Introduction to thrombosis in biomedical devices

Rodrigo Méndez Rojano*
Université de Montpellier
IMAG UMR CNRS 5149, France
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Thrombosis is a relevant concern in blood wetted medical devices. The present report aims to be an introduction of thrombosis in order to understand and situate the role of computational fluid dynamics in the development of biomedical devices. First, a general description of haemostasis and thrombosis is presented. Afterwards a brief summary of thrombosis, modelling is reviewed. Types of modelling strategies are presented for each type of modelling challenge that thrombosis comprises.

* http://www.math.univ-montp2.fr/~yales2bio/index.html

CONTENTS

NOMENCLATURE

FDA Food and Drug Administration

HMWK High molecular weight kininogen

LVADs Left ventricular assist devices

SS shear stress

TFPI Tissue Factor pathway inhibitor

TF Tissue Factor

VDAs Ventricular assist devices

I. FACTORS TABLE

Factor	Trivial name	Role
I	Fibrinogen	Activated by thrombin to form fibrin clot
II	Prothrombin	In the presence of FXa\Va converts to thrombin
III	Tissue factor	Initiates extrinsic pathway by forming a compound with Factor VIIa
V	Labile factor	Activated by thrombin; factor Va is a cofactor in the activation of prothrombin by factor Xa
VII	Proconvertin	Activated by TF and activates Factor X as a cofactor with Ca^{2+} and phospholipids
VIII	Antihaemophilic factor	Activated by thrombin; factor VIIIa is a cofactor in the activation of factor X by factor IXa and Ca^{2+}
IX	Christmas factor	Activated by factor XIa, as a cofactor with Factor activates Factor X
X	Stuart-Power factor	Activated by complex TF\FVIIa in presence of Ca^{2+}
XI	Plasma thromboplastin antecedent	Activated by factor XIIa and activates Factor X
XII	Hageman (contact factor)	Binds to exposed collagen or an artificial surface, activated by HMWK and kallikrein
XIII	Fibrin-stabilizing factor, Prekallikrein, HMWK	Activated by thrombin in presence of Ca^{2+} stabilizes fibrin clot by covalent cross-linking

TABLE I.

II. THROMBOSIS IN BIOMEDICAL DEVICES

Coagulation is the biological process by which blood is transformed into a clot. The purpose of coagulation is to cease blood loss from a damaged vessel. When coagulation results into the stop of bleeding the process is called haemostasis. Hoffbrand and H. [1] defines the haemostatic system as a delicate balance between procoagulant and anticoagulant mechanisms allied to a process for fibrinolysis. In a simple direct definition haemostasis is the assembly of processes that hold the blood in a fluid state inside the blood vessel. The five major components of haemostasis are: platelets, coagulation factors, coagulation inhibitors, fibrinolysis and blood vessels. These major components participate in the three stages of haemostasis: initiation, amplification and regulation. A simpler pedagogic division can be found in three stages: primary haemostasis (vasoconstriction, platelet adhesion and activation), coagulation and fibrinolysis. Haemostasis is triggered naturally when an injury is present at the vessel wall, however, it can also be caused by the interaction of blood with an artificial surface; for instance a medical device.
In medical practice the main concerns related to thrombosis when using medical devices are:

- Thrombosis deposition that can lead to device malfunction
- Thromboembolism which leads to ischemic strokes, myocardial infarction or pulmonary embolism.
- Hemorrhagic stroke due to anti-coagulant or anti-platelet therapy

Thrombus formation has been observed in several biomedical devices and clinical procedures like stents, grafts, cathethers, haemodialysis, bypass or in ventricular assist devices (VDAs). The probability of thrombus formation depends a lot on the procedure and on the device. For instance in stents implants Wilson and Cruden [2] thrombosis was reported to occur in only $1-2\%$ of the patients. In endovascular grafts the American Food and Drug Administration (FDA) reported thrombus formation for 34.8% of the patients; this value was found to be due to a manufacturing imperfection that induced high shear stress values and therefore platelet activation. Chan *et al.* [3] showed that the high shear stress induced during catheterization resulted in platelet activation which is relevant for several procedures for instance hemodialysis. In left ventricular assist devices (LVADs) implants, a particular trend was reported by Mehra *et al.* [4] showing an increase in thrombus formation causing mechanical failures of the devices. In the United States closed to 25% of patient hospitalizations are due to thrombus complications and result in a cost close to 1 billion of U. S. dollars per year. Considering a global scale optimizing medical devices to reduce the thrombus formation is an alternative to reduce hospitalizations cost and improve the service life of the biomedical devices.
In this section coagulation is presented paying close attention to thrombosis in biomedical devices. For the sake of understanding the normal in vivo coagulation process is presented. Variations due to biomedical devices are explained when convenient.

A. Thrombosis: a chemical process

Thrombosis is the pathological process that forms a clot inside a blood vessel. The key component in coagulation is thrombin. Thrombin is an enzyme that amplifies the cascade of reactions that lead to coagulation, it also regulates the conversion of fibrinogen to fibrin. The haemostatic equilibrium between coagulants agonist and anticoagulants is broken when excessive quantities of thrombin are produced (hence thrombosis). Full non-thrombogenic surfaces remain unavailable today. One reason of this is that the complicated coagulation process has not been fully understood. Several interactions between blood components, artificial surfaces, flow properties and different time scales make coagulation a difficult multi-physic problem. A general explanation of coagulation is presented bellow to understand each part of the haemostatic system and their interactions. For a deeper description of the haemostatic system one can refer to haematology textbooks for instance [1].

1. Coagulation Cascade

Coagulation proteins circulate in the blood in their inactive form. When an injury at the wall takes place, they are involved in a cascade of reactions that lead to coagulation and to thrombin formation. These reactions are known as the coagulation cascade which is conformed by two systems that converge into a common pathway. The intrinsic and the extrinsic system pathways converge into the common pathway to form fibrin clot.

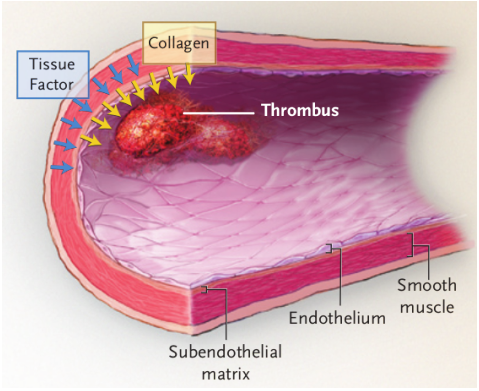


FIG. 1. Vessel wall showing the collagen and Tissue Factor locations (image from Furie and Furie [5])

a. Intrinsic system (pathway): In vivo the intrinsic pathway system is initiated by the exposure of collagen under the endothelium as in figure 1. In particular when the endothelium is damaged, contact activation (activation by negatively charged surfaces) occurs. The importance of the intrinsic pathway remains speculative in vivo because of the difficulty to measure contact activation in the blood vessels. However, for in vitro cases, contact activation is always present thus initiating the cascade of reactions that lead to coagulation. A recent model of the intrinsic pathway for artificial surfaces was proposed by Chatterjee *et al.* [6]. Figure 2 shows the intrinsic pathway including the three enzymatic reactions (auto-activation, auto-hydrolysis and reciprocal activation) that activate factor XII and begin the coagulation cascade in biomedical devices. At the artificial surface factor XII follows a surface mediated reaction to form factor XIIa (auto-activation). Also at the surface high molecular weight kininogen (HMWK) binds to prekallikrein (PK) and to factor XI. Once PK is bind to HMWK it transforms into Kallikrein (Kal). Activation of factor XII by Kal and auto-hydrolysis of factor XII complete the three different mechanisms of factor XII activation. In addition Kal transform factor XIIa to XIIf (fragmented) which serves as a regulator of factor XIIa.
Factor XI is transformed to XIa by the presence of factor XIIa. Activated factor XI transform IX to IXa and diffuses, then factor IXa forms a complex with calcium and VIIIa (which is a result of the initiation of the extrinsic system). Subsequently complex IXa\VIIa\Ca activate factor X. The intrinsic and extrinsic pathways merge in the production of factor Xa.

b. Extrinsic system (pathway): This pathway is triggered by the presence of Tissue Factor (TF) which is present at the sub-endothelium (see Figure 1), in leukocytes and under some pathological conditions in monocytes. TF is also known as factor III or thromboplastin. When TF is exposed to blood flow, it binds to plasma factor VII to form the TF\VII complex. TF \VII complex promotes the activation of factor VII forming the complex TF\VIIa. It is important to mention that pico-molar concentrations of VIIa circulate normally in the blood thus allowing, in the presence of TF, the direct formation of TF\VIIa complex [7]. In the presence of calcium and phospholipids TF\VIIa complex activate factor X, as pointed out before, here is where the intrinsic and extrinsic pathways come together. In addition TF\VIIa complex can activate factor IX, hence communication between extrinsic and intrinsic systems take place. Figure 3 shows a diagram of the extrinsic pathway.

c. Common pathway: Factor Xa forms a complex with activated factor Va. In the presence of calcium complex Xa\Va converts prothrombin into Thrombin which is the master regulation of coagulation. Thrombin cleaves activation peptides from Fibrinogen to form fibrin monomers that result into a clot at the site of the injury. It also activates factor XIII that gives mechanical structure to the fibrin clot. In addition thrombin activates surrounding platelets that seal the fibrin clot. In order to form an amplification feedback loop, thrombin activates factor V, factor XI and factor VIII. Figure 4 shows the coagulation cascade involving the three pathways previously mentioned.[1]

d. Inhibitors of coagulation As we have seen, the coagulation events are amplified by pro-coagulant activity, therefore a counterpart that slows down the coagulation reactions is present in blood in order to reach a balance. The main inhibitors of coagulation are: Protein C, Protein S, Antithrombin and Tissue factor pathway inhibitor (TFPI).

- **Protein C** is a vitamin K-dependent protein that inactivates factors Va and VIIIa.

[1] A really good graphical effort from the Johns Hopkins University to explain the coagulation cascade can be found in `http://www.hopkinsmedicine.org/hematology/Coagulation.swf`

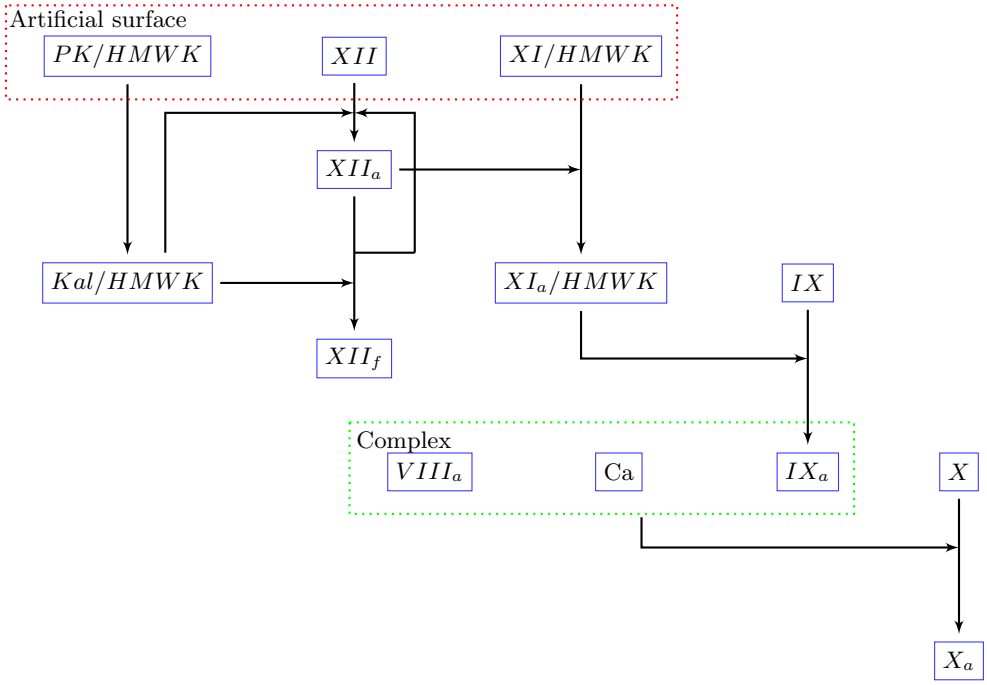


FIG. 2. Intrinsic pathway, sometimes refer as contact pathway, based on the model presented by [6] and traditional biochemical theory.

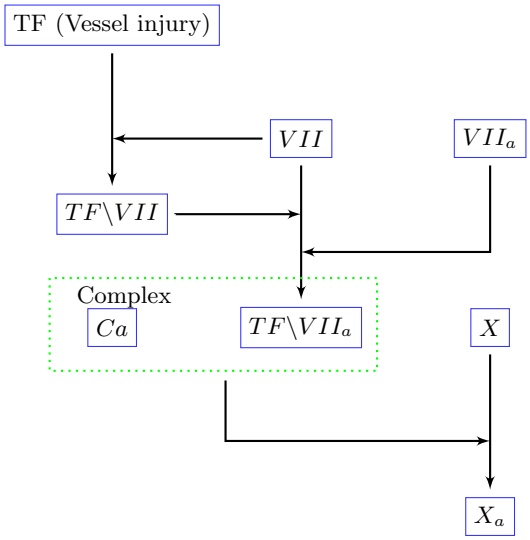


FIG. 3. Extrinsic system pathway (sometimes refer as TF pathway).

- **Protein S** is also a vitamin K-dependent protein that is a cofactor of protein C.
- **Antithrombin** is contained in blood plasma, it neutralizes factor Xa and Thrombin by forming a complex with both enzymes (Xa and Thrombin), thus blocking the active site. It is also capable of inhibiting factors IXa, XIa and XIIa.
- **TFPI** is the main inhibitor of TF*backslash*VIIa complex and factor Xa. TFPI is present on the lumminal surface of the vascular endothelium, also in platelets and plasma. At the time of their activation, monocytes can release TFPI.

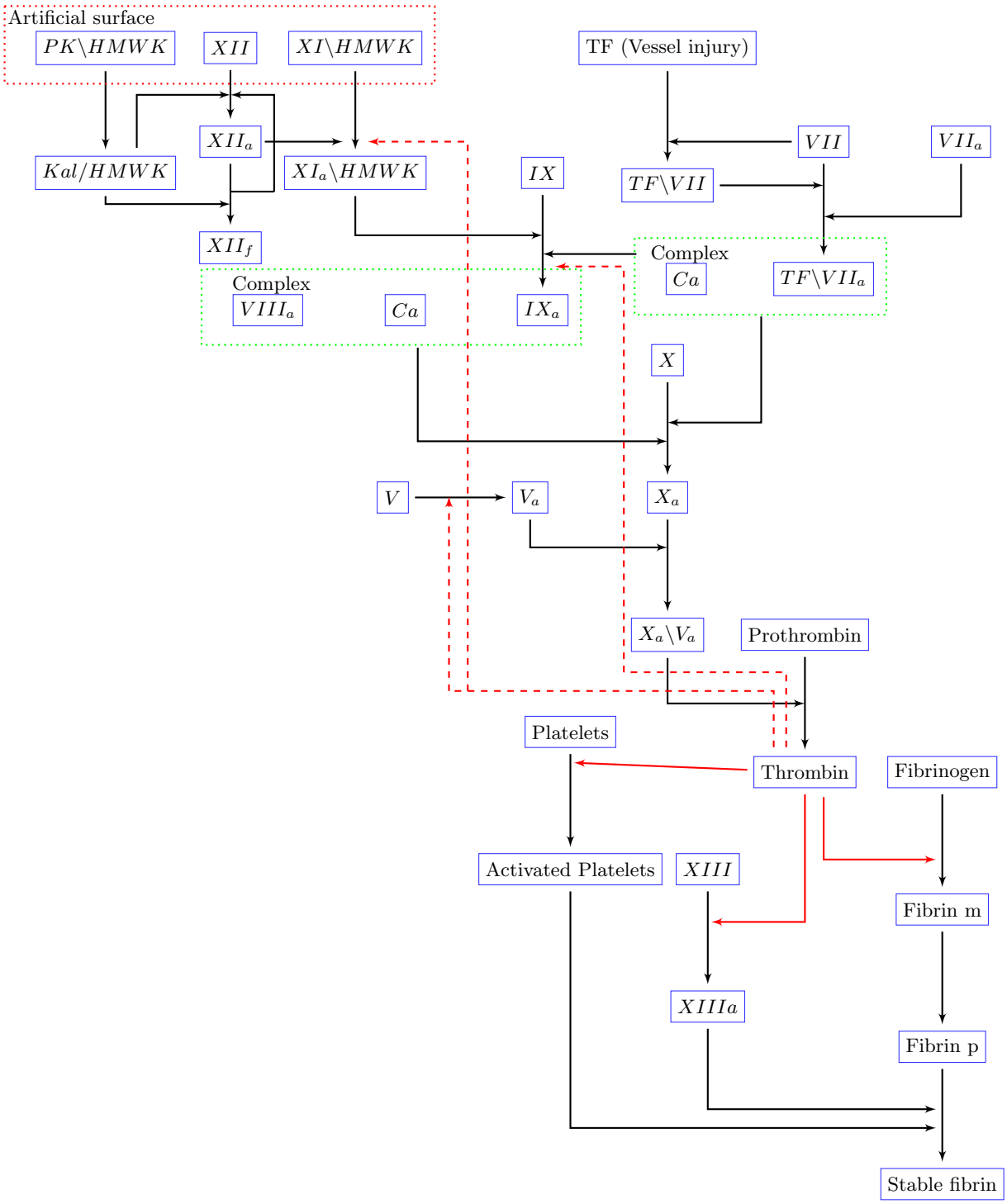


FIG. 4. Blood-coagulation cascade (intrinsic, extrinsic and common pathways) and fibrin production.

e. Bio-material effects in coagulation pathways In order to trigger the intrinsic system, contact activation by negative charged surfaces has to be present. This event is not confirmed in vivo. However in the presence of an artificial surface, an absorbed protein layer appears and the required negatively charge surface is present, hence initiation of the intrinsic pathway presented above. Furthermore TF expression by monocytes was observed by Wilhelm *et al.* [8] and correlated to the presence of bio-materials boosting the extrinsic pathway.

2. Platelet activation

Platelets act together with the fibrin plug in haemostatic process to preserve the integrity of the vascular wall. Normally non-activated platelets circulate in the blood flow and they become active in the first instants of haemostasis (in what is call primary haemostasis). Platelets are recruited to the injury in order to seal the fibrin clot; therefore they become a major component of the thrombus. Platelets become activated when contacting any type of thrombogenic surface, they play a critical role in the amplification of the coagulation cascade by providing a fundamental base in which reactions of coagulation can take place (we had referred to this base as a phospholipid surface). There exist two pathways to platelet activation [5]. One pathway is due to the interactions of von Willebrand factor (vWF) and glycoprotein VI with collagen; this pathway is independent of thrombin and its result is the adhesion of platelets to the site of injury. A second pathway for platelet activation is related to the extrinsic system which ends up in the production of thrombin. Thrombin activates platelets directly but it also produces serotonin and thromboxane A_2 that amplify platelet activation.
In addition platelets can be mechanically activated by the flow. Hellums [9] identify a shear stress threshold that depend on the stress exposure time.

a. Effect of bio-materials in platelets Platelet activation has been observed in several clinical procedures and biomechanical devices. Once activated, platelets may attach to the wall vessel or be swept away by high blood flow rates. They also can form microemboli that flow in the circulation system. The bouncing off or adhesion of platelets to the thrombus is regulated by the interaction of GPIIb\IIIa complex with fibrinogen and by the interaction of GPIIb\IIa complex with vWF.
Another event that affect platelets takes place when artificial hydrophilic surfaces are exposed to normal plasma Vroman effect. Vroman *et al.* [10] observed the replacement of fibrinogen in an attempt to identify the pathway of proteins deposited by plasma to artificial surfaces. The process that was used to track the proteins revealed an alteration in the fibrinogen deposited onto the surface. HMWK apparition and fibrinogen disappearance was observed when fibrinogen was deposited onto hydrophilic glass-like surfaces and put in contact with plasma. The process of fibrinogen alteration was clear when HMWK deficient plasma was used and the deposited fibrinogen remain unaltered. This event suggest that HMWK is the agent responsible of altering fibrinogen. The importance of the Vroman effect to platelets relays on the fact that platelets have a strong affinity to adhere with fibrinogen. For instance if a deficient HMWK plasma is present, platelets will interact with fibrinogen.

3. Complement system

The complement system allows antibodies to kill some bacteria. This activity was said to "complement" the antibacterial activity of the antibody and hence the name. It has fundamental clinical implications in the context of life-threatening tissue injury and inflammation. In the last years an important relation of the complement system and the coagulation process has been observed.
Complement system is conformed by the classical and the alternative pathways see Figure 5. The classical pathway is triggered by antigen-antibody complexes while the alternative pathway is activated by foreign surfaces such as fungal, bacterial polyssaccharides, lipopolysaccharides, particles and **bio-material surfaces**.
The complement system relates to the coagulation system in the form of a feedback loop. Thrombin and coagulation Factors XIa, Xa, IXa and plasmin were all found to effectively cleave C3 and C5 molecules which are central components of the complement system. In Table II all the interactions of the complement system with the coagulation systems are shown [7].

Protein	Type of interaction
Thrombin	Proteolysis of C3, C5, C6 and factor B
Factor XIIa	Proteolysis of C1r, C1s and C3
Kallikrein	Proteolysis of C1, C5 and Factor B
Antithrombin III	Protect RBC form lysis by mC5b-9
Bb	Proteolysis of prothrombin
C3bBb	Proteolysis of prothrombin
C1 inhibitor	Inactivates FXIIa and kallikrein
S protein (vitronectin)	Stabilizes plasminogen activator inhibitor 1
C4b-binding protein	Binds to the vitamin K-dependant protein S

TABLE II. Interactions between complement and coagulation systems [7]

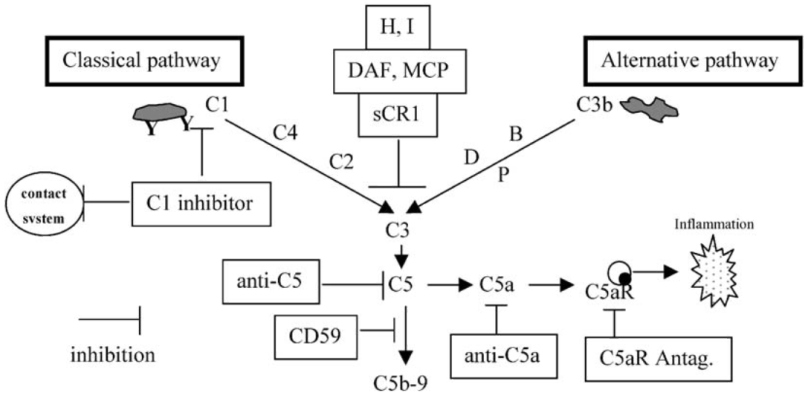


FIG. 5. Complement system diagram from [7] (Kirschfink M)

a. Effect of biomedical devices in the Complement system: Gorbet and Sefton [7] pointed out the importance to account for complement system interaction with the coagulation process when artificial surfaces are present. In particular an inflammatory response is observed in the presence of bio-materials. This inflammation is due to the complement activation by the alternative pathway. Interactions of the Factor H and the C3b molecule (see figure 5) with the artificial surface trigger the complement system. In addition the complement activation by biomedical means has an important role in leukocyte activity meaning possible TF expression and therefore the initiation of the extrinsic system pathway.

4. Leukocytes

Several types of leukocytes are present in the circulatory system: neutrophils, monocytes, lymphocytes, basophils and eosinophils. Artificial surfaces interaction with Neutrophils($40-60\%$ of leukocytes population) and monocytes (5% of leukocyte population) may be the reason of leukocyte activation. One of the most important effects of leukocyte activation to thrombosis is the expression and synthesis of TF. Leukocyte adhesion may also participate in inflammation (increasing the reactive surface) and therefore promoting the thrombogenic activity.

a. Biomedical effects of devices in Leukocytes activation

5. Blood flow influence in thrombosis

Flow enhances the transport of coagulation factors (pro coagulants and inhibitors) to the surface (vessel wall injury or the artificial surface) and therefore is a crucial factor in the coagulation process. When it comes to the extrinsic pathway, it is found that for high shear rates the activation of factor Xa by the complex TF\VIIa increases. Basmadjian *et al.* [11] showed the relation between the artificial surface reactivity and the flow. At low flow rates, activation rates of Factor IX (intrinsic system) are high and do not depend on the surface reactivity. However, as the flow shear rate increases, the activation of factor IX depends a lot on the surface reactivity. This findings are really interesting because even when the activation rate of Factor XII is close to zero (almost anti-thrombogenic surface), the activation of factor IX continues. This supports the fact that the best way to design non-thrombogenic surfaces is to include both the reactivity of the tissue and the characteristics of the flow.
A clear influence of the flow in platelet activation, aggregation and adhesion is present [9, 12, 13]. Fluid mechanical shear stress can be pictured as a platelet agonist that will increase binding affinity between the different platelet agonists. Furthermore a clear interaction of platelet activation and shear stress has been observed at some particular threshold shear stress (SS) levels. Measurable changes in the platelet response are seen when the thresholds of SS are reached, these thresholds depending strongly on the time of exposure. Figure 6 shows the dependency of the platelet serotonin release (activation of platelets) to the shear stress and the exposure time. In particular a key event of the stress-induce activation and aggregation is the binding of vWF to platelet membrane glycoprotein Ib. Grabowski *et al.* [13] demonstrated that increasing shear rate may increase the flux of platelets to a foreign surface not only by diminishing the thickness of the platelet concentration boundary layer but also by simultaneously augmenting the platelet diffusion coefficient; a dependency of the platelet adhesion to shear rate is therefore present.

In addition thrombus architecture is greatly influenced by how the fibrin plug and platelets adhere to thrombogenic surface, therefore the characteristics of the flow like wall shear or turbulence are extremely important to understand the dynamic process of thrombus formation. Similar studies as for platelets have been done in order to evaluate the

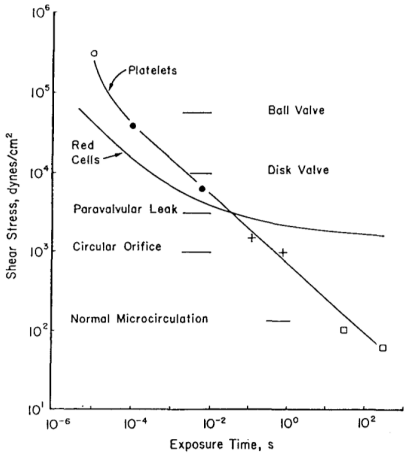


FIG. 6.

influence of the flow on leukocyte adhesion, suggesting an important connection; however a bigger effort needs to be done. Finally, turbulence may have an effect on the recirculation zones that result in hemolysis and cell activation but its influence in thrombus growth is poorly understood and research is still on going.

6. Virchow's triad and coagulation tests

There are several test and criteria that allow us to test the risk of thrombosis from a biomedical device. For instance Virchow's triad consist of three risk elements that build a criteria for venous thrombosis. Virchow's components are:

- Slowing down of the local blood flow
- Hypercoagulatibity of the blood
- Vessel damage

Assessment of the biomedical devices needs to be performed in order to test the thrombogenicity. This test vary according the device and procedure in which the device will be use. In Table III several examples of device testing are presented.

Device	**Test**
Intervention Catheters	4 hour canine NAVI study
Indewelling Catheters	30 day animal study with platelet activation and leukocyte information
Stents-Grafts	Large animal studies
VADs	Large animal studies
Bypass circuit components	In vitro coagulation assays

TABLE III. Thrombogenicity testing from the FDA for several biomedical devices

7. Conclusion

B. Thrombosis Modelling

The modelling of thrombosis can easily turn into complicated mathematical models, therefore an isolated analysis of each component of thrombosis may be easier and more clear to present. In this section the state of the art in

thrombosis modelling is presented paying closed attention to the multi-physic nature of the problem.

1. Biochemistry of intrinsic, extrinsic and common pathways

One of the first models of thrombin generation was presented by Jones and Mann [14]. This model simulates the TF pathway (extrinsic pathway) including 18 species and 20 differential equations that describe the coagulation reactions. The model is solved using a Runge-Kutta integration technique.
A specific model of the intrinsic and common pathways was presented by Gregory and Basmadjian [15]. The model is comprised of 20 dominant reactions with 11 components that can be reduce to 4 coupled ODEs with Leveque's regime hypothesis. A polynomial algebraic equation can be obtained and 3 steady state concentrations for coagulants are analysed. The central coagulant in this model is Factor XII which was considered in 3 states (activated, bind to the surface and fragmented).
Another model of the intrinsic pathway was developed by Zarnitsina *et al.* [16]. In this model 8 differential equations account for the activation of factors XI, IX, X, II, I, VIII, V protein C. Tenase and prothrombinase complex are calculated as a function of calcium concentration. The model assumes a constant flux at the injury site of activated factor XI.
Kuharsky and Fogelson [17] developed a physical and chemical model that accounts for platelet and coagulation events that occur in a thin layer, called the reaction zone, just above a small vascular injury. The KF model takes into account the plasma-phase, subendothelial-bound and platelet-bound enzymes and zymogens as well as activated and unactivated platelets. All species in the reaction zone are assumed to be well mixed; each species is characterized by its concentration that is tracked in time using an ordinary differential equation. Advective and diffusive transport of fluid-phase species (chemicals and platelets) into or out of the reaction zone is modelled by a mass-transfer term in which the mass-transfer coefficient depends on flow and diffusion parameters. The disadvantage of this model is the poor treatment of the flow.
In the work of Xu *et al.* [18] a two dimensional model is presented where a macroscopic view of the flow is described by the NS equations. However, for the for the microscale interactions between the platelets and coagulation reactions, an extended stochastic discrete model was used.
Anand *et al.* [19–21] biochemical reactions and rheological aspects are taken into account, in addition of reactions for the production of fibrin. The model of Anand [19] was used in a simplified way by Bodnár and Sequeira [22] to study the clot formation and growth of thrombus in the vicinity of an injured vessel wall.
A mathematical model for the contact activation of factor XII by a pro-coagulant surface was developed by Guo *et al.* [23]. The model of Guo uses a Michaelis-Menten kinetic mechanism simplifying the coagulation cascade of enzymatic reactions in a single enzymatic reaction. Therefore the model can be divided in two steps; first the activation of FXIIa as function of a catalytic surface potential (that variates according to the water-weattability of the surface) is calculated and then FXIIa interacts with the rest of the cascade of reactions in the form of a substrate. These two steps are combined to predict the coagulation time. Guo concludes that the material induced coagulation is a surface mediated event thus the coagulation times depends strongly on the surface area and the properties of the surface. Finally the results suggest that procoagulant surfaces have no influence in enzymatic reactions other than FXII activation

2. Platelet activation and adhesion

Sorensen *et al.* [24] developed a two dimensional model of a coupled set of convection-diffusion-reaction equations, which attempts to simulate platelet-platelet and platelet-surface adhesion as well as platelet activation by relevant agonist (RP, AP, a_{pr}, a_{ps}). The model also accounts for platelet-phospholipid-dependent thrombin generation and thrombin inhibition by antithrombin III. The velocity fields come from the well know Poiseuille solution.
Mandrusov *et al.* [25] studied the Vroman effect in a shear flow chamber for a mixture of plasma and saline solution. Experiments were compared against numerical simulations to study the kinetics of plasma protein deposition. A band of fibrinogen moving downstream was observed and calculated. This band promotes platelet adhesion that was also observed in the experiments. A single-component unsteady convective-diffusion equation was solved for a two dimensional domain. Deposition of fibrinogen and HMWK was calculated at the wall using the composition of the species. Natural convection had a great effect in the experiments, therefore, the experimental and numerical results showed important differences.
Fogelson and Guy [26] presented a model that account for platelet adhesion in an injured vessel using distributions of elastic links which generate stresses that influenced the fluid motion. This method is interested at the microscale of platelets events and considers the wall and the flow as a continuum.

A backward-facing step (BFS) configuration was studied by Taylor *et al.* [27]. In this work thrombus growth is investigated using an magnetic resonance imaging (MRI). The acrylic BFS configuration is connected to a pump in a closed loop in which bovine blood circulate for 90 minutes. Several MRI were performed to capture the thrombus growth and then simulations were performed with the segmentation geometry. The simulations where performed at a Reynolds number of 490 and the wall shear stress distribution over the thrombus was calculated observing a clear dependence on the thrombus topology. In an posterior work Taylor *et al.* [28] used a simplified form the model of Fogelson and Guy[26]. A modified Brinkman term was added to the equations in order to account for thrombus growth; This term act as a momentum sink in regions with a high concentration of platelet-platelet links. The advantage of this treatment is that it allows to keep the original mesh.

3. Thrombus growth

Goodman *et al.* [29] present a model in which thrombus growth is handled by increasing the viscosity in mesh cells where the volume of adherent platelets was grater than the volume of the grid. This model also takes into account embolization, platelet adhesion and platelet activation. Transport properties were taken as in [30]. The model does not account for protein absorption it assumes proteins at the surface are in equilibrium. Finally the model of Goodman *et al.* [29] is compared with experimental results showing a good agreement for the thrombus growth.
Leiderman and Folgelson [31] present an extension of the Kuharsky and Fogelson [17] model that incorporates spatial variations and explicitly models the growth of a thrombus and how this is coupled with the local fluid dynamics; the platelet adhesion is model as in Fogelson and Guy [26].

4. Complement system activation

5. Leukocyte activation and TF expression

6. Thrombosis risk assessment in biomedical devices

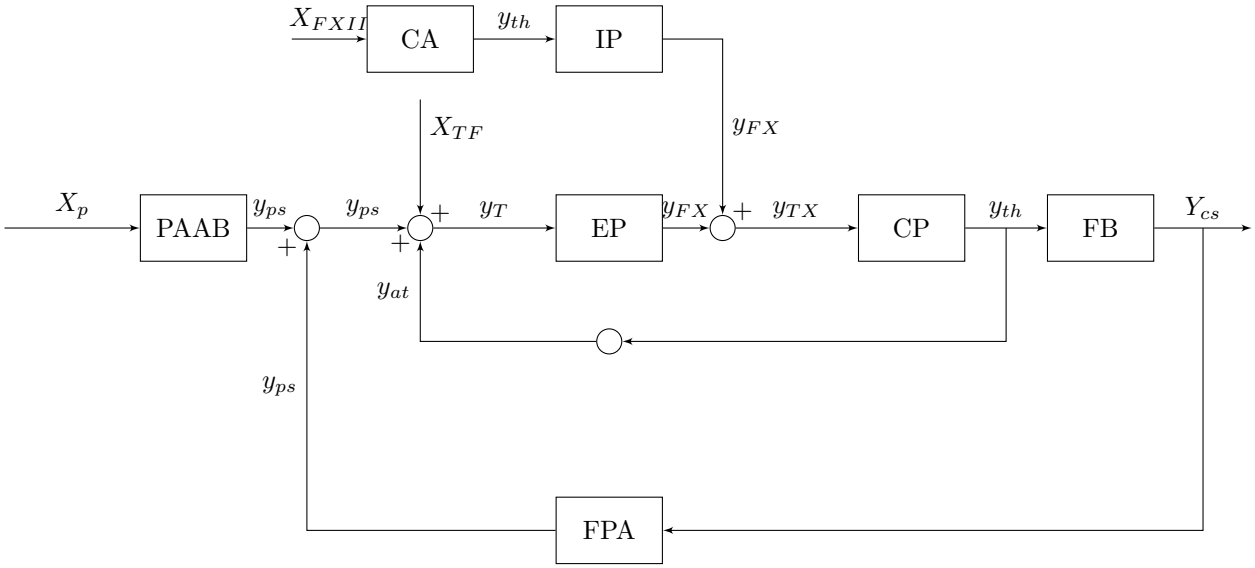
Biasetti *et al.* [32] studied an unsteady blood flow in aneurysmatic aortas using a Newtonian and a non newtonian model for the blood using the λ_2 criteria for vortex-eduction. Then a possible relation between vortex and intraluminal thrombus (ILT) formation was investigated. In a posteriori work Biasetti *et al.* [33] present a model in which biochemical reaction were added with a set of convection-diffusion-reaction equations from [14]. The results showed a big influence of the flow (shear rates and vortex) on the production of thrombin and the ILT growth.
In contrast, Achille *et al.* [34] presented a predictor of intraluminal thrombus formation in abdominal aortic aneurysms using a chemistry-free approach. It mimics the platelets activation due to flow-induce shear and platelet adhesion at the walls where the haemodynamic activity is favourable (recirculation zones). Achille *et al.* applied the model to 10 carotid arteries and 6 abdominal aortic aneurysms from which half of them where healthy. The results show an impressive effectiveness of the predictor; however more studies have to be done to include nascent thrombus that were not include in the study and that are crucial for medical practice.

7. Conclusion

C. A mathematical model for thrombosis in medical devices

1. Thrombosis block diagram

In order to have a graphical representation of the mathematical modelling of thrombosis a diagram of thrombosis is presented with the inputs, outputs and processes involved.



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Process	Meaning
PAAB	Platelet Activation Aggregation and Binding
EP	Extrinsic Pathway
AA	Adsorption and activation of factor XII
IP	Intrinsic Pathway
CP	Common Pathway
FB	Fibrinolysis
FPA	Feedback Platelet Activation by Thrombin

TABLE IV. Principal process of clot formation diagram

Inputs	Meaning
X_{FXII}	Concentration of Factor XII in blood
S	Artificial Surface
K_m	Michaelis-Menten constant
X_p	Platelet concentration in blood
D_i	Diffusion coefficients
C_i	Concentration of species (Platelets or coagulation enzymes and complex)
k_i	Reaction rate
X_{TF}	Concentration of Tissue Factor (at the surface and in the blood stream)

TABLE V. Principal inputs of clot formation diagram

can see from TableVII most of the models are focused on the extrinsic and common pathways thrombosis. Very few articles study thrombosis due to an artificial surface or in other words the intrinsic pathways. In addition complex flow configurations (which is the real case for biomedical devices) and activation of factor XII are not considered in the articles that study the intrinsic pathway [15, 16, 25, 35, 36].
The role of turbulence and pulsate flows in platelet dynamics and coagulation pathways as well as the leukocyte expression of tissue factor and the complement system interactions with the coagulation cascade remain to be elucidated. In the next section two models to account for protein adsorption dynamics will be presented.

Outputs	Meaning
y_{ps}	Phospholipid surface (activated platelet concentration at the surface)
y_{at}	Activated platelet by thrombin concentration at the surface
y_T	Total activated platelet concentration at the surface
y_{FX}	Concentration of FX
y_{TX}	Total concentration of FX
y_{th}	Thrombin concentration (at the surface and in the blood stream)
Y_{cs}	Final output clot surface

TABLE VI. Principal outputs of clot formation diagram

Article	Process	Summary
Jones and Mann [14]	EP, CP	Phospolipid excess considered.
Chatterjee *et al.* [35]	AA, IP, EP, CP	Transport due to the flow are not taken into account. Influence of different plasma donors is shown.
Guo *et al.* [23]	AA, IP, EP, CP	Properties of the surface taken into account. Coagulation cascade reactions are taken as a single Michaelis-Menten reaction.
Kogan *et al.* [36]	AA, IP, EP, CP	Transport due to the flow are not taken into account.
Zarnitsina *et al.* [16]	IP, EP, CP	Constant concentration of activated factor XI as input.
Gregory and Basmadjian [15]	CA, IP	Léveque transport regime. FXII (binded to the wall) considered constant and equal to saturation level. HMWK considered as activated. All PK is complexed with HMWK.
Mandrusov *et al.* [25]	(Vroman effect protein adsorption model)	Transient Leveque problem accounting for Fibrinogen and HMWK deposition (Vroman effect)
Sorensen *et al.* [24]	PAAB,EP,CP,FB,FPA	Model focus in describing platelet dynamics (activated, adhere and resting) EP and CP simplified (only Thrombin, ATII and FII are accounted)
Kuharsky and Fogelson [17]	PAAB, EP, CP	Léveque transport regime. Platelets as pro-coagulant surfaces.
Xu *et al.* [18]	PAAB, EP, CP, FB	NS for the flow. PAAB does not communicate with EP or FB. Clot interface tracked.
Anand *et al.* [19–21]	EP, CP, PAAB, FB	Shear-thinning visco-elastic fluid. Platelet activation by thrombin, and by shear stress criteria. Constitutive model for the clot. Clott growth and dissolution.
Bodnár and Sequeira [22]	EP,CP,FB	Clot growth with a viscosity constitutive law. Simplification of Anand *et al.* model
Fogelson and Guy [26]	PAAB	Model for platelet wall interaction (adhesion and aggregation)
Wootton *et al.* [30]	PAAB, EP, CP, FB	Wall shear stress is correlated with lysis rate of mural thrombi
Goodman *et al.* [29]	PAAB, EP, CP, FB	3D simulation of a conduct with variable cross section, platelet transport, adhesion and shear activation are taken into account. Thrombin production, emboli and thrombus growth are calculated and compared against experimental values
Biasetti *et al.* [33]	EP, CP	Study the effect of flow transport in coagulation (in vivo) ussing the model of [14]
Leiderman and Fogelson [31]	PAAB, EP, CP, FB, FPA	Two way communication between the growing thrombus and the flow. The porus nature of the clott is taking into account.
Taylor *et al.* [28]	PAAB, FB	BFS incompressible NS for a laminar configuration, the model uses a simplified version of Fogelson and Guy [26] including a Brinkman term to account for thrombus growth

TABLE VII. Summary of models presenting relating them with the block diagram

D. Mathematical model for protein adsorption on artificial surfaces

A mathematical model involving the initiation of the coagulation process and the dynamics of the flow remains absent in the literature. Most of the models consider a source of activated factor XIIa or a posterior activated factor. In order to investigate the contact pathway initiation in realistic flow regimes a kinetic enzymatic mechanism of factor XII activation can be couple in the form of a convection diffusion reaction equation communicating with the Navier Stokes equations.

1. Convection diffusion reaction model

One of the most common techniques to model thrombosis is the convection diffusion reaction model. This type of model considers a reaction network that is transported by a fluid in the form of diffusion and convection that yields to the following equation.

$$\frac{\partial C_i}{\partial t} + \nabla \cdot (C_i u) = \nabla \cdot (D_i \nabla C_i) + R_i \tag{1}$$

Where:
C_i : Concentration of i species
D_i : Diffusion coefficient
R_i : Source or sinks of species i
The source terms are obtained from a enzymatic kinetic scheme. Then initial conditions of the species concentrations are given as an input (free flow concentrations or wall concentrations in the case of Factor XII). As we can see from equation 1 the diffusion coefficients and the velocity field are as well inputs in the model. In our case the Navier-Stokes equations for an incompressible fluid are solved to calculate the velocity fields.
A kinetic scheme of the intrinsic pathway can be used to investigate possible effects in the coagulation cascade due to the transport of enzymes. Two models for the activation of factor XII are presented. The first kinetical scheme was presented by Guo *et al.* [23] in which the catalytic potential is taken into account depending on the surface properties. A second scheme is taken from Chatterjee *et al.* [35] in which activation of factor XII is inhibited by two anti-thrombogenic enzymes and a relations with the complement system are also present.

2. Activation of Factor XII

Up to date it is accepted that there are three enzymatic events that conduct to factor XII activation (auto-activation, auto-hydrolysis and reciprocal activation of factor XII) as it is shown in figure 7.
The second model presented is a portion of Chatterjee *et al.* [35] model that was used to predict the thrombin pro-

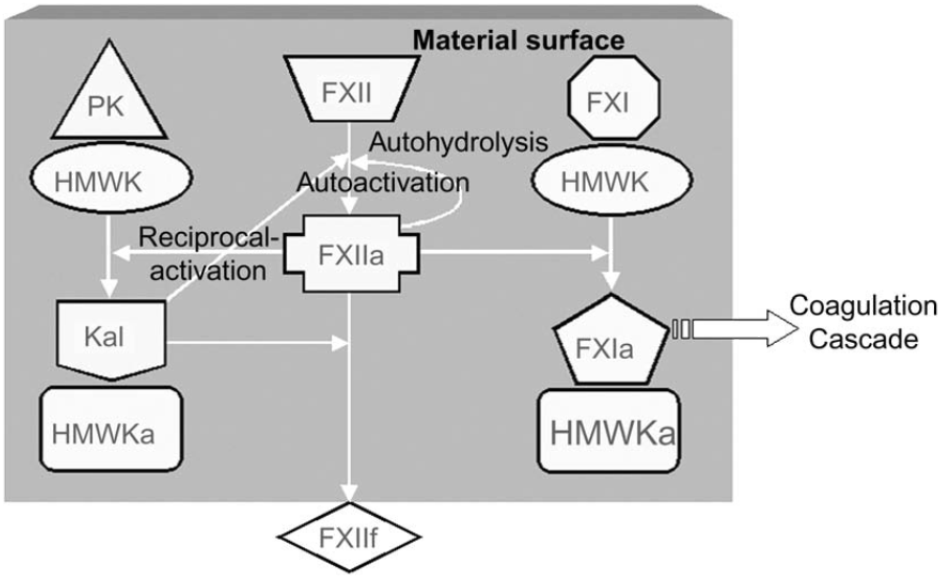

FIG. 7. Enzymatic reactions for activation of factor XII from Chatterjee *et al.* [6]

duction in the absence of tissue factor suggesting that the possible mechanism for thrombin formation was activation of factor XII. This model also includes inhibitors for factor XII. Initiation of the intrinsic pathway was taken from the model and is presented bellow.

In addition to Table X the boundary condition at the wall for factor XII is $\frac{\partial C_{XII}}{\partial t} = 0$ thus the concentration of factor XII at the wall is constant and with a value of $C_{XII} = xxx$. The boundary condition for all the species at the bulk is $\frac{\partial C_i}{\partial t} = 0$.

Reaction	$M^{-1}s^{-1}$	s^{-1}	s^{-1}
$XII \rightarrow XII_a$		$k_1 = 5.0 \times 10^{-4}$	
$XII_a + XII \leftrightarrow XII_a/XII \rightarrow XII_a + XII_a$	$k_2 = 1 \times 10^8$	$k_3 = 750$	$k_4 = 3.3 \times 10^{-2}$
$XII_a + PK \leftrightarrow XII_a/PK \rightarrow XII_a + K$	$k_5 = 1 \times 10^8$	$k_6 = 3.6 \times 10^3$	$k_7 = 40$
$XII + K \leftrightarrow XII/K \rightarrow XII_a + K$	$k_8 = 1 \times 10^8$	$k_9 = 45.3$	$k_{10} = 5.7$
$PK + K \rightarrow K + K$	$k_{11} = 2.7 \times 10^4$		
$K \rightarrow K.Inhibited$		$k_{12} = 1.1 \times 10^{-2}$	
$XII_a + CTI \leftrightarrow XII_a/CTI$	$k_{13} = 1 \times 10^8$	$k_{14} = 2.4$	
$XII_a + C1_{inh} \rightarrow XII_a/C1_{inh}$	$k_{15} = 3.6 \times 10^3$		
$XII_a + ATIII \rightarrow XII_a/ATIII$	$k_{16} = 21.6$		
$XII_a + XI \leftrightarrow XII_a/XI \rightarrow XII_a + XI_a$	$k_{17} = 1 \times 10^8$	$k_{18} = 200$	$k_{19} = 5.7 \times 10^{-4}$

TABLE VIII. Kinetic constants for first, second order and Michaelis-Menten enzymatic reaction from Chatterjee *et al.* [35]

Species	R_i
XII	$-k_1 C_{XII} - \frac{k_4 C_{XII} C_{XII_a}}{km_1 + C_{XII}} - \frac{k_{10} C_{XII} C_K}{km_3 + C_{XII}}$
XII_a	$k_1 C_{XII} + \frac{k_4 C_{XII} C_{XII_a}}{km_1 + C_{XII}} + \frac{k_{10} C_{XII} C_K}{km_3 + C_{XII}} - k_{13} C_{CTI} C_{XII_a} + k_{14} C_{CTI/XII_a} - k_{15} C_{C1_{inh}} C_{XII_a} - k_{16} C_{ATIII} C_{XII_a}$
XII_a/XII	$k_2 C_{XII_a} C_{XII} - k_3 C_{XII_a/XII} - k_4 C_{XII_a/XII} - k_5 C_{XII_a} C_{PK} + k_6 C_{XII_a/PK} + k_{10} C_{K/XII} - k_{13} C_{CTI} C_{XII_a} + k_{14} C_{CTI/XII_a} - k_{15} C_{C1_{inh}} - k_{16} C_{ATIII} C_{XII_a} - k_{17} C_{XI} C_{XII_a} + k_{18} C_{XI/XII_a}$
PK	$-\frac{k_7 C_{PK} C_{XII_a}}{km_2 + C_{PK}} - k_{11} C_{PK} C_K$
PK/XII_a	$k_5 C_{XII_a} C_{PK} - k_6 C_{XII_a/PK} - k_7 C_{PK/XII_a}$
K	$\frac{k_7 C_{PK} C_{XII_a}}{km_2 + C_{PK}} + k_{11} C_{PK} C_K - k_{12} C_K$
K/XII	$k_8 C_K C_{XII} - k_9 C_{K/XII} - k_{10} C_{K/XII}$
$K.Inhibited$	$k_{12} C_K$
CTI	$-k_{13} C_{CTI} C_{XII_a} + k_{14} C_{CTI/XII_a}$
CTI/XII_a	$k_{13} C_{CTI} C_{XII_a} - k_{14} C_{CTI/XII_a}$
$C1_{inh}$	$-k_{15} C_{C1_{inh}} C_{XII_a}$
$C1_{inh}/XII_a$	$k_{15} C_{C1_{inh}} C_{XII_a}$
$ATIII$	$-k_{16} C_{ATIII} C_{XII_a}$
$ATIII/XII_a$	$k_{16} C_{ATIII} C_{XII_a}$
XI	$-\frac{k_{19} C_{XI} C_{XII_a}}{km_1 + C_{XI}}$
XI	$-k_{17} C_{XI} C_{XII_a} + k_{18} C_{XI/XII_a}$
XII_a/XI	$k_{17} C_{XI} C_{XII_a} - k_{18} C_{XI/XII_a} - k_{19} C_{XI/XII_a}$
XI_a	$\frac{k_{19} C_{XI} C_{XII_a}}{km_1 + C_{XI}}$

TABLE IX. Source terms inferred from Chatterjee *et al.* [35] kinetic scheme. Only intrinsic pathway reactions where consider and that involve XII_a. Michaelis-Menten constant are: $km_1 = \frac{k_4 + k_3}{k_2}$, $km_2 = \frac{k_7 + k_6}{k_5}$, $km_3 = \frac{k_{10} + k_{11}}{k_8}$

The model of Guo *et al.* [23] predicts the amount of FXIIa produced by a surface of pro-coagulant materials. In this model the pro-coagulant surface is model as an enzyme. Auto-hydrolysis is not taken into account because the production of activated factor XII is marginal next to the production due to auto-activation and reciprocal-activation. Another interesting aspect of this model is that a catalytic potential that takes into account wet-ability is included in the model. The production of factor XIIa due to auto-activation can be expressed in the form of a Michaelis-Menten

Enzyme	Initial concentration $[\mu M]$	Diffusion Coefficient $[cm^2/s]$	Reference
XII	0.34	5.0×10^{-7}	[**?**] [a]
XII_a	0.0	5.0×10^{-7}	[**?**]
PK	0.45	4.46×10^{-7}	[**?**]
K	0.0	4.59×10^{-7}	[**?**]
CTI	4.2	9.28×10^{-7}	[**?**]
CTI/XII_a	0.0	9.28×10^{-7}	[**?**]
$C1_{inh}$	2.5	4.57×10^{-7}	[**?**]
$ATIII$	3.4	5.57×10^{-7}	[19]
XI	0.031	3.97×10^{-7}	[19]
XI_a	0.0	5.0×10^{-7}	[19]

[a] Molecular Weight

TABLE X. Initial bulk concentrations for blood proteins from [35] and Diffusion Coefficients (in some cases the value was calculated using the correlation of [**?**] with the molecular weight.)

mechanism that writes:

$$\mathrm{XII+A} \overset{\mathrm{k_1}}{\rightleftharpoons} \mathrm{(XII/A)} \overset{\mathrm{k_2}}{\rightarrow} \mathrm{XII_a+A} \qquad \{1\}$$

in which the FXIIa will be expressed as:

$$R_{XII_a} = \frac{k_2 C_{XII} A_0}{k_s + A_0} \tag{2}$$

if k_s is admitted to be the same across different pro-coagulant materials the product of $k_2 C_{XII}$ can be expressed as a single constant K_1

$$R_{XII_a} = \frac{K_1 A_0}{k_s + A_0} \tag{3}$$

which is the source term (R_{XII_a}) for equation 1, the variables used in the equations are:

- C_{XII} concentration of Zymogen factor XII μM
- A_O initial surface area m^2
- K_1 catalytic potential of the pro-coagulant material $\frac{\mu M}{min^{-1}}$
- k_s Michaeles Menten dissociation constant m^2

It is important to mention that the source terms must be added specifically at the artificial surface and not in the complete fluid domain. An interesting work perspective will be to add proper steps of the coagulation cascade until thrombin or fibrin production considering platelet activation by thrombin and due to the shear flow. Also by considering the effects of the shear flow, a criteria could be added for leukocyte expression of tissue factor due to high shear rates hence the amplification of the extrinsic pathway due to leukocyte expression could be study. Finally a kinetic model for the complement system could also be included to address the role of the complement system in thrombin production.

III. APPENDIX ENZYME KINETICS

3. Enzymatic reactions

In order to understand the source terms equation 1 a basic introduction to enzyme kinetics is presented. The complex behaviour of the enzymes present in blood flow can be analysed using basic chemical principles. The simplest enzyme mechanism that provides a description of individual chemical steps that make up the overall reaction can be explained as follows: substrate S will be transformed into a product P going through an intermediate step where a complex of enzyme E and S is formed:

$$\mathrm{E+S} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \overset{k_3}{\rightarrow} \mathrm{P+E} \qquad \{2\}$$

where:

- E - Enzyme
- S - Substrate
- ES - Complex
- P - Product
- k_{+1} reaction rate

In order to advance step by step in the understanding of the previous kinetic mechanism a table with the different types of reactions is presented:

Order	**Production Rate**	**Equation**
first	rate $= k_2 A$	$A \rightarrow B$
second	rate $= k_1 ES$	$E + S \leftrightarrow ES$
Michaelis-Menten	$\frac{k_3 E_t S}{k_m S} = \frac{V_m S}{k_m + S}$	$E + S \leftrightarrow ES \rightarrow P$

TABLE XI. Enzyme reactions, k_1, k_1 are in s^{-1} whereas the units of k_2 are s^{-1}. V_m is the maximum rate of reaction and $k_m = \frac{k_2 + k_3}{k_1}$

An important concept that needs to be include in the enzymatic reaction network is the competitive inhibition. This event occurs when the a substance resembling the substrate occupies the enzyme thus acting as a lock in the active site. This kind of locking is critical for haemostasis and thrombosis and needs to be taken into account in the reaction networks.

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