Modeling collective biophysical behavior of platelets in blood clotting

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Keywords: Blood flow, blood clotting, mesoscale modelling

Blood clotting disorders prevent the body’s natural ability to achieve hemostasis and lead to bleeding 1, stroke or heart attack 2. Other blood clotting disorders cause formation of undesired blood clots inside blood vessels defer blood flow from normal condition and lead to thrombosis diseases 3. Understanding the underlying physics behind the clotting process plays an important role in developing treatment of these disorders. Interactions between platelet and fibrin network leading to blood clotting are a complex multiscale process taking place in blood flow (Fig 1), preventing the development of atomistic-scale models of fibrin clot contraction. We employ a mesoscale computational approach based on dissipative particle dynamics (DPD) 4,5 to examine the biophysics of clot contraction that links two dramatically different spatial scales.

During clot contraction, platelets extend filopodia to various points in the surrounding fibrin mesh and then contract the mesh leading to clot contraction. We use 3D confocal images of platelets and fibrin 6 to create computational replicas of fibrin meshes with distributed platelets and to analyze platelet filopodia kinetics, filopodia numbers, and filopodia lengths. Fibrin mesh is modeled as semi-flexible polymers branched from crosslinks 7-10. Platelets are modeled as clusters of DPD beads with stiff internal bonds, placed into the network to the sites found in confocal image analysis. Fig 2a shows that initial fibrin mesh (green) with distributed platelets (blue). Filopodia retraction is simulated as reducing the length of bonds connecting platelets and the fibrin network. Clotting effectiveness is quantified by clot contraction ratio, defined as the ratio of final clot volume to its initial volume. The model allows us to probe the effects of filopodia length, filopodia number, and dynamics of filopodia retraction on fibrin clot microstructure (Fig 2).

To study the effects of platelet concentration, filopodia numbers, and filopodia lengths, we use a model in which all platelets and filopodia are activated simultaneously. Fig 3 shows that when we use 6 µm filopodia corresponding to the experimental conditions, clot volume decreases only to about 22% of the initial volume. In the experiments, clot contracts to about 6% of the volume. To achieve such contraction in our model we need to increase the filopodia length to 10 µm which is significantly longer than the experimental value. We also simulated platelets with different number of filopodia per platelet. As shown in Fig 3, increasing the number of filopodia from 10 to 28 has a minor effect on clot contraction. In other words, these excessive filopodia remain unutilized. Furthermore, this model predicts that contraction will be completed in about 20 min whereas in experiments contraction takes about 90 min. This points to the fact that this simple model...
assuming simultaneous activation and action of platelets cannot correctly describe fibrin-network interactions.

Experiments show that platelets are rather heterogeneous and typically activate at different times during clot contraction. Furthermore, activated platelets do not grow all filipodia simultaneously, but rather continuously add new filipodia through the period of time they stay active. To examine the effects of the temporal variation in platelet activation and filipodia growth, we construct two models that examine these processes. In the first model, platelets are activated at different times while all filipodia grow once a platelet gets activated. In the second model, filopodia grow at different times while all platelets get activated immediately after clotting starts. As shown in Fig 4, with the same number of platelets and filopodia, significant enhancement of clot contraction is observed using delayed activation of platelets and filopodia that are divided into groups that are activated sequentially. We find that delayed filopodia growth and activation converges faster the final clot ratio indication that delayed activation is less important for filipodia than for platelets.

We note that using models with delayed platelet and filopodia activation we are able to reproduce clot contraction that is similar to that observed in the experiments. Thus, we conclude that our relatively simple model reveals a strong dependence of clot contraction on platelet heterogeneity and activation pattern.

Acknowledgements

Financial support from the National Science Foundation (CAREER Award DMR-1255288) is gratefully acknowledged.

References


