Biophysicists develop a model for arterial thrombus formation

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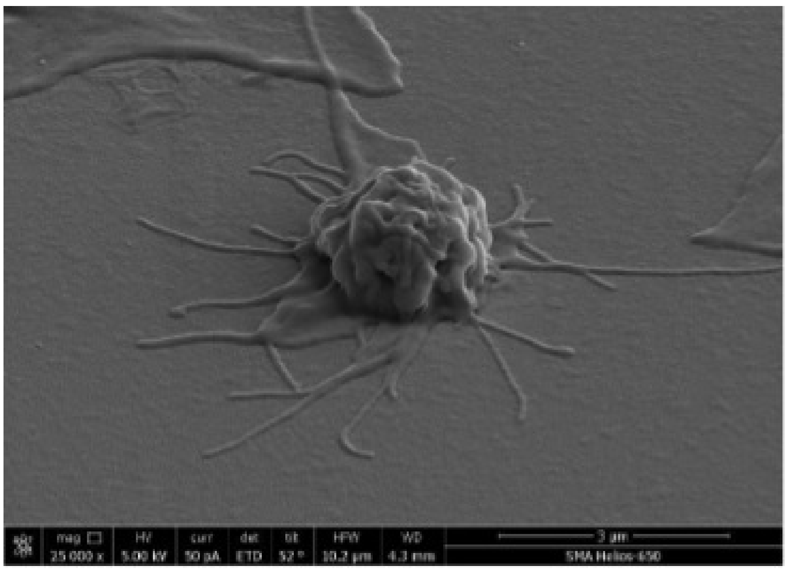


Activated thrombocyte on a slide with immobilized fibrinogen, one of the proteins found in the blood. Scanning electron microscopy. Credit: Sergey Obydenny / Wikimedia

A group of biophysicists, including representatives from Moscow Institute of Physics and Technology, have developed a mathematical model of arterial thrombus formation, which is the main cause of heart attacks and strokes. The scientists described the process of platelet aggregation as being similar to the popular video game Tetris and derived equations that allowed them to reproduce the wave process of platelet aggregate formation in a blood vessel.

Researchers described the new model in the journal *PLOS ONE*. When discussing the development of the model and the members of the research team, Mikhail Panteleev, one of the authors of the publication, said, "Fazly Ataullakhanov and I formulated the problem and established the equation, and Evgenia Babushkina, under the guidance of her teacher Nikolay Bessonov, developed solution methods in the two-dimensional case taking into account the hydrodynamics of the flow in which the thrombus is formed. She performed all the calculations herself; Fazly and I are professors of the Department of Translational and Regenerative Medicine of MIPT's Faculty of Biological and Medical Physics, which is based at FRCC PHOI—we work in a lot of different places…"

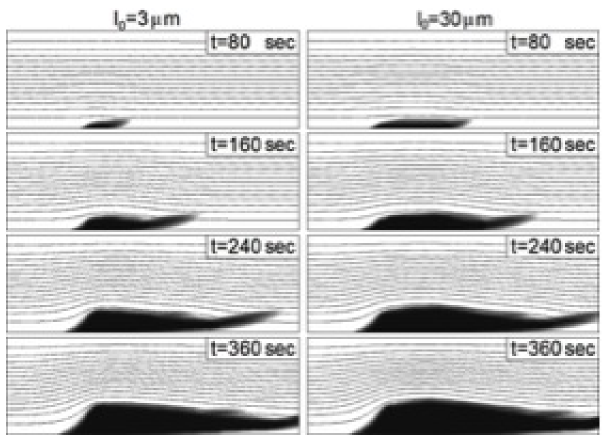
The new model regards thrombus formation as akin to the way that tiles become stacked up in the classic video game Tetris. In Tetris, the tiles either drop down onto a flat surface, or become attached to parts sticking out from the rest of the block. The only difference between thrombus formation and the game is that when a layer is complete, it does not disappear; therefore, as time passes, a thrombus is capable of obstructing the space it is in. In addition, the falling shapes are always the same: The model describes the aggregation of thrombocytes, specialized blood cells.

Having described the mathematical process of how vacant areas on the surface of a growing thrombus are filled, the scientists were able to build a one-dimensional model (as in Tetris), and then a two-dimensional model (thrombocytes are deposited in a dimensional plane). And at one point, the scientists began to consider certain thrombocytes as being dimensionless, and the thrombus itself as being continuous; in other words, the scientists went from a *discrete* model to a *continuous* model.

In a discrete model, the system under study consists of individual particles, and the behaviour of each particle can be tracked individually.

This makes it possible to simulate, for example, gas molecules in the problem of Brownian motion, representing each molecule as a particle colliding with a larger particle.

In a continuous model, the system under study consists of solid objects that can freely change their size or any other characteristic. This can be used to model temperature increase in a functioning boiler, for example – the output will be the temperature field in the volume under study.



Thrombus formation in various circumstances: on the left, the area of the vascular wall that is damaged is ten times smaller than on the right. However, over time, the thrombus growth in both cases is approximately the same size. Image: 10.1371/journal.pone.0141068

The sequential solution of the equations obtained enabled the researchers to reproduce the dynamics of the growth of a real thrombus and study its behaviour under various conditions – during damage to the vascular wall, for example.

Active media and autowaves

In their paper, the researchers emphasize that the process of thrombus formation resembles a traveling wave, and this similarity is by no means accidental. They previously demonstrated that the thrombus formation process is like an autowave – the blood, which carries platelets and a number of special proteins for coagulation, is an active medium. At that time, the conclusion drawn by the researchers was concerned with blood coagulation as a result of a cascade of biochemical reactions involving proteins, but it is also possible to talk of an active medium in the case of adhered platelets.

The term "active medium" plays a key role in non-linear dynamics—the mathematical modeling of a whole range of systems, from mixtures of interacting chemicals and lasers to forest fires and even social networks. The easiest way to describe an active medium is to use the example of a forest fire: Every dry tree is not simply a passive object, but a potential source of thermal energy. If there is a fire near a dry tree, it, too, will start to burn and provide more heat, which can then ignite other trees. The ability of elements in the system to release energy is a key feature of an active medium.

In active media, a local event (lightning striking a tree for example) can initiate a transition process in a system from one state to another (in this case a dry tree becomes a burning tree). This process spreads like a wave in space and can be described mathematically regardless of the specific physical nature of the system; the same equation can be used to describe entirely different phenomena. The term "autowave" means that wave propagation process is not passive, as in the case of seismic waves travelling from an earthquake's epicentre, but active – at each point, the wave receives more energy. In the case of thrombus formation, instead of dry and burning trees, think of platelets flowing in blood plasma. These platelets can go from a free-flowing state to a deposited state.

Thrombi: essential, but also dangerous

Thrombocytes (blood platelets) play an important role in forming thrombi, which block the blood vessels by forming clots. Under normal circumstances, they flow freely in the bloodstream, but if the vascular wall becomes damaged, they adhere to one another and to the vascular wall; additionally, the blood also contains many proteins required for thrombus formation. Even if there are no platelets, reactions with these proteins help form a clot to block a damaged vessel, and these reactions also occur in the form of autowaves. Normally, thrombi prevent blood loss in the human body when a blood vessel has become damaged. Sometimes, however, thrombus formation occurs as a result of a reaction to a pathological process, such as the build-up of fatty plaque within an artery in cases of atherosclerosis. This type of thrombus formation can block a vessel completely and cut off the blood supply to tissues and organs. This, in turn, can lead to myocardial infarction (blockage of the arteries to the heart), stroke (blockage of the arteries supplying blood to the brain), or gangrene of the extremities. The new model correctly describes arterial thrombus formation – these particular thrombi consist mainly of platelets; blood proteins play a relatively small role in the process.

Prospects

Mikhail Panteleev also spoke about the prospects of studying thrombi and why the researchers chose to look at arteries, rather than venous thrombi or the blood clotting process in the capillaries: "We are working on various issues in the field of hemostasis – the 'physiological' process of wound clotting, as well as venous and arterial blood clots. Arterial blood clots, in particular, are very interesting, and have social importance in the case of heart attacks and ischemic strokes. Blood proteins also play a key role here that is not fully understood. However, we have always had difficulty working with arterial blood clots in particular, in terms of developing and implementing computer models, because they involve a very difficult combination of ell attachments, hydrodynamics with variable geometry, and biochemistry. There is no standard software program that can adequately address the problem."

Panteleev continues: "In our paper in *PLOS ONE*, we tried to use the most primitive description of a thrombus as a continuous medium, rather than discrete particles. This approximation is rough in many respects, and it limits the scope of the research, but it is able to give us some common patterns. On the one hand, we plan to continue to apply it to specific tasks, as far as is possible, and on the other hand, we are developing more sophisticated and advanced models with three-dimensional blood cells, the full mechanics of their interaction, and the proper biochemistry. This will be done on supercomputers, of course. Another aspect is the 'inside' of a thrombocyte, modeling intracellular signaling, calcium oscillations, and the collapse of mitochondria in thrombocytes. This topic has been addressed in a number of papers that have already been published, including a very recent paper in *Molecular BioSystems*. Over time, I hope that all these projects will merge together into full multi-scale model of thrombus formation."

In order to understand the social importance of the problem described by Mikhail Panteleev, note that every day, around 1000 people in Russia suffer a stroke and of those who survive, two-thirds are left with a disability. Contrary to popular belief, strokes not only affect the elderly; one in eight stroke victims are people under the age of 45. Signs of a stroke include partial paralysis and a sudden onset of weakness. In a number of cases, the symptoms, which include slurred speech and a staggering gait, may make it appear as if the sufferer is under the influence of alcohol: this error of judgment could cost the lives of victims of an acute cerebrovascular accident.

More information: Evgenia S. Babushkina et al. Continuous Modeling of Arterial Platelet Thrombus Formation Using a Spatial Adsorption

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