A Pharmacokinetic/Pharmacodynamic Model of Recombinant Batroxobin

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Background & Objective

- Batroxobin
  - It is a thrombin-like snake venom protein purified from the venom of *Bothrops atrox moojeni*.[2]
  - Hemostatic effect
    - ✓ cleaves fibrinogen
  - Anti-thrombotic effect[2,6]
    - ✓ Unlike thrombin which cleaves both fibrinopeptide A and B, batroxobin cleaves only fibrinopeptide A, which forms a more soluble fibrin web.[1,3]
    - ✓ Unlike thrombin, batroxobin does not cleave factor XIII.[1,3]
- Recombinant Batroxobin
  - yeast *Pichia pistoris* system [2,7]
- We attempted to build a nonlinear mixed effect model describing batroxobin and fibrinogen dynamics.

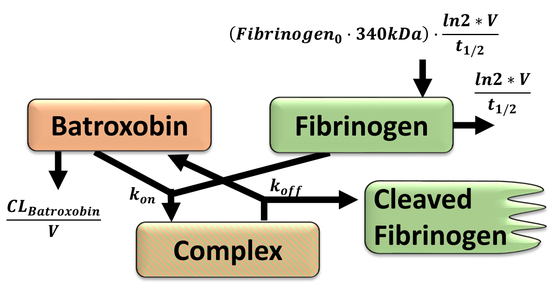
Method

- Step1: Data extraction from a publication
  - Data were extracted from the figures obtained from publication by Sugai et al[4]. The datapoints and the error bar lengths were extracted.
  - GetData Graph Digitizer (ver. 2.26.0.20, S.Fedorov)
- Step2: Fitting a semi-mechanistic model was carried out on the digitized data to generate a prior for downstream analysis.
  - $\hat{\theta} = \underset{\theta}{argmin}\left(\sum \frac{(observation - f(\theta))^2}{(error\ bar\ length)^2}\right)$
  - Nelder-Mead algorithm (Scipy v.1.9.3)
- Step3: Clinical trial data was provided by Severance Hospital Clinical Trial Center.
  - A paper describing the study results is published[2], but the data was not subjected to modeling.
  - Three dose groups were used with 2 placebo subjects for each group: placebo(n=6), 2.5 BU(n=6), 5.0 BU(n=6), 10.0 BU(n=6)
- Step4: Nonlinear mixed-effect modeling with SAEM algorithm with a Bayesian method
  - The parameter estimates from step 1 were used as typical values for the Bayesian priors with standard deviation 1.
  - Monolix (ver. 2023R1, Lixoft)

Result-1: Fitting a Semi-mechanistic Model on Data Extracted from a Publication, to Obtain a Prior for Downstream Analysis

- Based on the physiology of batroxobin and fibrinogen, a semi-mechanistic compartmental model was developed (Figure 1A), which showed good fit to the data extracted from a publication (Figure 1C). The estimated parameters (Figure 1B) were physiologically plausible.

(A)



(B)

Name	Unit	Estimates
$CL_{Batroxobin}$	L/h	3.3453
$t_{\frac{1}{2},Fibrinogen}$	Day	4.0963
V	L	3.3891
$Fibrinogen_0$	Mg/dL	227.34
k_{on}	/h	2.0692
k_{off}	/h	3092.8

(C)

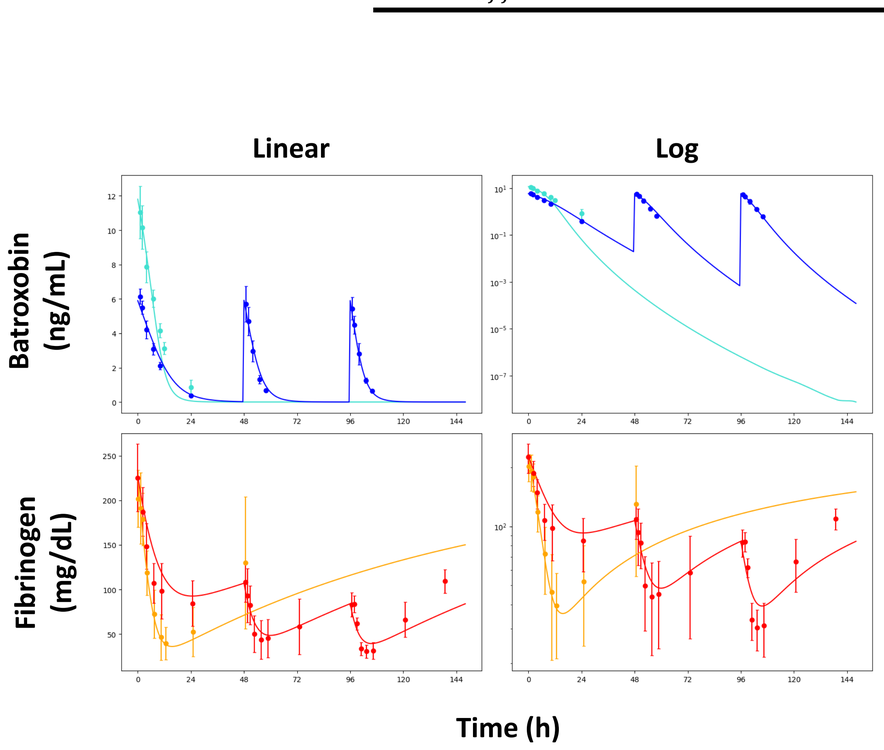


Fig1. Presented is the result of curve-fitting to data extracted from "Metabolic fate of Batroxobin in human" by Sugai, K. et al., 1986, *Yakugakuzasshi:Journal of the Pharmaceutical Society of Japan*, *106(4)*, 335-342. (A) The model used to fit the data is shown. (B) The estimated parameters are shown. (C) The mean observations by timepoint and the simulated time-course are overlayed. The left two subplots are plotted in the linear scale and the right two subplots are plotted in the semi-log scale. The top two subplots are for plasma batroxobin concentration and the bottom two subplots are for plasma fibrinogen concentration. The sky blue curve and the orange curve are for a single 20 BU i.v. administration of batroxobin and the deep blue and red curve are for a 3 multiple 10 BU i.v. administration of batroxobin with a 48h interval.

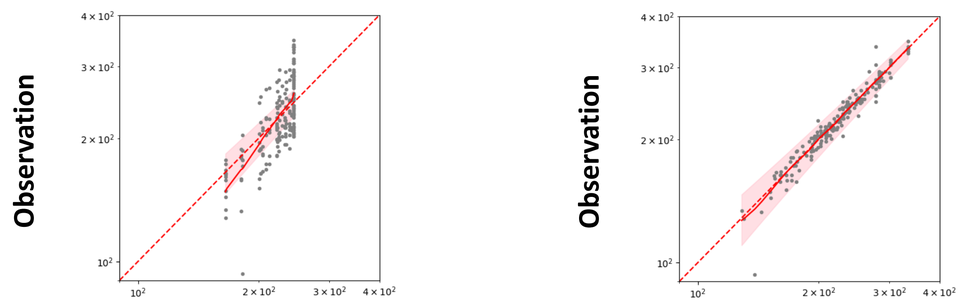
Result-2: Nonlinear Mixed Effect Modeling of Clinical Trial Data With a Bayesian Method Utilizing the Prior Obtained from Upstream Analysis

- Physiological Plausibility of the Estimated Parameters
  - Volume of distribution is similar to plasma volume, which is expected since batroxobin is a protein drug.(Figure 2A)
  - Estimated fibrinogen half-life is similar to former reported values (1~4 days) (Figure 2A)
  - the speed of cleaving fibrinogen once the complex has formed was estimated to be much faster than the speed of complex formation (Figure 2A)
- Goodness of Fit
  - The observation vs prediction, scatterplot of the residuals, and visual predictive check showed acceptable fit to the data. (Figure 2B, 2C)

(A)

Name	Unit	Estimates	RSE(%)
Typical Values for Structural Model Parameters			
$CL_{Batroxobin}$	L/h	2.79	2.88
$t_{\frac{1}{2},Fibrinogen}$	Day	1.31	2.28
V	L	1.8	1.56
$Fibrinogen_0$	Mg/dL	244.84	2.90
k_{on}	/h	3.81	6.07
k_{off}	/h	7504.99	15.2
Random Effects Parameters for Individual Parameter Model			
$\omega_{Fibrinogen_0}$	CV(%)	13.85	14.7
Random Effects Parameters for Residual Error Model			
$\sigma_{additive}$	mg/dL	0.6	5.44

(B)



(C)

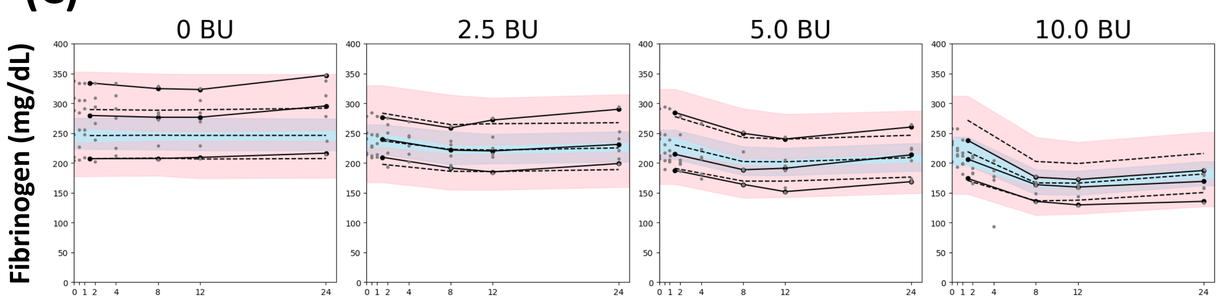


Fig2. Presented is the nonlinear mixed effect modeling result of the clinical trial data generated from Severance Hospital Clinical Trial Center. (A) The parameter estimates are shown. (B) The left subplot shows the observations versus the population prediction and the right subplot shows the observations versus the individual predictions. The red broken line is the y=x line, the solid red line is the spline, and the pink area is the 90% confidence interval. (C) The VPC is stratified by dose. The predicted 50 percentile confidence intervals are shown in blue and the 10, 90 percentile 90% confidence intervals are shown in pink. The empirical 10, 50, 90 percentiles are shown as solid black lines and the theoretical 10, 50, 90 percentiles are shown as broken black lines.

Conclusion

- A model of fibrinogen and batroxobin dynamics was successfully developed based on data extracted from a publication.
- Using the estimated parameters as the prior for the fixed effects, nonlinear mixed effects modeling was successfully carried out on data from a clinical trial for recombinant batroxobin, executed by Severence Hospital Clinical Trial Center.
- Future work should examine the feasibility of building a covariate model incorporating of the effect of the baseline lab test results and the demographics on the random effect to suggest an optimal dosage regimen for batroxobin.

Reference

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