Mathematical Modeling to Investigate Inhibition by Anticoagulant Drugs

Azlan Tubbs, Karin Leiderman, PhD

Department of Applied Mathematics and Statistics, Colorado School of Mines, Golden, CO, USA

Abstract

- Coagulation is the process by which a blood clot forms to stop bleeding from a blood vessel. Dozens of biochemical reactions must be carried out in fluid and on cell surfaces. Exposed tissue factor initiates the process and is followed by activation and aggregation of platelets. The major product of coagulation, **thrombin**, cleaves fibrinogen into fibrin, which polymerizes and forms a fibrin meshwork to physically stabilize the clot.
- Dual-pathway inhibition of coagulation whereby antiplatelet and anticoagulant drugs are both used, has been shown to produce optimal results in patients and promises therapies for reducing harmful clots. The underlying mechanisms of this inhibition has not been fully defined.
- To investigate this, we extended a previously published mathematical model of blood coagulation under flow to include rivaroxaban, an anticoagulant drug, and studied the effects on thrombin generation.
- We compared the effects of rivaroxaban inhibiting its targets in the fluid versus its targets that were bound to activated platelet surfaces. We found that the model coagulation system is sensitive to rivaroxaban levels and that the sensitivity is due entirely to the surface-mediated inhibitory reactions.
- Future work will include antiplatelet drugs to study dual-pathway inhibition.

Mathematical Model Overview

- The mathematical model uses differential equations to simulate reactions that occur at the site of vessel injury.
- At the injury site, tissue factor and collagen initiate the overlapping events that induce clotting.

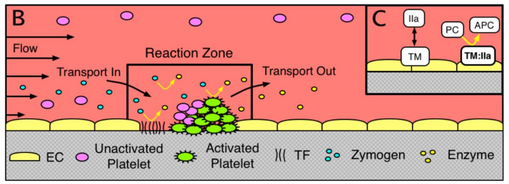


Figure 1. Biology schematic underlying the flow-mediated coagulation model.

- The mathematical equations determine the concentrations of biological species including platelets, coagulation factors, and inhibitors in time.
- The model's inputs include tissue factor concentration, appropriate initial conditions of concentrations, blood flow rate, and tissue factor density, and it outputs species in time. Thrombin concentration is an adequate representation of blood coagulation since this protein is used to mechanically stabilize the clot by forming a mesh.

New Inhibition Reactions

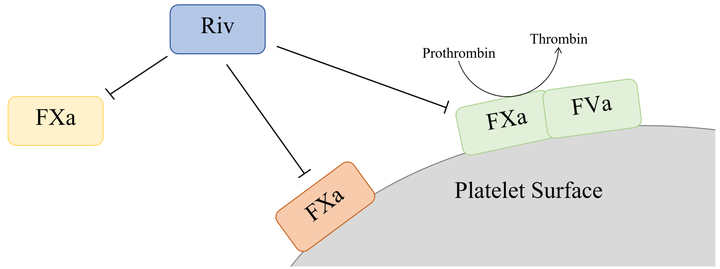


Figure 2. Three major rivaroxaban binding reactions considered in the mathematical model in this study: binding of Riv:FXa (left), binding of Riv:FXa on the activated platelet surface (middle), and binding of Riv:Prothrombinase, where the FXa:FVa complex is prothrombinase (right). Rivaroxaban inhibits coagulation through reversible binding with free FXa, platelet-bound FXa, and FXa within the prothrombinase complex (FXa:FVa).

Rivaroxaban Affects Thrombin

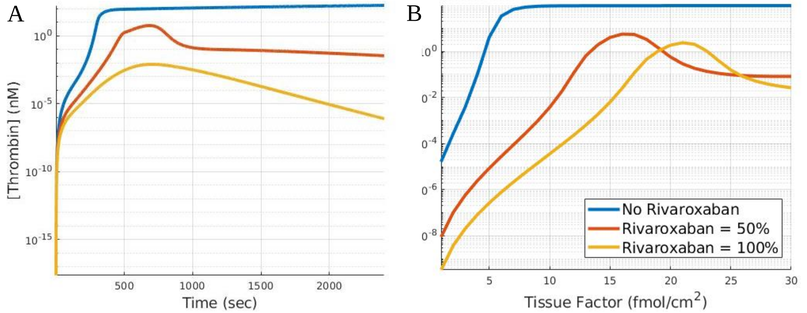
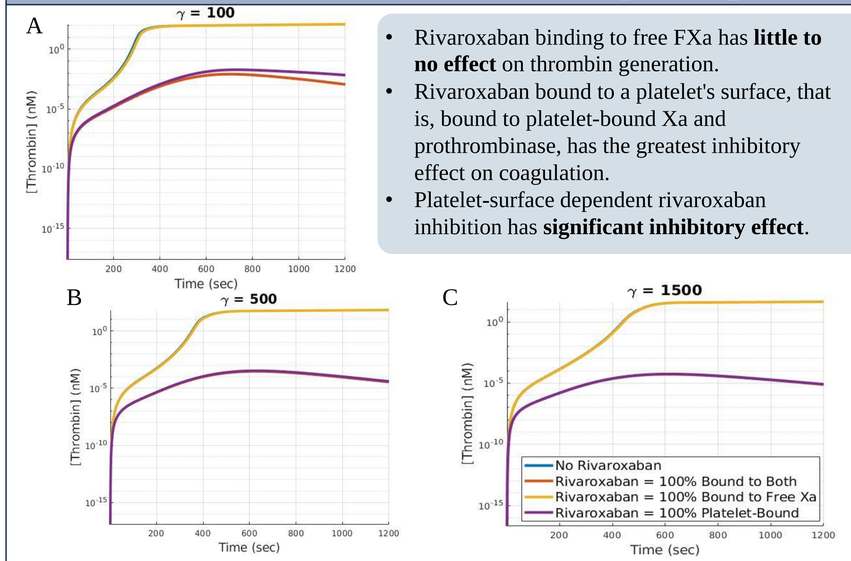


Figure 3. Thrombin concentration for tissue factor and rivaroxaban (upstream and initial) concentration variations with a TF density of 15 fmol/cm^2 (A), and tissue factor threshold plot at 10 minutes of clotting (B).

- **Increasing rivaroxaban concentrations decreases clotting time and clotting effectiveness.**
- A greater density of TF was required for the model to reach a thrombin plateau with increased rivaroxaban, and these thrombin plateaus became smaller with the increase of rivaroxaban.

Platelet-Bound Inhibition Has Largest Impact



- Rivaroxaban binding to free FXa has **little to no effect** on thrombin generation.
- Rivaroxaban bound to a platelet's surface, that is, bound to platelet-bound Xa and prothrombinase, has the greatest inhibitory effect on coagulation.
- Platelet-surface dependent rivaroxaban inhibition has **significant inhibitory effect**.

Figure 5. Thrombin generation with 100% of initial and upstream rivaroxaban concentrations and a TF density of 15 fmol/cm^2 with free Xa binding and platelet-bound binding with a shear rate of (A) 100 m/s, (B) 500 m/s, and (C) 1500 m/s.

- Rivaroxaban binding to platelet-bound complexes has a greater inhibitory effect on thrombin generation compared to its binding to free FXa only.

Conclusions and Future Work

- Rivaroxaban has a significant impact on coagulation inhibition while under flow. Platelet-dependent binding had the greatest inhibitory effect, compared with rivaroxaban bound to free FXa.
- Future work includes separating the platelet-bound complexes to determine whether rivaroxaban has the greatest effect on FXa or prothrombinase and the addition of the antiplatelet aspirin will also be used to elucidate the mechanisms underlying the dual-inhibition pathway of coagulation.

References

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