Biophysics 1971 Vol. 16 No. 3 pp. 500–506.

BIOPHYSICS OF COMPLEX SYSTEMS. MATHEMATICAL MODELS

MULTIBARRIER IMMUNITY

A. M. MOLCHANOV

Institute of Applied Mathematics, U.S.S.R. Academy of Sciences, Moscow
Institute of Biological Physics, U.S.S.R. Academy of Sciences, Pushchino (Moscow Region)

(*Received* 15 *June* 1970)

The general kinetic patterns of the course of immune processes have been considered. A close analogy with physical and biochemical oscillatory processes has been discerned. The conditions are indicated in which the kinetics of immune processes is of an auto-oscillatory character.

1. LEADING PROCESSES OF MULTIBARRIER IMMUNITY

THE kinetic model [1] of immunity is constructed on the assumption of the spontaneous course of the following processes. *A*. Multiplication of the infectious principle. *B*. Reproduction of the immune agents. *C*. Interaction of the infectious principle with the immune. *D*. Spontaneous death of the immune agents.

Denoting by x the number of microbes and by y the number of immune agents it is possible to write the differential equations describing the time course of the immune process as a whole:

$$\frac{dx}{dt} = A(x) - C(x, y),$$
$$\frac{dy}{dt} = B(x) - C(x, y) - D(y). \tag{1}$$

Immune phenomena even for their most intense development correspond in fact to very minor changes in the body as a whole. Therefore, it is possible in some respects—however, by no means not all—to confine oneself to simple assumptions corresponding to the scheme of linearization of the system close to the equilibrium position.

This primarily applies to process *A* which it suffices to describe within the frames of a crude approximation corresponding to the "law of mass action":

$$A(x) = \alpha x. \tag{2}$$

* Biofizika **16**: No. 3, 482–487, 1971.

The parameter α sets the tempo of multiplication of the infectious principle in the given "medium"—the body studied—and characterizes the reciprocal property of infection and the medium.

A quite similar assumption must be made concerning process D:

$$D(y)=\varepsilon y . \tag{3}$$

However, the coefficient ε is deliberately noted by the letter, traditionally reserved for designating small values. It must be assumed that the tempo of spontaneous death of immune agents is small, otherwise there would be no immune process at all.

A somewhat more precise assumption must be adopted for describing the mechanism

$$C(x, y)=\gamma(x)y . \tag{4}$$

As the base as before, we take the "law of mass action" (number of destroyed microbes is proportional to the number of immune factors present) although it is necessary to take in mind the fall in the efficiency of the immune principle at low concentrations x

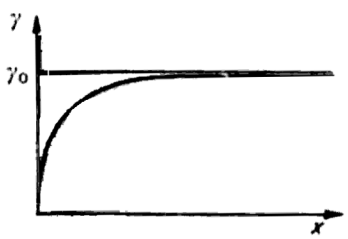

FIG. 1

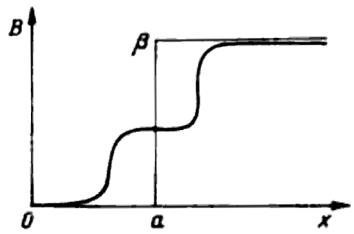

FIG. 2

FIG. 1. Effectiveness of immune principle $\gamma(x)$ tends to zero for vanishing concentrations x and to arrive at the limiting value γ_0 with shortening of the "enemy search time".

FIG. 2. Power of immune protection B. Broken line $O\alpha\beta$ corresponds to "disrupted interpretation" in the sense of the all or none principle. Two-stepped model would give better approximation of this "two-barrier" immunity.

associated with reduction in the "probability of encounter". It is natural to assume the existence of limiting efficiency γ_0 which corresponds to the "immediate" inclusion In the struggle of each newly appearing immune agent (Fig. 1).

The main role in the model proposed is played by the description of the process B. In the mechanism of the reproduction of immune agents the body acts as a single whole with substantial non-linear characteristics of biological systems. The immune process is very complex. It includes the work of certain receptors tracking the level of the infectious danger and effector organs producing different types of immune agents. An important role is played by the nervous system, humoral regulation, the specific and nonspecific reaction of the cells of the lymphoid series, the incorporation of various tissue barriers. The complete and detailed allowance for all these factors is impossible. Fortunately, it is not necessary for the problem posed. All these systems in the problem of immunity are of interest to us only from the point of view of their contribution to

the production of immune agents. It is therefore possible to speak simply of the "immune protection" and measure its intensity in certain general arbitrary units, for example, in killing strength (Fig. 2).

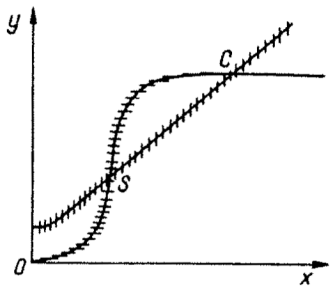

FIG. 3. Isoclines "zero" and "infinity". Steady points O, S and C.

The main assumption—the dependence of B only on x—corresponds to the hypothesis of the ideal work of all tracking and controlling systems which actuate the next "echelon" of protection as soon as the need arises. This of course is an idealized concept but it allows us to draw important conclusions on the character of the course of immune processes.

2. PHASIC PORTRAIT OF THE ONE-BARRIER IMMUNITY

In the mathematical analysis of the model an important role is played by two curves, One of them "isocline zero" is determined by the equation:

$$B(x)-C(x,y)-D(y)=0\,. \tag{5}$$

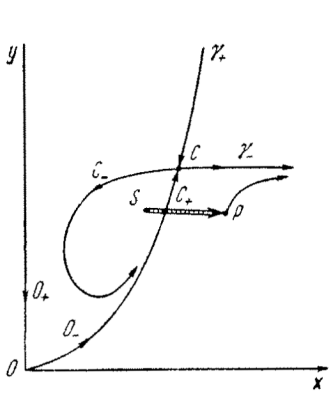

FIG. 4

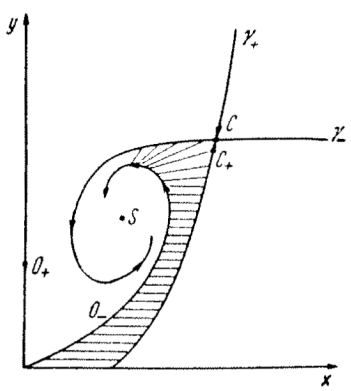

FIG. 5

FIG. 4. Between separatrices O_- and O_+ is the region of non-sterile immunity. All the trajectories extend to the stable point S. Infection SP throwing the body through separatrix C_+ will lead to death.

FIG. 5. Increase in "safety margin" of immunity with shift in separatrix O_- within region encompassed by the separatrix C_+.

Above this line the number of immune agents diminishes and below it increases. In Fig. 3 this line is denoted by a horizontal hatching.

The "isocline in infinity" (vertical hatching)

$$A(x)-C(x, y)=0 \tag{6}$$

plays a similar role but now in relation to the infectious principle. The right of this line is "good" for the microbes and left of it is "poor". Intersection of these two lines de-

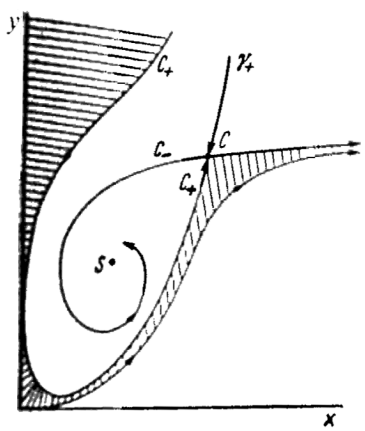

FIG. 6

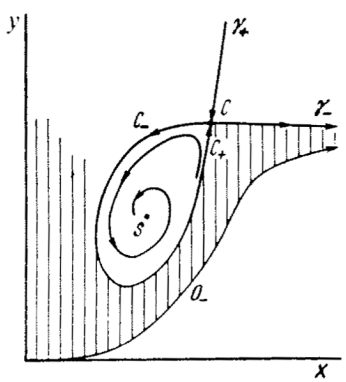

FIG. 7

FIG. 6. Latent period—region between O_+ and C_+ (shaded region on left) and progressive disease for region between C_+ and O_-) leading to death—movement of O_- and γ_- (shaded region on right).

FIG. 7. Moment of generation of unstable limiting cycle of loop of separatrices.

termines the steady points S and C. The two integral curves ${}_+\gamma$ and C_+ enter the critical point C (saddle) (entry separatrices). There are also two exit separatrices C_- and γ_-.

The structure of the field of the integral curves—the phasic portrait of the system—is determined by the reciprocal position of the steady points and the behaviour of the separatrices (see also Fig. 10). The most important types of kinetics are depicted in Figs. 4-9. Particularly important are the critical (transition) situations arising on coincidence of the separatrix C_+ with O_- (Fig. 4) or with C_- (Fig. 7).

3. SPECIAL FEATURES OF MULTIBARRIER IMMUNITY

The main feature of the multibarrier immunity is the presence of the several steady points. This sharply increases the number of possible types and course of immune processes. Thus, for example, already in the simplest case of a two-barrier immunity three saddle points are possible between which are located two steady points of the focus type. Such a situation appears if in Fig. 2 we draw the "isocline infinity" which intersects the "isocline zero" at five points (Fig. 10).

As we have seen from the example of one-barrier immunity the "switching" of the types of behaviour occurs at the moment of fusion of one of the emerging separatrices

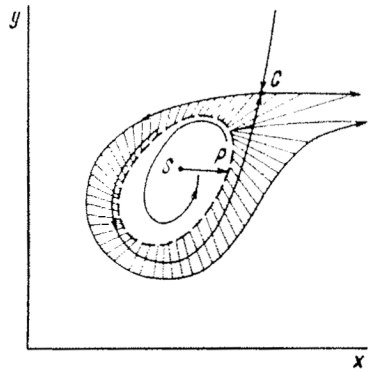

FIG. 8

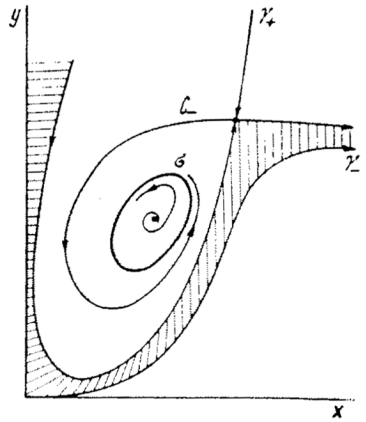

FIG. 9

FIG. 8. "Islet of health" within unstable limiting cycle covering the stable point S. The segment SP gives the limiting value of the permissible dose of infection.

FIG. 9. Stable mode corresponds to periodic inclusion and exclusion of immune protection—movement over stable limiting cycle δ. In other respects the picture is quite similar to that in Fig. 6.

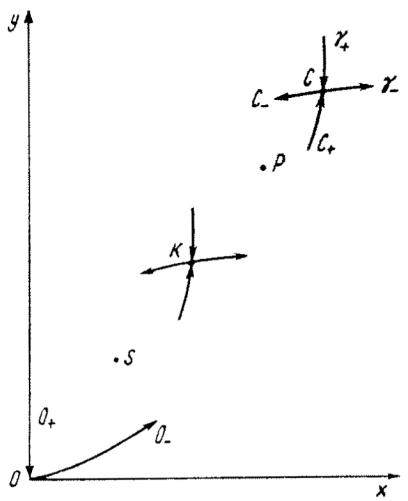

FIG. 10

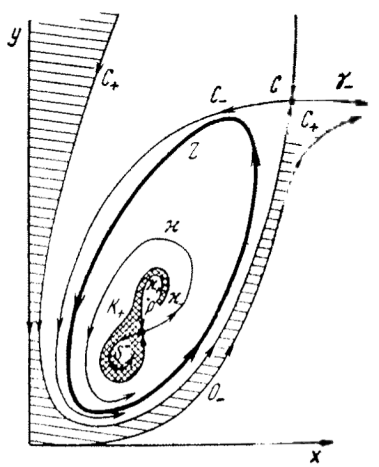

FIG. 11

FIG. 10. Relative position of separatrices of saddle points O, K and C determines the structure of the field, the integral curves and the picture of the immune process.

FIG. 11. Curves beginning within separatrix C_+ "wind" to the limiting cycle Z. Thin strip between separatrices K_+ and κ_+ "winds" to stable focus S.

with one of the incoming. The two-barrier immunity has seven "switching" separatrices. In all, it has ten separatrices but three of them (O_+, γ_- and γ_+) have no inflience on the qualitative picture. The enumeration of all the possibilities and even more so, their analysis does not come within the scope of the present work.

However, one of the types of the course of the process is of fundamental interest became of the deep biological meaning of the regimes appearing. We shall consider the critical point in space of the parameters to which corresponds the coincidence of the separatrices C_- and C_+ forming a single loop embracing the points C, K and P. We shall shift a small parameter in such a way that on "splitting" of the separatrices the line C_- just passes above C_+ in the region where C_+ enters the point C. It is not difficult to show that with such a shift of the loop C_- C_+ generates a stable limiting cycle Z, embracing the steady points S, K and P (Fig. 11).

If in addition the point P is unstable and point S is stable, then the picture obtained causes involuntary association with the chronic course of the disease. A small region of self-recovery bounded by the separatrix K is little stable. A small dose of infection throws the body from the point S to the region where the development of the disease takes the system to the limiting cycle Z. The temporary improvements corresponding to the passage of part of the cycle lying to the left of point S alternate with considerably more prolonged periods of deterioration. Particularly dangerous (and prolonged) is stay of the system in the environs of the critical point C. A small dose of infection (or a certain weakening of the overstrained immune protection) suffices for the system to enter the destructive zone behind the separatrix C_+.

4. COMPARISON WITH EXPERIMENT

The model discussed demonstrates the considerable diversity of the types of behaviour. It is therefore necessary to treat the already existing statistical data and particularly the directed design of the experiment in animals in order to classify the types of immunity. Theoretical analysis shows that strategy and tactics of treatment decisively depend on the character of the course of the immune process.

It is therefore desirable to make a radical simplification of the model to obtain the simplest quantitative characteristics. The most convenient model of such a kind is the "discontinuous interpretation" of the one-barrier immunity:

$$\begin{aligned} \dot{x} &= \alpha x \gamma y , \\ \dot{y} &= \beta(x) - \gamma y , \end{aligned} \tag{7}$$

where the function $\beta(x)$ is discontinuous

$$\beta(x) = \begin{cases} 0 & x \leqslant a \\ \beta & x > a . \end{cases} \tag{8}$$

Detailed quantitative analysis of this model forms the theme of a separate publication. Here we shall confine ourselves to a note on the number of important parameters in the model. Formally, it includes four parameters α, β, γ and a. However, by scale transformation the number of parameters can be reduced to two:

$$\frac{d\xi}{dt} = \alpha\xi - \eta , \tag{9}$$

$$\frac{d\eta}{dt}=\beta(\xi)-\eta\,,$$

where the function $\beta(\xi)$ is "stepped".

$$\beta(\xi)=\begin{cases}0 & \xi\leqslant 1\\ \beta & \beta>1\,.\end{cases} \tag{10}$$

The simplest quantitative classification of the forms of immunity may be based on this model.

In conclusion, we would note that the epidemiological aspect of the problem has a long history of mathematic modelling.

The author is grateful to Ye. Ye. Sel'kov who sought out the old paper of Lotka [2]. The author is grateful to Academician of Medical Sciences V. R. Levin and Doctor of Biological Sciences, S. E. Schnol' for useful discussion of the general problem of immunity. Very stimulating was the friendly discussion of the work in the Central Institute of Tuberculosis, U.S.S.R. Ministry of Health on 9 January 1970.

REFERENCES

1. **MOLCHANOV, A. M.**, Kinet. mod. immunit. (Kinetic Model of Immunity). Preprint of IPM, 1970
2. **LOTKA, A. J.**, Elements of Physical Biology, Baltimore, 1925