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BIOPHYSICS OF COMPLEX SYSTEMS. MATHEMATICAL MODELS

ANALYSIS OF THE MODEL OF SINGLE-BARRIER IMMUNITY*

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An investigation has been made on the types of dynamic behaviour of the elementary model of single-barrier immunity considered in [1, 2]. A formula has been derived for evaluating the stability margin of non-sterile immunity.

1. NORMALIZING OF THE SYSTEM OR REDUCTION TO THE INHERENT TIMES AND SCALES

WE SHALL consider a set of differential equations describing simple single-barrier immunity [2]:

$$\dot{\tilde{X}} = \tilde{\alpha}\tilde{X} - \gamma_1 \tilde{Y},$$
$$\dot{\tilde{Y}} = \tilde{\beta}(\tilde{X}) - \gamma_2 \tilde{Y}, \qquad (1)$$

where $\tilde{X}$—amount of the infectious principle; $\tilde{Y}$—amount of immune factor; $\tilde{\alpha}, \gamma_1, \gamma_2$—coefficients characterizing the multiplication and loss of the infectious principle and death of the immune factor; $\tilde{\beta}(\tilde{X})$—immune force of the body depending on the critical value $\tilde{X}$.

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Two main assumptions are made on $\beta(\tilde{X})$: the existence of the critical value $\tilde{X}=a$ when immune protection is actuated and the stepped pattern of the immune protection:

$$\tilde{\beta}(\tilde{X})=\begin{cases}0 & \tilde{X}\leqslant a \\ \tilde{\beta} & \tilde{X}>a\end{cases}. \tag{2}$$

We shall reduce system (1) to inherent times and scales. Dividing both equations by γ_2 and introducing the new time $\tau=\gamma_2 t$ we reduce the time to the scale in which as time unit we take the depletion of the immune force by e time. The scale for X and Y is so chosen that the critical value of infection is equal to unity and the coefficient for Y in the first equation is also unity.

In sum, we obtain a system with two parameters α and β

$$\begin{aligned}\dot{X}&=\alpha X-Y,\\ \dot{Y}&=\beta(X)-Y.\end{aligned} \tag{3}$$

The phase plane (X, Y) of the system (3) is divided into two parts: for X from 0 to 1—the zone of excluded immunity and for $X\geqslant 1$—the zone of included immunity.

The behaviour of the system will depend on the value of the dimensionless parameters α and β. The curves on this plane separating the zones with uniform dynamic behaviour form the "structural portrait" of the system in the plane (X, Y) for the given values of the parameters.

We know nothing beforehand about the value of the parameters α and β and therefore we shall investigate all the parametric plane. The value α is determined not only by the infectious principle but depends on the medium and it is quite possible that α for the same infectious principle may strongly differ. It may be assumed that the actual values of α and β will be close to unity. Herein lies one of the main advantages of systems reduced to inherent times and characteristic scales.

2. STRUCTURAL AND PHASE PORTRAITS OF THE SYSTEM

We shall investigate the system (3), it has one or three equilibrium points, the boundary is the condition $\alpha=\beta$. We shall denote the equilibrium points by O, S and C. It is possible to verify that the points O and C are saddles, the point S may be either a focus or a centre [3].

It is easy to show that the slope of the separatrices of the saddles is equal to $K=0$ and $K=1+\alpha$. We shall denote the separatrices entering the saddle by the sign $(+)$ and those emerging by the sign $(-)$ with the corresponding letter of the saddle. We shall be interested in the relative position of the separatrices $(C_+, C_-\ O_+, O_-)$.

We shall begin with the case of the maximum degeneration when the separatrix C_+ coincides with O_- and the separatrix C_- with O_+. The condition for coincidence for the separatrices C_- and O_+ is $\beta=1+\alpha$ and for O_- and C_+, $\beta=\alpha\ (1+\alpha)$. In the structural portrait (Fig. 1) the point of maximum degeneration is $\alpha=1$, $\beta=2$.

The lines $\beta=1+\alpha$ and $\beta=\alpha(1+\alpha)$ are the boundaries where the change of the order of passage of the separatrices occurs. In the structural portrait we shall draw a further line of neutrality $\alpha=1$ for the point S.

We shall obtain the breakdown of the structural portrait into zones (Fig. 1) with uniform dynamic behaviour. The whole system has seven main types of phase portraits.

It should be noted that in the system two types of recovery are possible: sterile, when the infectious principle is completely suppressed and non-sterile, when equilibrium is set

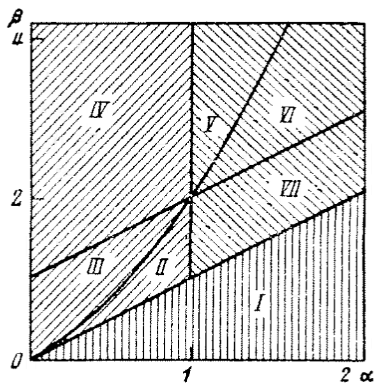

FIG. 1. Structural portrait of system: I–VII—zones of main types of dynamic behaviour.

up between the synthesis of immune protection and the multiplication of the microbes and, finally, a third outcome is possible when the system does not cope with the infection.

In our system sterile immunity corresponds to the negative values of X, this occurs because of the failure to allow for the inversion to zero of y_1 for small values of X.

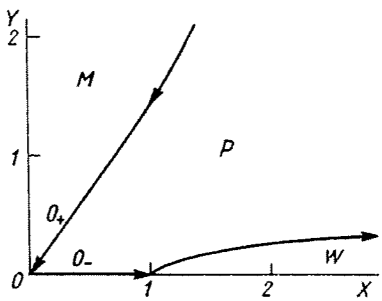

FIG. 2

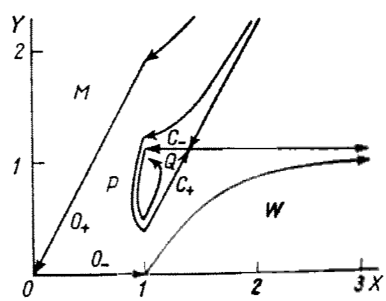

FIG. 3

FIG. 2. Phase portrait of system for $\alpha = 0{\cdot}8$, $\beta = 0{\cdot}4$ (zone I). P—main zone of course of illness (unstable), M—zone of sterile immunity; W—zone of absolute instability.

FIG. 3. Phase portrait of system for $\alpha = 0{\cdot}8$, $\beta = 1{\cdot}12$ (zone II). The appearance of the region of sterile immunity Q is characteristic.

Figure 2 shows the phase portrait for the zone I: it has one steady point O. The Figure shows that the system in this zone of parameters is quite unstable, and separatrices O_+ and O_- form the region P. This portrait has regions of sterile immunity M and absolute instability W characteristic of all the phase portraits and the entry into these regions is due either to the large store of immunity or to the very heavy initial infection.

The zone II has the phase portrait shown in Fig. 3. The zone is located together with III and IV in that part of the plane where $\alpha < 1$ and there are three equilibrium points. Figure 2 shows that in the region of instability P, a region of non-sterile immunity Q appears formed by the separatrix C_+ and characterized by the store of resistance in relation to the infection.

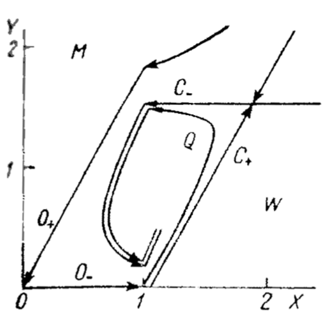

FIG. 4

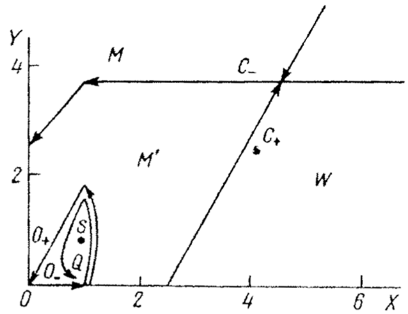

FIG. 5

FIG. 4. Phase portrait of system for $\alpha = 0{\cdot}8$; $\beta = 1{\cdot}5$ (zone III). The region P is ousted by the region Q.
FIG. 5. Phase portrait of system for $\alpha = 0{\cdot}8$, $\beta = 3{\cdot}6$ (zone IV); M'—region of sterile immunity.

Figure 4 presents the phase portrait for the zone III. It will be seen that the unstable region P is ousted by the region of non-sterile immunity Q and the store of resistance increases. From Fig. 5 for the phase portrait of zone IV it will be seen that the region

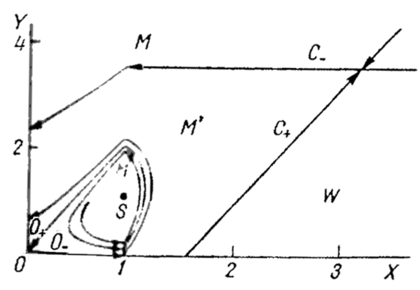

FIG. 6

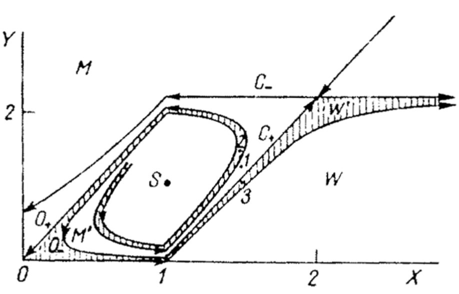

FIG. 7

FIG. 6. Phase portrait of system for $\alpha = 1{\cdot}1$, $\beta = 3{\cdot}6$ (zone V). Region M' ousts region Q.
FIG. 7. Phase portrait of system for $\alpha = 1{\cdot}1$, $\beta = 2{\cdot}25$ (zone VI). W'—region of instability.

of non-sterile immunity is surrounded by a region of sterile immunity M which increases like the store of resistances with rise in β.

For $\alpha > 1$ we move from the zone IV to V. The zones V, VI and VII lie in that part of the plane where the point S is unstable.

For $\alpha = 1$ the separatrix O_- coincides with the separatrix O_+ which corresponds to the neutrality of the point S and the presence of closed integral curves within the loop of the separatrices.

For $\alpha > 1$ the separatrix O_- shifts to the outside while the separatrix O_+ runs into the saddle unwinding from the point S and the region of non-sterile immunity Q is converted to the sterile immunity M' (Fig. 6).

With fall in β we pass to the zone VI, of most interest in its dynamic behaviour (Fig. 7).

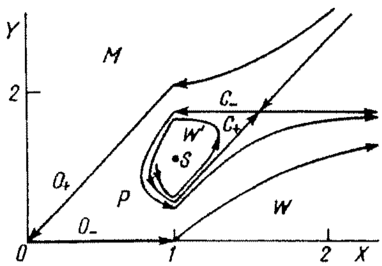

Fig. 8. Phase portrait of system for $\alpha = 1{\cdot}1$, $\beta = 1{\cdot}75$ (zone VII). The predominance of the regions of instability P and W' is characteristic.

In this case the separatrix C_- overrides the separatrix O_+ running from the point S and produces a flux of self-recovery M'. The separatrix O_- overrides C_+ running from the same point S, producing a flux with a fatal outcome W'.

The phase portrait of the zone VII (Fig. 8) is characterized by the fact that the separatrices O_+ and O_- override separatrix C_- and produce a fatal flux P. The separatrix C_- in turn forces C_+ to unwind from the point S producing the fatal flux W'.

To compare the phase portraits with a region of non-sterile immunity it is desirable to obtain a quantitative evaluation of resistance.

We present the formula

$$s = \frac{\beta - \alpha}{\alpha(1+\alpha)} . \tag{4}$$

This formula determines the store of resistance in relation to infections in zones III and IV.

For the zone II we shall write the following formula:

$$s = \frac{2\alpha^2 + \alpha - \beta}{\alpha(1+\alpha)} , \tag{5}$$

which represents the distance from the point S to the separatrix C_+ in the direction X.

It should be noted that these formulae are meaningfull for $\alpha \leqslant 1$. For $\alpha > 1$ the point S becomes unstable and therefore in this case there is no point in speaking of the resistance store.

DISCUSSION

From the phase portraits considered it will be seen that the immune protection of the body may be of an oscillatory character and oscillations may be decaying and unstable. The dying oscillations lead to non-sterile immunity while the unstable may lead both to death and sterile immunity. Incorrect treatment may result in relapses. For example, if we give a drug at point *1* (Fig. 7) where there are many microbes and a good level of the immune factor (in which self-recovery is possible) then we may enter point *2* from which the patient comes into the zone of relative health but then after a certain time, the disease is again exacerbated (point *3*).

In conclusion, it should be noted that the model considered does not give a complete description of immunity in view of the complexity of the process (see multi-barrier pattern [2]) although some types may be described by the model presented on the basis of which it is possible to choose a definite strategy and tactic of treatment.

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