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Initiation of reaction–diffusion waves of blood coagulation

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Formation of blood clot in response to the vessel damage is triggered by the complex network of biochemical reactions of the coagulation cascade. The process of clot growth can be modeled as a traveling wave solution of the bistable reaction–diffusion system. The critical value of the initial condition which leads to convergence of the solution to the traveling wave corresponds to the pulse solution of the corresponding stationary problem. In the current study we prove the existence of the pulse solution for the stationary problem in the model of the main reactions of the blood coagulation cascade using the Leray–Schauder method.

1. Introduction

The main function of blood coagulation is the formation of blood clot covering the injury site and preventing further blood leak in case of vessel damage. One can define three main stages of the blood coagulation process: initiation of the clotting process, amplification of clot formation and clot growth arrest [1,2]. Clot growth is triggered by the enzyme thrombin that catalyzes fibrinogen conversion to fibrin which leads to blood gelation [3,4]. During each stage of the coagulation process the speed of thrombin formation is determined by the action of different proteins. Initial amount of thrombin is formed in response to the exposure of the tissue factor to blood plasma with help of factors VIIa and Xa [5,6], or as the result of factor XI activation on the foreign surface through the reactions of the contact system [7]. Amplification phase takes place thanks to the positive feedback loops of the blood coagulation cascade with participation of factors XI, X, IX, VIII, V and their complexes [8]. The main mechanisms of the clot growth arrest are

the action of the direct thrombin inhibitors such as antithrombin [9], the mechanical removal of the active substances by the blood flow and the active protein C pathway [2]. Whether the amplification phase of the coagulation cascade will be launched or not depends on the amount of thrombin formed during the initiation stage [5]. In the current study we address triggering of the coagulation system from the initiation to the amplification phase using a mathematical model.

Clot growth can be described as a reaction–diffusion wave for the concentrations of blood factors [10–12]. Under certain assumptions we can prove existence and stability of such solutions for the model system of coagulation cascade [13]. We suppose that thrombin production during the coagulation process is described by a bistable system. Indeed, under normal conditions, accelerated thrombin formation occurs only in response to the significantly important initial stimuli [5,14,15]. Under this assumption, the convergence of the solution of the model system to a traveling wave takes place only for the sufficiently large initial condition. In terms of biochemical process, the amount of thrombin formed during the initiation stage must exceed some threshold value to launch the amplification phase of blood coagulation process. The threshold value for the initial conditions that guarantees convergence of the

Dedicated to Professor Edriss S. Titi on the occasion of his 60th birthday.

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solution to the traveling wave in case of one PDE is a stationary solution of the system in particular form called pulse solution. The similar criteria was proven for the system of two equations in particular form [16]. In the current study we consider the existence of pulse solutions for a system of PDE describing the action of the coagulation cascade.

Thrombin production in quiescent plasma during the amplification phase of blood coagulation can be described by the following system of PDEs:

$$\begin{aligned}
\frac{\partial v_1}{\partial t} &= D \frac{\partial^2 v_1}{\partial x^2} + k_V T - h_V v_1, \\
\frac{\partial v_2}{\partial t} &= D \frac{\partial^2 v_2}{\partial x^2} + k_{VIII} T - h_{VIII} v_2, \\
\frac{\partial v_3}{\partial t} &= D \frac{\partial^2 v_3}{\partial x^2} + k_{XI} T - h_{XI} v_3, \\
\frac{\partial v_4}{\partial t} &= D \frac{\partial^2 v_4}{\partial x^2} + k_{IX} v_3 - h_{IX} v_4, \\
\frac{\partial v_5}{\partial t} &= D \frac{\partial^2 v_5}{\partial x^2} + k_X v_4 + k_X^* v_2 v_4 - h_X v_5, \\
\frac{\partial T}{\partial t} &= D \frac{\partial^2 T}{\partial x^2} + (k_{II} v_5 + k_{II}^* v_1 v_5) \left(1 - \frac{T}{T_0}\right) - h_{II} T.
\end{aligned} \tag{1.1}$$

Here T denotes thrombin concentration, v_i , $i = 1, \dots, 5$, respectively denote concentrations of the activated forms of factors V, VIII, XI, IX and X. The constant T_0 denotes the maximal available concentration of thrombin taken equal to the initial concentration of prothrombin in blood plasma.

The diffusion coefficient D is a positive number. We suppose that all the diffusion coefficients are equal to each other. Such assumption is relevant for the coagulation cascade reaction since all the participating proteins have approximately the same size. All results remain valid in the case of different diffusion coefficients.

We consider a one-dimensional case with x axis perpendicular to the vessel wall and directed from the wall to the vascular lumen.

A more detailed discussion of the model can be found in [13], see also Appendix of this paper.

Let us set $\mathbf{w} = (w_1, \dots, w_5, T)$ (alternatively we will also denote $w_6 = T$). Then, system (1.1) can be written in the vector form:

$$\frac{\partial \mathbf{w}}{\partial t} = D \frac{\partial^2 \mathbf{w}}{\partial x^2} + \mathbf{F}(\mathbf{w}), \tag{1.2}$$

where $\mathbf{F} = (F_1, \dots, F_6)$, is the vector of reaction rates in Eqs. (1.1). The functions F_i take the form:

$$\begin{aligned}
F_1(\mathbf{w}) &= \alpha_i(\beta_i T - w_i) \text{ for } i = 1, 2, 3, \\
F_4(\mathbf{w}) &= \alpha_4(\beta_4 w_3 - w_4), \\
F_5(\mathbf{w}) &= \alpha_5(\beta_5 w_4 + \gamma w_2 w_4 - w_5), \\
F_6(\mathbf{w}) &= \alpha_6 w_5 (1 + \delta w_1) \left(1 - \frac{T}{T_0}\right) - \sigma T,
\end{aligned} \tag{1.3}$$

where the different constants are positive and are given by

$$\begin{aligned}
\alpha_1 &= h_V, \alpha_2 = h_{VIII}, \alpha_3 = h_{XI}, \alpha_4 = h_{IX}, \alpha_5 = h_X, \alpha_6 = k_{II}, \\
\beta_1 &= \frac{k_V}{h_V}, \beta_2 = \frac{k_{VIII}}{h_{VIII}}, \beta_3 = \frac{k_{XI}}{h_{XI}}, \beta_4 = \frac{k_{IX}}{h_{IX}}, \beta_5 = \frac{k_X}{h_X}, \\
\gamma &= \frac{k_X^*}{h_X}, \delta = \frac{k_{II}^*}{k_{II}}, \sigma = h_{II}.
\end{aligned}$$

The zeros $\mathbf{w}^* = (w_1^*, \dots, w_5^*, T^*)$ of \mathbf{F} satisfy the equations

$$\begin{aligned}
w_1^* &= \beta_1 T^*, \quad w_2^* = \beta_2 T^*, \quad w_3^* = \beta_3 T^*, \quad w_4^* = \beta_3 \beta_4 T^*, \\
w_5^* &= \beta_3 \beta_4 T^* (\beta_5 + \gamma \beta_2 T^*).
\end{aligned} \tag{1.4}$$

Furthermore by expressing that $F_6(\mathbf{w}^*) = 0$ we find that T^* is a root of some polynomial P of order four which takes the form:

$$P(T) = TQ(T) \text{ with } Q(T) = aT^3 + bT^2 + cT + d. \tag{1.5}$$

Here $a < 0$ while the other coefficients of P have no a priori signs (see Section 2.2 for the explicit values of the coefficients of P). Consequently the zeros of F are in one-to-one correspondence with the ones of P . Clearly 0 is always a zero of P and the corresponding zero of F is the origin $\mathbf{0}$ of \mathbb{R}^6 .

Hereafter we will focus on the case where P has exactly two positive zeros denoted by $0 < \bar{T} < T^-$. We will also assume that

$$Q(0) < 0, \quad Q'(\bar{T}) > 0, \quad Q'(T^-) < 0, \tag{1.6}$$

(recall that Q is some polynomial of order three with negative leading coefficient). It can be easily shown that $T^- < T_0$ (see Section 2.2).

Consequently, \mathbf{F} has exactly three zeros in \mathbb{R}_+^6 . Let us denote them by \mathbf{w}^- , $\bar{\mathbf{w}}$ and \mathbf{w}^+ where $\mathbf{w}^+ = \mathbf{0} < \bar{\mathbf{w}} < \mathbf{w}^-$ (here and everywhere below inequalities for vectors mean that each component of the vectors satisfies this inequality). Furthermore, assumptions (1.6) guarantee that the principal eigenvalue of the Jacobian matrix of \mathbf{F} at \mathbf{w}^\pm (resp. $\bar{\mathbf{w}}$) is negative (resp. positive) (see Section 3.3). Hence the nonlinearity \mathbf{F} is of the bistable type.

It is easy to check that F_i satisfy the following property for all $j \neq i$:

$$\frac{\partial F_i}{\partial w_j}(\mathbf{w}) \geq 0 \text{ if } w_k \geq 0 \text{ for } 1 \leq k \leq 5 \text{ and } T < T_0. \tag{1.7}$$

Hence the system is monotone in that region of \mathbb{R}^6 containing the positive zeros of \mathbf{F} . It has a number of properties similar to those for scalar equations including the maximum principle.

By virtue of the above properties, system (1.2) possesses a unique traveling wave solution $\mathbf{u}(z)$, $z = x - ct$, satisfying the following equations and limits at infinity:

$$D\mathbf{u}'' + c\mathbf{u}' + \mathbf{F}(\mathbf{u}) = \mathbf{0}, \quad \mathbf{u}(\pm\infty) = \mathbf{w}^\pm, \tag{1.8}$$

(up to some translation in space for \mathbf{u}).

The stationary solutions of system (1.2) satisfy the elliptic system:

$$\begin{aligned}
Dw_1'' + \alpha_1(\beta_1 T - w_1) &= 0, \quad i = 1, 2, 3, \\
Dw_4'' + \alpha_4(\beta_4 w_3 - w_4) &= 0, \\
Dw_5'' + \alpha_5(\beta_5 w_4 + \gamma w_2 w_4 - w_5) &= 0, \\
DT'' + \alpha_6 w_5 (1 + \delta w_1) \left(1 - \frac{T}{T_0}\right) - \sigma T &= 0.
\end{aligned} \tag{1.9}$$

Hereafter we consider system (1.9) on the real axis and look for an even positive solution vanishing at infinity:

$$\mathbf{w}(x) > \mathbf{0}, \quad \mathbf{w}(x) = \mathbf{w}(-x), \quad x \in \mathbb{R}, \quad \mathbf{w}(\pm\infty) = \mathbf{0}.$$

We will call such solutions pulses. Instead of the problem on the whole axis, we can consider system (1.9) on the half-axis \mathbb{R}_+ with the boundary condition

$$\mathbf{w}'(0) = \mathbf{0}. \tag{1.10}$$

We will look for the decreasing solutions defined on \mathbb{R}_+ and require:

$$\begin{aligned}
\mathbf{w}'(0) &= \mathbf{0}, \quad \mathbf{w}(x) > \mathbf{0} \text{ and } \mathbf{w}'(x) < \mathbf{0} \text{ for } x > 0, \\
\mathbf{w}(\infty) &= \mathbf{0}.
\end{aligned} \tag{1.11}$$

Then the pulse is obtained by extending this function on \mathbb{R} by symmetry.

We can now formulate the principal result of this work.

Theorem 1.1. *Under assumption (1.6), problem (1.9) has a solution on \mathbb{R}_+ satisfying (1.11) if and only if the value of the speed c in problem (1.8) is positive.*

Theorem 1.1 can be easily proved for scalar equations. Indeed, suppose that we deal with some scalar equation with a nonlinearity F of bistable type with a single intermediate zero. Then it is well known that the speed c of the scalar traveling wave problem (1.8) has the sign of the integral $\int_0^w F(s)ds$. Besides, if we rewrite the scalar equation for the pulse in the form:

$$\begin{cases} w' = p, \\ p' = -F(w), \end{cases} \quad (1.12)$$

it is easy to see that:

$$\frac{w'(x)^2}{2} = - \int_0^{w(x)} F(s)ds.$$

From there it follows that the condition $\int_0^w F(s)ds > 0$ is necessary and sufficient for the existence of the pulse solutions. This provides the conclusion of Theorem 1.1 for the bistable scalar equations.

For systems of equations, the positiveness of the integral cannot be used anymore to conclude that the pulse exists and/or the speed of the wave is positive. Nevertheless, the relation between the sign of the wave speed and the existence of pulses may remain true. This was first proved in [16] and [17] for monotone systems of two equations. The proofs are much more involved than in the scalar case and rely on the Leray–Schauder method.

In this work we aim to derive such a result for the system describing main reactions of the blood coagulation cascade. In particular, the method supposes to construct some appropriate homotopy deformation. The key idea here will be to reduce the last equation in system (1.9) to some scalar equation that only depends on T . Meanwhile we will want the properties of the initial system to remain unchanged and we will have to track the sign of the wave speed when assuming $c > 0$ for problem (1.8). We start the description of the homotopy in Section 2. Then, in Section 3 we show separation of monotone solutions and we obtain a priori estimates of these solutions independently of the homotopy parameter. Section 4 is devoted to the proof of the existence part in Theorem 1.1. Finally we make some concluding remarks in Section 5 while the model is briefly discussed in Appendix.

2. Homotopy

2.1. Description

We introduce some homotopy of system (1.9) of the form:

$$D\mathbf{w}'' + \mathbf{F}^\tau(\mathbf{w}) = \mathbf{0}, \quad \tau \in [0, 1], \quad (2.1)$$

for which only the last component of the reaction term, that is $F_6^\tau(\mathbf{w})$, will vary with $\tau \in [0, 1]$. Hence the homotopy reads

$$\begin{aligned} Dw_1'' + \alpha_1(\beta_1 T - w_1) &= 0, \\ Dw_2'' + \alpha_2(\beta_2 T - w_2) &= 0, \\ Dw_3'' + \alpha_3(\beta_3 T - w_3) &= 0, \\ Dw_4'' + \alpha_4(\beta_4 w_3 - w_4) &= 0, \\ Dw_5'' + \alpha_5(\beta_5 w_4 + \gamma w_2 w_4 - w_5) &= 0, \\ DT'' + F_6^\tau(w) &= 0. \end{aligned} \quad (2.2)$$

As usual, the value $\tau = 0$ corresponds to the initial system (1.9) so that

$$F_6^0(\mathbf{w}) = F_6(\mathbf{w}) = \alpha_6 w_5 (1 + \delta w_1) \left(1 - \frac{T}{T_0}\right) - \sigma T. \quad (2.3)$$

Clearly F_6^0 is a nonlinear function of w_1, w_5 and T .

In the homotopy process we will reduce F_6^0 to some final nonlinearity F_6^1 that will only depend on T . Also we will require the zeros of F^τ in \mathbb{R}_+^6 to remain unchanged as τ varies between 0 and 1 and to be the ones of the initial nonlinearity $\mathbf{F} = (F_1, \dots, F_6)$.

In order to define the function $F_6^\tau(\mathbf{w})$, we introduce the auxiliary functions $\varphi_i(T), i = 1, \dots, 5$, determined by the equalities $F_i(\mathbf{w}) = 0$ for $i = 1, \dots, 5$, that is:

$$\begin{aligned} w_i &= \beta_i T \equiv \varphi_i(T), \quad i = 1, 2, 3, \\ w_4 &= \beta_4 \beta_3 T \equiv \varphi_4(T), \\ w_5 &= \beta_4 \beta_3 T (\beta_5 + \gamma \beta_2 T) \equiv \varphi_5(T). \end{aligned} \quad (2.4)$$

In addition we introduce some smooth function $g(T)$ which will be specified below in such a way that it does not change the zeros during the homotopy (other properties related to the positiveness of the wave speed will be required in Section 4.1).

The homotopy is defined as follows: for $\tau \in [0, \tau_1]$ where $\tau_1 \in (0, 1)$ ($\tau_1 = 1/2$ for example) we set

$$F_6^\tau(\mathbf{w}) = \alpha_6 w_5 (1 + \delta w_1) \left(1 - \frac{T}{T_0}\right) - \sigma T + \tau g(T), \quad (2.5)$$

while for $\tau \in (\tau_1, 1]$ we consider

$$\begin{aligned} F_6^\tau(\mathbf{w}) &= \alpha_6 [\alpha^\tau w_5 + \beta^\tau \varphi_5(T)] (1 + \delta [\alpha^\tau w_1 + \beta^\tau \varphi_1(T)]) \\ &\quad \times \left(1 - \frac{T}{T_0}\right) - \sigma T + \tau_1 g(T), \end{aligned} \quad (2.6)$$

$$\text{with } \alpha^\tau = \frac{1 - \tau}{1 - \tau_1}, \quad \beta^\tau = \frac{\tau - \tau_1}{1 - \tau_1}.$$

For $\tau \in [0, \tau_1]$ it will be convenient to set $\alpha^\tau = 1$ and $\beta^\tau = 0$ so that formula (2.6) is also valid for $\tau \in [0, \tau_1]$.

For some appropriate choice of the function $g(T)$ (see (2.12)), the nonlinearity F^τ will remain of bistable type (with unchanged zeros and unchanged stability properties of the zeros). Also F^τ will satisfy the same monotony property as \mathbf{F} (see (1.7)). Consequently the traveling wave problem (1.8) with \mathbf{F} replaced by \mathbf{F}^τ will possess some unique solution $(c^\tau, \mathbf{u}^\tau)$ (up to some translation in space for \mathbf{u}^τ).

These properties of \mathbf{F}^τ are derived in the following sections.

2.2. Stationary points

To investigate the zeros of \mathbf{F}^τ let us start with some preliminary remarks. For $\tau = 0$, the zeros are given by the equations

$$\begin{aligned} w_i &= \varphi_i(T) \text{ for } 1 \leq i \leq 5, \quad \alpha_6 \varphi_5(T) (1 + \delta \varphi_1(T)) \\ &\quad \times \left(1 - \frac{T}{T_0}\right) - \sigma T = 0. \end{aligned}$$

Here, a straightforward computation yields that

$$\begin{aligned} \alpha_6 \varphi_5(T) (1 + \delta \varphi_1(T)) \left(1 - \frac{T}{T_0}\right) - \sigma T &\equiv P(T) \\ &= aT^4 + bT^3 + cT^2 + dT, \end{aligned} \quad (2.7)$$

with

$$\begin{aligned} a &= -\alpha_6 \beta_1 \beta_2 \beta_3 \beta_4 \gamma \delta T_0^{-1}, \quad c = \alpha_6 \beta_2 \beta_3 \beta_4 \gamma \\ &\quad + \alpha_6 \beta_1 \beta_3 \beta_4 \beta_5 \delta - \alpha_6 \beta_3 \beta_4 \beta_5 T_0^{-1}, \\ b &= -\alpha_6 \beta_1 \beta_3 \beta_4 \beta_5 \delta T_0^{-1} + \alpha_6 \beta_1 \beta_2 \beta_3 \beta_4 \gamma \delta \\ &\quad - \alpha_6 \beta_2 \beta_3 \beta_4 \gamma T_0^{-1}, \quad d = \alpha_6 \beta_3 \beta_4 \beta_5 - \sigma. \end{aligned} \quad (2.8)$$

Recall that we suppose that the polynomial $P(T) = TQ(T)$ has exactly two positive zeros $0 < \bar{T} < T^-$. Since Q is a polynomial of degree three with negative leading coefficient it is straightforward that

$$P < 0 \text{ on } (0, \bar{T}), \quad P > 0 \text{ on } (\bar{T}, T^-), \quad P < 0 \text{ on } (T^-, \infty). \quad (2.9)$$

Also it is worth noting that

$$T^- < T^0. \quad (2.10)$$

Indeed, in view of definition (2.7) it is clear that $P(T) \leq -\sigma T < 0$ for $T \geq T^0$. Also recall that we assumed (1.6) which implies the following condition on the parameters

$$Q(0) = \alpha_6 \beta_3 \beta_4 \beta_5 - \sigma < 0. \quad (2.11)$$

Then the zeros of $\mathbf{F} = (F_1, \dots, F_6)$ remain unchanged if we replace F_6 by the following function

$$\alpha_6 [\alpha w_5 + \beta \varphi_5(T)] (1 + \delta [\alpha w_1 + \beta \varphi_1(T)]) \left(1 - \frac{T}{T_0}\right) - \sigma T,$$

where $0 \leq \alpha \leq 1$, $\beta = 1 - \alpha$. The same remains true if we replace F_6 by

$$\begin{aligned} & \alpha_6 [\alpha w_5 + \beta \varphi_5(T)] (1 + \delta [\alpha w_1 + \beta \varphi_1(T)]) \\ & \times \left(1 - \frac{T}{T_0}\right) - \sigma T + g(T) \end{aligned}$$

provided the function $g = g(s)$ is such that

$$g(s) \geq 0 \text{ for } s \geq 0, \quad \text{Supp } g \subset (\bar{T}, T^-). \quad (2.12)$$

Indeed, in that case in the equations for the zeros, $P(T)$ is modified in a region where $P(T) > 0$ by adding some non-negative term.

Hereafter we will suppose that function g satisfies (2.12). Then, the zeros of functions $\mathbf{F}^\tau = (F_1, \dots, F_5, F_6^\tau)$ where F_6^τ is given by (2.5) or (2.6) coincide with the ones of \mathbf{F} . In particular, these functions possess exactly three zeros in \mathbb{R}_+^6 which are \mathbf{w}^- , $\bar{\mathbf{w}}$ and \mathbf{w}^+ .

2.3. Monotony of the system and stability of the stationary points

Recalling that \mathbf{F} is given by (1.3) it is clear that

$$\frac{\partial F_i}{\partial w_j}(\mathbf{w}) \geq 0 \text{ for } i, j = 1, \dots, 6, \quad i \neq j,$$

provided that

$$\begin{aligned} w \in \mathcal{D} = \{ \mathbf{w} = (w_1, \dots, w_5, T), \quad w_k \geq 0 \\ \text{for } 1 \leq k \leq 5, \quad 0 \leq T < T_0 \}. \end{aligned}$$

This monotony property remains valid for the homotopy function \mathbf{F}^τ . Indeed $F_1^\tau, \dots, F_5^\tau$ remain unchanged while for the last component the positivity property is easily checked. Hence, for all $\tau \in [0, 1]$, the system is monotone in \mathcal{D} :

$$\frac{\partial F_i^\tau}{\partial w_j}(\mathbf{w}) \geq 0 \text{ for } i \neq j \text{ and } \mathbf{w} \in \mathcal{D}. \quad (2.13)$$

Let us now investigate the stability properties of the three zeros of \mathbf{F}^τ in \mathbb{R}_+^6 . Note that thanks to (2.10) these zeros belong to \mathcal{D} so that the off-diagonal terms of the Jacobian matrices at these points are non-negative. Hence by the Perron Frobenius Theorem the principal eigenvalue – that is the eigenvalue with maximal real part – is real.

The stability properties of the zeros remain unchanged as τ varies as stated in the following proposition.

Proposition 2.1. *For $\tau \in [0, 1]$, the three zeros \mathbf{w}^- , $\bar{\mathbf{w}}$ and \mathbf{w}^+ of \mathbf{F}^τ are such that*

$$\begin{aligned} & \text{the eigenvalues of the matrices } (\mathbf{F}^\tau)'(\mathbf{w}^\pm) \\ & \text{have negative real parts,} \end{aligned} \quad (2.14)$$

$$\text{the matrix } (\mathbf{F}^\tau)'(\bar{\mathbf{w}}) \text{ has a positive eigenvalue.} \quad (2.15)$$

Proof. We claim that, for all zeros, the sign of the principal eigenvalue does not change as τ varies. Indeed, let us denote by \mathbf{w}^* some zero of \mathbf{F}^τ in \mathbb{R}_+^6 . When computing the Jacobian matrix $(\mathbf{F}^\tau)'(\mathbf{w}^*)$ the terms related to g disappear due to (2.12). Hence, the Jacobian matrix remains unchanged when τ varies between 0 and τ_1 . Then, by investigating the kernel of this matrix for $\tau \in [\tau_1, 1]$ it can be shown that

$$\text{Ker } (\mathbf{F}^\tau)'(\mathbf{w}^*) = \text{Ker } \mathbf{F}'(\mathbf{w}^*) \text{ for } \tau \in [0, 1].$$

Hence, the determinants satisfy

$$\begin{aligned} \text{Det } (\mathbf{F}^\tau)'(\mathbf{w}^*) \neq 0 & \Leftrightarrow \text{Det } \mathbf{F}'(\mathbf{w}^*) \neq 0 \\ & \Leftrightarrow \text{Det } (\mathbf{F}^1)'(\mathbf{w}^*) \neq 0, \quad \tau \in [0, 1]. \end{aligned}$$

If these determinants are not equal to zero, then the sign of the principal eigenvalue cannot change as τ varies and the stability property of the zero will remain unchanged. This property was first noted in [13].

For the various zeros the possible nullity of the determinants and the sign of the principal eigenvalue are now determined by considering $\tau = 1$. By construction of the homotopy, for $\tau = 1$, $F_6^1(\mathbf{w})$ only depends on T and $F_6^1(\mathbf{w}) = P(T) = TQ(T)$ given by (2.7). It is easy to check that the eigenvalues of $(\mathbf{F}^1)'(\mathbf{w}^*)$ are $-\alpha_i$ with $1 \leq i \leq 5$ and $P'(T^*)$. Recall that we assumed (1.6) which implies that for $T^* = T^+, \bar{T}$ and T^- we have

$$P'(T^+) < 0, \quad P'(\bar{T}) > 0, \quad P'(T^-) < 0. \quad (2.16)$$

Hence, the determinants are not equal to zero and the principal eigenvalue has the sign of $P'(T^*)$. In view of (2.16) this provides readily (2.14) and (2.15). \square

3. Functional spaces and estimates of solutions

3.1. Operators and spaces

We consider the system

$$D\mathbf{w}'' + \mathbf{F}^\tau(\mathbf{w}) = \mathbf{0}, \quad (3.1)$$

where for $\tau \in [0, 1]$ the nonlinearity \mathbf{F}^τ is defined as above. We aim to investigate the solutions of (3.1) defined on the half-axis $x \geq 0$ and such that:

$$\mathbf{w}(x) > \mathbf{0} \text{ for } x \in \mathbb{R}_+, \quad \mathbf{w}'(0) = \mathbf{0}, \quad \mathbf{w}(\infty) = \mathbf{0}. \quad (3.2)$$

For the functional setting let us introduce the Hölder space $C^{k+\alpha}(\mathbb{R}_+)$ consisting of vector-functions of class C^k , which are continuous and bounded on the half-axis \mathbb{R}_+ together with their derivatives of order k , and such that the derivatives of order k satisfy the Hölder condition with the exponent $\alpha \in (0, 1)$. The norm in this space is the usual Hölder norm. Set

$$E^1 = \{ \mathbf{w} \in C^{2+\alpha}(\mathbb{R}_+), \quad \mathbf{w}'(0) = \mathbf{0} \}, \quad E^2 = C^\alpha(\mathbb{R}_+).$$

Next, we introduce the weighted spaces E_μ^1 and E_μ^2 with $\mu(x) = \sqrt{1+x^2}$ which are equipped with the norms:

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

In view of (3.1), let us consider the operator

$$\mathbf{A}^\tau(\mathbf{w}) = D\mathbf{w}'' + \mathbf{F}^\tau(\mathbf{w}), \quad (3.3)$$

acting from E_μ^1 into E_μ^2 . Then, the linearized operator about any function in E_μ^1 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_μ^1 .

3.2. A priori estimates for monotone solutions

In this section we consider solutions of (3.1)–(3.2) that are furthermore decreasing on \mathbb{R}_+ . Such solutions are the pulses we are interested in. Let us first derive some L^∞ bound for these pulses.

Proposition 3.1. *Assume that problem (3.1) has a solution $\mathbf{w}(x)$ defined for $x \geq 0$ satisfying (1.11). Then*

$$\mathbf{w}(x) \leq \mathbf{w}^- \text{ for } x \geq 0, \quad (3.4)$$

where \mathbf{w}^- is the largest zero of \mathbf{F} . In particular $\mathbf{w}(x) \in \mathcal{D}$ for all $x \geq 0$.

Proof. Recall that the coordinates of \mathbf{w}^- are $\varphi_i(T^-)$, $1 \leq i \leq 5$, and T^- where T^- is the largest root of P . We start with some preliminary result.

Lemma 3.1. *There exists some smooth function $\Psi(s) = (\psi_1(s), \dots, \psi_6(s))$ defined for $s \geq 0$ such that*

$$\begin{aligned} \Psi(0) &= \mathbf{w}^-, \quad \psi_i'(s) > 0 \text{ for } s > 0, \quad \psi_i(s) \rightarrow \infty \text{ as } s \rightarrow \infty, \\ \mathbf{F}^\tau(\Psi(s)) &< 0 \text{ for } s > 0 \text{ and } \tau \in [0, 1]. \end{aligned} \quad (3.5)$$

In particular $\Psi(s) > \mathbf{w}^-$ for $s > 0$.

Proof. Let us first consider the function Ψ^0 with coordinates:

$$\psi_i^0(s) = \varphi_i(T^- + s), \quad i = 1, \dots, 5, \quad \psi_6^0(s) = T^- + s. \quad (3.6)$$

It is easy to see that

$$\begin{aligned} \Psi^0(0) &= \mathbf{w}^-, \quad (\psi_i^0)'(s) > 0 \text{ for } s > 0, \\ \psi_i^0(s) &\rightarrow \infty \text{ as } s \rightarrow \infty, \end{aligned} \quad (3.7)$$

and since $P < 0$ on (T^-, ∞) (see (2.9))

$$\begin{aligned} F_i(\Psi^0(s)) &= 0, \quad F_6^\tau(\Psi^0(s)) = P(T^- + s) < 0 \\ \text{for } s > 0 \text{ and } \tau \in [0, 1]. \end{aligned} \quad (3.8)$$

Let us then introduce the following modification of the functions Ψ^0 :

$$\psi_i(s) = \varphi_i(T^- + \kappa_i s) \text{ for } i = 1, \dots, 5, \quad \psi_6(s) = T^- + \kappa_6 s, \quad (3.9)$$

where κ_i , $i = 1, \dots, 6$, are some positive coefficients. Under the conditions

$$\kappa_i > \kappa_6 \text{ for } i = 1, 2, 3, \quad \kappa_3 < \kappa_4, \quad \kappa_2 < \kappa_5, \quad \kappa_4 < \kappa_5, \quad (3.10)$$

we can see that

$$F_i(\Psi(s)) < 0 \text{ for } s > 0 \text{ and } i = 1, \dots, 5. \quad (3.11)$$

It remains to investigate the sign of $F_6^\tau(\Psi(s))$. In view of definitions (2.5) and (2.6) of F_6^τ it is clear that for $\mathbf{w} \geq \mathbf{0}$ and $T \geq T_0$ we have $g(T) = 0$ and $F_6^\tau(\mathbf{w}) < 0$. Consequently, $F_6^\tau(\Psi(s)) < 0$ for $s \geq s_*$ with $s_* = (T_0 - T^-)/\kappa_6$. Let us now study this inequality on the bounded interval $0 < s < s_*$. For this purpose we set $\kappa_i = 1 + \epsilon \rho_i$, $i = 1, \dots, 6$, where $\epsilon > 0$ is sufficiently small and the constants $\rho_i > 0$ are chosen in such a way that condition (3.10) are satisfied for any ϵ . We note that s_* depends on ϵ but we can neglect this dependence for ϵ small enough. Thus,

$$\psi_i(s) = \psi_i^0(s) + \epsilon s \psi_i^1(s), \quad \psi_i^1(s) > 0 \text{ for } s > 0,$$

where $\psi_i^1(s)$ are some bounded positive functions on the interval $0 \leq s \leq s_*$ (some of them are constants). Hence,

$$F_6^\tau(\Psi(s)) = F_6^\tau(\Psi^0(s)) + \epsilon s H^\tau(s),$$

where $H^\tau(s)$ is a bounded function for $s \in [0, s_*]$ and $\tau \in [0, 1]$. Here $F_6^\tau(\Psi^0(s)) < 0$ on $(0, s_*]$ thanks to (3.8). Furthermore, the derivative of function $s \rightarrow F_6^\tau(\Psi(s))$ at $s = 0$ reads

$$\begin{aligned} (F_6^\tau \circ \Psi)'(0) &= \nabla F_6^\tau(\mathbf{w}^-) \cdot (\Psi^0)'(0) + \epsilon \nabla F_6^\tau(\mathbf{w}^-) \cdot \Psi^1(0) = \\ &P'(T^-) + \epsilon \nabla F_6^\tau(\mathbf{w}^-) \cdot \Psi^1(0), \end{aligned} \quad (3.12)$$

where $P'(T^-) < 0$. These properties yield readily that $F_6^\tau(\Psi(s)) < 0$ on $(0, s_*]$ for all $\tau \in [0, 1]$ if ϵ is sufficiently small. \square

Let us get back to the proof of Proposition 3.1. Let $\tilde{\mathbf{w}}$ denote some solution of (3.1) satisfying (1.11). Then, to derive (3.4) it is sufficient to prove that

$$\tilde{\mathbf{w}}(0) \leq \mathbf{w}^-. \quad (3.13)$$

Considering the function Ψ given by Lemma 3.1, for $s \geq 0$ let us introduce the set

$$\mathcal{E}(s) = \{\mathbf{w} \mid \mathbf{0} \leq \mathbf{w} \leq \Psi(s)\},$$

with the boundary hyperplanes denoted as

$$\Gamma^i(s) = \{\mathbf{w} \mid w_i = \Psi_i(s), \quad 0 \leq w_j \leq \Psi_j(s), \quad j = 1, \dots, 6, \quad j \neq i\}.$$

Note that for $0 \leq s_1 \leq s_2$ we have $\mathcal{E}(s_1) \subset \mathcal{E}(s_2)$.

Let us argue by contradiction and assume that (3.13) is not true. Note that this is equivalent to $\tilde{\mathbf{w}}(0) \notin \mathcal{E}(0)$. Clearly, for $s > 0$ sufficiently large, we have $\tilde{\mathbf{w}}(0) < \Psi(s)$ and $\tilde{\mathbf{w}}(0) \in \mathcal{E}(s)$. Let us choose the minimal value of s for which $\tilde{\mathbf{w}}(0) \in \mathcal{E}(s)$. Then, for some i we have $\tilde{w}_i(0) > w_i^-$ and $\tilde{w}_i(0) \in \Gamma^i(s)$. We claim that

$$F_i^\tau(\tilde{\mathbf{w}}(0)) < 0. \quad (3.14)$$

Suppose that this is proved. Since $\tilde{w}_i'(0) = 0$ and $\tilde{w}_i'(x) < 0$ for $x > 0$ we also have $\tilde{w}_i''(0) \leq 0$. Thus, we have a contradiction in signs in the i th equation of system (3.1).

It remains to check (3.14). Let us come back to the monotony property (2.13) and note that, for $1 \leq i \leq 5$, it is valid provided that $\mathbf{w} \geq \mathbf{0}$. Consequently, if $\tilde{w}_i(0) \in \Gamma^i(s)$ for some $1 \leq i \leq 5$, the monotony property yields that $F_i^\tau(\tilde{\mathbf{w}}(0)) \leq F_i^\tau(\Psi(s)) < 0$. Suppose now that $\tilde{w}_6(0) = \Psi_6(s)$ and $\tilde{w}_i(0) < \Psi_i(s)$ for $1 \leq i \leq 5$. The nonlinearity F_6^τ is such that $F_6^\tau(\mathbf{w}) < 0$ if $\mathbf{w} \geq \mathbf{0}$ and $w_6 \geq T^0$. Hence, due to the maximum principle the solution $\tilde{\mathbf{w}}$ satisfies $\tilde{w}_6(x) < T^0$ for $x \geq 0$. In particular, $\tilde{w}_6(0) = \Psi_6(s) \leq T_0$. Hence the same monotony argument applies and provides that $F_6^\tau(\tilde{\mathbf{w}}(0)) < 0$. This concludes the proof of Proposition 3.1. \square

In view of (2.14)–(2.15), the nonlinearity \mathbf{F}^τ is of bistable type while by (2.13) it is monotone in \mathcal{D} . Consequently, the traveling wave problem:

$$D\mathbf{u}'' + c^\tau \mathbf{u}' + \mathbf{F}^\tau(\mathbf{u}) = \mathbf{0}, \quad \mathbf{u}(\pm\infty) = \mathbf{w}^\pm, \quad (3.15)$$

possesses a unique solution denoted by $(c^\tau, \mathbf{u}^\tau)$ (up to some translation in space for \mathbf{u}^τ) [20].

Estimates for monotone pulses in E_μ^1 can be obtained by imposing positiveness conditions on c^τ . The following result is proved in [16] and remains true here thanks to Proposition 3.1).

Theorem 3.1. *Under assumption (1.6), moreover suppose that $c^\tau > 0$ for all $\tau \in [0, 1]$. Then, there exists some constant $R > 0$ such that for all $\tau \in [0, 1]$ and for all monotone solution \mathbf{w} of (3.1) satisfying (1.11) the following estimate holds:*

$$\|\mathbf{w}\|_{E_\mu^1} \leq R.$$

Since the proof of this theorem is given in [16], we will recall here only its main idea. Solutions of Eq. (3.1) are uniformly bounded in the $\mathbb{C}(\mathbb{R}_+)$ -norm due to Proposition 3.1. However, this is not sufficient to conclude that the solutions are uniformly

bounded in the weighted space E_μ^1 . Indeed, if there is a sequence \mathbf{u}^k of solutions which converge to \mathbf{w}^- on any bounded interval (and to $\mathbf{w}^+ = \mathbf{0}$ at ∞), then this sequence is uniformly bounded in the uniform norm but not in the weighted space. Let us explain why this situation is not possible. Suppose that such sequence exists. Consider then a sequence of shifted functions $\mathbf{v}^k(x) = \mathbf{u}^k(x + h_k)$, where h_k is a real number chosen in such a way that $\|\mathbf{u}^k(h_k)\| = \|\mathbf{w}^-\|/2$ (where $\|\cdot\|$ denotes the Euclidean norm in \mathbb{R}^6). Since the sequence $\mathbf{u}^k(x)$ converges to \mathbf{w}^- uniformly in every bounded interval (in positive half-axis), then $h_k \rightarrow \infty$ as $k \rightarrow \infty$. Hence, the functions $\mathbf{v}^k(x)$ are defined for $x \geq -h_k$. Choosing a locally convergent subsequence of the sequence $\mathbf{v}^k(x)$, we obtain a function $\mathbf{v}^0(x)$ defined on the whole axis and satisfying (3.15) with $c^\tau = 0$. This conclusion contradicts the assumptions of the theorem.

3.3. Separation of monotone solutions

Let us suppose that all monotone solutions of (3.1)–(3.2) are uniformly bounded in space E_μ^1 (Theorem 3.1 provides conditions that guarantee this property and will be investigated in Section 4.1).

We aim to derive a result of separation between the solutions of (3.1)–(3.2) that are monotonically decreasing for all their components that will be denoted by $\mathbf{w}^M(x)$, and the solutions of (3.1)–(3.2) which do not satisfy this condition that will be denoted by $\mathbf{w}^N(x)$. We will call the latter ones non-monotone solutions.

Theorem 3.2. *Suppose that all monotone solutions of (3.1)–(3.2) are uniformly bounded 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 $\mathbf{w}^M(x)$ and any non-monotone solution $\mathbf{w}^N(x)$ of (3.1)–(3.2), we have*

$$\|\mathbf{w}^M - \mathbf{w}^N\|_{E_\mu^1} \geq r. \quad (3.16)$$

Proof. Let us start with two preliminary results.

Lemma 3.2. *Suppose that \mathbf{w} is some solution of problem (3.1) for $0 \leq \tau \leq 1$ and satisfies*

$$\mathbf{w}(x) \in \mathcal{D} \text{ for } x \in \mathbb{R}^+, \quad \mathbf{w}'(0) = \mathbf{0}. \quad (3.17)$$

Then, either all the components of \mathbf{w} are positive for all $x \geq 0$ or all of them are identically equal to 0.

Proof. Each of the equations of system (3.1) or equivalently (2.2) can be written in the form

$$Dz'' - \gamma z + f(x) = 0, \quad z'(0) = 0, \quad (3.18)$$

where γ is a positive constant and $f(x) \geq 0$ for all $x \geq 0$. It can be easily verified 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 (2.2) it follows that $T(x) \equiv 0$. Hence, from second and third equations of (2.2) we can conclude that $w_2(x) \equiv w_3(x) \equiv 0$ since the only bounded solutions of these equations are decaying exponentials. In order to satisfy the boundary conditions, these functions should be identically 0. From the next two equations we get $w_4(x) \equiv w_5(x) \equiv 0$. Thus, the lemma is proved if $w_1(x) \equiv 0$. Similar arguments are applicable if $w_2(x) \equiv 0$ or $w_3(x) \equiv 0$.

If $w_4(x) \equiv 0$, then we conclude from fourth equation of (2.2) that $w_3(x) \equiv 0$, and we return to the previous case. If $w_5(x) \equiv 0$, then we conclude from the fifth equation of (2.2) that $w_4(x) \equiv 0$.

As before, the previous arguments are applicable here. Finally, if $T(x) \equiv 0$, then $w_1(x) \equiv 0$ from the first equation of (2.2), and we proceed as above. \square

Lemma 3.3. *There exists some vector $\mathbf{q} > \mathbf{0}$ such that for all $\tau \in [0, 1]$ we have $(\mathbf{F}^\tau)'(\mathbf{0})\mathbf{q} < \mathbf{0}$.*

Proof. For $\tau \in [0, 1]$ the matrix $(\mathbf{F}^\tau)'(\mathbf{0})$ reads

$$(\mathbf{F}^\tau)'(\mathbf{0}) = \begin{pmatrix} -\alpha_1 & 0 & 0 & 0 & 0 & \alpha_1\beta_1 \\ 0 & -\alpha_2 & 0 & 0 & 0 & \alpha_2\beta_2 \\ 0 & 0 & -\alpha_3 & 0 & 0 & \alpha_3\beta_3 \\ 0 & 0 & \alpha_4\beta_4 & -\alpha_4 & 0 & 0 \\ 0 & 0 & 0 & \alpha_5\beta_5 & -\alpha_5 & 0 \\ 0 & 0 & 0 & 0 & \alpha_6\alpha^\tau & \alpha_6\beta_3\beta_4\beta_5\beta^\tau - \sigma \end{pmatrix} \quad (3.19)$$

We look for a positive vector $\mathbf{q} = (q_1, \dots, q_6)$ such that $(\mathbf{F}^\tau)'(\mathbf{0})\mathbf{q} < \mathbf{0}$. The following inequalities should be satisfied:

$$\begin{aligned} \beta_i q_6 < q_i \text{ for } i = 1, 2, 3, \quad \beta_4 q_3 < q_4, \quad \beta_5 q_4 < q_5, \\ \alpha_6 \alpha^\tau q_5 < (\sigma - \alpha_6 \beta_3 \beta_4 \beta_5 \beta^\tau) q_6. \end{aligned} \quad (3.20)$$

For $\tau = 1$ we have $\alpha^\tau = 0$ and the existence of reals $q_i > 0$ satisfying (3.20) follows readily from (2.11). Let us verify it for $\tau \in [0, 1)$. From the last four inequalities in (3.20) we obtain:

$$q_6 < \frac{\sigma - \alpha_6 \beta_3 \beta_4 \beta_5 \beta^\tau}{\beta_3 \beta_4 \beta_5 \alpha_6 \alpha^\tau} q_6, \quad (3.21)$$

while the first two inequalities are independent. Hence, the required q_i exist if and only if

$$1 < \frac{\sigma - \alpha_6 \beta_3 \beta_4 \beta_5 \beta^\tau}{\beta_3 \beta_4 \beta_5 \alpha_6 \alpha^\tau}. \quad (3.22)$$

For $\tau \in [0, \tau_1]$ we have $\alpha^\tau = 1, \beta^\tau = 0$ and inequality (3.22) holds true by virtue of (2.11). Since the function in the right-hand side increases for $\tau \in [\tau_1, 1)$, then it also holds true for all τ from this interval. \square

We aim now to derive (3.16). 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:

$$\|\mathbf{w}^{M,k} - \mathbf{w}^{N,k}\|_{E_\mu^1} \rightarrow 0 \text{ as } k \rightarrow \infty. \quad (3.23)$$

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_μ^1 . Consequently, there exists some subsequence of the monotone solutions still denoted by $\mathbf{w}^{M,k}$ converging to some function $\hat{\mathbf{w}}(x)$.

Clearly, the limit function $\hat{\mathbf{w}}(x)$ is a solution of system (3.1) for some $\tau = \tau_0$; furthermore it satisfies $\hat{\mathbf{w}}(x) \geq \mathbf{0}$, $\hat{\mathbf{w}}(x) \in \mathcal{D}$, $\hat{\mathbf{w}}'(x) \leq \mathbf{0}$ for $x \geq 0$, $\hat{\mathbf{w}}'(0) = \mathbf{0}$, $\hat{\mathbf{w}}(\infty) = \mathbf{0}$. This concludes the proof of Theorem 3.2.

The next two lemmas provide more precise properties of the function $\hat{\mathbf{w}}(x)$.

Lemma 3.4. *The limit function $\hat{\mathbf{w}}$ is positive: for all $x \geq 0$, $\hat{\mathbf{w}}(x) > \mathbf{0}$.*

Proof. Let us first check that $\hat{\mathbf{w}}(0) \neq \mathbf{0}$. Arguing by contradiction suppose that $\mathbf{w}^{M,k}(0) \rightarrow \mathbf{0}$. It follows from Lemma 3.3 that there exists a vector $\mathbf{q} > \mathbf{0}$ such that $(\mathbf{F}^{\tau_0})'(\mathbf{0})\mathbf{q} < \mathbf{0}$. Due to the continuity of $\mathbf{F}^\tau(\mathbf{w})$ and its derivatives, for τ close to τ_0 and sufficiently small ε , we have $\mathbf{F}^\tau(\varepsilon\mathbf{q}) < \mathbf{0}$. Then, the monotony property (2.13) guarantees that for any $\mathbf{w} \in B_\varepsilon = [0, \varepsilon\mathbf{q}]$, $\mathbf{w} \neq \mathbf{0}$ at least one component of $\mathbf{F}^\tau(\mathbf{w})$ is negative. Since $\mathbf{w}^{M,k}(0)$ converges to $\mathbf{0}$, then, for sufficiently large k , $\mathbf{w}^{M,k}(0)$ enters B_ε . Consequently, for some k and some i we see that $F_i^{\tau_0}(\mathbf{w}^{M,k}(0)) < 0$. Thus, from (3.1) we conclude that $w_i^{M,k}(0) > 0$ and $w_i^{M,k}(0)$ cannot be decreasing that contradicts (3.2). Thus, $\hat{\mathbf{w}}(0)$ is different from $\mathbf{0}$.

In view of Lemma 3.2 this implies the positiveness of $\hat{\mathbf{w}}$. \square

Lemma 3.5. *The limit function $\hat{\mathbf{w}}$ is decreasing: for all $x > 0$, $\hat{\mathbf{w}}'(x) < \mathbf{0}$.*

Proof. Recall that the function $\hat{\mathbf{w}}$ satisfies (3.1) for some $\tau = \tau_0$. Suppose that $\hat{w}'_i(x_0) = 0$ for some point $x_0 > 0$ and for some i . By differentiating the i th equation of system (3.1) for $\tau = \tau_0$, we see that $v(x) = -\hat{w}'_i(x)$ satisfies:

$$-Dv'' - \frac{\partial F_i^{\tau_0}}{\partial w_i}(\hat{\mathbf{w}})v = - \sum_{j=1, j \neq i}^6 \frac{\partial F_i^{\tau_0}}{\partial w_j}(\hat{\mathbf{w}})\hat{w}'_j. \quad (3.24)$$

Here $v(x) \geq 0$, $v(x_0) = 0$ for $x_0 > 0$ and from (2.13) the right hand-side of (3.24) is non-negative. Hence, the positiveness theorem guarantees that $v \equiv 0$. Consequently, in view of the limit at infinity we have that $\hat{w}'_i(x) \equiv 0$ and this contradicts Lemma 3.4. \square

Consider now a sequence of non-monotone functions $\mathbf{w}^{N,k}$ converging to the monotone function $\hat{\mathbf{w}}$ as $k \rightarrow \infty$. Without loss of generality, we can suppose that the first components of the solutions are not monotone. Then, there are values $x_k > 0$ such that $w_1^{N,k'}(x_k) = 0$ and up to some subsequence we have either $x_k \rightarrow x_* > 0$ or $x_k \rightarrow \infty$ or $x_k \rightarrow 0$ as $k \rightarrow \infty$.

If $x_k \rightarrow x_*$ for some $x_* > 0$, then $\hat{w}'_1(x_*) = 0$ and we obtain a contradiction with Lemma 3.4. Next, we claim that for sufficiently large $y > 0$ and for sufficiently large k ,

$$(\mathbf{w}^{N,k})' < \mathbf{0} \text{ on } [y, \infty[. \quad (3.25)$$

Therefore, the convergence $x_k \rightarrow \infty$ cannot hold.

Indeed, considering again the positive \mathbf{q} given by Lemma 3.3, we have $(\mathbf{F}^{\tau_0})(\mathbf{0})\mathbf{q} < \mathbf{0}$. Thus, there exists $k_0 > 0$ and $\delta > 0$ such that $(\mathbf{F}^{\tau_k})(\mathbf{w})\mathbf{q} < \mathbf{0}$ for $k \geq k_0$ and for $\|\mathbf{w}\| \leq \delta$ (where $\|\cdot\|$ denotes the Euclidean norm in \mathbb{R}^6). Since $\hat{\mathbf{w}}(x)$ is a solution of (3.1)–(3.2) for some $\tau = \tau_0$, then it is exponentially decreasing and we can choose \tilde{y} such that $\|\hat{\mathbf{w}}(x)\| < \delta$ for $x \geq \tilde{y}$. Since $\mathbf{w}^{N,k}$ converges to the monotone function $\hat{\mathbf{w}}$, we can choose $y \geq \tilde{y}$ and $k_1 \geq k_0$ such that $\|\mathbf{w}^{N,k}(x)\| \leq \delta$ for $x \geq y$ and $k \geq k_1$ and $\mathbf{w}^{N,k'}(y) < \mathbf{0}$ for $k \geq k_1$. Let us check that these properties lead to

$$\mathbf{w}^{N,k'}(x) < \mathbf{0} \text{ for } x \geq y \text{ and } k \geq k_1, \quad (3.26)$$

whence (3.25). Indeed, the function $\mathbf{v}^k(x) = -(\mathbf{w}^{N,k})'(x)$ is a solution of:

$$D\mathbf{v}^{k''} + (\mathbf{F}^{\tau_k})'(\mathbf{w}^{N,k})\mathbf{v}^k = 0. \quad (3.27)$$

Let us suppose that $\mathbf{v}^k(x)$ is not positive for some $x > y$ and $k \geq k_1$. Since $\mathbf{v}^k(y) > \mathbf{0}$ and $\mathbf{v}^k(+\infty) = \mathbf{0}$ (due to the exponential decay of \mathbf{v}^k), we can choose some $\alpha > 0$ such that the shifted function $\mathbf{u}^k(x) \equiv \mathbf{v}^k(x) + \alpha\mathbf{q}$ satisfies $\mathbf{u}^k(x) \geq \mathbf{0}$ for all $x \geq y$, and $\mathbf{u}^k(x_1) = \mathbf{0}$ for some $x_1 > y$ (for at least one of the components of this vector). Taking into account system (3.27), we see that

$$D(\mathbf{u}^k)'' + (\mathbf{F}^{\tau_k})'(\mathbf{w}^{N,k})\mathbf{u}^k + \mathbf{b}_k(x) = 0, \quad (3.28)$$

where the second term in (3.28) is positive thanks to (2.13) and $\mathbf{b}_k(x) = -\alpha(\mathbf{F}^{\tau_k})'(\mathbf{w}^{N,k})\mathbf{q} > \mathbf{0}$ on $[y, +\infty)$. Then, $(\mathbf{u}^k)''(x_1)$ must be negative and we obtain a contradiction in signs in the equation for the component of the vector-function \mathbf{u}^k which has a minimum at $x = x_1$.

It remains to study the case $x_k \rightarrow 0$. Let us verify that

$$\mathbf{F}^{\tau_0}(\hat{\mathbf{w}}(0)) > \mathbf{0}. \quad (3.29)$$

Obviously, the inequality $\mathbf{F}^{\tau_0}(\hat{\mathbf{w}}(0)) \geq \mathbf{0}$ holds because otherwise, if at least one of the components of this vector is negative, then the corresponding component of the vector $\hat{\mathbf{w}}''(0)$ is positive. Since $\hat{\mathbf{w}}'(0) = \mathbf{0}$, this would contradict the assumption that the function $\hat{\mathbf{w}}$ is decreasing. Thus, we need to verify that the components of

the vector $\mathbf{F}^{\tau_0}(\hat{\mathbf{w}}(0))$ cannot equal zero. Suppose that this is not true, and $F_i^{\tau_0}(\hat{\mathbf{w}}(0)) = 0$ for some i so that $\hat{w}_i''(0) = 0$. Then $v(x) = -\hat{w}_i'(x)$ satisfies

$$Dv'' + \frac{\partial F_i^{\tau_0}}{\partial w_i}(\hat{\mathbf{w}})v + b(x) = 0,$$

where

$$b(x) = - \sum_{j=1, j \neq i}^6 \frac{\partial F_i^{\tau_0}}{\partial w_j}(\hat{\mathbf{w}})\hat{w}'_j \geq 0.$$

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

Thus, we proved that all the components of the vector $\mathbf{F}^{\tau_0}(\hat{\mathbf{w}}(0))$ are positive. Since the functions $\mathbf{w}^{N,k}$ converge to $\hat{\mathbf{w}}$, then for all k sufficiently large, $\mathbf{F}^{\tau_k}(\mathbf{w}^{N,k}(0)) > \mathbf{0}$. Therefore, $\mathbf{w}^{N,k}(x)' < \mathbf{0}$ in some interval $0 < x < \delta$ independent of k . Hence $\mathbf{w}^{N,k}(x)' < \mathbf{0}$ in this interval and the convergence $x_k \rightarrow 0$ cannot hold. This contradiction completes the proof of the lemma. \square

Remark. The monotone solutions are also separated from the trivial solution $\mathbf{w} \equiv \mathbf{0}$ of (3.1)–(3.2). Indeed, by virtue of the arguments in the proof of Theorem 3.2, there exists some constant $\eta > 0$ such that for any monotone solution \mathbf{w}^M and all $\tau \in [0, 1]$:

$$w_i^M(0) > \eta, \text{ for } i = 1, \dots, 6. \quad (3.30)$$

Indeed, otherwise there exists a sequence of monotone solutions $\mathbf{w}^{M,k}$ converging to some $\hat{\mathbf{w}}$ in E_μ^1 and at least one component of $\hat{\mathbf{w}}(0)$ vanishes. This would contradict Lemma 3.4.

4. Proof of Theorem 1.1

The non-existence part in Theorem 1.1 for $c \leq 0$ can be proved as in [16] to which the reader is referred.

Hereafter we assume that the speed of the traveling wave solution of (1.8) is positive:

$$c > 0, \quad (4.1)$$

and we aim to derive the existence of a monotonically decreasing pulse. The proof relies on the Leray–Schauder method. The key step consists in the construction of a continuous deformation (homotopy) of our problem to a model problem for which we will be able to prove that the value of the topological degree is different from zero.

The continuous deformation has been introduced in Section 2. There in definitions (2.5) and (2.6) for F_6^τ , the function g is still at hand provided it satisfies (2.12). We will first show how g can be chosen so that the speed c^τ in (3.15) remains positive as τ varies (Section 4.1). Thanks to Theorem 3.1 this will yield a priori estimates in E_μ^1 of the monotonically decreasing solutions. Then in Section 4.2 we will investigate the limit problem ($\tau = 1$) and in particular some spectral properties. They will allow us to conclude the proof of the existence of a monotone pulse in Section 4.3.

4.1. Positiveness of the wave speed

As already mentioned, we come back to the definition of the homotopy and aim to check that by some appropriate choice of the function g we will have $c^\tau > 0$ for all $\tau \in [0, 1]$.

Recall that for $\tau \in [0, \tau_1]$ the function F_6^τ is given by

$$F_6^\tau(\mathbf{w}) = \alpha_6 w_5 (1 + \delta w_1) \left(1 - \frac{T}{T_0} \right) - \sigma T + \tau g(T),$$

where g satisfies (2.12). Since $g \geq 0$, we have $F_6^\tau(\mathbf{w}) \geq F_6(\mathbf{w})$. A classical result on monotone systems (see [18]) provides that $c^\tau \geq c$. Consequently, by virtue of (4.1) we conclude that

$$c^\tau > 0 \text{ for } \tau \in [0, \tau_1]. \quad (4.2)$$

It is worth noting that the above positiveness result did not need to require any additional condition on g . This will be different for $\tau \in (\tau_1, 1]$ where F_6^τ takes the form

$$F_6^\tau(\mathbf{w}) = \alpha_6 [\alpha^\tau w_5 + \beta^\tau \varphi_5(T)] (1 + \delta [\alpha^\tau w_1 + \beta^\tau \varphi_1(T)]) \\ \times \left(1 - \frac{T}{T_0} \right) - \sigma T + \tau_1 g(T),$$

with $\alpha^\tau, \beta^\tau \geq 0$ and $\alpha^\tau + \beta^\tau = 1$. Let us note that for $\mathbf{w} \in \mathcal{D}$ and $\tau \in (\tau_1, 1]$

$$F_6^\tau(\mathbf{w}) \geq G(T) \equiv \tau_1 g(T) - \sigma T. \quad (4.3)$$

By virtue of conditions (2.12) on g , we have $G(0) = 0$ and $G'(0) < 0$. Clearly we can also assume that the nonlinearity G is of bistable type: more precisely, there exists $\tilde{T} < T_* < T^-$ such that

$$\text{function } G(T) = \tau_1 g(T) - \sigma T \text{ possesses three zeros in} \\ [0, T^-]: 0, \tilde{T} \text{ and } T_*, \\ G(T) < 0 \text{ for } 0 < T < \tilde{T}, \quad G(T) > 0 \text{ for } \tilde{T} < T < T_*, \\ G(T) < 0 \text{ for } T_* < T \leq T^-. \quad (4.4)$$

Proposition 4.1. *Suppose that g satisfies (2.12), (4.4) and furthermore*

$$\int_0^{T_*} G(s) ds > 0. \quad (4.5)$$

Then, $c^\tau > 0$ for $\tau \in [\tau_1, 1]$.

Proof. Consider the scalar parabolic equation

$$\frac{\partial \theta}{\partial t} = D \frac{\partial^2 \theta}{\partial x^2} + G(\theta), \quad (4.6)$$

on the whole axis together with some initial condition $\theta(x, 0)$ that it is a monotonically decreasing function converging to 0 at ∞ and to T_* at $-\infty$. By virtue of conditions (4.4) on the function G , its solution converges to some traveling wave solution $\theta_*(x - c_* t)$ of this equation. The speed c_* has the sign of the integral in (4.5) so that condition (4.5) guarantees that $c_* > 0$.

We claim that

$$c^\tau > c_* \text{ for } \tau \in [\tau_1, 1]. \quad (4.7)$$

Indeed, let us consider the parabolic problem

$$\frac{\partial \mathbf{v}^\tau}{\partial t} = D \frac{\partial^2 \mathbf{v}^\tau}{\partial x^2} + \mathbf{F}^\tau(\mathbf{v}^\tau), \quad \mathbf{v}^\tau(x, 0) = \hat{\mathbf{v}}(x). \quad (4.8)$$

If $\hat{\mathbf{v}}(-\infty) = \mathbf{w}^-$ and $\hat{\mathbf{v}}(\infty) = \mathbf{w}^+ = \mathbf{0}$, then $\mathbf{v}^\tau(x, t)$ converges to some wave solution $\mathbf{u}^\tau(x - c^\tau t)$ with c^τ being the speed of the wave propagation.

Along with system (4.8) consider also the system

$$\frac{\partial \mathbf{z}^\tau}{\partial t} = D \frac{\partial^2 \mathbf{z}^\tau}{\partial x^2} + \Phi^\tau(\mathbf{z}^\tau), \quad \mathbf{z}^\tau(x, 0) = \hat{\mathbf{z}}(x), \quad (4.9)$$

where $F_6^\tau(\mathbf{w})$ is replaced by $G(z_6^\tau)$ and all other components of this vector-function do not change. We set $\hat{z}_i(x) \equiv 0$ for $i = 1, \dots, 5$ while the last component of the initial condition is the same as for Eq. (4.6), that is:

$$\hat{z}_6(x) = \theta(x, 0).$$

Let us suppose that $\hat{v}_6(x) \geq \hat{z}_6(x)$ for all $x \in \mathbb{R}$. Since $\mathbf{F}^\tau(\mathbf{w}) \geq \Phi^\tau(\mathbf{w})$ and $\hat{\mathbf{v}}(x) \geq \hat{\mathbf{z}}(x)$, then $\mathbf{v}^\tau(x, t) > \mathbf{z}^\tau(x, t)$ for all $x \in \mathbb{R}$ and $t > 0$. Since $\mathbf{v}^\tau(x, t)$ converges to the wave with the speed c^τ and $u_6^\tau(x, t)$ to the wave with the speed c_* , then $c^\tau \geq c_* > 0$. \square

Hereafter we suppose that the function g is chosen so that conditions (2.12), (4.4) and (4.5) are satisfied. This guarantees that

$$c^\tau > 0 \text{ for } \tau \in [0, 1]. \quad (4.10)$$

4.2. The limit system $\tau = 1$

The system for $\tau = 1$ reads

$$D\mathbf{w}'' + \mathbf{F}^1(\mathbf{w}) = \mathbf{0}, \quad (4.11)$$

on the half-axis $x > 0$ with the boundary conditions

$$\mathbf{w}'(0) = \mathbf{0}. \quad (4.12)$$

Proposition 4.2. *Problem (4.11)–(4.12) has a unique monotonically decreasing pulse solution.*

Proof. According to the definition of \mathbf{F}^1 the last equation in (4.11) reads

$$DT'' + P(T) + \tau_1 g(T) = 0. \quad (4.13)$$

Here the function $T \rightarrow P(T) + \tau_1 g(T)$ is of the bistable type. Moreover due to (4.5)

$$\int_0^{T^-} (P(s) + \tau_1 g(s)) ds > 0.$$

As recalled in the introduction, it follows that the scalar equation (4.13) possesses a unique pulse solution on \mathbb{R}_+ . Let us denote this solution by $T(x)$. Then, equations for w_i , $i = 1, 2, 3$ take the form:

$$Dw_i''(x) - \alpha_i w_i(x) = -\alpha_i \beta_i T(x), \quad w_i'(0) = 0. \quad (4.14)$$

Since the operators corresponding to the left-hand sides of these equations are invertible from E_μ^1 into E_μ^2 and $T(x) \in E_\mu^2$, then they also possess unique solutions $w_1(x), w_2(x), w_3(x) \in E_\mu^1$ (here the spaces E_μ^i are scalar functions spaces analog to the ones in Section 3.1). Next, we proceed to the equation for $w_4(x)$:

$$Dw_4''(x) - \alpha_4 w_4(x) = -\alpha_4 \beta_4 w_3(x), \quad w_4'(0) = 0, \quad (4.15)$$

which in turn has a unique solution $w_4(x)$, and the equation for w_5 :

$$Dw_5''(x) - \alpha_5 w_5(x) = -\alpha_5 \beta_5 w_4(x) - \alpha_5 \gamma w_2(x) w_4(x), \\ w_5'(0) = 0, \quad (4.16)$$

has a unique solution $w_5(x)$.

It remains to verify that functions $w_i(x)$ are monotonically decreasing. Let us begin with $w_1(x)$. Set $v_1(x) = -w_1'(x)$. Differentiating the first equation in (4.11) we get:

$$Dv_1' - \alpha_1 v_1 + h(x) = 0, \quad v_1(0) = 0,$$

where $h(x) = -\alpha_1 \beta_1 T'(x) > 0$. The only bounded solution of this problem is positive. Therefore, $w_1'(x) < 0$. Similarly, this can be verified for other components of the solution. \square

Next, consider the eigenvalue problem for the linearization of system (4.11)–(4.12) at the pulse solution $\mathbf{w}(x)$ given by Proposition 4.2:

$$D\mathbf{v}'' + (\mathbf{F}^1)'(\mathbf{w})\mathbf{v} = \lambda \mathbf{v}, \quad (4.17)$$

on the half-axis $x > 0$ with the boundary conditions

$$\mathbf{v}'(0) = \mathbf{0}, \quad \mathbf{v}(\infty) = \mathbf{0}. \quad (4.18)$$

Lemma 4.1. *All the eigenvalues of the linearized problem (4.17)–(4.18) are different from zero.*

Proof. Let us argue by contradiction and suppose that the linearized problem (4.17)–(4.18) has a zero eigenvalue. In particular, considering the last equation in (4.17) for $\lambda = 0$ there exists some scalar function $v_6(x)$ such that:

$$Dv_6''(x) + \delta(x)v_6(x) = 0, \quad v_6'(0) = 0, \quad v_6(\infty) = 0, \quad (4.19)$$

where $\delta(x) = (F_6^1)'(T(x))$. We will show that this assumption leads to a contradiction.

Consider also the function $v(x) = -T'(x)$. Differentiating (4.13) we get:

$$Dv''(x) + \delta(x)v(x) = 0, \quad (4.20)$$

$$v(0) = 0, \quad v(x) > 0 \text{ for } x > 0, \quad v(\infty) = 0. \quad (4.21)$$

Let us choose x_* in the way that $\delta(x) < 0$ for all $x > x_*$.

Suppose first that $v_6(x) > 0$ for all $x \geq 0$. Then, we can choose k large enough so that

$$kv_6(x) > v(x) \text{ for } 0 \leq x \leq x_*. \quad (4.22)$$

Denote by k_0 the infimum of all values k for which (4.22) holds true. Then, $k_0 v_6(x) \geq v(x)$ and there exists x_0 such that $k_0 v_6(x_0) = v(x_0)$. From Lemma 4.2 it follows, that $k_0 v_6(x_*) \geq v(x_*)$ leads $k_0 v_6(x) > v(x)$ for all $x > x_*$. Then, $x_0 \in [0, x_*]$. We exclude the case $x_0 = 0$ since it contradicts (4.21). Thus, there exists $x_0 \in (0, x_*)$ such that $k v_6(x_0) = v(x_0)$, this contradicts the positiveness theorem.

Consider now the case where the function $v_6(x)$ has variable sign. Let us note that $v_6(0) \neq 0$. Otherwise, $v_6(x) \equiv 0$. Without loss of generality we can assume that $v_6(0) < 0$. Indeed, otherwise we can multiply it by -1 . Hence, we can choose k sufficiently large such that $kv(x) > v_6(x)$ for $0 \leq x \leq x_*$. We repeat the construction of the previous paragraph where the functions $v(x)$ and $v_6(x)$ replace each other. We obtain a contradiction, as above. This contradiction proves the lemma. \square

Lemma 4.2. *Let us consider the equation*

$$Dz''(x) + \delta(x)z(x) = 0, \quad z(\infty) = 0. \quad (4.23)$$

If there exists some N such that $\delta(x) < 0$ for $x > N$ and $z(N) \geq 0$, then $z(x) > 0$ for all $x > N$.

Proof. Let us suppose the opposite: $\exists x_0 > N$ such that $z(x_0) < 0$. Since $z(N) \geq 0$ and $z(\infty) = 0$, then there exists a negative minimum of this function reached at some $x_1 > N$. Then, $z''(x_1) \geq 0$ and $\delta(x_1) < 0$, this gives a contradiction with (4.23). \square

4.3. Proof of the existence of pulses

In Sections 2 and 4.1 we constructed the homotopy \mathbf{F}^τ with $c^\tau > 0$ for $\tau \in [0, 1]$. Recall the operator \mathbf{A}^τ given by (3.3) and the corresponding functional spaces.

In view of Theorem 3.1 there exists a ball \mathbf{B} in the weighted space containing all the monotone solutions of $\mathbf{A}^\tau(\mathbf{w}) = \mathbf{0}$. The operator \mathbf{A}^τ is proper on closed bounded sets with respect to both variables \mathbf{w} and τ so that the set of the monotone solutions of $\mathbf{A}^\tau(\mathbf{w}) = \mathbf{0}$ is compact. Thus, thanks to Theorem 3.2, we can construct a domain $\tilde{\mathbf{B}}$ that contains all the monotone solutions and its closure does not contain any non-monotone solutions for all $\tau \in [0, 1]$. Indeed, let us take as $\tilde{\mathbf{B}}$ a union of balls with radius r determined in Theorem 3.2. For this domain we define the topological degree $\gamma(\mathbf{A}^\tau, \tilde{\mathbf{B}})$ which preserves its value for all $\tau \in [0, 1]$:

$$\gamma(\mathbf{A}^0, \tilde{\mathbf{B}}) = \gamma(\mathbf{A}^\tau, \tilde{\mathbf{B}}) = \gamma(\mathbf{A}^1, \tilde{\mathbf{B}}). \quad (4.24)$$

Since the limit problem ($\tau = 1$) has a unique solution and the operator linearized about this solution does not have zero eigenvalues, the topological degree for the limit problem is given by

$$\gamma(\mathbf{A}^1, \tilde{\mathbf{B}}) = (-1)^{v_k},$$

where v_k is the number of positive eigenvalues of the operator linearized about this solution together with their multiplicity.

It follows that $\gamma(\mathbf{A}^1, \tilde{\mathbf{B}}) \neq 0$. Hence, the degree $\gamma(\mathbf{A}^0, \tilde{\mathbf{B}})$ is also different from 0. This guarantees that the problem $\mathbf{A}^0(\mathbf{w}) = \mathbf{0}$ has (at least) a solution in $\tilde{\mathbf{B}}$. This concludes the proof of the existence result in Theorem 1.1.

5. Concluding remarks

In this work we proved that the pulse solution of the reaction–diffusion system modeling the main reactions of the blood coagulation cascade exists if and only if the traveling wave solution of this system has a positive speed.

The speed of the reaction–diffusion wave of blood coagulation determines the rate of clot growth. If it is too large, then various thrombotic events can occur, if it is too low, then this can lead to hemophilia and to other bleeding disorders. Therefore, the estimation of the speed of the traveling wave is important both for the theory and the applications. The methods to estimate the wave speed of blood coagulation are developed in [13]. They allow the derivation of some analytical expressions for the speed which provide good approximations as evidenced thanks to numerical simulations and some experimental results. Moreover, in [13] the dependence of the wave speed on the various physiological parameters is analyzed.

As shown in [13,19], the wave speed can be approximated by considering the single equation for the thrombin concentration. Indeed the traveling wave is a solution of the system

$$\begin{aligned} Du_i'' + cu_i' + \alpha_i(\beta_i u_6 - u_i) &= 0, \quad i = 1, 2, 3, \\ Du_4'' + cu_4' + \alpha_4(\beta_4 u_3 - u_4) &= 0, \\ Du_5'' + cu_5' + \alpha_5(\beta_5 u_4 + \gamma u_2 u_4 - u_5) &= 0, \\ Du_6'' + cu_6' + \alpha_6 u_5(1 + \delta u_1) \left(1 - \frac{u_6}{T_0}\right) - \sigma u_6 &= 0, \end{aligned} \quad (5.1)$$

where u_6 is the thrombin concentration, supplemented with the limits at infinity:

$$\mathbf{u}(\pm\infty) = \mathbf{w}^\pm.$$

If we set $\alpha_i = \alpha_i^0/\epsilon$, $i = 1, \dots, 5$, and consider a formal limit as $\epsilon \rightarrow 0$, then we can express the variables u_1 and u_5 through u_6 and substitute in the last equation, which becomes as follows:

$$Du_6'' + cu_6' + P(u_6) = 0, \quad u_6(\pm\infty) = T^\pm, \quad (5.2)$$

where the polynomial P is given by (2.7). It is proved in [19] that the speed of the wave for system (5.1) converges to the speed of the wave for Eq. (5.2) as $\epsilon \rightarrow 0$. Moreover, it is shown that this approach gives a good approximation of the speed of clot growth for the realistic physiological values of parameters. The wave speed for Eq. (5.2) is positive if and only if

$$\int_{T^+}^{T^-} P(s) ds > 0.$$

Therefore, we obtain an approximate positiveness condition for the wave speed of the original system.

The pulse solution $\mathbf{w}(x)$ is a positive stationary solution of the parabolic system

$$\frac{\partial \mathbf{v}}{\partial t} = D \frac{\partial^2 \mathbf{v}}{\partial x^2} + \mathbf{F}(\mathbf{v}), \quad (5.3)$$

on the whole axis with the zero limits at infinity. This solution is unstable with respect to small perturbations. Indeed, differentiating the system $D\mathbf{w}'' + \mathbf{F}(\mathbf{w}) = 0$, we conclude that $\mathbf{w}'(x)$ is an eigenfunction corresponding to the zero eigenvalue of the corresponding linearized operator. This eigenfunction has an alternating sign. On the other hand, the eigenfunction corresponding to the eigenvalue with the maximal real part is positive [20,18]. Hence, we can conclude that 0 is not the principal eigenvalue, and there exists a positive eigenvalue of the linearized operator.

Thus, the solution of the Cauchy problem for Eq. (5.3) with an initial condition $\mathbf{v}(x, 0) = \mathbf{w}(x) + \mathbf{s}(x)$, where $\mathbf{s}(x)$ is a small perturbation, in general will not converge to $\mathbf{w}(x)$. In order to determine the behavior of the solutions of the parabolic system, let us consider the two following initial conditions:

$$\mathbf{u}^1(x, 0) = \min(\mathbf{w}(x), \mathbf{w}(x + h)), \quad \mathbf{u}^2(x, 0) = \max(\mathbf{w}(x), \mathbf{w}(x + h)),$$

where h is some real number. In particular, we have two small perturbations of the pulse solution for small values of h . It can be easily verified that $\mathbf{u}^1(x, 0)$ is an upper function, and the corresponding solution decays in time and converges to $\mathbf{w}^+ = \mathbf{0}$ uniformly on the whole axis. Similarly, $\mathbf{u}^2(x, 0)$ is a lower function. The corresponding solution grows in time and converges to \mathbf{w}^- uniformly on every bounded interval. The convergence of this solution to the two traveling waves propagating in the opposite directions is proved for the scalar equation [21,22]. We can expect a similar behavior for the system under consideration but it is not proved. Propagation of the reaction-diffusion waves of blood coagulation was studied in several works (e.g. [23,12,10]). Convergence to a single wave in 1D and to the 2D waves was observed in [24]. Strictly speaking, numerical results on the convergence to the two waves propagating in the opposite directions in 1D was not presented in these publications. However, this case can be approximately considered as 1D cross section of the 2D radially symmetric case [24].

Thus, the unstable pulse solution separates decaying and growing solutions. From the point of view of applications to blood coagulation, it determines the initial concentration of thrombin, which is necessary to initiate blood coagulation under the condition that the wave speed is positive. If it is negative or if the initial thrombin concentration is not sufficient, then the clot will not form possibly resulting in bleeding and other physiological complications [12]. At the same time, for the positive wave speed, solutions of system (5.1) are well approximated by the traveling wave solutions of the simplified one-equation model on the thrombin concentration studied in details in [13]:

$$D\tilde{T}'' + b\tilde{T}^3(1 - \tilde{T}) - \sigma\tilde{T} = 0. \quad (5.4)$$

The kinetics of thrombin production in this model is regulated by two principal parameters: the rate of thrombin production b and the rate of thrombin inhibition σ . The pulse solution increases with the increase of σ and with the decrease of b . This effect can be interpreted as an increase of the critical value of the coagulation system disturbance necessary for the beginning of the clot formation under the additional activation of the anticoagulation mechanisms or under the inhibition of procoagulation mechanisms. We expect the similar properties to be true for the system (1.1).

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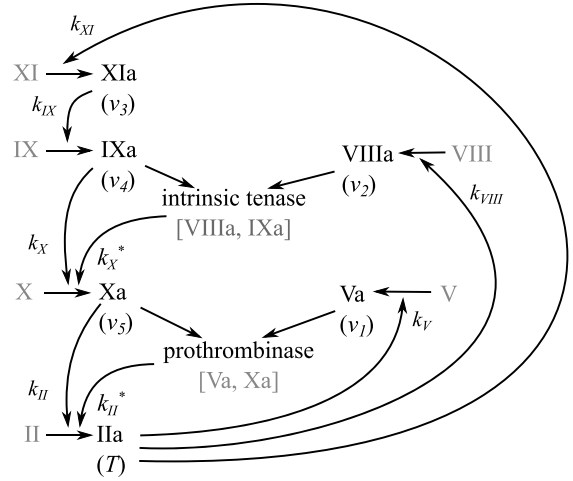


Fig. 1. The main activation reactions of the coagulation cascade.

Appendix

The model system is derived from the previously published model [25] as described in [13]. Clot formation is due to fibrin polymerization and the key enzyme of the coagulation is thrombin. During the amplification phase that we investigate in this paper formation of thrombin appears due to the prothrombin activation in the coagulation cascade. It involves activation of factors V, VIII, XI, IX and X as described by the following system of PDEs:

$$\begin{aligned} \frac{\partial U_V}{\partial t} &= D \frac{\partial^2 U_V}{\partial x^2} + k_V U_{II} - h_V U_V, \\ \frac{\partial U_{VIII}}{\partial t} &= D \frac{\partial^2 U_{VIII}}{\partial x^2} + k_{VIII} U_{II} - h_{VIII} U_{VIII}, \\ \frac{\partial U_{XI}}{\partial t} &= D \frac{\partial^2 U_{XI}}{\partial x^2} + k_{XI} U_{II} - h_{XI} U_{XI}, \\ \frac{\partial U_{IX}}{\partial t} &= D \frac{\partial^2 U_{IX}}{\partial x^2} + k_{IX} U_{XI} - h_{IX} U_{IX}, \\ \frac{\partial U_X}{\partial t} &= D \frac{\partial^2 U_X}{\partial x^2} + k_X U_{IX} + k_X^* U_{VIII} U_{IX} - h_X U_X, \\ \frac{\partial U_{II}}{\partial t} &= D \frac{\partial^2 U_{II}}{\partial x^2} + (k_{II} U_X + k_{II}^* U_V U_X) \left(1 - \frac{U_{II}}{T_0}\right) - h_{II} U_{II}. \end{aligned}$$

Here U_{II} denotes the concentration of the activated form of thrombin while $U_V, U_{VIII}, U_{XI}, U_{IX}, U_X$ respectively denote the concentrations of the activated forms of factors V, VIII, XI, IX, X. These variables correspond to the variables $T, v_1, v_2, v_3, v_4, v_5$ in system (1.1) respectively.

The coagulation cascade is described in Fig. 1. Straight arrows indicate factors activation, curved arrows indicate the catalytic actions on factors on other factors activation reactions. IIa, Va, VIIIa, XIa, IXa, Xa denote the concentrations of activated forms and II, V, VIII, XI, IX, X denote the inactivated forms. The factors in gray are not explicitly incorporated to the model by opposition to the ones in black (together with the notations for the model variables used in the system (1.1) in brackets).

Thrombin (IIa) catalyzes activation of factors V, VIII, XI. Factor XIa catalyzes activation of factor IX. Factors IXa and Xa form active complexes with factors VIIIa and Va respectively and further increase thrombin production. Here reactions of formation of the intrinsic tenase and prothrombinase complexes are fast and thus their concentrations are provided by the product of the concentrations of the participating factors ($U_{VIII} U_{IX}$ and $U_V U_X$ respectively).

The constant T_0 denotes the maximal available concentration of thrombin taken equal to the initial concentration of prothrombin in blood plasma.

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