ZOOMING IN ON BLOOD COAGULATION AND VISCOSITY:
Computation Takes On Blood Behavior

By Alexander Gelfand

Understanding blood flow and coagulation is crucial to treating blood disorders such as hemophilia and thrombosis, and to dealing with diseases such as AIDS, malaria, and diabetes that have hematologic consequences.

It's also bloody difficult. Although it behaves like a homogeneous fluid in large vessels such as arteries, human blood is really a suspension of solids (blood cells, platelets) that can alter their characteristics in response to chemical and physical provocation. In smaller vessels such as capillaries and arterioles, those particles cause blood to act like a non-Newtonian fluid, similar to ketchup, whose viscosity is subject to change. Coagulation, meanwhile, involves a complicated dance between cell membranes and biological molecules.

Fortunately, advances in computational modeling are helping to clarify the behavior of blood under both healthy and unhealthy conditions. Two researchers in particular are modeling blood's component parts, albeit at slightly different scales. One is trying to describe the molecular mechanisms that drive coagulation, while the other is trying to predict changes in blood viscosity by modeling individual red blood cells and their interactions. Like microscopes that offer different levels of magnification, their simulations illuminate the inner workings of blood at multiple levels.

Extreme Close-Up: Molecular Dynamics of Coagulation's Early Stages

Emad Tajkhorshid, PhD, professor of biochemistry, biophysics, and pharmacol-

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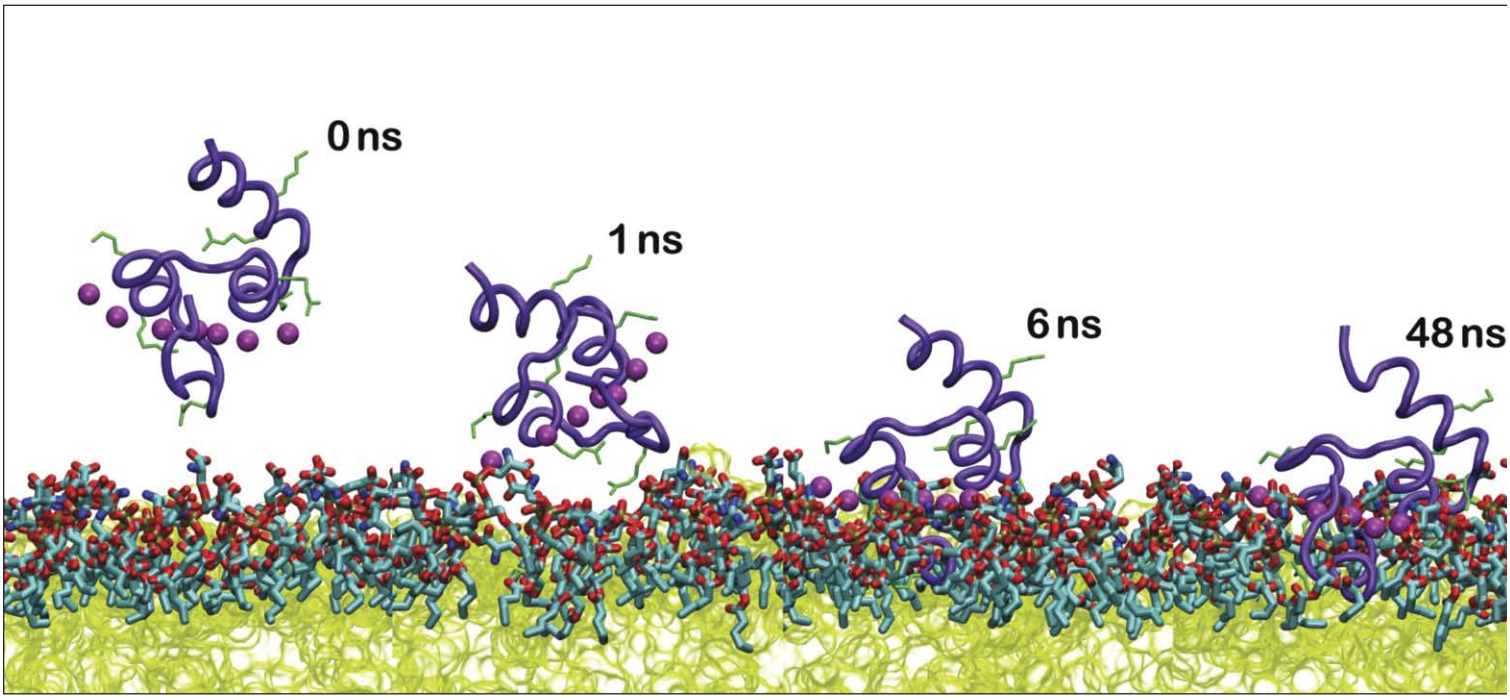
In unbiased full-atom simulations using a novel membrane representation, Tajkhorshid's team captured a peripheral membrane protein (purple) spontaneously binding and inserting into the platelet membrane. The model replaces the lipid tails in the membrane's hydrophobic core with an organic solvent, while preserving a full representation of lipid headgroups. This treatment enhances the lateral diffusion of lipid molecules by one to two orders of magnitude (compared to conventional full-tail membrane models) without compromising atomic details, and improves the efficiency of simulation studies of diverse membrane-associated phenomena. The work is described in Ohkubo YZ, et al., Accelerating membrane insertion of peripheral proteins with a novel membrane mimetic model. **Biophysical Journal,** ***102: 2130-2139 (2012). Image courtesy of Y. Zenmei Ohkubo, Taras V. Pogorelov, Mark J. Arcario, and Emad Tajkhorshid.***



ogy at the University of Illinois, has been using molecular dynamics (MD) modeling to simulate the earliest stages in the coagulation cascade. The process begins when blood-clotting proteins bind to the membranes of activated platelets. They do so with the help of lipid molecules that ordinarily lie buried within the membranes themselves, rising to the surface only when needed—a regulatory mechanism that prevents your blood from clotting in your veins as you read this.

Divining the mechanics of that binding process, and the specific sites on the membrane where binding occurs, could lead to the development of better anticoagulant drugs with fewer side effects. But the process is difficult to characterize experimentally because the platelets' membrane surface is a semi-fluid platform; the relevant lipids and proteins are in constant motion, and it is difficult to determine which parts of the molecules bind to one another, and where.

MD modeling, which allows scientists to simulate interactions at the molecular level, would seem to present the perfect solution. Yet the extraordinarily high resolution afforded by molecular dynamics comes at a correspondingly high cost. Tajkhorshid's models, for example, must calculate the forces between almost every pair of atoms in a system comprising hundreds of thousands of them. And they must do so at time intervals measured in quadrillionths of a second. Generating even one nanosecond's worth of simulation time requires performing those calculations millions of times.

"That's really, really expensive," says Tajkhorshid, adding that the computational burden is so high that the simulations are currently limited to timescales of hundreds of nanoseconds—"maybe a microsecond, if you really push it." The binding process itself plays out over tens of microseconds, however, which presents an obvious problem—one that Tajkhorshid's group has solved by means of an ingenious computational trick.

By replacing a portion of the virtual platelet membrane with a more fluid organic solvent, Tajkhorshid has sped up the rate at which his simulated lipids move.

"Suddenly everything is ten times faster, at least," Tajkhorshid says. "Things that usually happen at the microsecond scale are happening at the nanosecond scale." This artificial accelerant has enabled Tajkhorshid and his colleagues to simulate the interaction between platelet membrane and lipid molecules, and to work out how coagulating proteins bind to the membrane surface. Tajkhorshid is currently using his lubed-up model to pursue an even more ambitious goal: simulating how different coagulation proteins form complexes on the membrane surface in order to become fully activated, thereby driving the coagulation cascade forward.

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Medium Close-Up: Modeling Blood Viscosity

George Karniadakis, PhD, professor of applied mathematics at Brown University, also found himself bumping up against the limits of molecular dynamics when attempting to model hematological phenomena. His solution? Study blood at a coarser level of granularity. This lets him cover a larger territory in the circulatory system at a longer timescale, modeling changes in blood viscosity and simulating the kinds of abnormal red blood cell aggregation that occurs in diseases such as atherosclerosis, AIDS, myeloma, and diabetes mellitus.

To create his multiscale models, Karniadakis simulates everything from the biomechanics of individual red blood cells to their passage *en masse* through the human body's arterial tree. The method he uses, known as dissipative particle dynamics (DPD), was originally developed by a pair of Dutch chemical engineers for the purpose of modeling polymers. Sometimes called a coarse-grained molecular dynamics approach, DPD relies on virtual particles that represent clusters, or lumps, of atoms and molecules rather than delving into too much microscopic detail. "Instead of every droplet in a cloud interacting with every droplet in another cloud, we have two small clouds interacting with each other," Karniadakis says. As that metaphor suggests, DPD offers a mesoscopic or intermediate-scale tool for bridging the gap between the high-powered zoom of true MD modeling and the standard fluid models that are used to simulate blood flow writ large.

Last year, Karniadakis and his colleagues constructed a multiscale model that simulates the growth and rupture of a brain aneurysm by using DPD to capture cell-to-cell interactions within the aneurysm and classical fluid mechanics to represent the flow of blood in the brain. Now he has developed two different DPD-based models for simulating individual red blood cells and predicting their aggregate behavior.

The first model, which Karniadakis calls "cheap blood," uses only 10 DPD particles to represent each cell. (By contrast, Karniadakis says, some 30,000 points would be required to faithfully replicate the protein structure of the surface of a single red blood cell.) Yet this bare-bones model still permits accurate simulations of blood flow down to the level of capillaries. "It's not exactly the geometry you want, but it's pretty close," Karniadakis says.

The second model uses several hundred particles to accurately represent the cytoskeletal structure of a red blood cell. Though considerably more expensive, it can be used to predict the flow of blood through even the smallest vessels. By toggling between the two models, Karniadakis can tailor the degree of resolution to the

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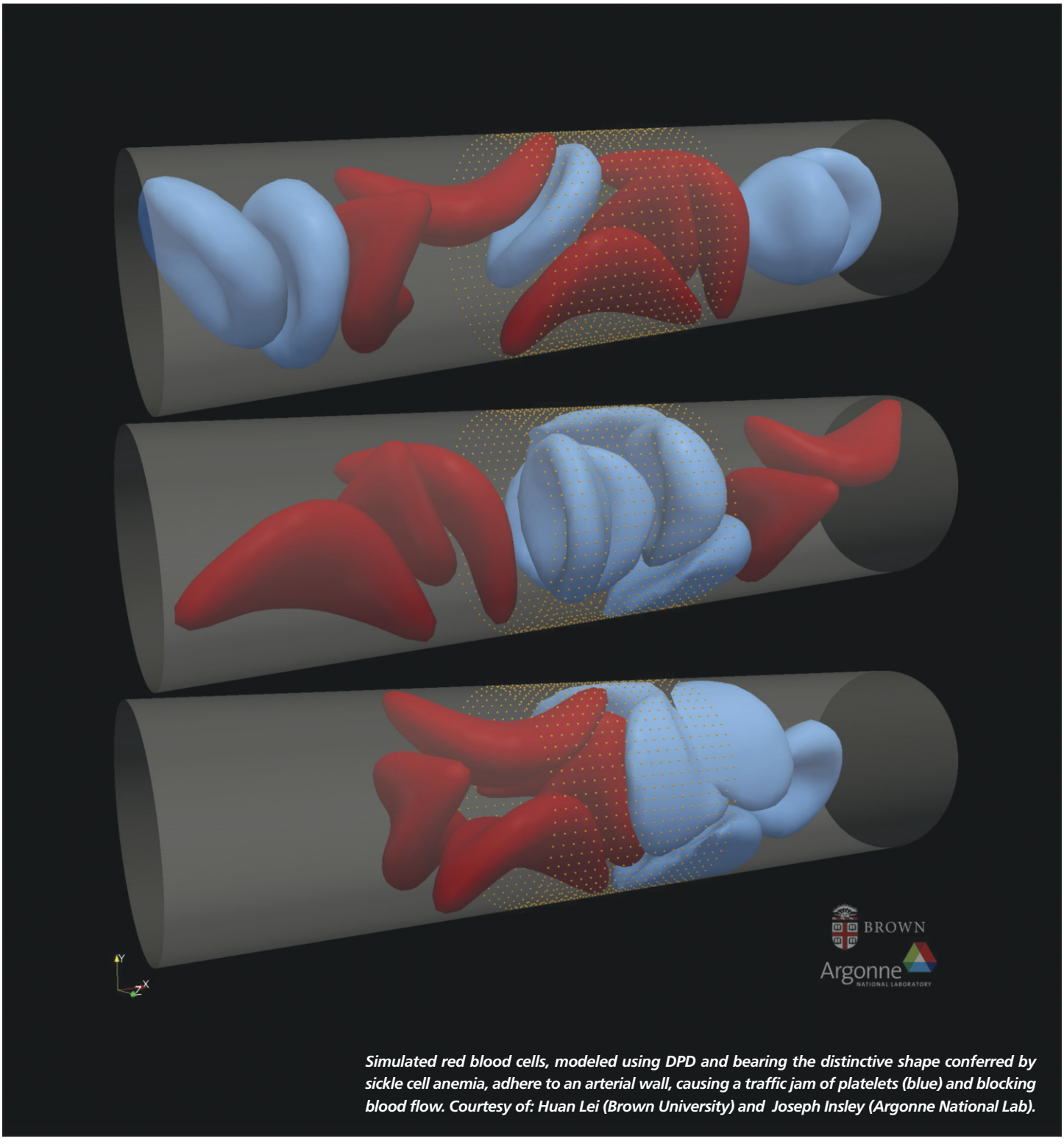
task at hand and avoid eating up more computational resources than necessary.

Using methods developed in collaboration with **Subra Suresh**, **PhD**, current director of the National Science Foundation, Karniadakis calibrates his models with biomechanical data gathered from experiments on individual red blood cells, then predicts the collective behavior of blood under both healthy and diseased conditions. By tweaking his models to reflect the stiffening of red blood cells infected with malaria, for example, or varying levels of a protein called fibrinogen that plays a key role in coagulation, Karniadakis has successfully predicted changes in blood viscosity—and accurately modeled, for the first time, the microscopic physical processes that cause those changes, such as the formation and destruction of "rouleaux," or stacks of red blood cells. The abnormal aggregation of red blood cells is a symptom of many diseases, and better modeling of how and why that aggregation occurs could lead to more precise diagnoses.

In addition to unpacking the physics of blood flow and coagulation, Karniadakis is also using his DPD models to figure out how diseased red blood cells interact with arterial walls and white blood cells—information that could lead to more effective treatments for both malaria and sickle cell anemia.

Now that would be bloody brilliant. □



Simulated red blood cells, modeled using DPD and bearing the distinctive shape conferred by sickle cell anemia, adhere to an arterial wall, causing a traffic jam of platelets (blue) and blocking blood flow. Courtesy of: Huan Lei (Brown University) and Joseph Insley (Argonne National Lab).