Using chemistry to predict the dynamics of clotting in human blood

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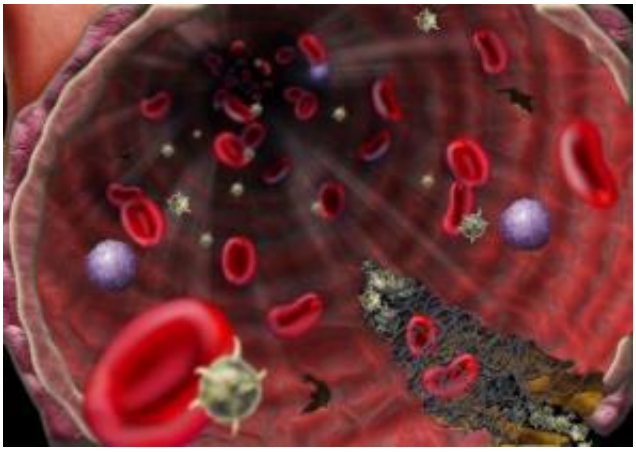
A microfluidic chip. Microfluidics is the science of manipulating fluids on the micron scale, a unit of measurement much narrower than the diameter of a human hair. Credit: Photo by Peter Kiar

University of Chicago chemists have demonstrated for the first time how to use a simple laboratory model consisting of only a few chemical reactions to predict when and where blood clotting will occur. The scientists used microfluidics, a technique that allowed them to probe blood clotting on surfaces that mimic vascular damage on the micron scale.

Although scientists understand what occurs during many of the 80 individual chemical reactions involved in blood clotting, many questions about the dynamics of the entire reaction network remain. Rustem Ismagilov, Associate Professor in Chemistry at the University of Chicago, and graduate students Christian Kastrup, Matthew Runyon and Feng Shen have now developed a technique that will enable scientists to understand the rules governing complex biological reaction networks. They will detail their technique in the online early edition of the Oct. 16-20 issue of the *Proceedings of the National Academy of Sciences*.

Life and death literally depend on a finely tuned blood-clotting system. "Clotting has to occur at the right place at the right time," Ismagilov said. "A strong, rapid clotting response is essential to stop bleeding at a wound, but such a clotting response at the wrong spot can block blood vessels and can be life-threatening."

In the past, scientists have typically examined the blood-clotting network using flasks containing homogenous mixtures-the test fluids were the same throughout. But the contents of the circulatory system are not homogeneous, said Kastrup, a Ph.D. student in chemistry and the PNAS article's lead author. One of the great virtues of microfluidics technology is its ability to control complex reactions at critical times and locations.



This image shows clotting occurring on a large area of vascular damage, but not small areas. A chemical model for blood clotting developed at the University of Chicago predicted this phenomenon. The Chicago scientists verified this prediction in the laboratory using their microfluidic system, which enables them to manipulate fluids on a minute scale. The team's in vitro experiments -- conducting in an artificial environment -- may also apply in vivo, or in the living body. Credit: Nicolle Rager Fuller, National Science Foundation

"The blood-clotting system contains both fluids and surfaces in an elaborate spatial environment, where localization of chemicals is very important," he said. Microfluidic technology can address this issue through its ability to control complex reactions at critical times and locations.

In previous work, the Ismagilov group designed a simple laboratory model to simulate blood clotting. In this model, Ph.D. student Runyon and his associates devised three modules that correspond to the three major stages of clotting: production of chemicals that activate clotting, the inhibition of these activators, and formation of the solid clot.

In this model, the scientists used only one chemical reaction in each module instead of the 20-to-30 biochemical reactions that the modules represent. Surprisingly, this simple model adequately reproduced many features of blood clotting.

"There's a long history in chemistry of using simple models to understand more complex behavior," Kastrup said. "Instead of looking at hundreds of equations for blood clotting, we reduced it down to three main equations. From these equations we were able to describe a lot of the dynamics of clotting."

The ability of microfluidics to mimic the flow and geometry of human blood vessels also proved critical.

"We had to use microfluidics to do all of this because that's how we controlled where everything is," Ismagilov said of Runyon's previous work. "It turned out that we got appropriate behavior only if we used geometry similar to those observed in our vascular system. If we changed the geometry to something that didn't look like a biological system, the chemical system couldn't function. So geometry and flow were very important."

In the latest advance, Kastrup used Runyon's model to see if he could predict when clotting would occur in human blood. The team predicted and verified that clotting occurs only at locations of vascular damage larger than a critical size. "Surprisingly, this simple model made correct, quantitative predictions about blood clotting," Kastrup said.

Furthermore, the model provided new details about the dynamics of clotting. A big question in blood-clotting studies is the role of a protein called tissue factor. Can tissue factor exist in blood without the presence of clotting?

"From our experiments we see that it's not the overall concentration of tissue factor that matters, but it's the localization of it that makes a difference," Kastrup explained. That means a high concentration of tissue factor at one location will result in clotting, while the same number of molecules spread farther apart will not.

In the future, chemists might now be able to apply microfluidics to the study of other complex reaction networks that control various biological functions. And in the medical arena, the technique could become a way to perform rapid and detailed diagnostic tests. "We'd love to see that happen," Kastrup said.

Source: University of Chicago