1 SUPPLEMENTARY MATERIAL

Title: Synergy Between Tissue Factor and Exogenous Factor XIa in Initiating Coagulation
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The simulations performed for this Supplement were conducted using the mathematical model described in [1]. A complete listing of the reactions included in the model and of the parameter values used in the simulations is in the Methods and Materials Supplement (Tables M-I – M-VII). See [1] for a listing of the model's differential equations, and [1, 2, 3] for further discussions of the model's derivation and behavior. The mathematical model simulates the clotting response due to a small injury to a vessel wall, as depicted in Fig. M-I in the Methods and Materials Supplement.

1.1 Effect of Shear Rate on Synergistic Thrombin Burst

Here we show the results of simulations at shear rates 50/sec and 10/sec. These should be compared with Fig. 1 in the main paper which shows results for shear rate 100/sec. The figures demonstrate that the synergistic response occurs at shear rates much lower than that looked at in the main paper.

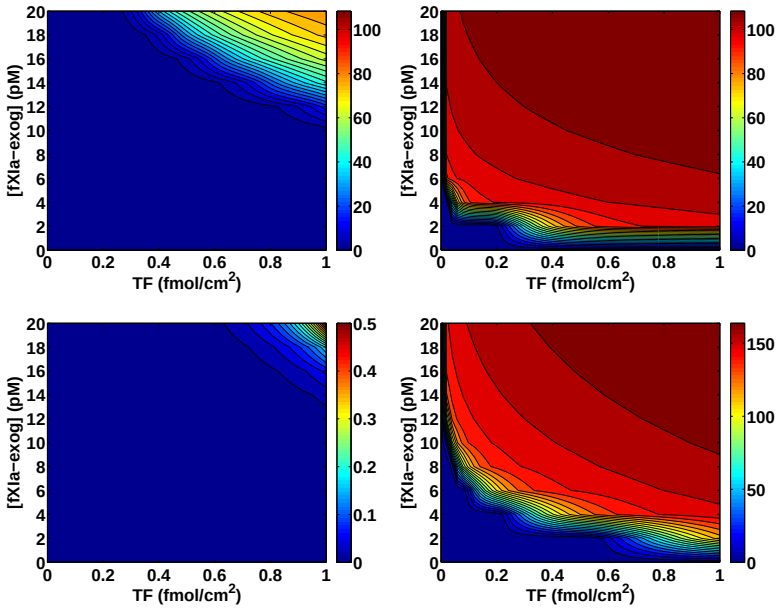

Figure S-I: Effects of TF and FXIa on intravascular thrombin generation in *in silico* experiments for shear rates 50/sec and 10/sec. Plasma thrombin concentration at 10 min (Top Left) and 20 min (Top Right) for $[TF]_d$ between 0 and 1 fmol/cm^2 and [E-FXIa] between 0 and 20 pM and shear rate 50/sec. Plasma thrombin concentration at 10 min (Bottom Left) and 20 min (Bottom Right) for $[TF]_d$ between 0 and 1 fmol/cm^2 and [E-FXIa] between 0 and 20 pM and shear rate 10/sec. Each point on the heat-maps was obtained from a single simulation with specified values of $[TF]_d$ and [E-FXIa]. Platelet count 250,000/μL.

1.2 Rate of thrombin increase during burst

To better understand the sensitivity of the maximum relative rate of thrombin increase during a burst shown in Fig. 1H, in Fig. S-II we plot the plasma thrombin, and platelet prothrombinase and tenase concentrations from these simulations in a different way. For each simulation, we determined the time t_1 at which the thrombin concentration reached 1 nM, which we regard as the start of the thrombin burst, and we plotted the concentrations starting at t_1 as a function of the *elapsed* time $t_{\text{elapsed}} = t - t_1$. Thus the plots for the different simulations were aligned with $t_{\text{elapsed}} = 0$ indicating when for each simulation, the thrombin concentration reached 1 nM. Fig. S-II shows that there was little difference among the prothrombinase concentrations at the start of the burst, but that the tenase concentrations at that time were clustered into distinct groups determined by [E-FXIa]. Within a cluster, the variation with $[\text{TF}]_{\text{d}}$ was small. The different tenase concentrations at the start of the bursts were the cause of the subsequent differences in *rates of increase* of prothrombinase and thrombin during the bursts. Higher concentrations of E-FXIa led to greater availability of Plt-FIXa early in the simulations and to the higher concentrations of tenase at the starts of the corresponding bursts. For these simulations, the availability of Plt-FVIIIa, due to activation by Plt-FXa, was sufficient at all $[\text{TF}]_{\text{d}}$ considered.

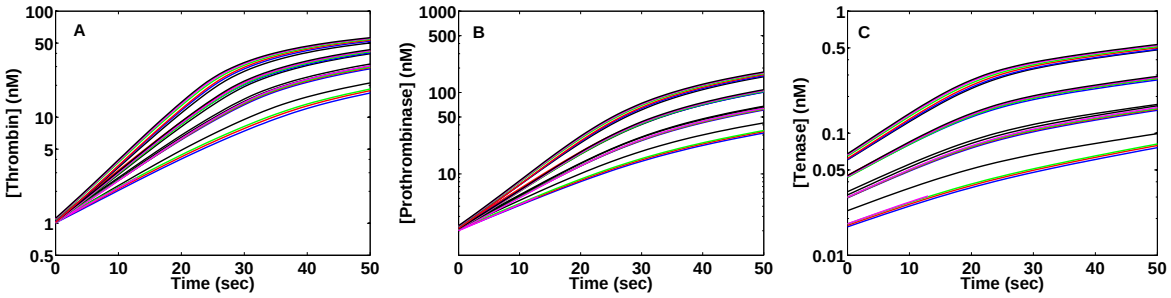

Figure S-II: Concentrations as functions of the elaspsed time since the thrombin concentration reached 1 nM for $[\text{TF}]_{\text{d}}$ = 10.0, 3.0, 1.0, 0.5, 0.1, 0.02 fmol/cm^2 and [E-FXIa]= 2, 5, 10, 20 pM. Each cluster of curves corresponds to one of the [E-FXIa] values. (A) Plasma thrombin concentrations vs elapsed time. (B) Prothrombinase concentrations vs elapsed time. (C) Tenase complex concentrations vs elapsed time. The tenase and prothrombinase concentrations include those of the complexes bound to their substrates, FX and prothrombin, respectively. Platelet count 250,000/μL. Shear rate 100/sec.

Here, we show the results of a series of simulations conducted to examine the relative rate of increase of thrombin during a thrombin burst in situations without E-FXIa. Fig. S-III shows that this rate increases with increasing $[\text{TF}]_{\text{d}}$. Here, $[\text{TF}]_{\text{d}}$ is the dominant determinant, early in each simulation, of the availability

of *both* Plt-FVIIIa and Plt-FIXa, and thus the rate of formation of the platelet-bound tenase complexes.

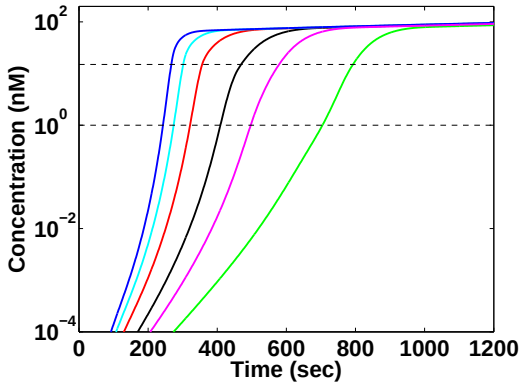

Figure S-III: For simulations with no exogenenous E-FXIa, time course of plasma thrombin concentration for $[TF]_d$ = 25 (blue), 20 (cyan), 15 (red) , 10 (black), 7.5 (magenta), 5 (green) fmol/cm^2 . Dashed lines show 1 nM and 15 nM concentrations. The steepness of the curves between these levels increases with $[TF]_d$. Platelet count 250,000/μL. Shear rate 100/sec.

1.3 Effect of FIXa binding sites on platelets

Simulations were performed in which i) FIX had 250 binding sites and fIXa had 250 binding sites per activated platelet, and ii) in which each activated platelet had 500 binding sites for which FIX and FIXa compete. Results are shown in Fig. S-IV. They should be compared with Fig. 1 in the main paper which shows results from simulations in which each activated platelet had 250 binding sites for which FIX and FIXa compete and 250 additional sites to which only FIXa could bind. The synergistic response to low $[\mathrm{TF}]_{\mathrm{d}}$ and [E-FXIa] is seen for all of these cases.

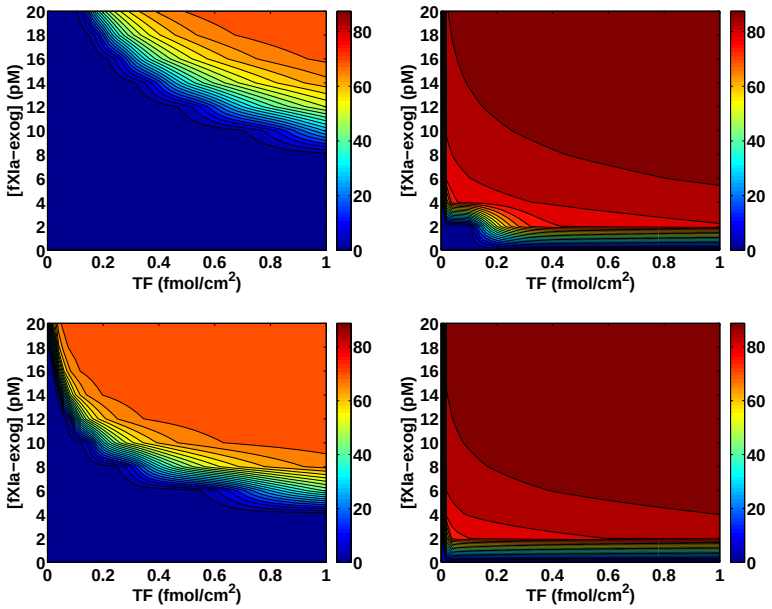

Figure S-IV: Effects of TF and FXIa on intravascular thrombin generation in *in silico* experiments for different assumptions about FIXa binding sites. Plasma thrombin concentration at 10 min (Top Left) and 20 min (Top Right) for $[\mathrm{TF}]_{\mathrm{d}}$ between 0 and 1 fmol/cm^2 and [E-FXIa] between 0 and 20 pM when each platelet has 250 binding sites only for FIX and 250 binding sites only for FIXa. Plasma thrombin concentration at 10 min (Bottom Left) and 20 min (Bottom Right) for $[\mathrm{TF}]_{\mathrm{d}}$ between 0 and 2.5 fmol/cm^2 and [E-FXIa] between 0 and 20 pM when each platelet has 500 binding sites for which FIX and FIXa compete. Each point on the heat-maps was obtained from a single simulation with specified values of $[\mathrm{TF}]_{\mathrm{d}}$ and [E-FXIa]. Platelet count 250,000/μL.

References

[1] A.L. Fogelson, Y.H. Hussain, and K. Leiderman. Blood clot formation under flow: The importance of factor XI depends strongly on platelet count. *Biophys J*, 102:10–18, 2012.

[2] A.L. Fogelson and N. Tania. Coagulation under flow: The influence of flow-mediated transport on the initiation and inhibition of coagulation. *Pathophysiol Haemost Thromb*, 34:91–108, 2005.

[3] A.L. Kuharsky and A.L. Fogelson. Surface-mediated control of blood coagulation: The role of binding site densities and platelet deposition. *Biophys J*, 80:1050–1074, 2001.