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STRUCTURE OF PHASIC SPACE OF MODELS OF THE PEROXIDASE–OXIDASE REACTION*

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A seventh-order model of the peroxidase–oxidase reaction is considered based on a previously proposed scheme. The structure of the phasic space of this system has been investigated. It is shown that all the observed oscillatory regimes in this reaction may be explained by two main types of oscillations and their interaction: the first type are close to sinusoidal oscillations with a comparatively low amplitude (establishment occurs softly through the Hopf supercritical bifurcation); the second is the strongly relaxing oscillations of high amplitude (established rigidly through non-steady bifurcation).

It has been established that the relaxation oscillations appear in the system on introducing reactions of breakdown of the enzyme–substrate complex III (CoIII) or other reactions removing degeneration occurring in the absence of these reactions. It is shown that the presence of the two types of oscillations indicated is common to all models previously considered by us for this reaction, and that all types of more complex oscillations (oscillations of the type "one major limiting cycle plus several minor ones" and chaos) are explained within the proposed seventh-order model in which both the main types of auto-oscillations indicated are possible.

Peroxidase catalyses the oxidation of a number of substrates by hydrogen peroxide. For some substrates the reaction proceeds without the addition of peroxide and oxygen serves as its source. A reaction with the participation of oxygen is called peroxidase–oxidase. In this reaction with NAD·H complex dynamic regimes are observed as the oxidizable substrate: auto-oscillatory [1–3], trigger [1, 4, 5], regime of complex oscillations [1] and chaos [1].

Modelling of auto-oscillations in the peroxidase–oxidase reaction has at different times engaged the attention of several groups of authors: Yamazaki *et al.* [6], ourselves [7–13], Degn and Olsen [1, 14], Aguda and Larter [15, 16]. The model of Yamazaki *et al.* and our models are based on the real scheme of the reaction and are recorded in elementary reactions while the Degn and Olsen models are based on abstract schemes formally describing the dynamics observed in the experiment. Aguda and Larter considered both our seventh-order model [4, 15] serving for the reduction to second-order systems in [8, 9] and the model of Olsen *et al.* [16].

In our work we obtained all the main oscillatory regimes observed in the peroxidase–oxidase reaction: simple oscillations [8, 9], complex oscillations in a limiting cycle [10–12] and chaos [12] and also oscillations with exposure of the system to light of constant and variable intensity [13].

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The simplest model describing auto-oscillations in the peroxidase–oxidase reaction is based on the real elementary stages — seventh-order system considered in [4, 8, 9, 15]. In the present work this model is explored in detail (model (1)), in particular, those properties which disappear in second-order models obtained by reduction [8, 9] are discussed. We shall also look at the seventh-order model (model (2)) into which is introduced the reaction of monomolecular breakdown of the enzyme–substrate complex III (CoIII). The elementary stages making up the models and sets of values of constants are given below

$$PO^{3+} + H_2O_2 \xrightarrow{k_1'} CoI, \tag{1}$$

$$CoI + YH \xrightarrow{k_2'} CoII + Y^{\cdot}, \tag{2}$$

$$CoII + YH \xrightarrow{k_3'} CoIII + Y^{\cdot}, \tag{3}$$

$$O_2 + Y^{\cdot} \xrightarrow{k_4'} O_2^{\cdot-} + Y, \tag{4}$$

$$O_2^{\cdot-} + YH \xrightarrow{k_5'} Y^{\cdot} + H_2O_2, \tag{5}$$

$$Y^{\cdot} + Y^{\cdot} \xrightarrow{k_6'} YH + Y, \tag{6}$$

$$PO^{3+} + O_2^{\cdot-} \xrightarrow{k_7'} Co(III), \tag{7}$$

$$CoIII + Y^{\cdot} \xrightarrow{k_8'} CoI + Y, \tag{8}$$

$$CoIII \xrightarrow{k_9'} CoII + H_2O_2, \tag{9}$$

$$\xrightarrow{G'([O_2]_0 - [O_2])} O_2, \tag{10}$$

where PO^{3+} is the oxidized form of peroxidase; CoI, CoII, CoIII are the enzyme substrate complexes I, II and III respectively; YH, $Y^{\cdot}$ and Y are the substrate oxidizable in the peroxidase reaction, its radical and oxidized form; $O_2^{\cdot-}$ is the superoxide radical; k_i' are the rate constants of the corresponding reaction; G' is the rate constant of influx of oxygen; $[O_2]_0$ is the saturating concentration of oxygen for a set composition of the gas mixture with which the reaction medium contacts. Let us introduce the notations: $[PO^{3+}]+[CoI]+[CoII]+[CoIII]=E_0$ is the total concentration of enzyme; $[H_2O_2]_0$ is the initial concentration of hydrogen peroxide; $[YH]_0$ is the initial concentration of the oxidizable substrate; $[O_2]_0+[H_2O_2]_0=\Sigma$ is the total concentration of all forms of oxidant and the dimensionless variables:

$$x_1 = [CoI]/E_0,\ x_2 = [CoII]/E_0,\ x_3 = [CoIII]/E_0,\ z = [PO^{3+}]/E_0,$$

$$x_4 = [H_2O_2]/\Sigma,\ x_5 = [O_2]/\Sigma,\ x_6 = [Y^{\cdot}]/\Sigma,\ x_7 = [O_2^{\cdot-}]/\Sigma,$$

$$\tau = k_1E_0t,\ e_1 = E_0/[YH]_0,\ e_2 = k_9'/k_1',\ e_3 = \Sigma/[YH]_0,$$

$$S = [O_2]_0/\Sigma,\ G = G'/(k_1'E_0),\ k_i = k_i'/k_1', \text{ where } i = 1, 2, \ldots, 8$$

Let us designate the derivative $dx_i/dt=\dot{x}_i$.

In the new notations the systems of differential equations studied corresponding to the models (1) and (2) have the following form:

System (1)	Reactions appearing in system (2)	
$\dot{x}_1 = (1/\varepsilon_1)(\varepsilon_3 z x_4 - k_2 x_1 + k_8 \varepsilon_3 x_3 x_6)$,		(11)
$\dot{x}_2 = (1/\varepsilon_1)(k_2 x_1 - k_3 x_2)$	$+ (\varepsilon_2/\varepsilon_1)x_3$,	(12)
$\dot{x}_3 = (\varepsilon_3/\varepsilon_1)(k_7 z x_7 - k_8 x_3 x_6)$	$- (\varepsilon_2/\varepsilon_1)x_3$,	(13)
$\dot{x}_4 = (1/\varepsilon_1)k_5 x_7 - z x_4$	$+ (\varepsilon_2/\varepsilon_3)x_3$,	(14)
$\dot{x}_5 = G(S - x_5) - (\varepsilon_3/\varepsilon_1)k_4 x_5 x_6$,		(15)
$\dot{x}_6 = (1/\varepsilon_3)(k_2 x_1 + k_3 x_2) - (1/\varepsilon_1)(\varepsilon_3 k_4 x_5 x_6 - k_5 x_7) - -k_8 x_3 x_6 - 2k_6 x_6^2$,		(16)
$\dot{x}_7 = (1/\varepsilon_1)(\varepsilon_3 k_4 x_5 x_6 - k_5 x_7) - k_7 z x_7$,		(17)
$z = E_0 - x_1 - x_2 - x_3$.		(18)

Preliminary investigations of the space of the parameters of the models allow three sets of constants to be chosen describing the most characteristic regimes in the systems studied:

Set	(1)	(2)	(3)
$k_1' \cdot 10^{-7}$	1	1	1
k_1	1	1	1,8
k_2	0,1	0,1	$3 \cdot 10^{-4}$
$k_3 \cdot 10^5$	1	100	4
k_4	10^{-3}	10^{-3}	111
$k_5 \cdot 10^5$	1	1	30
k_6	$5 \cdot 10^{-4}$	$5 \cdot 10^{-4}$	3
k_7	2	2	0,1
k_8	10^{-3}	10^{-3}	7
$k_9 \cdot 10^8$	0	1	5
$G \cdot 10^5$	5	5	1
S	0,758	0,758	0,912
ε_1	0,01	0,01	0,05
$\varepsilon_2 \cdot 10^8$	0	1	5
ε_3	0,1	0,1	0,2

Steady points of system (1)

In system (1) there may be from one to three non-trivial steady states and a line of trivial steady states not previously considered [4, 8, 9, 15]. Let us designate the region of phasic space in which the non-trivial steady states R and the line of the trivial, Q, are observed (Fig. 1).

Region R. In region R, depending on the values of the parameters, either one steady point (stable or unstable) exists or three. The values of the parameters for which the system has three steady points were found in [15]. In [4], it was shown that bistability may be observed between the oscillatory and stable states of equilibrium, i.e. about one of the unstable points there is a stable limiting cycle.

If the system has one steady point it may be stable and unstable. When the single steady point is unstable, a limiting cycle may be in the system. Figure 1 gives an example of such a cycle. In the projection $\{x_3, x_4, x_5\}$ it practically lies in the plane forming with the plane $\{x_3, x_5\}$ a small angle (3–5°).

Region Q. Line of steady states. System (1) has a line of steady states ($x_4 z = 0$; $x_3 = 1 - z$; $x_1 = x_2 = x_6 = x_7 = 0$; $x_5 = S$); in which one of the roots of the characteristic equation tends to zero. It has two branches: stable ($x_1 = x_2 = x_6 = x_7 = 0$, $x_5 = S$, $0 \leqslant x_3 < 1$, $x_4 = 0$) and unstable ($x_1 = x_2 = x_6 = x_7 = 0$; $x_5 = S$; $x_3 = 1$; x_4 — any > 0). The steady states on this line are trivial: the rate

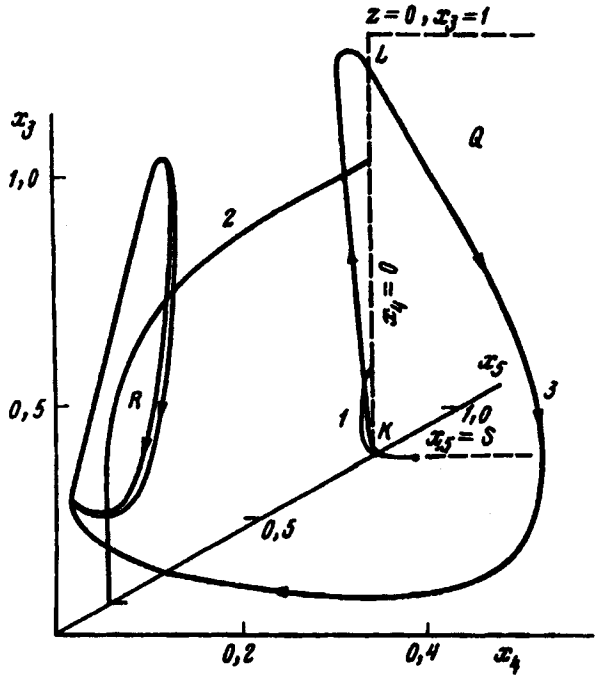

Fig. 1. Main types of behaviour in the system (*1*) for the case when both regions R and Q contain attracting multiplicities (stable limiting cycle and the segment KL, respectively). The projection of the seventh-dimensional phasic space onto the three-dimensional space of the variables $\{x_3, x_4, x_5\}$ is depicted. Broken line denotes the line of steady states. The trajectories (1–3) running from different points of phasic space are shown. Set of constants (*1*). Initial conditions: $x_3 = 10^{-5}$ (*1*, *3*) and 10^{-2} (*2*); $x_4 = 10^{-2}$ (*1*, *2*) and 10^{-1} (*3*); $x_5 = 0.758$ (*1*, *3*) and 0.1 (*2*); $x_1 = x_2 = x_6 = x_7 = 10^{-5}$.

of all the elementary reactions on it is equal to zero because of the equality to zero of all concentrations apart from those of oxygen, CoIII and H_2O_2. In the stable portion of the line of steady states (KL in Fig. 1) the concentration of CoIII is equal to that reached by the end of the reaction and does not change since the breakdown of CoIII is possible only in the reaction with $Y^{\cdot}$ the concentration of which on this line is equal to zero.

On the unstable branch the store of active particles is not equal to zero since $[H_2O_2] \neq 0$, there is plenty of oxygen and a negligible fraction of free peroxidase PO^{3+} suffices (the slightest deviation from zero of the value z) for the reaction to proceed and the system to leave the steady point. Only at $z = 0$ ($x_3 = 1$) is the rate equal to zero.

Thus, system (1) has two attracting multiplicities: the region R and the stable branch of region Q (the segment KL in Fig. 1). They are heavily dispersed in phasic space. To the multiplicity R correspond a low oxygen concentration and non-zero concentrations of active particles (H_2O_2, $Y^{\cdot}$, O^{-}_2), the reaction rate is high. To the segment KL correspond the limiting concentration of oxygen ($x_5 = S$), zero concentration of active particles and an arbitrary concentration of CoIII, the reaction rate is equal to zero (the complex CoIII remains in the state in which the end of the reaction found it).

Thus, the depicting point in system (1) depending on the initial conditions may move either to the stable branch of the line of the stationaries (the segment KL) or to the region R if there is an attracting multiplicity in it. This may be called "major" bistability as distinct from "minor" considered in [4, 15], where the steady points all lie in the region R and are practically unresolved. If the single steady point in region R is unstable and there is no limiting cycle (or it

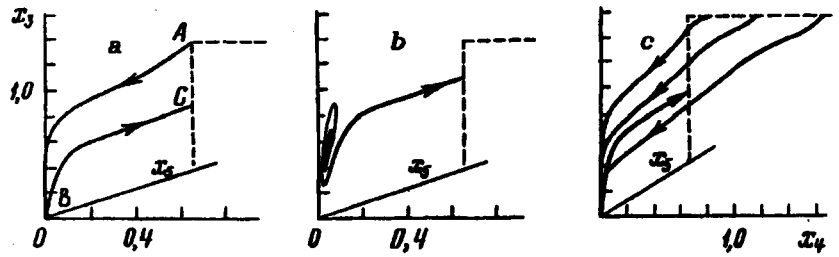

Fig. 2. Phase trajectories of system (*1*) in different initial conditions. The set of constants (*2*) corresponding to the case when the sole steady point of region *R* is unstable. Trajectories emerging: *a*, from the point close to the saddle ($x_1=x_2=x_4=x_6=x_7=0$, $x_5=S$, $x_3=1$), — actually from the point ($x_1=x_2=x_4=x_6=x_7=10^{-5}$, $x_5=S$, $x_3=1$); *b*, from the point corresponding to the unstable state of equilibrium from region *R* ($x_1=3.54\times10^{-5}$; $x_2=3.54\times10^{-3}$; $x_4=7.16063\times10^{-8}$; $x_6=0.0708$; $x_7=3.55831\times10^{-5}$; $x_5=0.05$; $x_3=0.499497$); *c*, phase trajectories starting on the unstable branch of the line of steady states. It will be seen that they all come to a common curve.

is unstable) then the trajectory running from it ends in the stable branch of the line of the steady states (the segment *KL*) which in the particular case is the sole attracting multiplicity (Fig. 2).

Figure 1 shows several trajectories which, depending on the initial conditions, arrive in the region *R* or *Q* (the set of constants corresponds to the case when the limiting cycle is stable). Figure 2 depicts the trajectories corresponding to the set of constants when in the region *R* both the special point and limiting cycle are unstable. Evidently there is an interface of the regions of attraction of the multiplicities *R* and *Q*. It was not found. It is merely shown that for initial conditions from which the reaction is usually triggered in the experiment ($x_1=x_2=x_3=x_6=x_7=0$; $x_4=x_{40}$; $x_5=S$), the system comes to the segment *KL* if $x_{40}<x_{40\,\min}$ (curves *1* and *2* in Fig. 1) and to the limiting cycle if $x_{40}\geqslant x_{40\,\min}$ (curve *3* in Fig. 1), i.e. auto-oscillations in this model may be obtained for not all the initial conditions even when they exist in the system. For releasing the reaction natural for the experiment, hydrogen peroxide is not added and its concentration in the system may be below the threshold value for which the auto-oscillations begin.

The line of steady states exists in all the models previously considered by us [7–13] for $\varepsilon_2=0$, i.e. their behaviour at $\varepsilon_2=0$ is also essentially determined by the two attracting multiplicities indicated.

Thus, in models not containing the reaction of monomolecular breakdown of CoIII the following main types of behaviour are possible: "major bistability" between the two attracting multiplicities *R* and *Q*, one of the possible types of behaviour being in the region *R* — auto-oscillations. These auto-oscillations appear softly through the Hopf supercritical bifurcation and their form is quasisinusoidal.

Model (2) (removal of degeneration)

Let us consider the result of the removal of degeneration ($\lambda=0$) consisting in the existence of a line of steady states. This occurs, for example, on introducing the reaction of monomolecular breakdown of CoIII (system (2)) or photoreactions in an eight-order system [13].

At $\varepsilon_2\neq0$ the line of steady states disappears, it is drawn into a point ($x_1=x_2=x_3=x_4=x_6=x_7=0$, $x_5=S$), which is always unstable — a saddle. In the system the sole attracting multiplicity *R* remains. The former stable segment *KL* of the steady state line (Fig. 1) is converted to a slow manifold (for small ε_2). In the system (2) there appears a limiting cycle of a new type not present in system (1). This occurs for those values of the constants when the sole attracting multiplicity at $\varepsilon_2=0$ is the segment *KL*, i.e. the sole steady point of *R* is unstable and there is no small limiting cycle or it is unstable (Fig. 2).

Figure 2*a*, *b* for the case $\varepsilon_2=0$ gives two trajectories emerging from the nearest vicinity of the two saddle points: the saddle focus of the region *R* (Fig. 2*b*) and the point ($x_1=x_2=x_4=x_6=x_7=0$, $x_5=S$, $x_3=1$) of the unstable branch of the line of stationaries (Fig. 2*a*, point *A*). They both terminate in the attracting multiplicity singular for this case — the segment *KL*. At $\varepsilon_2\neq 0$ in this system the possibility of movement appears though slowly (for $\varepsilon_2\to 0$) along the segment *KL*. "Rupture" of the trajectory existing at $\varepsilon_2=0$ is eliminated, the trajectory closes (over the segment *CA*, Fig. 2*a*) forming a limiting cycle which hereafter will be called "major". The trajectory of the major cycle is the "former" separatrix *ABC* emerging from the saddle *A* plus the segment *CA* (Fig. 2*a*, Fig. 3). It does not pass through the "new" saddle ($x_1=x_2=x_4=x_6=x_7=0$, $x_5=S$, $x_3=0$). With change in ε_2 from zero to an infinitely small value the strongly relaxational oscillations of high amplitude rigidly appear. The period of these oscillations is determined, in the main, by movement over the segment *CA*. At the boundary of the region $\varepsilon_2\to 0$ it grows in inverse proportion to ε_2. Thus, with perturbation of the system ($\varepsilon_2\neq 0$) from the invariant manifold formed by the separatrix of the saddle focus and the segment of immobile points is separated the limiting cycle. This bifurcation is non-standard.

The advent of oscillations with high amplitude requires (besides the fact that $\varepsilon_2\neq 0$) that the sole steady point of the region *R* be unstable and the small limiting cycle about this point also be unstable (Fig. 3*b*).

The analysis made shows that in seventh-order models in the form they are considered in [4, 8, 9, 15], i.e. without monomolecular breakdown of CoIII only the "minor" limiting cycle is

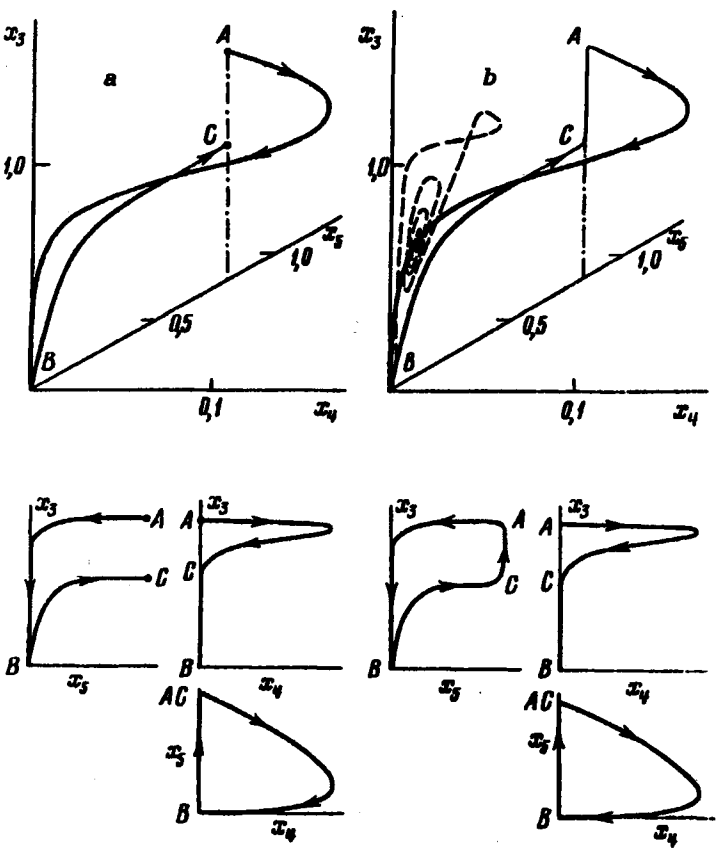

Fig. 3. Projections of: *a*, "separatrix" of system (*1*); *b*, limiting cycle in the system (*2*) in the space $\{x_3, x_4, x_5\}$. It will be seen that they coincide with an accuracy to the segment *CA*. Set of constants (*2*). Broken line in *b*, indicates passage to the limiting cycle from the point close to the saddle focus of region *R*. The trajectory of the "major" cycle passes far from the saddle focus from region *R*.

possible. Such regimes are presented in [4, 15]. Addition of the reaction of monomolecular breakdown of CoIII without changing the order of the system of differential equations makes possible the appearance of a "major" cycle together with the "minor". The description of all the regimes observed in the absence of this reaction is maintained but a new oscillatory regime appears interacting with the old one. The "major" bistability disappears and the "minor" remains.

Comparison with second-order models

In [8, 9] the seventh-order system was reduced to a second-order system in which oscillations were obtained but they were not considered in the initial model. Therefore, in this work we give examples of oscillatory regimes in the initial seventh-order model (with linear discharge of the radicals Y·) for the same sets of constants as in [8, 9] (Fig. 3).

In [9] x_5 and x_6 were chosen as slow variables. The set of constants for which oscillations are observed in this system corresponds to the case when the initial seventh-order system has a minor limiting cycle in the region R (set of constants (1), Fig. 4*a*) but not all the initial conditions lead to this cycle (see Fig. 1).

In the second-order system considered in [8] the slow variables are x_4, x_6. Both sets of constants for which oscillations occur correspond to the major cycle. But in the initial seventh-order system for these values of the constants there are no oscillations at $\varepsilon_2 = 0$. They appear, as pointed out, only at $\varepsilon_2 \neq 0$, i.e. during reduction degeneration is removed: the cycle "open" in the initial system "closes" in the second-order system. Successive reduction and integration of the systems obtained show that at $\varepsilon_2 = 0$ the cycle "closes" in the fourth-order system at $\dot{x}_1 = \dot{x}_2 = \dot{x}_3 = 0$. In the sixth-order ($\dot{x}_1 = 0$) and fifth-order ($\dot{x}_1 = \dot{x}_2 = 0$) systems there are no oscillations at $\varepsilon_2 = 0$, i.e. the cycle does not close.

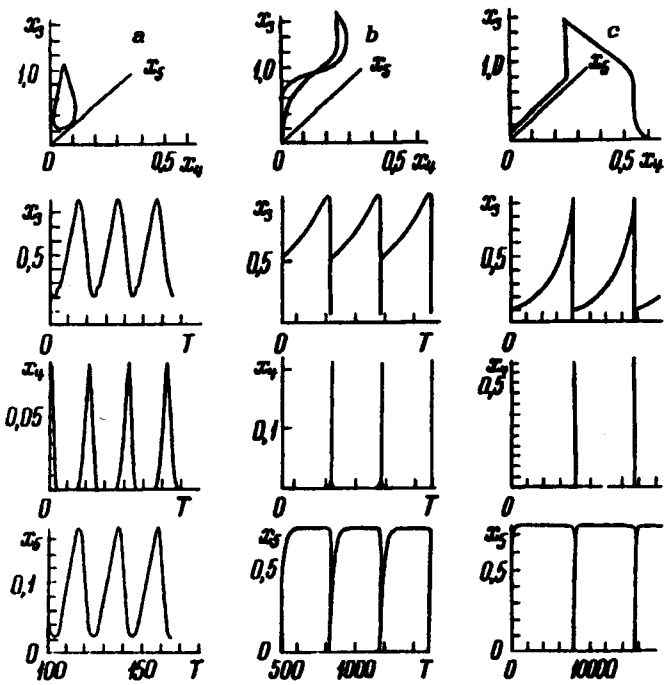

Fig. 4. Three-dimensional projections of the limiting cycles and the form of the oscillations: *a*, "minor" cycle, system (*1*), set of constants (*1*); *b*, *c*, "major" cycle, system (*2*) with sets of constants (*2*) and (*3*) respectively.

Other systems

As well as the seventh-order model, we previously also considered several eighth-order models, where to the reactions of the model (1) are added the reactions:

(1) with the participation of the reduced form of peroxidase (PO^{2+}) [10–13]

$$PO^{3+} + Y^{\cdot} \xrightarrow{k_{11}'} PO^{2+}, \quad k_{11}' = 10^4,$$

$$PO^{2+} + O_2 \xrightarrow{k_{12}'} CoIII, \quad k_{12}' = 10^5;$$

(2) the model including photoreactions [13];

(3) eighth-order model differing from the minimal only in the fact that in it the concentration of oxidizable substrate is not constant and represents the eighth variable of the system [10, 11].

In the models of [10–13] complex oscillatory regimes and chaos [12, 13] are observed. The model containing the photoreactions [13] is interesting in that in it there is no reaction of monomolecular breakdown of CoIII and the role of the factor removing degeneration is played by the action of light of constant intensity. For a very low, differing from zero, intensity of light there rigidly appear auto-oscillations the form of which coincides for identical values of the parameters with the form of the oscillations in the seventh-order system at $\varepsilon_2 \neq 0$ (Fig. 3*b*).

Common to all the models considered is that depending on the parameters oscillations in the "minor" or in the "major" cycle are observed. There are also values of the parameters for which the trajectory of the "major" cycle closely approaches the saddle focus of the region R and we see complex oscillations of the type "one major limiting cycle plus several minor" (Fig. 5).

Thus, qualitatively, the type of behaviour does not change in the systems considered (in the sense that there are two basic forms of the oscillations and their interaction). Only the quantitative characteristics change: the region of existence of the oscillations, the period of the oscillations, and so forth.

CONCLUSION

The investigations of the structure of the phasic space for the seventh-order model of the peroxidase–oxidase reaction have shown that there is a minor parameter with zero value of which a characteristic of the system is a line of degenerate steady states ($\lambda = 0$) consisting of two branches stable and unstable. In the unperturbed systems two invariant manifolds exist —

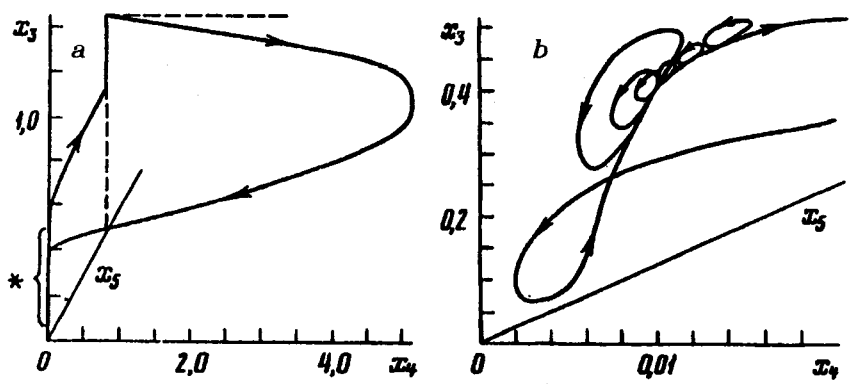

Fig. 5. Three-dimensional projection of the limiting cycle corresponding to complex oscillations in an eighth-order system containing the reactions (1)–(10), (19) and (20) (Table 1), set of constants (2); *a*, general appearance; *b*, increase in the region denoted by asterisk, spiral twisting and untwisting of the trajectory close to the saddle focus of region R are seen.

a special point which may be stable and unstable and the line of stationaries. Around the special point a limiting cycle may appear through the Hopf supercritical bifurcation. The oscillations in this cycle are quasisinusoidal with a comparatively small amplitude. Such behaviour was considered in [4, 5, 8, 9].

In the system oscillations of a fundamentally different type may be observed [10–13], relaxational with high amplitude. This work has shown that the limiting cycle corresponding to these oscillations forms for a non-standard bifurcation. In this case on perturbation of the system from an invariant manifold formed by the separatrix of the saddle focus and the segment of immobile points is separated a limiting cycle movement along which represents relaxational oscillations of high amplitude.

The perturbing agent may be the reaction of monomolecular breakdown of CoIII [10–12] or the action of light of constant intensity [13]. Earlier these two basic forms of oscillatory movements were considered in different models: in [4, 5, 8, 9] only the behaviour of the system determined by the special point and the "minor" limiting cycle, while in [10–13] only the "major" cycle. This work presents the whole picture of how and when a particular oscillatory movement appears and their interaction is realized.

Failure to allow for the second attracting multiplicity and its perturbations leads to loss of a whole class of oscillatory movements in the system considered: "major" bistability in the unperturbed system and relaxational oscillations of high amplitude in the perturbed.

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