

# An Individualized Blood Coagulation Model to Predict INR Therapeutic Range During Warfarin Treatment

A. Bouchnita<sup>1,2,3,4\*</sup>, K. Bouzaachane<sup>3,5,6</sup>, T. Galochkina<sup>2,4,7,8</sup>, P. Kurbatova<sup>1</sup>, P. Nony<sup>1,9</sup>, V. Volpert<sup>2,4,10</sup>

<sup>1</sup> Laboratoire de Biométrie et Biologie Evolutive, UMR 5558 CNRS  
University Lyon 1, 69376 Lyon, France

<sup>2</sup> Institut Camille Jordan, UMR 5208 CNRS, University Lyon 1, 69622 Villeurbanne, France

<sup>3</sup> Laboratory of Study and Research in Applied Mathematics, Mohammadia School of Engineers  
Mohamed V university, Rabat, Morocco

<sup>4</sup> INRIA Team Dracula, INRIA Antenne Lyon la Doua, Villeurbanne, France

<sup>5</sup> Laboratoire de Mathématiques Appliquées et Informatique, Faculté des Sciences et Techniques  
Caddi Ayyad University, Marrakech, Morocco

<sup>6</sup> Ecole Supérieure de Technologie, Cadi Ayyad University, Marrakech, Morocco

<sup>7</sup> Department of Biophysics, Faculty of Biology, M.V. Lomonosov Moscow State University  
Leninskie gory 1, Moscow, Russia

<sup>8</sup> Federal Research Clinical Center of Federal Medical & Biological Agency of Russia  
Orekhovy boulevard 28, Moscow, Russia

<sup>9</sup> Hospices Civils de Lyon, Service de Pharmacologie Clinique, Lyon, France

<sup>10</sup> Laboratoire Poncelet, UMI 2615 CNRS, Bolshoy Vlashevskiy Pereulok 11, 119002 Moscow, Russia

**Abstract.** Deep venous thrombosis (DVT) is characterized by formation of blood clot within a deep vein. The resulting thrombus can partially or completely block blood circulation. It can also detach and migrate with the flow resulting in pulmonary embolism. Anticoagulant drugs such as warfarin are usually prescribed to prevent recurrent thrombosis. The action of warfarin is monitored using a blood test for the International Normalized Ratio (INR) which is based on prothrombin time measurement. A high INR indicates a predisposition of the patient to bleeding, while a low INR shows that the warfarin dose is insufficient to prevent thromboembolic events. The therapeutic target of INR varies from case to case depending on clinical indications. It tends to be in the range 2.0 – 3.0 in most conditions. In this work we develop a model describing blood clotting during warfarin treatment. The action of warfarin is introduced by a Pharmacokinetics-Pharmacodynamics (PK-PD) sub-model. It describes the inhibition of synthesis of the vitamin K dependent factors by warfarin in the liver. We generate a population of patients with individual characteristics and assess their response to warfarin treatment by comparing the simulated INR and the corresponding developed clot height. Using this approach, we determine the underlying causes behind thrombosis and bleeding persistence even for an INR in the normal range. Thus, we suggest a novel methodology to predict the targeted INR depending on individual patient characteristics.

**Keywords and phrases:** blood coagulation, warfarin, PK-PD

**Mathematics Subject Classification:** 35Q53, 34B20, 35G31

## 1. Introduction

If a blood vessel wall is damaged, hemostasis is preserved due to clot formation. Clot growth involves several mechanisms including blood coagulation and platelet aggregation. After some time, when the injury is healed, the clot is dissolved. In some pathological conditions, if the clot forms spontaneously or if it is not dissolved, then various physiological complications can emerge possibly demanding medical treatment. Deep venous thrombosis (DVT) is a blood clotting disorder that occurs when excessive blood clotting occurs inside deep veins. It can provoke embolisms where a part of the clot breaks off and subsequently blocks blood circulation in smaller vessels.

Under normal conditions, clot formation is initiated when tissue factor is exposed to bloodstream. It forms a complex with factor VIIa which activates the factors IX and X resulting in the generation of an initial concentration of thrombin. If the produced thrombin concentration in the initiation phase is sufficiently high, it activates other factors in the amplification phase leading to self-accelerating thrombin production through a positive feedback [3]. Other mechanisms act to stop clot growth. Activated protein C inhibits thrombin generation in the amplification phase, while antithrombin inactivates thrombin itself by binding to it. In addition, blood flow limits clot growth by transporting thrombin and other clotting factors away from the injury site.

The risk factors for developing deep venous thrombosis can be obesity, cancer, injury, slow blood flow due to the lack of physical activity, among the others. Recurrent thrombi can be prevented by controlling these risk factors or by anticoagulant drugs. There are several anticoagulant drugs that can have different mechanisms of action. They can inhibit the activation of the factor X or thrombin such as the new oral anticoagulants [13]. Others like heparin increase the activity of antithrombin [14]. Another important type of anticoagulant drugs is vitamin K antagonist (AVK) drugs such as warfarin. It acts by reducing vitamin K-dependant factors synthesis in the liver [7]. As a result, the concentrations of the key blood clotting factors such as prothrombin and factors IX and X are decreased.

The advantage of warfarin based treatments is that they can be monitored by blood testing for the International Normalized Ratio (INR). It is an *in vitro* assay based on the measurement of the prothrombin time (PT). The latter characterizes the time interval necessary to convert prothrombin into thrombin under specific experimental conditions. Depending on the measured value of INR, the administrated dose of warfarin is adjusted in order to reach a therapeutic range. In DVT, the targeted level of INR is between 2.0 and 3.0 [36]. A lower than 2.0 value of INR indicates the predisposition of the patient to develop recurrent thrombosis while a higher than 3.0 value signifies a high risk of bleeding. Furthermore, the difference between the experimental settings under which the INR is measured and *in vivo* physiological conditions can result in cardio-vascular events even for a normal INR level. In particular, these tests do not consider the effect of blood flow and the direct inhibition of thrombin by antithrombin.

Mathematical models of blood coagulation represent three main categories depending on the purpose of modelling. The first type of models uses ordinary or partial differential equations to describe clot formation at the injury site [1], [9], [15], [20], [22], [29]. The action of flow and platelets is introduced in [4], [5], [8], [17], [25], [30], [31]-[33]. The second type is pharmacokinetics-pharmacodynamics (PK-PD) models developed to describe the response to anticoagulant drugs [11], [27], [21]. These models can suggest a practical solution to medical questions such as predicting the appropriate dose for individual patients, but they do not take into account the complexity of physiological processes. Such limitation complicates the interpretation of the obtained results. Finally, integrative models combine several aspects related to

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\*Corresponding author. E-mail:

the blood clotting including synthesis of vitamin-K dependent factors in the liver and their effects on clot formation [28], [35].

The present study is devoted to the development of an individualized model describing blood clotting dynamics during warfarin therapy. It consists of three components: clot formation at the injury site, vitamin-K dependent factors synthesis in the liver, blood testing for INR. We will be particularly interested by the effects of blood flow and direct thrombin inhibition by antithrombin on blood clotting during warfarin treatment. We will explore the patho-physiological conditions resulting in thromboembolic events in spite of the INR values corresponding to appropriate anticoagulant target values during warfarin treatment. Finally, we will suggest an *in silico* framework to accurately predict the appropriate therapeutic range for INR depending on the characteristics of the patient.

## 2. Individualized PK-PD blood coagulation model

To study the effect of warfarin on the coagulation process, we develop a blood coagulation model taking into account the main features of clot formation under warfarin treatment. The model consists of three sub-models. The first one is devoted to blood clotting at the injury site. The second one is a PK-PD model that describes synthesis of the vitamin K-dependent blood factors in the liver and the action of warfarin. The third model simulates *in vitro* blood testing for INR. These three components of the individualized model are connected with each other as shown in Figure 1.

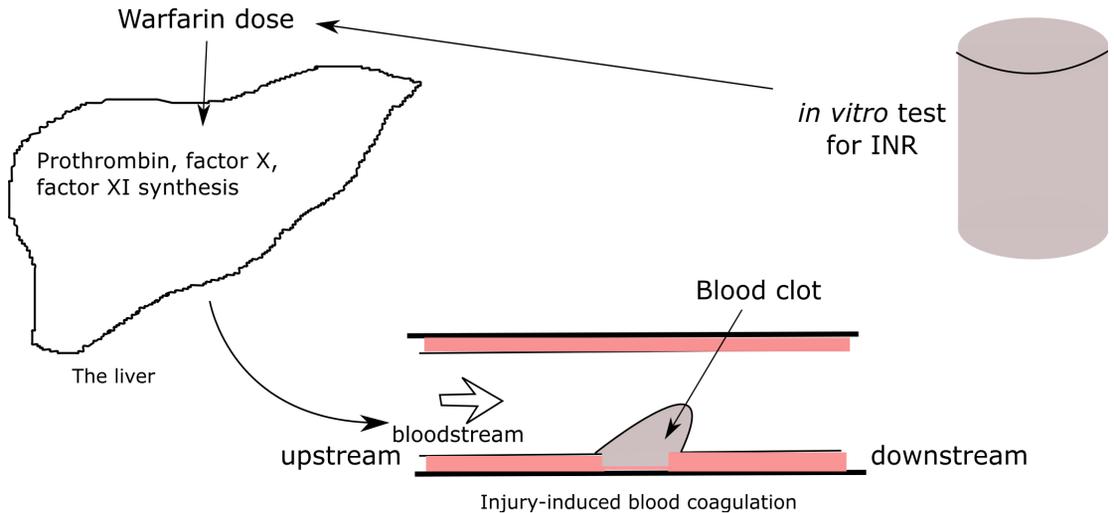


FIGURE 1. The structure of the model indicating the interaction between warfarin, vitamin-K dependent factors synthesis in the liver, INR tests and blood coagulation.

### 2.1. Blood clotting dynamics at the injury site

We use a previously developed model [6] to describe clot formation initiated by a damage of the blood vessel wall. It consists of reaction-diffusion equations for the concentrations of clotting factors coupled with the Navier-Stokes equations for blood flow. Clot is considered as a partially penetrable medium where flow velocity decelerates. We represent the vein by a 2-D rectangle where a part of the wall is damaged. Tissue factor is exposed to the bloodstream at the damaged part of the wall. The blood clotting pathway considered in the model is shown in Figure 2 (left). We consider the following equations for the concentrations of prothrombin  $P$ , thrombin  $T$ , antithrombin  $A$ , factors IX and X with their total

concentration denoted by  $B$  and their active form  $B_a$ , protein C denoted by  $C$  and its active form  $C_a$ , fibrinogen  $F_g$ , fibrin  $F$  and fibrin polymer  $F_p$ :

Prothrombin

$$\frac{\partial P}{\partial t} + \nabla \cdot (vP) = D\Delta P - \Phi(T, B_a, C_a)P, \quad (2.1)$$

Thrombin

$$\frac{\partial T}{\partial t} + \nabla \cdot (vT) = D\Delta T + \Phi(T, B_a, C_a)P - k_a^0 AT, \quad (2.2)$$

Antithrombin

$$\frac{\partial A}{\partial t} + \nabla \cdot (vT) = D\Delta A - k_a^0 AT, \quad (2.3)$$

Factors IX, X and IXa, Xa

$$\frac{\partial B}{\partial t} + \nabla \cdot (vB) = D\Delta B - k_b^0 B, \quad \frac{\partial B_a}{\partial t} + \nabla \cdot (vB_a) = D\Delta B_a k_b^0 B_a, \quad (2.4)$$

Protein C and its active form

$$\frac{\partial C}{\partial t} + \nabla \cdot (vC) = D\Delta C - k_c^0 C, \quad \frac{\partial C_a}{\partial t} + \nabla \cdot (vC_a) = D\Delta C_a - k_c^0 C_a, \quad (2.5)$$

Fibrinogen

$$\frac{\partial F_g}{\partial t} + \nabla \cdot (vF_g) = D\Delta F_g - k_1^0 TF_g, \quad (2.6)$$

Fibrin

$$\frac{\partial F}{\partial t} + \nabla \cdot (vF) = D\Delta F + k_1^0 TF_g - k_2^0 F, \quad (2.7)$$

Fibrin polymer

$$\frac{\partial F_p}{\partial t} = K_2 F. \quad (2.8)$$

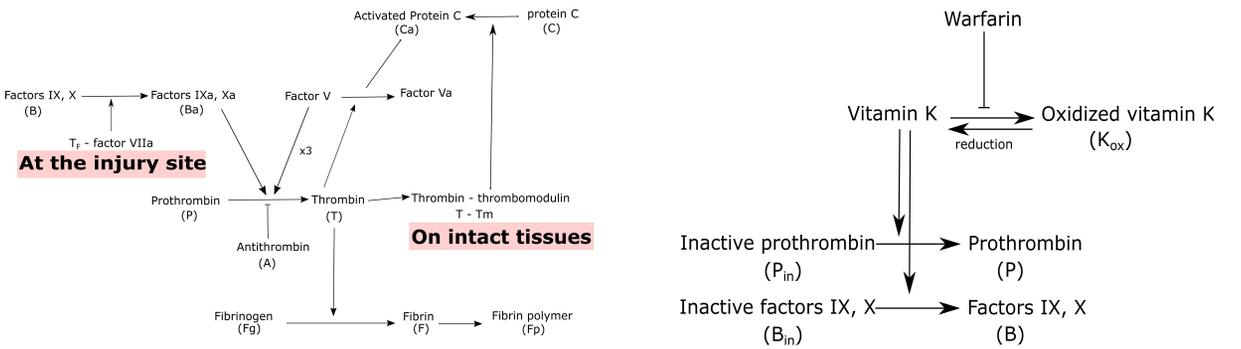


FIGURE 2. Blood clotting pathway (left) and synthesis of the vitamin-K dependent factors in the liver under warfarin therapy (right).

All these concentrations are normalized. Here  $v$  is the flow velocity,  $k_i^0$  denote reaction rate constants,  $D$  is the diffusion coefficient taken the same for all concentrations except for fibrin polymer. The latter forms a solid clot, it does not diffuse and it is not transported by flow. In equations (2.1) and (2.2), the reaction term  $\Phi(T, B_a, C_a)$  is given by the function:

$$\Phi(T, B_a, C_a) = \underbrace{k_3^0 B_a}_{\text{initiation phase}} + \frac{\overbrace{k_4^0 T^3}^{\text{self-accelerated production}}}{\underbrace{1 + k_5^0 C_a}_{\text{inhibition by APC}}}.$$

The boundary conditions for the activated factors IX and X depend on the amount of tissue factor at the damaged part of the wall:

$$\frac{\partial B_a}{\partial n} \Big|_{\Gamma_d} = \frac{k_6^0 (B^0 - B_a)}{1 + k_7^0 (B^0 - B_a)}, \quad (2.9)$$

where  $K_6 = K_7^- K_7 T_F^*$ . The activation of protein C depends on the complex of thrombin and thrombomodulin at the intact wall:

$$\frac{\partial C_a}{\partial n} \Big|_{\Gamma_u} = \frac{k_8^0 (C^0 - C) [TT_m]}{1 + k_9^0 (C^0 - C_a)}, \quad (2.10)$$

$$[TT_m] = \frac{k_T^0 TT_m}{1 + k_T^0 TT_m}, \quad (2.11)$$

where  $[TT_m]$  is the complex thrombin-thrombomodulin. The concentrations of prothrombin, fibrinogen and antithrombin are fixed at the inlet of the domain to  $P_0$ ,  $A_0$  and  $F_{g0}$ , respectively. No flux boundary conditions are prescribed at the other boundaries for these variables and at all boundaries for the other variables. We consider zero initial conditions for all variables except for prothrombin, fibrinogen and antithrombin for which the same initial values are prescribed as their values at the boundary.

Blood flow is modelled with the Navier-Stokes equations for the incompressible fluid. We describe the thrombus as a porous medium whose permeability depends on the concentration of fibrin polymer. To model the interplay between clot growth and venous hemodynamics, an additional term was added to the Navier-Stokes equations describing fluid deceleration by the porous medium

$$\rho \left( \frac{\partial v}{\partial t} + v \nabla v \right) = -\nabla p + \mu \Delta v - \frac{\mu}{K_f(\mathbf{x})} v, \quad (2.12)$$

$$\nabla v = 0.$$

Here  $v$  is the velocity vector,  $p$  is the pressure,  $\rho$  is the blood plasma density,  $\mu$  is the blood viscosity,  $K_f$  is the permeability of fibrin polymer which depends on its concentration  $F_p$  [37]:

$$\frac{1}{K_f(\mathbf{x})} = \alpha^2 16 F_p(\mathbf{x})^{1.5} (1 + 56 F_p(\mathbf{x})^3), \quad (2.13)$$

where  $\alpha$  is the fiber radius. One of the advantages of this method is enabling the use of the same model in the entire computational domain. We prescribe the condition of constant pressure difference between the inlet and the outlet

$$p_{out} - p_{in} = \Delta p,$$

and we use the periodic boundary conditions for the velocity at the inlet and the outlet of the flow and the no-slip condition at the top and bottom walls.

**Simplified model.** Along with the complete model (2.1) - (2.12), we consider a simplified 1-D model of thrombin production consisting of a single reaction-diffusion equation:

$$\frac{\partial T}{\partial t} = D \frac{\partial^2 T}{\partial y^2} + (k_1 B_a + k_2 T^3)(P_0 - T) - (\alpha_1 A + \alpha_2 v)T, \quad (2.14)$$

where  $D$  is the diffusion coefficient,  $P_0$  is the prothrombin concentration initially present in blood flow,  $\alpha_1$  and  $\alpha_2$  are the coefficients representing thrombin inhibition by antithrombin and blood flow respectively,  $k_1$  and  $k_2$  are kinetic coefficients,  $B_a(y)$  express the initiation of thrombin generation by factors IXa and Xa and is given as a function of  $y$ :  $B_a(y) = Be^{-y/\sigma}$  where  $\sigma = \sqrt{\frac{D}{k_b}}$ . Blood flow velocity is introduced as a Poiseuille flow  $v(y) = Ay(H - y)$ , where  $H$  is the vessel diameter. We denote by  $v(H/2) = v_m$  the maximal value of blood flow velocity in the middle of the vessel.

This equation describes thrombin distribution in the cross section of the vessel. In spite of the simplicity of the model, it gives a good approximation of the complete model. On the other hand, it will allow us to obtain analytical conditions of thrombosis and bleeding. We have represented the maximal height reached by the clot as we increase prothrombin concentration in plasma in Figure 3. We compared the prothrombin effects on injury-induced clotting by using simulations of both the complete and 1-D models. The similarity between the results obtained by the two models will allow us to use the simplified 1-D model in what follows.

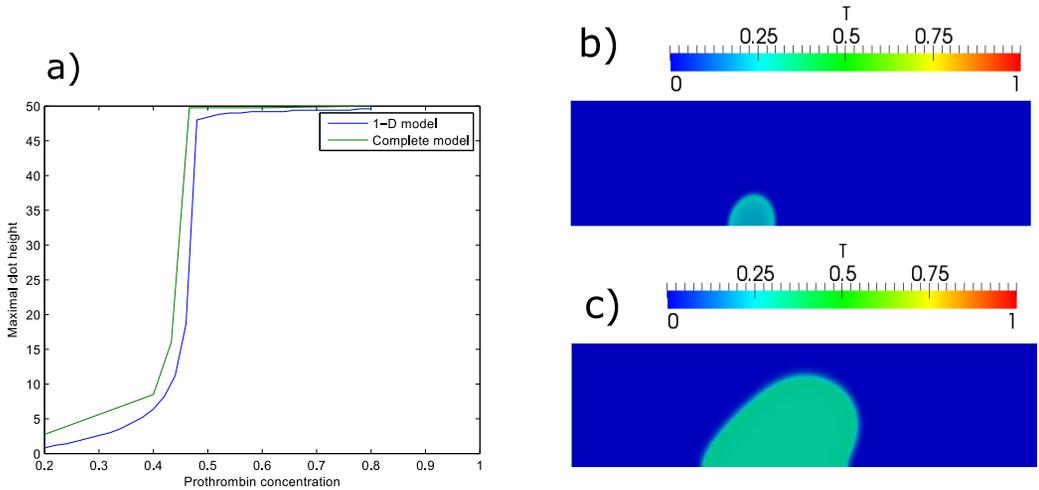


FIGURE 3. a) Comparison of the clot height in the simplified and complete models for an initial parabolic flow of  $v_m = 200 \mu\text{m/s}$ . The maximal heights reached by the clot as a function of prothrombin concentration in plasma  $P_0$ ; b) distribution of thrombin concentration obtained using the complete model for  $P_0 = 0.4$ ; c) snapshot of thrombin distribution using the complete model for  $P_0 = 0.6$ .

Let us note that prothrombin is a zymogen that is converted to thrombin which plays an important role in the formation of blood clot. Prothrombin is activated by both factors IX, X (initiation phase) as well as factors that are subsequently activated by thrombin itself (amplification phase). When prothrombin concentration is low, it is insufficient to trigger clotting and thus bleeding is observed. As we increase prothrombin in the plasma, a small clot forms. The thrombin wave is not strong enough to withstand removal by blood flow and thus it stops propagating. This corresponds to normal blood clotting. As prothrombin concentration increases in blood plasma, thrombin generation becomes sufficiently high to resist to blood flow. Then partial or complete occlusions of the vein can occur. This corresponds to deep venous thrombosis.

## 2.2. PK-PD model of warfarin action on vitamin-K dependent factors synthesis

Warfarin is one of the common anticoagulants whose mechanism of action implies the inhibition of synthesis of vitamin K in the liver. As a result, it downregulates the production of thrombin and factors IX and X. Below we develop a PK-PD model that reflects main features of warfarin treatment.

### 2.2.1. Warfarin pharmacokinetics

A knowledge of the pharmacokinetics of warfarin is helpful in understanding the initial response to therapy. Warfarin can be detected in the plasma one hour after oral administration, and peak concentrations occur in two to six hours [19].

Warfarin is a racemic mixture of stereo isomers, which are 99 percent bound to albumin. The drug is metabolized in the liver and kidneys, with the subsequent production of inactive metabolites that are excreted in the urine and stool [23]. It is almost completely absorbed, reaching a maximum plasma concentration between 2 and 6 hours after administration. It has a small volume of distribution (10 L/70kg) and it is eliminated by hepatic metabolism with a very small clearance (0.2 L/h/70kg). Its elimination half-life is about 35 hours [16]. We describe warfarin concentration in the body by the following equation:

$$\frac{dW}{dt} = mW_{ex}(t) - nW, \quad (2.15)$$

where  $W$  is warfarin concentration in plasma,  $W_{ex}(t)$  equals some constant value during first 4 hours after administration and 0 after 4 hours because warfarin concentration in plasma reaches its maximal value after 2-6 hours of the administration time,  $m$  and  $n$  are two positive constants.

### 2.2.2. Warfarin pharmacodynamics

Vitamin K is used for synthesis of some of the clotting factors in the liver such as factors II, IX and X [7]. It is formed in the reversible reaction of oxidized vitamin K reduction [26]. Warfarin inhibits vitamin K activity in the liver (Figure 2, right). We consider the following reactions taking place in the liver:



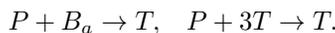
Here  $P^{in}$  and  $B^{in}$  are the inactive forms of prothrombin and factors IX and X in the liver,  $P$  and  $B$  are their active forms and due to mass balance we have the relations:  $P^{in} + P = P_0$  and  $B^{in} + B = B_0$ . Taking into account that  $K^0 = K + K_{ox}$  where  $K_{ox}$  is the concentration of oxidized vitamin-K, we have the following equations for these concentrations:

$$\frac{dK}{dt} = \beta_1^0(K_0 - K) - (\beta_1^1(P_0 - P) + \beta_1^2(B_0 - B))K - \beta_2^0WK, \quad (2.16)$$

$$\frac{dP}{dt} = \beta_1^1(P_0 - P)K - \beta_2^1P, \quad \frac{dB}{dt} = \beta_1^2(B_0 - B)K - \beta_2^2B, \quad (2.17)$$

## 2.3. INR and PT estimation

Prothrombin is converted into thrombin in the initiation and amplification phases of the coagulation cascade. In a quiescent platelet free plasma, this process can be approximated with:



We get the following equation for the concentration of prothrombin ( $P$ ):

$$\frac{dP}{dt} = -k_1 B_a P - k_2 T^3 P. \quad (2.18)$$

Replacing  $T$  in the right-hand side by its maximal value  $P_0$ , we find:

$$P = P_0 e^{-(k_1 B_a + k_2 P_0^3)t}. \quad (2.19)$$

Prothrombin time (PT) characterizes plasma tendency to clotting. It shows how much time is necessary to reach some given concentration  $P_\tau$  of prothrombin [24]. Set  $P_0/P_\tau = \beta$ . Then from (2.19) we find PT:

$$PT = \frac{\ln(\beta)}{k_1 B_a + k_2 P_0^3}. \quad (2.20)$$

The International Normalized Ratio (INR) is given by the expression

$$INR = \left( \frac{PT}{PT_{ref}} \right)^{ISI},$$

where  $PT_{ref}$  is the reference prothrombin time and ISI indicates the increase in tissue factor in comparison with reference factor. We consider the prothrombin time at the beginning of treatment

$$PT_{ref} = \frac{\ln(\beta)}{k_1 B_a^* + k_2 P_*^3},$$

where  $B_a^*$  and  $P_*$  are the reference pre-treatment concentrations of activated factors IX and X and prothrombin, and set  $ISI = 1$ . Then

$$INR = \frac{k_1 B_a^* + k_2 P_*^3}{k_1 B_a + k_2 P_0^3}. \quad (2.21)$$

### 3. Results

In order to study the action of warfarin on blood clotting, we first determine the role of vitamin-K dependent coagulation factors on thrombosis and bleeding. We use numerical simulations and analytical estimates to derive the conditions on the existence of different regimes of blood clotting. We consider two main factors arresting clot growth: direct inhibition of blood factors by antithrombin and the role of blood flow. The latter is of particular interest since INR testing is measured in quiescent plasma while flow effect can have significant influence on the clotting dynamics. Then, we study the action of warfarin on blood coagulation combining three sub-models: *in situ* thrombus development submodel (Section 2.1), PK-PD submodel of warfarin action (Section 2.2), INR *in vitro* assay submodel (Section 2.3). We also address the problem of thrombosis persistence in patients with normal INR. We demonstrate the difference of PT measurement in artificial *in vitro* conditions as compared to the physiological conditions.

#### 3.1. The levels of prothrombin and factors IX, X in plasma determine the regimes of blood coagulation

Using the simplified model given by equation (2.14), we will determine conditions on  $P$  and  $B$  which provide thrombosis or bleeding. Bleeding occurs if the initiation of blood clotting fails. This happens near the endothelial wall ( $y = 0$ ), where  $B_a(y) = B$  and  $v(y) = 0$ . Equation (2.14) in this case is written as follows:

$$\frac{\partial T}{\partial t} = D \frac{\partial^2 T}{\partial y^2} + (k_1 B + k_2 T^3)(P - T) - \alpha_1 AT. \quad (3.1)$$

This reaction-diffusion equation describes thrombin distribution. Set

$$\Phi(T) = (k_1 B + k_2 T^3)(P - T) - \alpha_1 AT.$$

This nonlinearity can have up to three zeros  $0, T_1, T_2$  depending on the values of parameters. It can have travelling wave solutions corresponding to clot growth. The thrombin wave will either propagate and then will be followed by fibrinogen conversion into fibrin leading to clot formation. Otherwise, the wave does not propagate, thrombin will diffuse in the plasma without initiating self-sustained reaction and resulting in formation of a small clot or no clot formation at all (bleeding). In order to have a travelling wave solution with a positive speed, we impose the following condition [34]:

$$\int_0^{T_2} \Phi(T) > 0. \quad (3.2)$$

If this inequality is opposite, then the speed of the wave is negative, and thrombin wave does not propagate. In this case, the clot does not form even near the wall where the flow velocity is zero. This situation will result in complete clot absence and severe bleeding. In Section 3.3 below we will consider a more general case of insufficient clot formation where a small clot is formed near the wall but it cannot grow further.

**Conditions of bleeding.** If inequality (3.2) does not hold, then we obtain conditions on  $B$  or  $P$  when bleeding occurs:

$$B_a \leq \frac{1}{4k_1 P - k_1 T_2^3} \left( \frac{4k_2 T_2^4}{5} - k_2 P T_2^3 + 2\alpha_1 A T_2 \right) \quad (3.3)$$

or

$$P \leq \frac{1}{4k_1 B + k_2 T_2^3} \left( k_1 B_a T_2^3 + \frac{4k_2}{5} T_2^4 + 2\alpha_1 A T_2 \right). \quad (3.4)$$

**Conditions of thrombosis.** Deep venous thrombosis (DVT) occurs if clot fills the whole cross section of the vessel or its essential part. In the framework of the considered model, this situation corresponds to the travelling wave propagating across the vessel. Since the flow velocity depends on the distance from the vessel wall, conditions on thrombin wave propagation should also be given depending on this distance. We assume here that thrombin gradient is sufficiently large, and condition (3.2) can be considered for fixed values of  $y$ . Therefore we obtain the following conditions of thrombosis formulated either in terms of  $B_a$  or  $P$ :

$$B_a(y) > \frac{1}{4k_1 P - k_1 T_2^3} \left( \frac{4k_2 T_2^4}{5} - k_2 P T_2^3 + 2\alpha_1 A T_2 + 2\alpha_2 v(y) \right), \quad (3.5)$$

$$P > \frac{1}{4k_1 B_a(y) + k_2 T_2^3} \left( 2k_1 B_a(y) T_2^2 + \frac{4k_2}{5} T_2^4 + 2\alpha_1 A + 2\alpha_2 v(y) \right). \quad (3.6)$$

In order to have complete occlusion, conditions (3.5) or (3.6) should be verified for the maximal value of flow velocity in the middle of the vein  $v(H/2) = v_{max}$ . Otherwise, we obtain a partial occlusion depending on the blood flow velocity. As we increase it, more prothrombin and factors IX, X concentrations are required for thrombosis to occur, and the regime of normal hemostasis is more likely to take place. Hence, blood flow plays a vital role in normal hemostasis providing an additional mechanism limiting clot growth. When blood flow is slower than normal, clot growth is not stopped and the thrombus completely occludes the vein. If flow velocity is sufficiently high, it limits clot growth at the middle of the vessel. We show the clot height for different prothrombin concentrations and flow velocities in Figure 4.

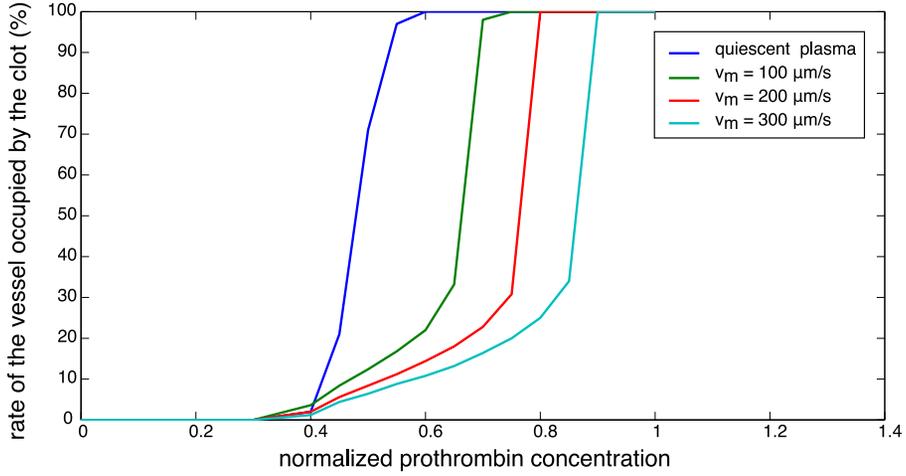


FIGURE 4. The final clot size (relative to the vein width) as a function of the concentration of prothrombin in blood plasma for different blood flow velocities.

### 3.2. Warfarin reduces synthesis of the vitamin-K dependent factors

Warfarin concentration is determined by equation (2.15). We simulate synthesis of the vitamin-K dependent factors with equations (2.16) and (2.17). The concentration of warfarin in bloodstream increases after each administration, and then decreases during the next several hours (Figure 5, left). Its average value increases during the first 10 days and then oscillates around some constant value ( $0.8 \text{ mg/l}$ ) for a daily dose of  $4 \text{ mg}$ . The vitamin-K concentration in the liver is affected by warfarin, and it is reduced by half after the first ten days (Figure 5, right). As a result, the amounts of factors IX, X and prothrombin released to bloodstream are reduced by 70% (Figure 6).

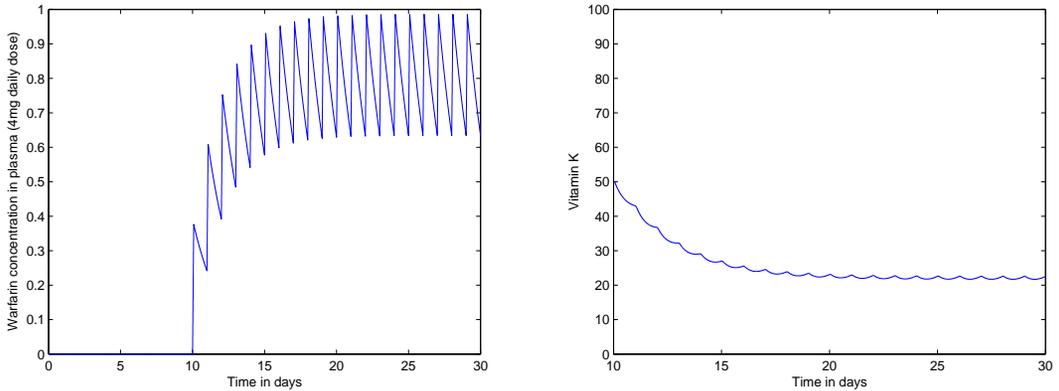


FIGURE 5. Prothrombin synthesis under warfarin treatment. Left: warfarin concentration in plasma ( $\text{mg/l}$ ) during a protocol of daily administration of a  $4 \text{ mg}$  dose starting from day 10; right: vitamin K concentration in the liver (% of the maximal value).

INR measures the concentrations of vitamin-K dependent factors in bloodstream. When the concentrations of prothrombin and factors IX, X are below their reference value, INR increases. After 10 days of

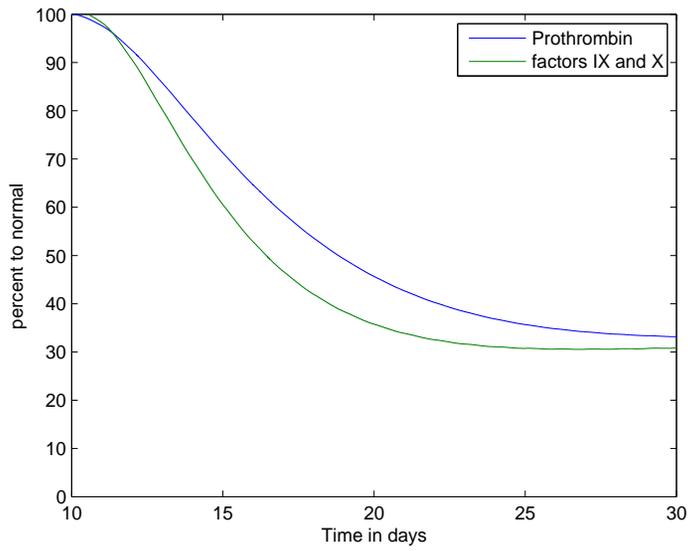


FIGURE 6. Prothrombin and factors IX and X percent of initial concentration during treatment.

warfarin daily intake, INR reaches a stable value. In thrombosis prevention, warfarin daily dose is chosen in order to reach the required INR level (Figure 7).

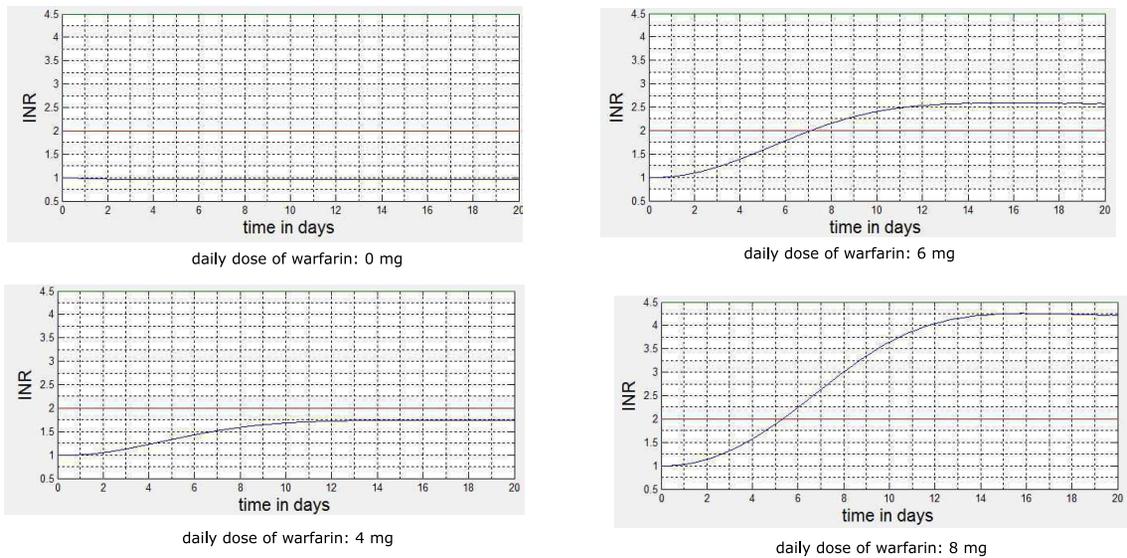


FIGURE 7. INR levels over time for different daily doses of warfarin.

### 3.3. Thrombosis and bleeding can persist even for the normal INR therapeutic range

Blood tests for INR are based on prothrombin time measurement. This time depends on the concentrations of vitamin-K dependent factors in blood. The model described in Section 3.2 provides the dynamics by which warfarin inhibits the production of prothrombin and factors IX and X. Using the conditions of bleeding and thrombosis on vitamin-K factors obtained in Section 3.1 and the INR formula, we derive conditions under which thromboembolic events can still occur even for the normal INR level. From (2.21) and equality in (3.2), we get:

$$A = \frac{1}{2k_1\alpha_1T_2} \left( \frac{k_1B_a^* + k_2P_*^3 - INRk_2P^3}{INR} - \frac{4k_2T_2^4}{5} + k_2T_0T_2^3 - 2\alpha_2vT_2 \right). \quad (3.7)$$

To simplify its interpretation, we consider a constant blood flow velocity  $v$ .

We consider the antithrombin concentration  $A$  as a function of INR for different values of  $v$ . Set  $v = v_m$ , where  $v_m$  is the maximal flow velocity reached at the center of the vessel. The corresponding curve in Figure 8 (dashed curve) separates the regions of parameters where the clot continues its growth (below the curve) and where it stops (above the curve) for this value of flow velocity. The first case corresponds to complete vessel occlusion where the clot fills the whole cross section of the vessel. In the second case the clot is stopped before it reaches the center of the vessel.

Next, we determine the region of insufficient clot formation. We set  $v = v_m/8$  and draw the corresponding curve (solid curve in Figure 8). In the region of parameters above this curve, clot growth is stopped near the vessel wall even though the flow velocity there is low. In particular this region includes the bleeding conditions suggested in Section 3.1 where clot does not form at all. The remaining region between the curves obtained for  $v = v_m$  and  $v = v_m/8$  we split by the curve for  $v = v_m/4$  and consider that normal clot growth occurs above it and partial occlusion occurs below it. The choice of the values  $v_m/8$  and  $v_m/4$  is to some extent arbitrary with some low and intermediate flow velocities.

Thus, we identify four regions in the parameters plane: partial or complete occlusion, insufficient and normal clot growth. If  $INR > 3$ , then bleeding or insufficient clotting occurs for most values of antithrombin concentration. If  $INR < 2$ , then partial or complete occlusion occurs in the wide range of values of  $A$ . In the normal therapeutic range  $2 < INR < 3$ , insufficient, normal or excessive clotting can occur depending on the values of antithrombin concentration and flow velocity. This analysis confirms that low INR is specific for thrombosis and high INR to bleeding. However it also indicates that a more precise specification is required in the normal INR range.

### 3.4. Patients response to warfarin treatment

We consider a cohort of  $n = 200$  patients with random characteristics. These patients are exposed to the risk of thrombosis in deep vein (due to inflammation, cancer, chemotherapy or other thrombosis inducing disease). Physiological characteristics of these patients are chosen randomly with a normal distribution. The population is divided into four groups based on the daily intake dose of warfarin. The prescribed doses for each of the these groups are 0, 4, 6, 8 mg, respectively. The average values of the simulated variables for each group of patients are shown in Table 1.

TABLE 1. Baseline average characteristics of the virtual patients.

Characteristic	average ( $\pm s.d.$ )
Prothrombin (normalized)	0.69 ( $\pm 0.09$ )
Factors IX and X (normalized)	0.69 ( $\pm 0.09$ )
Antithrombin (normalized)	0.48 ( $\pm 0.1$ )
Blood flow velocity ( $\mu m/s$ )	311 ( $\pm 101$ )
Vessel diameter (mm)	7.47 ( $\pm 0.39$ )

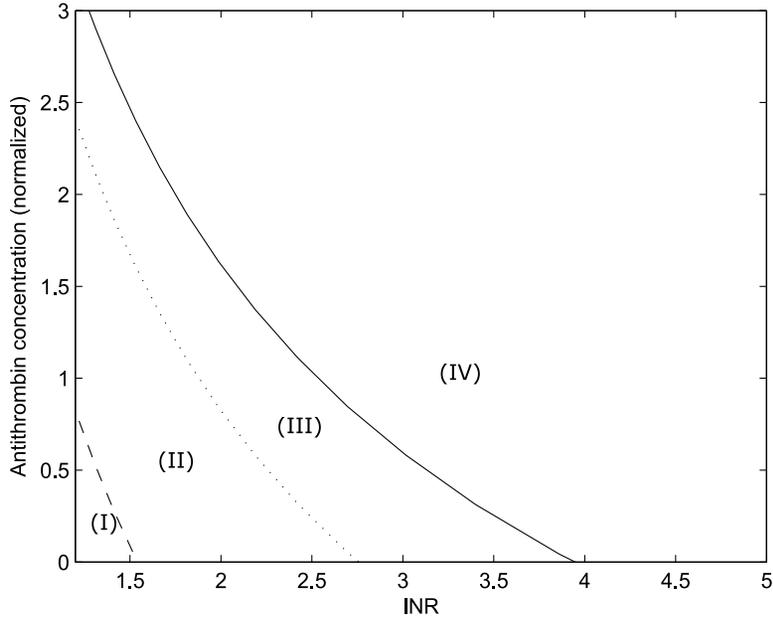


FIGURE 8. The regions with different regimes of blood clotting depending on INR and antithrombin concentration for a parabolic blood flow with a velocity  $v_m = 400 \mu m/s$ . (I) Complete thrombosis, (II) partial thrombosis, (III) normal hemostasis, (IV) insufficient clotting. Solid line is obtained from 3.7 for  $v = v_m/8$ , dotted line for  $v = v_m/4$ , dashed line for  $v = v_m$ .

Depending on the part of the vessel cross section occupied by the clot ( $r$ ), the patients are divided into four different categories depending on the observed regime of clot growth: (i) bleeding for  $r < 0.5\%$ , (ii) hemostasis for  $0.5\% \leq r \leq 5\%$ , (iii) partially occlusive thrombosis for  $5\% < r < 100\%$ , (iv) completely occlusive thrombosis for  $r = 100\%$ .

We compare the outputs of the two sub-models corresponding to the determination of the INR value and to the clot growth. For most patients, an INR value around 2.5 results in normal haemostatic response. Still, our modelling results suggest that blood flow velocity (related to venous pressure) should be considered in adjusting warfarin treatment as well as the level of antithrombin in plasma. Slow blood flow or low antithrombin concentration characterized the five patients that developed thrombosis among the fifty patients that presented an INR value targeted at 2.5. By contrast, nine of them developed bleeding. These patients all showed high blood flow velocities or high antithrombin levels. Interestingly, few normal hemostatic responses were observed for an INR below 2.0 or above 3.0. Overall, the majority of patients with an INR higher than 4.0 developed bleeding. This confirms the validity of our model as well as clinical indications for predicting the therapeutic range of INR. These clinical indications were adjusted for normal blood circulation and average antithrombin concentration in plasma.

#### 4. Discussion

The model developed in this work provides two ways of assessing warfarin action on blood clotting. In the injury-induced blood clotting model, we evaluated the patient response by simulating the percent of the vessel occupied by the clot after a potential vein injury. In the INR test model, we measured the INR level targeted by different treatment protocols. These two sub-models are connected by a PK-PD

TABLE 2. Average INR and clot vein percent occupied by the clot for the different groups of patients.

Population	INR	Percent of vessel occupied by the clot
Total ( $n = 200$ )	2.36( $\pm 1.16$ )	4%( $\pm 4\%$ )
Group 1 ( $n = 50$ )	1( $\pm 0$ )	13.7%( $\pm 2.3\%$ )
Group 2 ( $n = 50$ )	1.72( $\pm 0.009$ )	4.2%( $\pm 2.1\%$ )
Group 3 ( $n = 50$ )	2.54( $\pm 0.03$ )	1.5%( $\pm 1.4\%$ )
Group 4 ( $n = 50$ )	4.14( $\pm 0.09$ )	0.2%( $\pm 0.2\%$ )

model describing vitamin-K dependent factors synthesis in the liver during warfarin treatment. Using mathematical investigation of simplified models, we obtained the exact patho-physiological conditions of thrombosis and bleeding on vitamin-K dependent factors, blood flow and antithrombin. Then, we have described the dynamics of blood clotting during warfarin treatment. As a result, we have explained why bleeding and thrombosis persist even for appropriate INR values. In this context, there is a major distinction between the INR measurement model and the injury-induced blood clotting model. It is the absence of the effects of blood flow and direct thrombin inhibition by antithrombin in the first case. During *in vivo* blood clotting, blood flow plays an important role removing blood factors away from the injured zone and thus limiting clot growth. As a result, normal hemostasis is observed. The medical indications on the *in vitro* INR test were adjusted to correspond to normal levels of blood flow. Furthermore, antithrombin also plays an important role inactivating some of the coagulation factors. In this regard, the direct inhibition of thrombin by antithrombin is not considered in the prothrombin time measurements. Our results suggest that higher INR should be counterbalanced by low antithrombin levels or slow blood flow and vice versa.

The role of blood flow in thrombosis development is well known. It is mainly linked to haemostasis pathophysiology [18]. The clinical indications are only valid for average blood flow velocities as it was shown in our simulations. However, in case where blood flow is slow (usually  $v_m < 100\mu m/s$ ), partially occlusive thrombosis was developed in some patients showing an INR close to 2.5. On the other hand, bleeding was also observed in patients with high blood flow or high antithrombin concentrations for the same INR range. This suggests that blood flow velocity should be considered in targeting the appropriate INR therapeutic range. We indicated the regions where each of the different regimes of clot growth will supposedly take place for individual patients in order to help choosing the appropriate INR value. We concluded that the clinical indications correspond exclusively to patients with normal blood circulation and antithrombin levels. Similar conclusions were highlighted in another work [28] using different models especially regarding the effect of blood flow: in both studies, we recommended that targeting an INR above 3.0 should be considered in case of slow blood circulation. The results presented in another comprehensive model [35] are in good agreement with our modelling especially those regarding the action warfarin on vitamin-K dependent synthesis.

Several assumptions were made when developing the model in order to be able study a complex system such as blood coagulation. While blood is known for its Non-Newtonian rheological properties, it was considered to be Newtonian flow in our model. This is a valid hypothesis because we do not consider blood cells. Next, the *in vivo* clot growth model is exclusively devoted to thrombus formation upon the rupture of endothelial tissues (extrinsic pathway). Other mechanisms of blood clotting initiation such as thrombin activation by contact with artificial surfaces or by ADP are not taken into consideration. To further simplify the study, we restrict the studied coagulation cascade to the most important proteins. This allowed us to interpret the obtained numerical results and to derive the simplified model. Finally, venous walls were considered to be rigid and not deformable by the flow.

Although our model encompasses the main features of injury-induced blood clotting, it does not include platelets and their role in the coagulation process. Platelets increase the strength of the clot by aggregating and forming a plug [32]. They detach when exposed to high shear stress and migrate with blood flow

leading to embolisms. They may stimulate clot growth to a certain level. Still, they are affected by blood flow similarly to thrombin and the other factors. Hence, considering blood clotting without platelets is still valid for an initial approach. We will include the effect of platelets aggregation in a more complete model of coagulation in a forthcoming work and the study the action of combined anticoagulant and antiplatelet treatments. Another limitation of our model is the considered vitamin-K dependent factors. In order to use mathematical investigations, we assumed that warfarin only reduces the concentrations of factors IX, X and prothrombin. In reality, warfarin treatment downregulates the synthesis of other factors such as protein C and S as well as factor VII. The reduction of the anti-coagulant proteins C and S in bloodstream is observed only the first three days of the treatment (hypercoagulation phase) [2]. Then, the reduction of procoagulant factors IX, X and prothrombin overshadows the decrease in the anticoagulant proteins. Lastly, in our model, the role of antithrombin was reduced to the direct inhibition of thrombin. In reality, antithrombin also inhibits factors of the initiation phase such as factors IX, X and XI [12]. We have studied the direct inhibition of thrombin by antithrombin since it is exclusively present in the real *in vivo* blood clotting and not considered in INR tests.

Our results not only explain the persistence of recurrent thrombosis and bleeding during warfarin treatment, but can also serve as a basis for individualized INR prediction. This methodology can be used by clinicians to adjust the administrated warfarin dose, especially for those with an embolic risk higher than 3. We suggest that the current test for INR should be accompanied with venous pressure as well as antithrombin measurements. Our computational models can be used then to predict the appropriate INR that should be targeted during warfarin therapy.

## Appendix: Simulations parameters

All concentrations used in the simulations are normalized, the reference units are  $\mu m$  and  $10^{-2} s$ . The values of reaction rate constants are taken from [6], [10], [15].

Simulation	Numerical value	Description
$dx$	0.2	spatial step
$dt$	0.02	time step in haemostatis simulations
$dt$	0.00069	time step of PK-PD model
$D$	0.5	diffusion coefficient for all proteins
Reactions coefficients	Numerical value	Description
$k_1$	1	generation of thrombin in the initiation phase
$k_2$	22.5	generation of thrombin in the propagation phase
$\alpha_1$	0.63	thrombin-antithrombin binding reaction rate
$\alpha_2$	0.658	thrombin removal rate by blood flow
$\beta_1^0$	0.01	oxidized vitamin K reduction
$\beta_2^0$	0.3	oxidized vitamin K reduction inhibition by warfarin
$\beta_1^1$	0.0037	prothrombin activation by vitamin K
$\beta_2^1$	0.23	prothrombin inactivation
$\beta_1^1$	0.0056	factors IX and X activation by vitamin K
$\beta_2^1$	0.48	factors IX and X inactivation
Warfarin treatment	Numerical value	Description
$m$	1.15	warfarin distribution in blood rate
$n$	0.48	warfarin elimination by clearance rate

TABLE 3. The values of parameters used for the 1-D simplified model and the PK-PD model of warfarin.

Simulation	Numerical value	Description
$dx$	0.25	spatial step
$dt$	0.005	time step
$H$	50	diameter of the vessel
$L$	250	length of the vessel
$D$	0.5	diffusion coefficient for all proteins
$\rho$	1.025e-15	blood plasma density
$\nu = \mu/\rho$	2.8e4	blood plasma viscosity
Reactions coefficients	Numerical value	Description
$k_1^0$	0.1	conversion of fibrinogen into fibrin
$k_2^0$	1	generation of fibrin polymer from fibrin
$k_3^0$	2500	activation of prothrombin during the initiation phase
$k_4^0$	22.5	activation of prothrombin during the amplification phase
$k_5^0$	3122.2	inactivation of V by APC
$k_b^0$	0.05	IXa and Xa inactivation
$k_c^0$	0.05	APC inactivation
$k_7^0$	40	$T_F - VIIa$ binding with IXa and Xa
$k_8^0$	9400	$k_8 = k_9^- k_9$
$k_9^0$	9400	APC activation by thrombin-thrombomodulin
$k_a^0$	0.68	Inactivation of thrombin by antithrombin
$k_T^0$	10000	thrombin binding with thrombomodulin
Physiological values	Numerical value	Description
$VIIa$	0.5	factor VIIa concentration on the damaged tissue
$P_0$	varied	prothrombin concentration in blood plasma
$A_0$	0.4	antithrombin concentration in blood plasma
$B_0$	1	initial concentrations of factors IX and X
$C_0$	1	initial concentration of APC
$F_{g0}$	1	fibrinogen concentration in blood
$F_p^*$	0.8	level of fibrin polymer forming the clot

TABLE 4. The values of parameters used in numerical simulations of the 2-D model (Figure 3).

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