WFH 2016
Hemostasis
tests and assays
73-PP-M

A validated patient-specific numerical model of thrombin generation for the management of hemophilia

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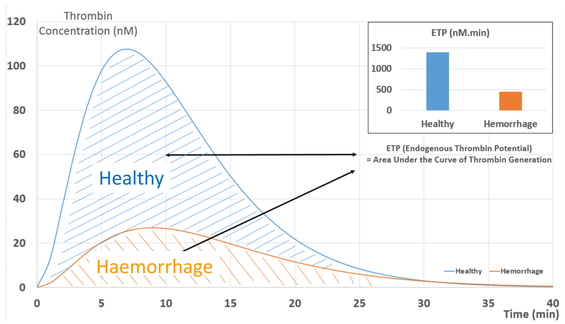
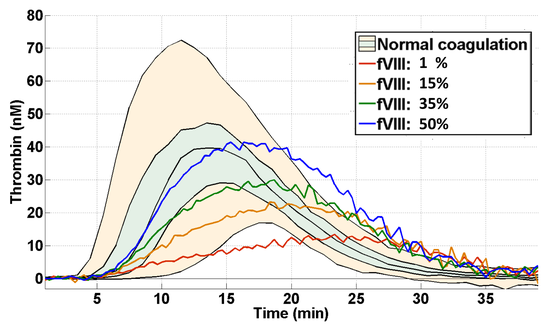
INTRODUCTION AND OBJECTIVES

- Thrombin Generation (TG) = test assessing the coagulation phenotype

→ Use TG as target for hemophilic treatment





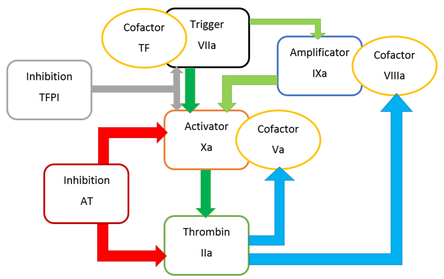
- Build a mathematical model that predicts the TG from the concentrations of coagulation factors
- Use this model to individualize the hemophilic treatment

METHODS

Model Definition :

Accounted reactions:

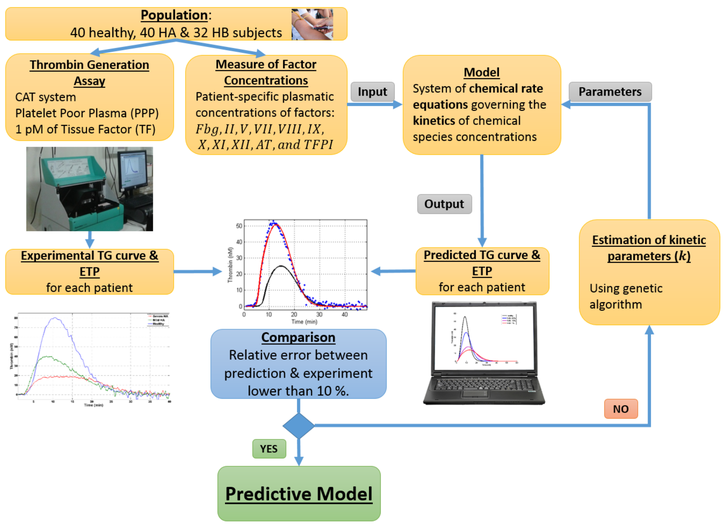
- Thrombin activation (green)
- Amplification loops (blue)
- Inhibition (red and grey)



Simplified scheme of the coagulation cascade representing the pattern of reactions of the model

- Kinetic laws as $v(x) = \frac{V_{max}\, x}{K + x}$ with K and V_{max} kinetic parameters and x the reactant concentration
- The model involves 11 parameters
  - 8 population parameters (fixed)
  - 3 patient-specific parameters

Model evaluation :



- ETP = Area under the curve of TG
- Uncertainties on measures :
  - CV~2% on factors concentrations (input)
  - CV<7% on ETP

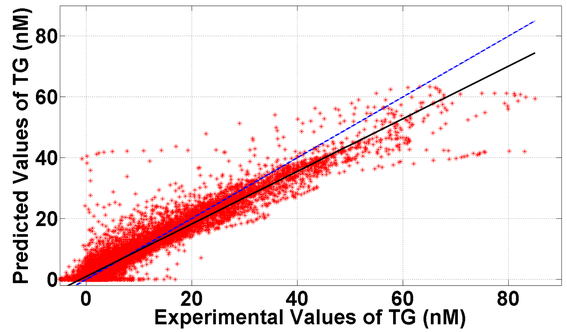
→ 10 % tolerance on the predicted ETP

RESULTS

- Good agreement between prediction and experiment: Comparison on the 112 TG curves :

→ $R^2 = 0{,}950$

- Errors of prediction on ETP:
- Mean relative error on ETP = 7,29 %
- 75 % of predicted TG with relative error on ETP <10%



Prediction vs experiment

- Experimental uncertainties on the factors concentrations taken into account

→ Confidence intervals

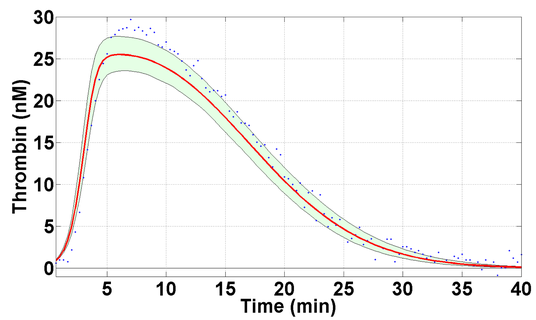
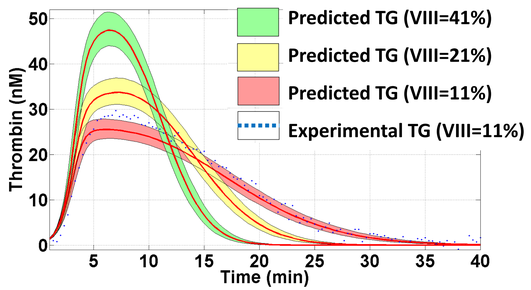


Illustration : predicted TG of HA patient (with uncertainties)

- Predictions of treatment :

→ Simulations of factor VIII or IX variation



Simulation of treatment predictions

CONCLUSIONS

- Model dedicated only to the prediction of the TG of hemophilic patients and their treatment
- Future work : validation using experimental data of patients with treatment

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