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Qualitative analysis of two systems of nonlinear first-order ordinary differential equations for biological systems

Benjamin Wacker[1,2] | **Jan Christian Schlüter**[2,3,4,5]

[1]Department of Engineering and Natural Sciences, University of Applied Sciences Merseburg, Merseburg, Germany

[2]Next Generation Mobility Group, Department of Dynamics of Complex Fluids, Max-Planck-Institute for Dynamics and Self-Organization, Göttingen, Germany

[3]Econophysics Lab, Chair of Network Dynamics, Center for Advancing Electronics Dresden (CFAED), Technical University of Dresden, Dresden, Germany

[4]Flexible Transport Systems and Complex Urban Dynamics Research Group, 'Friedrich List' Faculty of Transport and Traffic Sciences, Technical University of Dresden, Dresden, Germany

[5]Institute for Medical Epidemiology, Biometrics and Informatics, Interdisciplinary Center for Health Sciences, Martin Luther University of Halle-Wittenberg, Halle, Germany

Correspondence
Benjamin Wacker, Department of Engineering and Natural Sciences, University of Applied Sciences Merseburg, Eberhard-Leibnitz-Str. 2, D-06217 Merseburg, Germany.
Email: benjamin.wacker@hs-merseburg.de

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We consider two systems of nonlinear first-order ordinary differential equations proposed to describe Ca^{2+}-levels in renal vascular smooth muscle cells and in liver cells. Initially, we present the models and its assumptions. We next investigate an approach to local solvability by Picard–Lindelöf 's Theorem. Further, we prove nonnegativity of the systems' possible solutions and we especially conclude global unique existence of the models' solutions by Gronwall-type arguments and the concept of trapping regions. After finishing our theoretical part with some aspects of stability analysis, we provide evidence of our findings by some numerical experiments.

KEYWORDS

dynamical systems, first-order nonlinear ordinary differential equations, nonnegativity, oscillations, solvability, stability, uniqueness

MSC CLASSIFICATION

34A12; 34A34; 65L05; 65L06; 92C45

1 | INTRODUCTION

In this article, we first examine the initial value problem of the system

$$\begin{cases} x'(t) &= -\beta x(t) - \gamma x(t) + k_0 + k_s y(t) + f\,(x(t))\,y(t), \\ y'(t) &= \gamma x(t) - k_s y(t) - f\,(x(t))\,y(t), \\ x(0) &= x_0, \\ y(0) &= y_0 \end{cases} \tag{1}$$

of nonlinear first-order ordinary differential equations for Ca^{2+}-levels in renal vascular smooth muscle cells as depicted by Layton and Edwards.[1] This model was first proposed by Somogyi and Stucki[2] to describe hormone-induced calcium oscillations in liver cells. Here, $\beta,\ \gamma,\ k_0$, and k_s are positive constants as model parameters and the scalar-valued function $f\ :\ [0,\infty) \rightarrow [0,1]$ is a suitable model transfer rate function as defined in Section 2. We assume nonnegative initial conditions x_0 and y_0.

Additionally, we investigate the initial value problem of the system

$$\begin{cases} x'(t) &= k_1 + k_2 x(t) - k_3 \frac{x(t)y(t)}{x(t)+k_4} - k_5 \frac{x(t)z(t)}{x(t)+k_6}, \\ y'(t) &= k_7 x(t) - k_8 \frac{y(t)}{y(t)+k_9}, \\ z'(t) &= k_{10} x(t) - k_{11} \frac{z(t)}{z(t)+k_{12}}, \\ x(0) &= x_0, \\ y(0) &= y_0, \\ z(0) &= z_0 \end{cases} \tag{2}$$

of nonlinear first-order ordinary differential equations for Ca^{2+}-levels in liver cells as proposed by Kummer and co-authors.[3] Here, k_j for $j \in \{1, \dots, 12\}$ are positive constants as model parameters. We assume nonnegative initial conditions $x_0,\ y_0$, and z_0.

In both systems, we assume spatial homogeneity of signaling processes. For motivational purposes, we restrict our short motivational introduction to System (1).

1.1 | Motivation

Modeling with differential equations is a versatile tool in all natural sciences with a traditional history.[1–22] Especially in pharmacokinetics or systems biology, one often uses the tool of compartmental models for modeling different types of systems.[23] From a compartmental model approach, System (1) is derived under certain assumptions by Layton and Edwards.[1] We illustrate this compartmental approach for System (1) in Figure 1.

We follow the description by Layton and Edwards.[1] x denotes Ca^{2+}-concentration in the cytosol, and y denotes Ca^{2+}-concentration in the sarcoplasmic reticulum (SR). We abbreviate the plasma membrane Ca^{2+} pump by PCMA (plasma membrane **Ca^{2+}**) and the sarcoplasmic reticulum Ca^{2+} pump by SERCA (sarcoplasmic reticulum **Ca^{2+}**). We assume that the last two mentioned pumps pump Ca^{2+} at linear rates β and γ. At the same time, there are two passive Ca^{2+} fluxes into the cells of the cytosol. The one flux transports Ca^{2+} at a linear rate k_0 from the extracellular compartment into the cytosol, while the other flux transports Ca^{2+} at a linear rate k_s from the SR into the cytosol. At last, we assume that receptor-mediated Ca^{2+} release into the cytosol is given by a transfer rate function $f(x)$. For further details, we refer the reader to the book by Layton and Edwards[1] or the work by Somogyi and Stucki.[2]

From a biological or medical viewpoint, transfer coefficients might be indicators of cell healthfulness. If some coefficients leave certain parameter ranges, medical scientists will be able to predict abnormalities that indicate need of medical

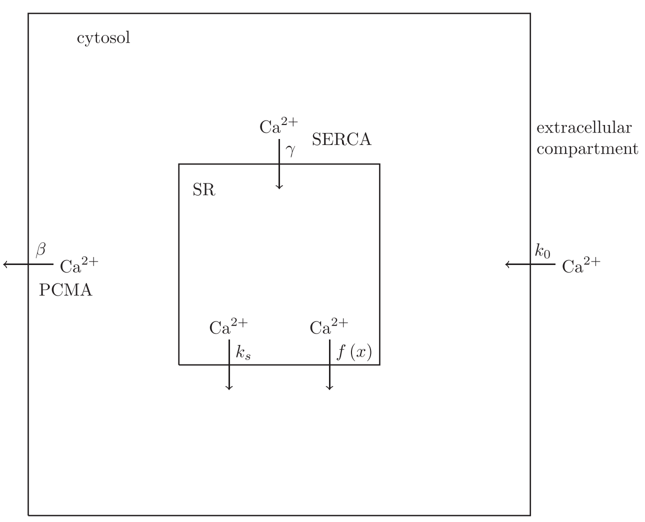


FIGURE 1 A simplified representation of intracellular calcium signaling described through System (1). This illustration is modified from Figure 6.4 by Layton and Edwards [1]

treatment. However, we restrict our work to mathematical aspects and discuss later some important implications which can be drawn from our findings.

1.2 | Contributions and outline

We often answer the following mathematical questions when dealing with nonlinear systems of first-order ordinary differential equations:

- Does there exist a solution locally? Is this solution locally unique? Are there special properties?
- Are we able to extend a local solution globally in time? Is this solution unique for all time? Can we prove some special properties like nonnegativity?
- Are stationary points of the right-hand side vector field stable or unstable?

Hereafter, we are going to answer these questions as they were not addressed by Layton and Edwards[1] or by Somogyi and Stucki.[2] Answers to these questions are important for applications as some properties like nonnegativity of solutions are essential for meaningfulness of mathematical models. For that reason, we give detailed analysis to both systems which we investigate in this work.

Our article is structured as follows. After our introduction in Section 1, we carry out a detailed analysis of System (1) in Section 2. Afterwards, we give a thorough analysis of System (2) in Section 3. Finally, we draw some similarities and differences between those two systems by numerical experiments. We summarize our findings, draw conclusions from them, and provide some further research directions regarding dynamical systems in biological systems in Section 4.

2 | FIRST SYSTEM: Ca^{2+} LEVELS IN RENAL VASCULAR SMOOTH MUSCLE CELLS

2.1 | Mathematical preliminaries

Here, we recall Lipschitz continuity of a function.

Definition 1 ([24, Definition 1]). Let (X, d_X) and (Y, d_Y) be two metric spaces with corresponding metrics d_X and d_Y on the sets X and Y. We call a function $h : X \to Y$ Lipschitz continuous if there exists a real constant $L \geq 0$ such that

$$d_Y\left(h\left(x_1\right), h\left(x_2\right)\right) \leq L d_X\left(x_1, x_2\right) \tag{3}$$

holds for all $x_1, x_2 \in X$. We refer to L as a Lipschitz constant for the function h. If there exists for every $x \in X$, a neighborhood U of x such that h restricted to U is Lipschitz continuous, we call h *locally Lipschitz continuous*.

As we work on Euclidean spaces $\mathbb{R}^d$ with $d \in \mathbb{N}$, we can restrict the aforementioned definition and inequality (3) to this case.

Definition 2 ([16, Subsection 3.2]). Let $d_1, d_2 \in \mathbb{N}$. If $S \subset \mathbb{R}^{d_1}$, a function $\mathbf{F} : S \to \mathbb{R}^{d_2}$ is called *Lipschitz continuous on S* if there exists a nonnegative constant $L \geq 0$ such that

$$\|\mathbf{F}(\mathbf{x}) - \mathbf{F}(\mathbf{y})\|_{\mathbb{R}^{d_2}} \leq L\|\mathbf{x} - \mathbf{y}\|_{\mathbb{R}^{d_1}} \tag{4}$$

holds for all $\mathbf{x}, \mathbf{y} \in S$. Here, $\|\cdot\|$ denotes a suitable norm on the corresponding Euclidean space.

Let $U \subset \mathbb{R}^{d_1}$ be open, let $\mathbf{F} : U \to \mathbb{R}^{d_2}$. We shall call $\mathbf{F}$ locally Lipschitz continuous if for every point $x_0 \in U$ there exists a neighborhood V of x_0 such that the restriction of $\mathbf{F}$ to V is Lipschitz continuous on V.

2.2 | Model equations

As a reminder, our model equations read

$$\begin{cases} x'(t) &= -\beta x(t) - \gamma x(t) + k_0 + k_s y(t) + f\left(x(t)\right) y(t), \\ y'(t) &= \gamma x(t) - k_s y(t) - f\left(x(t)\right) y(t), \\ x(0) &= x_0, \\ y(0) &= y_0, \end{cases} \tag{5}$$

where we seek two continuously differentiable functions $x : [0, \infty) \to \mathbb{R}$ and $y : [0, \infty) \to \mathbb{R}$. System (5) consists of two first-order nonlinear ordinary differential equations. Investigating properties of this system's solutions, we must take additional assumptions into account.

Assumption 1. Let β, γ, k_0, k_s be positive real constants. Likewise, we assume $x_0, y_0 > 0$ for our initial conditions. Let the function $f : [0, \infty) \to [0, 1]$ be a continuously differentiable function with $f(0) = 0$ and whose first derivative is bounded, that is, there exists a positive real constant $M \geq 0$ such that

$$\left| f'(z) \right| \leq M \tag{6}$$

holds for all $z \in [0, \infty)$.

If we follow Somogyi's work[2] or Problem 6.5 from Layton's book,[1] a suitable transfer rate function choice for f is

$$f : [0, \infty) \to [0, 1], \, z \mapsto \frac{z^n}{\alpha^n + z^n} \tag{7}$$

for a positive real constant $\alpha > 0$ and an arbitrary $n \in \mathbb{N}$. We summarize the following properties.

Lemma 1. *The function defined in (7) fulfills Assumption 1.*

Proof. By definition, we see $f : [0, \infty) \to \mathbb{R}$. Obviously, $f(0) = 0$ is satisfied. Additionally, we conclude that

$$0 \leq f(z) = \frac{z^n}{\alpha^n + z^n} \leq \frac{z^n}{z^n} = 1$$

holds for all $z \in [0, \infty)$. This shows boundedness of f.

Finally, we prove that (6) is valid. We have

$$f'(z) = \frac{n\alpha^n z^{n-1}}{(\alpha^n + z^n)^2}$$

for the first derivative. This means that f is monotonically increasing for all $z \in [0, \infty)$ and for every $n \in \mathbb{N}$. The second derivative depends on $n \in \mathbb{N}$. If $n = 1$, we get

$$f''(z) = -\frac{2\alpha}{(\alpha + z)^3} \leq 0$$

for all $z \in [0, \infty)$. For $n \geq 2$, the second derivative reads

$$f''(z) = \frac{n\alpha^n z^{n-2} \left((n-1)\, \alpha^n - (n+1) z^n \right)}{(\alpha^n + z^n)^3}$$

for all $z \in [0, \infty)$. Thus, f' is monotonically increasing on $\left[0, \sqrt[n]{\frac{n-1}{n+1}}\,\alpha\right]$, whereas it is monotonically decreasing on $\left[\sqrt[n]{\frac{n-1}{n+1}}\,\alpha, \infty\right)$. It immediately follows for every $n \in \mathbb{N}$ that there exists a real constant $M(n) > 0$ such that

$$\left| f'(z) \right| \leq M(n)$$

holds for all $z \in [0, \infty)$ which finishes our proof. □

2.3 | Local unique solvability

In this section, proof of local unique existence is provided by Picard–Lindelöf 's Theorem. We consider the initial value problem

$$\begin{cases} \mathbf{z}'(t) &= \mathbf{G}\left(\mathbf{z}(t)\right), \\ \mathbf{z}(0) &= \mathbf{z_0}, \end{cases} \tag{8}$$

where we define $\mathbf{z}(t) = (x(t), y(t))$ and $\mathbf{G}\left(\mathbf{z}(t)\right) = \left(g_1\left(x(t), y(t)\right), g_2\left(x(t), y(t)\right)\right)$. Here, the functions

$$g_1, g_2 : \mathbb{R}^2 \to \mathbb{R}$$

are given by

$$g_1\left(x(t), y(t)\right) = -\beta x(t) - \gamma x(t) + k_0 + k_s y(t) + f\left(x(t)\right) y(t) \tag{9}$$

and

$$g_2\left(x(t), y(t)\right) = \gamma x(t) - k_s y(t) - f\left(x(t)\right) y(t). \tag{10}$$

System (8) is therefore a reformulation of System (5).

We state Picard–Lindelöf 's Theorem for proving local unique existence.

Theorem 1 ([16, Theorem 3.2.1]). *Suppose that $U \subset \mathbb{R}^d$ is open and it holds $z_0 \in U$ for our initial condition. Let $\mathbf{G} : (-\varepsilon, \varepsilon) \times U \to U$ be locally Lipschitz continuous. Then there exists a unique continuously differentiable function $\mathbf{z} : (-\varepsilon, \varepsilon) \to \mathbb{R}^d$ which satisfies*

$$\begin{cases} \mathbf{z}'(t) &= \mathbf{G}\left(t, \mathbf{z}\right), \\ \mathbf{z}(0) &= \mathbf{z_0}, \end{cases} \tag{11}$$

that is, satisfaction of our initial value problem in shortened notation.

We are now able to show that the initial value problem (8) has a unique local solution.

Lemma 2. *We consider the initial value problem (8) with right-hand side functions (9) and (10). This initial value problem possesses a unique local solution.*

Proof. As our initial conditions x_0 and y_0 are nonnegative by Assumption 1 and both functions

$$g_1 : \mathbb{R} \times \mathbb{R}^2 \to \mathbb{R} \text{ in (9) and } g_2 : \mathbb{R} \times \mathbb{R}^2 \to \mathbb{R} \text{ in (10)}$$

are continuously differentiable as sums and products of continuously differentiable functions and locally Lipschitz continuous by ([16, Proposition 3.2.3]), we are able to apply Picard–Lindelöf 's Theorem 1 and this yields the unique local existence. □

2.4 | Boundedness and nonnegativity

We examine the behavior of System (8) with right-hand side functions (9) and (10), where Assumption 1 is fulfilled.

In order to provide boundedness, we have to state one variant of Gronwall's Lemma.

Theorem 2 ([16, Lemma 3.3.1]). *Let $g : [0, T] \to \mathbb{R}$ be continuous and suppose that there are nonnegative real constants C and K such that*

$$g(t) \le C + K \int_0^t g(s)\,\mathrm{d}s \tag{12}$$

holds for all $t \in \mathbb{R}$ with $0 \le t \le T$. This then implies

$$g(t) \le C \exp(Kt) \tag{13}$$

for all $t \in \mathbb{R}$ with $0 \le t \le T$.

Now, we prove a generalization of Gronwall's Lemma as it is only given as Exercise 8a in Subsection 3.5 of Schaeffer's book.[16]

Lemma 3 ([16, Subsection 3.5, Exercise 8a]). *Let g : [0, T]→ be continuous and suppose that there are nonnegative real constants B, C, K such that*

$$g(t) \leq C + Bt + K \int_0^t g(s)\,\mathrm{d}s \tag{14}$$

holds for all $t \in \mathbb{R}$ with $0 \leq t \leq T$. Then it holds

$$g(t) \leq C \exp(Kt) + B \frac{\exp(Kt) - 1}{K} \tag{15}$$

for all $t \in \mathbb{R}$ with $0 \leq t \leq T$.

Proof. Define the function $h : [0, T] \to \mathbb{R}, t \mapsto g(t) + \frac{B}{K}$. Obviously, this function is continuous. We have

$$\begin{aligned} h(t) = g(t) + \frac{B}{K} &\leq C + Bt + K \int_0^t g(s)\,\mathrm{d}s + \frac{B}{K} \\ &= C + K \left(\int_0^t g(s) + \frac{B}{K}\,\mathrm{d}s \right) + \frac{B}{K} = \left(C + \frac{B}{K} \right) + K \int_0^t h(s)\,\mathrm{d}s. \end{aligned}$$

from application of inequality (14). By the aforementioned version of Gronwall's Lemma, we get

$$g(t) + \frac{B}{K} = h(t) \leq \left(C + \frac{B}{K} \right) \exp(Kt)$$

and this implies

$$g(t) \leq C \exp(Kt) + B \frac{\exp(Kt) - 1}{K}$$

which shows our assertion of inequality (15). □

For boundedness, we need the following lemma. We consider the autonomous initial value problem

$$\begin{cases} \mathbf{z}'(t) = \mathbf{F}(\mathbf{z}(t)), \\ \mathbf{z}(0) = \mathbf{z_0}. \end{cases} \tag{16}$$

It is a consequence of the generalization of Gronwall's Lemma.

Lemma 4 ([16, Theorem 4.2.1]). *If $\mathbf{F} : \mathbb{R}^d \to \mathbb{R}^d$ is locally Lipschitz continuous and if there exist nonnegative real constants B and K such that*

$$\|\mathbf{F}(\mathbf{z})\|_{\mathbb{R}^d} \leq K \|\mathbf{z}\|_{\mathbb{R}^d} + B \tag{17}$$

holds for all $\mathbf{z} \in \mathbb{R}^d$, then the solution of the aforementioned initial value problem (16) exists for all time $t \in \mathbb{R}$ and moreover, it holds

$$\|\mathbf{z}(t)\|_{\mathbb{R}^d} \leq \|\mathbf{z_0}\|_{\mathbb{R}^d} \exp(K|t|) + \frac{B}{K}(\exp(K|t|) - 1) \tag{18}$$

for all $t \in \mathbb{R}$.

Proof. As depicted in Theorem 4.2.1 of Schaeffer's book,[16] this inequality is a direct consequence of Lemma 3. □

We introduce the concept of *trapping regions* from Section 4.2 of Schaeffer's book[16] in order to provide an alternative approach to boundedness.

Definition 3. Consider an initial value problem

$$\begin{cases} \mathbf{z}'(t) &= \mathbf{G}\left(\mathbf{z}(t)\right), \\ \mathbf{z}(0) &= \mathbf{z_0}, \end{cases}$$

where the right-hand side function $\mathbf{G} : U \rightarrow \mathbb{R}^d$ is defined on an open set $U \subset \mathbb{R}^d$. Let $K \subset U$ be a compact set with a piecewise smooth boundary ∂K. Let $\mathbf{x} \in \partial K$ and N_x be an inward pointing normal to ∂K at x. We shall call K a trapping region for the initial value problem if

$$\langle \mathbf{N_x}, \mathbf{G}\left(\mathbf{x}\right)\rangle_{\mathbb{R}^d \times \mathbb{R}^d} \geq 0$$

holds for all $x \in \partial K$. Here, $\langle \cdot, \cdot \rangle_{\mathbb{R}^d \times \mathbb{R}^d}$ denotes the inner product on Euclidean space $\mathbb{R}^d$.

A consequence of this introduced concept is the following theorem.

Theorem 3 ([16, Theorem 4.2.3]). *Suppose that* $\mathbf{G} : U \rightarrow \mathbb{R}^2$ *is continuously differentiable on a domain* $U \subset \mathbb{R}^2$ *and that* $K \subset U$ *is a compact region with a piecewise smooth boundary such that*

$$\langle \mathbf{N_x}, \mathbf{G}\left(\mathbf{x}\right)\rangle_{\mathbb{R}^2 \times \mathbb{R}^2} \geq 0$$

holds for all $x \in \partial K$ *that are regular points. If the initial data lie in the interior of K, then the solution* $\mathbf{x}(t)$ *to the initial value problem* $\mathbf{x}'(t) = \mathbf{G}\left(\mathbf{x}(t)\right), \mathbf{x}(0) = \mathbf{x_0}$ *exists for all nonnegative time and remains in K.*

2.4.1 | Nonnegativity

As nonnegativity is an important feature of biological systems such as in epidemiology[21,25] or population dynamics,[22] we want to demonstrate that solutions to System (8) never leave the first quadrant, that is, that solutions are nonnegative.

Theorem 4. *We consider system (8) under Assumption 1. If we have a solution in regard of Lemma 2, this solution remains nonnegative.*

Proof. Let us assume that there is a time $\hat{t} > 0$ such that $x\left(\hat{t}\right) = 0$ or $y\left(\hat{t}\right) = 0$. We have to distinguish three different cases.

Case 1: Let $x\left(\hat{t}\right) = 0$ and $y\left(\hat{t}\right) = 0$. This yields

$$\begin{aligned} x'\left(\hat{t}\right) &= -\beta x\left(\hat{t}\right) - \gamma x\left(\hat{t}\right) + k_0 + k_s y\left(\hat{t}\right) + f\left(x\left(\hat{t}\right)\right) y\left(\hat{t}\right) \\ &= k_0 \\ &> 0 \end{aligned}$$

and

$$\begin{aligned} y'\left(\hat{t}\right) &= \gamma x\left(\hat{t}\right) - k_s y\left(\hat{t}\right) - f\left(x\left(\hat{t}\right)\right) y\left(\hat{t}\right) \\ &= 0. \end{aligned}$$

Continuity of x' implies that there exists a positive constant $\delta_1 > 0$ such that $x(t) > 0$ for all $t \in \mathbb{R}$ with $\hat{t} < t < \hat{t} + \delta_1$. By the following, we are also going to notice that $y(t)$ is positive.

Case 2: Let $x\left(\hat{t}\right) > 0$ and $y\left(\hat{t}\right) = 0$. This implies

$$\begin{aligned} x'\left(\hat{t}\right) &= -\beta x\left(\hat{t}\right) - \gamma x\left(\hat{t}\right) + k_0 + k_s y\left(\hat{t}\right) + f\left(x\left(\hat{t}\right)\right) y\left(\hat{t}\right) \\ &= -\beta x\left(\hat{t}\right) - \gamma x\left(\hat{t}\right) + k_0 \end{aligned}$$

and

$$\begin{aligned} y'\left(\hat{t}\right) &= \gamma x\left(\hat{t}\right) - k_s y\left(\hat{t}\right) - f\left(x\left(\hat{t}\right)\right) y\left(\hat{t}\right) \\ &= \gamma x\left(\hat{t}\right) \\ &> 0. \end{aligned}$$

Continuity of x' and y' yields that there exists a positive constant $\delta_2 > 0$ such that $x(t) > 0$ and $y(t) > 0$ for all $t \in \mathbb{R}$ with $\hat{t} < t < \hat{t} + \delta_2$.

Case 3: Let $x\left(\hat{t}\right) = 0$ and $y\left(\hat{t}\right) > 0$. This gives

$$\begin{aligned} x'\left(\hat{t}\right) &= -\beta x\left(\hat{t}\right) - \gamma x\left(\hat{t}\right) + k_0 + k_s y\left(\hat{t}\right) + f\left(x\left(\hat{t}\right)\right) y\left(\hat{t}\right) \\ &= k_0 + k_s y\left(\hat{t}\right) \\ &> 0 \end{aligned}$$

and

$$\begin{aligned} y'\left(\hat{t}\right) &= \gamma x\left(\hat{t}\right) - k_s y\left(\hat{t}\right) - f\left(x\left(\hat{t}\right)\right) y\left(\hat{t}\right) \\ &= -k_s y\left(\hat{t}\right) \\ &< 0. \end{aligned}$$

From continuity of x' and y', we conclude that there exists a positive constant $\delta_3 > 0$ such that $x(t) > 0$ and $y(t) > 0$ for all $t \in \mathbb{R}$ with $\hat{t} < t < \hat{t} + \delta_3$. □

2.4.2 | First approach to boundedness: Gronwall-type arguments

We start with local Lipschitz continuity of G defined in (8) by (9) and (10).

Lemma 5. *The function* $\mathbf{G}$ *defined in (8) by (9) and (10) is locally Lipschitz on every compact set* K *with* $K \subset [0, \infty) \times [0, \infty)$.

Proof. $\mathbf{G} : [0, \infty) \times [0, \infty) \to \mathbb{R}^2$ is continuously differentiable for every open set $U \subset [0, \infty) \times [0, \infty)$. Thus, $\mathbf{G}$ is locally Lipschitz continuous on every compact set K with $K \subset U$ by application of Proposition 3.2.2 from Schaeffer's book.[16] □

Additionally, we state that $\mathbf{G}$ fulfills the assumed inequality in Lemma 4.

Lemma 6. *The function* $\mathbf{G}$ *defined in (8) by (9) and (10) fulfills*

$$\|\mathbf{G}(\mathbf{z}(t))\|_\infty \leq (1 + \beta + \gamma + k_s) \|\mathbf{z}(t)\|_\infty + k_0 \tag{19}$$

for all $\mathbf{z} \in \mathbb{R}^2$ *and for all* $t \in \mathbb{R}$. *Here,* $\|\cdot\|_\infty$ *denotes the maximum norm.*

Proof. Denote $\mathbf{z}(t) = (x(t), y(t))$. We remind ourselves that $\mathbf{G}$ is defined by (9) and (10) and the maximum norm is given by

$$\|(x(t), y(t))\|_\infty := \max\{|x(t)|, |y(t)|\}.$$

Consequently, we investigate

$$\|\mathbf{G}(x(t), y(t))\|_\infty = \max\{|g_1(x(t), y(t))|, |g_2(x(t), y(t))|\}.$$

By applying the triangle inequality, we get

$$\begin{aligned} |g_1(\mathbf{z}(t))| &= |g_1(x(t), y(t))| \\ &= |-\beta x(t) - \gamma x(t) + k_0 + k_s y(t) + f(x(t))\, y(t)| \\ &\leq \beta |x(t)| + \gamma |x(t)| + k_0 + k_s |y(t)| + |y(t)| \\ &\leq (1 + \beta + \gamma + k_s) \|(x(t), y(t))\|_\infty + k_0 \\ &= (1 + \beta + \gamma + k_s) \|\mathbf{z}(t)\|_\infty + k_0 \end{aligned}$$

and

$$\begin{aligned}|g_2(\mathbf{z}(t))| &= |g_2(x(t), y(t))| \\ &= |\gamma x(t) - k_s y(t) - f(x(t))\, y(t)| \\ &\leq \gamma\, |x(t)| + k_s\, |y(t)| + |y(t)| \\ &\leq (1+\gamma+k_s)\, \|(x(t), y(t))\|_\infty \\ &\leq (1+\beta+\gamma+k_s)\, \|\mathbf{z}(t)\|_\infty + k_0.\end{aligned}$$

Thus, we conclude

$$\|\mathbf{G}(\mathbf{z}(t))\|_\infty = \|\mathbf{G}(x(t), y(t))\|_\infty \leq (1+\beta+\gamma+k_s)\, \|\mathbf{z}(t)\|_\infty + k_0$$

and this proves our assertion of inequality (19). □

Finally, we are able to state our boundedness result.

Theorem 5. *Solutions of system (8) are bounded for all times $t \in \mathbb{R}$ and fulfill the inequality*

$$\|\mathbf{z}(t)\|_\infty \leq \|\mathbf{z_0}\|_\infty \cdot \exp((1+\beta+\gamma+k_s)\,|t|) + \frac{k_0\,(\exp((1+\beta+\gamma+k_s)\,|t|) - 1)}{(1+\beta+\gamma+k_s)} \tag{20}$$

for all times $t \in \mathbb{R}$.

Proof. By Lemmas 5 and 6, we know that all assumptions of Lemma 4 are fulfilled. This implies that

$$\|\mathbf{z}(t)\|_\infty \leq \|\mathbf{z_0}\|_\infty \exp((1+\beta+\gamma+k_s)\,|t|) + \frac{k_0\,(\exp((1+\beta+\gamma+k_s)\,|t|) - 1)}{(1+\beta+\gamma+k_s)}$$

holds for all $t \in \mathbb{R}$ which proves our assertion of (20). □

2.4.3 | Second approach to boundedness: Trapping regions

Alternatively, we can use the concept of trapping regions.

Theorem 6. *Define the domain boundary*

$$\begin{aligned}\partial K :=& \left\{(x,y) \in \mathbb{R}^2 \,:\, 0 \leq x \leq N\frac{k_0}{\beta}\left(1 + 2\frac{\gamma}{k_s}\right),\, y = 0\right\} \\ &\cup \left\{(x,y) \in \mathbb{R}^2 \,:\, x = 0,\, 0 \leq y \leq 2N\frac{\gamma k_0}{k_s \beta}\right\} \\ &\cup \left\{(x,y) \in \mathbb{R}^2 \,:\, 0 \leq x \leq N\frac{k_0}{\beta},\, y = 2N\frac{\gamma k_0}{k_s\beta}\right\} \\ &\cup \left\{(x,y) \in \mathbb{R}^2 \,:\, x + y = N\frac{k_0}{\beta}\left(1 + 2\frac{\gamma}{k_s}\right),\, N\frac{k_0}{\beta} \leq x \leq N\frac{k_0}{\beta}\left(1 + 2\frac{\gamma}{k_s}\right)\right\} \\ &= \partial K_1 \cup \partial K_2 \cup \partial K_3 \cup \partial K_4\end{aligned}$$

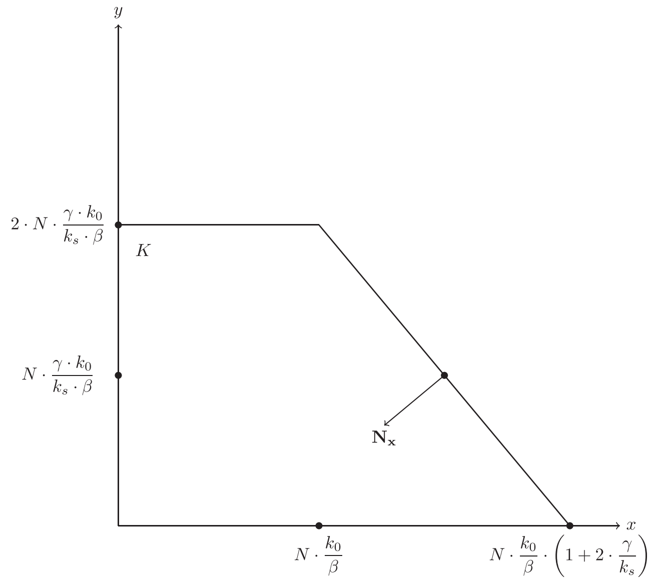
for an arbitrary $N \in \mathbb{N}$. It follows that K is a trapping region for system (8).

Proof. By construction, K is compact. The domain K and an example of an inward pointing normal vector N_x are shown in Figure 2. We have to check that

$$\langle \mathbf{N_x}, \mathbf{G}(\mathbf{x})\rangle_{\mathbb{R}^2\times\mathbb{R}^2} \geq 0$$

holds for all $x \in \partial K$. Thus, we distinguish four cases.

FIGURE 2 A sketch of the trapping region K



Case 1: Let $\mathbf{x} \in \partial K_1$. It holds

$$\langle \mathbf{N_x}, \mathbf{G}(\mathbf{x}) \rangle_{\mathbb{R}^2 \times \mathbb{R}^2} = \left\langle \begin{pmatrix} 0 \\ 1 \end{pmatrix}, \begin{pmatrix} x'(t) \\ y'(t) \end{pmatrix} \right\rangle_{\mathbb{R}^2 \times \mathbb{R}^2}$$
$$= y'(t)$$
$$= \gamma x(t)$$
$$\geq 0,$$

which proves our assertion in this case.

Case 2: Let $\mathbf{x} \in \partial K_2$. We get

$$\langle \mathbf{N_x}, \mathbf{G}(\mathbf{x}) \rangle_{\mathbb{R}^2 \times \mathbb{R}^2} = \left\langle \begin{pmatrix} 1 \\ 0 \end{pmatrix}, \begin{pmatrix} x'(t) \\ y'(t) \end{pmatrix} \right\rangle_{\mathbb{R}^2 \times \mathbb{R}^2}$$
$$= x'(t)$$
$$= k_0 + k_s y(t)$$
$$\geq k_0$$
$$> 0,$$

which finishes this case's proof.

Case 3: Let $\mathbf{x} \in \partial K_3$. This implies

$$\langle \mathbf{N_x}, \mathbf{G}(\mathbf{x}) \rangle_{\mathbb{R}^2 \times \mathbb{R}^2} = \left\langle \begin{pmatrix} 0 \\ -1 \end{pmatrix}, \begin{pmatrix} x'(t) \\ y'(t) \end{pmatrix} \right\rangle_{\mathbb{R}^2 \times \mathbb{R}^2}$$
$$= -y'(t)$$
$$= -\gamma x(t) + k_s y(t) + f(x(t))\, y(t)$$
$$\geq -\gamma x(t) + k_s y(t)$$
$$\geq -\gamma N \frac{k_0}{\beta} + 2 k_s N \frac{\gamma k_0}{k_s \beta}$$
$$= N\gamma \frac{k_0}{\beta}$$
$$> 0$$

from which we conclude our assertion in this case.

Case 4: Let $\mathbf{x} \in \partial K_4$. This yields

$$\begin{aligned}\langle \mathbf{N_x}, \mathbf{G}(\mathbf{x}) \rangle_{\mathbb{R}^2\times\mathbb{R}^2} &= \left\langle \begin{pmatrix} -1 \\ -1 \end{pmatrix}, \begin{pmatrix} x'(t) \\ y'(t) \end{pmatrix} \right\rangle_{\mathbb{R}^2\times\mathbb{R}^2} \\ &= -x'(t) - y'(t) \\ &= \beta x(t) - k_0 \\ &\geq \beta N \frac{k_0}{\beta} - k_0 \\ &= (N-1)\, k_0 \\ &\geq 0,\end{aligned}$$

and our final case is proved. □

As $N \in \mathbb{N}$ in our aforementioned theorem can be any arbitrary natural number, we are always able to define trapping regions K for arbitrary nonnegative initial values x_0 and y_0.

2.5 | Global unique solvability

All our foregoing results can be summarized in our main Theorem.

Theorem 7. *We consider the initial value problem (8) where the functions $g_1, g_2 : \mathbb{R}^2 \to \mathbb{R}$ are given by (9) and (10). Then, this initial value problem has a unique nonnegative solution which exists for all $t \geq 0$ and is bounded above according to (20).*

2.6 | Stability analysis

Again, we consider the initial value problem

$$\mathbf{z}'(t) = \begin{pmatrix} x'(t) \\ y'(t) \end{pmatrix} = \begin{pmatrix} -\beta x(t) - \gamma x(t) + k_0 + k_s y(t) + f(x(t))\, y(t) \\ \gamma x(t) - k_s y(t) - f(x(t))\, y(t) \end{pmatrix} = \begin{pmatrix} g_1(x(t), y(t)) \\ g_2(x(t), y(t)) \end{pmatrix} = \mathbf{G}(\mathbf{z}(t)) \tag{21}$$

with initial conditions

$$\mathbf{z}(0) = \begin{pmatrix} x(0) \\ y(0) \end{pmatrix} = \begin{pmatrix} x_0 \\ y_0 \end{pmatrix}. \tag{22}$$

Now, we are interested in stationary points of the vector field $\mathbf{G}$. This means that we want to find $\mathbf{z}^\star = (x^\star, y^\star)$ such that

$$\mathbf{G}(\mathbf{z}^\star) = \begin{pmatrix} g_1(x^\star, y^\star) \\ g_2(x^\star, y^\star) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix} \tag{23}$$

holds.

Lemma 7. *A stationary point of the vector field $\mathbf{G}$ is given by*

$$\mathbf{z}_s = \begin{pmatrix} x_s \\ y_s \end{pmatrix} = \begin{pmatrix} \frac{k_0}{\beta} \\ \frac{\gamma k_0}{\beta k_s + \beta f\left(\frac{k_0}{\beta}\right)} \end{pmatrix}. \tag{24}$$

Proof. We have to investigate the nonlinear system

$$\begin{aligned} -\beta x_s - \gamma x_s + k_0 + k_s y_s + f(x_s)\, y_s &= 0, \\ \gamma x_s - k_s y_s - f(x_s)\, y_s &= 0 \end{aligned}$$

of equations from (23). The second equation implies

$$k_s y_s + f(x_s)\, y_s = \gamma x_s$$

and plugging this result into our first equation yields

$$k_0 - \beta x_s = 0.$$

Thus, we infer

$$x_s = \frac{k_0}{\beta}.$$

As it holds

$$y_s = \frac{\gamma x_s}{k_s + f(x_s)}$$

from our second equation, we conclude that

$$y_s = \frac{\gamma k_0}{\beta k_s + \beta f\left(\frac{k_0}{\beta}\right)}$$

is valid. This proves (24). □

We further follow the lines of Layton's book[1] on pages 133–135. Let J denote the Jacobian of our system and I the identity matrix. As the oscillatory behavior of the system depends on the eigenvalues λ of the Jacobian J at stationary points, we consider the characteristic equation

$$\det(J - \lambda I) = 0.$$

Thus, we compute the Jacobian

$$J = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} = \begin{pmatrix} \frac{\partial g_1(x,y)}{\partial x} & \frac{\partial g_1(x,y)}{\partial y} \\ \frac{\partial g_2(x,y)}{\partial x} & \frac{\partial g_2(x,y)}{\partial y} \end{pmatrix}$$
$$= \begin{pmatrix} -\beta - \gamma + f'(x)y & k_s + f(x) \\ \gamma - f'(x)y & -k_s - f(x) \end{pmatrix}$$

and evaluating the Jacobian at (x_s, y_s) leads to

$$J_s = \begin{pmatrix} -\beta - \gamma + f'\left(\frac{k_0}{\beta}\right) \frac{\gamma k_0}{\beta k_s + \beta f\left(\frac{k_0}{\beta}\right)} & k_s + f\left(\frac{k_0}{\beta}\right) \\ \gamma - f'\left(\frac{k_0}{\beta}\right) \frac{\gamma k_0}{\beta k_s + \beta f\left(\frac{k_0}{\beta}\right)} & -k_s - f\left(\frac{k_0}{\beta}\right) \end{pmatrix}.$$

Consequently, the matrix $J_s - \lambda \cdot I$ reads

$$J_s - \lambda \cdot I = \begin{pmatrix} -\beta - \gamma + f'\left(\frac{k_0}{\beta}\right) \frac{\gamma k_0}{\beta k_s + \beta f\left(\frac{k_0}{\beta}\right)} - \lambda & k_s + f\left(\frac{k_0}{\beta}\right) \\ \gamma - f'\left(\frac{k_0}{\beta}\right) \frac{\gamma k_0}{\beta k_s + \beta f\left(\frac{k_0}{\beta}\right)} & -k_s - f\left(\frac{k_0}{\beta}\right) - \lambda \end{pmatrix}.$$

We get

$$\det(J_s-\lambda I) = \det\begin{pmatrix} -\beta-\gamma+f'\left(\frac{k_0}{\beta}\right)\frac{\gamma k_0}{\beta k_s+\beta f\left(\frac{k_0}{\beta}\right)}-\lambda & k_s+f\left(\frac{k_0}{\beta}\right) \\ \gamma-f'\left(\frac{k_0}{\beta}\right)\frac{\gamma k_0}{\beta k_s+\beta f\left(\frac{k_0}{\beta}\right)} & -k_s-f\left(\frac{k_0}{\beta}\right)-\lambda \end{pmatrix}$$

$$= \left(-\beta-\gamma+f'\left(\frac{k_0}{\beta}\right)\frac{\gamma k_0}{\beta k_s+\beta f\left(\frac{k_0}{\beta}\right)}-\lambda\right)\left(-k_s-f\left(\frac{k_0}{\beta}\right)-\lambda\right)$$

$$-\left(\gamma-f'\left(\frac{k_0}{\beta}\right)\frac{\gamma k_0}{\beta k_s+\beta f\left(\frac{k_0}{\beta}\right)}\right)\left(k_s+f\left(\frac{k_0}{\beta}\right)\right).$$

Summarizing all terms, we end up with the characteristic equation

$$\begin{aligned}\det(J_s-\lambda I) &= \lambda^2+\lambda\left(\beta+\gamma+k_s+f\left(\frac{k_0}{\beta}\right)-f'\left(\frac{k_0}{\beta}\right)\frac{\gamma k_0}{\beta k_s+\beta f\left(\frac{k_0}{\beta}\right)}\right) \\ &\quad+\left(\beta k_s+\beta f\left(\frac{k_0}{\beta}\right)\right) \\ &= \lambda^2-\lambda\underbrace{\left(f'\left(\frac{k_0}{\beta}\right)\frac{\gamma k_0}{\beta k_s+\beta f\left(\frac{k_0}{\beta}\right)}-\beta-\gamma-k_s-f\left(\frac{k_0}{\beta}\right)\right)}_{=:b} \\ &\quad+\underbrace{\left(\beta k_s+\beta f\left(\frac{k_0}{\beta}\right)\right)}_{=:c} \\ &= \lambda^2-\lambda b+c \\ &= 0.\end{aligned} \tag{25}$$

The solutions for the eigenvalues λ read

$$\lambda = \frac{b\pm\sqrt{b^2-4c}}{2}.$$

As $c>0$ in all cases, we have to distinguish the two cases $b^2<4c$ and $b^2\geq 4c$.

- If $b^2<4c$, we have a pair of complex conjugates. Its real part equals $\frac{b}{2}$ and thus, the system is stable if $b<0$ and unstable if $b>0$.
- If $b^2\geq 4c$, both solutions are real and have the same sign as b. Again, the system is stable if $b<0$ and unstable if $b>0$.

Finally, we can state our main Theorem regarding stability.

Theorem 8. *The nonlinear system is stable if $b<0$ and is unstable if $b>0$.*

2.7 | Numerical experiments

We apply the function ODE15S of GNU Octave Version 5.1.0.[26] For further information on ODE15S, we refer the reader to the work of Shampine and Reichelt.[27] Our short computation code reads

```
% Computation of System of Nonlinear First−Order Differential
% Equations for Ca^2+−Levels in Renal Vascular Smooth Muscle Cells
% as presented in our work on Qualitative Analysis on those
% Systems

% Definition of Parameters and ODE System

function r = renal_ode (t,z)
  alpha = 1.0;
  beta  = 1.0;
  gamma = 1.0;
  k_0   = 1.0;
  k_s   = 1.0;
  n     = 2.0;

% For presentational purpose, the first ODE is here split up into
% two lines of code

  r     = [−beta∗z(1)−gamma∗z(1)+k_0+
          k_s∗z(2)+((z(1))^n)/(alpha^n+(z(1))^n)∗z(2)
          gamma∗z(1)−k_s∗z(2)−((z(1))^n)/(alpha^n+(z(1))^n)∗z(2)];
endfunction

% Solution of system

[t,z] = ode15s(@renal_ode, [0, 50], [10; 2]);
```

and is given for completeness of presentation.

2.7.1 | Example of a stable solution

In this example, our parameters are set by $\alpha = 1.0$, $\beta = 1.0$, $\gamma = 1.0$, $k_0 = 1.0$, $k_s = 1.0$, and $n = 2$ with initial conditions $x_0 = 10$ and $y_0 = 2$. Our final simulation time T is $T = 50$. We use the transfer rate function as defined in (7). The corresponding vector field is plotted in Figure 3. The resulting solution can be seen in Figure 4.

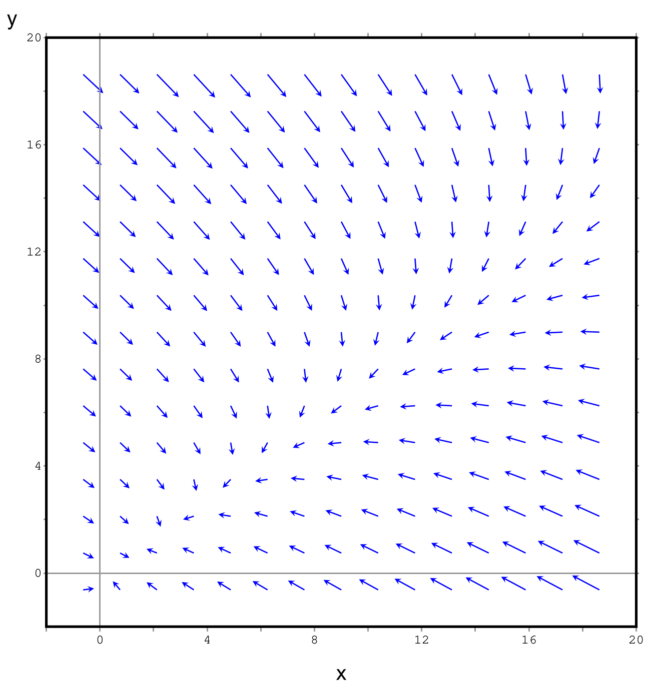


FIGURE 3 A plot of the vector field **G** for the example in Section 2.7.1 [Colour figure can be viewed at wileyonlinelibrary.com]

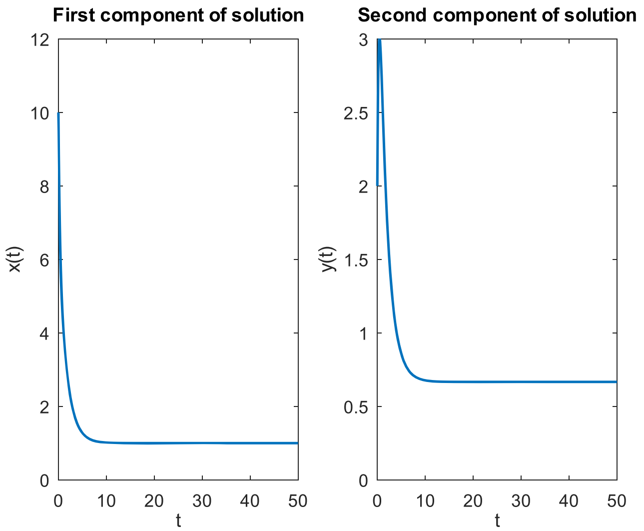


FIGURE 4 A plot of the stable solution components for the example in Section 2.7.1 [Colour figure can be viewed at wileyonlinelibrary.com]

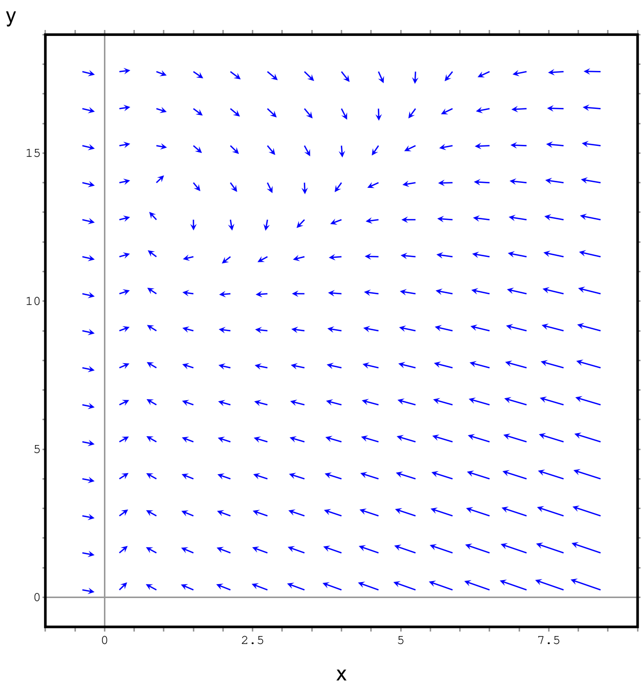


FIGURE 5 A plot of the vector field **G** for the example in Section 2.7.2 [Colour figure can be viewed at wileyonlinelibrary.com]

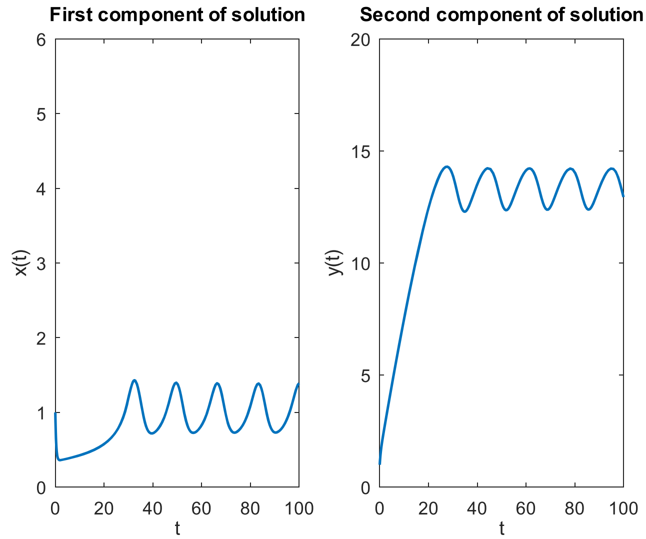
As the constant b in our characteristic Equation (25) is $b = -\frac{11}{12} < 0$, we expect the solution to be stable as shown in Figure 4.

2.7.2 | Example of an oscillatory solution

In this example, our parameters are set by $\alpha = 2.5$, $\beta = 1.0$, $\gamma = 2.0$, $k_0 = 1.0$, $k_s = 0.01$, and $n = 2$ with initial conditions $x_0 = 1$ and $y_0 = 1$. Our final simulation time T is $T = 100$. We use the transfer rate function as defined in (7). The corresponding vector field is plotted in Figure 5. The resulting solution can be seen in Figure 6.

As the constant b in our characteristic Equation (25) is $b = 0.0673 > 0$, we expect an oscillatory solution as depicted in Figure 6. Under a given trapping region K for nonnegative initial values x_0 and y_0, we can deduce by Bendixson's Theorem that K must contain a closed orbit.

FIGURE 6 A plot of the unstable solution components for the example in Section 2.7.2 [Colour figure can be viewed at wileyonlinelibrary.com]



3 | SECOND SYSTEM: Ca^{2+} LEVELS IN LIVER CELLS

3.1 | Model equations

Our model equations read

$$\begin{cases} x'(t) = k_1 + k_2 x(t) - k_3 \dfrac{x(t)y(t)}{x(t)+k_4} - k_5 \dfrac{x(t)z(t)}{x(t)+k_6}, \\ y'(t) = k_7 x(t) - k_8 \dfrac{y(t)}{y(t)+k_9}, \\ z'(t) = k_{10} x(t) - k_{11} \dfrac{z(t)}{z(t)+k_{12}}, \\ x(0) = x_0, \\ y(0) = y_0, \\ z(0) = z_0, \end{cases} \tag{26}$$

where we seek three continuously differentiable functions $x, y, z : [0, \infty) \to \mathbb{R}$ with positive model parameters $k_1, \ldots, k_{12}$ and nonnegative initial conditions x_0, y_0, z_0. Here, x denotes concentration of a certain G-protein, y represents concentration of phospholipase C (GLC), and z stands for Ca^{2+}-concentrations. For further details, we refer interested readers to Kummer's work.[3]

3.2 | Local unique solvability

We define a vector-valued function $\mathbf{H} : \mathbb{R}^3 \to \mathbb{R}^3$ by

$$\mathbf{H}\left(\begin{pmatrix} x(t) \\ y(t) \\ z(t) \end{pmatrix}\right) = \begin{pmatrix} h_1(x(t), y(t), z(t)) \\ h_2(x(t), y(t), z(t)) \\ h_3(x(t), y(t), z(t)) \end{pmatrix}$$

with right-hand side functions

$$h_1(x(t), y(t), z(t)) = k_1 + k_2 x(t) - k_3 \frac{x(t)y(t)}{x(t)+k_4} - k_5 \frac{x(t)z(t)}{x(t)+k_6}, \tag{27}$$

$$h_2(x(t), y(t), z(t)) = k_7 x(t) - k_8 \frac{y(t)}{y(t)+k_9}, \tag{28}$$

$$h_3(x(t), y(t), z(t)) = k_{10} x(t) - k_{11} \frac{z(t)}{z(t)+k_{12}}. \tag{29}$$

As our model parameters $k_1, \dots, k_{12}$ are all positive and our initial conditions are nonnegative, there exists a small neighborhood around the zero vector such that our vector-valued right-hand side function $\mathbf{H}$ restricted to this neighborhood is locally Lipschitz continuous as a product and sum of continuously differentiable functions. As a result, we get local unique solvability by Picard–Lindelöf 's Theorem.

Lemma 8. *There exists a neighborhood around the zero vector such that* $\boldsymbol{H}$ *restricted to this neighborhood is locally Lipschitz continuous. By Picard–Lindelöf 's Theorem, this yields local unique solvability of system (26).*

3.3 | Nonnegativity and boundedness

3.3.1 | Nonnegativity

Analogously to Theorem 4, we achieve nonnegativity of solutions.

Theorem 9. *Consider (26) under nonnegative initial values* x_0, y_0, z_0 *and positive constants* k_j *for all* $j \in \{1, 2, \dots, 12\}$. *With respect to Lemma 8, this solution remains nonnegative.*

Proof. We have to distinguish three cases.

Case 1: Let $x(0) = 0$ and $0 \le y(0), z(0) \le \infty$. This yields

$$x'(0) = k_1 > 0,$$
$$y'(0) = -k_8 \frac{y(0)}{y(0) + k_9},$$
$$z'(0) = -k_{11} \frac{z(0)}{z(0) + k_{12}},$$

and we get a small time $\varepsilon > 0$ such that $x(t), y(t), z(t)$ remain nonnegative by continuously differentiability of these functions for all $t \in [0, \varepsilon]$.

Case 2: Let $y(0) = 0$ and $0 \le x(0), z(0) \le \infty$. This implies

$$x'(0) = k_1 + k_2 x(0) - k_5 \frac{x(0)z(0)}{x(0) + k_6},$$
$$y'(0) = k_7 x(0) \ge 0,$$
$$z'(0) = k_{10} x(0) - k_{11} \frac{z(0)}{z(0) + k_{12}}$$

which results in the existence of a small time $\varepsilon > 0$ such that $x(t), y(t), z(t)$ remain nonnegative by continuously differentiability of these functions for all $t \in [0, \varepsilon]$.

Case 3: Let $z(0) = 0$ and $0 \le x(0), y(0) \le \infty$. We have

$$x'(0) = k_1 + k_2 x(0) - k_3 \frac{x(0)y(0)}{y(0) + k_4},$$
$$y'(0) = k_7 x(0) - k_8 \frac{y(0)}{y(0) + k_9},$$
$$z'(0) = k_{10} x(0) \ge 0.$$

We conclude the existence of a small time $\varepsilon > 0$ such that $x(t), y(t), z(t)$ remain nonnegative by continuously differentiability of these functions for all $t \in [0, \varepsilon]$.

Hence, we conclude that these arguments can be established on sequent time intervals such that solutions remain nonnegative for all times $t \ge 0$. This finishes our proof. □

We infer that the nonnegative orthant is a positively invariant set for system (26).

3.3.2 | Boundedness

We follow the lines of Lemma 6.

Lemma 9. *The function* $\mathbf{H}$ *defined in (27)–(29) fulfills*

$$\|\mathbf{H}(\mathbf{z}(t))\|_\infty \leq \max\{k_2+k_3+k_5; k_7; k_{10}\}\,\|\mathbf{z}(t)\|_\infty + \max\{k_1; k_8; k_{11}\} \tag{30}$$

for all $\mathbf{z} \in ([0,\infty))^3$ *and for all* $t \in \mathbb{R}$. *Here,* $\|\cdot\|_\infty$ *denotes the maximum norm.*

Proof. Denote $\mathbf{z}(t) = (x(t), y(t), z(t))$. We remind ourselves that $\mathbf{H}$ is defined by (27)–(29), and the maximum norm is given by

$$\|(x(t), y(t), z(t))\|_\infty := \max\{|x(t)|, |y(t)|, |z(t)|\}.$$

Consequently, we investigate

$$\|\mathbf{H}(x(t), y(t), z(t))\|_\infty = \max\{|h_1(x(t), y(t), z(t))|, |h_2(x(t), y(t), z(t))|, |h_3(x(t), y(t), z(t))|\}.$$

By applying the triangle inequality, we get

$$\begin{aligned}
|h_1(\mathbf{z}(t))| &= |h_1(x(t), y(t), z(t))| \\
&= \left|k_1 + k_2 x(t) - k_3\frac{x(t)y(t)}{x(t)+k_4} - k_5\frac{x(t)z(t)}{x(t)+k_6}\right| \\
&\leq k_1 + k_2|x(t)| + k_3|y(t)| + k_5|z(t)|, \\
|h_2(\mathbf{z}(t))| &= |h_2(x(t), y(t), z(t))| \\
&= \left|k_7 x(t) - k_8\frac{y(t)}{y(t)+k_9}\right| \\
&\leq k_7 \cdot |x(t)| + k_8
\end{aligned}$$

and

$$\begin{aligned}
|h_3(\mathbf{z}(t))| &= |h_3(x(t), y(t), z(t))| \\
&= \left|k_{10} x(t) - k_{11}\frac{z(t)}{z(t)+k_{12}}\right| \\
&\leq k_{10} \cdot |x(t)| + k_{11}.
\end{aligned}$$

Thus, we conclude

$$\|\mathbf{H}(\mathbf{z}(t))\|_\infty \leq \max\{k_2+k_3+k_5; k_7; k_{10}\}\,\|\mathbf{z}(t)\|_\infty + \max\{k_1; k_8; k_{11}\}$$

and this finishes our assertion. □

A direction consequence of this result is the following theorem on global boundedness by application of Gronwall's Lemma.

Theorem 10. *Solutions of system (26) are bounded according to the inequality*

$$\|\mathbf{z}(t)\|_\infty \leq \|\mathbf{z_0}\|_\infty \exp(\max\{k_2+k_3+k_5; k_7; k_{10}\}\,|t|) + \frac{\max\{k_1; k_8; k_{11}\}(\exp(\max\{k_2+k_3+k_5; k_7; k_{10}\}\,|t|) - 1)}{\max\{k_2+k_3+k_5; k_7; k_{10}\}}. \tag{31}$$

3.4 | Global unique solvability

By applying Theorems 9 and 10, we conclude the following result.

Theorem 11. *We consider the initial value problem (26)*

$$\begin{cases} \mathbf{z}'(t) = \mathbf{H}(\mathbf{z}(t)), \\ \mathbf{z}(0) = \mathbf{z_0} \end{cases}$$

and define $\mathbf{z}(t) = (x(t), y(t), z(t))$ *and* $\mathbf{H}(\mathbf{z}(t)) = (h_1(x(t), y(t), z(t)), h_2(x(t), y(t), z(t)), h_3(x(t), y(t), z(t)))$. *Here, the functions* $h_1, h_2, h_3 : \mathbb{R}^3 \to \mathbb{R}$ *are given by (27)–(29). Assume nonnegative initial values* x_0, y_0, z_0 *and positive constants* k_j *for all* $j \in \{1, 2, \dots, 12\}$. *Then, this initial value problem has a unique nonnegative solution which exists for all* $t \geq 0$.

3.5 | Some results on stability analysis

We want to remark that stability analysis for higher-dimensional dynamical system becomes more delicate. We begin with existence of equilibrium states of our system (26) with nonnegative initial values $x_0,\ y_0,\ z_0$ and positive constants k_j for all $j \in \{1, 2, \dots, 12\}$.

3.5.1 | Existence and uniqueness of equilibrium states

We denote equilibrium states by $\mathbf{z}_s = (x_s, y_s, z_s)$. For these stationary points of our system (26), we obtain the system

$$\begin{cases} k_1 + k_2 x_s - k_3 \frac{x_s y_s}{x_s + k_4} - k_5 \frac{x_s z_s}{x_s + k_6} = 0, \\ k_7 x_s - k_8 \frac{y_s}{y_s + k_9} = 0, \\ k_{10} x_s - k_{11} \frac{z_s}{z_s + k_{12}} = 0 \end{cases} \tag{32}$$

of nonlinear equations. From the last two equations, we conclude

$$y_s = \frac{k_7 k_9 x_s}{k_8 - k_7 x_s} \tag{33}$$

and

$$z_s = \frac{k_{10} k_{12} x_s}{k_{11} - k_{10} x_s}. \tag{34}$$

Plugging these results (33) and (34) into the first equation of (32), we have to investigate

$$k_1 + k_2 x_s - \frac{k_3 k_7 k_9 x_s^2}{(x_s + k_4)(k_8 - k_7 x_s)} - \frac{k_5 k_{10} k_{12} x_s^2}{(x_s + k_6)(k_{11} - k_{10} x_s)} = 0.$$

We define the function

$$q : \mathbb{R} \backslash \left\{ \frac{k_8}{k_7}, \frac{k_{11}}{k_{10}} \right\} \to \mathbb{R},\ x_s \mapsto k_1 + k_2 x_s - \frac{k_3 k_7 k_9 x_s^2}{(x_s + k_4)(k_8 - k_7 x_s)} - \frac{k_5 k_{10} k_{12} x_s^2}{(x_s + k_6)(k_{11} - k_{10} x_s)}. \tag{35}$$

Theorem 12. *Let all constants* k_j *be positive for all* $j \in \{1, 2, \dots, 12\}$ *and all initial values* $x_0,\ y_0,\ z_0$ *be nonnegative. Then all equilibrium states of our system (26) can be written as*

$$\mathbf{z}_s = \begin{pmatrix} x_s \\ y_s \\ z_s \end{pmatrix} = \begin{pmatrix} x_s \\ \frac{k_7 k_9 x_s}{k_8 - k_7 x_s} \\ \frac{k_{10} k_{12} x_s}{k_{11} - k_{10} x_s} \end{pmatrix} \tag{36}$$

with $x_s \in \left(0, \min\left\{\frac{k_8}{k_7}, \frac{k_{11}}{k_{10}}\right\}\right)$.

Proof. As our initial values are nonnegative, Theorem 9 implies nonnegativity of solutions for all times $t \geq 0$ and we conclude that $x_s \geq 0$ follows. Furthermore, it must hold $x_s < \min\left\{\frac{k_8}{k_7}, \frac{k_{11}}{k_{10}}\right\}$. If we assume $x_s > \min\left\{\frac{k_8}{k_7}, \frac{k_{11}}{k_{10}}\right\}$, we then obtain $y_s < 0$ or $z_s < 0$ by (33) and (34). Hence, we conclude that all interesting equilibrium states for our system (26) need to have $x_s \in \left(0, \min\left\{\frac{k_8}{k_7}, \frac{k_{11}}{k_{10}}\right\}\right)$. Finally, we prove that at least one $x_s \in \left(0, \min\left\{\frac{k_8}{k_7}, \frac{k_{11}}{k_{10}}\right\}\right)$ exists such that we obtain an equilibrium state of type (36). We consider our function q defined by (35). On the one hand, it holds $q(0) = k_1 > 0$. On the other hand, by denoting $E := \min\left\{\frac{k_8}{k_7}, \frac{k_{11}}{k_{10}}\right\}$ in this proof, we notice that

$$\lim_{x_s \to E} q\left(x_s\right) = -\infty$$

is valid. By continuity of our function q defined by (35) and application of the intermediate value theorem, we conclude existence of at least one $x_s \in \left(0, \min\left\{\frac{k_8}{k_7}, \frac{k_{11}}{k_{10}}\right\}\right)$ such that the first equation of (32) is fulfilled. Hence, this proves our assertion. □

Furthermore, we can establish a sufficient condition for uniqueness of equilibrium states.

Theorem 13. *Let all constants k_j be positive for all $j \in \{1, 2, \ldots, 12\}$ and all initial values x_0, y_0, z_0 be nonnegative. Then our system (26) has a unique equilibrium point.*

Proof. Consider

$$k_1 + k_2 x_s - x_s \left\{ \frac{k_3 k_7 k_9 x_s}{\left(x_s + k_4\right)\left(k_8 - k_7 x_s\right)} + \frac{k_5 k_{10} k_{12} x_s}{\left(x_s + k_6\right)\left(k_{11} - k_{10} x_s\right)} \right\} = 0,$$

which is equivalent to

$$k_1 + k_2 x_s = x_s \left\{ \frac{k_3 k_7 k_9 x_s}{\left(x_s + k_4\right)\left(k_8 - k_7 x_s\right)} + \frac{k_5 k_{10} k_{12} x_s}{\left(x_s + k_6\right)\left(k_{11} - k_{10} x_s\right)} \right\}. \tag{37}$$

We define

$$r : \left[0, \min\left\{\frac{k_8}{k_7}, \frac{k_{11}}{k_{10}}\right\}\right) \to \mathbb{R},\ r\left(x_s\right) = \frac{k_3 k_7 k_9 x_s}{\left(x_s + k_4\right)\left(k_8 - k_7 x_s\right)} + \frac{k_5 k_{10} k_{12} x_s}{\left(x_s + k_6\right)\left(k_{11} - k_{10} x_s\right)}.$$

Obviously, $r(0) = 0$ and it holds $\lim_{x \to E} r(x) = +\infty$ for $E := \min\left\{\frac{k_8}{k_7}, \frac{k_{11}}{k_{10}}\right\}$. Differentiation of this function yields

$$\begin{aligned} r'\left(x_s\right) &= k_3 k_7 k_9 ((x_s + k_4)(k_8 - k_7 x_s))^{-1} + k_3 k_7 k_9 x_s (-1)\left\{(k_8 - k_7 x_s) - k_7 (x_s + k_4)\right\}((x_s + k_4)(k_8 - k_7 x_s))^{-2} \\ &\quad + k_5 k_{10} k_{12} ((x_s + k_6)(k_{11} - k_{10} x_s))^{-1} + k_5 k_{10} k_{12} x_s (-1)\left\{(k_{11} - k_{10} x_s) - k_{10}(x_s + k_6)\right\}((x_s + k_6)(k_{11} - k_{10} x_s))^{-2} \\ &= \frac{k_3 k_7 k_9 \left\{(x_s + k_4)(k_8 - k_7 x_s) + \left(2 k_7 x_s^2 + k_4 k_7 x_s - k_8 x_s\right)\right\}}{(x_s + k_4)^2 (k_8 - k_7 x_s)^2} \\ &\quad + \frac{k_5 k_{10} k_{12} \left\{(x_s + k_6)(k_{11} - k_{10} x_s) + \left(2 k_{10} x_s^2 + k_6 k_{10} x_s - k_{11} x_s\right)\right\}}{(x_s + k_6)^2 (k_{11} - k_{10} x_s)^2} \\ &= \frac{k_3 k_7 k_9 \left(k_7 x_s^2 + k_4 k_8\right)}{(x_s + k_4)^2 (k_8 - k_7 x_s)^2} + \frac{k_5 k_{10} k_{12} \left(k_{10} x_s^2 + k_6 k_{11}\right)}{(x_s + k_6)^2 (k_{11} - k_{10} x_s)^2} \\ &> 0 \end{aligned}$$

for all $x_s \in \left(0, \min\left\{\frac{k_8}{k_7}, \frac{k_{11}}{k_{10}}\right\}\right)$. At first, the second derivative of r reads

$$\begin{aligned}
r''(x_s) &= k_3k_7k_9(2k_7x_s)(x_s+k_4)^{-2}(k_8-k_7x_s)^{-2} \\
&\quad + k_3k_7k_9\left(k_7x_s^2+k_4k_8\right)(-2)(x_s+k_4)^{-3}(k_8-k_7x_s)^{-2} \\
&\quad + k_3k_7k_9\left(k_7x_s^2+k_4k_8\right)(x_s+k_4)^{-2}(2k_7)(k_8-k_7x_s)^{-3} \\
&\quad + k_5k_{10}k_{12}(2k_{10}x_s)(x_s+k_6)^{-2}(k_{11}-k_{10}x_s)^{-2} \\
&\quad + k_5k_{10}k_{12}\left(k_{10}x_s^2+k_6k_{11}\right)(-2)(x_s+k_6)^{-3}(k_{11}-k_{10}x_s)^{-2} \\
&\quad + k_5k_{10}k_{12}\left(k_{10}x_s^2+k_6k_{11}\right)(x_s+k_6)^{-2}(2k_{10})(k_{11}-k_{10}x_s)^{-3} \\
&= 2k_3k_7k_9(x_s+k_4)^{-3}(k_8-k_7x_s)^{-3}\{k_7x_s(x_s+k_4)(k_8-k_7x_s) \\
&\quad -\left(k_7x_s^2+k_4k_8\right)(k_8-k_7x_s)+k_7\left(k_7x_s^2+k_4k_8\right)(x_s+k_4)\} \\
&\quad + 2k_5k_{10}k_{12}(x_s+k_6)^{-3}(k_{11}-k_{10}x_s)^{-3}\{k_{10}x_s(x_s+k_6)(k_{11}-k_{10}x_s) \\
&\quad -\left(k_{10}x_s^2+k_6k_{11}\right)(k_{11}-k_{10}x_s)+k_{10}\left(k_{10}x_s^2+k_6k_{11}\right)(x_s+k_6)\}.
\end{aligned}$$

Some manipulations show

$$\begin{aligned}
&k_7x_s(x_s+k_4)(k_8-k_7x_s)-\left(k_7x_s^2+k_4k_8\right)(k_8-k_7x_s)+k_7\left(k_7x_s^2+k_4k_8\right)(x_s+k_4) \\
&= k_4^2k_7k_8+k_7^2x_s^3+3k_4k_7k_8x_s-k_4k_8^2
\end{aligned}$$

and

$$\begin{aligned}
&k_{10}x_s(x_s+k_6)(k_{11}-k_{10}x_s)-\left(k_{10}x_s^2+k_6k_{11}\right)(k_{11}-k_{10}x_s)+k_{10}\left(k_{10}x_s^2+k_6k_{11}\right)(x_s+k_6) \\
&= k_6^2k_{10}k_{11}+k_{10}^2x_s^3+3k_6k_{10}k_{11}x_s-k_6k_{11}^2.
\end{aligned}$$

Both results are confirmed by Mathematica through SIMPLIFY. Hence, we obtain

$$\begin{aligned}
r''(x_s) &= 2k_3k_7k_9(x_s+k_4)^{-3}(k_8-k_7x_s)^{-3}\left(k_4^2k_7k_8+k_7^2x_s^3+3k_4k_7k_8x_s-k_4k_8^2\right) \\
&\quad + 2k_5k_{10}k_{12}(x_s+k_6)^{-3}(k_{11}-k_{10}x_s)^{-3}\left(k_6^2k_{10}k_{11}+k_{10}^2x_s^3+3k_6k_{10}k_{11}x_s-k_6k_{11}^2\right).
\end{aligned}$$

Now, we define

$$v : \left[0, \min\left\{\frac{k_8}{k_7}, \frac{k_{11}}{k_{10}}\right\}\right) \to \mathbb{R},\ v(x_s) = x_s r(x_s).$$

It holds

$$\begin{aligned}
v''(x_s) &= 2r'(x_s)+x_sr''(x_s) \\
&= 2k_3k_7k_9\left(k_7x_s^2+k_4k_8\right)(x_s+k_4)^{-2}(k_8-k_7x_s)^{-2} \\
&\quad + 2k_5k_{10}k_{12}\left(k_{10}x_s^2+k_6k_{11}\right)(x_s+k_6)^{-2}(k_{11}-k_{10}x_s)^{-2} \\
&\quad + 2x_sk_3k_7k_9(x_s+k_4)^{-3}(k_8-k_7x_s)^{-3}\left(k_4^2k_7k_8+k_7^2x_s^3+3k_4k_7k_8x_s-k_4k_8^2\right) \\
&\quad + 2x_sk_5k_{10}k_{12}(x_s+k_6)^{-3}(k_{11}-k_{10}x_s)^{-3}\left(k_6^2k_{10}k_{11}+k_{10}^2x_s^3+3k_6k_{10}k_{11}x_s-k_6k_{11}^2\right) \\
&= 2k_3k_7k_9(x_s+k_4)^{-3}(k_8-k_7x_s)^{-3}\left\{\left(k_7x_s^2+k_4k_8\right)(x_s+k_4)(k_8-k_7x_s)\right. \\
&\quad \left.+x_s\left(k_4^2k_7k_8+k_7^2x_s^3+3k_4k_7k_8x_s-k_4k_8^2\right)\right\} \\
&\quad + 2k_5k_{10}k_{12}(x_s+k_6)^{-3}(k_{11}-k_{10}x_s)^{-3}\left\{\left(k_{10}x_s^2+k_6k_{11}\right)(x_s+k_6)(k_{11}-k_{10}x_s)\right. \\
&\quad \left.+x_s\left(k_6^2k_{10}k_{11}+k_{10}^2x_s^3+3k_6k_{10}k_{11}x_s-k_6k_{11}^2\right)\right\}.
\end{aligned}$$

Again, some manipulations show

$$\begin{aligned}&\left(k_7x_s^2+k_4k_8\right)(x_s+k_4)(k_8-k_7x_s)+x_s\left(k_4^2k_7k_8+k_7^2x_s^3+3k_4k_7k_8x_s-k_4k_8^2\right)\\&=k_4^2k_8^2+k_7k_8x_s^3+k_4k_7x_s^2\underbrace{(3k_8-k_7x_s)}_{>0}\end{aligned}$$

and

$$\begin{aligned}&\left(k_{10}x_s^2+k_6k_{11}\right)(x_s+k_6)(k_{11}-k_{10}x_s)+x_s\left(k_6^2k_{10}k_{11}+k_{10}^2x_s^3+3k_6k_{10}k_{11}x_s-k_6k_{11}^2\right)\\&=k_6^2k_{11}^2+k_{10}k_{11}x_s^3+k_6k_{10}x_s^2\underbrace{(3k_{11}-k_{10}x_s)}_{>0}\end{aligned}$$

as $k_8-k_7x_s>0$ and $k_{11}-k_{10}x_s>0$ hold due to $x_s\in\left(0,\min\left\{\frac{k_8}{k_7},\frac{k_{11}}{k_{10}}\right\}\right)$ by applying SIMPLIFY from Mathematica. Thus, $v''(x_s)>0$ is valid for all $x_s\in\left(0,\min\left\{\frac{k_8}{k_7},\frac{k_{11}}{k_{10}}\right\}\right)$. This implies that the left-hand side function and right-hand side function of (37) only intersect once on $\left(0,\min\left\{\frac{k_8}{k_7},\frac{k_{11}}{k_{10}}\right\}\right)$ due to convexity of v. Hence, our assertion is proven. □

3.5.2 | Computational stability analysis

Now, we consider our right-hand side function $\mathbf{H}$ of our system (26) which is defined by (27)–(29). For abbreviation, we neglect time dependence of $x(t),\ y(t),\ z(t)$ and simply write $x,\ y,\ z$. The Jacobian of $\mathbf{H}$ reads

$$\begin{aligned}J_{\mathbf{H}}(x,y,z)&=\begin{pmatrix}\frac{\partial h_1}{\partial x}(x,y,z)&\frac{\partial h_1}{\partial y}(x,y,z)&\frac{\partial h_1}{\partial z}(x,y,z)\\\frac{\partial h_2}{\partial x}(x,y,z)&\frac{\partial h_2}{\partial y}(x,y,z)&\frac{\partial h_2}{\partial z}(x,y,z)\\\frac{\partial h_3}{\partial x}(x,y,z)&\frac{\partial h_3}{\partial y}(x,y,z)&\frac{\partial h_3}{\partial z}(x,y,z)\end{pmatrix}\\&=\begin{pmatrix}k_2-\frac{k_3k_4y}{(x+k_4)^2}-\frac{k_5k_6z}{(x+k_6)^2}&-\frac{k_3x}{x+k_4}&-\frac{k_5x}{x+k_6}\\k_7&-\frac{k_8k_9}{(y+k_9)^2}&0\\k_{10}&0&-\frac{k_{11}k_{12}}{(z+k_{12})^2}\end{pmatrix}.\end{aligned}\tag{38}$$

We seek eigenvalues of (38) at stationary points of type (36) computationally because it is difficult to prove or disprove the hypothesis of negative real parts for all eigenvalues analytically. Our applied GNU Octave-code reads

```
% Computational Code for Stationary Point of Autonomous ODE
% System and Eigenvalues of Jacobian Matrix

% Step 1: Defining All Constant Coefficients

% Just an example, one has to change values accordingly

k01 = 1.0;
k02 = 1.0;
k03 = 1.0;
k04 = 1.0;
k05 = 1.0;
k06 = 1.0;
k07 = 1.0;
k08 = 1.0;
k09 = 1.0;
k10 = 1.0;
k11 = 1.0;
k12 = 1.0;

% Step 2: Equilibrium States (Newton-Type Method for
% x_s - for that reason, a local starting point is needed)

% For presentational purpose, the code for x_s is split up
% into different lines

x_s = fzero(@(x) k01 + k02*x
      - (k03*k07*k09*x^2)/((x+k04)*(k08-k07*x))
      - (k05*k10*k12*x^2)/((x+k06)*(k11-k10*x)),
      0.75*min(k08/k07,k11/k10));
y_s = (k07*k09*x_s)/(k08-k07*x_s);
z_s = (k10*k12*x_s)/(k11-k10*x_s);

% Step 3: Computation of Jacobian's Eigenvalues

% Step 3.1: Definition of Jacobian

% For presentational purpose, our Jacobian Matrix is split up
% into different lines

J = [k02-(k03*k04*y_s)/((x_s+k04)^2)-(k05*k06*z_s)/((x_s+k06)^2),
     -(k03*x_s)/(x_s+k04), -(k05*x_s)/(x_s+k06);
     k07, -(k08*k09)/((y_s+k09)^2), 0;
     k10, 0, -(k11*k12)/((z_s+k12)^2)];

% Step 3.2: Compuation of Eigenvalues

lambda = eig(J);
```

and is given for completeness of presentation.

3.6 | Numerical experiments

After computing the unique equilibrium state and all eigenvalues of the Jacobian, we apply the function ODE15S of GNU Octave Version 5.1.0[26] to solve our system (26). For further information on ODE15S, we refer the reader to the work of Shampine and Reichelt.[27] Our short computation code reads

```
% Computation of System of Nonlinear First-Order Differential
% Equations for Ca^2+-Levels in Liver Cells
% as presented in our work on Qualitative Analysis on those
% Systems

% Definition of Parameters and ODE System

function r = liver_ode (t,z)
  k01  = 1.0;
  k02  = 1.0;
  k03  = 1.0;
  k04  = 1.0;
  k05  = 1.0;
  k06  = 1.0;
  k07  = 1.0;
  k08  = 1.0;
  k09  = 1.0;
  k10  = 1.0;
  k11  = 1.0;
  k12  = 1.0;

% For presentational purpose, the first ODE is here split up into
% three lines of code

  r = [k01+k02*z(1)-k03*(z(1)*z(2))/(z(1)+k04)-k05*(z(1)*z(3))/(z(1)+k06)
        k07*z(1)-k08*(z(2))/(z(2)+k09)
        k10*z(1)-k11*(z(3))/(z(3)+k12)];
endfunction

% Solution of system

[t,z] = ode15s(@liver_ode, [0, 50], [0.1; 0.0; 0.0]);
```

and is given for completeness of presentation.

3.6.1 | Example with bounded solution for all time

In this example, our parameters are set by $k_j = 1.0$ for all $j \in \{1, \dots, 12\}$ with initial conditions $x_0 = 0.1$, $y_0 = 0.0$ and $z(0) = 0.0$. Our final simulation time T is $T = 50$. The starting point for our root finding function FZERO reads $0.8 \min\left\{\frac{k_8}{k_7}; \frac{k_{11}}{k_{10}}\right\}$. We obtain stationary coordinates $x_s \approx 0.6751$, $y_s \approx 2.0782$ and $z_s \approx 2.0782$. Additionally, all real parts of the Jacobian's eigenvalues are negative. The resulting solution can be seen in Figure 7.

This setting yields a solution which converges to a bounded equilibrium point.

3.6.2 | Example with periodic orbit solution

In this example, our parameters are set by $k_1 = 1.0$, $k_2 = 2.25$ and $k_j = 1.0$ for all $j \in \{3, \dots, 12\}$ with initial conditions $x_0 = 0.1$, $y_0 = 0.0$ and $z(0) = 0.0$. Our final simulation time T is $T = 400$. The starting point for our root finding function FZERO reads $0.8 \min\left\{\frac{k_8}{k_7}; \frac{k_{11}}{k_{10}}\right\}$. We obtain stationary coordinates $x_s \approx 0.7583$, $y_s \approx 3.1375$ and $z_s \approx 3.1375$. The resulting solution can be seen in Figure 8.

This setting seems to give us a solution with a periodic orbit.

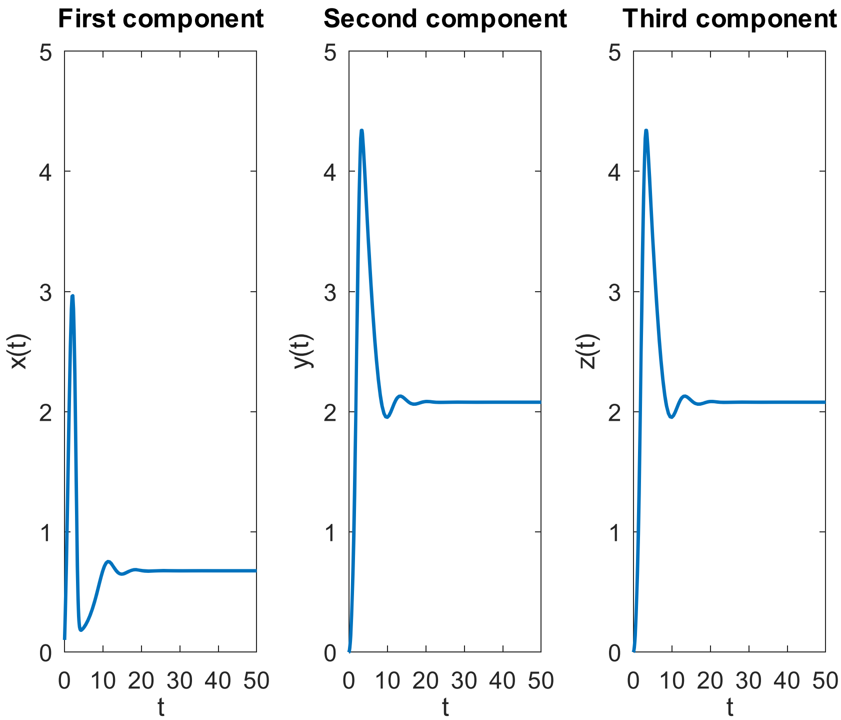


FIGURE 7 A plot of the stable solution components for the example in Section 3.6.1 [Colour figure can be viewed at wileyonlinelibrary.com]

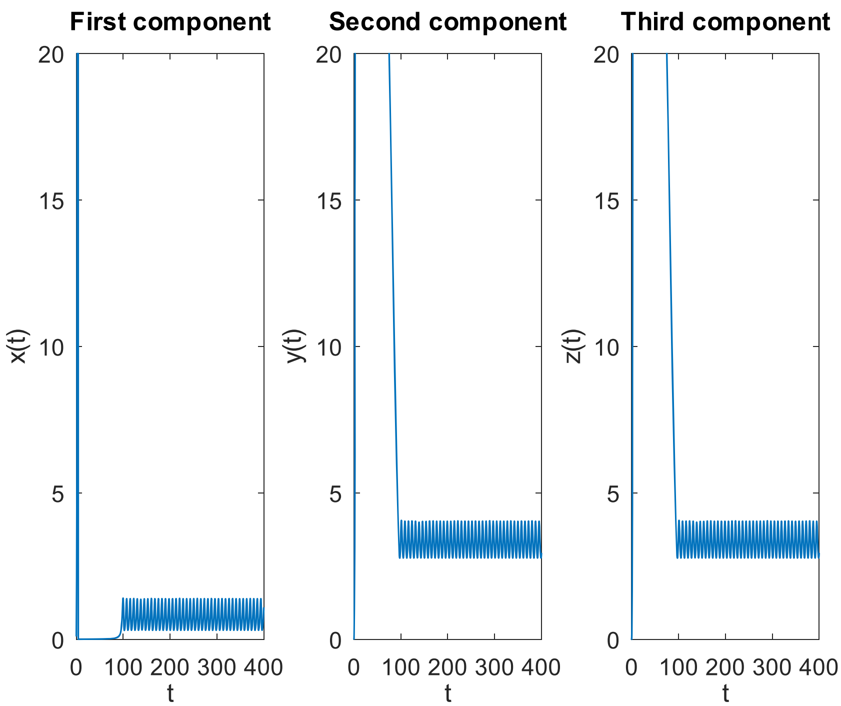


FIGURE 8 A plot of the solution components with periodic orbit for the example in Section 3.6.2 [Colour figure can be viewed at wileyonlinelibrary.com]

3.6.3 | Example with unbounded solution as time approaches infinity

In this example, our parameters are set by $k_1 = 1.0$, $k_2 = 5.0$ and $k_j = 1.0$ for all $j \in \{3, \dots, 12\}$ with initial conditions $x_0 = 0.1$, $y_0 = 0.0$ and $z(0) = 0.0$. Our final simulation time T is $T = 5$. The starting point for our root finding function FZERO reads $0.8 \min\left\{\frac{k_8}{k_7}; \frac{k_{11}}{k_{10}}\right\}$. We obtain stationary coordinates $x_s \approx 0.8511$, $y_s \approx 5.7152$ and $z_s \approx 5.7152$. The resulting solution can be seen in Figure 9.

This setting results in an unbounded solution as $t \to +\infty$. This example indicates that convergence to stationary points seems to hold only locally for this dynamical system.

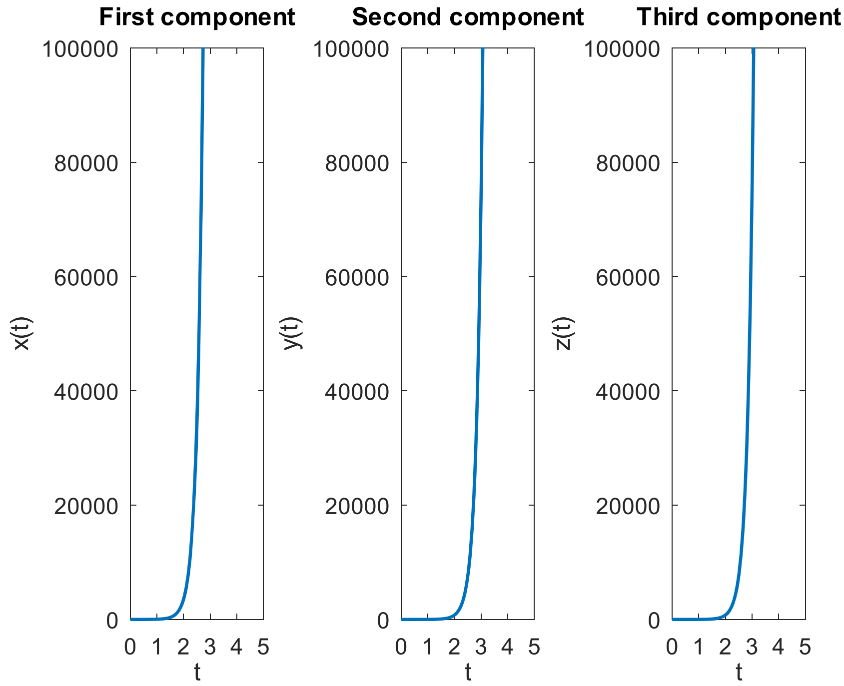


FIGURE 9 A plot of the unbounded solution components for the example in Section 3.6.3 [Colour figure can be viewed at wileyonlinelibrary.com]

4 | CONCLUSIONS AND OUTLOOK

4.1 | Conclusions

As noted in Section 1.2, we first established global unique existence of nonnegative solutions to our system (1) of first-order nonlinear ordinary differential equations in time for Ca^{2+}-concentrations in renal smooth muscle cells. We additionally provided a stability analysis to predict stability of stationary points which depends on the sign of the constant b from the characteristic equation. Finally, we gave two numerical examples which strengthen our theoretical findings from our analytical observations as we investigated one stable and one oscillatory solution for system (1).

Later, we investigated System (26) and proved global unique existence of nonnegative solutions as well. However, as this system is higher-dimensional in contrast to (1) system, we could also demonstrate by numerical examples that unbounded solutions are possible as depicted in Section 3.6.3.

Summarizing our results, we state that a thorough detailed analysis of biological dynamical systems is of importance to predict different solutions' behaviors. These findings further show that we need to careful choose our transfer parameters in dynamical systems as a small change might lead to totally different solutions. If we want to estimate parameters for those systems by experimental observations, this fact needs to be taken into consideration. For further details on parameter estimation of dynamical systems, we refer interested readers to the book by Schittkowski.[28]

4.2 | Outlook

Regarding our analytical findings, it might be of interest to investigate the behavior of our system (26) in further detail. Especially, we think that a thorough analysis of stability points might give us insight into the system's dynamics. This can be regarded as an interesting future research direction. In addition to that, higher-order time-stepping schemes might be of practical interest as well.[29]

We further stress that an adaption of this system to fractional derivates would lead to a different analysis and might provide further insight into the adapted system's dynamics.[7,13,30,31] If we examine different numerical methods for our nonlinear system or a variant with fractional derivates, this will eventually be a research topic in its own right.

Additionally, coupling our systems' dynamics with partial differential operators adds different effects like diffusion through Laplacian operators or its fractional operators can introduce spatial inhomogeneities to these dynamics.

Concluding our remarks, investigations with respect to numerical methods might be an interesting research direction in its own right as especially high-dimensional dynamical systems lack analytical results. Numerical observations might help giving insights into systems and stimulate ideas for future analytical findings.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ORCID

Benjamin Wacker https://orcid.org/0000-0002-0071-8819
Jan Christian Schlüter https://orcid.org/0000-0002-3363-8663

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