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Mathematical model of blood clotting in the portal vein

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Portal vein thrombosis (PVT) is a significant complication during both the pre-transplant and postoperative periods of liver transplantation. The multifactorial etiology of PVT, the paradoxical hemostatic state in liver cirrhosis and the limited usefulness of standard coagulation tests highlight the necessity of formalized models to assess thrombosis risk.

Objective: Using a mathematical model of the blood coagulation system, investigate the influence of hemodynamic conditions and coagulation factor levels on the likelihood of thrombus formation in the portal vein.

The portal vein is modelled as a flow-through reactor with rapid convective mixing. The mathematical model is based on Panteleev et al. (2010) detailed kinetic scheme, incorporating equations for the extrinsic pathway of coagulation activation, positive and negative feedback loops, and inhibition of active factors. The resulting system of ordinary differential equations was integrated using a one-stage Rosenbrock method with complex coefficients.

Thrombin generation was shown to exhibit threshold dependence on blood flow velocity. Above a critical velocity, the initiation phase does not transition to the amplification phase. This corresponds to physiological conditions that prevent thrombus formation. We demonstrated that, at reduced fibrinogen concentrations characteristic of hepatic dysfunction, the critical velocity threshold above which thrombus formation is suppressed increases. This indicates the system's heightened susceptibility to stasis. Protein C deficiency had minimal effect on thrombogenesis dynamics under the modeled conditions. The modeling results qualitatively agree with clinical data on fibrinogen distribution in PVT patients ($n = 932$, Sklifosovsky Research Institute).

Keywords: blood clotting system, thrombin generation, flow-through reactor, portal vein, vein thrombosis

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Математическая модель свертывания крови в воротной вене

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Тромбоз воротной вены (ТВВ) является значимым осложнением как в претрансплантационном, так и в послеоперационном периоде трансплантации печени. Многофакторная этиология ТВВ, парадоксальное состояние гемостаза при циррозе печени и ограниченная информативность стандартных коагулологических тестов определяют необходимость разработки формализованных моделей для оценки риска тромбообразования.

Цель работы — на основе математической модели системы свертывания крови исследовать влияние гидродинамических условий и уровней факторов коагуляции на возможность формирования тромба в воротной вене.

Воротная вена рассматривается как проточный реактор с быстрым конвективным перемешиванием. Математическая модель основана на детализированной кинетической схеме, включающей уравнения для внешнего пути активации свертывания, петель положительных и отрицательной обратной связи, ингибирования активных факторов. Система обыкновенных дифференциальных уравнений интегрировалась одностадийным методом Розенброка с комплексными коэффициентами.

Показан пороговый характер генерации тромбина в зависимости от скорости кровотока. При превышении критической скорости фаза инициации не переходит в фазу амплификации, что соответствует физиологическим условиям, препятствующим тромбообразованию. Продemonстрировано, что при пониженной концентрации фибриногена (характерной для дисфункции печени) порог скорости, выше которого тромб не формируется, возрастает, что означает повышенную чувствительность системы к стазу. Дефицит протеина C в моделируемых условиях оказывает минимальное влияние на динамику тромбообразования. Результаты моделирования качественно согласуются с клиническими данными по распределению пациентов с ТВВ по уровню фибриногена ($n = 932$, НИИ им. Склифосовского).

Математическое моделирование позволяет формализовать связь между гемодинамическими и биохимическими факторами риска ТВВ. Пониженный уровень фибриногена идентифицирован как фактор, усиливающий тромботический потенциал при условиях стаза. Полученные результаты открывают перспективы для пациент-ориентированного прогнозирования риска ТВВ у кандидатов на трансплантацию печени.

Ключевые слова: система свертывания крови, производство тромбина, проточный реактор, воротная вена, венозный тромбоз

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Introduction

The portal vein (PV) is a large blood vessel that collects blood from the abdominal organs and transports it to the liver. Unlike other veins, the PV system is located between two networks of capillaries. The first network gives rise to the venous trunks that make up the PV, and the second network is located within the liver parenchyma where the PV divides into its terminal branches. The portal vein is a large vessel. Its normal dimensions are a length of 6–8 centimeters and a diameter of about 1.5 centimeters. The average linear blood flow velocity in the portal vein is approximately 15–20 cm/min and depends heavily on the vein's geometry.

Portal vein thrombosis (PVT) is an occlusion or partial obstruction of the portal vein by thrombotic masses. For liver transplantation (LT), this condition is significant in two ways: it acts both as a pre-transplant complication (in patients with liver cirrhosis and portal hypertension) and as a postoperative complication that directly threatens the viability of the transplant.

The prevalence of PVT in patients with liver cirrhosis awaiting transplantation varies widely, from 5 % to 26 %, depending on the stage of the disease and the diagnostic criteria used [Francoz et al., 2012; Sarin et al., 2016]. In patients with decompensated cirrhosis, the incidence of PVT is significantly higher, exceeding 30 % [Nery et al., 2015]. After transplantation, portal vein thrombosis develops in 2–13 % of cases. Early postoperative PVT (within the first 30 days) is associated with graft loss in 50–80 % of cases when diagnosis is delayed [Hibi et al., 2014; Englesbe et al., 2010].

Pre-transplant portal vein thrombosis

The etiology of PVT in liver cirrhosis is multifactorial and can be formalized using Virchow's classic triad, each component of which undergoes significant changes in cirrhosis:

Blood flow stasis. Portal hypertension leads to a progressive slowing of the linear blood flow velocity in the portal vein. It has been shown that a flow velocity of less than 15 cm/s is an independent predictor of PVT development [Zocco et al., 2009]. Decreased flow velocity increases contact time between procoagulant factors and the endothelium, raising the likelihood of initiating the coagulation cascade.

There are few studies of processes in PV depending on the time of contact of procoagulant factors with the subendothelium. This work is devoted to a model study of such a dependence.

Changes in the vascular wall. Chronic inflammation, fibrosis of periportal tissues, and endothelial dysfunction in the portal vein basin create conditions conducive to platelet adhesion and activation of the intrinsic coagulation pathway [Tripodi, Mannucci, 2011].

We believe that blood clots, consisting mainly of fibrin fibers, form in the portal vein. We will disregard platelet adhesion. Below, we will focus solely on studying the extrinsic pathway of coagulation.

Hemostatic disorders. This component is the most paradoxical and deserves separate consideration. Liver cirrhosis is accompanied by a simultaneous deficiency of both procoagulant and anticoagulant factors simultaneously, resulting in a state of so-called "rebalanced hemostasis", which can shift toward either bleeding or thrombosis [Lisman, Porte, 2010].

In the present article we will examine how the body's response is affected by a deficiency of key clotting factors produced by the liver — fibrinogen and protein C. Protein C is one of the main inhibitors of the coagulation system.

Additional risk factors for pre-transplant PVT include: previous abdominal surgery (particularly splenectomy), hepatocellular carcinoma (HCC) with tumor invasion of the portal vein, hereditary thrombophilias (Factor V Leiden mutation, prothrombin gene G20210A mutation, protein C and S deficiency), and myeloproliferative disorders, including latent forms with the JAK2V617F mutation [Qi et al., 2015; Kiladjian et al., 2008].

[Boccatonda et al., 2024] lists the main risk factors considered in predicting PVT. The authors divide all risk factors into three groups. The first — acquired permanent risk factors — is associated with liver diseases, such as cirrhosis, or oncological diseases. The second group — transient acquired risk factors — is associated with surgical procedures, sports injuries, and the use of hormonal medications. The group of inherited (genetically determined) risk factors is directly related to the functioning of the blood coagulation system (BCS). The mutations mentioned above are classified as genetic factors.

It should be noted that this list of risk factors boils down to a reduced ability of activated protein C to halt the rapid clotting process. The Leiden mutation, for example, prevents normal binding of factor V to protein C [De Stefano, Leone, 1995]. The prothrombin G20210A mutation is associated with elevated prothrombin levels in the blood and may be accompanied by reduced protein C levels [Rosendaal, Reitsma, 2009].

The JAK2V617F mutation is directly linked to red blood cell production and, consequently, to hematocrit [Nielsen et al., 2010]. Using rheological models such as the Quemada model [Quemada, 1978], it is hematocrit that determines the rheological properties of blood and the progression of the disease [Hund et al., 2017]. Among the listed hereditary risk factors, only the JAK2V617F mutation is associated with portal vein hemodynamics; the other mutations are associated with slow inhibition of coagulation factors. According to [Manzano-Robleda et al., 2015], the JAK2V617F mutation and other myeloproliferative disorders occur in approximately 40 % of portal vein thrombosis cases. These disorders are the primary risk factor in PVT. The next most significant risk factors, according to [Manzano-Robleda et al., 2015], are prothrombin mutations (40 %) and the Leiden factor V mutation (32 %). The least significant factors are protein C and S deficiency (less than 30 % each). Since the total percentage of all factors significantly exceeds 100 %, it can be concluded that clinical cases typically involved a combination of the listed factors.

Unfortunately, data on genetic mutations in patients with PVT are not available. Therefore, in this work we will focus on studying the effect of fibrinogen and protein C. These data can be compared with known clinical cases.

Post-transplant portal vein thrombosis

The etiology of early post-transplant PVT differs from that of pre-transplant PVT and primarily involves surgical and anatomical factors:

- Technical aspects of portal anastomosis creation: size mismatch, excessive vessel length resulting in kinking, vessel rotation;
- Presence of residual thrombus in the recipient's portal vein;
- Low portal blood flow, including that caused by persistent splenorenal or gastro-renal collaterals “stealing” blood from the portal bed (portal steal phenomenon);
- Small-for-size syndrome, in which excessive portal flow through a relatively small volume of parenchyma causes damage to the sinusoidal endothelium with subsequent activation of coagulation [Kazymov et al., 2025; Ghabril et al., 2016];
- Use of vascular conduits in portal vein reconstruction — synthetic grafts in this location carry a high risk of thrombosis due to the absence of an endothelial lining and contact with the contaminated environment of the abdominal cavity [Zilla et al., 2007].

To predict post-transplantation deep vein thrombosis, it is necessary to develop mathematical models that would allow for the assessment of the likelihood of thrombotic complications.

Paradoxes

The hemostatic paradox of cirrhosis

For decades, classical hepatology considered liver cirrhosis to be a condition that increases the risk of bleeding, based on prolonged prothrombin times, decreased fibrinogen levels, and thrombocytopenia. However, this interpretation proved to be overly simplistic.

The liver synthesizes not only procoagulant factors (II, V, VII, IX, X, XI) but also key natural anticoagulants (antithrombin III, protein C, protein S). In cirrhosis, there is a parallel decrease in both groups of factors, resulting in the hemostatic system reaching a new state of equilibrium — an unstable one, with a small “safety margin” in both directions [Lisman, Porte, 2010; Tripodi et al., 2009]. Standard coagulation tests (INR and APTT) only reflect the procoagulant component and cannot assess anticoagulant potential. This creates a false impression of hypocoagulation. The issue of hemostatic paradoxes in liver disease is discussed in detail in the review by [Hoffman, 2015].

The paradox of “protective” thrombosis

A number of observations suggest that partial (non-occlusive) portal vein thrombosis in patients with cirrhosis may resolve spontaneously in 40–45 % of cases [Luca et al., 2012]. Furthermore, some authors hypothesize that the organization of a mural thrombus may contribute to the remodeling of the portal vein wall — a process remotely analogous to physiological vascular remodeling via the “thrombus → organization → neointima” mechanism. The clinical significance of this phenomenon remains controversial. However, it raises the question of whether PVT is always pathological and requires aggressive treatment or if, in some cases, it is an adaptive response.

The paradox of anticoagulant therapy

Until recently, it was considered contraindicated to prescribe anticoagulants to patients with liver cirrhosis and portal vein thrombosis (PVT) due to the presumed high risk of bleeding. However, recent studies have demonstrated that anticoagulant therapy (low-molecular-weight heparins, direct oral anticoagulants) is not only effective in achieving portal vein recanalization (recanalization rate of 42–75 % versus 0–40 % without treatment). Furthermore, these therapies are not associated with a statistically significant increase in the incidence of clinically significant bleeding when variceal bleeding is adequately prevented [Delgado et al., 2012; Pettinari et al., 2019].

Furthermore, several studies have shown that anticoagulant therapy in patients with cirrhosis may exert an antifibrotic effect by inhibiting thrombin-mediated activation of hepatic stellate cells and reducing microthrombus formation in the sinusoids — a mechanism known as “parenchymal extinction” [Villa et al., 2012; Wanless et al., 1995]. Thus, anticoagulants potentially affect not only thrombosis itself but also the underlying disease that created the conditions for thrombosis.

The three paradoxes described above can be resolved by developing patient-oriented mathematical models. In particular, even the simplest zero-dimensional mathematical models can describe hemostatic paradoxes and (with the necessary modifications) the paradoxes of anticoagulant therapy. To investigate the role of protective thrombi, it is necessary to develop more detailed models that account for the spatial heterogeneity of the distribution of key coagulation factors.

The paradox of classification and stratification

Existing PVT classifications [Kazymov et al., 2022; Sarin et al., 2016] are primarily based on the anatomical extent of the thrombus [Kazymov et al., 2022]. However, clinical outcomes do not always correlate with the anatomical extent of the process. For example, partial thrombosis involving the confluence of the superior mesenteric vein may have a worse prognosis than complete thrombosis of the main portal vein trunk with preserved mesenteric inflow. Without a comprehensive classification system that simultaneously accounts for anatomy, hemodynamics, etiology, and the chronology of

thrombosis, patient stratification and decision-making regarding management strategies are significantly more complicated.

In response to these limitations, the N. V. Sklifosovsky Research Institute of Emergency Medicine has developed and implemented the MLTR classification, in which each capital letter denotes an anatomical segment of the portal system: M (mesenteric) — mesenteric venous basin, L (lienalis) — splenic venous basin, T (truncus) — portal vein trunk, R (ramus) — portal vein branches. Each segment is assessed on a three-point scale: 0 — no thrombosis, 1 — mural thrombosis with lumen stenosis of less than 50 %, 2 — subtotal or total thrombosis; an additional modifier C indicates calcification. Thus, a four-letter code with numbers unambiguously characterizes the condition of the entire portal basin of each specific patient and directly correlates with the reconstruction strategy. The MLTR classification was published in [Kazymov et al., 2022] and, unlike the Yerdel (2000) classification, which did not account for L-segment involvement and calcification, provides complete anatomical mapping while maintaining clinical simplicity.

Impact on transplant outcomes

Historically, the presence of PVT at the time of transplantation has been considered a relative or absolute contraindication to transplantation. However, as surgical experience has grown, this position has been revised. Nevertheless, PVT remains associated with increased intraoperative blood loss, longer operative times, higher rates of postoperative complications, and the need for complex vascular reconstructions [Zanetto et al., 2018; Bhangu et al., 2019].

Recent meta-analyses have shown that the presence of pre-transplant PVT is associated with an increased 30-day mortality rate (odds ratio: 1.5–2.1) and reduced five-year survival. The degree of prognosis deterioration correlates with the severity of thrombosis according to the MLTR classification: minimal impact in M₀T₁ (isolated trunk thrombosis) and significant impact in M₂T₂ (occlusive thrombosis of the trunk and mesenteric veins) [Ravaioli et al., 2011; Rodríguez-Castro et al., 2012].

Complete portal vein and superior mesenteric vein thrombosis (M₂T₂) requires non-standard surgical approaches, such as multivisceral transplantation, portal vein arterialization, reno-portal anastomosis, or caval-portal hemitransposition. Each approach carries specific risks and debatable efficacy [Selvaggi et al., 2007].

Current trends and unresolved issues

The following key research areas have emerged in recent years:

- The development of predictive models (including those using machine learning methods) to assess the risk of venous thromboembolism (PVT) in patients on the transplant waiting list [Stine, Northup, 2019];
- Investigation of the role of direct oral anticoagulants (DOACs) in PVT in patients with cirrhosis, taking into account altered drug metabolism in the liver [Kazymov et al., 2022];
- Investigation of the value of thromboelastography (TEG) and rotational thromboelastometry (ROTEM) as more adequate methods for assessing “global” hemostatic potential in cirrhosis than standard coagulation tests [De Pietri et al., 2016];
- Optimization of surgical strategies for various degrees of VTE, including preoperative and intraoperative thromboectomy, selection of vascular conduits, and issues related to postoperative anticoagulant prophylaxis [European Association for the Study of the Liver, 2016].

Thus, portal vein thrombosis in the context of liver transplantation is a clinically problematic condition with unclear causal relationships, limited value of classic diagnostic tests, and counterintuitive standard therapeutic approaches. The multifactorial etiology, the paradoxical state of hemostasis in cirrhosis, the heterogeneity of classification approaches, and the dependence of outcomes on surgical technique highlight the need for further clinical research and the development of formalized decision-making models.

The aim of this study is to use a simple mathematical model to examine the influence of various coagulation factors on the likelihood of thrombus formation in the portal vein in the presence of fluid flow. Based on numerical simulations, the study aims to determine the significance of potential risk factors for thrombus formation in a large blood vessel.

Mathematical models of coagulation dynamics in blood vessels

There is an extensive body of literature on the mathematical modeling of blood coagulation dynamics and fibrin clot growth in an in vitro system. Some of the current mathematical models of thrombin generation are analyzed in the review [Owen et al., 2024]. Twenty-four mathematical models were examined, and a historical retrospective of model development was provided. Patient-oriented testing of some of the models was conducted. Predictive properties were investigated using 348 datasets from healthy donors. None of the mathematical models examined provides complete agreement with laboratory data. A comparison based on the value of endogenous thrombin potential (ETP) showed that the model [Panteleev et al., 2010] provides the best agreement with laboratory data. For this reason, we will use this model to describe the reaction kinetics.

To describe thrombus growth in blood vessels, simplified (reduced) systems for thrombin production are typically used. Accounting for spatial effects is reduced to incorporating diffusion for coagulation factors and describing the passive convective transport of these factors. For small blood vessels with low Reynolds numbers, “reaction – diffusion – convection” models with a simplified description of thrombin production were considered in [Чуличков и др., 2000]. Most modern mathematical models are based precisely on the consideration of systems of partial differential equations of the “convection – reaction – diffusion” type. Among the works in this area, we note the articles [Rukhlenko et al., 2015; Bouchnita et al., 2020; Bouchnita et al., 2023; Terekhov et al., 2023]. In [Rukhlenko et al., 2015], based on numerical experiments with the equations of the mathematical model, a threshold dependence of the thrombus formation scenario is established as a function of the Reynolds number, which is equivalent to a dependence on a specific vein. A phenomenological model of thrombin production is used [Атауллаханов и др., 1994].

In a series of studies [Bouchnita et al., 2020; Bouchnita et al., 2023; Terekhov et al., 2023], the problem of fibrin clot growth in a flow was examined based on a reduced mathematical model of thrombin production. The parameters of the mathematical model were selected based on experimental results [Shen et al., 2008]. In [Bouchnita et al., 2023], neural network technologies were used to estimate the parameters of the mathematical model. Based on this selection of mathematical model coefficients, calculations of fibrin clot growth in veins were performed [Terekhov et al., 2023]. In doing so, changes in flow characteristics during clot growth were taken into account. Veins with non-cylindrical shapes were considered. To describe fibrin polymerization, a very simple approach was used, in which the concentration of the fibrin polymer was assumed to be proportional to the time integral of the fibrin-monomer concentration.

Another approach to mathematical modeling of fibrin clot growth in blood vessels also relies on reaction-diffusion-convection equations. The model considers a large blood vessel with a fast blood flow. It is assumed that coagulation reactions are initiated via the intrinsic pathway (on the damaged vascular endothelium). It is further assumed that all reactions occur only within a thin reaction layer.

The size of the layer is determined by the diffusion coefficients of the factors and the shear rate of the flow near the vessel wall. The work in this series began with the article [Fogelson, Tania, 2005]. Since this approach involves mathematical models of the flow-through reactor type, which reduce to systems of ODE, it became possible to use detailed mathematical models of thrombin generation. Modern mathematical models account for membrane reactions on the surface of platelets, in particular, the role of TFPI [Miyazawa et al., 2023a] and a detailed description of the inhibition of coagulation reactions by antithrombin, including upon the administration of heparin [Miyazawa et al., 2023b]. It should be noted that mathematical models of this type have been used only to describe the formation of fibrin layers several micrometers thick on the damaged endothelial surface. Thus, these models are used primarily to describe hemostatic processes in the case of minor injuries, rather than to describe thrombus growth.

Problem statement and mathematical model

We are considering a straight segment of a large vein with a circular endothelial injury. Such a case may correspond, for example, to a circular anastomosis (Fig. 1, *a*). We assume that the geometric characteristics of the damaged section are known — length L and radius R . In the section under consideration, blood flows at a constant average velocity v across the vessel cross-section. A diagram of the model vessel is shown in Fig. 1, *b*.

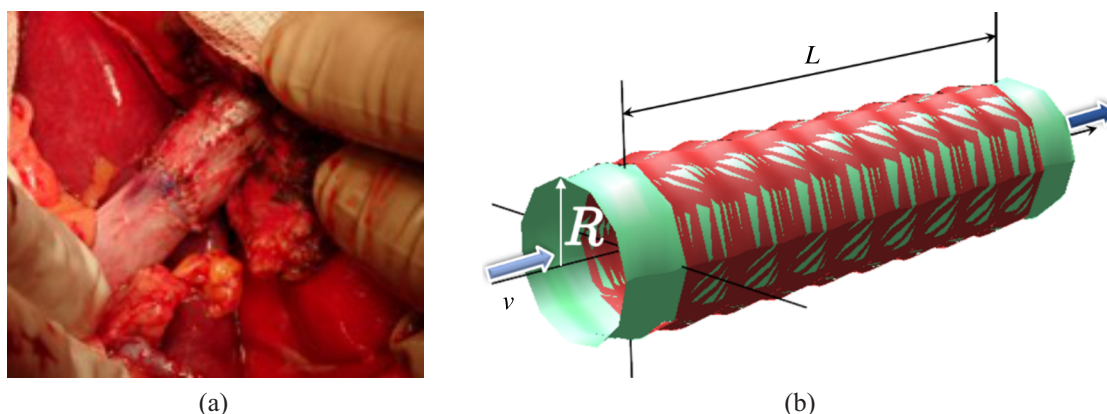


Figure 1. a) Circular anastomosis during transplantation. b) Model of a damaged vascular segment. A flow with an average velocity v passes through the damaged vascular segment, which is L units long and has a radius of R

The coagulation reactions that occur during the formation of a fibrin clot can be divided into three broad groups. Some of these reactions occur in blood plasma. Others occur on the surface of activated platelet membranes and/or extracellular vesicles. Tissue factor (TF) complex formation and breakdown occur on the surface of a vessel with damaged endothelium. Both volume-dependent and membrane-bound reactions can be described by identical “convection – reaction” equations. The Peclet number for the transport of coagulation factors can be estimated as

$$Pe = \frac{vL}{D},$$

where D is the characteristic value of the diffusion coefficient. The characteristic flow velocity in the portal vein is approximately 15–20 cm/min. Assuming a characteristic length of the portal vein of 10 cm and a diffusion coefficient of thrombin of 10^{-6} cm²/min (according to estimates from [Zarnitsina et al., 2001]), we can estimate the Peclet number. The diffusion coefficient for platelets is at least two orders of magnitude smaller [Menichini, Xu, 2016]. Thus, the estimated Peclet number for coagulation

factors is on the order of 10^8 . Convection dominates to such an extent that diffusion transport can be neglected. For platelets and extracellular vesicles, the Peclet number is significantly larger.

The flow in the portal vein is highly non-stationary. This is due to the vessel's location in the abdominal cavity, in close proximity to the diaphragm. Respiratory rhythms superimpose on the flow in the portal vein. In healthy individuals, the amplitude of respiratory modulation is 20–40 % of the mean flow velocity [Abu-Yousef, 1992]. Normally, the transmission of cardiac pulsation to the portal blood flow is minimal. The appearance of marked cardiac pulsatility is a pathological sign. The shape of the portal vein differs from a cylinder. Reverse blood flow is possible within the vessel. The complex, non-stationary flow in the portal vein leads to significant convective mixing. The characteristic mixing time is on the order of the duration of a respiratory cycle (1–5 s). During this time, the blood does not have time to leave the portal vein. We assume that due to rapid convective mixing, coagulation factors and activated platelets are uniformly distributed throughout the vessel's volume. Under these assumptions, the model can be considered zero-dimensional. Since the time required for a fibrin clot to form in the portal vein exceeds the duration of the respiratory cycle by several orders of magnitude, when studying the basic patterns using numerical modeling, time-averaged flows can be taken into account. Under conditions of significant convective mixing, the entire vessel acts as the reaction volume, whereas when convective mixing plays a minor role, the main coagulation reactions will occur in relatively thin reaction layers. Under conditions of significant convective mixing, the entire vessel acts as the reaction volume, whereas when convective mixing plays a minor role, the main coagulation reactions will occur in relatively thin reaction layers.

Let us consider the extrinsic pathway of coagulation initiation, which begins with the contact of coagulation factor VII with tissue factor TF on the surface of the damaged endothelium. Tissue factor is present in all cells of the body, except for blood cells and the monolayer of vascular endothelial cells. Reactions involving TF and its complexes occur only on appropriate surfaces. Exchange with coagulation factors VII, VIIa, IX, and X present in the plasma occurs only upon the formation of the corresponding complexes.

Some of the cascade reactions occur in the plasma volume and on the membranes of active platelets upon the entry of active forms of factors IX and X into the circulation. These reactions may be flow-sensitive. The intrinsic coagulation pathway, initiated by Hageman factor, leads to a faster cascade activation compared to the extrinsic pathway [Panteleev et al., 2020].

Given these assumptions, the system of differential equations for the mathematical model of a vein as a flow reactor takes the following form.

1. Initiation of the coagulation cascade. Reactions in the subendothelium:

$$\begin{aligned} \frac{d[TF]}{dt} &= -k_a^{VII,TF}[VII][TF] + k_d^{VII-TF}[VII-TF] - k_a^{VIIa,TF}[VIIa][TF] + k_d^{VIIa-TF}[VIIa-TF], \\ \frac{d[VII-TF]}{dt} &= k_a^{VII,TF}[VII][TF] - k_d^{VII-TF}[VII-TF] - \frac{k_{cat}^{VII-TF,Xa}[VII-TF][Xa]}{K_M^{VII-TF,Xa} + [Xa]}, \\ \frac{d[VIIa-TF]}{dt} &= k_a^{VIIa,TF}[VIIa][TF] - k_d^{VIIa-TF}[VIIa-TF] - \\ &- \frac{k_a^{Xa-VIIa-TF,TFPI}[TFPI] \frac{k_{cat}^{Xa-VIIa-TF}}{k_a^{Xa-VIIa-TF}}[X][VIIa-TF]}{K_M^{X,VIIa-TF} \left(1 + \frac{[IX]}{K_M^{IX,VIIa-TF}} + \frac{[X]}{K_M^{X,VIIa-TF}} \right)} + \frac{k_{cat}^{VII-TF,Xa}[VII-TF][Xa]}{K_M^{VII-TF,Xa} + [Xa]}. \end{aligned}$$

This set of equations includes differential equations for the surface density of the tissue factor $[TF]$ on the vascular subendothelium. All coagulation factor complexes with TF are

also bound to the vascular wall. The variables have the meaning of the surface density of the corresponding complex.

2. Initiation of the coagulation cascade. Exchange between plasma volume and subendothelium. In all equations here and below, $\frac{1}{\tau} = \frac{v}{L}$, v is the average flow velocity in the vessel, L is the length of the damaged section, then τ has the meaning of the average residence time of the liquid particle in the reaction zone. For the zero-dimensional model, the convective term $(v\nabla)c$ is replaced by the value averaged over the volume of the portal vein, $\frac{c(L)-c(0)}{\tau}$:

$$\begin{aligned}\frac{d[VII]}{dt} &= \frac{-2}{R}k_a^{VII,TF}[VII][TF] + \frac{2}{R}k_d^{VII-TF}[VII-TF] - \frac{1}{\tau}([VII] - [VII](0)), \\ \frac{d[VII_a]}{dt} &= \frac{-2}{R}k_a^{VIIa,TF}[VII_a][TF] + \frac{2}{R}k_d^{VIIa-TF}[VII_a-TF] - \frac{1}{\tau}([VII_a] - [VII_a](0)).\end{aligned}$$

In this block, the variables have the meaning of the volumetric concentration of different forms of coagulation factor VII. When taking into account the exchange between the reaction volume and the reacting surface, the equations include the ratio of volume to surface area. In the case of a cylindrical vessel, it is equal to $\frac{2}{R}$, R is the radius of the vessel.

3. Activation of factors by extrinsic tenase and the transition of active factors into volume, initiating a positive feedback loop. All model variables, except TF complexes, have the meaning of volumetric concentrations of the corresponding coagulation factors:

$$\begin{aligned}\frac{d[IX]}{dt} &= \frac{-2}{R} \frac{k_{cat}^{IX,VIIa-TF}[VII_a-TF][IX]}{K_M^{IX,VIIa-TF} \left(1 + \frac{[IX]}{K_M^{IX,VIIa-TF}} + \frac{[X]}{K_M^{X,VIIa-TF}}\right)} - \frac{k_{cat}^{IX,XIa}[XI_a][IX]}{K_M^{IX,XIa} + [IX]} - \frac{1}{\tau}([IX] - [IX](0)), \\ \frac{d[IX_a]}{dt} &= \frac{2}{R} \frac{k_{cat}^{IX,VIIa-TF}[VII_a-TF][IX]}{K_M^{IX,VIIa-TF} \left(1 + \frac{[IX]}{K_M^{IX,VIIa-TF}} + \frac{[X]}{K_M^{X,VIIa-TF}}\right)} + \frac{k_{cat}^{IX,XIa}[XI_a][IX]}{K_M^{IX,XIa} + [IX]} - \\ &\quad - h_a^{IXa}[IX_a] - \frac{1}{\tau}([IX_a] - [IX_a](0)), \\ \frac{d[X]}{dt} &= \frac{-2}{R} \frac{k_{cat}^{X,VIIa-TF}[VII_a-TF][X]}{K_M^{X,VIIa-TF} \left(1 + \frac{[IX]}{K_M^{IX,VIIa-TF}} + \frac{[X]}{K_M^{X,VIIa-TF}}\right)} - \frac{k_{cat}^{X,IXa}[IX_a][X]}{K_M^{X,IXa} + [X]} - \\ &\quad - \frac{k_{cat}^{X,IXa-VIIIa}[IX_a][VIII_a][X]}{(K_M^{IXa-VIIIa} + [IX_a] + [VIII_a])(K_M^{X,IXa-VIIIa} + [X])} - \frac{1}{\tau}([X] - [X](0)), \\ \frac{d[X_a]}{dt} &= \frac{2}{R} \frac{k_{cat}^{X,VIIa-TF}[VII_a-TF][X]}{K_M^{X,VIIa-TF} \left(1 + \frac{[IX]}{K_M^{IX,VIIa-TF}} + \frac{[X]}{K_M^{X,VIIa-TF}}\right)} + \frac{k_{cat}^{X,IXa}[IX_a][X]}{K_M^{X,IXa} + [X]} + \\ &\quad + \frac{k_{cat}^{X,IXa-VIIIa}[IX_a][VIII_a][X]}{(K_M^{IXa-VIIIa} + [IX_a] + [VIII_a])(K_M^{X,IXa-VIIIa} + [X])} - h_a^{Xa}[X_a] - \frac{1}{\tau}([X_a] - [X_a](0)).\end{aligned}$$

4. Thrombin production. Positive feedback loops:

$$\frac{d[II]}{dt} = \frac{-k_{cat}^{II,Xa}[X_a][II]}{K_M^{II,Xa} + [II]} - \frac{k_{cat}^{II,Xa-Va}[X_a][V_a][II]}{(K_d^{Xa-Va} + [X_a] + [V_a])(K_M^{II,Xa-Va} + [II])} - \frac{1}{\tau}([II] - [II](0)),$$

$$\begin{aligned}
\frac{d[II_a]}{dt} &= \frac{k_{cat}^{II,Xa}[X_a][II]}{K_M^{II,Xa} + [II]} + \frac{k_{cat}^{II,Xa-Va}[X_a][V_a][II]}{(K_d^{Xa-Va} + [X_a] + [V_a])(K_M^{II,Xa-Va} + [II])} - h_a^{IIa}[II_a] - \\
&\quad - \frac{1}{\tau}([II_a] - [II_a](0)), \\
\frac{d[V]}{dt} &= \frac{-k_{cat}^{V,Xa}[V][X_a]}{K_M^{V,Xa} + [X_a]} - \frac{k_{cat}^{V,IIa}[V][II_a]}{K_M^{V,IIa}\left(1 + \frac{[Fg]}{K_M^{Fg,IIa}}\right) + [II_a]} - \frac{1}{\tau}([V] - [V](0)), \\
\frac{d[V_a]}{dt} &= \frac{k_{cat}^{V,Xa}[V][X_a]}{K_M^{V,Xa} + [X_a]} + \frac{k_{cat}^{V,IIa}[V][II_a]}{K_M^{V,IIa}\left(1 + \frac{[Fg]}{K_M^{Fg,IIa}}\right) + [II_a]} - \frac{k_{cat}^{Va,PCa}[V_a][PC_a]}{K_M^{Va,PCa} + [V_a]} - \frac{1}{\tau}([V_a] - [V_a](0)), \\
\frac{d[VIII]}{dt} &= \frac{-k_{cat}^{VIII,IIa}[VIII][II_a]}{K_M^{VIII,IIa}\left(1 + \frac{[Fg]}{K_M^{Fg,IIa}}\right) + [II_a]} - \frac{1}{\tau}([VIII] - [VIII](0)), \\
\frac{d[VIII_a]}{dt} &= \frac{k_{cat}^{VIII,IIa}[VIII][II_a]}{K_M^{VIII,IIa}\left(1 + \frac{[Fg]}{K_M^{Fg,IIa}}\right) + [II_a]} - h^{VIIIa}[VIII_a] - \frac{k_{cat}^{VIIIa,PCa}[VIII_a][PC_a]}{K_M^{VIIIa,PCa} + [VIII_a]} - \\
&\quad - \frac{1}{\tau}([VIII_a] - [VIII_a](0)), \\
\frac{d[XI]}{dt} &= \frac{-k_{eff}^{XI,IIa}[XI][II_a]}{1 + \frac{[Fg]}{K_M^{Fg,IIa}}} - \frac{1}{\tau}([XI] - [XI](0)), \\
\frac{d[XI_a]}{dt} &= \frac{k_{eff}^{XI,IIa}[XI][II_a]}{1 + \frac{[Fg]}{K_M^{Fg,IIa}}} - h^{XIa}[XI_a] - \frac{1}{\tau}([XI_a] - [XI_a](0)).
\end{aligned}$$

5. Fibrinogen cleavage:

$$\begin{aligned}
\frac{d[Fg]}{dt} &= \frac{-k_{cat}^{Fg,IIa}[Fg][II_a]}{K_M^{Fg,IIa}\left(1 + \frac{[Fg]}{K_M^{Fg,IIa}}\right)} - \frac{1}{\tau}([Fg] - [Fg](0)), \\
\frac{d[Fn]}{dt} &= \frac{k_{cat}^{Fg,IIa}[Fg][II_a]}{K_M^{Fg,IIa}\left(1 + \frac{[Fg]}{K_M^{Fg,IIa}}\right)} - \frac{1}{\tau}([Fn] - [Fn](0)).
\end{aligned}$$

6. Activation of protein C. Activation of the negative feedback loop:

$$\begin{aligned}
\frac{d[PC]}{dt} &= \frac{-k_{cat}^{PC,IIa}[PC][II_a]}{K_M^{PC,IIa}\left(1 + \frac{[Fg]}{K_M^{Fg,IIa}}\right) + [II_a]} - \frac{1}{\tau}([PC] - [PC](0)), \\
\frac{d[PC_a]}{dt} &= \frac{k_{cat}^{PC,IIa}[PC][II_a]}{K_M^{PC,IIa}\left(1 + \frac{[Fg]}{K_M^{Fg,IIa}}\right) + [II_a]} - h^{PCa}[PC_a] - \frac{1}{\tau}([PC_a] - [PC_a](0)).
\end{aligned}$$

The constants of the mathematical model are given in Tables 1–3. The initial concentrations of the factors for the physiological norm are given in Table 4. In the case of a reversible reaction,

Table 1. Formation of external tenase. Activation of factors IX and X by external tenase

Reaction	Constants	Values	Source
$[VII] + [TF] \leftrightarrow [VII - TF]$	$k_a^{VII,TF}$, k_d^{VII-TF}	$0.155 \text{ nmol}^{-1} \text{ L min}^{-1}$, 0.014 min^{-1}	[Sen et al., 2010]
$[VII_a] + [TF] \leftrightarrow [VII_a - TF]$	$k_a^{VIIa,TF}$, $k_d^{VIIa-TF}$	$0.155 \text{ nmol}^{-1} \text{ L min}^{-1}$, 0.014 min^{-1}	[Sen et al., 2010]
$[VII - TF] + [X_a] \rightarrow [VII - TF - X_a]$	$k_{cat}^{VII-TF,Xa}$, $K_M^{VII-TF,Xa}$	912 min^{-1} , 1200 nmol/L	[Butenas, Mann, 1996]
$[VII_a - TF] + [X] \rightarrow [VII_a - TF - X]$	$k_{cat}^{X,VIIa-TF}$, $K_M^{X,VIIa-TF}$	435 min^{-1} , 238 nmol/L	[Baugh, Krishnaswamy, 1996]
$[VII_a - TF] + [IX] \rightarrow [VII_a - TF - IX]$	$k_{cat}^{IX,VIIa-TF}$, $K_M^{IX,VIIa-TF}$	5.8 min^{-1} , 200 nmol/L	[Warn-Cramer, Bajaj, 1986]
$[VII_a - TF - X] \rightarrow [VII_a - TF] + [X_a]$	$k_d^{Xa-VIIa-TF}$	770 min^{-1}	[Panteleev et al., 2002]
$[VII_a - TF - X_a] + [TFPI] \rightarrow [VII_a - TF - X_a - TFPI]$	$k_a^{Xa-VIIa-TF,TFPI}$	$6 \text{ nmol}^{-1} \text{ L min}^{-1}$	[Panteleev et al., 2002]

the forward reaction constant is listed first, followed by the reverse reaction constant. For enzymatic kinetics described by the Michaelis – Menten model, the first constant listed is the catalytic reaction constant, and the second is the Michaelis constant. When factors IX and X are activated by the external tenase complex, it is assumed that only free (unbound to tenase) molecules of the corresponding factors can participate in the reaction. The number of free molecules is estimated in accordance with the Michaelis – Menten kinetic model [Michaelis et al., 2011]. This accounts for the appearance of characteristic denominators in the equation. Therefore, Table 1 does not list the values for the forward and reverse reactions for reactions 3–5, but only provides estimates of the product formation rate (subscript *cat*) and the Michaelis constant.

Although the rate of the reaction involving the activation of factor XI by thrombin is small, it cannot be ignored – if this reaction is neglected, the simulation results do not match the experimental data for the intrinsic pathway [Андреева и др., 2022].

For most reversible reactions, the arrows corresponding to the reverse reactions are not shown in the table. For such reactions, only estimates of the product formation rate (subscript *cat*) and the Michaelis constant are provided. For the factor XI activation reaction, the effective reaction constant is given as

$$k_{eff}^{XI,IIa} = \frac{k_{cat}^{XI,IIa}}{K_M^{XI,IIa}}.$$

The mathematical model accounts for the fact that thrombin can form complexes with fibrinogen and fibrin monomers. The estimation of free thrombin for the mathematical model variant used was performed under the assumption that the thrombin monomer rapidly undergoes polymerization and its concentration is negligible; therefore, the concentration of free thrombin depends only on the current concentration of fibrinogen.

The final system of equations does not include equations for the intrinsic tenase $IX_a - VIII_a$ and prothrombinase $V_a - X_a$ complexes. When reducing the system of equations, it was assumed that for these complexes, there is equilibrium between the forward and reverse reactions, and the concentration

Table 2. Thrombin activation and positive feedback loops

Reaction	Constants	Values	Source
$[II] + [X_a] \rightarrow [II_a] + [X_a]$	$k_{cat}^{II,Xa}, K_M^{II,Xa}$	$1 \text{ min}^{-1}, 32 \text{ nmol/L}$	[Rosing et al., 1980]
$[V] + [II_a] \rightarrow [V_a] + [II_a]$	$k_{cat}^{V,IIa}, K_M^{V,IIa}$	$14 \text{ min}^{-1}, 72 \text{ nmol/L}$	[Monković, Tracy, 1990]
$[VIII] + [II_a] \rightarrow [VIII_a] + [II_a]$	$k_{cat}^{VIII,IIa}, K_M^{VIII,IIa}$	$54 \text{ min}^{-1}, 147 \text{ nmol/L}$	[Hill-Eubanks, Lollar, 1990]
$[XI] + [II_a] \rightarrow [XI_a] + [II_a]$	$k_{eff}^{XI,IIa}$	$1.5 \cdot 10^{-7} \text{ nmol}^{-1} \text{ L min}^{-1}$	[Panteleev et al., 2010]
$[V] + [X_a] \rightarrow [V_a] + [X_a]$	$k_{cat}^{V,Xa}, K_M^{V,Xa}$	$2.6 \text{ min}^{-1}, 10.4 \text{ nmol/L}$	[Monković, Tracy, 1990]
$[V_a] + [X_a] \leftrightarrow [V_a - X_a]$	$K_d^{Xa-Va} = \frac{k_{-d}^{Xa-Va}}{k_d^{Xa-Va}}$	1 nmol/L	[Krishnaswamy, 1990]
$[II] + [V_a - X_a] \rightarrow [II_a] + [V_a - X_a]$	$k_{cat}^{II,Xa-Va}, K_M^{II,Xa-Va}$	$1919 \text{ min}^{-1}, 72 \text{ nmol/L}$	[Rosing et al., 1980]
$[IX] + [XI_a] \rightarrow [IX_a] + [XI_a]$	$k_{cat}^{IX,XIa}, K_M^{IX,XIa}$	$20 \text{ min}^{-1}, 2100 \text{ nmol/L}$	[Bajaj, 1982]
$[X] + [IX_a] \rightarrow [X_a] + [IX_a]$	$k_{cat}^{X,IXa}, K_M^{X,IXa}$	$0.00247 \text{ min}^{-1}, 58 \text{ nmol/L}$	[van Dieijen et al., 1981]
$[IX_a] + [VIII_a] \leftrightarrow [IX_a - VIII_a]$	$K_d^{IXa-VIIIa} = \frac{k_{-d}^{IXa-VIIIa}}{k_d^{IXa-VIIIa}}$	0.07 nmol/L	[Mathur et al., 1997]
$[X] + [IX_a - VIII_a] \rightarrow [X_a] + [IX_a - VIII_a]$	$k_{cat}^{X,IXa-VIIIa}, K_M^{X,IXa-VIIIa}$	$73 \text{ min}^{-1}, 18 \text{ nmol/L}$	[Panteleev et al., 2006a]
$[Fg] + [II_a] \rightarrow [Fn] + [II_a]$	$k_{cat}^{Fg,IIa}, K_M^{Fg,IIa}$	$5040 \text{ min}^{-1}, 7200 \text{ nmol/L}$	[Higgins et al., 1983]

of the complexes will be directly proportional to the product of the concentrations of the corresponding factors. Since the complexes form primarily on the membranes of activated platelets, the proportionality coefficient can vary over a fairly wide range depending on platelet concentration. Table 4 lists the corresponding constant values for the physiological norm.

The mathematical model incorporates the effective inhibition constants for all inhibitors, including antithrombin III. These effective constants are denoted by the letter h . A negative feedback loop is identified separately. Thrombin is an activator of proprotein C. Proprotein C, in turn, inhibits the active forms of factors V and VIII, which ultimately leads to a slowing of thrombin generation. The concentration of TFPI is considered a parameter. Its value, according to [Panteleev et al., 2002], is 1.6 nmol/L.

The surface density of tissue factor $[TF](0) = 2 \mu\text{m}^{-2}$ [Govindarajan et al., 2018]. For calculations in more convenient units, $[TF](0) = 3.32 \cdot 10^{-7} \text{ nmol/cm}^2$ was assumed. The initial concentrations of the remaining active blood coagulation factors, as well as all complexes, are zero. The system of ODEs was solved numerically using the one-step Rosenbrock method with complex coefficients. The properties of the method are described in detail in [Альшин и др., 2006].

Table 3. Inhibition. Negative feedback loop

Reaction	Constants	Values	Source
Thrombin inhibition by all the inhibitors	h_a^{IIa}	0.94 min^{-1}	[Panteleev et al., 2010]
Factor IX_a inhibition by all the inhibitors	h_a^{IXa}	0.01 min^{-1}	[Lipets et al., 2014]
Factor X_a inhibition by all the inhibitors	h_a^{Xa}	1 min^{-1}	[Panteleev et al., 2006b]
Factor XI_a inhibition by all the inhibitors	h_a^{XIa}	0.01 min^{-1}	[Lipets et al., 2014]
Factor $VIII_a$ inhibition by all the inhibitors except of the PC_a	h_a^{VIIIa}	0.35 min^{-1}	[Panteleev et al., 2006b]
$[PC] + [II_a] \rightarrow [PC_a] + [II_a]$	$k_{cat}^{PC,IIa}, K_M^{PC,IIa}$	$1.2 \text{ min}^{-1}, 60\,000 \text{ nmol/L}$	[Panteleev et al., 2006b]
$[VIII_a] + [PC_a] \rightarrow [VIII_a - PC_a]$	$k_{cat}^{VIIIa,PCa}, K_M^{VIIIa,PCa}$	$7.5 \cdot 10^{-7} \text{ min}^{-1}, 2.5 \cdot 10^{-5} \text{ nmol/L}$	[O'Brien et al., 2000]
$[V_a] + [PC_a] \rightarrow [V_a - PC_a]$	$k_{cat}^{Va,PCa}, K_M^{Va,PCa}$	$19.7 \text{ min}^{-1}, 23.7 \text{ nmol/L}$	[Solymoss et al., 1988]
PC_a inhibition by all the inhibitors	h^{PCa}	0.034 min^{-1}	[Panteleev et al., 2006b]

Table 4. Initial concentrations of blood clotting factors for the physiological norm

Factor	Initial value, nmol/L
II	1400
V	20
VII	10
VII_a	0.1
VIII	0.7
IX	90
X	170
XI	30
PC	60
Fg	7600

According to the current classification [Park, Park, 2024], the process of fibrin clot growth can be broadly divided into three stages. The first is the initiation stage. During this stage, the concentration of thrombin rises from zero to a threshold value of 1 nmol/L, which can be experimentally determined. This phase corresponds to the thrombin lag period. The amplification stage is characterized by accelerated thrombin growth. It is for this stage that the auto-modeling solutions were developed [Andreeva et al., 2025]. During the propagation phase, active forms of factors (primarily factor V) are transferred to the membranes of activated platelets. Since the mathematical model used does not explicitly account for the platelet component of the cascade, there is no distinction between the amplification and propagation phases in our calculations.

Sometimes, in addition to these three phases, the clot stabilization phase is also included in the analysis [Furie, Furie, 2008; Versteeg et al., 2013]. During this stage, protein C is activated, halting

the growth of the clot. Factor XIII is activated, leading to thrombus contraction. The lysis process is initiated.

In our calculations, we will focus primarily on the process of thrombin generation. We assume that mixing processes in the blood are rapid. The main focus is on the initiation and amplification stages. When considering a mathematical model of a flow reactor with rapid mixing, there is no need to distinguish a propagation stage.

Calculation results

For the model calculations, the length of the portal vein was assumed to be 8 cm and its radius 0.6 cm, which corresponds to anatomical measurements. Let us examine the main patterns of thrombus formation in a system with a flow channel.

The case of a physiological norm

Figure 2 shows the calculated dynamics of thrombin for the case of a physiological norm. All constants and initial conditions correspond to the data in Tables 1–4. The normal level of fibrinogen in the blood, according to various sources, ranges from 1.8–2 g/L to 4 g/L. The value chosen for calculation was 2.5 g/L. For ease of perception, the graph is shown in double logarithmic coordinates.

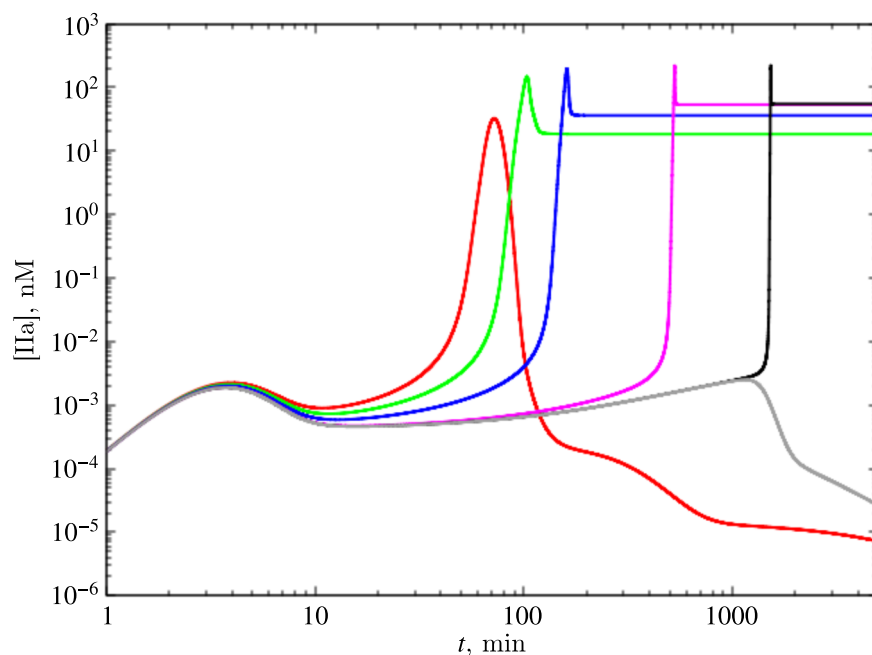


Figure 2. Thrombin production dynamics for the case of physiological norm (fibrinogen concentration of 7600 nmol/L or 2.5 g/L) at different flow rates. The colors correspond to the following flow rates: red — $v = 0$ (stationary fluid), green — $v = 0.1$ cm/min, blue — $v = 0.2$ cm/min, purple — $v = 0.3$ cm/min. The black curve corresponds to the subthreshold flow rate, and the gray curve to the threshold flow rate. For this fibrinogen concentration, these values are 0.30904 cm/min (black curve) and 0.30905 cm/min (gray curve)

The flow rate values are given in the figure caption. In the absence of flow, thrombin production ceases after a finite time. This is due to the depletion of prothrombin in a closed system. In the case of a flow reactor, a significant amount of unactivated factors is introduced into the reaction zone, where they undergo reactions. In addition, active factors are always carried out of the reaction zone, where they are deactivated on the surface of healthy endothelium. At relatively low flow rates, the inflow of active forms of coagulation factors due to volume reactions dominates over the convective outflow of

these active factors. As a result, an equilibrium configuration of all coagulation factors, in particular thrombin, is established in the system.

The initial rising phase of all curves corresponds to the formation of TF-factor VII complexes, in both active and inactive forms, on the subendothelial surface and the subsequent activation of the factor VII–TF complex. These reactions depend neither on flow rate nor on wall shear rate and are determined solely by TF density and the concentration of factor VII forms. The appearance of the external factor VII_a–TF complex in the system triggers the activation of factor X and, consequently, the initiation of thrombin production. The peak in Fig. 2, occurring at times of the order of several minutes, corresponds to the active inhibition of external tenase complexes by the tissue factor pathway inhibitor (TFPI). Since these reactions involve complexes located on the vascular wall and factors in blood plasma, the rate of such inhibition depends on the flow rate in the flow-through reactor. This region determines the duration of the lag period (the initiation phase of coagulation).

When the thrombin concentration increases to a certain value (in the calculation provided, this is approximately 10^{-2} nmol/L), the initiation phase is replaced by the amplification phase — a rapid increase in thrombin concentration. Positive feedback loops are activated. Note that in experiments, the lag period is defined as the time it takes for thrombin to reach a concentration of 1 nmol/L [Wolberg, Campbell, 2008]. According to our simulation results, this value is already reached during the amplification phase.

As the flow rate increases, the initiation time of the cascade (lag period) increases. At the same time, the equilibrium concentration of thrombin also rises slightly as the flow rate in the blood vessel increases. When the flow rate exceeds its threshold value, the convective transport of active factors begins to dominate over the reactions occurring within the blood volume. In this case, the initiation phase is not followed by an amplification phase (accelerated growth of thrombin concentration). The thrombin concentration drops to low levels.

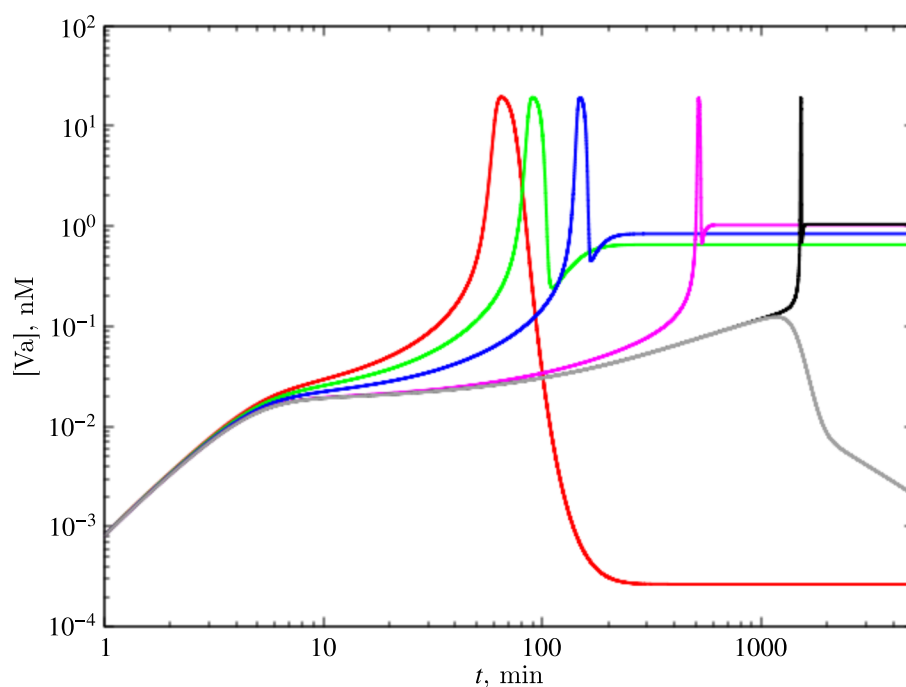


Figure 3. Production dynamics of the active form of factor V for the physiological norm (fibrinogen concentration of 7600 nmol/L or 2.5 g/L) at different flow rates. The colors correspond to the same average flow rate values as in Fig. 2

The threshold nature of the phenomenon is clearly evident in the dynamics of factor V concentration (Fig. 3). It can be seen that, at a subthreshold velocity, following a prolonged lag period, the concentration of the active form of factor V rises sharply, reaches its maximum value, and then approaches the equilibrium value. The threshold value of the rate (black curve in Fig. 3) is characterized by a long lag period. With a slight increase in the rate, the threshold value is already exceeded, and after the initiation stage, the concentration of the active form of factor V rapidly approaches zero (gray curve in Fig. 3).

It should be noted that the flow velocity (the residence time of a liquid particle in the reaction zone) acts as a bifurcation parameter. However, due to the high dimensionality of the system's phase space, it is difficult to conduct an analytical study of this type of bifurcation.

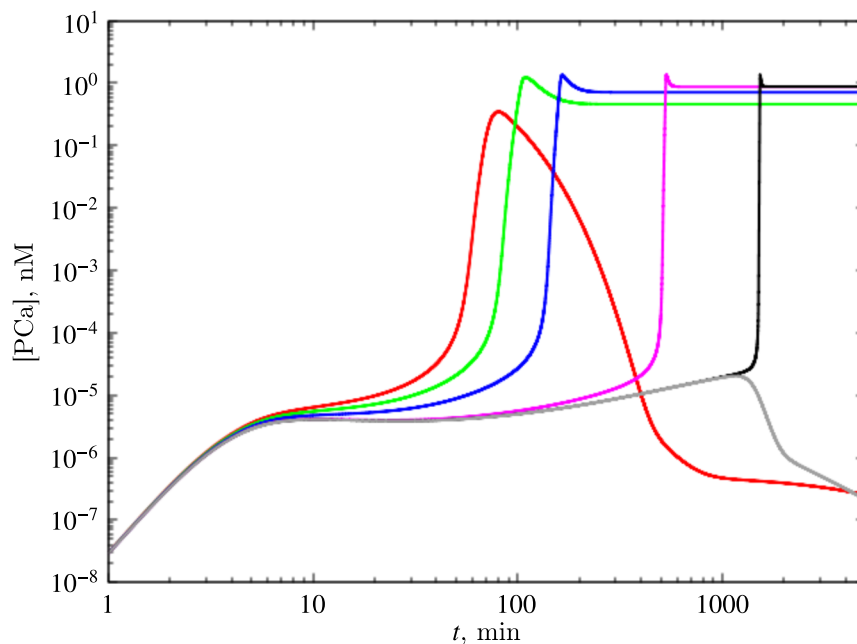


Figure 4. Concentration profile of activated protein C for a physiologically normal case (fibrinogen concentration of 7600 nmol/L or 2.5 g/L) at various flow rates. The colors correspond to the same flow rate values as in Fig. 2

Figure 4 shows the dynamics of production in the system of active forms of protein C (PC_a). It can be seen that, for all subcritical flow rates, an equilibrium concentration is established that is low compared to the initial value (approximately 1 nmol/L for PC_a at an initial concentration of 60 nmol/L). It can be concluded that a change in the initial concentration of protein C in the system has a negligible effect on thrombin production and its equilibrium concentration at subthreshold flow rates. Unlike the other factors, the final equilibrium concentration of protein C is almost independent of the flow rate.

Numerical calculations based on reducing the initial protein C concentration to 40 and 20 nmol/L confirm this hypothesis. In these calculations, a deficiency of protein C resulted in only a slight increase in the equilibrium concentration of factor V_a .

Low fibrinogen levels

It is known that a fibrin polymer network can form even in the presence of fibrinogen deficiency, down to levels as low as 0.2 g/L.

Fibrinogen is a glycoprotein produced by the liver. In cases of liver dysfunction, fibrinogen concentrations may deviate significantly from the physiological norm. Let us assume that the

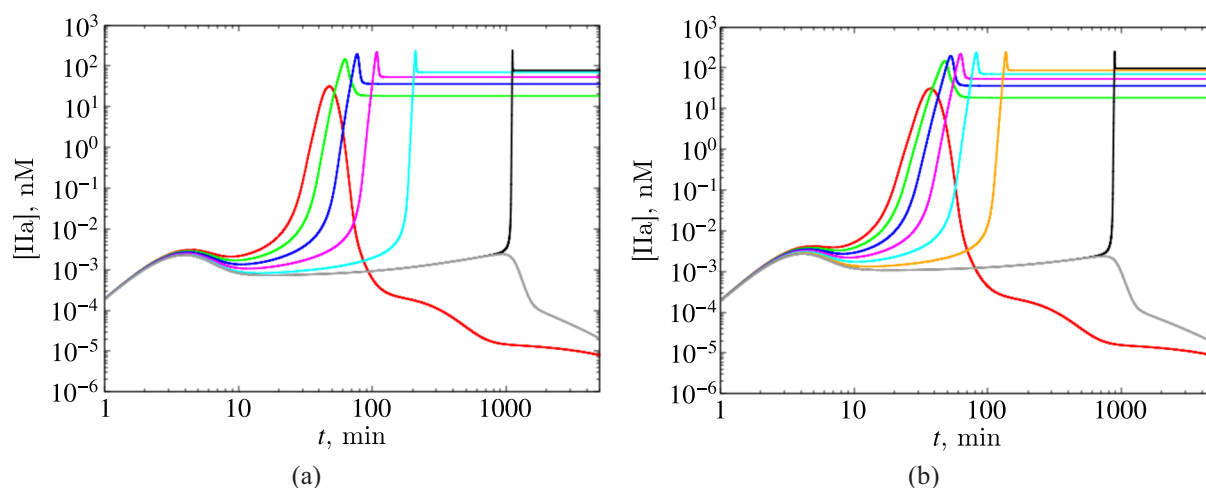


Figure 5. Thrombin dynamics as fibrinogen concentration decreases. Initial prothrombin concentration: a) 3000 nmol or 1 g/L and b) 760 nmol or 0.25 g/L. Colors correspond to the following flow rates: red — $v = 0$ (stationary fluid), green — $v = 0.1$ cm/min, blue — $v = 0.2$ cm/min, purple — $v = 0.3$ cm/min, light blue — $v = 0.4$ cm/min, yellow — $v = 0.5$ cm/min. The black curve corresponds to the subthreshold flow velocity value, the gray curve to the threshold value. Flow rate threshold values for a fibrinogen concentration of 1 g/L, top panel: 0.44435 (black curve) and 0.44435 (gray curve). Flow rate threshold values for a fibrinogen concentration of 0.25 g/L, bottom panel: 0.56510 (black curve) and 0.56511 (gray curve)

concentrations of the other coagulation factors have not changed compared to the physiological norm, and consider the effect of fibrinogen concentration on the dynamics of blood coagulation.

Figure 5 shows the results of calculations of thrombin production dynamics in the PV model as a flow-through reactor for initial concentrations of 3000 nmol/L (1 g/L) and 760 nmol/L (0.25 g/L). In this case, the equilibrium concentrations of thrombin do not depend on the initial fibrinogen concentration but depend on the flow rate. In turn, the threshold (bifurcation) value of the flow rate depends on the initial fibrinogen concentration. As the initial fibrinogen concentration decreases, the flow rate threshold increases. The dependence of this threshold on the fibrinogen concentration is given by a simple formula obtained by interpolation of experimental data

$$v = \frac{0.026}{[Fg](0) + 2.5},$$

where fibrinogen concentration is measured in g/L and velocity in centimeters per second.

It can be concluded that at reduced fibrinogen concentrations, the system becomes more sensitive to stasis. When fibrinogen concentration is reduced, the risk of thrombus formation in the venous system arises over a wider range of flow velocities than under normal conditions; even minor reductions in velocity can trigger activation of the extrinsic coagulation pathway.

A model of thrombocytopenia

It is known that in most cases, PVT is accompanied by thrombocytopenia — a disorder of the platelet component of hemostasis characterized by a decrease in the number of platelets per unit volume of blood. Although the platelet count is not explicitly included in the system of equations, it can be accounted for within the system. External tenase (the $IX_a - VIII_a$ factor complex) is formed on the membranes of activated platelets. Therefore, a decrease in platelet concentration should cause a decrease in the rates of the corresponding reactions, which is accounted for by the constant $K_d^{IXa-VIIIa} = \frac{k_d^{IXa-VIIIa}}{k_a^{IXa-VIIIa}}$. The calculations performed showed that a simple account of

thrombocytopenia confirms these qualitative conclusions. Thrombin generation in these cases slows down as expected, and the equilibrium concentration of thrombin in the flow reactor decreases.

Discussion and conclusions

The results of our calculations using a mathematical model lead to the conclusion that protein C deficiency does not affect the nature of thrombus formation in the portal vein. This conclusion is consistent with the findings of [Manzano-Robleda et al., 2015] regarding the low significance of protein C deficiency for assessing the risk of PVT. Furthermore, [Manzano-Robleda et al., 2015] do not provide data on the presence of other risk factors in patients with protein C deficiency.

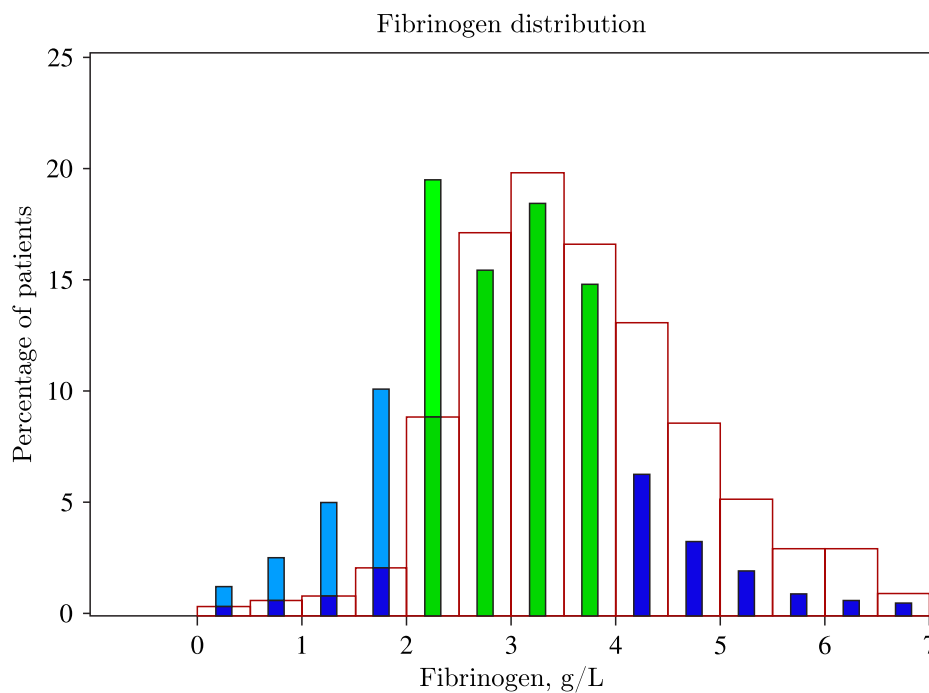


Figure 6. Histogram showing the distribution of patients by fibrinogen level. The wide red bars in the chart correspond to blood fibrinogen levels for a sample of 3693 patients, according to [Saadalla et al., 2025]. The thin bars represent data for 932 patients diagnosed with “portal vein thrombosis” according to data from the N. V. Sklifosovsky Research Institute of Emergency Medicine. The green bars correspond to the physiological norm

Based on the calculations performed, we can formulate a hypothesis regarding the increased sensitivity of the coagulation system in DVT to stasis in the presence of low fibrinogen levels. Figure 6 shows a distribution chart of patients in the population by blood fibrinogen level. The light red bars show data [Saadalla et al., 2025] for a sample of 3693 patients in the United States, characterizing the distribution in the population. The blue and green bars show the distribution by fibrinogen level of patients diagnosed with “portal vein thrombosis” according to data from the N. V. Sklifosovsky Research Institute of Emergency Medicine (932 patients). The green bars correspond to the physiological norm.

A shift in the distribution toward lower values is to be expected — as noted above, fibrinogen is produced by the liver. The fact that a larger proportion of patients have fibrinogen deficiency compared to the general population does not contradict the hypothesis that these patients are more susceptible to stasis.

Data on patients with DVT were obtained using different methods for determining fibrinogen levels. To test the hypothesis of increased susceptibility to stasis, it is necessary to carefully account for the errors introduced by different methods in the range of elevated or reduced fibrinogen levels.

The introduction above noted some paradoxes of DVT. For example, a decrease in the procoagulant activity of the main factors of the coagulation system does not necessarily lead to hypocoagulation. The conclusion drawn regarding susceptibility to stasis at reduced fibrinogen levels falls within the scope of these paradoxes. To draw definitive conclusions about the role of fibrinogen in DVT, it is necessary to conduct a modeling study of the influence of other coagulation factors on the rate of thrombin formation. In addition, it appears necessary to consider models of the “protective thrombus” separately. Concurrently with modeling, a specialized analysis of the accumulated clinical data is required.

In [Wachsberg et al., 1995], the portal vein pulsatility index (PPI) was proposed as a quantitative marker. In [McNaughton, Abu-Yousef, 2011], the resistance index (RI) is introduced alongside the PPI:

$$RI = \frac{V_{\max} - V_{\min}}{V_{\max}}.$$

A normal RI value ranges from 0.55 to 0.7. A high RI value ($RI > 0.7$) may correspond to a postprandial state (immediately after a meal), peripheral vasoconstriction, or a post-transplant state. In such cases, the minimum blood flow velocity in the VV decreases compared to normal levels. For low blood flow velocities and small shear stresses, rheological models of the [Quemada, 1978] type show a significant deviation from the ideal fluid model. In this case, under non-stationary flow conditions, convective mixing occurs throughout the entire volume of the blood vessel. At normal or reduced RI values, convective mixing occurs in a relatively thin layer near the vessel wall. In this case, the mathematical model described in the article must be modified — the volume of the mixing layer should be selected as the reaction volume. In this case, the nature of thrombus growth will be determined by the wall shear rate, as in the experiments [Shen et al., 2008]. If, at high RI values, thrombi are pathological in nature, then at low RI values, protective thrombi should primarily form.

To validate the model, it is necessary to account for the resistance index, and for the same patients, the composition of the blood in the portal vein should be determined. Unfortunately, obtaining such a dataset is difficult. The response of the blood coagulation system depends on the magnitude of the stimulus (for example, on the size and nature of endothelial damage). The extent of endothelial damage can only be assessed for models of postoperative thrombosis. Unfortunately, data are not available for preoperative thrombosis.

The following areas could be identified as directions for further research. The mathematical model should be modified to account for the thickness of the convective mixing layer as a function of RI. It is necessary to account for reduced levels in the blood not only of fibrinogen but also of other coagulation factors produced by the liver. A thorough analysis of the simulation results is required, based on clinical data from specific patients.

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