Mathematical Modeling to Investigate Dual Pathway Inhibition by Anticoagulant and Antiplatelet Drugs

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Motivation

- 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, in which 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.

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.

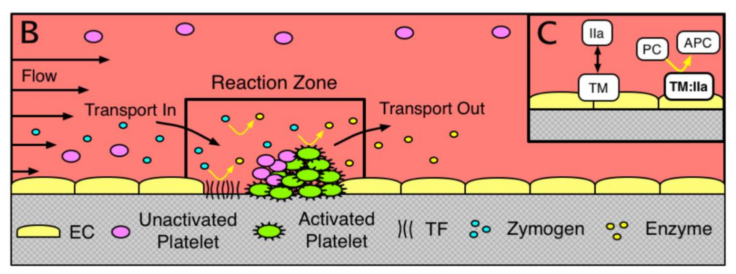


Figure 1. Biology schematic underlying the flow-mediated coagulation model.

- 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 cleaves fibrin, and other species in the model including activated platelets and prothrombinase also elucidate the mechanism of action.

$$\begin{array}{c}\text{rate of change of}\\ \text{concentrations in}\\ \text{reaction zone}\end{array} = \left(\text{rate of supply}\right) - \left(\text{rate of removal}\right) \pm \left(\begin{array}{c}\text{rate of generation,}\\ \text{inhibition, etc.}\end{array}\right)$$

$$\frac{d\mathbf{c}}{dt} = f(\mathbf{c}, plts, tf, flow)$$

- The above equation demonstrates the mathematics used in the model, where **c** represents all species concentrations. The rate of change of reaction zone species depends on other species leaving and entering the zone.

Rivaroxaban and Aspirin Inhibition Reactions

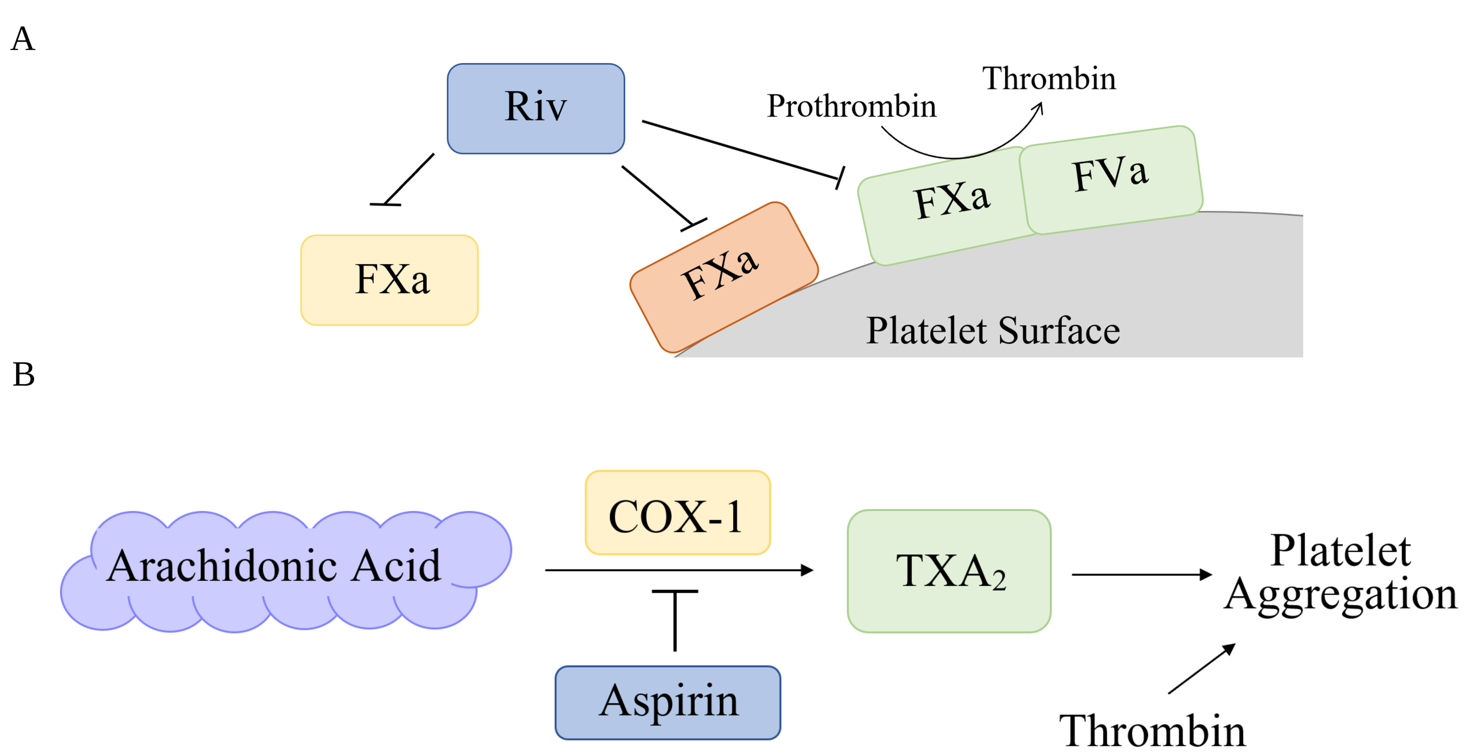


Figure 2. Three major rivaroxaban binding reactions considered in the model: reversible binding of rivaroxaban to free FXa (left), FXa on the activated platelet surface (middle), and the prothrombinase complex FXa:FVa (right) (A). Aspirin most affects coagulation by irreversibly inhibiting cyclooxygenase-1 (COX-1), which stops the generation of thromboxane A_2 (TXA_2) (B).

Rivaroxaban and Aspirin Affects Thrombin

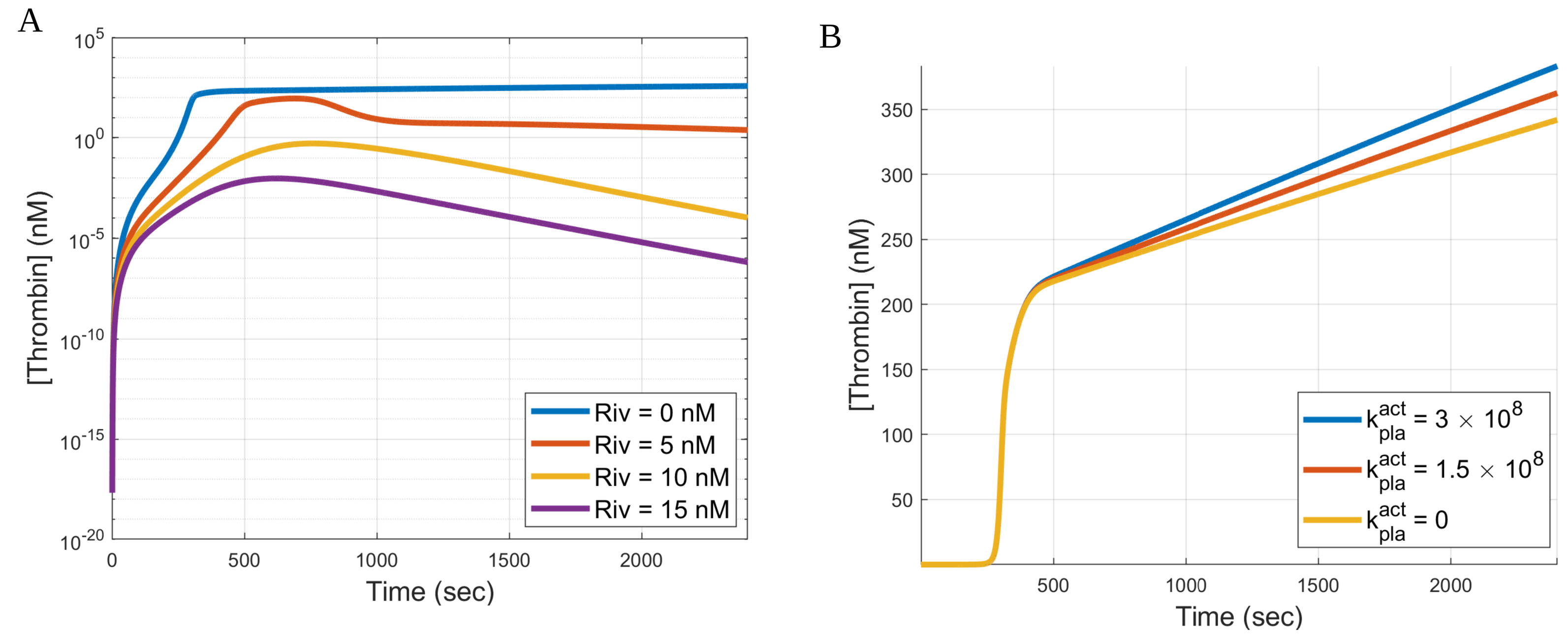
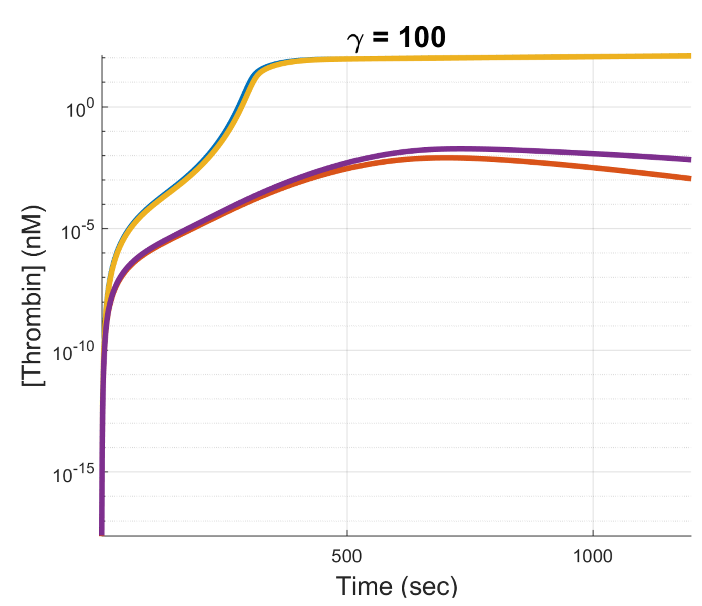


Figure 3. Thrombin concentration for rivaroxaban (upstream and initial) concentration (A) and k_{pla}^{act}, the rate of reaction for activated platelets which inversely demonstrates aspirin effects, (B) variations with a TF density of 15 fmol/cm^2 .

- Increasing rivaroxaban concentrations decreases clotting time and clotting effectiveness.
- Increasing aspirin decreases clotting effectiveness.
- Rivaroxaban affects thrombin more than aspirin.
- Aspirin inhibits an enzyme before thrombin can be activated, reducing the number of platelets available for clotting.

Rivaroxaban and Platelet-Bound Inhibition



- Rivaroxaban binding to free FXa has little to no effect on thrombin generation.
- Rivaroxaban bound to free FXa causes slight delay in thrombin response.
- 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.

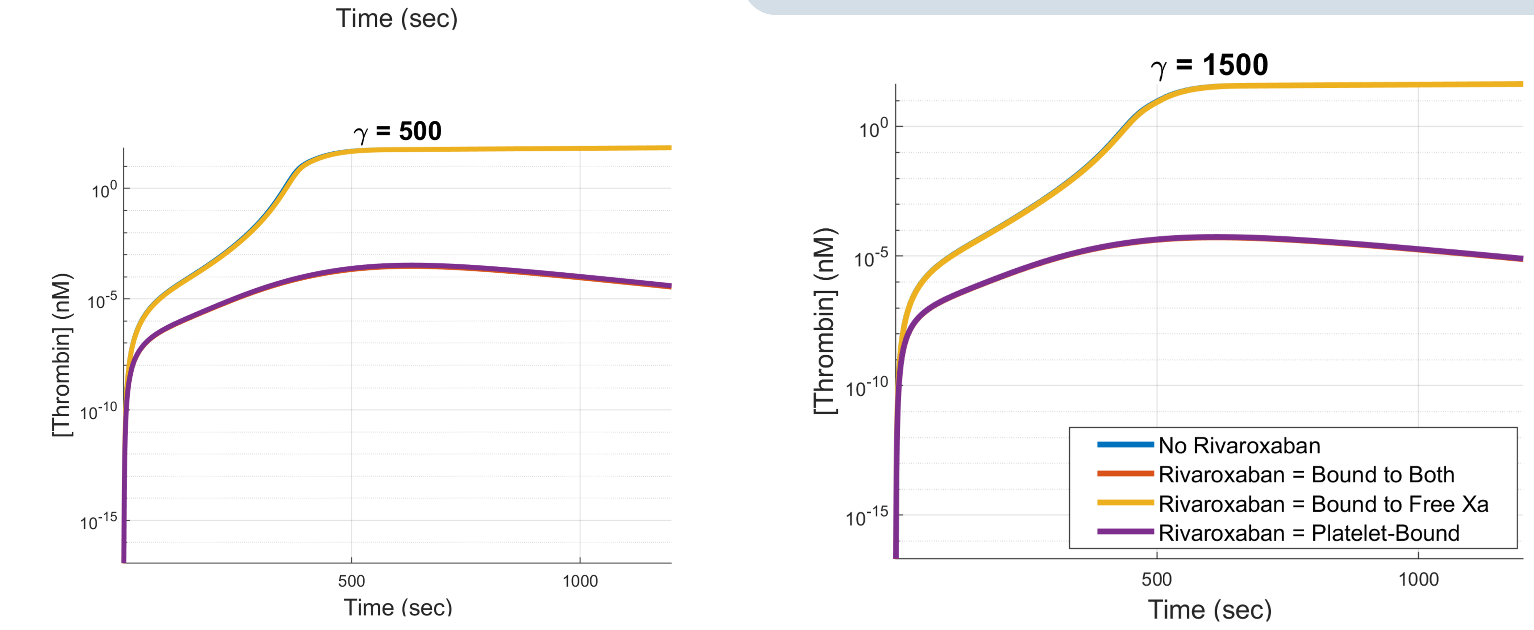


Figure 4. Thrombin generation with 100% of initial and upstream rivaroxaban concentrations and a TF density of 15 fmol/cm^2 with free Xa binding and platelet-bound binding with a shear rate of (A) 100 m/s, (B) 500 m/s, and (C) 1500 m/s.

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

Combination Inhibition Has Largest Impact

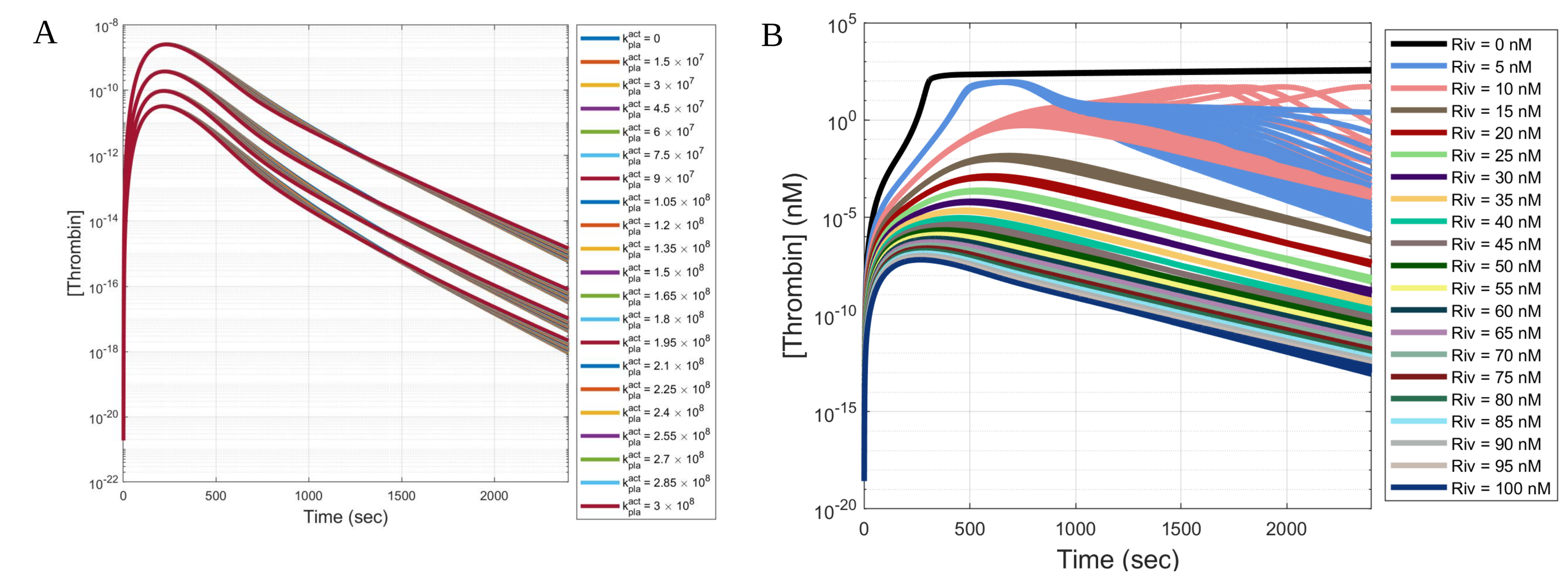


Figure 5. Thrombin concentration for rivaroxaban of greater concentrations is shown in (A), where the top red line represents 200 nM rivaroxaban and 0 nM aspirin, and rivaroxaban proceeds in increments of 100 nM as the red lines decrease. Thrombin concentration of smaller rivaroxaban concentrations, from 0 nM to 100 nM, is shown in (B).

- Greater rivaroxaban influences as shown in (A) demonstrate what is to be expected, where greater rivaroxaban with greater aspirin results in reduced thrombin and thus a reduced clotting response.
- In rivaroxaban concentrations greater than 5 nM, (B) shows the same expected pattern.

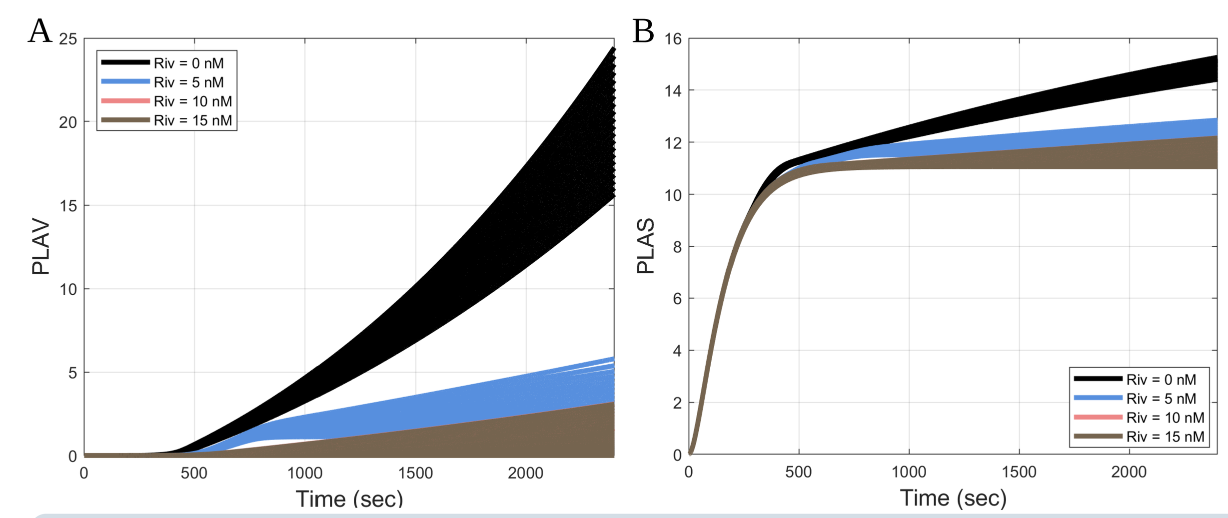


Figure 6. Activated platelets in volume (A) and on subendothelium (B) for all aspirin cases.

- As rivaroxaban and aspirin increase, there is a decrease in activated platelets in volume. Aspirin results in a reduced number of activated platelets of volume (PLAV). PLAV can become subendothelial-bound, PLAS, which also decreases as rivaroxaban and aspirin increase.
- Less PLAS leads to more subendothelial activity since more surface area is available.

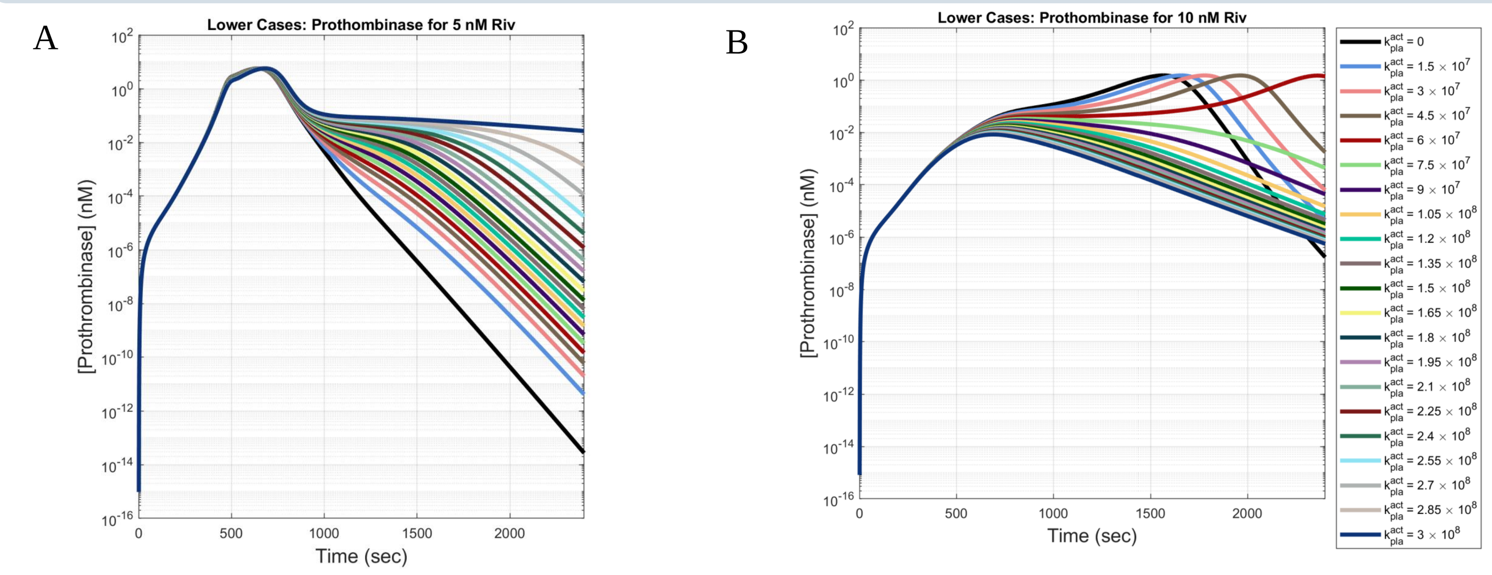


Figure 7. Prothombinase concentration for 5 nM rivaroxaban (C) and 15 nM rivaroxaban (D). As rivaroxaban increases from 5 nM to 10 nM, the prothrombinase concentration generally decreases. The effects of aspirin, shown by k_{pla}^{act}, reverse as rivaroxaban increases from 5 nM to 10 nM.

- The delay in prothombinase production, and hence thrombin production, between the 5 nM and 10 nM rivaroxaban cases may result in unintentional bleeding.
- This lag time is impacted by the tissue factor concentration present in the vessel as rivaroxaban is more affected by tissue factor than aspirin.

Conclusions and Future Work

- Rivaroxaban and aspirin prevent coagulation more effectively in combination than alone, though both rivaroxaban and aspirin affect clotting independently.
- Future work includes expanding understanding of the anticoagulant mechanism by studying more instances of how rivaroxaban and aspirin affect model species in different doses to discover optimal doses of each drug for greatest anticoagulation.