A Comprehensive Model for the Humoral Coagulation Network in Humans

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Introduction

- Experimental tests of clotting are either difficult to conduct or interpret, because of:
  1) complex series of interaction of positive feedforward, negative feedforward, positive feedback and negative feedback reactions
  2) reaction ranges are a wide time frame of seconds to days
- A mathematical representation of the system therefore serves as a direct source from which cause-effect relationships can be assessed as well as providing quantitative information.

Objective

- To develop a mathematical model for the comprehensive humoral coagulation network based on mechanisms

Model Development and Simulation

- The model was developed based on mechanisms (Figure 1).
- The general equation[1] for activation processes
  - Saturable conversion of inactivated factors
  - Time-varying activation

$$\text{Activation rate} = k(t)\cdot[\text{inactivated factor}]$$

$$k(t) = \frac{V_{max}\cdot[\text{enzyme}]}{K_m + [\text{enzyme}]}$$

- For steady state of the system
  - A turn over model[2] for inactivated factors
  - Assumed initial concentrations of activated factors are zero

$$p = d\cdot[Y(0)],\quad [Ya(0)] = 0$$

$[Y(0)]$: steady state concentration of inactivated factor 'Y'
$[Ya(0)]$: initial concentration of activated factor 'Y'
p: production rate, d: degradation rate constant

- Complex formation: Stoichiometric reaction (1:1 molar ratio)
- Subsystems
  - Vitamin K cycle: for warfarin simulation
  - AT-III:Heparin complex: for heparins simulation
  - Tissue factor (TF): extrinsic activation (e.g. INR test)
  - Contact system activator (CA): intrinsic activation (e.g. aPTT test)
- *in vitro* blood tests (INR & aPTT)
  - Simulated by setting the initial conditions (e.g. TF, CA, etc.)

Abbreviations
PT: prothrombin time, aPTT: activated partial thromboplastin time, INR: international normalized ratio, UFH: unfractionated heparin, Fg: fibrinogen, F: fibrin, XF: cross-linked fibrin, II: prothrombin, IIa: thrombin, TF: tissue factor, TFPI: tissue factor pathway inhibitor, Pg: plasminogen, P: plasmin, PC: protein C, PS:, protein S, APC: activated protein C, TAT: thrombin-antithrombin complex, VK: vitamin K, VKH2; vitamin K hydroquinone, VKO: vitamin K epoxide, AT-III: antithrombin-III, Tmod: thrombomodulin, DP: degradation product, Pk: prekallikrein, K: kallikrein; CA: activator for contact system

Coagulation Network Model

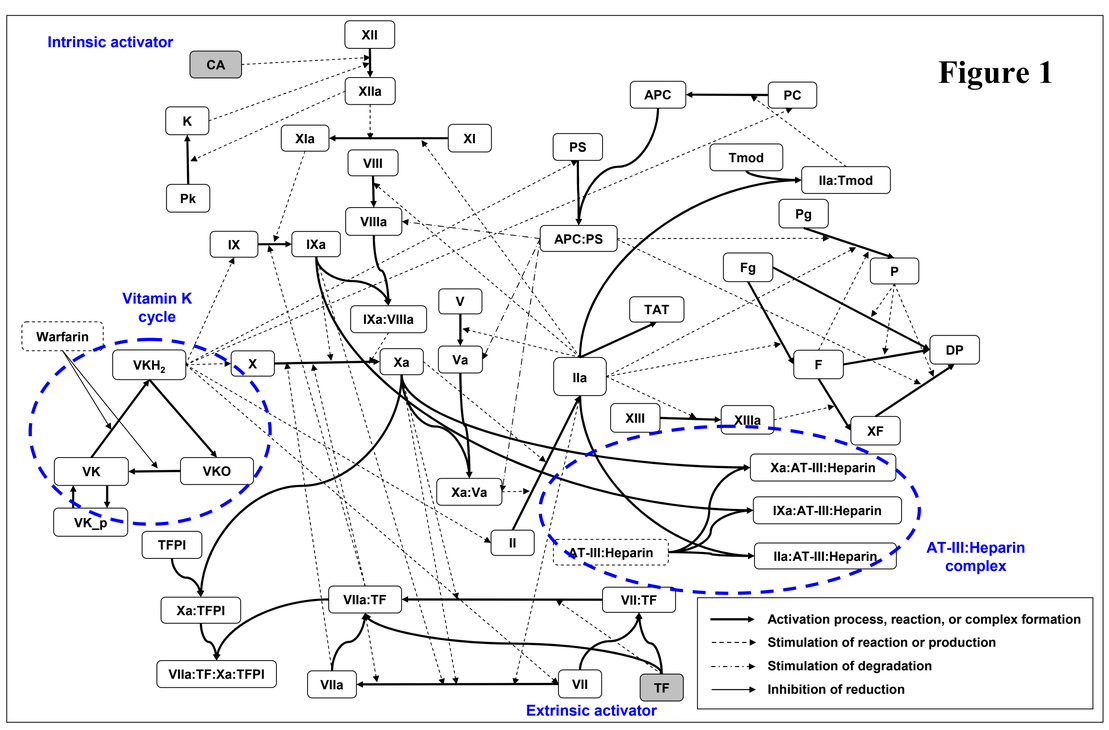

Figure 1

Simulation of Drug Therapy

- Time courses after warfarin dosing were simulated (Figure 2).
- Time courses after administration of heparins (unfractionated heparin [UFH], enoxaparin) were simulated (Figure 3).

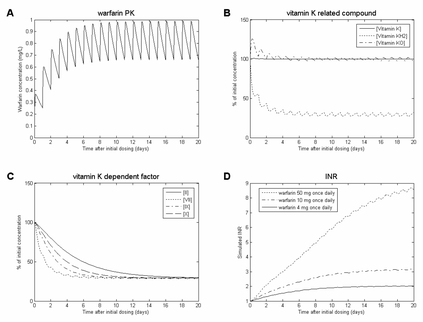

Figure 2. The time courses after warfarin dosing

$INR = (PT_{test}/PT_{standard})^{ISI}$
$PT_{standard}$: PT in standard plasma
ISI: international standardized index
assumed '1' in this study

INR at 4 mg once daily: ~ 2.0
For PK steady state: ~ 1 week
For INR steady state at 4 mg daily: ~ 2 weeks
INR at 12 times over-exposure: ~ 9.0

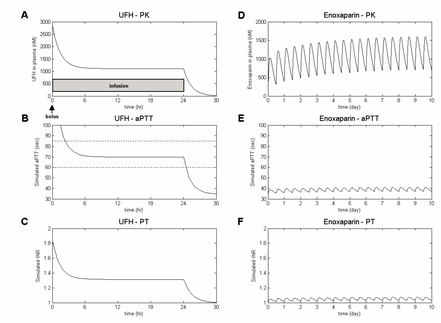

Figure 3. The time courses after heparin dosing

UFH: 5000 U bolus + 32000 U/24 hr inf.
Enoxaparin: 1 mg/kg twice daily (s.c.)

INR by UFH: minimal
aPTT by UFH: prolonged to ~ 70 sec
INR by enoxaparin: minimal
aPTT by enoxaparin: minimal

Application to the Actual Data

- The model was applied for simulating INR (PT) and aPTT from factor concentrations (Figure 4).
- The model was applied for simulating the time courses of coagulation factors after envenomation by taipan snake bite (Figure 5).
- The model was used for simulating aPTT for haemophilias A & B (Table 1).

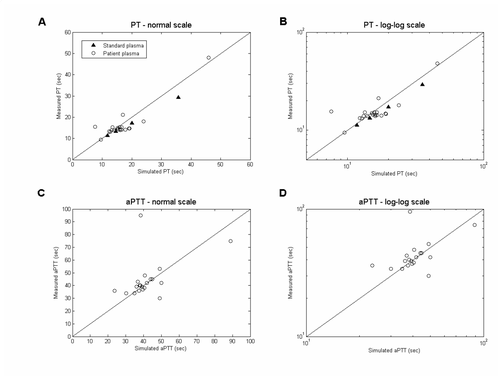

Figure 4. INR (PT) and aPTT simulation
The data were derived from the reference 3

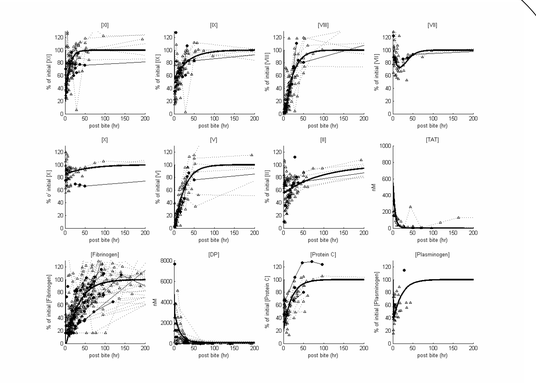

Figure 5. Simulation for snake bite data
The data were derived from reference 4

Severity (% level of factor)	Haemophilia A (VIII deficiency)		Haemophilia B (IX deficiency)	
	Simulated	Observed[4]	Simulated	Observed[4]
severe (<1%)	73-98	>60	79-123	>80
moderate (1-5%)	56-73	40-80	59-79	40-80
mild (5-25%)	43-56	40-60	44-59	40-60

Table 1. aPTT simulation for haemophilia
The data were derived from reference 5

Conclusions

- The model developed in this study is the first comprehensive description of the *in vivo* coagulation network and the time course of changes in the clotting factors.
- The model was effective at describing the effects of anticoagulants (warfarin and heparins) on the *in vitro* tests of INR and aPTT.
- The model would be useful for clinical situations and for drug development.

References

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