Predicting complex biology with simple chemistry

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One of the most important activities in science is the development of models, i.e., simpler representations, often by mathematical equations, of more complex systems, which capture key aspects of those systems. A model, of course, cannot be identical to its target system and must discard at least some of the features of the full system while focusing on those characteristics that the modeler considers essential. A successful model not only reproduces the desired behavior(s) but also provides insight into the workings of the system and, ideally, generates testable predictions about the system. In this issue of PNAS, Kastrup *et al.* (1) design a set of chemical reactions coupled to a microfluidic system to model the initiation of blood clotting in the complex network of hemostasis. This tour de force significantly extends the scope of chemical reactions as a source of fruitful models for complex biological processes.

The use of chemical models for biological phenomena goes back at least to Luther's effort a century ago (2) to elucidate the conduction of nerve impulses by demonstrating before the Deutsche Bunsengesellschaft a traveling wave propagating in an autocatalytic mixture of oxalic acid and potassium permanganate. Rebek and coworkers (3) showed how relatively simple acyl transfer reactions could exhibit the "biological" phenomenon of self-replication. More recent work has exploited the richness of nonlinear chemical dynamics (4), with its oscillatory, bistable, and chaotic temporal behavior and striking spatial pattern formation, to mimic, and occasionally offer explanations for, a variety of phenomena in living systems. Fig. 1 demonstrates how pattern formation in the classic Belousov–Zhabotinsky oscillating reaction in a Petri dish captures, at least visually, the spatial behavior of the aggregating slime mold *Dictyostelium discoideum*. This same reaction has been used to model such complex activities as myocardial fibrillation (5), counting (6), and maze solving (7), while the oscillatory chlorite–iodide reaction has served as a model for the characteristic bursting output of neurons (8). One must, of course, be wary of the "same behavior implies same mechanism" fallacy because a given phenomenon may arise via more than one pathway. Nevertheless, the ability to mimic a biological function with a reaction or a coupled set of chemical reactions offers at least the possibility of understanding that phenomenon at a deeper level than is likely to be achieved with, for example, a set of partial differential equations.

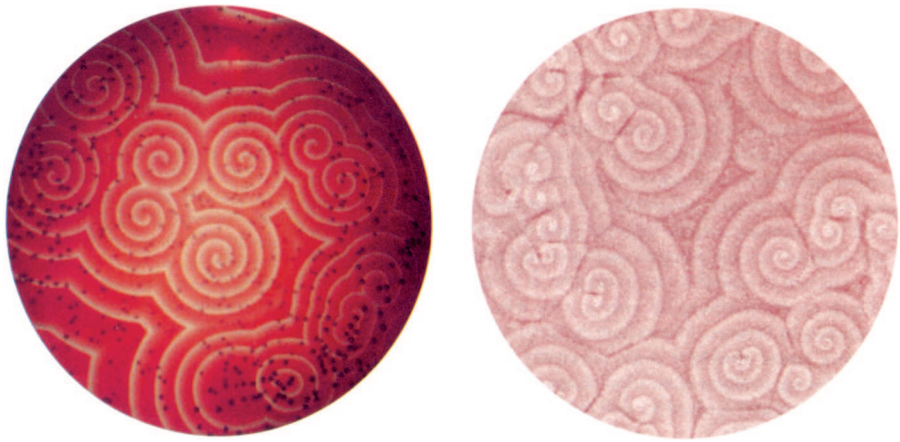

Fig. 1. Spiral waves in the Belousov–Zhabotinsky reaction (*Left*) and in *D. discoideum* (*Right*).

What is most impressive about the study of Kastrup *et al.* (1) is that by combining the power of microfluidic technology (9) with nonlinear chemical dynamics, they are able to model multiple aspects of a system as complex as hemostasis and make and test detailed predictions about the behavior of that system. Their approach is a modular one. They identify, separately model, and then link three processes crucial to clotting: autocatalytic production of activators, simple (linear) consumption of activators, and formation of a clot at sufficiently high activator concentration. By replacing the 80 or so reactions of the actual hemostasis process (10) with three key chemical reactions—(*i*) the autocatalytic chlorite–thiosulfate reaction, which generates the "activator" H^+, (*ii*) the pH-controlled gelling ("clotting") of alginic acid, and (*iii*) the photoisomerization of 2-nitrobenzaldehyde to create patches of "clotting stimuli"—the authors are able to generate a remarkably accurate replica of actual clotting behavior. They focus on the issue of thresholds for clotting. How large an insult is required to initiate a clot? Experiments on the chemical model predict not only the minimum size necessary for a single patch of "clotting stimulus" to generate a "clot" but also that multiple subthreshold patches whose total area exceeds the threshold will not cause clotting unless they are sufficiently close together to form an effective single patch. The authors then test their predictions on preparations of blood plasma and obtain not only qualitative confirmation but also semiquantitative accuracy in predicting the threshold size of patches in plasma by using scaling arguments and the known diffusion coefficient of thrombin. It is shown that clotting is highly sensitive to the spatial distribution of tissue factor, whereas knowing only the total amount of this clotting stimulus in the experiment is not sufficient to predict whether clotting will occur. This result may have profound implications for relating results of biochemical experiments, typically done under homogeneous conditions, to coagulation. One of the key insights of nonlinear chemical dynamics is that average concentrations are insufficient to predict the behavior of nonlinear reaction–diffusion systems. Spatial information is essential (11).

In an earlier investigation (12), the same group used their chemical model to suggest novel design principles that may have governed the evolution of the vascular system's geometry. Can one hope to obtain even more insight from models such as these? Could they, for example, guide us in designing improved diagnostic methods and therapies for clotting diseases or recipes for blood substitutes? Clearly, questions of bio-

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compatibility come into play as one seeks applications to real biological systems, but the possibilities are intriguing. By combining the modular approach to analyzing complex biological systems with an understanding of nonlinear chemical dynamics and a mastery of microfluidic technology, we may now hope to construct fruitful chemical models in the not too distant future for such complex processes as photosynthesis, respiration, development, and apoptosis.

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