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Impulsive Delayed Lasota-Wazewska Fractional Models: Global Stability of Integral Manifolds

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Abstract: In this paper we deal with the problems of existence, boundedness and global stability of integral manifolds for impulsive Lasota–Wazewska equations of fractional order with time-varying delays and variable impulsive perturbations. The main results are obtained by employing the fractional Lyapunov method and comparison principle for impulsive fractional differential equations. With this research we generalize and improve some existing results on fractional-order models of cell production systems. These models and applied technique can be used in the investigation of integral manifolds in a wide range of biological and chemical processes.

Keywords: global stability; integral manifolds; impulsive Lasota–Wazewska models; functional derivatives; variable impulsive perturbations; time-varying delays

MSC: 34K60; 34K20; 34K37; 34K45

1. Introduction

The intensive investigation of blood cell dynamics in numerous articles in the past 50 years leads to a huge forward movement in the growth of mathematical methods and models, numerical results, schemes to estimate parameters and prognosticate optimal treatments to particular diseases. The paper [1] offers a very completed overview of the main mathematical models related to blood formation, disorders and treatments.

A turning point in the establishment of new models and methods was the publication of the paper authored by Wazewska–Czyzewska and Lasota in 1976 [2]. In order to describe the survival of red blood cells in animals, Wazewska–Czyzewska and Lasota proposed in [2] the following delayed equation

$$\dot{x}(t) = -\gamma x(t) + \beta e^{-\alpha x(t-\tau)},\tag{1}$$

where x(t) represents the number of red blood cells at time t, $\gamma > 0$ is the death probability for a red blood cell, α and β are positive constants related to the production of red blood cells per unit time and τ is the time delay between the production of immature red blood cells and their maturation for release in circulating blood stream.

The well known Lasota–Wazewska model seen in Equation (1) was extended and generalized by many authors, see, for example, refs. [3–8], including some recent publications on the topic [9–13]. This model can be also considered as one of the motivations to the development of the theory of delay differential equations, since delays are often considered in the hematopoiesis processes.

One of the directions in which the Lasota–Wazewska models have been extended and generalized is related to considering impulsive effects in the cells dynamic. Indeed, momentary (impulsive) changes at certain instants exists and can often affect the behavior of a real-world process. That is

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why the impulsive mathematical models has attracted a large amount of research interest and has become an emerging trend [14–20]. For some excellent results on impulsive Lasota–Wazewska models, we refer the reader to [21–25]. However, in all of the existing results, the authors considered fixed moments of impulsive effects. The aim of our research is to study some qualitative properties of a generalized impulsive Lasota–Wazewska model with variable impulsive perturbations. Indeed, considering impulsive effects at variable times is more general and close to reality [26–28].

On the other hand, fractional-order models are found to provide more advantages in describing memory effects and chaos [29,30]. The last two decades witnessed the rise of the development of the theory of fractional-order models and equations involved in fractional-order modeling. See, for example some recent publications [31–35] and the references therein. Some researchers used classical fractional-order models while new fractional differential systems, including impulsive fractional models started to be explored [36–40].

In addition, in relation to mathematical simulations in biology, chemistry and medicine, fractional calculus has been incorporated into some population dynamics models [41–43]. Since the survival of red blood cells is a deeply composite process, different methods have been developed throughout the years to get the most appropriate answers to some particular practice problems. To better reflect the dependence of Lasota–Wazewska-type models on their past history, an impulsive Lasota–Wazewska model of fractional order with time-varying delays has been introduced in [44] and some results related to existence and stability of almost periodic solutions of the model have been established. To the best of our knowledge no work on fractional Lasota–Wazewska systems was developed besides the one found in [44]. However, the paper [44] considered only fixed moments of impulsive perturbations.

Our aim in this paper is to extend the results in [44], and to consider variable impulsive perturbations. Furthermore, we will investigate the global stability behavior of an integral manifold related to the model. Indeed, the concept of integral manifolds is more general and includes, as particular cases, the global stability of zero solutions, equilibrium states, almost periodic solutions and etc. [45–48]. Despite the high importance of the concept of global stability of integral manifolds, the theory is not yet developed for fractional-order biological systems and this is another aim of the proposed research.

In the present paper, motivated by the above considerations, we focus on an impulsive Lasota–Wazewska model of fractional order with time-varying delays and variable impulsive perturbations. The remainder of this paper is organized as follows. In Section 2, we introduce the fractional Lasota–Wazewska model under consideration. Some notations and preliminaries are also given. In Section 3 first existence and boundedness results are proposed. Also, we obtain conditions for an integral manifold to be a global attractor of the survival model of red blood cells proposed by Wazewska and Lasota. The conditions are used in our global asymptotic stability analysis. In addition, the notion of global Mittag–Lerffler stability is defined and criteria for global Mittag–Lerffler stability of integral manifolds with respect to the model are also proved. An example is presented in Section 4, to show the validity and efficiency of the obtained results. Finally, some ending remarks are stressed in Section 5.

2. Preliminaries

Let $\mathbb{R} = (-\infty, \infty)$, $\mathbb{R}_+ = [0, \infty)$, $t_0 \in \mathbb{R}_+$ and let h = const > 0. Here and in what follows we will use the Caputo fractional derivative of order q, 0 < q < 1 with the lower limit t_0 for a function $l \in C^1[[t_0, b], \mathbb{R}]$, $b > t_0$,

$${}_{t_0}^C D_t^q l(t) = \frac{1}{\Gamma(1-q)} \int_{t_0}^t \frac{l'(\sigma)}{(t-\sigma)^q} d\sigma,$$

where Γ as usually means the Gamma function.

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Using the above fractional derivative, to consider long range memory in the survival of red blood cells, we introduce the following impulsive fractional-order Lasota–Wazewska model with time-varying delays and variable impulsive perturbations

$$\begin{cases}
 C_{t_0} D_t^q x(t) = -\gamma(t) x(t) + \sum_{j=1}^m \beta_j(t) e^{-\alpha_j(t) x(t-s_j(t))}, \ t \neq \tau_k(x(t)), \\
 \Delta x(t) = \alpha_k x(t) + \nu_k, \ t = \tau_k(x(t)), \ k = 1, 2, \dots,
\end{cases}$$
(2)

where:

(i) the model's parameters $\alpha_{j}(t)$, $\beta_{j}(t)$, $\gamma(t)$, $s_{j}(t) \in C[\mathbb{R}_{+}, \mathbb{R}_{+}]$, $0 \leq s_{j}(t) \leq h$, j = 1, 2, ..., m, h = const > 0, $\tau_{k} : \mathbb{R}_{+} \to (t_{0}, \infty)$, k = 1, 2, ...;

(ii)
$$\Delta x(t) = x(t^+) - x(t), \ \alpha_k, \ \nu_k \in \mathbb{R}, \ k = 1, 2, ...$$

The second equation of the impulsive system in Equation (2) is considered as a *control* or *jump condition*. The parameters α_k and ν_k , determine the controlled outputs $x(t^+)$. In an impulsive control system of type seen in Equation (2), the functions $\Delta x(t)$ are considered as control forces at the variable times for $t = \tau_k(x(t))$, $k = 1, 2, \ldots$ For the basic concepts and theorems of such systems, we refer the reader to [14,20–25].

The model in Equation (2) is a generalization of many existing integer-order Lasota–Wazewska models with time-varying delays and impulsive perturbations. The consideration of time-varying delays $s_j(t)$ is motivated by the fact that "a long time delay will increase the length of time a population will spend in the neighborhood of an unstable steady state ..." examined in [49]. The studies in [13,23,25] and some of the references therein also support the viewpoint that equations with time-varying delays provide a more realistic description for blood flow models.

Also, the fractional-order approach will better model the long-term memory phenomena and provides with a conceptually straightforward mathematical representation of rather complex processes. Indeed, a large number of empirical studies have investigated the long-term dependence of red blood cells and cell production systems in general. We refer the reader to [50–52] for some studies on long-range feedback effects in such systems. The very comprehensive analysis made in [44] shows that the population size of the red blood cells in an erythropoietic system has a very long memory. Therefore, the formulated fractional-order model in [44] of blood flow phenomenon is more realistic and takes into account the long-range hereditary properties of red blood cells populations. In addition, we consider variable impulsive perturbations in our research which are more useful and applicable in biological systems. Thus, our results will improve and generalize some known results obtained in [2,3,5,20–25,44]. For equations with non-fixed moments of impulsive perturbations, a number of difficulties related to the phenomena of 'beating' of the solutions, bifurcation, loss of the property of autonomy, etc. appeared. But the wide application of this type of equation requires their study.

The solutions x(t) of impulsive models with variable impulsive perturbations of the type in Equation (2) are piecewise continuous functions [14,20,26,28] that have first kind points of discontinuity at which they are continuous from the left, i.e., at the moments t_{l_k} when the integral curve of a solution x(t) meets the hypersurfaces

$$\sigma_k = \{(t, x) \in [t_0, \infty) \times \Omega : t = \tau_k(x)\},$$

where it is continuous from the left, the following relations are satisfied:

$$x(t_{l_k}^-) = x(t_{l_k}), \ x(t_{l_k}^+) = x(t_{l_k}) + I_{l_k}(x(t_{l_k})).$$

The points t_{l_1} , t_{l_2} , ... $(t_0 < t_{l_1} < t_{l_2} < ...)$ are the impulsive control instants. Let us note that, in general, $k \neq l_k$.

Let $J \subset \mathbb{R}_+$ be an interval. Define the following classes of piecewise continuous functions:

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 $PC[J,\mathbb{R}^n] = \{\sigma: J \to \mathbb{R}^n: \sigma(t) \text{ is continuous everywhere except at some points } t_{l_k} \in J \text{ at which } \sigma(t_{l_k}^-) \text{ and } \sigma(t_{l_k}^+) \text{ exist and } \sigma(t_{l_k}^-) = \sigma(t_{l_k})\};$

 $\mathcal{PC} = PC[[-h, 0], \mathbb{R}_+];$

 $PCB[J, \mathbb{R}_+] = \{ \sigma \in PC[J, \mathbb{R}_+] : \sigma(t) \text{ is bounded on } J \}.$

Let $\varphi_0 \in PCB[[-h,0],\mathbb{R}_+]$. Denote by $x(t) = x(t;t_0,\varphi_0)$, $x \in \mathbb{R}_+$ the solution of the system in Equation (2) that satisfies the initial conditions:

$$\begin{cases} x(t;t_0,\varphi_0) = \varphi_0(t-t_0), \ t_0-h \le t \le t_0, \\ x(t_0^+;t_0,\varphi_0) = \varphi_0(0). \end{cases}$$
 (3)

In this paper, we will investigate such trajectories of solutions x(t) the motion along with which must be ensured by an appropriate choice of impulsive forces. To guarantee the existence, uniqueness and continuability of the solution $x(t) = x(t;t_0,\varphi_0)$ of the initial value problem (IVP) in Equation (2), Equation (3) on the interval $[t_0,\infty)$ for $\varphi_0 \in PCB[[-h,0],\mathbb{R}_+]$ and $t_0 \in \mathbb{R}_+$, as well as, the absence of the phenomenon 'beating', we assume that:

1. $\tau_0(x) \equiv t_0$ for $x \in \mathbb{R}_+$, the functions $\tau_k(x)$ are continuous and the following relations hold

$$t_0 < \tau_1(x) < \tau_2(x) < \dots, \ \tau_k(x) \to \infty \text{ as } k \to \infty$$

uniformly on $x \in \mathbb{R}_+$.

2. The functions $\alpha(t)$, $\beta_i(t)$, $\gamma_i(t)$, $s_i(t)$ and τ_k are continuous on \mathbb{R}_+ .

For $\varphi \in \mathcal{PC}$, we define $|.|_h$ as $|\varphi|_h = \sup_{-h \leq \xi \leq 0} |\varphi(\xi)|$. In the case $h = \infty$ we have $|\varphi|_h = |\varphi|_\infty = \sup_{\xi \in (-\infty,0]} |\varphi(\xi)|$.

We shall use the following definition for integral manifolds connected with Equation (2) [20,48].

Definition 1. An arbitrary manifold M in the extended phase space $[t_0 - h, \infty) \times \mathbb{R}_+$ of (3) is called an integral manifold, if for any solution $x(t) = x(t;t_0, \varphi_0)$, $(t, \varphi_0(t-t_0)) \in M$, $t \in [t_0 - h, t_0]$ implies $(t, x(t)) \in M$, $t \ge t_0$.

For a manifold $M \subset [t_0 - h, \infty) \times \mathbb{R}_+$ we introduce the following sets and distances:

M(t) is the set of all $x \in \mathbb{R}_+$ such that $(t, x) \in M$ for $t \in [t_0, \infty)$;

 $M_0(t)$ is the set of all $x \in \mathbb{R}_+$ such that $(t, x) \in M$ for $t \in [t_0 - h, t_0]$;

 $d(x, M(t)) = \inf_{y \in M(t)} |x - y|$ is the distance between $x \in \mathbb{R}_+$ and M(t);

 $M(t,\varepsilon) = \{x \in \mathbb{R}_+ : d(x,M(t)) < \varepsilon\} \ (\varepsilon > 0) \text{ is an } \varepsilon\text{-neighborhood of } M(t);$

 $d_0(\varphi, M_0(t)) = \sup_{t \in [t_0 - h, t_0]} d(\varphi(t - t_0), M_0(t))$ is the distance between a function $\varphi \in PC[[-h, 0], \mathbb{R}_+]$ and $M_0(t)$;

 $M_0(t,\varepsilon) = \{ \varphi \in PC[[-h,0], \mathbb{R}_+] : d_0(\varphi, M_0(t)) < \varepsilon \}$ is an ε -neighborhood of $M_0(t)$;

 $\overline{S_a}(PC_0) = \{ \varphi \in \mathcal{PC} : |\varphi|_h \le a, \ a = const > 0 \}.$

In order to realize our investigations we will need the following assumptions:

A1. The set M(t) is nonempty for $t \in [t_0, \infty)$.

A2. The set $M_0(t)$ is nonempty for $t \in [t_0 - h, t_0]$.

A3. The distance d(x, M(t)) is Lipschitz with respect to t on any compact subset F of $[t_0, \infty) \times \mathbb{R}_+$. We also will use the following definitions.

Definition 2. The integral manifold M of system in Equation (2) is said to be:

- (a) equi-bounded, if for any initial point $t_0 \in \mathbb{R}_+$ and any positive constants $\eta > 0$ and a > 0 there exists a positive number $b = b(t_0, \eta, a) > 0$ such that for any initial function $\varphi \in \overline{S_a}(PC_0) \cap M_0(t, \eta)$ the solution $x(t; t_0, \varphi) \in M(t, b)$ for all $t \geq t_0$;
 - (b) t (or a)- uniformly bounded, if the number b from (a) is independent of t_0 (or of a);
 - (c) uniformly bounded, if the number b from (a) depends only on η .

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Definition 3. *The integral manifold M is said to be:*

(a) stable with respect to the system in Equation (2), if for any initial point $t_0 \in \mathbb{R}_+$ and any positive constants a > 0 and $\varepsilon > 0$ there exists a positive $\delta = \delta(t_0, a, \varepsilon) > 0$ such that for any initial function such that $\varphi \in \overline{S_a}(PC_0) \cap M_0(t, \delta)$ the solution $x(t; t_0, \varphi) \in M(t, \varepsilon)$ for all $t \ge t_0$;

- (b) uniformly stable with respect to the system in Equation (2) if the number δ from (a) depends only on ε ;
- (c) uniformly globally attractive with respect to the system in Equation (2), if for any $\eta > 0$ and $\varepsilon > 0$ there exists a positive number $T = T(\eta, \varepsilon) > 0$ such that for any initial point $t_0 \in \mathbb{R}_+$, any constant a > 0 and any initial function such that $\varphi \in \overline{S_a}(PC_0) \cap M_0(t, \eta)$ the solution $x(t; t_0, \varphi) \in M(t, \varepsilon)$ for all $t \geq t_0 + T$;
- (d) uniformly globally asymptotically stable with respect to the system in Equation (2) if M is a uniformly stable, uniformly globally attractive and uniformly bounded with respect to the system in Equation (2).

Remark 1. *Point (d) of Definition 3 can be reduced to the following specific stability notions:*

1. Lyapunov uniform global asymptotic stability of the zero solution of Equation (2), if

$$M = [t_0 - h, \infty) \times \{x \equiv 0\}.$$

2. Lyapunov uniform global asymptotic stability of a non-zero equilibrium state $x^* = x^*(t)$ of Equation (2), if

$$M = [t_0 - h, \infty) \times \{x \in \mathbb{R}_+ : x \equiv x^*\}.$$

3. Uniform global asymptotic stability of conditionally integral manifold B with respect to a integral manifold A, where $A \subset B \subset \mathbb{R}_+$, if M(t) = B for $t \geq t_0$ and $M_0(t) = A$ for $t \in [t_0 - h, t_0]$.

Next, motivated by [38,53], for an integral manifold M with respect to Equation (2) we will define a generalization of the global exponential stability notion to the fractional-order case, called global Mittag–Leffler stability. To this end we will need the Mittag–Leffler function [29,30] defined as

$$E_q(z) = \sum_{\kappa=0}^{\infty} \frac{z^{\kappa}}{\Gamma(q\kappa+1)}, \ q > 0.$$

Definition 4. The integral manifold M is said to be globally Mittag–Leffler stable with respect to Equation (2), if there exist constants $\mu > 0$ and $\tilde{d} > 0$ such that

$$x(t;t_0,\varphi_0) \in M(t,\{m[\varphi_0]E_q(-\mu(t-t_0)^q)\}^{\tilde{d}}), t \geq t_0,$$

where E_q is the corresponding Mittag–Leffler function, $\varphi_0 \in PCB[[-h,0],\mathbb{R}_+]$, m(0) = 0, $m(\varphi) \geq 0$ and $m(\varphi)$ is Lipschitz with respect to $\varphi \in PCB[[-h,0],\mathbb{R}_+]$.

Let $\tau_0(x) = t_0$, $x \in \mathbb{R}_+$. Next, we need the following sets

$$\mathcal{G}_k = \{(t,x) \in [t_0,\infty) \times \mathbb{R}_+: \ \tau_{k-1}(x) < t < \tau_k(x)\}, \ k = 1,2,\ldots, \ \mathcal{G} = \bigcup_{k=1}^{\infty} \mathcal{G}_k$$

and in the future considerations, we will adopt the Lyapunov–Razumikhin approach. That is why in the proofs of our main results we will use the class of piecewise continuous auxiliary functions given as:

$$V_M = \{ V : [t_0, \infty) \times \mathbb{R}_+ \to \mathbb{R}_+ : V \in C[G, \mathbb{R}_+], t \in [t_0, \infty), \}$$

V is locally Lipschitz with respect to its second argument on each of the sets G_k ; V(t,x)=0 for $(t,x)\in M$, $t\geq t_0$, V(t,x)>0 for $(t,x)\in [t_0,\infty)\times \mathbb{R}_+\setminus M$, for $(t_0^*,x_0^*)\in \sigma_k$, $V(t_0^{*-},x_0^*)$ and $V(t_0^{*+},x_0^*)$ exist and $V(t_0^{*-},x_0^*)=V(t_0^*,x_0^*)$.

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Lets, for simplicity, denote

$$X(t,x) = -\gamma(t)x(t) + \sum_{j=1}^{m} \beta_j(t)e^{-\alpha_j(t)x(t-s_j(t))}, \ t \neq \tau_k(x), \ x \in \mathbb{R}_+.$$

Using the above notation, for a function $V \in V_M$ we define the following fractional-order derivative.

Definition 5. Let $t \in (\tau_{k-1}(x), \tau_k(x))$, $k = 1, 2, ..., x \in \mathbb{R}_+$ and $\varphi \in \mathcal{PC}$. For $V \in V_M$ the upper right-hand derivative of V in Caputo's sense of order q, 0 < q < 1 with respect to the system in Equation (2) is defined by

$${}^{C}D_{+}^{q}V(t,\varphi(0)) = \lim_{\chi \to 0^{+}} \sup \frac{1}{\chi^{q}} \big[V(t,\varphi(0)) - V(t-\chi,\varphi(0) - \chi^{q}X(t,\varphi)) \big].$$

The following class of weight functions will also be useful in the proofs of our main theorems: $\mathcal{K} = \{w \in C[\mathbb{R}_+, \mathbb{R}_+] : w(r) \text{ is strictly increasing and } w(0) = 0, w(r) \to \infty, r \to \infty\}.$

Let t_1, t_2, \ldots ($t_0 < t_1 < t_2 < \ldots$) be the impulsive control instants at which the integral curve ($t, x(t; t_0, \varphi_0)$) of the IVP Equation (2), Equation (3) meets the hypersurfaces $\sigma_k, k = 1, 2, \ldots$, i.e., each of the points t_k is a solution of some of the equations $t = \tau_k(x(t)), k = 1, 2, \ldots$

In the next section we shall use the following Lemma from [38]. Similar comparison results can be found in [44] and the references therein.

Lemma 1. Assume that the function $V \in V_M$ is such that for $t \in [t_0, \infty)$, $\varphi \in \mathcal{PC}$,

$$V(t^+, \varphi(0) + \Delta \varphi) \le V(t, \varphi(0)), \ t = t_k,$$

and for a continuous function $\lambda:[t_0,\infty)\to\mathbb{R}$ the inequality

$$^{C}D_{+}^{q}V(t,\varphi(0)) \leq \lambda(t)V(t,\varphi(0)), t \neq t_{k}, k = 1,2,...$$

is valid whenever $V(t + \xi, \varphi(\xi)) \leq V(t, \varphi(0))$ for $-h \leq \xi \leq 0$.

Then $\sup_{-h<\xi\leq 0}V(t_0+\xi,\varphi_0(\xi))\leq V(t,\varphi(0))$ implies

$$V(t,x(t;t_{0},\varphi_{0}))\leq sup_{-h\leq \xi\leq 0}V(t_{0}^{+},\varphi_{0}(\xi))E_{q}(\lambda(t)(t-t_{0})^{q}),\,t\in [t_{0},\infty).$$

In the case when $\lambda(t) = 0$ for $t \in [t_0, \infty)$ the following corollary follows directly from Lemma 1.

Corollary 1. Assume that the function $V \in V_M$ is such that for $t \in [t_0, \infty)$, $\varphi \in \mathcal{PC}$,

$$V(t^+, \varphi(0) + \Delta \varphi) \le V(t, \varphi(0)), \ t = t_k,$$

and the inequality

$$^{C}D_{+}^{q}V(t,\varphi(0)) \leq 0, \ t \neq t_{k}, \ k = 1,2,...$$

is valid whenever $V(t + \xi, \varphi(\xi)) \leq V(t, \varphi(0))$ for $-h \leq \xi \leq 0$.

Then

$$V(t, x(t; t_0, \varphi_0)) \le \sup_{-h \le \xi \le 0} V(t_0^+, \varphi_0(\xi)), t \in [t_0, \infty).$$

3. Main Results

In this section, for a bounded continuous function f defined on \mathbb{R}_+ , we set

$$\overline{f} = \sup_{t \in \mathbb{R}_+} f(t), \ \underline{f} = \inf_{t \in \mathbb{R}_+} f(t).$$

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3.1. Existence and Boundedness Results

Theorem 1. Assume that:

- 1. Assumptions A1–A3 are satisfied.
- 2. M is a manifold in the extended phase space of the system in Equation (2).
- 3. The functions $\alpha_j(t)$, $\beta_j(t)$, $\gamma(t)$, $s_j(t)$ are bounded on \mathbb{R}_+ , $s_j(t) < \min\{t,h\}$, $j = 1,2,\ldots,m$, $t \in [t_0,\infty)$.
 - 4. The sequences of constants $\{\alpha_k\}$ are such that

$$-1 < \alpha_k \le 0, \ k = 1, 2, \dots$$

5. The model's parameters are such that for $t \neq \tau_k(x)$, $k = 1, 2, ..., x \in \mathbb{R}_+$

$$\frac{\sum_{j=1}^{m} \overline{\beta_j \alpha_j}}{\gamma} < 1.$$

Then M is an integral manifold of Equation (2).

Proof. Let $t_0 \in \mathbb{R}_+$, $\varphi_0 \in \mathcal{P}C$. Let $x(t;t_0,\varphi_0)$ be the solution of the IVP Equation (2), Equation (3) and $(t,\varphi_0(t-t_0)) \in M$ for $t \in [t_0-h,t_0]$. We will prove that M is an integral manifold of Equation (2). If we suppose that this is not true, then there exists a t', $t' > t_0$ such that $(t,x(t;t_0,\varphi_0)) \in M$ for $t_0 < t \le t'$ and $(t,x(t;t_0,\varphi_0)) \notin M$ for t > t'.

Consider the Lyapunov function $V \in V_M$ defined as

$$V(t,x) = d(x,M(t)), (4)$$

where $t \in [t_0 - h, \infty)$.

It is easy to see that there exists t'', t'' > t' such that $(t'', x(t''; t_0, \varphi_0)) \notin M$ and $V(t'', x(t''; t_0, \varphi_0)) > 0$.

In the case when $t = \tau_k(x)$, $x \in \mathbb{R}_+$, by condition 4, we get

$$V(t^{+}, \varphi(0) + \Delta\varphi) = d(\varphi(0) + \Delta\varphi, M(t^{+}))$$

$$\inf_{\varphi_{1}(0) \in M(t)} |\varphi(0) + \Delta\varphi - \varphi_{1}(0) - \Delta\varphi_{1}(0)| = \inf_{\varphi_{1}(0) \in M(t)} |\varphi(0) + \alpha_{k}\varphi(0) - \varphi_{1}(0) - \alpha_{k}\varphi_{1}(0)|$$

$$\leq (1 + \alpha_{k}) \inf_{\varphi_{1}(0) \in M(t)} |\varphi(0) - \varphi_{1}(0)| \leq V(t, \varphi(0)). \tag{5}$$

Let $t \geq t_0$, $t \neq \tau_k(x)$, $x \in \mathbb{R}_+$. We can see that

$${_{t_0}^CD_t^q|x(t) - x^*(t)| = sign(x(t) - x^*(t))_{t_0}^CD_t^q(x(t) - x^*(t))}.$$

Then for $t \ge t_0$ and $t \in (\tau_{k-1}(x), \tau_k(x))$ and for the derivative ${}^CD_+^qV(t, \varphi(0))$ along the solutions of the system in Equation (2) we have

$${}^{C}D_{+}^{q}V(t,\varphi(0)) \leq -\gamma(t)|\varphi(0)-\varphi_{1}(0)| + \sum_{i=1}^{m}\beta_{j}(t)\Big|e^{-\alpha_{j}(t)\varphi(-s_{j}(0))} - e^{-\alpha_{j}(t)\varphi_{1}(-s_{j}(0))}\Big|$$

$$\leq -\gamma(t)|\varphi(0)-\varphi_1(0)|+\sum_{j=1}^m\beta_j(t)\alpha_j(t)|\varphi(-s_j(0))-\varphi_1(-s_j(0))|,\;\varphi_1(0)\in M(t).$$

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From the above estimate, we have

$$^{C}D_{+}^{q}V(t,\varphi(0)) \leq -\underline{\gamma}V(t,\varphi(0)) + \sum_{j=1}^{m} \overline{\beta_{j}\alpha_{j}} \sup_{-h \leq \xi \leq 0} V(t+\xi,\varphi(\xi))$$

and for any solution x(t) that satisfies the Razumikhin condition

$$V(t+\xi,\varphi(\xi)) < V(t,\varphi(0)), -h < \xi < 0$$

by virtue of condition 5 of Theorem 1, it follows that

$${}^{C}D_{+}^{q}V(t,\varphi(0)) \le 0, \ t \ne \tau_{k}(x), \ t > t_{0}.$$
 (6)

Then using Equations (5) and (6) and Corollary 1, we get

$$V(t, x(t)) \le \sup_{-h < \xi < 0} V(t_0^+, \varphi_0(\xi)), \ t \in [t_0, \infty). \tag{7}$$

From the last inequality we get $V(t'',x(t'';t_0,\varphi_0)) \leq \sup_{-h \leq \xi \leq 0} V(t_0^+,\varphi_0(\xi)) = 0$, $t \in [t_0,\infty)$ which contradicts the fact that $V(t'',x(t'';t_0,\varphi_0)) > 0$ and therefore, it shows that M is an integral manifold of Equation (2).

The proof of Theorem 1 is complete. \Box

Now, we will proof some boundedness results.

Theorem 2. Let conditions of Theorem 1 are satisfied. Then the integral manifold M of Equation (2) is uniformly bounded.

Proof. Let a > 0, $\eta > 0$ and $t_0 \in \mathbb{R}_+$. Consider again the Lyapunov function seen in Equation (4). It follows from the choice of the function V that there exist functions $w_1, w_2 \in \mathcal{K}$ that satisfy

$$w_1(d(x, M(t))) \le V(t, x) \le w_2(d(x, M(t))), (t, x) \in [t_0, \infty) \times \mathbb{R}_+.$$
 (8)

Now, we suppose that $x(t) = x(t; t_0, \varphi_0)$ is a solution of problem Equations (2) and (3). From the definition of the weight functions $w_1, w_2 \in \mathcal{K}$, it follows that we can choose the number $b = b(\eta) > 0$ so that $w_2(\eta) < w_1(b)$.

Let $\varphi_0 \in \overline{S_a}(PC_0) \cap M_0(t,\eta)$. Since all conditions of Theorem 1 are satisfied, we get Equations (5) and (7). Then by Equations (5), (7) and (8), we have

$$w_1(d(x(t), M(t))) \le V(t, x(t)) \le \sup_{-h \le \xi \le 0} V(t_0^+, \varphi_0(\xi))$$

$$\leq w_2(d_0(\varphi_0, M_0(t))) \leq w_2(\eta) < w_1(b), t \geq t_0.$$

Therefore, $x(t;t_0,\varphi_0) \in M(t,b)$ for $t \in [t_0,\infty)$ and the theorem is proved. \square

The proofs of the next two theorems is analogous to the proof of Theorem 2. They present sufficient conditions for t (respectively for a)-uniform boundedness of the integral manifold M with respect to Equation (2).

Theorem 3. Let the conditions of Theorem 2 hold and for the Lyapunov function in Equation (4) there exists $w_2(.,s) \in \mathcal{K}$ such that for each fixed $s \ge 0$

$$V(t,x) < w_2(d(x,M(t)),x)$$
 for $(t,x) \in [t_0,\infty) \times \mathbb{R}_+$.

Then the integral manifold M of Equation (2) is t-uniformly bounded.

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Theorem 4. Let the conditions of Theorem 2 hold and for the Lyapunov function in Equation (4) there exists $w_2(t,.) \in \mathcal{K}$ such that for each $t \in [t_0, \infty)$

$$V(t,x) \leq w_2(t,d(x,M(t)))$$
 for $(t,x) \in [t_0,\infty) \times \mathbb{R}_+$.

Then the integral manifold M of Equation (2) is α - uniformly bounded.

Remark 2. Theorems 1–4 offer efficient criteria for existence and boundedness of integral manifolds related to the fractional-order Lasota-Wazewska model in Equation (2). It is well known that boundedness is an important property that plays a significant role in the existence of permanent, periodic and almost-periodic solutions of different systems [20,38,54–57]. Since integral manifolds are sets of solutions of the system (see, [45–48]), our results generalize and complement the existing qualitative results for separate solutions of Equation (2), biological models [4,10–12,19–25,38,44].

3.2. Global Asymptotic Stability

In this section, we shall use the measurable function $\lambda : [t_0, \infty) \to \mathbb{R}_+$. It is integrally positive if

$$\int_{\hat{I}} \lambda(t)dt = \infty$$

whenever
$$\hat{J} = \bigcup_{k=1}^{\infty} [a_k, b_k]$$
, $a_k < b_k < a_{k+1}$ and $b_k - a_k \ge \theta > 0$, $k = 1, 2, ...$

Theorem 5. Assume that:

- 1. Conditions 1-4 of Theorem 1 are satisfied.
- 2. There exists an integrally positive function $\lambda = \lambda(t) : \mathbb{R}_+ \to \mathbb{R}_+$ such that for $t \neq \tau_k(x)$, $k = 1, 2, \ldots$, $x \in \mathbb{R}_+$

$$\underline{\gamma} - \sum_{j=1}^{m} \overline{\beta_j \alpha_j} > \lambda(t) > 0.$$

3.
$$\frac{\eta}{\Gamma(q)}\int_0^\infty (t-s)^{q-1}\lambda(s)ds = \infty$$
 for sufficiently small values of $\eta>0$. Then the integral manifold M is uniformly globally asymptotically stable with respect to Equation (2).

Proof. Let $t_0 \in \mathbb{R}_+$. The fact that M is a uniformly bounded integral manifold of Equation (2) follows from Theorem 2.

Consider the Lyapunov function $V \in V_M$ defined by Equation (4).

We will first prove the uniform stability of the integral manifold M with respect to Equation (2). Let $\varepsilon > 0$ and take $\delta = \delta(\varepsilon) > 0$ so that $\delta < \varepsilon$.

Let a > 0 be arbitrary, $\varphi_0 \in \overline{S_a}(PC_0) \cap M_0(t,\delta)$ and $x(t) = x(t;t_0,\varphi_0)$ be the solution of Equation (2) through (t_0, φ_0) .

By condition 2 of Theorem 5, using similar arguments as in the proof of Theorem 1, for the case $t \ge t_0$, $t \ne \tau_k(x)$, $x \in \mathbb{R}_+$, we have

$${}^{C}D_{+}^{q}V(t,\varphi(0)) \le -\lambda(t)V(t,\varphi(0)), \ t \ne \tau_{k}(x), \ t > t_{0}.$$
 (9)

From Equations (5) and (9) and Corollary 1, we get

$$d(x(t;t_0,\varphi_0),M(t)) = V(t,x(t)) \le \sup_{-h<\xi<0} V(t_0^+,\varphi_0(\xi))$$

$$= \sup_{-h < \xi < 0} d(\varphi_0(\xi), M_0(t_0^+)) \le d_0(\varphi_0, M_0(t)) < \delta < \varepsilon, \ t \ge t_0,$$

hence the integral manifold *M* is uniformly stable with respect to Equation (2).

Next, for the given $\varepsilon > 0$ and $\eta < \varepsilon$, in view of condition 3 of Theorem 5, we can choose the number $T = T(\eta, \varepsilon) > 0$ so that

$$\frac{\varepsilon}{\Gamma(q)} \int_{t_0}^{t_0+T} (t_0 + T - s)^{q-1} \lambda(s) ds > \eta. \tag{10}$$

Let a>0 be arbitrary, $\varphi_0\in \overline{S_a}(PC_0)\cap M_0(t,\eta)$ and if we assume that for any $t\in [t_0,t_0+T]$ we have

$$d(x(t;t_0,\varphi_0),M(t)) \ge \varepsilon \tag{11}$$

then by Equations (5), (9) and (11) it follows that

$$\begin{split} V(t,x(t;t_0,\varphi_0)) &\leq V(t_0^+,\varphi_0) \\ &- \frac{1}{\Gamma(q)} \int_{t_0}^{t_0+T} (t_0+T-s)^{q-1} \lambda(s) d(x(s;t_0,\varphi_0),M(s)) ds \\ &\leq V(t_0^+,\varphi_0) - \frac{\varepsilon}{\Gamma(q)} \int_{t_0}^{t_0+T} (t_0+T-s)^{q-1} \lambda(s) ds, \ t \in [t_0,t_0+\mu]. \end{split}$$

From the above estimate, Equations (5) and (10) for $t = t_0 + T$ we obtain

$$V(t_0+T,x(t_0+T;t_0,\varphi_0)) \leq \eta - \frac{\varepsilon}{\Gamma(q)} \int_{t_0}^{t_0+T} (t_0+T-s)^{q-1} \lambda(s) ds < 0,$$

which contradicts the fact that $V \in V_M$. Hence, there exists a $t^* \in [t_0, t_0 + T]$, such that

$$d(x(t^*;t_0,\varphi_0),M(t^*))<\varepsilon.$$

From the lack of increase of the function V along the solution $x(t) = x(t; t_0, \varphi)$ it follows that for $t \ge t^*$ (hence for any $t \ge t_0 + T$ as well) we have

$$d(x(t;t_0,\varphi_0),M(t))) = V(t,x(t;t_0,\varphi_0)) \le \sup_{t^*-h \le t \le t^*} V(t^{*^+},x(t-t^*))$$
$$= \sup_{t^*-h \le t \le t^*} d(x(t-t^*),M(t-t^*)) < \eta < \varepsilon.$$

Therefore, $x(t) \in M(t, \epsilon)$ for $t \ge t_0 + T$. Hence, the integral manifold M is uniformly globally attractive with respect to Equation (2).

The proof is complete. \Box

The proof of the next theorem is similar to the proof of Theorem 5 and we will omit it here.

Theorem 6. Let the conditions 1 and 2 of Theorem 5 hold and for the Lyapunov function in Equation (4) there exists a function $w \in K$ and integrally positive functions $\zeta, \lambda : [t_0, \infty) \to \mathbb{R}_+$ such that

$$\zeta(t)w(d(x(t),M(t)))\lambda^{-1}(t) \leq V(t,x), \ t \neq \tau_k(x), \ k=1,2,...$$

for $t \in [t_0, \infty)$.

Then the integral manifold M is uniformly globally asymptotically stable with respect to Equation (2).

Remark 3. Theorems 5 and 6 offer new sufficient conditions on the model's parameters of the impulsive fractional Lasota–Wazewska Equation (2) that yield the global asymptotic stability of an integral manifold of states. Also, the obtained results extend the existing global attractivity and stability results for impulsive Lasota–Wazewska models [21–25] to the fractional-order case which better reflects the multiple history dependent phenomena in the red blood cells dynamics. In fact, stability properties are the most investigated qualitative properties of biological systems concerned with the study of their behavior over a finite or infinite interval of time.

Stability is also a very essential and crucial issue in control systems (such as impulsive control systems [20]). Hence, formulating rigorous stability results is a research problem of theoretical and practical significance.

Remark 4. With this research we generalize the results in [44], considering variable impulsive perturbations and integral manifolds. For example, if $M = [t_0 - h, \infty) \times \{x \in \mathbb{R}_+ : x \equiv x^*\}$, then two solutions x(t) and $x^*(t) \in M(t)$ may have different impulsive moments t_k and t_k^* which is more general than the case of fixed moments of impulsive perturbations, considered in [44]. Since taking into account variable impulsive perturbations in impulsive control systems is more natural and realistic, our results have great opportunities for applications. If the impulses are realized at fixed times, and the integral manifold $M = [t_0 - h, \infty) \times \{x \in \mathbb{R}_+ : x \equiv w\}$, where w is the unique almost periodic solution of the Lasota–Wazewska model, then the results in [44] follow as corollaries of our results.

3.3. Global Mittag-Leffler Stability

In this Section we will present our Mittag-Leffler stability results for the integral manifold M.

Theorem 7. *Assume that conditions* 1 *and* 2 *of Theorem* 5 *are met.*

Then the integral manifold M is globally Mittag-Leffler stable with respect to Equation (2).

Proof. Let $t_0 \in \mathbb{R}_+$ and $\varphi_0 \in PCB[[-h,0],\mathbb{R}_+]$ and $x(t) = x(t;t_0,\varphi_0)$ be the solution of the IVP Equations (2) and (3). From conditions 1 and 2 of Theorem 5 we get Equations (5) and (9).

Consider again the Lyapunov function Equation (4). For it there exists a constant $\nu > 0$ such that

$$V(t, x) < \nu |x|, t \in [t_0, \infty), x \in \mathbb{R}_+.$$

Then from the above estimate, Equations (5) and (9), using Lemma 1, we obtain

$$\begin{split} d(x(t;t_0,\varphi_0),M(t)) &= V(t,x(t)) \leq \sup_{-h \leq \xi \leq 0} V(t_0^+,\varphi_0(\xi)) E_q(-\lambda(t)(t-t_0)^q) \\ &< \nu |\varphi_0|_h E_q(-\lambda(t)(t-t_0)^q), \quad t \geq t_0. \end{split}$$

Let $m[\varphi_0] = \nu |\varphi_0|_h$. Then

$$d(x(t;t_0,\varphi_0),M(t)) < m[\varphi_0]E_q(-\lambda(t)(t-t_0)^q), t \ge t_0.$$

Since in the above estimate $m \ge 0$ and m = 0 is true only if $\varphi_0 = 0$, this proves that the integral manifold M is globally Mittag–Leffler stable with respect to Equation (2). \square

Remark 5. *If in Theorem 7 we consider* q = 1*, then we will have*

$$d(x(t;t_0,\varphi_0),M(t)) \le \nu |\varphi_0|_h \exp(-\lambda(t)(t-t_0)), t \ge t_0,$$

which implies the global exponential stability of the integral manifold M with respect to Equation (2). This shows that the notion of Mittag—Leffler stability for fractional-order differential equations is an extension of the notion of exponential stability for integer-order systems [20,53]. Therefore, with this research we generalize and improve the existing global exponential stability results for survival of red blood cells models [3,5,8,10,13,20,21,25] to the fractional-order case. It is also well known that the exponential stability guarantees the fast convergence rate which is preferable and desirable for mathematical models in biology, chemistry and medicine [20,24].

4. An Example

In this section, we present an example to illustrate the obtained results.

Consider the following impulsive Lasota–Wazewska fractional-order model with time-varying delays and variable impulsive perturbations:

$$\begin{cases}
CD_t^q x(t) = -(11 + \sin t)x(t) \\
+(3.5 + 0.4\sin t)e^{-(0.6 + 0.4\cos t)x(t - 2 - \cos t)} \\
+(3.1 + 0.2\cos t)e^{-(0.3 + 0.2\sin t)x(t - 2 - \sin t)}, \ t \neq \tau_k(x), \\
x(t^+) = \frac{1}{k}x(t) + \nu_k, \ t = \tau_k(x), \ k = 1, 2, \dots,
\end{cases}$$
(12)

where m = 2, $t \ge 0$, 0 < q < 1, $\gamma(t) = 11 + \sin t$, $\beta_1(t) = 3.5 + 0.4 \sin t$, $\beta_2(t) = 3.1 + 0.2 \cos t$, $\alpha_1(t) = 0.6 + 0.4 \cos t$, $\alpha_2(t) = 0.3 + 0.2 \sin t$, $s_1(t) = 2 + \cos t$, $s_2(t) = 2 + \sin t$, $v_k \in \mathbb{R}$, $\tau_k(x) = |x| + k$, k = 1, 2, ...

First, we have that the functions $\tau_k(x)$ are continuous on \mathbb{R}_+ and satisfy

$$\tau_1(x) < \tau_2(x) < \dots$$
, $\tau_k(x) \to \infty$ as $k \to \infty$.

Consider the manifold

$$M = [-3, \infty) \times \{ x \in \mathbb{R}_+ : \underline{M} \le x \le \overline{M} \}, \tag{13}$$

where \underline{M} , $\overline{M} \in \mathbb{R}_+$ are two constant solutions of Equation (12).

It is easy to check that for the manifold Equation (13) assumptions A1-A3 are satisfied.

Now, we have that $\overline{\alpha}_1 = 1$, $\overline{\alpha}_2 = 0.5$, $\overline{\beta}_1 = 3.9$, $\overline{\beta}_2 = 3.3$, $\gamma = 10$, and

$$\frac{\sum_{j=1}^{m} \overline{\beta_j \alpha_j}}{\gamma} = \frac{5.55}{10} < 1.$$

i.e., condition 5 of Theorem 1 is satisfied.

Moreover,

$$-1 < \alpha_k = \frac{1-k}{k} \le 0,$$

for k = 1, 2, ...

Therefore, according to Theorem 1, M is an integral manifold for Equation (12), and according to Theorem 2, M is uniformly bounded.

Also, if there exists an integrally positive function $\lambda = \lambda(t) : \mathbb{R}_+ \to \mathbb{R}_+$ such that for $t \neq \tau_k(x)$, $k = 1, 2, ..., x \in \mathbb{R}_+$

$$\underline{\gamma} - \sum_{j=1}^{m} \overline{\beta_j \alpha_j} = 4.45 > \lambda(t) > 0,$$

then according to Theorem 7 the integral manifold M is globally Mittag–Leffler stable with respect to Equation (12).

In addition, if the function λ is such that $\frac{\eta}{\Gamma(q)}\int_0^\infty (t-s)^{q-1}\lambda(s)ds=\infty$ for each sufficiently small value of $\eta>0$, the according to Theorem 5 the integral manifold M is uniformly globally asymptotically stable with respect to Equation (12).

Remark 6. With our example we illustrated the established theoretical results. Since the notion of stability of manifolds includes as particular cases stability of zero solutions, equilibrium states, almost periodic solutions, etc., our results have universal applicability and can be easily expanded in the study of many other fractional biochemical reactions processes.

5. Conclusions

A large number of empirical studies have investigated the long-term dependence of red blood cells and cell production systems in general. To better model the long-term memory phenomena in the survival of red blood cells models, in this paper we extend the existing impulsive Lasota–Wazewska models with time-varying delays to the fractional-order case. In addition, we consider variable

impulsive perturbations and integral manifolds in our analysis. Existence, boundedness, uniform global asymptotic stability and global Mittag–Leffler stability results are established. Since the notion of stability of integral manifolds is much more general than that of trivial solutions, equilibrium points, periodic and almost-periodic solutions, etc., our results generalized many existing boundedness and stability criteria. The generalized concept and the results obtained can be applied to study other types of impulsive control fractional biochemical systems.

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