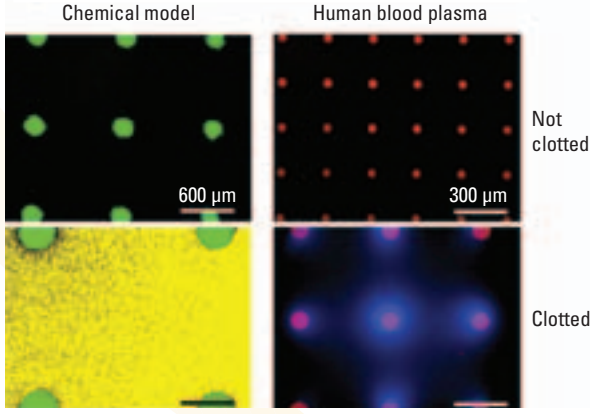
Probing complex biological systems with simple chemistry

A simplified chemical model helps elucidate the spatiotemporal dynamics of blood clotting.

Hemostasis, the process of blood clotting, plays a critical role in everything from healing a simple cut to causing life-threatening strokes. But the complex cascade of ~80 individual chemical reactions, with extensive positive and negative feedback controls and nonlinear dynamics, has been difficult to model mathematically. Rustem Ismagilov and colleagues at the University of Chicago previously developed a simplified chemical model that simulated the spatiotemporal dynamics of hemostasis (*Angew. Chem., Int. Ed.* **2004**, *43*, 1532–1536). Now, by using the chemical model and analyzing blood clotting in a microfluidic device, they've demonstrated that the model system can be used to predict clotting-initiation dynamics, including identification of a spatial threshold response that may have applications in medical diagnostics and treatment (*Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 15,747–15,752).



Fluorescent micrographs show that clotting initiation depends on the size of the activator patch rather than the total activator surface area. Results are shown for a chemical model (left, yellow = clotting) and human blood plasma (right, blue = clotting). (Adapted with permission. Copyright 2006 National Academy of Sciences, U.S.A.)

In nature, the blood-clotting cascade is initiated when damaged cells release the activator molecule, tissue factor. Christian Kastrup, first author on the current paper, says the fundamental question is, "Do you have to understand all the details of the system to predict its behavior, or can you reduce it down to more simple mechanisms?"

Coauthor Matthew Runyon had developed the chemical model of hemostasis by reducing the network to three functional modules: the autocatalytic production of activators, the linear consumption of activators, and the formation of a clot at high concentrations of activators. The investigators showed that the mechanisms in acidic gelling of alginic acid could be used as an analog of blood clotting. The ~80 steps of true clotting were drastically simplified, but the essential kinetics of the 3 modules was preserved.

In the current study, Ismagilov, Kastrup, Runyon, and Feng Shen proposed a spatial threshold effect for the initiation of clotting. By patterning small acidic patches ranging from 200 to 800 µm in diameter onto a photoacid layer to act as a "clotting" stimulus for alginic acid, they determined that gelling was initiated rapidly with patch diameters ≥400 µm but was not initiated with patch diameters ≤200 µm.

The investigators hypothesized competition between activator production and diffusion, and they found that even with many small patches, which produced more total acid than a large patch, gelling wasn't initiated unless the patches were located within diffusion distance of each other. "Using the chemical model, we realized that a threshold patch size could regulate clotting and that we could quantitatively predict the threshold value," says Kastrup. "So then we looked at human blood to test those predictions." Sure enough, when Ismagilov's group used a microfluidic device to expose blood plasma to patches of lipid and tissue factor patterned onto an inert lipid layer, they found that clotting followed the predicted spatiotemporal dynamics—it was initiated only above a minimum patch size threshold, regardless of total patch area.

"It's a very clever approach, and the results are a little surprising," says James Morrissey of the University of Illinois at Urbana–Champaign. "You get this 'go or no go' dynamic depending on the size of damage, rather than on the total amount of tissue factor produced." The finding may offer clues to long-standing mysteries about clotting regulation, Morrissey says, and the microfluidic device could potentially be developed into a diagnostic screen for elevated or reduced propensity to form blood clots. That's important clinical information with conditions such as stroke, myocardial infarction, and deep-vein thrombosis, but "there are so many reactions [in the clotting cascade] that it's hard to test for them all," says Morrissey. "This approach could look at the blood's overall ability to clot, rather than at individual reactions."

Ultimately, says Kenneth Showalter of West Virginia University, the current paper is confirmation of a long-standing assertion in nonlinear chemistry. "We've always been claiming that the dynamical behavior we see in chemical systems is relevant to what we see in biological systems but can't get a handle on because they are too complex to study," he says. The Ismagilov group's study, Showalter says, confirms that "these systems really can give us insights into what is and what is not possible in the spatiotemporal dynamics of complex biological systems." ◥

—Thomas Hayden