Existence of pulses for a reaction-diffusion system of blood coagulation in flow

N. Ratto[1], **M. Marion**[1], **V. Volpert**[2,3,4,5]

[1]Institut Camille Jordan, UMR 5585 CNRS, Ecole Centrale de Lyon
69134 Ecully, France
[2]Institut Camille Jordan, UMR 5585 CNRS, University Lyon 1
69622 Villeurbanne, France
[3] INRIA, Université de Lyon, Université Lyon 1, Institut Camille Jordan
43 Bd. du 11 Novembre 1918, 69200 Villeurbanne Cedex, France
[4] Peoples Friendship University of Russia (RUDN University)
6 Miklukho-Maklaya St, Moscow, 117198, Russian Federation
[5] Marchuk Institute of Numerical Mathematics of the RAS
ul. Gubkina 8, 119333 Moscow, Russian Federation

Abstract. A reaction-diffusion system describing blood coagulation in flow is studied. We prove the existence of stationary solutions provided that the speed of the travelling wave problem for the limiting value of the velocity is positive. The implications to the problem of clot growth are discussed.

Key words: reaction-diffusion system, blood coagulation in flow, existence of pulses, Leray-Schauder method

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1. Introduction

1.1. **Blood coagulation in flow.** Blood coagulation is an important physiological function preserving hemostasis in the case of injury. It consists of two main components: biochemical reactions in plasma leading to the formation of fibrin polymer and platelet aggregation. Though these two processes act together, the first one is more important in veins while the second one in arteries.

Blood coagulation is initiated at the vessel wall expressing tissue factor and propagates inside the vessel in the direction perpendicular to the vessel wall. After reaching certain size, clot growth stops. The balance between these three stages of clot growth (initiation, propagation, arrest) determines normal functioning of blood coagulation.

In this work we will study the influence of blood flow on clot growth taking into account the reactions of blood coagulation without platelet aggregation. We consider the reaction-diffusion system of equations for the concentrations of blood factors (proteins) [5, 18]:

$$\frac{\partial \mathbf{w}}{\partial t} = \mathbf{D}\frac{\partial^2 \mathbf{w}}{\partial x^2} + \mathbf{F}(\mathbf{w}) - \sigma(x)\mathbf{w}, \tag{1.1}$$

where $\mathbf{w} = (w_1, ..., w_8)$ and $\mathbf{F} = (F_1, ..., F_8)$ is given by:

$$\mathbf{F}(\mathbf{w}) = \begin{cases} F_1(\mathbf{w}) = k_1 w_3 w_6 - h_1 w_1 \\ F_2(\mathbf{w}) = k_2 w_4 w_5 - h_2 w_2 \\ F_3(\mathbf{w}) = k_3 w_8(\rho_3 - w_3) - h_3 w_3 \\ F_4(\mathbf{w}) = k_4 w_8(\rho_4 - w_4) - h_4 w_4 \\ F_5(\mathbf{w}) = k_5 w_7(\rho_5 - w_5) - h_5 w_5 \\ F_6(\mathbf{w}) = (k_6 w_5 + \overline{k}_6 w_2)(\rho_6 - w_6) - h_6 w_6 \\ F_7(\mathbf{w}) = k_7 w_8(\rho_7 - w_7) - h_7 w_7 \\ F_8(\mathbf{w}) = (k_8 w_6 + \overline{k}_8 w_1)(\rho_8 - w_8) - h_8 w_8 \end{cases}. \tag{1.2}$$

Here w_3, w_4, w_5, w_6 and w_7 are the concentrations of the activated Factors $Va, VIIIa, IXa, Xa$ and XIa, respectively, w_8 is the concentration of activated Factor IIa (thrombin), w_1 and w_2 are the concentrations of prothrombinase and intrinsic tenase complexes. The terms $(\rho_i - w_i)$ in the equations 3-8 represent the concentrations of the inactive factors. The total concentration of activated and inactivated factors equals the initial concentration of the inactive factor ρ_i in the absence of inhibition terms $h_i w_i$. This equality becomes approximate in the presence of the inhibition terms. The constants k_i and $\overline{k}_i$ are the activation rates of the corresponding factors by other factors or complexes, while the constants h_i are the rates of their inhibition, in particular by antithrombin. Parameters k_i, h_i, $\overline{k}_i$, and ρ_i are positive constants. The matrix $\mathbf{D}$ of diffusion coefficients is a diagonal matrix with positive coefficients.

This system of equations is considered on the half-axis $x \geq 0$ with the no-flux boundary condition $\mathbf{w}' = \mathbf{0}$ at $x = 0$ corresponding to the vessel wall (prime denotes the derivative with respect to x). Since reactions of blood coagulation are localized in a very narrow space interval compared to the vessel radius, the approximation of semi-infinite spatial domain is well justified.

Blood flow removes blood factors from the clot and decreases their concentrations. This effect is taken into account in the last term in the right-hand side of equation (1.1). The flow velocity $\sigma(x)$ depends on the distance from the wall. It is an increasing function such that $\sigma(0) = 0$.

Clot growth in a quiescent plasma ($\sigma(x) \equiv 0$) is described by reaction-diffusion waves [6], [10], [12], [17]. Existence of waves for the model (1.1)-(1.2) follows from the general results on the wave existence for the monotone reaction-diffusion systems [15], [7]. The wave speed can be approximated by the minimax method [15]. Solution of the initial-boundary value problem increases if the initial condition, which corresponds to the quantity of blood factors produced at the initiation stage, exceeds some threshold level, and vanishes if the initial condition is less than this threshold. The latter is given by the pulse solution which exists if and only if the wave speed is positive [11]. Thus, we obtain two conditions of clot growth: the wave speed should be positive, and the initial condition should exceed the pulse solution.

Blood flow influences the distribution of the concentrations of blood factors and the conditions of clot growth. The main result of this work states the existence of a stationary solution of the blood coagulation system assuming that the limiting value of the blood flow velocity at infinity preserves the positiveness of the wave speed. We will discuss the biological meaning of this result at the end of the paper.

1.2. **Formulation of the main result.** The stationary solutions of system (1.1) satisfy the elliptic system :

$$\begin{cases} D_1 w_1'' + k_1 w_3 w_6 - h_1 w_1 - \sigma(x) w_1 = 0, \\ D_2 w_2'' + k_2 w_4 w_5 - h_2 w_2 - \sigma(x) w_2 = 0, \\ D_3 w_3'' + k_3 w_8 (\rho_3 - w_3) - h_3 w_3 - \sigma(x) w_3 = 0, \\ D_4 w_4'' + k_4 w_8 (\rho_4 - w_4) - h_4 w_4 - \sigma(x) w_4 = 0, \\ D_5 w_5'' + k_5 w_7 (\rho_5 - w_5) - h_5 w_5 - \sigma(x) w_5 = 0, \\ D_6 w_6'' + (k_6 w_5 + \overline{k}_6 w_2)(\rho_6 - w_6) - h_6 w_6 - \sigma(x) w_6 = 0, \\ D_7 w_7'' + k_7 w_8 (\rho_7 - w_7) - h_7 w_7 - \sigma(x) w_7 = 0, \\ D_8 w_8'' + (k_8 w_6 + \overline{k}_8 w_1)(\rho_8 - w_8) - h_8 w_8 - \sigma(x) w_8 = 0. \end{cases} \quad . \tag{1.3}$$

It is convenient to set

$$\mathbf{G}(\mathbf{w}, x) = \mathbf{F}(\mathbf{w}) - \sigma(x)\mathbf{w}, \tag{1.4}$$

so that (1.3) reads

$$\mathbf{D}\mathbf{w}'' + \mathbf{G}(\mathbf{w}, \mathbf{x}) = \mathbf{0}. \tag{1.5}$$

Hereafter, we consider system (1.5) on the half-axis $\mathbb{R}^+$, and look for a solution which satisfies the following conditions:

$$\mathbf{w}'(0) = \mathbf{0}, \quad \lim_{x \to \infty} \mathbf{w}(x) = \mathbf{0}, \tag{1.6}$$

$$\mathbf{w}(x) > \mathbf{0} \text{ and } \mathbf{w}'(x) < \mathbf{0} \text{ for } x > 0. \tag{1.7}$$

Such a solution will be called a pulse.

We assume that the function $\sigma(x)$ satisfies the following conditions:

$$\sigma(0) = 0, \quad \lim_{x\to\infty} \sigma(x) = \sigma_0 > 0, \quad \sigma'(x) \geq 0. \tag{1.8}$$

In view of the limiting value of the blood flow velocity at infinity we introduce the following nonlinearity :

$$\mathbf{G}^0(\mathbf{w}) = \lim_{x\to\infty} \mathbf{G}(x, \mathbf{w}) = \mathbf{F}(\mathbf{w}) - \sigma_0 \mathbf{w}. \tag{1.9}$$

Note that the origin in $\mathbb{R}^8$ is a zero of both $\mathbf{F}$ and $\mathbf{G}^0$. In what follows we assume that

$$\text{the Jacobian matrix } \mathbf{F}'(\mathbf{0}) \text{ has all eigenvalues in the left-half plane.} \tag{1.10}$$

We will also assume that the nonlinearity $\mathbf{G}^0$ is of bistable type. More precisely, as detailed in the appendix, the nonnegative zeros of $\mathbf{G}^0$ are in one-to-one correspondence with the zeros of some appropriate polynomial P^0 of one variable. Namely, setting $T = v_8$ (thrombin concentration), we conclude that $(w_1, w_2, ..., w_7, T)$ is a zero of $\mathbf{G}^0$ if and only if $P^0(T) = 0$ and, for $1 \leq i \leq 7$, $w_i = \phi_i(T)$, where the corresponding functions P^0 and ϕ_i are given in the appendix (see (A.2)-(A.8), (A.11)). The polynomial $P^0(T)$ reads $P^0(T) = (aT^3 + bT^2 + cT + d)T$ with some negative leading coefficient a. We make the following assumptions on P^0:

$$\begin{cases} P^0(T) \text{ possesses exactly three non-negative roots: } 0 < \bar{T} < T^0, \\ P^{0\prime}(0) < 0, \ P^{0\prime}(\bar{T}) > 0, \ P^{0\prime}(T^0) < 0. \end{cases} \tag{1.11}$$

Then, due to the correspondence with the zeros of $\mathbf{G}^0$, the vector-valued function $\mathbf{G}^0$ has exactly three nonnegative zeros : $\mathbf{0} < \bar{\mathbf{w}} < \mathbf{w}^0$. Here and below the inequalities between the vectors are understood component-wise. Furthermore, the Jacobian matrices $\mathbf{G}^{0\prime}(\mathbf{0})$ and $\mathbf{G}^{0\prime}(\mathbf{w}^0)$ have all eigenvalues in the left-half plane, while $\mathbf{G}^{0\prime}(\bar{\mathbf{w}})$ has a positive eigenvalue.

Under the conditions (1.11), it is well known that the travelling wave problem :

$$\mathbf{D}\mathbf{u}'' + c^0\mathbf{u}' + \mathbf{G^0}(\mathbf{u}) = \mathbf{0}, \tag{1.12}$$

$$\mathbf{u}(\infty) = \mathbf{0}, \ \mathbf{u}(-\infty) = \mathbf{w}^0 \tag{1.13}$$

possesses a unique solution $(\mathbf{u}, c^0)$ (up to some translation in space for the wave profile $\mathbf{u}$ that is defined on the whole real axis) (see Section 3.3).

We can now formulate the main result of this work.

Theorem 1.1. *Suppose that conditions* (1.8), (1.10)-(1.11) *are satisfied. If the wave speed* c^0 *in the problem* (1.12)-(1.13) *is positive, then problem* (1.5)-(1.7) *possesses a solution.*

The proof of this theorem mainly relies on the Leray-Schauder method. We first introduce some homotopy deformation in Section 2. In Section 3 we present some properties of solutions satisfied for all values of the homotopy parameter. In particular, we obtain a priori estimates of monotone solutions in some weighted Hölder spaces by using the positivity of the wave speed c^0. We conclude the proof of the existence of solutions of problem (1.5)-(1.7) in Section 4.

2. Homotopy and function spaces

We define the homotopy by setting:

$$\mathbf{G}^\tau(\mathbf{w}, x) = (1-\tau)\mathbf{G}(\mathbf{w}, x) + \tau\mathbf{G}^0(\mathbf{w}), \quad \tau \in [0,1]. \tag{2.1}$$

The function $\mathbf{G}^\tau$ also reads:

$$\mathbf{G}^\tau(\mathbf{w}, x) = \mathbf{F}(\mathbf{w}) - (1-\tau)\sigma(x)\mathbf{w} - \tau\sigma_0\mathbf{w}. \tag{2.2}$$

Thus, we consider the system

$$\mathbf{D}\mathbf{w}'' + \mathbf{G}^\tau(\mathbf{w}, \mathbf{x}) = \mathbf{0}. \tag{2.3}$$

Pulses are solutions of (2.3) defined on the half-axis $x \geq 0$ such that

$$\mathbf{w}'(0) = \mathbf{0}, \quad \lim_{x\to\infty} \mathbf{w}(x) = \mathbf{0}, \tag{2.4}$$

together with the monotonicity condition

$$\mathbf{w}'(x) < \mathbf{0} \text{ for } x > 0. \tag{2.5}$$

Here, for $\tau = 0$, we have the initial system (1.5). For $\tau = 1$ the nonlinearity $\mathbf{G}^0(\mathbf{w})$ does not depend on the space variable x. A problem similar to the one for $\tau = 1$ was studied in [11], and we will use some results from [11] in Section 4.

Note that the system (2.3) is monotone provided that $\mathbf{w}$ takes its values in an appropriate set. Indeed, let us introduce the set

$$\mathcal{D} = \{\mathbf{w} = (w_1, ..., w_8) \in \mathbb{R}^8_+ \mid w_i \leq \rho_i \text{ for } i \in \{3, ..., 8\}\}. \tag{2.6}$$

Recalling the definition (1.2) of $\mathbf{F} = (F_1, ..., F_8)$, it is straightforward that

$$\forall\, \mathbf{w} \in \mathcal{D}, \quad \frac{\partial F_i}{\partial w_j}(\mathbf{w}) \geq 0, \quad \forall i \neq j. \tag{2.7}$$

Therefore, since $\mathbf{w} \geq \mathbf{0}$ in $\mathcal{D}$:

$$\forall\, \mathbf{w} \in \mathcal{D},\ \forall\, \tau \in [0,1],\ \forall\, x \geq 0, \quad \frac{\partial G_i^\tau}{\partial w_j}(\mathbf{w}, x) \geq 0, \quad \forall i \neq j, \tag{2.8}$$

which provides the monotony property. This property will be very important in the sequel.

For the functional setting we introduce the Hölder space $\mathcal{C}^{k+\alpha}(\mathbb{R}_+)$, $\alpha \in (0,1)$, consisting of vector-functions of class $\mathcal{C}^k$, which are continuous and bounded on $\mathbb{R}_+$ together with their derivatives up to the order k, and such that the derivative of order k satisfies the Hölder condition with the exponent α. This space is equipped with the usual Hölder norm. We set:

$$\begin{cases} E^1 = \{\mathbf{w} \in \mathcal{C}^{2+\alpha}(\mathbb{R}_+), \mathbf{w}'(0) = \mathbf{0}\}, \\ E^2 = \mathcal{C}^{\alpha}(\mathbb{R}_+). \end{cases} \tag{2.9}$$

We now introduce the weighted spaces E^1_μ and E^2_μ where μ is the weight function, $\mu(x) = \sqrt{1+x^2}$. The norm in these spaces is defined by the equality:

$$\|\mathbf{w}\|_{E^i_\mu} = \|\mathbf{w}\mu\|_{E^i}, \quad i = 1, 2. \tag{2.10}$$

In view of (2.3), let us consider the operator A^τ acting from E^1_μ into E^2_μ which is given by:

$$A^\tau(\mathbf{w}) : x \to \mathbf{D}\mathbf{w}''(x) + \mathbf{G}^\tau(\mathbf{w}(x), x). \tag{2.11}$$

Then the operator linearized about any function in E^1_μ satisfies the Fredholm property and has the zero index. The nonlinear operator is proper on closed bounded sets. This means that the inverse image of a compact set is compact in any closed bounded set in E^1_μ. Finally, the topological degree can be defined for this operator. All these properties can be found in [13], [14].

We aim to prove the existence of a monotonically decreasing solution $\mathbf{w} \in E^1_\mu$ satisfying the equation $A^\tau(\mathbf{w}) = \mathbf{0}$.

3. A priori estimates

3.1. **First properties of the solutions of (2.3)-(2.4).** A non-negative solution of (2.3)-(2.4) is either positive or identically equal to zero as stated in the next lemma.

Lemma 3.1. *Let $\mathbf{w}(x)$ be a solution of problem (2.3)-(2.4) (for some $\tau \in [0,1]$) such that $\mathbf{w}(x) \geq \mathbf{0}$ for $x \geq 0$. Then one of the two following conclusions holds:*

- *either $\mathbf{w}(x) \equiv 0$,*
- *or $\mathbf{w}(x) > 0$ for all $x \geq 0$.*

Proof. Let $\mathbf{w}(x) \geq \mathbf{0}$ be a solution of (2.3)-(2.4). Recalling that for $\tau = 0$ the system is explicitly given by (1.3), it is straightforward that every equation of system (2.3) takes the form

$$dz'' - \gamma(x)z + f(x) = 0, \quad z'(0) = 0, \tag{3.1}$$

where $d > 0$, $\gamma(x) \geq h > 0$ and $f(x) \geq 0$ for all $x \geq 0$. It can be easily checked that either $z(x) > 0$ for all $x \geq 0$ or $z(x) \equiv 0$. Let us verify that all components of the solution are similar from the point of view of the choice between these two options. In the other words, if one of the components is identically zero, then all other components are also identically zero.

Suppose that $w_1(x) \equiv 0$. Then, from the first equation in (2.3) it follows that $w_3(x)w_6(x) \equiv 0$, which implies that $w_3(x) \equiv 0$ or $w_6(x) \equiv 0$.

- If $w_3(x) \equiv 0$, then the third equation readily provides $w_8(x) \equiv 0$. Then from the eighth equation we get $w_6(x) \equiv 0$, from the sixth equation, $w_2(x) \equiv w_5(x) \equiv 0$, and from the fifth equation, $w_7(x) \equiv 0$. Finally $w_4(x)$ satisfies the problem:

$$D_4 w_4'' - h_4 w_4 - \sigma(x) w_4 = 0, \; w_4 \geq 0, \; w_4'(0) = 0, \; w_4(\infty) = 0,$$

with $\sigma(x) \geq 0$ due to the assumption (1.8). Hence w_4 is non-decreasing and, consequently, $w_4(x) \equiv 0$.

- If $w_8(x) \equiv 0$, then the equations successively yield $w_6(x) = w_5(x) = w_2(x) = w_7(x) = w_8(x) = w_6(x) \equiv 0$ and, finally, as above for w_4, we obtain that $w_3(x) = w_4(x) \equiv 0$.

In the above argument we initially assumed that $w_1(x) \equiv 0$. The proof remains similar for all other values of i for which the component w_i is identically equal to zero. This concludes the proof of the lemma.

□

The next result provides some explicit upper bound for the monotone solutions of (2.3).

Proposition 3.2. *Let* $\mathbf{w}^+ = (w_1^+, ..., w_8^+)$ *be given by the equalities:*

$$w_1^+ = k_1 \rho_3 \rho_6 / h_1, \;\; w_2^+ = k_2 \rho_4 \rho_5 / h_2, \;\; w_i^+ = \rho_i \text{ for } i \geq 3. \tag{3.2}$$

Then all solutions $\mathbf{w}(x)$ *of the problem* (2.3)-(2.5) *admit the estimate:*

$$\mathbf{w}(x) \leq \mathbf{w}^+ \;\; \text{for} \;\; x \geq 0, \tag{3.3}$$

where $\mathbf{w}^+$ *is given by* (3.2)*. Consequently,* $\mathbf{w}(x) \in \mathcal{D}$ *for* $x \geq 0$.

Proof. Let $\mathbf{w}(x)$ be some solution of the problem (2.3)-(2.5). Since $\mathbf{w}'(0) = \mathbf{0}$ and $\mathbf{w}'(x) < \mathbf{0}$ for $x > 0$, we necessarily have $\mathbf{w}''(0) \leq \mathbf{0}$ and $\mathbf{G}^\tau(\mathbf{w}(\mathbf{0}), \mathbf{0}) \geq \mathbf{0}$. Next, in view of (2.2) and (1.8), we see that $\mathbf{G}^\tau(\mathbf{w}(0), 0) = \mathbf{F}(\mathbf{w}(0))$. Then recalling the definition (1.2) of $\mathbf{F}$, we conclude that for $i \in \{3, ..., 8\}$, $w_i(0) \leq \rho_i$ and for $i \in \{1, 2\}$, $w_i(0) \leq w_i^+$ given by (3.2). Since $\mathbf{w}(x)$ is decreasing, (3.3) follows readily.

□

Finally, a positive, non-increasing solution with values in $\mathcal{D}$ and zero limit at infinity is necessarily monotone as stated in the next lemma.

Lemma 3.3. *Let* $\mathbf{w}(x)$ *be a solution of problem* (2.3) *satisfying*

$$\mathbf{w}(x) > 0, \ \ \mathbf{w}(x) \in \mathcal{D}, \ \ \mathbf{w}'(x) \le 0 \text{ for } x > 0, \ \ \mathbf{w}(\infty) = \mathbf{0}.$$

Then $\mathbf{w}'(x) < 0$ *for* $x > 0$.

Proof. Suppose that there exists some component $w_i(x)$ of the solution and some $x_0 > 0$ such that $w_i'(x_0) = 0$. Denote $v = -w_i'$. Differentiating the ith equation of the system (2.3), we obtain the following equality:

$$D_i v''(x) + \frac{\partial G_i^\tau}{\partial w_i}(\mathbf{w}(x), x) v(x) = \sum_{j \ne i} \frac{\partial G_i^\tau}{\partial w_j}(\mathbf{w}(x), x) w_j'(x) - (1-\tau)\sigma'(x) w_i(x). \tag{3.4}$$

Here, for $x \ge 0$, $\mathbf{w}(x) \in \mathcal{D}$ so, thanks to the monotony property (2.8), $\frac{\partial G_i^\tau}{\partial w_j}(\mathbf{w}(x), x) \ge 0$ for all $j \ne i$. Also $w_j'(x) \le 0$ and $w_i(x) \ge 0$, while due to the assumption (1.8), $\sigma'(x) \ge 0$. Consequently the right hand-side of (3.4) is non-positive. Besides $v(x) \ge 0$ and $v(x_0) = 0$. From the maximum principle we conclude that $v = -w_i' \equiv 0$. Since w_i vanishes at infinity, it follows that $w_i \equiv 0$, which is impossible. □

3.2. **Separation between monotone and non-monotone solutions.** Let us suppose that all solutions of (2.3)-(2.5) are uniformly bounded in the space E_μ^1. Theorem 3.6 below will provide conditions that guarantee this property.

We aim to obtain a result on the separation between the monotonically decreasing solutions of (2.3)-(2.4) that will be denoted by $\mathbf{w}^M(x)$, and the solutions of (2.3)-(2.4) which do not satisfy this condition and will be denoted by $\mathbf{w}^N(x)$. We will call the latter ones non-monotone solutions.

Since we are concerned with the existence of decreasing solutions, we need to ensure that the Leray-Schauder method can be applied to some set containing only these solutions. The separation property will allow us to construct an open subset of E_μ^1 containing all the decreasing solutions and whose closure does not contain any non-monotone solution.

Theorem 3.4. *Suppose that the assumptions* (1.8), (1.10) *hold and, moreover, that all solutions of* (2.3)-(2.5) *are bounded independently of* τ *in the space* E_μ^1. *Then there exists a constant* $r > 0$ *such that, for all* $\tau \in [0, 1]$, *for any monotone solution* $\mathbf{w}^M(x)$ *of* (2.3)-(2.5) *and any non-monotone solution* $\mathbf{w}^N(x)$ *of* (2.3)-(2.4), *we have*

$$||\mathbf{w}^M - \mathbf{w}^N||_{E_\mu^1} \ge r. \tag{3.5}$$

Proof. Let us argue by contradiction and suppose that there exist some sequence of monotone solutions $\mathbf{w}^{M,k}(x)$ and some sequence of non-monotone solutions $\mathbf{w}^{N,k}(x)$ such that:

$$||\mathbf{w}^{M,k} - \mathbf{w}^{N,k}||_{E^1_\mu} \to 0 \text{ as } k \to \infty. \tag{3.6}$$

Since monotone solutions are uniformly bounded and the operator is proper, the set $\{\mathbf{w}^{M,k},\ k \in \mathbb{N}\}$ is relatively compact in E^1_μ. Consequently, there exists some subsequence still denoted by $\mathbf{w}^{M,k}(x)$ converging to some function $\widehat{\mathbf{w}}(x)$:

$$||\mathbf{w}^{M,k} - \widehat{\mathbf{w}}||_{E^1_\mu} \to 0 \text{ as } k \to \infty. \tag{3.7}$$

Clearly, the limit function $\widehat{\mathbf{w}}(x)$ is a solution of system (2.3) for some $\tau = \hat{\tau}$; furthermore it satisfies

$$\widehat{\mathbf{w}}(x) \geq \mathbf{0} \text{ for } x \geq 0,\ \widehat{\mathbf{w}}'(x) \leq \mathbf{0} \text{ for } x > 0,\ \widehat{\mathbf{w}}'(0) = \mathbf{0},\ \widehat{\mathbf{w}}(\infty) = \mathbf{0}, \tag{3.8}$$

and, in view of Proposition 3.2, $\widehat{\mathbf{w}}(x) \in \mathcal{D}$ for $x \geq 0$.

We claim that $\widehat{\mathbf{w}}$ is not identically equal to zero and that it is a monotonically decreasing solution of (2.3)-(2.4), as stated in the following lemma.

Lemma 3.5. *We have* $\widehat{\mathbf{w}}(x) > \mathbf{0}$ *and* $\widehat{\mathbf{w}}'(x) < \mathbf{0}$ *for* $x > 0$.

Proof. Let us first check that $\widehat{\mathbf{w}}(0) \not\equiv \mathbf{0}$. Arguing by contradiction suppose that $\mathbf{w}^{M,k}(0) \to \mathbf{0}$.

Due to the assumption (1.10) and the monotony property (2.8), the principal eigenvalue of the Jacobian matrix $\mathbf{F}'(\mathbf{0})$ is real and negative. Consequently, there exists a constant vector $\mathbf{q} > \mathbf{0}$ such that

$$\mathbf{F}'(\mathbf{0})\mathbf{q} < \mathbf{0}. \tag{3.9}$$

Since $\mathbf{F}(\mathbf{0}) = \mathbf{0}$ and the nonlinearity $\mathbf{F}$ is quadratic, we have $\mathbf{F}(\varepsilon\mathbf{q}) < \mathbf{0}$ for sufficiently small $\varepsilon \leq \varepsilon_0$. Here ε_0 can be chosen such that $\varepsilon_0\mathbf{q} \in \mathcal{D}$. Then for $\varepsilon \leq \varepsilon_0$, we have:

$$\forall\, \tau \in [0,1],\ \forall\, x \geq 0,\ \mathbf{G}^\tau(\varepsilon\mathbf{q}, x) \leq \mathbf{F}(\varepsilon\mathbf{q}) < \mathbf{0}.$$

Then the monotony property (2.8) guarantees that for any $\mathbf{w} \in I_\varepsilon = [\mathbf{0}, \varepsilon\mathbf{q}]$, $\mathbf{w} \neq 0$, at least one component of the vector $\mathbf{G}^\tau(\mathbf{w}, x)$ is negative. Since $\mathbf{w}^{M,k}(0)$ converges to $\mathbf{0}$, then, for sufficiently large k, $\mathbf{w}^{M,k}(0)$ enters I_ε. Consequently, for some k and some i, we see that $G_i^\tau(\mathbf{w}^{M,k}(0), 0) < 0$ (with τ corresponding to the solution $\mathbf{w}^{M,k}$). Thus, from (2.3) we conclude that $w_i^{M,k''}(0) > 0$ and $w_i^{M,k}(0)$ cannot be non-increasing (since $w_i^{M,k'}(0) = 0$), which contradicts (3.8). Thus, $\widehat{\mathbf{w}}(0)$ is different from $\mathbf{0}$.

Finally, since $\hat{\mathbf{w}}$ is not identically equal to zero, Lemma 3.1 guarantees its positiveness while Lemma 3.3 provides its monotony.

□

Next, due to (3.6) and (3.7) the monotone solution $\widehat{\mathbf{w}}$ is the limit of the non-monotone solutions

$$||\mathbf{w}^{N,k} - \widehat{\mathbf{w}}||_{E^1_\mu} \to 0 \text{ as } k \to \infty. \tag{3.10}$$

Here $\mathbf{w}^{N,k}$ is a solution of system (2.3) for some $\tau = \tau_k$. Let us show that this leads to a contradiction.

We claim that the convergence in (3.10) together with the properties of $\widehat{\mathbf{w}}$ yield the existence of two constants $a > 0$ and $b > 0$ such that for all sufficiently large k we have

$$\mathbf{w}^{N,k'}(x) < \mathbf{0} \text{ for } 0 < x < a \text{ and for all } x \geq b. \tag{3.11}$$

To derive the existence of $a > 0$, we first verify the following property of $\widehat{\mathbf{w}}(0)$:

$$\mathbf{G}^{\hat{\tau}}(\widehat{\mathbf{w}}(0), 0) > \mathbf{0}. \tag{3.12}$$

Indeed, the inequality $\mathbf{G}^{\hat{\tau}}(\widehat{\mathbf{w}}(0), 0) \geq \mathbf{0}$ holds because otherwise, if at least one of the components of this vector is negative, then the corresponding component of the vector $\widehat{\mathbf{w}}''(0)$ is positive. Since $\widehat{\mathbf{w}}'(0) = \mathbf{0}$, this would contradict the assumption that the function $\widehat{\mathbf{w}}$ is decreasing. Thus, we need to verify that the components of the vector $\mathbf{G}^{\hat{\tau}}(\widehat{\mathbf{w}}(0), 0)$ cannot equal zero. Suppose that this is not true, and $G_i^{\hat{\tau}}(\widehat{\mathbf{w}}(0), 0) = 0$ for some i so that $\widehat{w_i}''(0) = 0$. Then $v(x) = -\widehat{w_i}'(x)$ satisfies

$$D_i v'' + \frac{\partial G_i^{\hat{\tau}}}{\partial w_i}(\widehat{\mathbf{w}}(x), x)v(x) + g(x) = 0,$$

where

$$g(x) = -\sum_{j \neq i} \frac{\partial G_i^{\hat{\tau}}}{\partial w_j}(\widehat{\mathbf{w}}(x), x)\widehat{w}_j'(x) + (1 - \tau)\sigma'(x)\widehat{w}_i(x) \geq 0.$$

Since $v(0) = 0$ and $v'(0) = 0$, then we obtain a contradiction with the Hopf lemma.

Since the functions $\mathbf{w}^{N,k}(x)$ converge to $\widehat{\mathbf{w}}(x)$, then, for all k sufficiently large, we have $\mathbf{G}^{\tau_k}(\mathbf{w}^{N,k}(0), 0) > \mathbf{0}$. Hence, there exist some small enough $a > 0$ and a constant k_1 such that for $x \in]0, a[$ and $k \geq k_1$ we have $\mathbf{G}^{\tau_k}(\mathbf{w}^{N,k}(x), x) > \mathbf{0}$. Hence $(\mathbf{w}^{N,k})'(x) < \mathbf{0}$ in the interval $]0, a[$.

We now aim to prove the existence of $b > 0$ such that (3.11) holds for all sufficiently large k. Let us consider again the positive vector $\mathbf{q}$ such that $\mathbf{F}'(\mathbf{0})\mathbf{q} < \mathbf{0}$ (see (3.9)). Then for all $\tau \in [0, 1]$ and all $x \geq 0$, we have (recall (2.2))

$$(\mathbf{G}^\tau)'(\mathbf{w}, x)\mathbf{q} = \mathbf{F}'(\mathbf{w})\mathbf{q} - (1 - \tau)\sigma(x)\mathbf{q} - \tau\sigma_0\mathbf{q} \leq \mathbf{F}'(\mathbf{w})\mathbf{q},$$

where $(\mathbf{G}^\tau)'(\mathbf{w},x)$ denotes the Jacobian matrix of the function $\mathbf{w} \to \mathbf{G}^\tau(\mathbf{w},x)$. Consequently, there exists $\delta > 0$ such that:

$$\forall\, \tau \in [0,1],\ \forall\, x \geq 0,\ (\mathbf{G}^\tau)'(\mathbf{w},x)\mathbf{q} \leq \mathbf{F}'(\mathbf{w})\mathbf{q} < \mathbf{0} \ \text{ for } \|\mathbf{w}\| < \delta. \tag{3.13}$$

Here $||.||$ denotes the euclidian norm in $\mathbb{R}^8$. Besides, by choosing sufficiently small δ, we will have $\mathbf{w} \in \mathcal{D}$, if $\mathbf{w} \geq \mathbf{0}$ and $\|\mathbf{w}\| < \delta$.

Since $\widehat{\mathbf{w}}(x)$ is a solution of (2.3)-(2.4) for some τ, then it is exponentially decreasing and we can choose $\tilde{b}$ such that for all $x \geq \tilde{b}$ we have $||\widehat{\mathbf{w}}(x)|| < \delta$. Since $\mathbf{w}^{N,k}$ converges to the monotone function $\widehat{\mathbf{w}}$, we can choose $b \geq \tilde{b}$ and $k_1 \geq k_0$ such that

$$\mathbf{w}^{N,k}(b) > \mathbf{0},\ \ \mathbf{w}^{N,k\prime}(b) < \mathbf{0},\ \ ||\mathbf{w}^{N,k}(x)|| \leq \delta \ \text{ for } x \geq b \ \text{ and } k \geq k_2. \tag{3.14}$$

We claim that

$$\mathbf{w}^{N,k\prime}(x) < \mathbf{0} \ \text{ for } x \geq b \ \text{ and } k \geq k_1. \tag{3.15}$$

Let us first check that:

$$\mathbf{w}^{N,k}(x) > \mathbf{0} \ \text{ for } x \geq b \ \text{ and } k \geq k_1. \tag{3.16}$$

Suppose that for some k and some $y > b$ we have $\mathbf{w}^{N,k}(y) \leq \mathbf{0}$. We can choose $\beta > 0$ such that the function $\mathbf{z}^k(x) \equiv \mathbf{w}^{N,k}(x) + \beta\mathbf{q}$ satisfies the following conditions: $\mathbf{z}^k(x) \geq 0$ for all $x \geq b$ and $z_j^k(c) = 0$ for some component of z_j^k and some $c > b$. In view of the definition (2.2) of $\mathbf{G}^{\tau_k}$, the function $\mathbf{z}^k(x)$ satisfies the equation:

$$\mathbf{D}(\mathbf{z}^k)''(x) + \mathbf{F}(\mathbf{z}^k(x)) - \sigma^k(x)\mathbf{z}^k(x) + \mathbf{g}_k(x) = 0, \tag{3.17}$$

with $\sigma^k(x) = (1-\tau_k)\sigma(x) + \sigma_0$ and

$$\mathbf{g}_k(x) = \mathbf{F}(\mathbf{w}^{N,k}(x)) - \mathbf{F}(\mathbf{w}^{N,k}(x) + \beta\mathbf{q}) + \sigma^k(x)\beta\mathbf{q} =$$
$$-\beta\mathbf{F}'(\mathbf{w}^{N,k}(x))\mathbf{q} + \sigma^k(x)\beta\mathbf{q} + \mathbf{h}_k(x),$$

where

$$||\mathbf{h}_k(x)|| \leq M\beta^2||\mathbf{q}||^2.$$

For δ in (3.13) sufficiently small, β is also sufficiently small, so that $g_k(x) > 0$. Consequently, using the definition (1.2) of $\mathbf{F}$, we obtain that the jth equation in (3.17) takes the form

$$D_i z'' - \gamma(x)z + f(x) = 0$$

with $z(x) \geq 0$ and $f(x) > 0$ for $x \geq b$, $z(b) > 0$, $z(c) > 0$ for $c > b$. This leads to a contradiction in sign at the point where $z(x)$ reaches its minimum for $x \geq b$ and proves (3.16)

Now let us show that $\mathbf{w}^{N,k}$ is decreasing for $x \geq b$. The function $\mathbf{v}^k(x) = -(\mathbf{w}^{N,k})'(x)$ is a solution of the equation:

$$\mathbf{D}(\mathbf{v}^k)''(x) + (\mathbf{G}^{\tau_k})'(\mathbf{w}^{N,k}(x),x)\mathbf{v}^k(x) + (1-\tau)\sigma'(x)\mathbf{w}^{N,k}(x) = 0. \tag{3.18}$$

Let us suppose that $\mathbf{v}^k(x)$ is not positive for some $x > b$ and $k \geq k_1$. Since $\mathbf{v}^k(y) > 0$ and $\mathbf{v}^k(+\infty) = 0$ (due to the exponential decay of $\mathbf{v}^k$), we can choose some $\alpha > 0$ such that the function $\mathbf{u}^k(x) \equiv \mathbf{v}^k(x) + \alpha\mathbf{q}$ satisfies the following conditions: $\mathbf{u}^k(x) \geq \mathbf{0}$ for all $x \geq b$, and $\mathbf{u}^k(x_1) = \mathbf{0}$ for some $x_1 > b$ (for at least one of the components of this vector). Taking into account system (3.18), we see that

$$\mathbf{D}(\mathbf{u}^k)''(x) + (\mathbf{G}^{\tau_k})'(\mathbf{w}^{N,k}(x), x)\mathbf{u}^k(x) + \mathbf{f}_k(x) = 0, \tag{3.19}$$

where

$$\mathbf{f}_k(x) = -\alpha(\mathbf{G}^{\tau_k})'(\mathbf{w}^{N,k}(x), x)\mathbf{q} + (1-\tau)\sigma'(x)\mathbf{w}^{N,k}(x) > \mathbf{0} \text{ for } x > b.$$

Then we obtain a contradiction in signs in the equation for the component of the vector-function $\mathbf{u}^k$ which has a minimum at $x = x_1$. This yields (3.11).

We can now conclude the proof of Theorem 3.4. Since the solutions $\mathbf{w}^{N,k}$ are non-monotone, without loss of generality, we can suppose that the first components of these functions are not monotone. Then there are values $x_k > 0$ such that $w_1^{N,k'}(x_k) = 0$. In view of (3.11), we have $a < x_k < b$ and up to some subsequence $x_k \to x_* > 0$. Then $\widehat{w}_1'(x_*) = 0$ and we obtain a contradiction with Lemma 3.5.

□

Remark. Decreasing solutions of (2.3)-(2.4) are separated from the trivial solution $\mathbf{w} \equiv \mathbf{0}$. More particularly, by virtue of the arguments in the proof of Theorem 3.4, there exists some constant $\eta > 0$ such that for any solution $\mathbf{w}^M$ of (2.3)-(2.5) and all $\tau \in [0, 1]$:

$$w_i^M(0) > \eta, \text{ for } i = 1, \ldots, 8. \tag{3.20}$$

Indeed, otherwise there exists a sequence of monotone solutions $\mathbf{w}^{M,k}$ converging to some $\widehat{\mathbf{w}}$ in E^1_μ, and at least one component of $\widehat{\mathbf{w}}(0)$ vanishes. This would contradict Lemma 3.5.

3.3. **A priori estimates of monotone solutions.** Our aim is to obtain a priori estimates of solutions of problem (2.3)-(2.5) in the weighted Hölder space E^1_μ independent of the homotopy parameter τ. A crucial assumption will concern the speed c^0 in the traveling wave problem (1.12)-(1.13), that we rewrite here:

$$\mathbf{D}\mathbf{u}'' + c^0\mathbf{u}' + \mathbf{G}^{\mathbf{0}}(\mathbf{u}) = \mathbf{0},$$
$$\mathbf{u}(\infty) = \mathbf{0}, \ \mathbf{u}(-\infty) = \mathbf{w}^0.$$

Recall that $\mathbf{G}^0(\mathbf{w}) = \mathbf{F}(\mathbf{w}) - \sigma_0\mathbf{w}$. As stated in the introduction, due to the assumption (1.11), the function $\mathbf{G}^0$ has exactly three nonnegative zeros: $\mathbf{0} < \bar{\mathbf{w}} < \mathbf{w}^0$. The stability properties of these zeros together with the monotony of $\mathbf{G}^0$ guarantee the existence and uniqueness of the traveling wave solution (up to some translation in space for $\mathbf{u}$).

We can now state the main result of this section.

Theorem 3.6. *Under the assumptions* (1.8)*,* (1.10)-(1.11)*, suppose that the speed* c^0 *in problem* (1.12)-(1.13) *is positive. Then there exists a constant* R *such that for all* $\tau \in [0,1]$ *and all solutions* $\mathbf{w}$ *of problem* (2.3)-(2.5) *the following estimate holds:*

$$\|\mathbf{w}\|_{E^1_\mu} \le R. \tag{3.21}$$

Proof. From the uniform estimate of monotone solutions given by Proposition 3.2 it easily follows that solutions of problem (2.3)-(2.5) are uniformly bounded in the Hölder space without weight. Hence, to prove the theorem it is sufficient to show that $\sup_x ||\mathbf{w}(x)\mu(x)||$ is uniformly bounded.

The solutions decay exponentially at infinity. Therefore, the weighted norm $\sup_x ||\mathbf{w}(x)\mu(x)||$ is bounded for every solution. Suppose that the solutions are not bounded uniformly in the weighted norm. Then there exists a sequence $\mathbf{w}^k$ of solutions of (2.3)-(2.5) such that:

$$\sup_{x\ge 0} ||\mathbf{w}^k(x)\mu(x)|| \to \infty \ \text{ as } k \to \infty. \tag{3.22}$$

These solutions can correspond to different values of τ.

Let $\varepsilon > 0$ be small enough, so that exponential decay of the solutions gives the existence of a constant M, independent of k, such that the estimate

$$||\mathbf{w}^k(x)\mu(x)|| \le M \tag{3.23}$$

follows from the inequality $||\mathbf{w}^k(x)|| \le \varepsilon$. Choosing $\varepsilon < \eta$ given by (3.20) we can select $x_k > 0$ such that

$$||\mathbf{w}^k(x_k)|| = \varepsilon, \ ||\mathbf{w}^k(x)\mu(x-x_k)|| \le M \ \text{ for } x \ge x_k. \tag{3.24}$$

If the values x_k are uniformly bounded, then the values $||\mathbf{w}^k(x)\mu(x)||$ are uniformly bounded for $0 \le x \le x_k$ since $\mathbf{w}^k(x) < \mathbf{w}^+$ (see Lemma 3.2). Together with (3.24) this provides the required estimate for all $x \ge 0$.

Suppose now that $x_k \to \infty$. Consider the sequence of functions $\mathbf{z}^k(x) = \mathbf{w}^k(x+x_k)$ that satisfy the equation:

$$\mathbf{D}\mathbf{z}^{k''}(x) + \mathbf{F}(\mathbf{z}^k(x)) - (1-\tau_k)\sigma(x+x_k)\mathbf{z}^k(x) - \tau_k\sigma_0\mathbf{z}^k(x) = 0 \ \text{ for } x \ge -x_k, \tag{3.25}$$

for some $\tau_k \in [0,1]$. Up to some subsequence, the functions $\mathbf{z}^k$ converge to some limiting function $\mathbf{z}^0$ in $\mathcal{C}^2_{loc}(\mathbb{R})$ while τ_k converges to some τ_0. Then the limit $\mathbf{z}^0$ is non-increasing with $\mathbf{0} \le \mathbf{z}^0(x) \le \mathbf{w}^+$. Moreover, since $\lim\limits_{y\to\infty}\sigma(y) = \sigma_0$, $\mathbf{z}^0$ satisfies the equation

$$\mathbf{D}\mathbf{z}^{0''}(x) + \mathbf{F}(\mathbf{z}^0(x)) - \sigma_0\mathbf{z}^0(x) = 0 \ \text{ for } x \in \mathbb{R}. \tag{3.26}$$

Also, in view of (3.24), we have $||\mathbf{z}^0(0)|| = \varepsilon$ and $||\mathbf{z}^0(x)\mu(x)|| \le M$. Hence $\mathbf{z}^0(0) \ne \mathbf{0}$ and $\mathbf{z}^0(\infty) = \mathbf{0}$. Consequently, the non-increasing bounded function $\mathbf{z}^0(x)$ possesses some limit $\mathbf{z}^-$ as $x \to -\infty$ and this limit can not be $\mathbf{0}$. Since $\mathbf{z}^-$ is a non-negative zero of $\mathbf{G}^0$, then, either $\mathbf{z}^- = \bar{\mathbf{w}}$ or $\mathbf{z}^- = \mathbf{w}^0$. Both cases lead to a contradiction.

Indeed, $\mathbf{z}^0$ is a non-negative non-increasing solution of (3.26) with $\mathbf{z}^0(\infty) = \mathbf{0}$, $\mathbf{z}^0(-\infty) = \mathbf{z}^-$. If $\mathbf{z}^- = \bar{\mathbf{w}}$, then since $\bar{\mathbf{w}}$ is unstable such a solution can not exist [15]. If $\mathbf{z}^- = \mathbf{w}^0$, then this provides a solution of (1.12)-(1.13) with the speed $c^0 = 0$, which contradicts our assumption on the speed for this problem.

Hence the function $\mathbf{z}^0$ can not exist, and the sequence x_k is bounded. This completes the proof of Theorem 3.6. □

4. Proof of Theorem 1.1

4.1. **Existence of pulses for the limit problem ($\tau = 1$).** The final system in the homotopy reads

$$\mathbf{D}\mathbf{w}'' + \mathbf{G}^0(\mathbf{w}) = \mathbf{0}, \tag{4.1}$$

and we look for solutions satisfying the following conditions:

$$\mathbf{w}'(0) = \mathbf{0}, \;\; \mathbf{w}(\infty) = \mathbf{0}, \;\; \mathbf{w}'(x) < \mathbf{0} \text{ for } x > 0. \tag{4.2}$$

In [11], we studied an analogous problem with $\mathbf{F}$ instead of $\mathbf{G}^0$ in the equations. These two nonlinear functions are quite similar since we obtain $\mathbf{G}^0$ by replacing the positive constants h_i by $h_i + \sigma_0$ in the definition (1.2) of $\mathbf{F}$. Under the assumption (1.11) the results in [11] apply to the problem (4.1)-(4.2) and provide the following result.

Proposition 4.1. *Suppose that condition* (1.11) *is satisfied and let* $\sigma_0 > 0$ *be given. Then the problem* (4.1)-(4.2) *possesses a solution in the space* E^1_μ *if and only if the wave speed* c^0 *in the problem* (1.12)-(1.13) *is positive. Moreover, the value of the degree* $\gamma(A^1, \mathcal{O})$ *is different from zero for any bounded open set* $\mathcal{O} \subset E^1_\mu$ *which contains all monotone solutions and does not contain any non-monotone solution, with no solutions on its boundary.*

4.2. **Leray-Schauder method and the existence of pulses for $\tau = 0$.** Under the assumption $c^0 > 0$, we can now prove the existence of pulses for Problem (1.5).

In Section 2 we introduced the homotopy $\mathbf{G}^\tau$. From Theorem 3.6 it follows that there exists a ball $\mathcal{B}$ containing all the decreasing solutions of the equations $A^\tau(\mathbf{w}) = \mathbf{0}$ for all $\tau \in [0, 1]$. Since the operator A^τ is proper on closed bounded sets with respect to both variables $\mathbf{w}$ and τ, then the set of decreasing solutions of the equation $A^\tau(\mathbf{w}) = \mathbf{0}$ is compact. Since they are separated from non-monotone solutions, then we can construct a domain $\mathcal{O} \subset \mathcal{B} \subset E_\mu^1$ such that all monotone solutions (for all $\tau \in [0,1]$) are located inside $\mathcal{O}$ and there are no non-monotone solutions in the closure $\bar{\mathcal{O}}$. Indeed it is sufficient to take a union of small balls of the radius r (Theorem 3.4) around each monotone solution.

We can define the topological degree $\gamma(A^\tau, \mathcal{O})$ and it remains unchanged along the homotopy:

$$\forall \tau \in [0,1], \;\; \gamma(A^\tau, \mathcal{O}) = \gamma(A^1, \mathcal{O}). \tag{4.3}$$

Consequently, Proposition 4.1 yields that $\gamma(A^0, \mathcal{O}) \neq 0$, and problem (1.5)-(1.7) possesses a solution. This completes the proof of Theorem 1.1.

5. Discussion

There is a vast literature on modelling of blood coagulation devoted to different facets of this complex process including coagulation cascade, hemodynamics, the role of platelets, and so on (see, e.g., [1, 4, 8] and the references therein). In this work we study the existence of stationary solutions of the 1D reaction-diffusion model of blood coagulation.

Biological and modelling assumptions. Clot formation is an important and complex physiological process based on biochemical reactions in plasma and platelet aggregation. Insufficient clotting leads to various bleeding disorders including hemophilia, excessive clotting results in thrombosis. The latter can lead to stroke or heart attack. Overall, clotting disorders represent the major cause of mortality and morbidity. One of the important questions of biomedical research is to control clot growth and to prevent thrombosis. Mathematical modeling can help to understand some properties of this complex system and to estimate its quantitative characteristics.

Clot growth is initiated at the blood vessel wall when tissue factor expressed by the endothelial cells and subendothelial matrix comes into contact with blood plasma. The initial quantity of blood factors produced at the initiation stage should be sufficient to start self-sustained clot growth in the form of a travelling wave. In our previous work [11] we have shown that in quiescent plasma this threshold level is determined by a pulse solution. We proved that the pulse exists if and only if the speed of the corresponding wave is positive. Hence, we obtain two conditions of clot growth: positive wave speed and initial condition exceeding the pulse solution.

Once clot starts propagation, at some moment it should stop its growth in order to avoid vessel occlusion. There are two main physiological mechanisms of clot growth arrest. One of them acts near the blood vessel wall, and it is based on the activation of protein C. Another mechanism acts on a larger distance from the wall, and it is based on the influence of blood flow. The latter removes blood factors from the clot and decelerates chemical reactions of blood coagulation possibly leading to the complete growth arrest.

The model considered in this work corresponds to the one-dimensional cross section of the blood vessel perpendicular to the vessel wall. The corresponding system of equations is considered on the half-axis $x \geq 0$, where $x = 0$ corresponds to the wall. This semi-infinite domain provides a good approximation of the blood coagulation process since the width of the reaction zone, that is, the interval where the essential part of prothrombin is converted into thrombin, is narrow compared with the vessel radius. Also by considering a two-dimensional setting with convection terms and integrating the equations for the concentrations in the direction of the flow, one obtains approximate equations with the terms $-\sigma(x)\mathbf{w}$ (see (1.3)). This 1D model of blood coagulation gives a good qualitative and even quantitative approximation of more complete 2D and 3D problems with Navier-Stokes equations for blood flow [2].

Limitations of the model. Kinetics of blood coagulation is extremely complex, it includes dozens of blood factors and reactions. In this work we study the propagation phase of coagulation cascade, and we do not consider various factors acting at the vessel wall or near it, such as TFPI or activated protein C. Some other factors including blood borne tissue factor [9] or platelet derived polyphosphates [16] also influence the coagulation cascade, and they can be considered in the future investigations. Furthermore, fibrinolysis which consists in breaking fibrin clot by plasmin [3] occurs after clot formation and, therefore, it is separated in time with the process of coagulation propagation considered in this work.

Results. In this work, we study the influence of blood flow on clot growth. The main result of the work affirms the existence of a stationary solution of the reaction-diffusion system if the maximal blood flow velocity preserves the positiveness of the corresponding wave speed. By analogy with quiescent plasma, we call this stationary solution a pulse solution. As before, we can expect that this solution is unstable. However, the same method of stability analysis is not applicable here, and this question remains open. If this property holds, then the solution of the initial boundary value problem with some appropriate initial condition will grow and approach the travelling wave solution. Biologically, this means that clot growth cannot be stopped by blood flow, and it results in complete vessel occlusion. Thus, in order to provide normal physiological conditions of a limited clot growth, we need to assume that the wave speed for the maximal blood flow velocity is negative. Numerical simulations confirm this conjecture [2]. Its mathematical analysis is open for further investigations.

Finally, let us discuss the biological meaning of the conditions of Theorem 1.1 on the matrix $\mathbf{F}'(0)$ and on the polynomial $P^0(T)$. First of all, blood coagulation should not occur without initiation. Mathematically speaking, this means that $\mathbf{u} = \mathbf{0}$ is a stable stationary point of the ODE system $\mathrm{d}\mathbf{u}/\mathrm{d}t = \mathbf{F}(\mathbf{u})$. This condition is satisfied if all eigenvalues of the matrix $\mathbf{F}'(0)$ have negative real parts. Next, we study in this work the case where clot growth occurs even for the maximal flow velocity for the limiting nonlinearity $\mathbf{G}^0(\mathbf{u})$. Therefore, this vector-valued function should have at least one more stable stationary point. Since there is one-to-one correspondence between the stationary points of this vector-values function and the roots of the polynomial $P^0(T)$, including their stability, we arrive to the required condition. Thus, the conditions of the theorem are imposed by the biological meaning of the considered problem.

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References

[1] A.V. Belyaev, J.L. Dunster, J.M. Gibbins, M.A. Panteleev, V. Volpert. Modeling thrombosis in silico: Frontiers, challenges, unresolved problems and milestones. Physics of Life Reviews, 2018

[2] A. Bouchnita, T. Galochkina, P. Kurbatova, P. Nony and V. Volpert, Conditions of microvessel occlusion for blood coagulation in flow, *International Journal for Numerical Methods in Biomedical Engineering*, 2017, e2850.

[3] J.C. Chapin, K.A. Hajjar, Fibrinolysis and the control of blood coagulation, Blood Rev. 29 (2015) 17-24.

[4] A. Fasano, A. Sequeira Hemomath, the Mathematics of Blood. Springer, 2017.

[5] T. Galochkina, H. Ouzzane, A. Bouchnita and V. Volpert, Traveling wave solutions in the mathematical model of blood coagulation. *Applicable Analysis*, 96, 2017, no. 16, 2891-2905.

[6] Y. V. Krasotkina, E. I. Sinauridze and F. I. Ataullakhanov, Spatiotemporal dynamics of fibrin formation and spreading of active thrombin entering non-recalcified plasma by diffusion, *Biochimica et Biophysica Acta (BBA) - General Subjects*, 1474, 2000, no. 3, 337-345.

[7] M. Marion and V. Volpert, Existence of pulses for a monotone reaction-diffusion system. *J Pure and Applied Functional Analysis*, 1, 2016, 97-122.

[8] K.G. Mann, T. Orfeo, S. Butenas, A. Undas, K. Brummel-Ziedins, Blood coagulation dynamics in haemostasis, Hemostaseologie 29 (2009) 7-16

[9] B. Osterud, E.S. Breimo, J.O. Olsen. Blood borne tissue factor revisited, Thromb. Res. 122 (2008) 432-344.

[10] E. A. Pogorelova and A. I. Lobanov, Influence of enzymatic reactions on blood coagulation autowave, *Biophysics* , 59, 2014, no. 1, 10-118.

[11] N. Ratto, M. Marion and V. Volpert, Existence of pulses for a reaction-diffusion system of blood coagulation, 2018, submitted.

[12] A. A. Tokarev, Y. V. Krasotkina, M. V. Ovanesov, M. A. Panteleev, M. A. Azhigirova, V. A. Volpert, F. I. Ataullakhanov, and A. A. Butilin, Spatial dynamics of contact-activated fibrin clot formation in vitro and in silico in haemophilia b: Effects of severity and ahemphil b treatment, *Mathematical Modelling of Natural Phenomena*, 1, 2006, no. 2, 124-137.

[13] V. Volpert and A. Volpert, Properness and topological degree for general elliptic operators, *Abstract and Applied Analysis*, 3, 2003, 129-182.

[14] V. Volpert, *Elliptic partial differential equations. Volume 1. Fredholm theory of elliptic problems in unbounded domains*, Birkhäuser, Basel, 2011.

[15] A. I. Volpert, V. A. Volpert, V. A. and V. A.Volpert, *Traveling Wave Solutions of Parabolic Systems*, AMS, Translations of Mathematical Monographs, volume 140, Providence, 1994.

[16] J.I. Weitz, J.C. Fredenburgh. Platelet polyphosphate: the long and the short of it, Blood 129 (2017) 1574.

[17] V.I. Zarnitsina, F.I. Ataullakhanov, A.I. Lobanov, and 0.L. Morozova, Dynamics of spatially nonuniform patterning in the model of blood coagulation, *Chaos: An Interdisciplinary Journal of Nonlinear Science*, 11, 2001, no. 1, 57-70.

[18] V.I. Zarnitsina, A.V. Pokhilko, F.I. Ataullakhanov, *A mathematical model for the spatio-temporal dynamics of intrinsic pathway of blood coagulation. I. The model description*, Thromb Res. 84 (1996), 225-236.

Appendix A. Nonnegative zeros of $\mathbf{G}^0$

We aim to investigate non-negative zeros of the vector-valued function $\mathbf{G}^0$ given by (1.9). Setting $T = w_8$, we get the equations:

$$\begin{cases} G_1^0(\mathbf{w}) \equiv k_1 w_3 w_6 - h_1 w_1 - \sigma_0 w_1 = 0, \\ G_2^0(\mathbf{w}) \equiv k_2 w_4 w_5 - h_2 w_2 - \sigma_0 w_2 = 0, \\ G_3^0(\mathbf{w}) \equiv k_3 T(\rho_3 - w_3) - h_3 w_3 - \sigma_0 w_3 = 0, \\ G_4^0(\mathbf{w}) \equiv k_4 T \rho_4 - w_4) - h_4 w_4 - \sigma_0 w_4 = 0, \\ G_5^0(\mathbf{w}) \equiv k_5 v_7(\rho_5 - w_5) - h_5 w_5 - \sigma_0 w_5 = 0, \\ G_6^0(\mathbf{w}) \equiv (k_6 w_5 + \overline{k}_6 w_2)(\rho_6 - w_6) - h_6 w_6 - \sigma_0 w_6 = 0, \\ G_7^0(\mathbf{w}) \equiv k_7 T(\rho_7 - w_7) - h_7 w_7 - \sigma_0 w_7 \\ G_8^0(\mathbf{w}) \equiv (k_8 w_6 + \overline{k}_8 w_1)(\rho_8 - T) - h_8 T_8 - \sigma_0 T. \end{cases} . \tag{A.1}$$

First, we note that if $(w_1, w_2, ..., w_7, T)$ is a non-negative zero, then every w_i for $i = 1, 2, ..., 7$, can be expressed as a function of $T \geq 0$. Indeed, the third equation in (A.1) provides the equality:

$$w_3 = \frac{k_3 \rho_3 T}{k_3 T + h_3 + \sigma_0} \equiv \phi_3(T). \tag{A.2}$$

Solving consecutively the equations $G_i^0(w_1, w_2, ..., w_7, T) = 0$ for $i = 4, 7, 5, 2, 6, 1$, we obtain:

$$w_4 = \frac{k_4 \rho_4 T}{k_4 T + h_4 + \sigma_0} \equiv \phi_4(T), \tag{A.3}$$

$$w_7 = \frac{k_7 \rho_7 T}{k_7 T + h_7 + \sigma_0} \equiv \phi_7(T), \tag{A.4}$$

$$w_5 = \frac{k_5 \rho_5 \phi_7(T)}{k_5 \phi_7(T) + h_5 + \sigma_0} \equiv \phi_5(T), \tag{A.5}$$

$$w_2 = \frac{k_2}{h_2 + \sigma_0} \phi_4(T) \phi_5(T) \equiv \phi_2(T), \tag{A.6}$$

$$w_6 = \frac{\rho_6 (k_6 \phi_5(T) + \bar{k}_6 \phi_2(T))}{k_6 \phi_5(T) + \bar{k}_6 \phi_2(T) + h_6 + \sigma_0} \equiv \phi_6(T), \tag{A.7}$$

$$w_1 = \frac{k_1}{h_1 + \sigma_0} \phi_3(T) \phi_6(T) \equiv \phi_1(T). \tag{A.8}$$

It is worth noting that the functions ϕ_i are rational fractions with no positive poles. Also the following properties are straightforward:

$$\phi_i(0) = 0, \quad \phi_i(T) > 0 \text{ and } \phi_i'(T) > 0 \text{ for } T > 0.$$

Next, we consider the last equation $G_8^0(w_1, w_2, ..., w_7, T) = 0$ which can be written as follows:

$$R(T) \equiv G_8^0(\phi_1(T), \phi_2(T), ..., \phi_7(T), T) = 0,$$

or, using the explicit formula for G_8^0:

$$R(T) = (k_8\phi_6(T) + \overline{k}_8\phi_1(T))(\rho_8 - T) - h_8T - \sigma_0T = 0. \qquad \text{(A.9)}$$

From the equations of the system $\mathbf{G}^0(\mathbf{w}) = \mathbf{0}$ we conclude that $(w_1, w_2, ..., w_7, T)$ is a non-negative zero of $\mathbf{G}^0$ if and only if $w_i = \phi_i(T)$ for $i = 1, ..., 7$, and T is a non-negative solution of the equation $R(T) = 0$.

Let us investigate the equation $R(T) = 0$ more precisely. Since $\phi_1(T)$ and $\phi_6(T)$ are rational fractions with no positive poles, the same is true for $R(T)$. A straightforward but tedious computation based on the explicit forms of the $\phi_i(T)$ provides the equality

$$R(T) = \frac{P_1(T)(\rho_8 - T)}{P_2(T)} - (h_8 + \sigma_0)T, \qquad \text{(A.10)}$$

where P_1 and P_2 are third degree polynomials with positive coefficients. Hence, $P_2(T) > 0$ for $T \geq 0$. Here the numerator of R denoted by P^0 is given by the following expression:

$$P^0(T) \equiv P_1(T)(\rho_8 - T) - (h_8 + \sigma_0)P_2(T)T. \qquad \text{(A.11)}$$

and the equation $R(T) = 0$ is equivalent to $P^0(T) = 0$. The explicit computation of the coefficients of P^0 shows that it is a fourth degree polynomial of the form:

$$P^0(T) = aT^4 + bT^3 + cT^2 + dT, \qquad \text{(A.12)}$$

where the leading coefficient a is negative since the coefficients of P_1 and P_2 are positive.