Procoagulant control strategies for the human blood clotting process

Marco Laurino[1], Tommaso Menara[2], Alessandro Stella[2], Monica Betta[2], Alberto Landi[2]

Abstract— **This paper describes the comparison between two drug control strategies to hemophilia A. To emulate blood clotting and the pathological condition of hemophilia, a mathematical model composed by 14 ordinary differential equations is considered. We adopt a variable structure non-linear PID approach and a Model Predictive Control in order to control the dosage of procoagulant factor used in the treatment of hemophiliac patient. The two control actions are sampled for a practical application. Finally, we discuss and compare the results of the two control approaches, introducing a suited control index (eINR).**

I. INTRODUCTION

The blood coagulation is the physiological response to a damaged blood vessel, it involves the activation and aggregation of platelets adhering to damaged vessel wall (hemostasis process) [1], [2].

Platelets are cells suspended in the blood with an high concentration (about $250.000/\text{mm}^3$). Normally, circulating platelets are non-adherent to the vessel wall or to one another. When the endothelium lining the vessel is damaged, the underlying collagen activates the circulating platelets to secrete serotonin and Adenosine DiPhosphate (ADP). The serotonin is the vasoconstrictor factor and the ADP increases the attraction and aggregation of other unactivated platelets, forming a temporary plug at the site of damage; this is called *primary hemostasis*.

Simultaneously, the coagulation process of *secondary hemostasis* occurs. It is a cascade process with two initial pathways, called *Intrinsic* and *Extrinsic* [3] . Both the ways lead to fibrin formation from fibrinogen (see fig 1). The pathways are a series of reactions, in which an inactive enzyme precursor is activated to become active factor that then catalyze the next reaction in the cascade. The factors are generally indicated by Roman numerals.

In summary, the two pathways (see fig. 1) are:

- The Intrinsic way activated by contact factor. The collagen of the damaged vessel activates the XII factor, this start a cascade process: the factors XII, XI, IX, VIII and X are activated consecutively. The factor X, in presence of lipids, platelets, Calcium (Ca) and factor V, catalyses prothrombin (factor II) to thrombin that finally converts fibrinogen (factor I) to fibrin (factor IIa).
- The Extrinsic way activated by tissue factor (TF). After the vessel damage, stromal fibroblasts and leukocytes express TF forming an activated complex with factor VII (TF-FVIIa). The complex TF-FVIIa (in presence of Ca and factor V) activates factor X that (in presence of lipids,platelets Ca and factor V) activates prothrombin to thrombin that converts fibrinogen to fibrin.

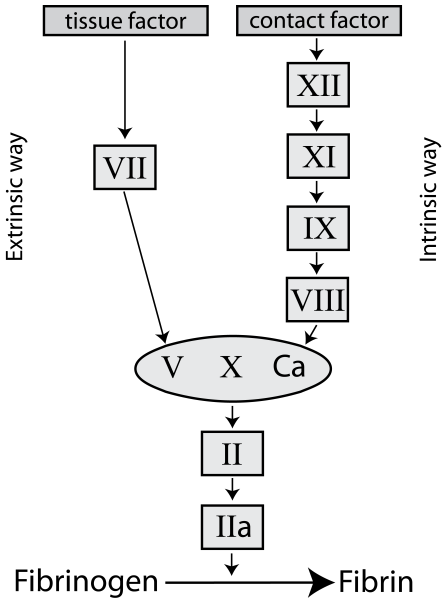

Fig. 1. Intrinsic and Extrinsic clotting pathway. Each factor is expressed by Roman numeral.

The procoagulants are substances or processes promoting the coagulation mechanism: the binding of thrombin to fibrin is thought to be an important mechanism by which thrombin exhibits procoagulant activity; the platelet membrane acts as one of the main contributors to coagulation by catalyzing several enzymatic steps in the coagulation cascade pathways.

To avoid accidental coagulation, there are several physiological antagonist of the coagulation factors or fibrinolytic enzyme, such as Antithrombin III (ATIII), Plasmin and Heparin (see fig. 1). In particular, ATIII combines with thrombin to avoid clot forming; Plasmin interacts with V factor, VIII factor, and the fibrinogen releasing substances that inhibits thrombin; Heparin amplifies the efficiency of ATIII and it inhibits IX factor, thrombin and aldosterone [5].

The main exogenous anticoagulants, used in therapies for thromboembolic pathology, are Heparin and Cumarin. The most common cumarin is Warfarin, it inhibits the vitamin K that is necessary for the activation of some coagulation factors (VII, IX ed X and prothrombin) [10], [11].

One of the most serious pathology related to coagulation process is the haemophilia A. It is an genetic disorder due to deficiency or inhibition of functional plasma clotting factor VIII [6]. The production of inhibitory antibodies to

[1] Institute of Life Sciences, Scuola Superiore Sant'Anna, Pisa, Italy marco.laurino@sssup.it

[2] Department of Information Engineering, University of Pisa, Pisa, Italy

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factor VIII can result in acquired hemophilia A or can complicate the treatment of genetic cases. The treatment of haemophilia A is performed with administration of Octocog Alfa (synthetic form of factor VIII) or Desmopressin (synthetic hormone). Desmopressin works by stimulating the production of clotting factor VIII and it has several side effects [7].

II. HUMAN BLOOD CLOTTING MODEL

A variety of mathematical models describing coagulation pathway has been developed starting from the second half of the 20th century [8], [9], [12].

In this work, the human clotting process is emulated using a model based on [4] composed by 14 ordinary differential equations (1). In model (1), each state describing a factor is indicated by a Roman numeral (with a lowercase *a* appended to indicate the active form) of the represented factor.

$$\begin{cases} \dot{II} = (-k1 \cdot X_a - k_{11} \cdot F_1) \cdot II + k_{12} \cdot F_2 \\ \dot{II}_a = k_1 \cdot II \cdot X_a + k_{14} \cdot F_1 \cdot mII_a \\ m\dot{II}_a = k_{13} \cdot F_2 - k14 \cdot F_1 \cdot mII_a \\ \dot{V} = -k_8 \cdot II_a \cdot V \\ \dot{V}_a = k_8 \cdot V \cdot II_a - k9 \cdot V_a \cdot X_a + k_{10} \cdot F_1 \\ \dot{VIII} = -k_2 \cdot II_a \cdot VIII \\ \dot{VIII}_a = k_2 \cdot II_a \cdot VIII - k_3 \cdot VIII_a \cdot IX_a + k_4 \cdot F_3 \\ \dot{IX}_a = k_4 \cdot F_3 - k_3 \cdot IX_a \cdot VIII_a \\ \dot{X} = k_6 \cdot F_4 - k_5 \cdot F_3 \cdot X \\ \dot{X}_a = k_7 \cdot F_4 + k_{10} \cdot F_1 - k_9 \cdot X_a \cdot V_a \\ \dot{F}_1 = k_9 \cdot X_a \cdot V_a + (k_{12} + k_{13}) \cdot F_2 - (k_{10} + k_{11} \cdot II) \cdot F_1 \\ \dot{F}_2 = k_{11} \cdot F_1 \cdot II - (k_{12} + k_{13}) \cdot F_2 \\ \dot{F}_3 = k_3 \cdot VIII_a \cdot IX_a + (k_7 + k_6) \cdot F_4 - (k_4 + k_5 \cdot X) \cdot F_3 \\ \dot{F}_4 = k_5 \cdot F_3 \cdot X - (k_6 + k_7) \cdot F_4 \end{cases} \tag{1}$$

The names and functions of each factor are summarized in table I. For the used numerical values of both parameters

TABLE I
CLOTTING FACTORS FUNCTIONS

Number: Name	Function
II: Prothrombin	Activates Fibrinogen, V, VII, VIII, XI, XIII, protein C, platelets
V: Proaccelerin	Co-factor of X
VII: Stable factor, Proconvertin	Activates IX, X
VIII: Antihemophilic factor A	Co-factor of IX
IX: Antihemophilic factor B	Activates X
X: Stuart-Prower factor	Activates II
XI: Plasma Thromboplastin Antecedent	Activates IX
XII: Hageman Factor	Activates XI, VII and prekallikrein
XIII: Fibrin-Stabilizing Factor	Crosslinks fibrin
F1 to F4: Intermediate complexes	Coordinates the factor reactions

and initial conditions see [4].

To simulate the alteration related to a pathology as haemophilia A, in the model (1) the value of initial condition for factor VII is reduced from $9 \cdot 10^{-9}$ [M] to $5 \cdot 10^{-12}$ [M].

III. FORMULATION OF CONTROL PROBLEM

To simulate the external control action of procoagulant drugs for haemophilia A, we hypothesize an increase of factor VIII both exogenous and physiologically induced by drug stimulation. In model (1), we change the dynamic equation of factor VIII introducing an external input as follow:

$$\dot{VIII} = -k_2 \cdot II_a \cdot VIII + u_H \tag{2}$$

The term u_H indicates the control input of factor VIII. It emulates an intravenous dispensing of the factor VIII during a clotting process, with maximum dosage of 10^{-5} [M/s].

In this work, to evaluate sub-optimal control strategies for drug administration for haemophilia A, we used two control strategy: a non-linear PID controller, and a model based predictive strategy. To check the status of the patient after the control action, we introduce a dedicated control index.

All the control strategies have been implemented by using Matlab/Simulink (MathWorks, Natick, MA, USA).

A. Effectiveness of the control actions

To compare the different control strategies, we discuss how to evaluate the effectiveness of the proposed control actions.

The most important parameter used to characterize the clotting dynamic is the *Prothrombin Time* (PT). PT is a blood test that measures how long it takes for the blood to clot. A standard prothrombin time test is called International Normalized Ratio (*INR*) test [13], [14]. INR can be used to check for internal bleeding problems or to test the efficiency of anticoagulant drug. The INR is the ratio between the Prothrombin time of the patient and a standard Prothrombin time (calculated on a healthy subject):

$$INR = \left(\frac{PT_{patient}}{PT_{reference}} \right)^{ISI} \tag{3}$$

where *ISI* is a parameter depending by reagents used in the laboratory procedure.

INR is an *a posteriori* bio-chemical test, so it must be modified to be used in the control problem. The hypothesis at hand is that the clot formation begins once factor *mIIa* (meizothrombin, the transitory state of prothrombin activation) reaches its maximum value, at a time defined as PT_P. We normalize this value with respect to the time of complete depletion of factor II (in a healthy subject about 143 sec), defined PT_R. This value represents the maximum time to certainly form the clot. Considering the previous definitions a new index is introduced and called *estimated International Normalized Ratio* (eINR):

$$eINR = \frac{PT_P}{PT_R} \tag{4}$$

In conclusion, we consider the eINR as the estimation of the ratio between the time when the formation of the clot starts and the time when the clotting process ends. As for the INR, three intervals of eINR values have been established to evaluate the condition of blood clotting process:

- $0 \leq eINR < 0.6$: thrombosis;

- $0.6 \leq eINR < 0.85$: normal clotting behavior;
- $eINR \geq 0.85$: hemophilia.

B. VS-PID

Following [16], [17] a variable structure standard non linear VS-PID controller is considered, in the general form:

$$C(s) = k_p e + \frac{k_i(e)}{s} + k_d s \tag{5}$$

where e is the error variable, i.e., the difference between the desired output and the actual response. A particular simple choice of nonlinear coefficients has been proposed as:

$$k_i(e) = \frac{k_{i0}}{1 + (c_i e)^2} \tag{6}$$

The overall logic of the modified integral action with respect to a standard PID is [18]:

1) for very large errors, the integral control action vanishes,
2) for small errors, the integral action becomes predominant and the wind-up problem is avoided.

The reference signal for factor *mIIa* (see model 1) is obtained from the evolution of the clotting model of a healthy subject. The proportional, integral and derivative coefficients (k_p, k_{i0} and k_d) used in the VS-PI controller are set via Auto Tune Variation (ATV) procedure [15]

The VS-PID control action is implemented via a sample-and-hold configuration. The sample time used in simulation is 20 seconds.

C. Model Predictive control

The Model predictive control (MPC) is a class of advanced algorithms typical of process control. In the MPC algorithm, a dynamic model of the system to be controlled is used to forecast the system evolution under a planned control trajectory. The control sequence is chosen by minimizing the value of a quadratic cost function over all the control input sequence u and the errors of the system outputs with respect to the desired references.

In the last years, MPC controllers have been widely applied to biomedical processes [19], [20].

In this work, the cost functional (J) evaluated over the finite prediction horizon N is:

$$J = \sum_{i=1}^{N-1} w_x (r_i - x_i)^2 + w_u u_i^2 \tag{7}$$

subject to the following input constrain:

$$0 \leq u \leq 10^{-5} M \tag{8}$$

The term r_i is the same reference state of VS-PID controller (*mIIa* in a healthy subject), x_i is the state *mIIa* and u_i is the external control sequence (u_H in 2). The weight terms w_x and w_u are both set to 1 for sake of simplicity.

The sample time of MPC control action is chosen as 20 seconds, as in VS-PID implementation. We set the prediction horizon (N) as 4, and the control horizon (the number of control inputs effectively administered to the real process) as 2.

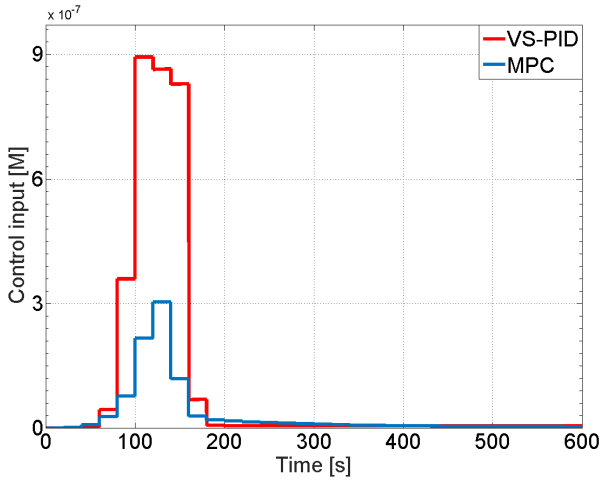

Fig. 2. Cases of VS-PID control (red line) and MPC (blue line). The control inputs are expressed in mole (M), maintaining the injection constant during each time step. The time is expressed in seconds (s).

IV. RESULTS, DISCUSSIONS AND CONCLUSIONS

Figure 2 shows the control action u_H for Factor VIII, in the case of both VS-PID and MPC controllers. The comparison of the eINR and total amount of administered drug between the two control strategies are shown in the table II. In terms of eINR value the VS-PID controller gives a lower value then MPC (see table II), however, both VS-PID and MPC controllers ensure that eINR value is included in the range of the normal clotting behavior.

TABLE II

COMPARISON OF EINR VALUE AND TOTAL ADMINISTERED DRUG AMOUNT BETWEEN THE TWO CONTROL STRATEGIES, WITH AND WITHOUT DISEASE

	eINR	Total Drug (M)
Healthy subject	0.80	0
Haemophiliac patient	2.00	0
Haemophiliac patient (VS-PID)	0.79	$6.16 * 10^{-5}$
Haemophiliac patient (MPC)	0.84	$1.82 * 10^{-5}$

Nevertheless, the total amount of administered drug is much lower using MPC than VS-PID (see table II and figure 2).

It is interesting to note that both controller actions administer the drug into the same timing window: between about 50 and 200 seconds.

Figure 3 shows the evolutions of first ten states of the model (1) in four cases: an healthy subject, an hemophiliac patient without any pharmacological treatment, an hemophiliac patient treated with a VS-PID controlled strategy and an hemophiliac patient treated with a MPC controlled strategy. It is possible to see how the factors and the end of the coagulation cascade process (factor *II*, *IIa* and *mIIa*) show the same dynamic of healthy subject in the case of both VS-PID and MPC controlled hemophiliac patients.

In case of treated hemophilia, both controller actions (VS-PID, MPC) boost the activation of the factor *II* increasing

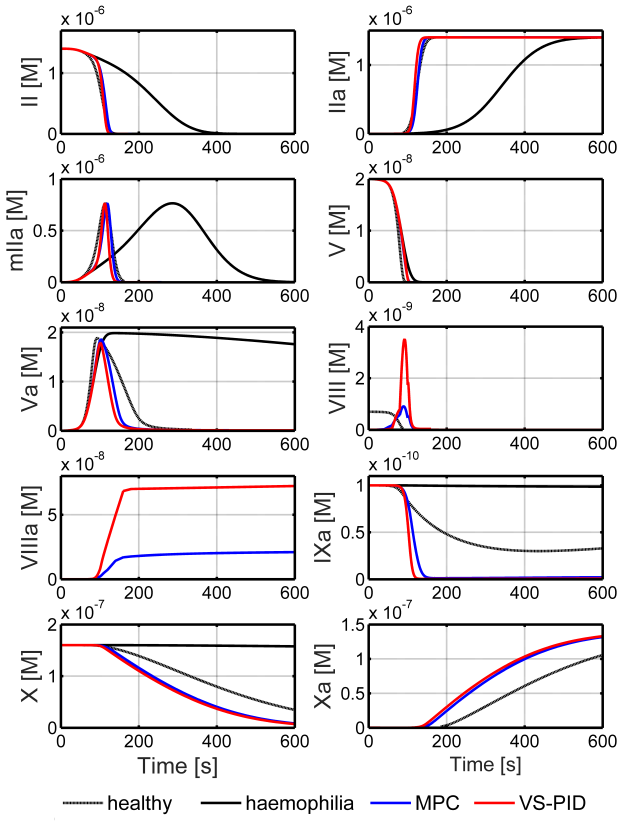

Fig. 3. Comparison of the evolutions of the first ten states of model 1 for a healthy subject (black dotted line), a hemophiliac patient without treatment (black continuous line), a hemophiliac patient with VS-PID controlled treatment (red continuous line) and a hemophiliac patient with MPC controlled treatment (blue dotted line). All the quantities are expressed in mole (M), and the time in seconds (s).

the amount of factor *VIIIa* (see figure 3).

We conclude that this preliminary study suggests that both control strategies are effective in the treatment of hemophiliac patients.

The MPC controller administers lower drug quantities obtaining similar results to the VS-PID controller. On the other hand the VS-PID controller has the advantage that it doesn't require the knowledge of a model of the process to be controlled. From the viewpoint of a practical implementation this last aspect constitutes an important issue.

Future work will consider in the model the small delay between injection and action of the administered drug.

A practical application of the proposed controllers will require a strict cooperation with clinical researchers, this future step is mandatory for their validation by experimental methods. From the viewpoint of clinical researchers the proposed controllers must be accurately discussed in terms of possible benefits, but we would like to highlight that this work represents an attempt for introducing advanced regulators for automatic control of administered drugs and that it could be applied and studied also in case of different physiological models.

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