcal{I}$ as the map in (2.4) with $m(z,\psi)(s) = (D_1 d - D_1^2 g)(z(s),\psi(-s))$, i.e.,

$$
\mathcal{I}(z,\psi,\chi)(t) := \int_0^t (D_1 d - D_1^2 g)(z(s),\psi(-s))\chi(-s)ds
$$

and note that m is continuous by Lemma 2.6 applied to $\tilde{m}(z,\psi) := m(z,\psi_-)$. Moreover

$$
\begin{aligned}
&\int_0^{\tau(\psi)} (D_1 d - D_1^2 g)(Y(\psi)(s),\psi(-s))D_e Y(\psi)\chi(s)ds\\
&= ev(\mathcal{I}(Y(\psi),\psi, D_e Y(\psi)\chi), \tau(\psi)).
\end{aligned}
$$

Hence,

$$
(\psi,\chi)\mapsto \int_0^{\tau(\psi)} (D_1 d - D_1^2 g)(Y(\psi)(s),\psi(-s))D_e Y(\psi)\chi(s)ds
$$

is continuous by continuity of $\mathcal{I}$, Y, $(\psi,\chi)\mapsto D_e Y(\psi,\chi)$, τ and ev. Continuity of the remaining terms can be shown similarly. □

We now turn to showing that the model ingredients satisfy property (sLb). First we will see how the boundedness properties that have been assumed for the derivatives in Theorem 1.13 (d) will be used. Further down it will become clear that in the following result (C^1-)boundedness in the statement would be sufficient, but the following proof makes clear that we get C-boundedness at no extra cost. Suppose for the remainder of the subsection that g satisfies (1.17) and that $D_2 g$ is bounded on $\overline{B(x_2, b)} \times A$ for any bounded $A \subset I$. We will use the assumptions for the maturation rate g to elaborate properties for the maturation function y and how these interact with the rates.

Lemma 2.10. *Suppose that $k : J \times I \longrightarrow \mathbb{R}$ is C^1 and that $D_i k$, $i = 1, 2$, are bounded on $\overline{B(x_2, b)} \times A$ for any bounded $A \subset I$. Then for any C-bounded $B \subset M$ there exist some $K_B, L_B \geq 0$ such that*

$$|y(s,\chi) - y(s,\psi)| \leq K_B \|\chi - \psi\|, \ \forall s \in [0,h],$$

$$\int_0^h |k(y(s,\psi), \psi(-s)) - k(y(s,\chi), \chi(-s))| ds \leq L_B \|\psi - \chi\|, \tag{2.10}$$

for all $\psi, \chi \in B$.

Proof. First, clearly $A := \{\psi(-s) : \psi \in B\}$ is bounded if B is C-bounded and hence so is its convex hull $conv(A)$. By the mean value theorem applied to $(x, y) \mapsto g(x, y)$ there exist two functions $[0, h] \to [0, 1]$; $s \mapsto \theta_s, \tilde{\theta}_s$ such that

$$\begin{aligned}
&|g(y(s,\chi), \chi(-s)) - g(y(s,\psi), \psi(-s))| \\
&\leq |D_1 g(y(s,\chi) + \theta_s(y(s,\psi) - y(s,\chi)), \chi(-s) + \tilde{\theta}_s(\psi(-s) - \chi(-s)))| \\
&\quad |y(s,\chi) - y(s,\psi)| + \\
&\quad |D_2 g(y(s,\chi) + \theta_s(y(s,\psi) - y(s,\chi)), \chi(-s) + \tilde{\theta}_s(\psi(-s) - \chi(-s)))| \\
&\quad |\psi(-s) - \chi(-s)| \\
&\leq \sup_{(x,y) \in \overline{B(x_2,b)} \times I} |D_1 g(x,y)| \|y(\cdot,\chi) - y(\cdot,\psi)\| \\
&\quad + \sup_{(x,y) \in \overline{B(x_2,b)} \times conv(A)} |D_2 g(x,y)| \|\psi - \chi\|.
\end{aligned}$$

It follows that

$$\begin{aligned}
&|y(t,\chi) - y(t,\psi)| \leq \int_0^h |g(y(s,\chi), \chi(-s)) - g(y(s,\psi), \psi(-s))| ds \\
&\leq h \sup_{(x,y) \in \overline{B(x_2,b)} \times I} |D_1 g(x,y)| \|y(\cdot,\chi) - y(\cdot,\psi)\| \\
&\quad + h \sup_{(x,y) \in \overline{B(x_2,b)} \times conv(A)} |D_2 g(x,y)| \|\psi - \chi\|.
\end{aligned}$$

This clearly yields

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$$\|y(\cdot,\chi)-y(\cdot,\psi)\|(1-h\sup_{(x,y)\in\overline{B(x_2,b)}\times I}|D_1g(x,y)|)$$
$$\le h\sup_{(x,y)\in\overline{B(x_2,b)}\times conv(A)}|D_2g(x,y)|\|\psi-\chi\|.$$

The first statement of the lemma follows if one uses that $h=\frac{b}{K}$ and (1.17). The second statement follows using similar arguments as well as the first statement. □

Next, recall that the delay $\tau=\tau(\psi)$ was defined via $y(\tau,\psi)=x_1$.

Lemma 2.11. *For any C-bounded $B\subset M$, there exists some $L_B\ge 0$, such that*

$$|\tau(\psi_1)-\tau(\psi_2)|\le L_B\|\psi_1-\psi_2\|, \textit{ for all } \psi_1,\psi_2\in B.$$

In particular, τ is (sLb).

Proof. Let $B\subset M$ be C-bounded, $\psi,\chi\in B$. We then get that

$$\int_{\tau(\chi)}^{\tau(\psi)} g(y(s,\psi),\psi(-s))ds$$
$$=\int_0^{\tau(\chi)} g(y(s,\chi),\chi(-s))-g(y(s,\psi),\psi(-s))ds.$$

This implies that by (G3) and (2.10) applied to $k=g$

$$|\tau(\psi)-\tau(\chi)|\le K\|\psi-\chi\|$$

for some $K\ge 0$, which proves the statement. □

Now consider $\mathcal{G}$ as defined in (1.12), suppose that $d, D_1g : J\times I\longrightarrow\mathbb{R}$ are C^1 and that d, D_id and D_iD_1g, $i=1,2$ are bounded on $\overline{B(x_2,b)}\times A$, whenever $A\subset I$ is bounded. The conditions guarantee that among others we can apply Lemma 2.10 to $k=d-D_1g$.

Lemma 2.12. *For any C-bounded $B\subset M$, there exists some $L_B\ge 0$, such that*

$$|\mathcal{G}(\psi_1)-\mathcal{G}(\psi_2)|\le L_B\|\psi_1-\psi_2\|, \textit{ for all } \psi_1,\psi_2\in B.$$

In particular, $\mathcal{G}$ is (sLb).

Proof. Let $B\subset M$ be C-bounded, $\psi,\chi\in B$. Then, note that the boundedness conditions for d and D_1g ensure that the map

$$\mathcal{J}:B\longrightarrow\mathbb{R};\ \psi\longmapsto\int_0^{\tau(\psi)}(d-D_1g)(y(s,\psi),\psi(-s))ds \tag{2.11}$$

is bounded. Then, by the mean value theorem applied to e,

$$M \longrightarrow \mathbb{R};\ \psi \longmapsto e^{\int_0^{\tau(\psi)}(d-D_1 g)(y(s,\psi),\psi(-s))ds} \tag{2.12}$$

satisfies the first of the two stated Lipschitz properties if $\mathcal{J}$ does. Moreover

$$|\mathcal{J}(\psi)-\mathcal{J}(\chi)| \le |\int_{\tau(\chi)}^{\tau(\psi)} (d-D_1 g)(y(s,\psi),\psi(-s))ds|$$
$$+\int_0^{\tau(\chi)} |(d-D_1 g)(y(s,\psi),\psi(-s))-(d-D_1 g)(y(s,\chi),\chi(-s))|ds.$$

The first integral is dominated by

$$K_1|\tau(\chi)-\tau(\psi)| \le K_2\|\psi-\chi\|$$

for some $K_i \ge 0$, $i=1,2$, by the boundedness properties of d and $D_1 g$ and Lemma 2.11. The second integral is dominated by

$$K_3\|\psi-\chi\|$$

for some $K_3 \ge 0$ by (2.10) applied to $d-D_1 g$ in place of k. In summary, $\mathcal{J}$ satisfies the Lipschitz property, hence so does (2.12). The mean value theorem applied to $y \longmapsto g(x,y)$ (similarly as in the proof of the first statement of Lemma 2.10) and the boundedness properties of $D_2 g$ imply that $M \longrightarrow \mathbb{R};\ \psi \mapsto g(x_2,\psi(0))$ satisfies the Lipschitz property. Now note that for this property there applies a similar product rule as stated for (sLb) in Lemma 1.6. By this product rule we now know that $\mathcal{G}$ satisfies the former property. □

Proof of Theorem 1.13 (d). By Lemmas 2.11 and 2.12, τ and $\mathcal{G}$ are (sLb). Next, note that the boundedness assumption for $D_2 g$ implies that $I \longrightarrow \mathbb{R}_+;\ y \mapsto g(x_1,y)$ is Lipschitz on bounded sets. Then, the Lipschitz properties of γ and $g(x_1,\cdot)$ on bounded sets along with the boundedness away from zero of g and the boundedness of γ imply that β as defined in (1.15) is Lipschitz on bounded sets and bounded. Since under the assumptions the functional $\mathcal{G}$ is bounded, also the remaining conditions of Theorem 1.8 (b) are satisfied and the theorem implies the statement. □

3. Discussion

In this paper we have elaborated a new general sufficient criterion for global existence (Theorem 1.7) for differential equations with state dependent delay. Moreover, we have analyzed a differential equation with implicitly defined delay with state dependence that describes the maturation process of a stem cell population. We have guaranteed existence of a local semiflow using a theorem from the literature and global existence via the above mentioned criterion, see Theorem 1.13. The computation of the derivative DF, which we used to verify the smoothness

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condition (S) (Theorem 1.13), of the functional inducing the DDE was the essential step in the specification of the linear variational equation (1.3). This equation could be important for future analysis (see below).

In [1] the authors analyzed oscillatory behavior, phenomena beyond the scope of this paper, for a comparable stem cell maturation model as a differential equation with state dependent delay. In difference to their model in this project we considered the case of a maturation rate that depends nonlinearly on both maturity and population. This leads to a merely implicitly defined delay as a function of the population history. It has become clear that an implicit definition of the delay complicates the verification of smoothness conditions (conditions (S) and (sLb)). As motivated by our example, such delays can be expected whenever the rate of individual development depends nonlinearly on the population state. In ecological (structured) population modeling such dependencies are typical [7,10,8,9]. Also in physics there are examples of implicitly defined state-dependent delays, see [19, Section 2.1] (two-body problem).

Most of the assumptions of Theorem 1.13 seem consistent with biological observation: The cell rates of production and development, considered as functions of both, cell maturity and the mature, i.e., the size of the mature cell population, should be smooth, bounded and not too wildly growing. In [2,12,13] is given a specification of the rates on the basis of empirical biological knowledge; in particular intracellular signaling should be reflected in the dependencies of the rates on the mature. It is not hard to see that under mild additional assumptions for the specifications the above mentioned assumptions for the present ingredients are satisfied.

In Theorem 1.13 we also have required (see (G3)) that there is a minimum positive value (ε) below which maturation (speed) cannot fall for any size of the mature within the range I, corresponding to the mature-component of the domain of g, and at any maturity (x). In [2] g is specified such that, as a function of the mature, it is decreasing and tending to zero at infinity, uniformly for all maturities. Under additional assumptions on maturity-dependence it is concluded there that maturation is bounded away from zero, since the range of the mature was assumed to lie within a finite interval $I = (R_-, R)$ and so the tending to zero is prevented. We have discussed biological relevance of the assumptions that guarantee local existence.

To discuss global existence note first that, if I is finite, for initial histories with large values of the mature a little population growth may lead to the latter assuming values beyond I. We propose two alternatives to avoid this, relating to the two possibilities of guaranteeing global existence that we have elaborated. One is to focus on those initial histories ϕ for which the orbit lies in the domain (condition $\overline{T}_\phi \subset U$ in Theorem 1.13 (d)), in particular for all times the mature assume only values in I. In parallel one can study whether these initial conditions capture the relevant situations. The second possibility is to guarantee global existence for all possible initial histories by modifying the specification such that an infinite interval $I = (R_-, \infty)$ (see again Theorem 1.13 (d)) is allowed for the values of the mature. With this modification the discussed specification for maturation velocity tends to zero at infinity and its boundedness from below is violated. To overcome this one may additionally slightly modify the specification, such that the limit is a (small) positive value. The biological interpretation seems not much affected, taking into account that very large sizes of the mature population may be irrelevant.

Note that (0.4) can be interpreted as a nonautonomous ODE depending on a parameter in a Banach space, i.e.,

$$\frac{dx}{dt} = f(t, x, \lambda), \quad x(0) = x_0, \text{ where } f(t, x, \lambda) := -g(x, \lambda(-t)), \quad x_0 := x_2. \tag{3.1}$$

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We have found established results for differentiability, with respect to infinite dimensional parameters, of solutions of more general classes than (3.1), which we will discuss in the following. We believe that in several cases the result could be applied to yield the differentiability statement in Proposition 1.9 but a precise formulation would lead to more technicalities than our proof contains.

[6, Theorem II 3.6.1] contains such a result for nonautonomous ODE. The initial data vector $(0, x_0, \lambda_0)$ is required to belong to the interior of the domain of f. This suggests to take $[-h, h]$ as the first component of the domain, which in turn suggests to consider also λ on $[-h, h]$. An application of the theorem in this way could proceed first extending the parameter function and then restricting solutions. In [11] the equation

$$x'(t) = f(x_t, p)$$

is analyzed, which is not a direct generalization of (3.1) as it does not allow explicit time dependence. [15, Theorem 4.6] contains a result for a class of neutral differential equations with state dependent delay that is much larger than (3.1). Differentiability is shown for a positive time of existence of solutions that is uniform locally around a given parameter. Here we would like to have differentiability for an existence time h that is uniform for all parameters in the set $C^1([-h, 0], I)$ (Proposition 1.9). After a personal communication with the author and a study of [15] we are confident that the result is essentially applicable.

For our model [2] Alarcón et al. have analyzed the possibility of a unique positive equilibrium (next to the trivial one) and computed representations of it. It is shown in [14,25] that for ODE variants of our model there is the possibility of destabilization of equilibria via Hopf bifurcation and the emergence of oscillations. As a future project we plan the local stability analysis of equilibria in the general setting of the present paper. We would like to investigate the existence of periodic solutions and how they relate to biological mechanisms at the cell level. As a first step there may be computed a characteristic equation from the linear variational equation computed in Theorem 1.13.

Note that the central equation of our studies, i.e., (0.1)–(0.2) is of the form

$$x'(t) = f(x_t, x(t - r(x_t)), r(x_t)), \tag{3.2}$$

where f, x and x_t are $\mathbb{R}^2$-valued and for $x = (w, v)$ we have $r(x_t) = \tau(v_t)$. Stability and oscillation as well as other much advanced topics for state dependent delays are analyzed in [5,16, 19–23,26]. However in most of the equations analyzed in these references there seems no formal allowance for a direct general dependence of f on x_t and in several references the delay functional r is only allowed to depend on $x(t)$, rather than on x_t. We hope that some of the established theory developed can be adapted to equations of the form (3.2).

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