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SPATIAL ASPECTS OF THE DYNAMICS OF BLOOD CLOTTING — II. PHENOMENOLOGICAL MODEL*

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The dynamics of the processes of structuring on blood clotting was investigated within a reaction–diffusion model based on current biochemical ideas. Analysis of the model shows that the mechanism of structuring in the blood fundamentally differs from the widely known mechanism discovered by Turing. It is shown that on clotting the blood behaves like a specific active medium of a new type in which the spatial structures form as a result of interaction of two concentration autowaves.

The possibility of formation of steady spatial structure in reaction–diffusion systems was first predicted by Turing in 1952 [1]. Later, it was shown theoretically that regular space–time structures may also form as spreading waves in such systems [2–4]. Such structures in the form of concentric and helical waves were discovered in the Belousov–Zhabotinskii chemical system [5, 6]. Then similar waves were also detected in populations of so-called "social" amoeba, *Dictyostelium discoideum* [7], in heart tissue [8], in individual cells [9] and some other systems commonly called active media. Recently, the steady structures predicted by Turing were also discovered in a real chemical system [10, 11].

Study of systems in which the effects of spatial or space–time self-organization have been observed shows that they all have similar principles of their kinetic arrangement [12–14]. Theoretical methods developed in connection with the solution of the problems of structuring [15, 16], in essence, generalize the known methods of non-linear dynamics [17–19] making up the current theory of dissipative structures — synergetics.

Analysis of current ideas on the blood clotting system showed that the biochemical kinetics of the coagulation processes has a number of features characteristic of active media governing the formation in them of space–time structures. The investigation presented in this paper of a mathematical model shows that the blood-clotting system possesses the necessary properties for forming localized and space–time dissipative structures in human blood. It turns out that the formation of these structures must follow a mechanism fundamentally different from that proposed by Turing. Investigation of this mechanism suggests that the blood represents a highly specific active medium of a new type in which structuring is the result of the interaction of spreading autowaves.

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MATHEMATICAL MODEL

The dynamics of the blood-clotting system is determined by the production and distribution in space of substances of two types: clotting factors and factors impeding clotting [20–22]. In real blood vessels clotting is activated by the factors released at the site of damage. These factors trigger a cascade of biochemical reactions, leading to the appearance of thrombin. The cascade is encompassed by positive feedback loops [23]. After activation, as shown by experiments *in vitro* in systems with total mixing, the kinetics of rise in the concentration of thrombin is of an explosive, self-accelerating exponential character [22, 25]. Activation of clotting occurs in a distinctly marked threshold manner [24, 25]. The subthreshold concentrations of activating factors in practice do not lead to the formation of thrombin.

The exponential growth of thrombin in time after activation gives way to an equally sharp drop linked with the appearance in the blood of thrombin inhibitors and factors impeding its production — anticoagulation factors [26]. Some components of the inhibitory system as, for example, protein C are enzymes, the activation of which is triggered directly by thrombin. As a result, the appearance in the plasma of high thrombin concentrations causes activation of the reactions blocking its production proper [27].

As is known from the general theory of active media, in reaction–diffusion systems with a self-accelerating character of point kinetics non-linear sustained, self-supported waves may exist — autowaves whose characteristics depend not on the mode of their initiation but on the kinetic arrangement of the system proper [12–15]. In line with this, the exponentiality of the kinetics of rise in the concentration of thrombin at each point and its diffusion make possible the autowave spread of thrombin in space. This means that in the blood the process of activation of clotting will spread in the form of fronts of non-linear self-sustained concentration thrombin autowaves. The propagation of the thrombin autowave ensures the movement of the front of polymerization of fibrin, that in itself controls the growth of the fibrin clot in the blood.

The fibrin clots (thrombi) formed in real blood represent spatially localized formations. In all active media studied to date, the autowaves spread without waning right up to the natural spatial boundaries of the system. In our concept this means that the clotting system ensures not only the appearance and spread of the thrombin autowave in the blood but also its arrest. Confinement of the distance of spread of the thrombin autowave is due, in our view, to the character of the kinetics of the reactions ensuring blocking of thrombin synthesis after it reaches its maximum value. A key role, as shown by analysis of the biochemical data, must be played by those reactions triggered by thrombin itself.

The mechanisms of the reactions ensuring the production of anticlotting factors have not been fully studied and, therefore, in this work we confine ourselves to a simplified mathematical model. It describes the kinetics of production and diffusion in space of only two factors: the clotting factor — thrombin — and a factor impeding clotting such as protein C. The model assumes that synthesis of the anticlotting factor is triggered by thrombin and is of an autocatalytic threshold character.

The mathematical model reduces to the equations:

$$\frac{\partial \theta}{\partial t} = \frac{\alpha \theta^2}{\theta + \theta_0} - \chi_1 \theta - \gamma \theta \varphi + D_1 \Delta \theta \tag{1}$$

$$\frac{\partial \varphi}{\partial t} = \beta \theta (1 - \varphi / C)[1 + (\varphi/\varphi_0)^2] - \chi_2 \varphi + D_2 \Delta \varphi \tag{2}$$

where Δ is the Laplace operator, $\theta \equiv \theta(\vec{r}, t)$ is the concentration of the key clotting factor — thrombin, $\varphi \equiv \varphi(\vec{r}, t)$ is the concentration of the anticlotting factor at the point of the system with the coordinates $\vec{r} = (x, y, z)$ at the moment of time t. The coefficients χ_1 and χ_2 reflect the passive leakages of the corresponding substances, α and β determine the rates of production of thrombin and the anticlotting factor respectively, γ reflects the influence of the anticlotting factor on decrease in the thrombin concentration, C characterizes the limiting concentration of the blood anticlotting factor, and D_1 and D_2 are diffusion coefficients. The magnitude θ_0 $\chi_1/(\alpha - \chi_1)$ corresponds to the threshold concentration of thrombin. In other words, the model allows for the fact that clotting, a threshold process, is triggered only if the initial stimulus is strong enough.

Simple analysis shows that the zero spatially uniform steady state of the system is stable in relation to minor perturbations. However, if as a result of fluctuation or stimulation from without in a certain region of space the thrombin concentration exceeds the threshold value, the thrombin autowave may form in the system. Using the known methods [28, 29] from equation (1) for the speed of the thrombin front, we obtain the evaluation:

$$v \sim 2\sqrt{\alpha D_1} \tag{3}$$

At each point through which the thrombin front passes, a rise in the thrombin concentration, as may be seen from equation (2), releases the explosive self-accelerating production of the anticlotting factor. This, in particular, makes possible the spread of the latter in space in an autowave manner. This can be simply demonstrated strictly mathematically. In fact equation (2), if one regards θ as a parameter in it, belongs in its form to a well-studied class of equations with bistable kinetics which, as is well known, permit solution in the form of an autowave [29]. From equation (2), it may also be seen that the wave of the anticlotting factor can spread only in the region in which the thrombin concentration is sufficiently high, i.e. where the thrombin wave had already passed.

To determine the speed of the second wave and the character of its interaction with the first, we made computer calculations. In a segment with a straight line of length $L = 1.5$ mm with impermeable boundary conditions, we examined the behaviour of the system (1)–(2) initially present in its stable steady state: $\theta_{st}(\vec{r}) = 0$, $\varphi_{st}(\vec{r}) = 0$. The wave was initiated by a local rise in the concentration of thrombin close to the left boundary. The calculations were based on the Euler scheme [30]. The parameters of the model used for numerical integration are given in Table 1. The evaluations of the parameters are based on work on the biochemistry and kinetics of coagulation processes [20–23].

Investigation of the mathematical model showed that, for sufficiently high values of the parameter $\theta_0 > 2.4$ characterizing the value of the threshold, in the coagulation system there is realized a regime in which the thrombin wave is at first formed from the initial perturbation

Table 1. Values of the parameters used in the mathematical model.

α, min^{-1}	β, min^{-1}	γ, min^{-1} nM^{-1}	θ_0, nM	φ_0, nM
2.0	0.0015	5.0	3.0	0.005
C, nM	χ_1, min^{-1}	χ_2,ii‡RçS 2[çS		
5.0	0.05	0.35	10^{-7}	10^{-7}

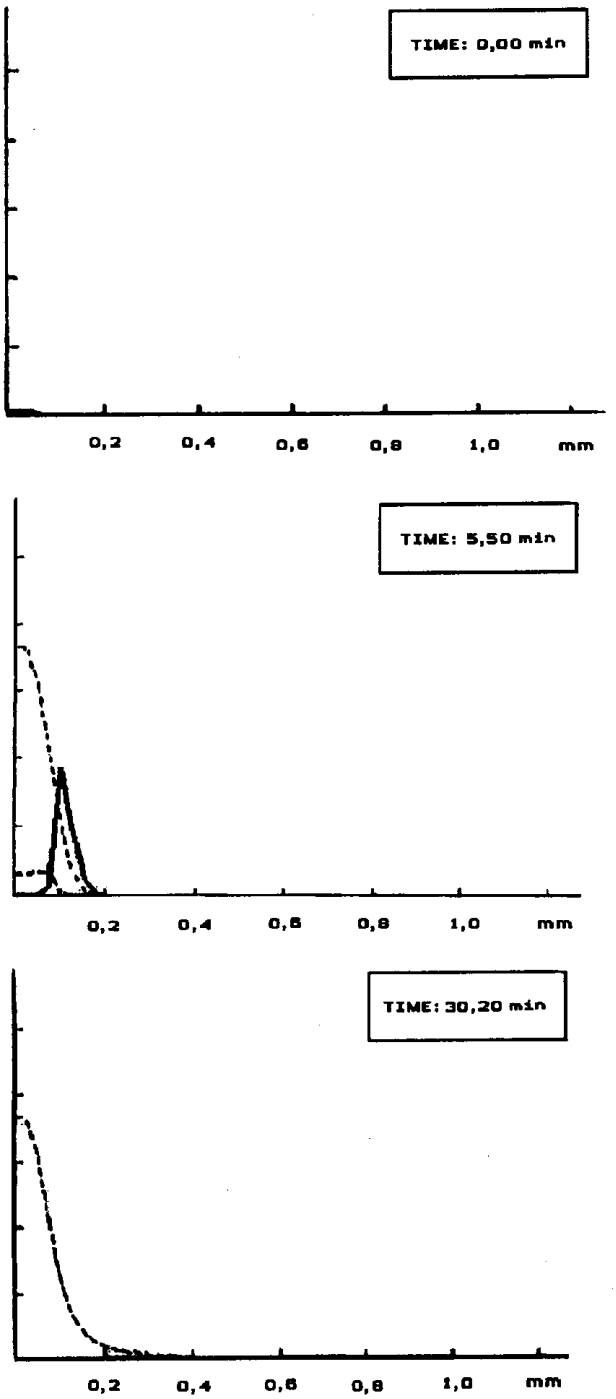

Fig. 1. Successive stages in the formation of the localized fibrin clot. Here and hereafter the continuous line shows concentration of thrombin, the bold broken line the concentration of the anticlotting factor and the thin broken line the distribution of fibrin. The calculations were made for the value of the parameter $\theta_0 = 3.0$. The values of the other parameters concur with those given in Table 1.

and, after a certain time, the anticlotting wave starts in its wake. The latter spreading at first quicker than the first wave as it approaches the leading edge appreciably weakens the thrombin wave in amplitude, so that at a certain moment the space distribution of thrombin everywhere is subthreshold. Then the thrombin wave and with it also the anticlotting wave themselves die away (Fig. 1). Experimentally this ought to correspond to the formation, in the region where the thrombin wave passed, of a solid clot with radius coinciding with the distance of spread of this wave.

Calculations show that change in the form of the initial pulse within wide limits insignificantly alters the distance of spread of the clotting wave. In other words, the size of the thrombus formed is determined not by the initial conditions but by the properties of equations (1)–(2) themselves, reflecting the kinetic structure of the system. In this sense the distance of spread of the wave, that is, the size of the clot, appears as an internal intrinsic characteristic of the system — its autoscale.

The numerical experiment reveals that, as a result of diffusion of the anticlotting factor into the region directly surrounding the clot formed, the clotting capacity is suppressed there. It is restored only a long time after the disappearance of the thrombin wave, so that the model considered describes the ability of the system to form a non-clotting zone, "liquid" zone around clots of finite size.

As well as describing the formation of a localized thrombus, the numerical investigation made also predicts the possibility of formation of other spatially regular structures. Thus, with fall in the parameter θ_0 below a defined value $\theta_0 < 2.3$ (in the range of values $\theta_0 > 1.3$) the behaviour of the system changes qualitatively. The second wave overtaking the first weakens it by several order in amplitude (and as a consequence weakens itself). However, this "weakened" low-amplitude thrombin wave still remains above threshold and continues to spread moving away from the solid clot formed in it backwards. By virtue of its low-amplitude nature this wave does not cause any appreciable blood clotting. When it moves from the primary clot over a distance of the order of its radius the influence of the anticlotting factor practically disappears. The thrombin wave begins to grow fast in amplitude, producing local clotting at the new site (Fig. 2).

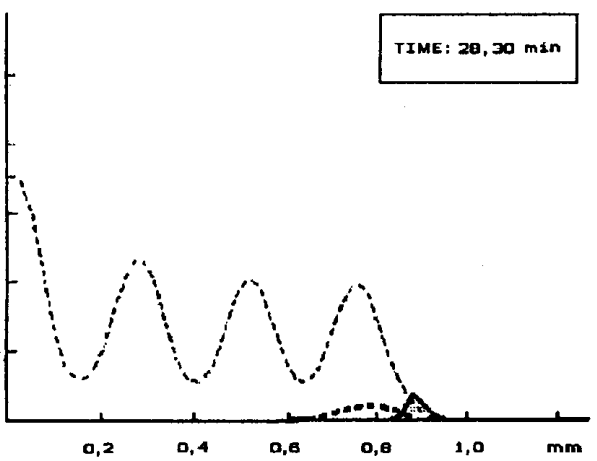

Fig. 2. Spatial-regular structure formed as successively appearing fibrin clots ($\theta_0 = 1.5$).

At the moment when the amplitude of the thrombin wave reaches a critical value at which the local concentration of the anticlotting factor exceeds the value φ_0, the anticlotting wave begins to form. The latter generated at the point of the thrombin maximum begins to spread both forwards and back splitting the thrombin "mound" into two parts. The anticlotting wave moving ahead overtaking the thrombin wave front sharply weakens it, but does not finally extinguish it. The previously described train of events is again repeated. Experimentally this must correspond to the case when as a result, after a second clot is formed, a third, then a fourth and so on (Fig. 2). In the two-dimensional case this would correspond to the formation of a system of concentric rings of polymerized blood.

The fate of the waves moving backwards is worth noting. It turns out that for some values of the parameters ($1.3 < \theta_0 < 1.8$) the backwave of the anticlotting factor overtakes the residue of the thrombin mound moving back and weakens it to subthreshold level (Fig. 2). Then both waves die out.

For values $1.9 < \theta_0 < 2.3$ in the numerical experiment we observe a distinctive effect of the echo type. The anticlotting wave is not able to suppress to the subthreshold value the amplitude of the thrombin maximum moving back (Fig. 3). And remaining transthreshold, it continues to move in low-amplitude form through the "non-clotting" zone gradually passing from the zone of the influence of the anticlotting factor. After the maximum of this wave has passed through the zone of diminished clotting, its amplitude begins to grow again. The amplitude of this backwave reaches its absolute maximum exactly at the point where it had already been. The thrombin wave for the first time appears in this zone coming from the opposite side. If in the zone reached by the echo, polymerization of fibrin had earlier not been complete, then with the arrival of the return echo-like wave the process of polymerization continues (Fig. 3).

Finally, it was found that when the threshold in relation to clotting is very low ($\theta_0 < 1.2$) the spatial pattern of blood clotting is determined by the following wave regime (Fig. 4). After local initiation of clotting, as usual, a thrombin wave of large amplitude forms causing the formation of the first clot. Then the wave of the anticlotting factor following it forms. The latter overtaking the first weakens but does not extinguish it. However, the low-amplitude

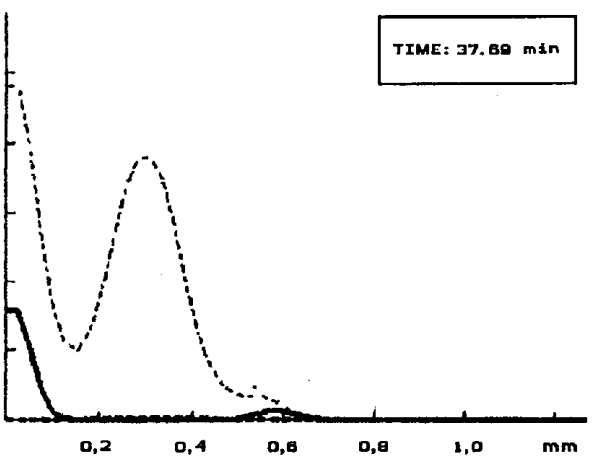

Fig. 3. Sequence of fibrin clots formed in the presence of an effect of the echo type ($\theta_0 = 2.2$).

thrombin wave henceforth never increases to amplitudes comparable with those occurring on formation of the primary clot. Undergoing periodic dying oscillations it passes to the steady propagation regime (Fig. 4). The low-amplitude wave of the anticlotting factor moves following it at the same speed.

This regime would correspond in the experiment to the rapid formation in the blood of a solid well-polymerized central clot and a zone slowly growing around it in which the degree of polymerization of fibrin is low. This zone gradually expands to the natural boundaries. The moving polymerization front behaves in this case exactly in the same way as the well-studied autowaves in active media [14, 31]. The speed of this front is an automodel variable depending not on the initial conditions but only on the intrinsic internal kinetics of the system.

DISCUSSION OF RESULTS

The theoretical analysis made of the kinetic arrangement of the clotting system showed that human blood offers all the necessary conditions for the formation both of localized and spatially regular dissipative structures. From our analysis it follows that the formation of these structures must occur by an essentially wave mechanism differing from the previously known mechanisms of structuring.

Outwardly the formation in the initially uniform medium of spatially ordered structures through the sequential generation one after the other of new structural elements resembles the growth of Liesiegang rings [32], although the mechanisms of these processes have nothing in common [33]. Nor can the strict successive spatial ordering in which new structural elements appear at a certain distance from those already formed be described in terms of the Turing theory [1]. This theory assumes that the conditions of structuring resulting from instability are total, i.e. uniform at all points of the system considered. Because of such transcritical bifurcation the generation of structures according to Turing may occur everywhere in space simultaneously, i.e. parallel in different parts of the system. In principle, it is not possible to

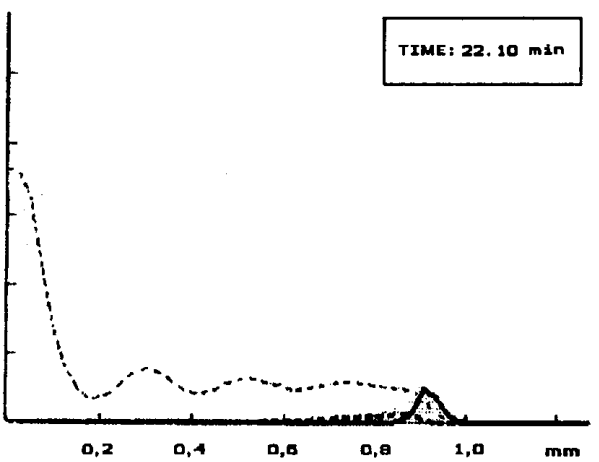

Fig. 4. Central well-polymerized clot formed and the zone successively forming around it with a low degree of polymerization ($\theta_0 = 0.5$).

describe the formation in an initially uniform unbounded system of localized dissipative structures of a finite size of the spheroidal clot type.

Investigation of the precritical bifurcations in reaction–diffusion systems showed that the growth of the spatial patterns occurs through division of the structural blocks already formed outwardly resembling cell division [34–36]. In contrast, in the system considered a regular spatial structure must be formed through addition of newly appearing structural elements to those earlier formed.

On formation in the system considered of localized dissipative structures (Fig. 1) to which in the experiment would correspond clots of finite dimensions, we, in essence, are dealing with a new unusual phenomenon when the finite size of the object depends not on the mode of initiation but on the kinetic arrangement of the system proper. In this sense the size of the clot is a typical inherent characteristic of the system — its internal scale (autoscale), i.e. a characteristic similar to the natural frequency of the auto-oscillations and the speed of the autowaves in known active media. In analysing the clotting system we thus came up against a new autocharacterization of non-equilibrium media — the distance of the spread of the wave.

We would note that not only the size of the clot but all other spatial scales of the structures in the system considered such as the thickness of the zone with diminished clotting capacity and widths of the rings formed do not depend on the mode of initiation of clotting. Therefore, it would be pertinent to call the phenomenon discovered a whole autoscaling.

The mechanism of structuring considered by us is sufficient for a mathematical description both of finite solitary objects of the clot type and successively formed concentric rings. Within this mechanism blood acts as a medium in the clotting dynamics of which two coupled self-accelerating threshold processes prove crucial. Because of this thrombus formation represents a kind of essentially biautowave process.

The general physicomathematical theory of such essentially biautocatalytic, biautowave media has not yet been developed. This is evidently connected with the fact that in all active media studied so far in detail only one variable has always acted as autocatalytic [12–14, 37–39]. As shown by investigation of the model proposed by us, an essentially biautocatalytic system has a number of new unexpected features.

(1) The presence in the active media of previously studied types of one autocatalytic variable predetermines the possibility of complete exhaustion of the resources of the system over the whole space. There is no self-limitation in these media. The waves and fronts formed in them spread to natural boundaries (such also is the actual situation in systems with branched chain reactions controlling the processes of combustion and explosion [37–40]).

Biautocatalyticity in the system considered by us determines the behaviour of the thrombin and anticlotting waves as independent when the distance between their fronts is large. The result of convergence of the fronts is that the waves become mutually dependent and evolve in the same way as they perish in coupled form. As a result objects of finite dimensions may form, i.e. an autonomous process self-limited in space may be realized.

(2) Unlike traditional uniform active media in which reduced excitability (refractoriness) is detected only behind the spreading front, in the system considered by us the mechanisms of braking of the wave are capable of ensuring reduction in clotting capacity also immediately before the thrombin front, i.e. a kind of "frontal" refractoriness. By virtue of this in the system considered we must have some sort of "repulsion" (slowing) of the fronts spreading towards each other and not their annihilation as occurs in active media of known types [12, 14].

(3) Analysis of the models showed that in the spatially uniform system considered by us the effect of generation of a return autowave of the echo type might operate. Such an effect [41] in active media known to date may occur only in the presence of spatial heterogeneity.

The above arguments show that in terms of the theory of self-organization blood may be regarded as an active medium of a fundamentally new type in which the formation of spatially dissipative structures must be ensured by essentially autowave mechanisms.

From the medical standpoint the task of investigating the mechanisms of the functioning of the blood-clotting system is exceptionally topical. We would merely note the well-known syndrome of disseminated intravascular clotting appearing in many pathological processes [42, 43]. We feel that the nature of this process is directly linked with the biwave mechanism of blood clotting.

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