Phase reversal in the Selkov model with inhomogeneous influx

A. I. Lavrova and L. Schimansky-Geier
Institute of Physics, Humboldt-University at Berlin, Newtonstr. 15, 12489 Berlin, Germany

E. B. Postnikov[†]
Department of Theoretical Physics, Kursk State University, Radishcheva Street, 33, 305000 Kursk, Russia

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The dynamical reaction-diffusion Selkov system as a model describing the complex traveling wave behavior is presented. The approximate amplitude-phase solution allows us to extract the base properties of the biochemical distributed system, which determines such patterns. It is shown that this relatively simple model could describe qualitatively the main features of the glycolysis waves observed in the experiments.

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I. INTRODUCTION

Glycolysis plays an important role in metabolism. It is connected to many different biochemical pathways representing a complex metabolic network. Temporal oscillations in glycolysis are one of the first types of metabolic rhythms that have been studied intensively in experiment and numerical simulations [1–4]. Also spatiotemporal dynamics has been observed in the yeast extracts, which is used as a model system in most experiments because it is possible to investigate the metabolic interactions on a subcellular level. It has been shown that waves can be induced by local perturbation on the activity of key enzyme, phosphofructokinase (PFK) [5]. Since the propagation dynamics and shape of traveling reaction-diffusion waves can contain information about the state of the system, it has been suggested that they can play an important role for biological information processing [5].

Several theoretical models have been developed to characterize the spatiotemporal dynamics in glycolysis [6,7], where various spatial patterns including propagating concentration waves, target waves, and chaotic waves due to different boundary or initial conditions have been observed.

To observe experimentally in detail the spatiotemporal patterns in glycolysis, the open spatial reactor has been used [5,8,9]. This reactor consisted of gel with yeast extract in contact with stirred reactor where it is permanently injected by substrates and cofactors for glycolysis. A permanent and constant supply of substrates and cofactors of glycolysis to the gel layer is provided by the diffusion of the substrates and cofactors of glycolysis from the reactor chamber into the gel. The spontaneous generation of traveling waves can be observed after an initial time period of about 10 min. They propagate from the border of the gel to the center (inward waves) [5,8]. Also a spontaneous change in the direction of wave propagation has been observed during one experiment in spite of the fact that the controlled influx was not changed. This leads to the generation of outwardly propagating waves [9]. The duration of one experiment is around 6–10 h [5,8].

Note that similar wave-antiwave exchange has been obtained in the experimental [10] and theoretical [11] investigations of the Belousov-Zhabotinsky reaction. However, the phenomenon described in this work has another origin as it will be discussed below.

Here we study the Selkov model [12] extended by diffusion terms [13] for reproduction and explanation of wave change direction described in experiment. It takes into account the PFK reaction in glykolysis, where the enzyme is inhibited by the substrate $x(r,t)$ and activated by the product $y(r,t)$, where substrate influx ν and product outflow w are considered as parameters,

$$\partial_t x = \nu - xy^2 + D\partial_r^2 x,$$

$$\partial_t y = xy^2 - wy + D\partial_r^2 y. \tag{1}$$

The model without diffusion terms (local model) reproduces self-sustained oscillations in glycolysis observed in experiment [2]. In dependence on parameter ν, harmonic and relaxation oscillations could be found.

In contrast to the developed models, we describe experimentally observed data using an inhomogeneous influx $\nu(r)$ of the substrate in the distributed model. Using amplitude phase representation helps us to understand mechanisms of a spontaneous change in the direction of wave propagation in experiments [9].

II. RESULTS

It is convenient to rewrite the original Selkov system (1) into new variables. First of all, we introduce $u=\nu-wy$ and $z=x+y-z_0$, where $z_0=w^2/\nu-\nu/w$. We assume that the diffusion coefficients D are equal for both substances. The next simplification follows from the experimental conditions. Note that the first two derivatives of the function $\nu(r)$ are small over the whole region of the reaction. This allows us to neglect spatial derivatives in system (1) and consider the coordinate transform as a linear one consisting of only shifts, rotation, and rescaling. Then, after summation of Eq. (1) and substitution of these variables, we simply get

$$\partial_t z = u + D\partial_r^2 z,$$

[†]postnicov@gmail.com

$$\partial_t u = 2\lambda(1 + c_1 u - c_2 u^2)u - [\Omega(1 - \nu^{-1}u)]^2 z + D\partial_r^2 u, \quad (2)$$

where $\lambda = (w - \nu^2 w^{-2})/2$, $c_1 = (3\nu - z_0 w)/2\lambda w^2$, $c_2 = w^{-2}/2\lambda$, and $\Omega = \nu/\sqrt{w}$.

This system can be considered as a kind of generalized Rayleigh equation [14]: the dissipative term also consists of the expansion up to the third power of velocity. But conversely to the classical form the square power is also kept. Additionally, Eq. (2) maintains the first (linear on u) term in the expansion of the frequency factor.

Let us start to analyze Eq. (2). As a first step, we consider a local model ($D=0$ and ν has a fixed value). It is easy to show that if $\lambda > 0$ this system has an unstable equilibrium point $u_1 = 0$, $z_1 = 0$. The existence of the negative cubic term leads to the compensation of an unbounded growth. Thus, there exists a stable limit cycle as an asymptotic solution in this case.

In the case if λ is a small parameter, a linear approximation of the system reduces it to the equation of harmonic oscillations with the frequency Ω. To find an approximate analytical solution of the local version of Eq. (2), we use an averaging method known as Krylov-Bogolyubov (KB) scheme [15]. Namely, we consider the representation of the solution in the form of simple harmonic function with variable amplitude and phase.

Note that the strictly non-negative term $2\lambda c_1$ plays a special role. It provides unidirectional acceleration from the unstable stationary point. This leads to an asymmetry in the limit cycle. The center of the cycle is shifted in the phase plane. Also this term influences in cycle's size. For this reason we add a shift,

$$z(t) = A(t)\cos[\Omega t - \phi(t)] + z_0(A),$$

$$u(t) = -\Omega A(t)\sin[\Omega t - \phi(t)].$$

In such a form, both variables actually are the decompositions in Fourier series (even and odd components) up to the main frequency Ω only. And the first term of the even part of Fourier expansion $z_0(A)$ plays a role of the slow amplitude-depended mean value (a shift of the limit-cycle center).

Both amplitude A and phase ϕ are changing little during the period of fast oscillations $2\pi/\Omega$. Thus, after averaging with respect to this period, we get the following equations for the slow amplitude and phase, which coincide formally with the corresponding representation of the Ginzburg-Landau equation,

$$d_t A = \lambda A\left(1 - k_1 \frac{3c_2}{4}\Omega^2 A^2\right), \quad (3)$$

$$d_t \phi = -k_2 \frac{\Omega^3}{8\nu^2} A^2. \quad (4)$$

We use the correcting factors $k_1 = c_2/c_1$ and $k_2 = 2c_1/\nu c_2$ to take into account an additional influence of unidirectional acceleration discussed above on the limit-cycle radius and phase shift.

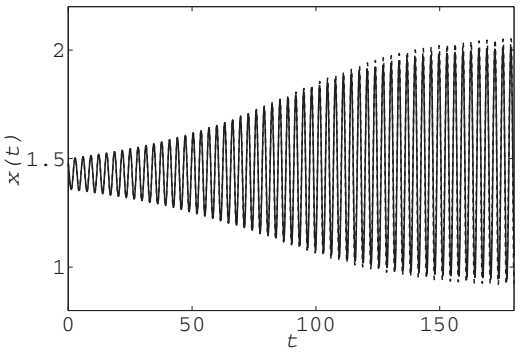

FIG. 1. The comparison of the approximate (solid line) and exact (dashed line) solutions for the substrate concentration in the local system. The parameters: $w=2$, $\nu=2.8$.

Having these solutions, one can transfer back to the initial concentration variables as $x = w^2\nu^{-1} + w^{-1}u + z$, $y = w^{-1}\nu - w^{-1}u$.

Let us consider two examples. We have chosen the parameter values as the boundaries between harmonic and relaxation oscillations. The initial conditions for both cases are identical: $A=0.05$, $\phi=0$. Figure 1 represents the transition to the limit cycle slightly below the critical value for Hopf bifurcation ($\nu_c = 2.82$).

One can see that the approximate solution obtained by KB method [Eqs. (3) and (4)] reproduces the exact one with the high accuracy. The second case represented in Fig. 2 corresponds to the oscillations close to relaxation ones. It is clear from the sufficiently asymmetric shape of peaks. Naturally, taking into account only first Fourier harmonic cannot reproduce such behavior. As a consequence the approximate solution deviates from the exact one in the region of the upper maxima, where this asymmetry is most clear. Nevertheless, the periods and phase of both solutions coincide quite well.

Note that the considered frequency of the main Fourier harmonic Ω (as well as the phase shift ϕ) sufficiently depends on the influx parameter. Consequently, there will be a difference in the motion of the near located even independent oscillators with various values of ν. This difference leads to the picture, which looks like as a phase wave for the series of oscillators.

Now let us consider distributed media described with the full Selkov system (2). In order to describe experimental data

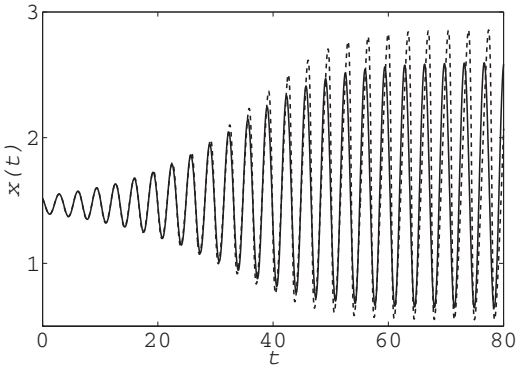

FIG. 2. The comparison of the approximate (solid line) and exact (dashed line) solutions for the substrate concentration in the local system. The parameters: $w=2$, $\nu=2.73$.

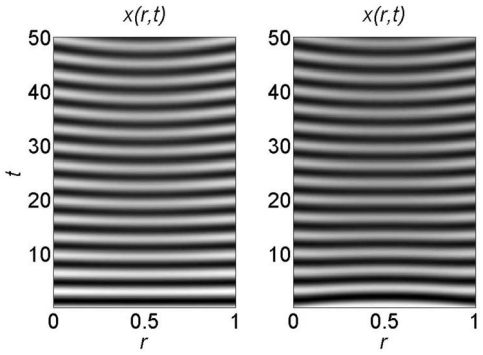

FIG. 3. Time space plots of traveling waves for $D=2.5\times10^{-3}$ and different initial conditions. Left: $A(r,0)=1$, $\phi(r,0)=1$. Right: $A(r,0)=1$, $\phi(r,0)=2\pi r(r-1)$.

we assume the inhomogeneous influx and model it as a parabola $\nu(r)=\nu_0+4(\nu_b-\nu_0)(r-0.5)^2$, where ν_0 and ν_b are the coefficients, defined maximum or minimum of parabola. Such suggestion can be conditioned by the following: (1) the substrate flux in the outer part of the reactor is laminar enough and can be considered as the parabolic Poiseuille flow; (2) even in more general case, there are weak disturbances of substrate percolation through the gel near the walls of gel-contained cylinder; therefore one can take parabola as the first small correction to the uniform influx. Thus, now parameters λ, c_1, c_2, and Ω depend on space coordinate.

Now substitute into Eq. (2) the amplitude-phase representation described by

$$z(r,t)=A(r,t)\cos[\Omega(r)t-\phi(r,t)]+z_0(A),$$

$$u(r,t)=-\Omega(r)A(r,t)\sin[\Omega(r)t-\phi(r,t)]$$

and get after the averaging equations for amplitude and phase dependent on space. These equations shape like Eqs. (3) and (4) supplemented by spatial derivatives: $(D/2)(\partial_r^2 A-A(\partial_r\phi)^2)$ will be added to Eq. (3) and $(D/2)(\partial_r^2\phi-\partial_r A\partial_r\phi)$ to Eq. (4).

Here, it is very important to take into account that the consideration of an inhomogeneous influx leads to a spatial distribution in frequencies, where Ω depends on space coordinate as $\Omega(r)=\nu(r)/\sqrt{w}$. Such spatial distribution in frequencies allows us to obtain phase waves observed in experiment.

We have solved equations for $A(r,t),\phi(r,t)$ numerically where the coordinate r has changed within the interval $[0,1]$. Zero fluxes have been used as boundary conditions. We have chosen coefficients for parabola as $\nu_0=2.8$ and $\nu_b=2.73$. The local oscillations for these values are considered in Sec. I above. We have studied the influence of various initial reagent distributions on the wave dynamics. For simplicity, we have changed the initial conditions for the amplitude and the phase. We can obtain wave solutions propagating in one direction for uniform initial conditions [Fig. 3 (left)] as well as for initial concave upward distribution of phases. To obtain the change in wave direction we should take initially a concave downward function [for example, see Fig. 3 (right)].

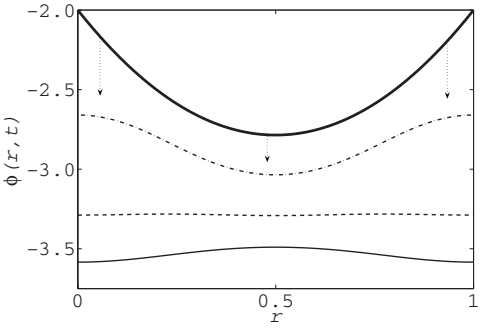

FIG. 4. Flip of the phase curve. The space distribution is presented at the following time steps: 0 (bold solid line), 10 (dashed-dotted line), 34 (dashed line), and 49 (thin solid line).

In numerical simulations it is shown that the dynamical behavior has a weak dependence on diffusion. This, it seems, stands in contrast with the diffusion-driven waves and antiwaves in the Belousov-Zhabotinsky (BZ) reaction [10,11]. Thus, one can neglect the diffusion and consider the origin of the wave reversal for fixed distribution of $\nu(r)$ at the other reasons. We return to Eqs. (3) and (4) with now space dependent amplitude and phase, and we distribute space dependent amplitude and phase depending on space $\nu(r)$ and $\Omega(r)$. As a solution we obtain

$$\phi(r,t)=\phi_0(r)-k_2\frac{\Omega(r)^3}{8\nu(r)^2}\int_0^t A^2(r,t)dt. \tag{5}$$

Here, the integral is a strongly monotonically negative growing function; its growth rate is very sensible to the substrate influx distribution $\nu(r)$. Since it has a maximum in the center of interval, this corresponds to the minimum of the phase change speed. The initial distribution $\phi_0(r)$ leads to inwardly propagating waves. However, the described heterogeneous growth of the phase results in a flip of the phase curve (see Fig. 4) (the phase change speed direction is denoted by arrows). It leads to an appearance of outwardly propagating waves.

To estimate the parameter requirement for the flip, let us consider the simplest case when all distributed oscillators reach the limit cycle $(dA/dt=0)$. Thereat, an amplitude, which coincides with the radius of limit cycle, does not depend on time. Consequently, substituting $A^2=4/(3k_1c_2\Omega^2)$ into Eq. (5), we obtain the explicit expression for the full phase $\varphi(r,t)=\Omega(r)t-\phi(r)$,

$$\varphi(r,t)=\frac{\nu(r)}{\sqrt{w}}\left[1-\frac{4w^2}{3\nu(r)}\left(w-\frac{\nu^2(r)}{w^2}\right)\right]t+\phi_0(r). \tag{6}$$

Here all the parameters are represented via original ones, i.e., via w and $\nu(r)$, which characterize the experimental conditions. Thus, the inhomogeneous influx $\nu(r)$ which is presented as parabola with minimum leads to two modifications in the phase growth: (1) it delays the growth of the speed of phase growth; (2) this delay is sufficiently smaller in the center of interval compared with values near the border. Therefore, if the initial phase distribution $\phi_0(r)$ and the influx $\nu(r)$ have contradistinct extrema in the center, then the

distribution of the phase growth speed will be sufficiently curved due to the damping near the borders. Such a shape results in a flip of the phase growth distribution.

Note that the different behavior of the growth of the phase is determined by the value of the amplitude. In particular, in the considered case of the formed limit-cycle motion (the maximal possible amplitude), this difference is so big that the phase flip occurs during times comparable with one period of oscillations. In experiments the change in wave propagation direction occurs after a certain number of periods of oscillations [9]. Therefore we need to take into account Eq. (3) which describes the growth of amplitude equation. The relatively slow growth of these solutions provides a necessary delay of the phase flip that leads to the change in the wave propagation direction. This situation is presented in Fig. 3 (right) where initially inwardly propagating waves change their direction. Such changes will take place before the distributed oscillators reach their limit cycles (see times in Fig. 4 and compare with the amplitude values in Figs. 1 and 2).

III. DISCUSSION AND CONCLUSION

Thus, we have found that the Selkov model with inhomogeneous influx describes the dynamical phenomena observed in the experiment. As it was shown in experiment, the waves propagate initially from borders to center (inward waves) and then, after 4–7 h, could change their direction (to outward waves); however the substrate influx and product degradation rates do not change during the experiment. For this reason present phenomenon differs from the situation observed in the BZ reaction [10]. Therefore, it cannot be explained in the frame of the theory suggested in work of Shao *et al.* [11], which considers the change in key influx parameter as the origin of the wave or antiwave behavior. Additionally, in the experimental cases described in [5,8,9], the diffusion of such big molecules as adenosine-5'-triphosphate (ATP) (substrate) and adenosine diphosphate (ADP) (product) is very slow in the gel dense structure. Therefore, we can suppose that diffusion processes play a small role in the wave-generating sources compared with the situation considered in [11]. We can explain the wave generation and reversal by our analysis of the initial condition influence. Usually, yeast extracts contain substrates, coenzymes, and enzymes for glycolysis pathway. It means only that the initial mixture should be described by a nonuniform initial distribution. We have shown that the phase shift is determined by the initial distribution of metabolites. Clearly, this function could be sufficiently large even for very small initial concentrations [and, correspondingly, the amplitudes in Eqs. (5) and (6)]. Thus, the time of wave change direction could be regulated by the adjustment of the coefficients ν_0 and ν_b in the influx function. For example, for the used parameters [see Fig. 3 (right)] the critical time is around 2 h, and for $\nu_0=2.82$, $\nu_b=2.81$ it will grow up to 9 h. We have showed that the properties of a wave propagation are not determined by diffusion processes but by speed of individual oscillator rotation in a phase plane. We can expect that the supposed distribution of influx and initial conditions can be defined by the inhomogeneity of diffusion coefficients or inhomogeneity of boundaries. This possible situation can correspond to the experimental conditions, where gel has a dense structure and enzymes of reaction could clog the gel pores. Finally, we can note that inhomogeneity may also affect on the break of axially symmetrical waves into spirals as it was found in some experiments [9].

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