Unstable Trigger Waves Induce Various Intricate Dynamic Regimes in a Reaction-Diffusion System of Blood Clotting

E. S. Lobanova[1] and F. I. Ataullakhanov[1,2]

[1]*Physics Department, Moscow State University, Moscow, 119899 Russia*

[2]*National Research Center for Hematology, Russian Academy of Medical Sciences, Moscow, 125167 Russia*

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In this work we demonstrate that the unstable trigger waves, connecting stable and unstable spatially uniform steady states, can create intricate dynamic regimes in one-dimensional three-component reaction-diffusion model describing blood clotting. Among the most interesting regimes are the composite and replicating waves running at a constant velocity. The front part of the running composite wave remains constant, while its rear part oscillates in a complex manner. The rear part of the running replicating wave periodically gives rise to new daughter waves, which propagate in the direction opposite the parent wave. The domain of these intricate regimes in parameter space lies in the region of monostability near the region of bistability.

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One of the well known solutions of one-dimensional reaction-diffusion models is a trigger wave. It is found in the models describing the bistable media with two stable spatially uniform steady states separated by the unstable spatially uniform steady state. A trigger wave propagates without changing its shape at a constant velocity switching medium between two stable states, called upper and lower states. The parameter values of the model determine whether the medium is switched from the lower into the upper state (the on wave), or from the upper into the lower state (the off wave). The on and off waves can coexist for certain parameter values and could be triggered by setting appropriate initial conditions [1]. In some models one of the stable steady states can lose its stability and continue to exist as an unstable state. Such models, with one stable and two unstable homogeneous steady states, can have solutions in the form of the unstable trigger waves connecting the stable and unstable steady states. In the Gray-Scott (GS) model the trigger waves of this kind can induce spatiotemporal chaos in the region of finite size [2]. While studying the reaction-diffusion model (1), originally constructed to describe blood clotting, we found that the unstable trigger wave can give rise not only to the chaotic behavior but also to the replicating waves as well as to the spatially localized waves, with a complicated waveform.

The biochemical pathway of blood clotting consists of the enzymatic cascade with several positive and negative feedbacks. This pathway cannot be described by the traditional model of active medium containing two variables: the activator and the inhibitor. The results of our previous studies led us to propose that blood should be viewed as active medium of a special kind [3,4]. The unique feature of this medium is that a self-sustained thrombin wave, which forms a solid fibrin clot, travels over a finite distance. This is critically important for normal clotting because the clot must remain localized at the site of injury. Normally, in other active media self-sustained waves propagate with a constant speed and amplitude up to the boundaries. To describe the blood clotting pathway we used the system of eleven equations [5,6]. When reduced, it led to a three-component set of equations (1) of the reaction-diffusion type [7], which we called the blood clotting (BC) model:

$$\begin{aligned}\frac{\partial u_1}{\partial t} &= D\frac{\partial^2 u_1}{\partial x^2} + K_1 u_1 u_2 (1-u_1)\frac{(1+K_2 u_1)}{(1+K_3 u_3)} - u_1,\\ \frac{\partial u_2}{\partial t} &= D\frac{\partial^2 u_2}{\partial x^2} + u_1 - K_4 u_2,\\ \frac{\partial u_3}{\partial t} &= D\frac{\partial^2 u_3}{\partial x^2} + K_5 u_1^2 - K_6 u_3.\end{aligned} \tag{1}$$

It contains three key variables that correspond to the concentrations of some proteins involved in blood clotting, and by analogy with traditional models can be called the activator (u_1) and the inhibitor (u_3), while u_2 is a new variable—the catalyst of the u_1 production. The chemical part of model (1) contains six parameters K_1–K_6. Model analysis has revealed that it exhibits several new regimes, which have not been observed in the reaction-diffusion systems seen thus far. Such regimes are likely to exist in various complex systems and, therefore, may be of interest to the researchers studying different active media.

For the numerical analysis of model (1) we replaced the partial differential equations with the difference equations and integrated them over a segment $0 \le x \le L$ for fixed values of four parameters ($K_1 = 6.85$, $K_3 = 2.36$, $K_4 = 0.1$, $K_5 = 14$) and of the diffusion coefficient ($D = 1$), with no-flux boundary conditions using a simple explicit finite difference scheme with spatial step $h = 0.25$ and temporal step $\tau = 0.01$. Only two parameters, K_2 and K_6, which describe the generation of the activator and the inactivation of the inhibitor, respectively, were

varied. These two parameters are the key determinants of the model dynamics because their variations allow obtaining all major characteristic regimes. The diffusion coefficients for all variables are assumed to be equal because the molecular weights of the enzymes corresponding to the main model variables are similar. The variations of the diffusion coefficients (up to 10%) in all three equations have shown that the observed dynamic modes continue to exist, but at slightly different parameters.

Figure 1 shows the results of mapping various regimes in the (K_2, K_6) parameter plane of Eqs. (1). Domain I is the region of spatially localized constant-amplitude pulses running at a constant velocity (autowaves, horizontal hatching). Domain II is the region of pulses running with periodically oscillating amplitude (oscillating autowaves). The value of the pulse's velocity is approximately constant. Standing spatially localized structures (peaks) are observed in domains III (vertical hatching) and IV. The peaks remain still in domain III but oscillate in domain IV. Domain V is the region of bistability, in which the solutions are in the form of the trigger waves. The large domain VI is the region of complex dynamic modes induced by the unstable on waves. Stable modes I–V are also known in other models of active media [1,8–11]. Therefore we focus on the results of detail examination of the intricate dynamic modes detected in domain VI.

To analyze solutions in the form of stationary waves moving with constant velocity c, we solved the ordinary differential equations derived from Eqs. (1) for the coordinate system moving with velocity c. By switching to the moving coordinate system we found in domain VI solutions in the form of unstable on waves. They connect the lower stable [trivial $(0, 0, 0)$] and the upper unstable spatially uniform steady states.

In subdomain VI*a* we distinguish two types of waves, both of which we call the composite waves. The waves of type I are found throughout subdomain VI*a* excluding the narrow zone at its bottom. This wave propagates from the site of activation at the boundary [Fig. 2(a)] [12]. The front part of the wave remains unchanged and runs at a constant velocity, whereas its rear part oscillates aperiodically in a complex manner. Initially, the rear part propagates slower than the front part, leading to the wave broadening, but later the broadening stops. In the coordinate system moving with the velocity of the leading wave, the total width of the leading wave oscillates around some average value. The farther the parameter points in the (K_2, K_6) plane from the domain of bistability, the narrower the width of the leading wave. The front part of the leading wave and its velocity [Fig. 2(a)] accurately coincide with the characteristics of unstable trigger on waves calculated for the same parameters [see Fig. 2(b)]. The pulses arising behind the leading wave of type I tend to develop into the secondary waves that are similar to the parent wave. The secondary waves propagate in the opposite direction and give birth to the tertiary waves, and so on. The arising numerous waves can either annihilate or fuse together. The fusion sites become the

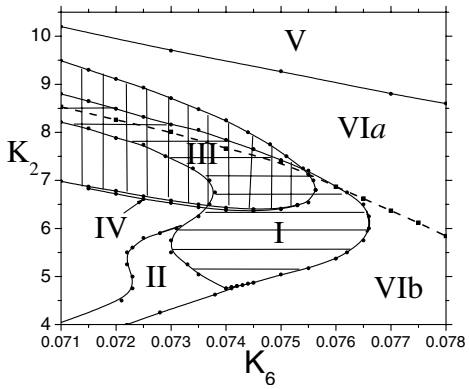

FIG. 1. Regions of the stable regimes in the (K_2, K_6) parameter plane (see text for details).

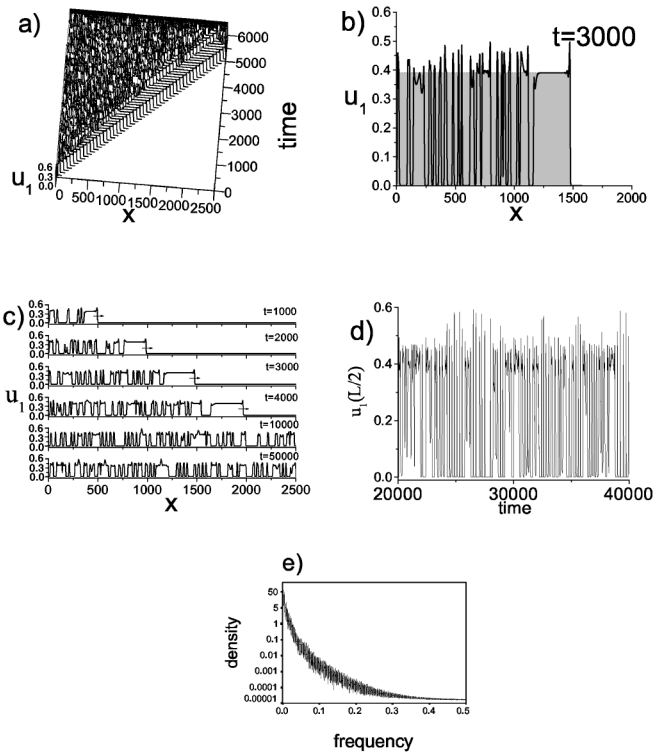

FIG. 2. Formation of the type I composite wave with the aperiodically oscillating rear part in response to a local rise in activator concentration at the end of the segment for $K_2 = 8.15$ and $K_6 = 0.075$. (a) Time series of the profiles for the activator. (b) Profile of the unstable trigger on wave shown along with the profile of the composite wave shown in (a) at $t = 3000$. (c) Snapshots of the dynamic pictures at indicated times. (d) Oscillations of the first variable in the center of the segment. (e) The example of the power spectrum for oscillations of activator concentration in the center of the segment.

foci for the birth of the new waves. On reaching the segment boundary the leading wave breaks down, resulting in the dynamic picture, which varies continuously in a complex manner. The interacting waves fill up the entire region [see Fig. 2(c); $t = 10\,000, 50\,000$) and give rise to oscillations of the variables in each point of space [Fig. 2(d)]. These oscillations have a broadband power spectrum [Fig. 2(e)], suggesting that their behavior is chaotic. This suggestion agrees well with the finding that at large times this dynamic regime is sensitive to perturbations imposed on the system: when we compared evolution of the temporal patterns of two equivalent systems we found that a minor initial perturbation in one of the systems resulted in their local exponential divergence with the largest Lyapunov exponent $\cong 5$ (not shown).

The model analysis has also revealed the existence of the second type of composite wave [12], which is produced by the unstable trigger wave in a narrow zone at the bottom of subdomain VI*a* [Fig. 3(a)]. As for the type I wave, the front part of the type II wave remains unchanged and coincides very accurately with the front part of the unstable on wave [Fig. 3(b)]. But, unlike the type I waves, the rear part of type II waves oscillates periodically. Since both types of waves contain two parts, the constant front part and the oscillating (periodically or aperiodically) rear part, we collectively call them the composite waves.

Figure 4(a) shows the regime, which is observed in subdomain VI*b* [12] and appears to be different from the composite waves. The secondary (daughter) wave is born in the rear part of the propagating parent wave. Gradually, it grows into a wave identical to the parent wave but running in the opposite direction. The parent wave gives birth to the new wave repeatedly, and its replica daughter waves also replicate themselves regularly. When two replicating waves collide, they annihilate each other [Fig. 4(b); compare $t = 1430$ and $t = 1500$] if they are well developed and run with only slightly varying profiles. However, if one of the two colliding waves is less well developed than the other, they merge and form a new wave of the parent type [Fig. 4(b); compare $t = 820$ and $t = 920$]. If both colliding waves are not well developed, they merge and form two waves moving in opposite directions [Fig. 4(b); compare $t = 1160$ and $t = 1250$). Gradually, the traveling replicating waves fill up the entire segment, causing the chaotic changes in variables at every point in space [the example of the power spectrum for oscillations in the center of the segment is shown in Fig. 4(c)]. As for the composite waves, the front part and the velocity of the replicating waves are very similar

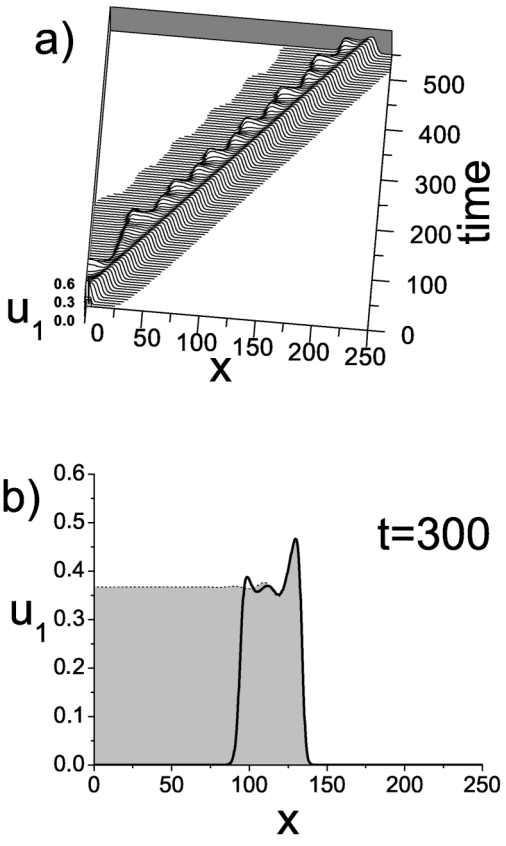

FIG. 3. Formation of the type II composite wave with the periodically oscillating rear part in response to a local rise in the activator concentration at the end of the segment for $K_2 = 7.6$ and $K_6 = 0.075$. (a) Time series of the profiles for the activator u_1 variable. (b) Profiles of the unstable trigger waves shown along with the profiles of the composite wave shown in (a) at $t = 300$.

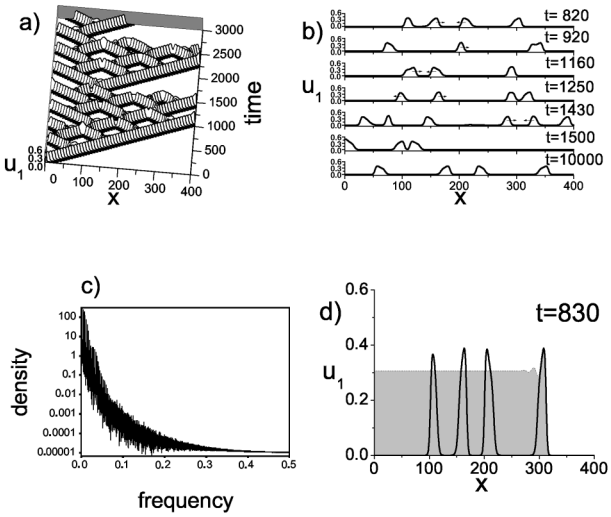

FIG. 4. Replicating waves in domain VI*b* for $K_2 = 6.0$ and $K_6 = 0.077$. (a) Time series of the profiles for the activator u_1. (b) Snapshots of the replication dynamics at different times. (c) The example of the power spectrum for oscillations of activator concentration in the center of the segment. (d) Profiles of the unstable trigger waves shown along with the profiles of the replicating wave shown in (a) at $t = 830$.

to those of the unstable on waves calculated for the same parameter values [see Fig. 4(d)].

It is noteworthy that the front part of the unstable trigger wave connecting the stable lower and the unstable upper spatially uniform steady states in the model (1) can be viewed as an essential component of the described dynamic regimes, and the front parts and velocities of the composite and replicating waves coincide very accurately with those of the unstable trigger waves. In other words, the unstable trigger waves can manifest themselves in direct simulations of the model (1) in the form of different dynamic regimes: they induce chaos at some parameters, give birth to replication dynamics at others, or they may exist in the form of spatially localized waves.

The trigger waves as part of spatiotemporal chaotic profiles were previously observed by other researchers in the GS model [2] and the model of catalytic CO oxidation on the platinum [13]. The same type of chaos we have found in the BC model (1) in the case of composite waves of the first type. In several models of active media were described self-replicating pulses with different dynamic behaviors (see [14,15] for classification). Replicating standing and propagating pulses were found in the GS model [16]; complicated replication of the oscillating pulses was observed in the Prague model [15]. Replication of breathing pulses was described in the Bonhoffer–van der Pol model [14]. Although the number of such examples is growing, the bifurcation mechanisms responsible for the self-replicating behavior remain poorly understood. In the so far best studied GS model, the replication dynamics is viewed as a transient process, which takes place near the hierarchically organized structure of fold bifurcations of multipulse solutions [16]. By examining the dynamic regimes arising in the BC model (1) we have established another bifurcation mechanism that causes replicating waves. The replicating waves in the BC model are the front parts of unstable trigger waves existing at these parameters. Since self-replicating dynamic regimes have also been observed in other models, it would be interesting to examine whether a similar bifurcation mechanism is also responsible for their dynamic properties.

Since model (1) has been obtained by reducing the full model of the blood clotting pathway, the uncovered dynamic regimes, in addition to their theoretical value, bear direct consequence in predicting various anomalies in blood clotting. These predictions can be tested in a recently developed experimental system for the *in vitro* study of the dynamics of blood clotting [17]. In order to observe the predicted regimes, the system parameters have to be changed so that the system is shifted close to the region of bistability. This boundary can be reached by increasing the value of either parameter K_2 or K_6. They correspond to the combinations of the reaction constants and concentrations of the precursors of blood clotting factors [7]. Therefore, K_2 and K_6 can be varied experimentally by changing the precursor's concentrations. We hope that such studies will help to shed light on the origin and treatment of different blood clotting pathologies, including the disseminated intravascular coagulation (DIC) syndrome.

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[12] See EPAPS Document No. E-PRLTAO-91-035336 for video files showing intricate dynamic regimes presented in Figs. 2(a), 3(a), and 4(a). A direct link to this document may be found in the online article's HTML reference section. The document may also be reached via the EPAPS homepage (http://www.aip.org/pubservs/epaps.html) or from ftp.aip.org in the directory /epaps/. See the EPAPS homepage for more information.
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