

Motivations

- Hemophilia A (HA) = deficiency of coagulation factor VIII (VIII)
 ➔ Bleeding tendency.
- Need to improve the management of HA patient's substitutive treatment by predicting its effect on the coagulation
- Thrombin Generation (TG) (see Figure 1):
 - Global Pharmacodynamic test of coagulation
 - Describes thrombin concentration as a function of time, $[IIa](t)$, in a plasma sample
 - Well correlated with bleeding severity, especially: $ETP = \int_{t=0}^{\infty} [IIa](t).dt$

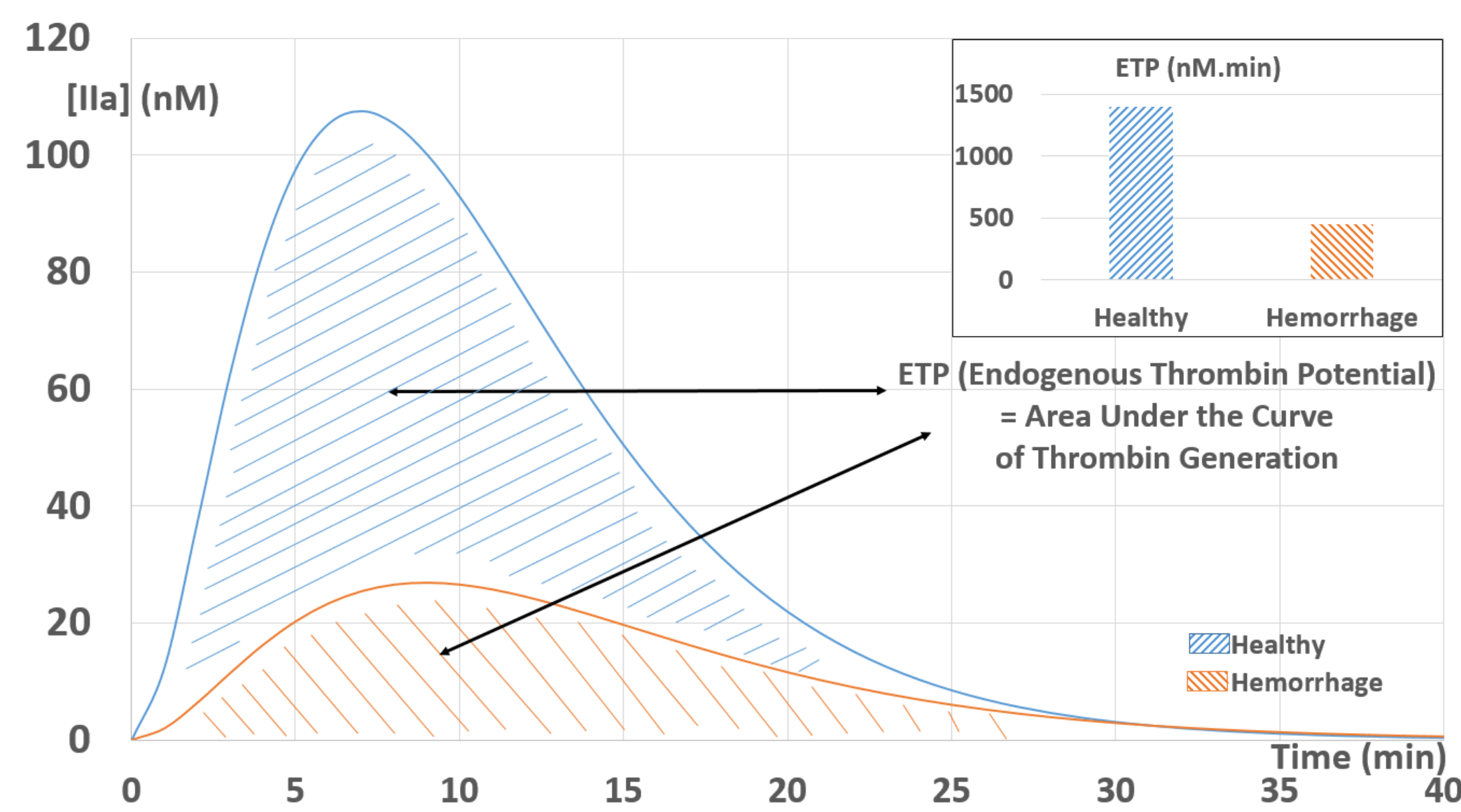


Figure 1: Thrombin Generation Curves for healthy and hemorrhagic phenotypes

- TG mechanistic model might be a good way to predict the level of factor VIII to be reached by the treatment.

Objective: Evaluate the predictive potential of a set of mechanistic numerical models to identify their capability to predict TG in HA patients.

Population & Methods

- Population:
 - Plasma samples of N=40 HA patients
- Method:
 - Measurement of ETP by means of a TG in Platelet Rich Plasma
 - Dosage of initial concentrations of coagulation factors: [I], [II], [V], [VII], [VIII], [IX], [X], [XI], [XII]
 - Dosage of initial concentrations of inhibitors [AT] and [TFPI]
 - Vector of initial concentrations for i-th patient:
 $C_i = \{[I], [II], [V], [VII], [VIII], [IX], [X], [XI], [XII], [AT], [TFPI]\}$
- Model description:
 - System of chemical rate equations (i.e. non-linear Ordinary Differential Equations characterized by the vector of kinetic parameters k) governing the kinetics of chemical species concentrations
 - Solution of the system with patient-specific coagulation factors and inhibitors input to determine the thrombin concentration as a function of time
Output: ETP as a function of the input concentrations and the set of kinetic parameters: $\overline{ETP}_i = f(C_i, k)$
- Performance before and after optimization of kinetic parameters:
 - For original and optimized sets of parameters, Mean Squared Error (MSE) and Stone-Geisser criterion, Q2 (normalized version of the MSE) were used to evaluate the accuracy of the estimations:
 $MSE = \frac{1}{N} \sum_{i=1}^N (\overline{ETP}_i - ETP_i)^2$ and $Q^2 = 1 - \frac{\sum_{i=1}^N (\overline{ETP}_i - ETP_i)^2}{\sum_{i=1}^N (\overline{ETP}_i - ETP_i)^2}$
 where $\overline{ETP}_i$ = mean of the N-1 ETP values when ETP_i is omitted.
 - Optimization of the set of kinetic parameters k on MSE criterion was realized using a genetic algorithm.
 - The most performant models will have the lowest MSE and the highest Q2.

Results

- Population (see Table 1):
 Concentrations are normalized with respect to the standard values from ISTH coagulation base Mean (μ) and Standard Deviation (σ) of experimental ETP are: 629 nM.min and 378 nM.min.

	VIII (x 100)	ETP (nM.min)	TFPI	I	II	V	VII	IX	X	XI	XII	AT
1 st quartile	0.27	336	0.88	0.78	0.98	1.04	0.91	0.86	0.99	0.76	0.80	1.01
Median	2.33	662	1.00	0.95	1.09	1.12	0.99	0.95	1.12	0.85	0.92	1.10
3 rd quartile	11.9	841	1.18	1.21	1.19	1.22	1.04	0.99	1.18	0.92	1.06	1.16

Table 1: Normalized concentrations of coagulation factors, inhibitors and ETP values.

- Model description and performance:

	Hockin [1]	Bungay [2]	Tyurin [3]	Panteleev [4]	Zhu [5]	Chatterjee [6]
Nb of chemical species	34	73	32	24	36	76
Nb of parameters	42	105	72	65	75	105
Q2	-1,08	-1,69	-3,29	-1,94	-8,21	0,14
Optimized Q2	0,37	-0,2	0,04	0,51	-0,25	0,26
√MSE (nM.min)	552	628	792	656	1161	355
Optimized √MSE (nM.min)	304	419	376	269	427	329
Improvement rate (as % of mean experimental ETP)	39	33	66	62	117	4

Table 2: Model performance before and after optimization.

- Q2 results indicate poor quality prediction for all the original models (Q2 < 0).
- For all models, optimization improved significantly the accuracy of the estimations.
- Models from Panteleev and Hockin have the lowest number of parameters and chemical species, and lead, on average, to the best agreement on ETP estimations after optimization (see Table 2 & Figure 2).
- Although the average error is decreased by the optimization process, a significant standard deviation on estimations errors is to be noticed (see Figures 2 and 3).

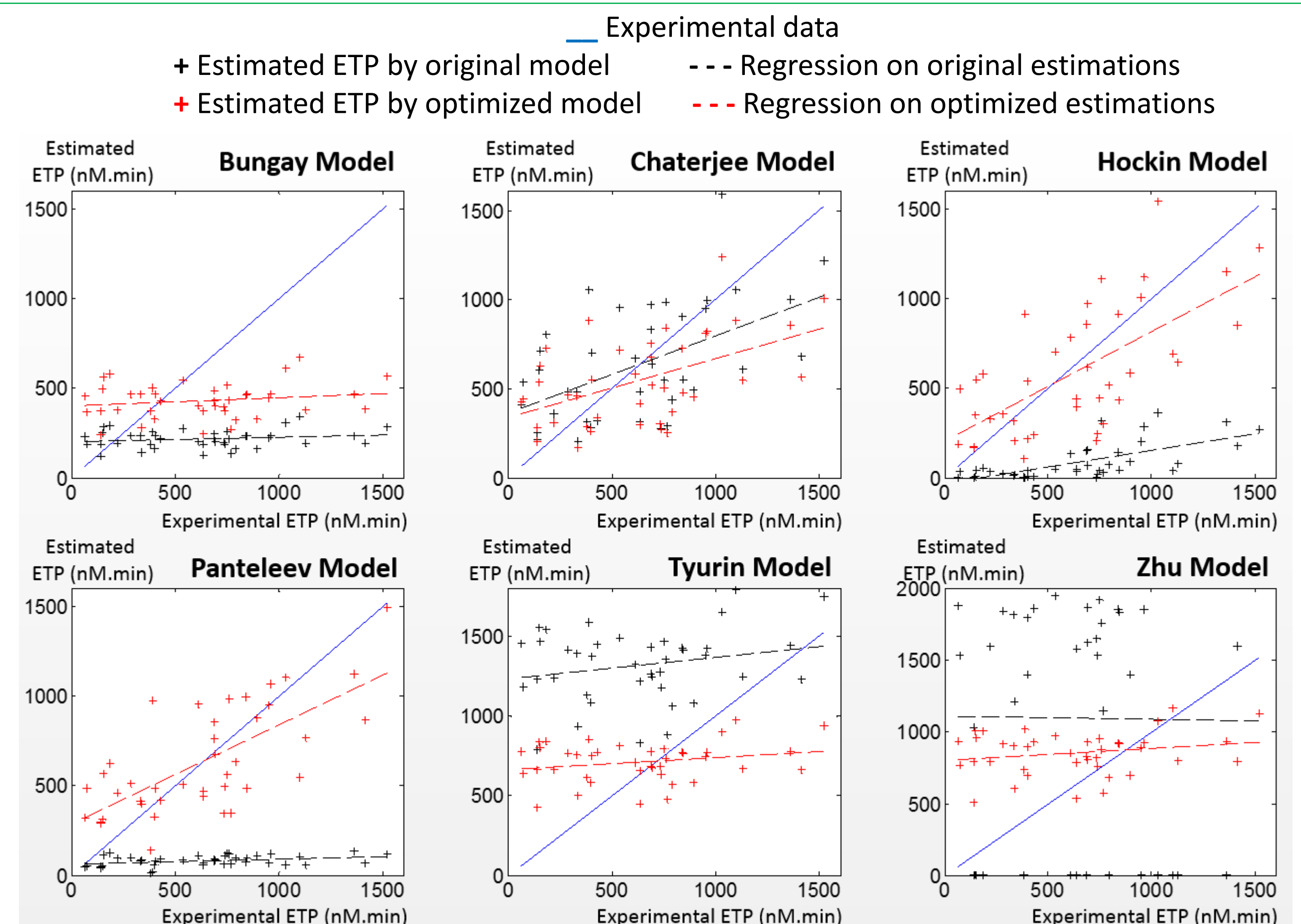


Figure 2: Estimated ETP vs Experimental ETP for each model

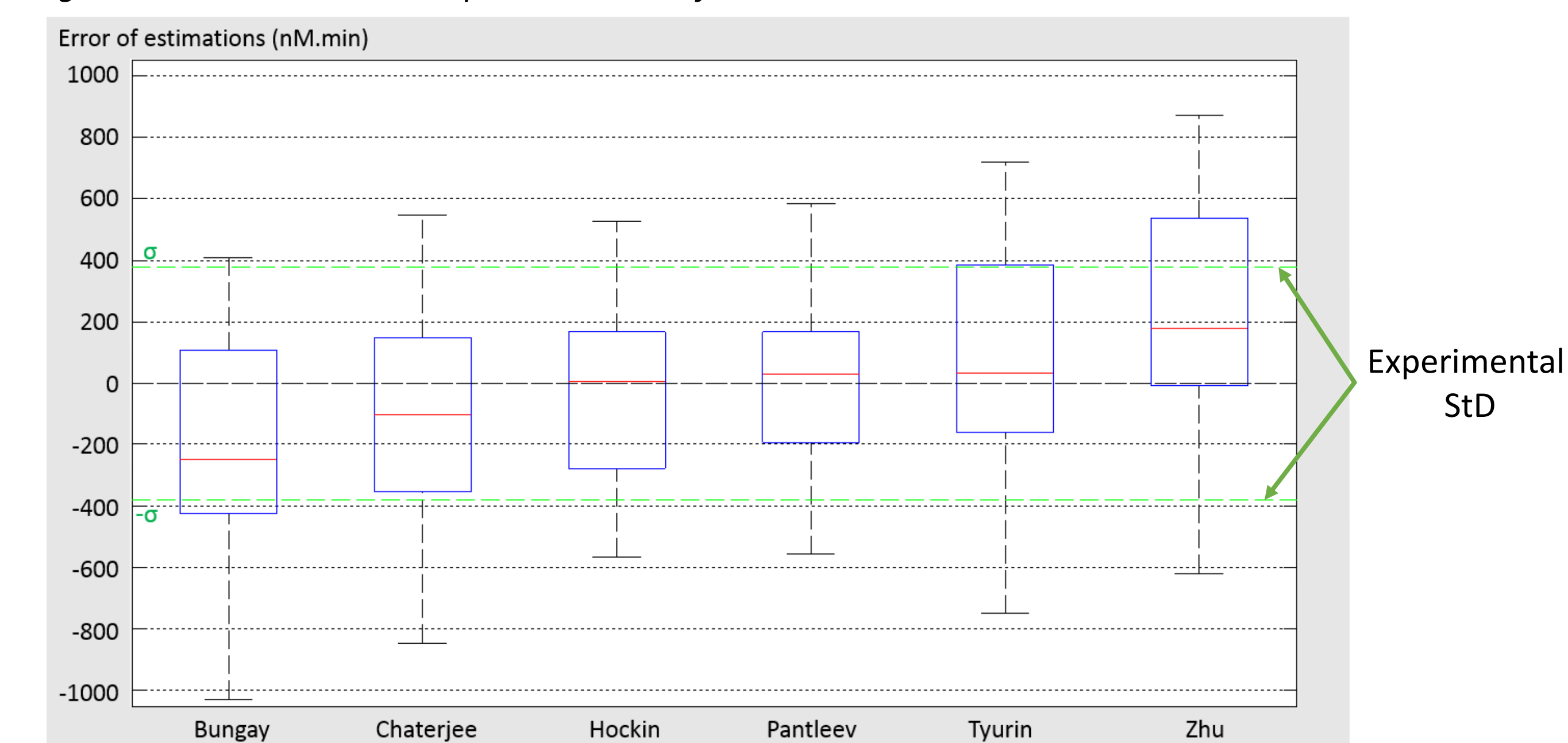


Figure 3: Distribution of errors on ETP estimations for optimized models

References

- [1] Hockin M, Jones K, Everse S, Mann K. A model for Stoichiometric Regulation of Blood Coagulation. Journal of Biological Chemistry 2002; 277 (21): 18322–18333
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Conclusion

- For mechanistic models, increasing the number of parameters does not lead to better estimations.
- Optimization by a genetic algorithm significantly improves ETP estimations.
- The wide variability of the observations can be only partially reproduced. Even after optimization, the square root of MSE is comparable to the experimental standard deviation.
- A simplified compartmental model with few parameters could estimate this variability (non-linear mixed effect model).
- Further work will use ETP coupled with other clinical relevant criteria to assess TG.
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