

BIOPHYSICS OF COMPLEX SYSTEMS. MATHEMATICAL MODELS

ENDOGENOUS BIOCHEMICAL FLUCTUATIONS AS THE POSSIBLE BASIS OF PHYSIOLOGICAL RHYTHMS*

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It is shown that the period of auto-oscillations may be sensitive to minor changes in the parameters of the biochemical system, for example, the activity of a key enzyme. An assumption is advanced on the possibility of evolutionary fixation in circadian rhythms of the properties of such critical endogenous oscillatory systems.

INTRODUCTION

THE literature, now voluminous [1], concerned with the biological clock and its mathematical models discusses the problem of evolutionary origin of biological rhythm. Circadian rhythms (considered as forced) are contrasted [2] with endogenous. It is considered almost axiomatic that these rhythms are of a different nature. It is implicitly assumed that the tremendous differences in the periods—days for circadian rhythms and fractions of a second for metabolic—automatically preclude even the posing of the problem of their generality.

Nevertheless, serious biological and mathematical grounds exist for discussing the problem of the evolutionary secondary nature of the circadian rhythms produced in the main by the daily periodicity of the light flux. However, photosynthesis appeared without any doubt in evolution considerably later than the other metabolic systems (for example, glycolytic). These systems had their own rhythms in no way connected with astronomical phenomena. It is, therefore, natural to suppose that circadian fluctuations appeared on the basis of the already existing endogenous rhythmic patterns. But if qualitatively such arguments are realistic then the quantitative gap

$$N = \frac{1 \text{ day}}{1 \text{ second}} = 86,400,$$

which separates the metabolic and circadian rhythms appears unbridgable. For most known physical phenomena or technical devices such a quantitative difference implies a different nature of the fluctuation.

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The aim of the present paper is to show that the biochemical systems may embrace tremendous frequency ranges (or amplitudes) on the basis of a single mechanism by a small change in its parameters. At the level of the organism a good illustration may be afforded by the organs of vision and hearing. The cause, mathematically speaking, consists in the fundamental non-linearity of biological and, in particular, biochemical systems.

2. MODEL OF THE GLYCOLYTIC SYSTEM

The author of [3] constructed a mathematical model of the glycolytic system. With certain simplifying assumptions the set of differential equations describing the kinetics of glycolysis has the form:

$$\left. \begin{aligned} \frac{dx}{dt} &= \beta - xy^2 \\ \frac{dy}{dt} &= xy^2 - y \end{aligned} \right\} \quad (1)$$

This set was numerically investigated with a computer with an acceptable accuracy (taking into account the approximate nature of the model). However, theoretical analysis was made only as a linear approximation and the qualitative picture was erroneously sketched. (The authors of the present paper (under whose guidance the work of Ye. Ye. Sel'kov was carried out) also bear responsibility for this. The error in the main is corrected in the article submitted for the attention of the reader. A more detailed publication is planned.) Yet the full analysis of the set (1) is highly instructive. It has a direct bearing on the theme under discussion on the relationship between endogenous and circadian rhythms. The most important aspect of this analysis is study of the system as a whole. This feature psychologically sharply conflicts with the usual practice of investigating physical systems when it suffices to study the small periphery of the steady state. The root of the error mentioned, we would note in parenthesis, lies in the habit of local investigation.

3. SPECIAL POINTS "TO INFINITY"

The phasic portrait of the system as a whole is more graphically depicted not in the initial variables but in variables similar to those of Poincare:

$$\left. \begin{aligned} \xi &= \frac{x}{1+x^2+y^2} \\ \eta &= \frac{y}{1+x^2+y^2} \end{aligned} \right\} \quad (2)$$

reflecting the whole plane (x, y) on a single circle of the plane (ξ, η) . For our purpose it suffices to consider a semi-circle since the trajectories beginning in the upper semi-plane are entirely accomodated in it. Below them the solution "is forbidden":

$$y=0, \quad (3)$$

which our system has.

In the semi-circle $\eta \gg 0$ the system studied has five special points (Fig. 1). One of them, point *F*, corresponding to the steady state,

$$\left. \begin{aligned} \beta - xy^2 = 0 \\ xy^2 - y = 0 \end{aligned} \right\}, \tag{4}$$

is located within the semi-circle and the others are at the boundary. The merit of Poincaré's variables is that these boundary special points become "clearly visible". In the initial variables it is easy to find only the steady point *F*:

$$\left. \begin{aligned} x = \frac{1}{\beta} \\ y = \beta \end{aligned} \right\}, \tag{5}$$

while the others are infinitely removed. Yet the kinetics of the system is determined by the structure precisely of these points.

The result of investigation of these points, the details of which we shall omit, is presented in Fig. 1. The infinitely removed special points retain their type for all values of the parameter β . As against this, the point *F* corresponding to the steady state and stable for $\beta > 1$ loses stability when β passes through the "linear" critical value.

$$\beta = 1. \tag{6}$$

As β at the top approaches unity the steady state becomes ever less stable. At the critical point there is "mild" generation of an auto-oscillatory regime—in this sense we are dealing with the "linear" critical value. The limiting cycle is generated with a zero

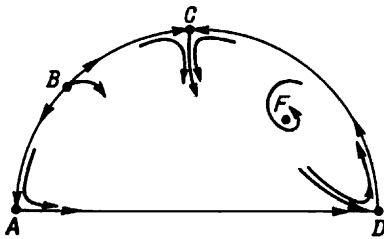


FIG. 1

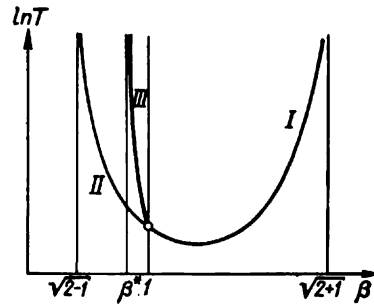


FIG. 2

FIG. 1. Special points in Poincaré semi-circle. For $\beta > 1$ steady point *F* is stable.

FIG. 2. Dependence on logarithmic scale of various periods on the parameter β : *I*—period of linearized fluctuations close to stable steady state; *II*—same for unstable state (for $\beta < 1$); *III*—period of auto-oscillations.

amplitude and "inherits" the period of low linear oscillation—the so-called characteristic time of the system. With rise in the amplitude of the auto-oscillations the difference between the period of the limiting cycle and the "characteristic time" of the system increases (Fig. 2).

It is therefore understandable that the very term "characteristic time" of the system is quite inapt in such situations since it is characteristic only of a certain small periphery of the steady (now unstable) state.

4. CRITICAL NON-LINEAR STATE

Numerical methods allow us to investigate the behaviour of the limiting cycle in relation to β immediately after generation of the auto-oscillatory state. (The communication by L. M. Kogan, L. V. Lunevskaya, A. M. Molchanov and Ye. Ye. Sel'kov was

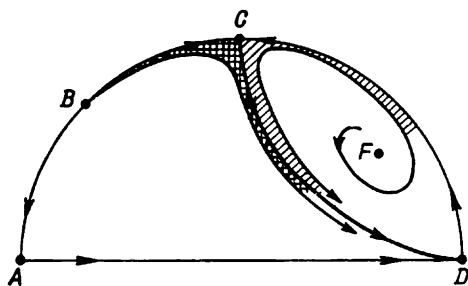


FIG. 3

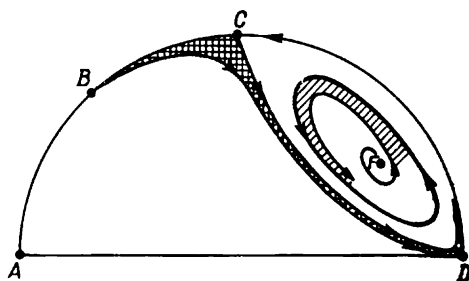


FIG. 4

FIG. 3. Separatrices form semi-stable limiting cycle "bull's eye" to use the terminology of Poincaré.

FIG. 4. Formation of limiting cycle on rupture of loop of separatrices.

presented to the Scientific Council of the Institute of Biological Physics, U.S.S.R. Academy of Sciences in Pushchino in 1970. The authors are grateful to G. A. Oskov for assistance.) However, direct numerical count very rapidly becomes impossible because of the sudden increase (with reduction in β) in the period and amplitude of the auto-oscillations. The need arises for theoretical analysis of the situation. This analysis reveals the existence of a further "non-linear" critical value of the parameter

$$\beta = \beta^*, \quad (7)$$

determined by the condition of fusion of two separatrices. One of them, CN , passes out of the saddle C and separates the flux coming from the node B from the flux occurring in the loop CD . The second separatrix MD separates the incoming and traversing curves in the vicinity of the complex special point—the saddle node D .

The fusion of the separatrices corresponds to the "equilibrium" of the two fluxes. The flux from B is wholly poured into D . The flux from the unstable focus F fills the loop CD twisting from within towards the semi-stable limiting cycle composed of the two separatrices. One begins in C and ends in D and the other is entirely accommodated in infinity—begins in D and ends in C . This remarkable situation is depicted in Fig. 3.

Change in the parameter β shifts the equilibrium. Small increase in this parameter leads to "flow" within the loop CD of a fine jet of the flux B . It "ousts" the flux F from the vicinity of the point D . The limiting cycle appears which is greater the closer the value of β to the critical (Fig. 4).

Reduction in β leads to the opposite effect. The flux F "breaks through" behind the separatrix flowing into D and discharges entirely into this special point. The closer

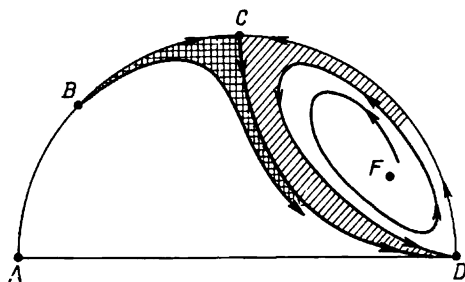


FIG. 5. Flux F ousts trajectories of flux B from loop CD .

β to β^* the more revolutions do the curves of the flux F perform before rushing to D . However, this is only a reminder of the destructive limiting cycle which no longer exists for $\beta < \beta^*$ (Fig. 5).

Numerical search for the critical value β^* represents a difficult problem of calculation consisting, in particular, in the search for the asymptotic resolutions of the separatrices of the points C and D . In addition, the instability of the count "from saddle to saddle" makes it necessary to resort to special procedures of calculation.

Nevertheless, in principle the critical value $\beta = \beta^*$ is similar to the "linear" critical value $\beta = 1$ in that they both determine the boundaries of stability of the steady states. The first relates to the limiting cycle and the second to the steady point. And both are therefore the roots of the equation

$$\operatorname{Re} \lambda(\beta) = 0, \quad (8)$$

where $\lambda(\beta)$ —inherent value determining the small fluctuations close to the steady state.

However, the stability of the steady point is determined by investigation of the algebraic equation. This property is local. Stability of the limiting cycle leads to study of the integral equations. This property is global. It is clear that such problems, typical apparently of biochemical systems, are more interesting, more difficult and more varied.

CONCLUSIONS

The example discussed illustrates the important feature of biochemical systems—sharp dependence of the characteristics of an auto-oscillatory state on the parameters of the system. Thus, for example, the period of auto-oscillations T has time to change from 2π to ∞ :

$$2\pi < T < +\infty,$$

with reduction in β from the first ("linear") critical value to the second ("non-linear")

$$1 > \beta > \beta^*.$$

The calculations show that β^* differs only by tens of percentages,

$$\beta^* \approx 0.9,$$

from unity—"the linear" critical value. Of course, not every non-linear system possesses such striking lability of the period. The system studied has a special individual feature—it belongs to the class of non-crude systems. One of its special points (namely D) for all values of the parameter β remains a complex special point—a saddle node—not breaking down into a saddle and a node. Practically any refinement of this undoubtedly approximate model will unfailingly lead to such breakdown. Of course, the period of the auto-oscillatory system is also stabilized—the variability will no longer be so sharp.

The system discussed is a particular case of a considerably wider class of "flow" systems:

$$\left. \begin{aligned} \frac{dx}{dt} &= S(x, y) - A(x, y) \\ \frac{dy}{dt} &= A(x, y) - P(x, y) \end{aligned} \right\} \quad (9)$$

These equations describe the kinetics of the following events. From the outside (and in the context of the present study it is not important to know from where and how) the flux S of the "substrate of the reaction x " is directed into the system. Then the "mechanism A of converting x to a semi-manufactured product" is actuated. Finally, the substance y is converted by the "mechanism P " into a certain "whole product" the nature and fate of which is of no interest to us. It, in particular, may coincide with y and the mechanism P (in this case) is the mechanism of release of the product from the system.

In our particular case

$$\left. \begin{aligned} S &= \beta \\ A &= xy^2 \\ P &= y \end{aligned} \right\} \quad (10)$$

This system well illustrates the general thesis [4] on the "difficult conditions" as the cause of the appearance of auto-oscillations. In this case the auto-oscillations appear when the system is "put on a hunger ration". In the system is "embodied" the competitive contradiction between the mechanisms A and P each of which requires the "semi-manufactured product" y but the mechanism A processes this compound while its flux P is taken out of the system. In addition, the "quadratic" mechanism A is stronger than the "linear" mechanism P at high concentrations of y and at low, on the other hand, P is stronger than A .

As a result, for large ($\beta > 1$) fluxes of the substrate, the mechanism A has time to "work up" a sufficient amount of y both for itself and for P . The system operates in the steady state.

Small ($\beta < 1$) fluxes of S are a different matter. It is necessary to wait a long time for an appreciable vitalization of A —until a sufficient quantity of substrate x "flows" to the system. However, increase in the production of y causes its rapid expulsion by the flux P . The productivity of A again falls. The system "drops" into the oscillatory state.

If we further reduce S the damage to the mechanism A becomes irreversible (for $\beta < \beta^*$). The flux P monotonically falls with slow unrestricted accumulation of the substrate x in the system. It is no longer capable of functioning.

These simple ideas admit of an evolutionary interpretation. It may be assumed that originally before the advent of photosynthesis various metabolic systems existed including "those entailing a miserable existence". Their oscillatory character not only did no good to them but was, as it were, a "mark of poverty". Among them were the most diverse and, in particular, those with periods close to daily. The latter were quite "weak" (a large period, in our example, denotes closeness to the fatal limit). However, after the appearance of photosynthesis with its forced daily rhythm they survived resonating with this external rhythm. We have no room here to discuss the details of the specific mechanism of survival.

The crux of the matter is the provision of a wide field of activity for the main creative force—natural selection. The difficult conditions (in this case the drop of the flux of the substrate) create a wide range of properties (in this case an unlimited set of periods of auto-oscillations) over which natural selection may "work".

The author is grateful for the useful discussion to many persons, in particular, V. L. Davydov, G. P. Kreitser, G. A. Ososkov, Ye. Ye. Sel'kov and E. E. Shnol', although they did not bear any responsibility for the perhaps risky speculations of the final paragraph.

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