Course project: Solving forward and inverse problems in mathematical modeling of blood coagulation

Contributed by Dr. He Li
School of Chemical, Materials, and Biomedical Engineering, University of Georgia

Project statement

In the last two decades, mathematical and computational modeling has been increasingly used to gain insights into hemostasis, a complex physiological mechanism that functions to maintain vascular integrity. Existing mathematical models for simulating coagulation pathways in hemostasis, including ordinary differential equation (ODE) models, mimicking thrombin and fibrin generation assays [12, 10, 6, 7, 11, 4], and partial differential equation (PDE) models, simulating thrombus growth under blood flow [18, 17, 14, 13, 15, 9].
In this project, we will first focus on implementing the existing ODE models to predict the generation of the key components of blood clots, such as thrombin, activated platelets and fibrin. Next, we will use system-biology informed neural networks (BINNs) to infer the unknown kinetic rates and missing dynamics of the species in the ODE models with a few noise-free data. Then, we will add different levels of noise to the data and examine the robustness of the BINNs model.

Coagulation models

Numerous coagulation models with varying levels of complexities, signified by the number of ODEs involved, have been developed over last 30 years. Some of the typical models are summarized in Table 1.

Table 1: Coagulation models with varying levels of complexities.

Number of Reaction Equations	Major Products	References
3	Thrombin	[3]
4	Activated platelets, Thrombin	[16]
8	Thrombin, Fibrin	[20]
18	Thrombin	[5]
23	Fibrin, Thrombin	[2]
24	Thrombin, Fibrin	[1]
27	Thrombin	[11]
59	Activated platelets, Thrombin	[12]

Let us consider the the set of equations that describe the thrombin generation in blood using the minimum possible number of parameters as given in [16].

$$\frac{\partial [IIa]}{\partial t} = -k_{\text{in}}\,[IIa] + \left(k_{\text{surf}} + k_{II}^{AP} \cdot [AP]\right) \cdot [II] \tag{1}$$

$$\frac{\partial [IIa]}{\partial t} = -\left(k_{\text{surf}} + k_{II}^{AP} \cdot [AP]\right) \cdot [II] \tag{2}$$

$$\frac{\partial [AP]}{\partial t} = k_{AP}^{AP} \cdot [AP] \cdot [RP] + k_{AP}^{IIa} \cdot [RP] \tag{3}$$

$$\frac{\partial [RP]}{\partial t} = -k_{AP}^{AP} \cdot [AP] \cdot [RP] - k_{AP}^{IIa} \cdot [RP], \tag{4}$$

where, IIa, II, AP and RP represents thrombin, prothrombin, activated platelets and resting platelets respectively. The values of the constants, parameters and the initial conditions are given as $k_{in} = 1.71 \times 10^{-2} - 0.2\ \text{s}^{-1}$, $k_{surf} = 10^{-5} s^{-1}$, $k_{II}^{AP} = 0.856 - 1.81\ \text{s}^{-1}$, $k_{AP}^{AP} = 5.24 \times 10^{-2}\ \text{s}^{-1}$,$[IIa]_{thr} =$

$1.75 - 4.18 \times 10^{-8}$ kg/kg($0.5 - 1.2$nM or $0.05 - 0.12$U/ml) and

$$k_{AP}^{IIa} = 0, if [IIa] < [\text{ IIa }]_{thr}$$
$$0.5, if [IIa] \geq [IIa]_{thr}.$$

For details please refer [16].

Tasks

1. Implement the coagulation model (ODE model) described above using Matlab or Python to make predictions of the generation of activated platelets, thrombin, prothrombin and resting platelets.
2. Perform a structural identifiability analysis to the coagulation model. Following the instructions in [8], a structural identifiability analysis is required to determine which parameters of the model are structurally identifiable.
3. Use the ODE model to generate sequential data for all the coagulation factors. Then, assume some of the factors and identifiable kinetic constants in the coagulation factors are unknown and use the known data to train a BINN model to infer the unknown kinetic rates and missing dynamics of the factors. The detailed implementation of BINNs is introduced in [19] and the source code can be found at https://github.com/alirezayazdani1/SBINNs. Explore the number training samples required for this task by training the model with 10, 20, 30, ..., 400 samples in the training dataset. Plot the Test Mean Squared Error against number of training samples. Report the time taken.
4. Perform an experiment to investigate the sensitivity of PINN to noise. Add Gaussian white noise with zero mean to coagulation factors. Vary the standard deviation of the noise and see how the PINN predictions change. Provide your observations.
5. Solve the same problem using PINNs with adaptive activation functions. Explain your implementation and report your observations. (*Hint:* related to model convergence while training).
6. Solve the same problem using PINNs with adaptive weights in the loss function. Explain your implementation and report your observations.

Programming Options

You may use TensorFlow, PyTorch or MODULUS for completing the tasks.

References

[1] M Anand, K Rajagopal, and KR Rajagopal. A model for the formation and lysis of blood clots. *Pathophysiology of haemostasis and thrombosis*, 34(2-3):109–120, 2005.

[2] M. Anand, K. Rajagopal, and K.R. Rajagopal. A model for the formation, growth, and lysis of clots in quiescent plasma. a comparison between the effects of antithrombin iii deficiency and protein c deficiency. *Journal of Theoretical Biology*, 253(4):725–738, 2008.

[3] FI Ataullakhanov, VI Zarnitsina, AV Pokhilko, AI Lobanov, and OL Morozova. Spatio-temporal dynamics of blood coagulation and pattern formation: a theoretical approach. *International Journal of Bifurcation and Chaos*, 12(09):1985–2002, 2002.

[4] Edward Beltrami and Jolyon Jesty. Mathematical analysis of activation thresholds in enzyme-catalyzed positive feedbacks: application to the feedbacks of blood coagulation. *Proceedings of the National Academy of Sciences*, 92(19):8744–8748, 1995.

[5] Jacopo Biasetti, Pier Giorgio Spazzini, Jesper Swedenborg, and Thomas Christian Gasser. An integrated fluid-chemical model toward modeling the formation of intra-luminal thrombus in abdominal aortic aneurysms. *Frontiers in physiology*, 3:266, 2012.

[6] Sharene D Bungay, Patricia A Gentry, and Rodney D Gentry. A mathematical model of lipid-mediated thrombin generation. *Mathematical Medicine and Biology*, 20(1):105–129, 2003.

[7] Manash S Chatterjee, Jeremy E Purvis, Lawrence F Brass, and Scott L Diamond. Pairwise agonist scanning predicts cellular signaling responses to combinatorial stimuli. *Nature Biotechnology*, 28(7):727–732, 2010.

[8] Mitchell Daneker, Zhen Zhang, George Em Karniadakis, and Lu Lu. Systems biology: Identifiability analysis and parameter identification via systems-biology informed neural networks. *arXiv preprint arXiv:2202.01723*, 2022.

[9] NM Dashkevich, MV Ovanesov, AN Balandina, SS Karamzin, PI Shestakov, NP Soshitova, AA Tokarev, MA Panteleev, and FI Ataullakhanov. Thrombin activity propagates in space during blood coagulation as an excitation wave. *Biophysical Journal*, 103(10):2233–2240, 2012.

[10] Aaron L Fogelson and Nessy Tania. Coagulation under flow: the influence of flow-mediated transport on the initiation and inhibition of coagulation. *Pathophysiology of Haemostasis and Thrombosis*, 34(2-3):91–108, 2005.

[11] Matthew F Hockin, Kenneth C Jones, Stephen J Everse, and Kenneth G Mann. A model for the stoichiometric regulation of blood coagulation. *Journal of Biological Chemistry*, 277(21):18322–18333, 2002.

[12] Andrew L Kuharsky and Aaron L Fogelson. Surface-mediated control of blood coagulation: the role of binding site densities and platelet deposition. *Biophysical Journal*, 80(3):1050–1074, 2001.

[13] Karin Leiderman and Aaron L Fogelson. Grow with the flow: a spatial–temporal model of platelet deposition and blood coagulation under flow. *Mathematical Medicine and Biology: a Journal of the IMA*, 28(1):47–84, 2011.

[14] Karin Leiderman and Aaron L Fogelson. The influence of hindered transport on the development of platelet thrombi under flow. *Bulletin of Mathematical Biology*, 75(8):1255–1283, 2013.

[15] Mikhail A Panteleev, Mikhail V Ovanesov, Dmitrii A Kireev, Aleksei M Shibeko, Elena I Sinauridze, Natalya M Ananyeva, Andrey A Butylin, Evgueni L Saenko, and Fazoil I Ataullakhanov. Spatial propagation and localization of blood coagulation are regulated by intrinsic and protein c pathways, respectively. *Biophysical journal*, 90(5):1489–1500, 2006.

[16] Konstantinos P Papadopoulos, Manolis Gavaises, and Chris Atkin. A simplified mathematical model for thrombin generation. *Medical engineering & physics*, 36(2):196–204, 2014.

[17] Z. Xu, N. Chen, M. M. Kamocka, E. D. Rosen, and M. Alber. A multiscale model of thrombus development. *Journal of the Royal Society Interface*, 5(24):705–722, 2008.

[18] Z. Xu, J. Lioi, J. Mu, M. M. Kamocka, X. Liu, D. Z. Chen, E. D. Rosen, and M. Alber. A multiscale model of venous thrombus formation with surface-mediated control of blood coagulation cascade. *Biophysical Journal*, 98(9):1723–1732, 2010.

[19] Alireza Yazdani, Lu Lu, Maziar Raissi, and George Em Karniadakis. Systems biology informed deep learning for inferring parameters and hidden dynamics. *PLoS Computational Biology*, 16(11):e1007575, 2020.

[20] VI Zarnitsina, AV Pokhilko, and FI Ataullakhanov. A mathematical model for the spatio-temporal dynamics of intrinsic pathway of blood coagulation. i. the model description. *Thrombosis Research*, 84(4):225–236, 1996.