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Detuning-dependent dominance of oscillation death in globally coupled synthetic genetic oscillators

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Abstract – We study dynamical regimes of globally coupled genetic relaxation oscillators in the presence of small detuning. Using bifurcation analysis, we find that under strong coupling via the slow variable, the detuning can eliminate standard oscillatory solutions in a large region of the parameter space, providing the dominance of oscillation death. This result is substantially different from previous results on oscillation quenching, where for homogeneous populations, the coexistence of oscillation death and limit cycle oscillations is always present. We propose further that this effect of detuning-dependent dominance could be a powerful regulator of genetic network's dynamics.

Since 1928 [1], the studies of coupled nonchaotic oscillators have provided a rich source of ideas and insights regarding the role of different coupling types as well as the dependence on the oscillator structure in the generation of new rhythms [2–4]. It has been shown that even ensembles consisting of identical oscillators may generate a variety of rhythms that differ in their period and phase relations [5–7]. Apart from such rhythmogenic activity, coupling can suppress oscillations in a network by different mechanisms. This particular behavior known as oscillation death (OD) was initially found by Prigogine and Lefever [8] for two identical Brusselators coupled in a diffusion-like manner. Their interaction can break symmetry, which leads to a stable *inhomogeneous* steady state. Furthermore, it has been shown theoretically that OD is model independent, persisting for a large parametric region in several models of diffusively coupled chemical [9] or biological oscillators [10]. Experimental results reported by Dolnik and Marek demonstrate the extinction of oscillations in chemical reactors coupled by mutual mass exchange [11]. Later, Crowley and Epstein demonstrated for two coupled, slightly nonidentical chemical oscillators that the basis for the OD is a specific, vector-type coupling, namely, coupling via a slow recovery variable [12]. Very recently, OD has been experimentally observed in chemical nano-oscillators (micro fluidic Belousov-Zhabotinsky-octane droplets), diffusively coupled via signaling species (Br_2 in this case) [13]. It is important to note that the OD in the investigated systems is always accompanied (coexists) in parameter space with stable synchronous oscillations [12,14].

Besides the OD phenomena, other types of coupling-dependent quenching of oscillations, called amplitude death (AD), are discussed in the literature [15,16]. It has been proven that for sufficiently strong coupling and sufficiently large variance of the distribution of the frequencies, AD can be observed – the oscillators pull each other off their limit cycles and into the origin, a stable equilibrium point [17]. Moreover, it has been shown that AD, in contrast to OD, is stable also for delayed coupling (scalar or vector) [18,19]. Thus, AD results in a *homogeneous* steady state (all oscillators in the system display identical steady-state behavior) and is therefore, principally different from the OD phenomena, which emerges from a symmetry-breaking bifurcation and is manifested as an *inhomogeneous* steady state (distinct steady-state levels are present in the system).

Recently, collective rhythms of regulatory genetic networks have been a subject of considerable interest

both to theoreticians and experimentalists, due to the rapid advancement in molecular-biology techniques, which allows the design and construction of *de novo* synthetic genetic circuits. Moreover, several theoretical models have been proposed to examine the dynamics of different types of synthetic oscillators, such as coupled repressilator [20–22] or relaxation oscillators of different types [23,24]. In these models, the role of what is known as a quorum sensing mechanism has been investigated in regulation of the dynamics on a population-wide scale. The quorum sensing mechanism underlying intercellular communication is accomplished by transmembrane diffusion of signaling molecules (autoinducer, AI) into extracellular medium, resulting in a coherent, in-phase dynamical behavior in networks of synthetic genetic circuits [20,23,24].

In [25], we have investigated the dynamics of globally coupled identical synthetic genetic relaxation oscillators [23] and showed that in addition to coherent behavior, there exist various other modes of organized collective behavior. However, we have also shown that OD coexists with these limit cycle oscillations (at most with in-phase oscillations) throughout the population (that is, their regions of stability coincide). In synthetic genetic networks, oscillators engaged in OD are distributed between two clusters, each of them being in a steady state, which corresponds to two different but constant protein synthesis levels [21,23,25]. We suppose that synthetic circuits in the OD mode are a promising tool for cell function regulation because they can provide for stable variability of protein concentration. Moreover, OD can be seen as an additional mechanism for genetic switch production composed of interacting limit cycles, which substantially differs from that of a standard genetic toggle switch [26].

Although all modern investigations demonstrate interesting prospects for further development of synthetic genetic circuits and their biotechnological applications, they are still limited to the study of identical elements. It is important to emphasize that this strong condition never holds in experiments or in nature. To that extent, in our present work we introduce detuning between the oscillators as an additional parameter to provide a more realistic view of interacting elements in a population. Unexpectedly, we observe that in a large part of the parameter interval this detuning can abolish limit cycle oscillations (in-phase and partial synchronization regimes), and replace them with OD at certain, appropriate magnitude of the coupling strength. This effect is sensitive to the extent of detuning, being observed even for small values of the detuning parameter. We propose furthermore, that this effect of detuning-dependent dominance could be used as a powerful regulator of genetic network's dynamics in the case of strong coupling.

The model considered here consists of hysteresis-based relaxation genetic oscillators coupled via quorum-sensing mechanism, as proposed in [23]. Namely, the system is constructed by combining two engineered gene networks, the toggle switch [26] and an intercell communication system, which have been implemented experimentally in *Escherichia coli* and *Vibrio fischeri* [27]. The synthesis of both repressor proteins which constitute the toggle switch, are regulated in such a way that the expression of both genes is mutually exclusive, and organizing bistability. The second network is based on the dynamics of an autoinducer (AI), which, on the one hand, drives the toggle switch through the hysteresis loop, and, on the other hand, provides an intercellular communication by diffusion through the cell membrane.

The time evolution of the elements in this system is governed by the dimensionless equations (see details in [23]):

$$\frac{\mathrm{d}u_i}{\mathrm{d}t} = \alpha_1^{(i)} f(v_i) - u_i + \alpha_3 h(w_i), \tag{1}$$

$$\frac{\mathrm{d}v_i}{\mathrm{d}t} = \alpha_2 g(u_i) - v_i, \tag{2}$$

$$\frac{\mathrm{d}w_i}{\mathrm{d}t} = \varepsilon(\alpha_4 g(u_i) - w_i) + 2d(w_e - w_i), \tag{3}$$

$$\frac{\mathrm{d}w_e}{\mathrm{d}t} = \frac{d_e}{N}\sum_{i=1}^{N}(w_i - w_e), \tag{4}$$

where N is the total number of cells (oscillators), u_i and v_i represent the proteins from which the toggle switch is constructed in the i-th cell, w_i represents the intracellular, and w_e the extracellular AI concentration. The mutual gene regulation is defined with the functions: $f(v) = 1/(1+v^\beta)$, $g(u) = 1/(1+u^\gamma)$ and $h(w) = w^\eta/(1+w^\eta)$. The coupling coefficients in the system are given by d and d_e (intracellular and extracellular) and depend mainly on the diffusion properties of the membrane, as well as on the ratio between the volume of the cells and the extracellular volume. The presence of multiple time scales in this system (achieved for $\varepsilon \ll 1$) allows to produce relaxation oscillations, which emerge via a Hopf bifurcation HB; (for a single oscillator, $\alpha_{1HB} \sim 1.18$). The dimensionless parameters $\alpha_1^{(i)}$ and α_2 regulate the repressor operation in the toggle switch, α_3 the activation due to the AI, and α_4 the repressing of the AI. Taking into account that the dynamics of the synthetic circuit is regulated by α_1, we assume that the detuning between different cells is expressed in the variability of the α_1-parameter values, thus defining the detuning measure between two cells as

$$d_{ij} = \frac{\alpha_1^{(i)}}{\alpha_1^{(j)}}. \tag{5}$$

The suggestion for introducing the variability in α_1 is realistic, because α_1, determining the expression strength of the gene is proportional to the concentration of the active promoters, thus proportional to the concentration of plasmids present in the cell. The control of the number of plasmid copies in experiment is elaborated in [28] and

it can be therefore coordinated with the cell's growth and division.

A detailed analysis of the deterministic model of identical, globally coupled relaxation genetic oscillators has revealed the presence of multistability, *i.e.* the appearance of several coexisting dynamical regimes (OD, in-phase, anti-phase and asymmetric oscillations; recall that, for two coupled cells, asymmetric oscillations are characterized by large excursions of one of the oscillators, while the other performs small-amplitude oscillations in the vicinity of a stable steady state). As shown in [25], the ability of the system to produce clustering and multiple rhythms is a result of the inhibitory, phase-repulsive coupling established through the AI diffusion. Moreover, the complex dynamic structures persists to exist when considering the more realistic assumption that a certain variability between cells is present (*e.g.* $d_{ij} = 0.98$ under small coupling, results not shown). We also observed in this case [29] a significant enlargement of the parametric area where the asymmetric solution is stable, with respect to the equivalent investigation for identical elements. It is noteworthy to mention that in both cases (identical and slightly nonidentical elements (for small coupling values, $d < 0.004$)), in line with the literature data on oscillation quenching, the OD *always* coexists with limit cycle oscillations (in-phase or quasi-in-phase for slightly nonidentical elements).

The primary focus of this study is the influence of detuning on oscillation quenching and the dynamics of the system under strong coupling, in general. Thus, as a result of the detuning, the homogeneous steady state corresponding to cells being identical here "splits" into slightly inhomogeneous steady states with different protein concentrations: "upper" (black line in fig. 1, region between $\alpha_1 = 2.8$ and $\alpha_1 = 2.85$) and "lower" (red line in fig. 1) levels. We show here in detail how the dynamical behavior of the two coupled cells (time series (ts) represented through conjecture lines in fig. 1 and bifurcation diagrams (fig. 2)) varies for fixed detuning between the cells ($d_{ij} = 0.96$) with increasing the coupling strength, starting from $d = 0.005$ (figs. 1, 2, top). The analysis is performed following the dynamical changes of the system through the "upper" level branch of the slightly inhomogeneous steady state (following variable u_1) using the *Xppaut* package [30].

We observed appearance of many oscillatory regimes on the branch emanating from the Hopf bifurcation HB_1 of the chosen inhomogeneous ("upper") steady state (fig. 2). As shown in the top frames of figs. 1 and 2, the branch of oscillatory solutions contains a simple asymmetric solution (stable between LP_1 and LP_2, ts in fig. 1 (top), for α_1 between 2.85 and 3.02), quasi-in-phase solution stable between PD_1 and PD_2 (ts for α_1 between 3.02 and 3.13), and dynamical regime characterized by synchronization of order 2 : 1, which is stable between the period doubling (PD_3) and saddle-node bifurcation (LP_3) (fig. 2 (top), ts for α_1 between 3.2 and 3.25). Despite the oscillatory

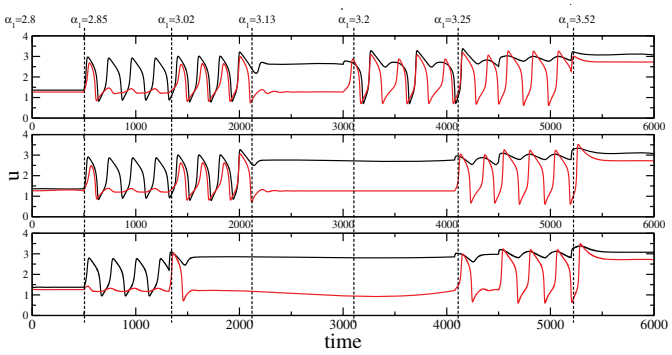

Fig. 1: (Colour on-line) Conjugation lines representing time series (ts) for different interval of α_1 values, which correspond to the qualitative changes of the dynamic of the system (1–4), for top: $d = 0.005$, middle: $d = 0.006$, bottom: $d = 0.008$ and $d_{ij} = 0.96$. These α_1 intervals (the vertical dashed lines) correspond to stable regimes for $d = 0.005$. We continue them below to show the dynamical changes in the system. Other parameters are: $N = 2$, $\varepsilon = 0.01$, $\alpha_2 = 5$, $\alpha_3 = 1$, $\alpha_4 = 4$, $\beta = \eta = \gamma = 2$, and $d_e = 1$.

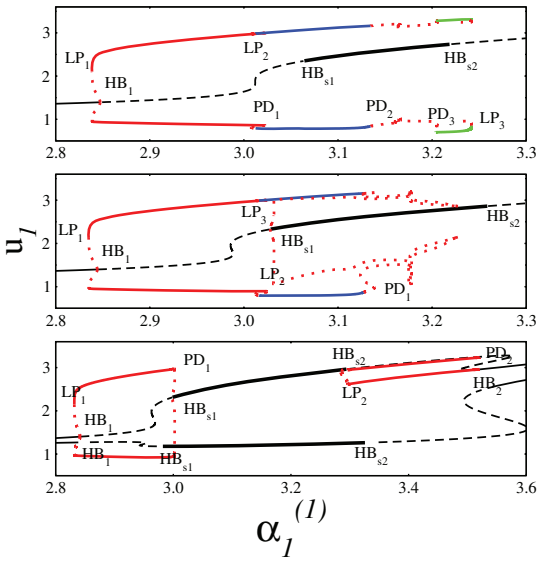

Fig. 2: (Colour on-line) The resulting bifurcation branch for top: $d = 0.005$, middle: $d = 0.006$, bottom: $d = 0.008$ and $d_{ij} = 0.96$. Other parameters as in fig. 1. The bifurcation analysis is performed on the upper branch of the inhomogeneous steady state. Note that we present only that part of the diagrams which is necessary for the results discussed, although the complete bifurcation analysis was performed. This is the reason why only one level of OD is shown on the top and middle diagram. Namely, the lower level of the OD, occupied by the second oscillator can be seen on the lower branch of the inhomogeneous steady state (as shown on the bottom figure).

regimes, the "upper" steady state stabilizes via another Hopf bifurcation, HB_{s1}, leading to the appearance of OD phenomena (solid black line in fig. 2, time series (ts) in fig. 1 (top), for α_1 between 3.13 and 3.2).

Unexpectedly we observed another, previously not reported phenomenon in systems of coupled oscillators. In contrast to the known results that the OD regime always coexists with in-phase oscillations, we show here (*e.g.* fig. 2, bottom) that oscillation quenching can gain dominance in phase space. The same feature can be observed also from the corresponding time series in fig. 1. The effect of the OD dominance is a result of the detuning present in the system and is dependent on the detuning value and the coupling strength. Thus, the small parameter region of OD dominance between PD_2 and PD_3 in fig. 2 (top) becomes significantly larger with increasing coupling strength. As shown in fig. 2 (middle), for slightly increased coupling values ($d = 0.006$), a qualitative difference in the particular branch is observed, which results in a subsequent loss of the $n:m$ synchronization regime on the one hand, and an expansion of the parameter region of OD dominance, on the other hand.

The dominance of the oscillation quenching regime is reinforced when the coupling strength in the system is further increased. For a given critical value (d_{crit}), the detuning abolishes completely the oscillatory solutions in a large part of the parameter plane, replacing them with OD (see fig. 2, bottom, for $d = 0.008$). Namely, the branch of the asymmetric limit cycle represents a link between two different Hopf bifurcations of stable asymmetric steady states: the slightly asymmetric solution before HB_1 and the OD stabilized through the other Hopf bifurcation, HB_{s1}. The detuning and the strong coupling provide the closed bifurcation branch between $HB_{1(2)}$ and $HB_{s1(2)}$, thus establishing the dominance of the OD regime. For comparison, the α_1 continuation of the HB_{s1} for identical elements always results in an unstable branch, not linked to other regimes.

The effect of OD dominance is observed even for small detuning between the oscillators, although a complete elimination of the oscillatory solutions from the middle of the parameter plane is established only for critical values of d_{ij} and d. By tracing the interdependence of d_{ij} and d, one can determine d_{min} for which OD phenomenon occurs for a fixed detuning between two coupled oscillators (black dotted line in fig. 3, top), as well as d_{crit} for which the OD dominance is established (red dotted line in fig. 3, top). In addition, we present here several examples for $N = 2$ and $d = 0.008$: in the case of identical elements ($d_{ij} = 1$), there is a coexistence of OD with in-phase oscillations (see fig. 3(a)). For $d_{ij} = 0.98$, only a partial dominance of OD is established (fig. 3(b)). However, for $d_{ij,crit} = 0.97$ and $d > d_{crit} = 0.0072$, OD abolishes completely the oscillatory solutions from the middle of the parameter interval, establishing a complete dominance of OD (see fig. 3(c)). Increased detuning between the oscillators, *e.g.*, $d_{ij} = 0.92$, results in an increased parameter region where the effect of OD dominance is manifested (fig. 3(d)).

In the generalized case of N coupled oscillators ($N > 2$), although the dynamics of the system becomes more complex, the dominance of the OD phenomena over given

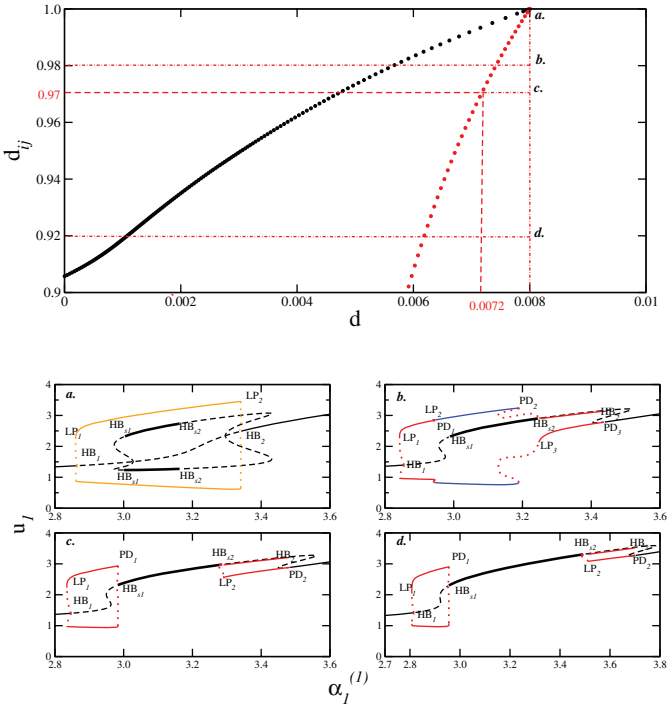

Fig. 3: (Colour on-line) Demonstrating OD dominance. Top figure: interdependence of d and d_{ij}, marking the relevant values from the examples on the bottom figure; bottom figure: a. coexistence of OD and oscillatory solution (in-phase) for $d_{ij} = 1$; b. partial OD dominance for $d_{ij} = 0.98$; c. complete OD dominance at $d_{ij,crit} = 0.97$; and d. reinforced OD dominance for increased detuning, $d_{ij} = 0.92$. The oscillatory branches (different oscillatory solutions) correspond to the discussed solutions in fig. 2.

parameter range persists to exist in the form of cluster formation. For inhomogeneous steady states (OD), the system demonstrates only two cluster decompositions, independently of N. As reported however [25], for N coupled oscillators there exist $N-1$ different distributions of the oscillators between the two stable clusters through which the OD is manifested. In the case of nonidentical elements, grouping of the oscillators between the "upper" and "lower" cluster in OD is still present, although, due to the parameter mismatches present in the system, the concentrations of the proteins produced by different oscillators are slightly inhomogeneous (note that for N cells, we define d_{ij} by fixing the $\alpha_1^{(1)}$ value, and further varying the remaining $N-1$ values of α_1 the range $[\alpha_1^{(1)} \pm 10\%]$). Again, $N-1$ different distributions of the oscillators between the two "cluster groupings" are possible with different stable cluster distributions in distinct parameter intervals (*e.g.*, for $N = 4$ given in fig. 4). The oscillatory solutions are in this case "pushed" between the stable OD distribution branches, thus establishing parameter regions with dominant OD regime. We note here that the effect of clustering in the case of nonidentical elements is out of the scope of the current manuscript, thus we limit here

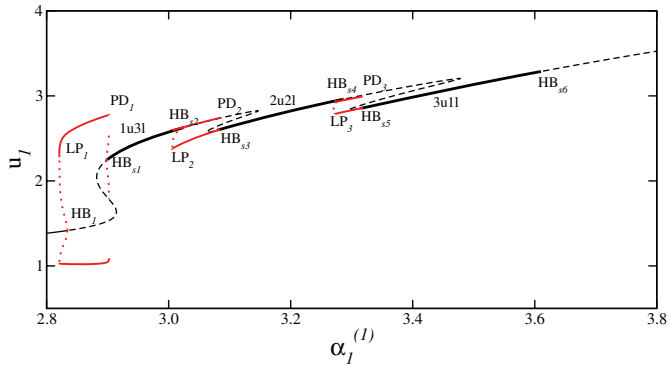

Fig. 4: (Colour on-line) Different stable cluster distributions for $N=4$ coupled oscillators (the bifurcation branch for one oscillator is plotted). From left to right: 1 oscillators located in the "(u)pper" OD cluster, 3 in the "(l)ower" one – $1u3l$ distribution, $2u2l$ and $3u1l$ distribution. The oscillatory solutions (asymmetric oscillations) are "pushed" between the stable distributions, establishing OD dominance. Parameters: $\alpha_1^{(1)}=2.7$, $\alpha_1^{(2)}=2.592$, $\alpha_1^{(3)}=2.646$, $\alpha_1^{(4)}=2.565$, and $d=0.007$. Other parameters as in fig. 1.

our discussions regarding this matter. Moreover, the accuracy of the OD dominance in a system of $N>2$ coupled nonidentical oscillators was re-confirmed by extensive numerical simulations. For example, in order to check for OD dominance in the case of $N=5$, 8 and 11 oscillators, we started from any of the limit cycles which are formed in this system under medium values of the coupling strength d. In contrast to the bifurcation analysis, the set of stable regimes in this method is generated by extensive probing of the large initial values set. Such method is effective for extracting the most probable attractors in cases of many oscillators, for which it is seemingly difficult to perform bifurcation analysis. Then we adiabatically increased the coupling strength and observed critical values of d which destabilized the given limit cycles that is manifested as the transition of phase points from limit cycle to the OD regime. We found that these critical values almost coincide with those found by *Xppaut* for destabilization of quasi-in-phase regime (*e.g.*, see fig. 4, PD_1 bifurcation).

In summary, we have demonstrated that coupling in the presence of detuning provides the dominance of OD, thus eliminating main periodic regimes from the middle part of the phase diagram for two coupled oscillators, whereas in the generalised case (N coupled oscillators), all oscillatory solutions are not removed from the middle of the parameter plane as in the previous case, but a clear dominance of OD is still established. However in both cases, this means that the stable steady states do not compete any longer with the full-amplitude periodic regimes in the phase space and, additionally, the bifurcation branches which start in the HBs through which OD is stabilized, are linked with the HBs of the emerging asymmetric limit cycle. These results are substantially different from previous works on oscillation quenching, where for homogeneous populations, OD always coexists with in-phase oscillations. Moreover, the particular detuning-dependent dominance of OD demonstrates once more the difference between the OD and AD regimes, since disorder of frequency dispersion eliminates AD [31]. Due to the effective realization of the detuning-dependent dominance, we suggest this mechanism as a powerful regulator of the genetic network's dynamics in case of a strong coupling.

In this paper we have devoted special attention to OD, which (in contrast to AD) is poorly investigated in population of globally coupled oscillators. The OD for these systems, as mentioned earlier, manifests itself as a set of two cluster decompositions, with different distributions of cells between them. Both clusters have different stable steady protein concentrations, which might be biologically interpreted as dynamical differentiation. Namely, OD, as a stable inhomogeneous steady state, resembles Turing's dissipative structure [32], only without space variables. In a sense, instead of the space Turing structure, in OD, a set of clusters is present. However, both phenomena are intrinsically related to fast diffusion of the slow variable. The fast diffusion of AI in the problem investigated is a natural process, and the model structure is typical for relaxation oscillators. Therefore we suggest that the phenomenon of OD dominance is rather general (we have confirmed it on other models as well) and the main results presented here will be valid not only for the particular genetic circuit, but, *e.g.*, in general synthetic genetic networks, chemical models and other systems where global intensive inhibitor diffusion takes place.

* * *

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REFERENCES

[1] Van der Pol B. and Van der Mark J., *Philos. Mag.*, **6** (1928) 763.
[2] Ermentrout G. B. and Kopell N., *SIAM J. Appl. Math.*, **54** (1994) 478.
[3] Golubitsky M., Nicol M. and Stewart I., *J. Nonlinear Sci.*, **14** (2004) 207.
[4] Casagrande V. and Mikhailov A. S., *Physica D*, **205** (2005) 154.
[5] Collins J. J. and Stewart I., *J. Nonlinear Sci.*, **3** (1993) 349.
[6] Elson R. C. *et al.*, *Phys. Rev. Lett.*, **81** (1998) 154.
[7] Volkov E. I. and Stolyarov M. N., *Biol. Cybern.*, **71** (1994) 451.
[8] Prigogine I. and Lefever R., *J. Chem. Phys.*, **48** (1968) 1695.

[9] Bar-Eli K., *Physica D*, **14** (1985) 242.
[10] Tsaneva-Atanasova K., Zimliki C. L., Bertram R. and Sherman A., *Biophys. J.*, **90** (2006) 3434.
[11] Dolnik M. and Marek M., *J. Phys. Chem.*, **92** (1988) 2452.
[12] Crowley M. F. and Epstein I. R., *J. Phys. Chem.*, **93** (1989) 2496.
[13] Toiya M., Vanag V. K. and Epstein I. R., *Angew. Chem., Int. Ed.*, **47** (2008) 7753.
[14] Volkov E. I. and Romanov V. A., *Phys. Scr.*, **51** (1995) 19.
[15] Zhai Y., Kiss I. Z. and Hudson J. L., *Phys. Rev. E*, **69** (2004) 026208.
[16] Herrero R. *et al.*, *Phys. Rev. Lett.*, **84** (2000) 5312.
[17] Mirollo R. E. and Strogatz S. H., *J. Stat. Phys.*, **60** (1990) 245.
[18] Ramana Redy D. V., Sen A. and Johnston G. L., *Phys. Rev. Lett.*, **80** (1998) 5109.
[19] Atay F. M., *Phys. Rev. Lett.*, **91** (2003) 094101.
[20] García-Ojalvo J., Elowitz m. B. and Strogatz S. H., *Proc. Natl. Acad. Sci. U.S.A.*, **101** (2004) 10955.
[21] Ullner E., Zaikin A., Volkov E. I. and García-Ojalvo J., *Phys. Rev. Lett.*, **99** (2007) 148103.
[22] Wang R. and Chen L., *J. Biol. Rhythms*, **20** (2005) 257.
[23] Kuznetsov A., Kaern M. and Kopell N., *SIAM J. Appl. Math.*, **65** (2005) 392.
[24] McMillen D., Kopell N., Hasty J. and Collins J. J., *Proc. Natl. Acad. Sci. U.S.A.*, **99** (2002) 679.
[25] Koseska A., Volkov E. I., Zaikin A. and Kurths J., *Phys. Rev. E.*, **75** (2007) 031916.
[26] Gardner T. S., Cantor C. R. and Collins J. J., *Nature*, **403** (2000) 339.
[27] Fuqua C. and Greenberg P., *Nat. Rev. Mol. Cell Biol.*, **3** (2002) 685.
[28] Paulsson J. and Ehrenberg M., *Q. Rev. Biophys.*, **34** (2001) 1.
[29] Koseska A., Volkov E. I., Zaikin A. and Kurths J., *Phys. Rev. E.*, **76 R** (2007) 020901.
[30] Ermentrout B., *Simulating, Analyzing, and Animating Dynamical Systems: A Guide to Xppaut for Researchers and Students (Software, Environments, Tools)* (SIAM Press) 2002.
[31] Rubchinsky L. and Sushchik M., *Phys. Rev. E.*, **62** (2000) 6440.
[32] Turing A., *Philos Trans. R. Soc. London*, **237** (1952) 37.