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Parameter mismatches and oscillation death in coupled oscillators

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We use a set of qualitatively different models of coupled oscillators (genetic, membrane, Ca-metabolism, and chemical oscillators) to study dynamical regimes in the presence of small detuning. In particular, we focus on a distinct oscillation quenching mechanism, the oscillation death phenomenon. Using bifurcation analysis in general, we demonstrate that under strong coupling via slow variable detuning can eliminate standard oscillatory solutions from a large region of the parameter space, establishing the dominance of oscillation death. We argue furthermore that the oscillation death dominance effect provides a reliable dynamical control mechanism in the general case of *N* coupled oscillators. © *2010 American Institute of Physics*. [doi:10.1063/1.3456937]

The dynamical behavior of complex systems has been extensively studied in a vast variety of natural and artificial systems. Despite various rhythmogenic activity which can occur as a response from the interactions among the coupled units, special attention has also been devoted to suppression of oscillations, and the mechanisms for emergence of this phenomenon. We focus here on one of the fairly less studied mechanisms, the oscillation death (OD) phenomenon. Using a set of qualitatively different systems of coupled oscillators (genetic, membrane, Ca-metabolism, and chemical oscillators), we demonstrate that under strong coupling via slow variable detuning can eliminate standard oscillatory solutions from a large region of the parameter space, establishing the dominance of OD. Moreover, we generalize that the effect of OD dominance is independent of the model structure, as well as of the model details and the coupling type. Thus, we propose this effect as an efficient regulator of the system's dynamics. Additionally, since the OD can be considered as an extension of Turing's mechanism in oscillatory media, it can be stated that on one hand, the OD dominance enlarges the robustness of the Turing's structures, and on the other hand, it provides a control for the transition between the steady and oscillating states in developing.

I. INTRODUCTION

Complex system's responses emerging from interactions among coupled units have been extensively studied in various fields, including coupled solid-state lasers,[1] chemical and electrochemical systems,[2,3] heart pacemakers,[4] etc. The dynamical behavior observed in different cases depends both on the coupling organization and strength as well as on the characteristics of the individual oscillators composing the system. Despite various rhythmogenic activities which can occur in coupled systems (e.g., synchronization, as one of the most studied phenomena[5]), special attention has also been paid to the suppression of oscillations, whereby individual oscillators cease to oscillate when coupled and go to one or more equilibrium solutions. In the literature, two main manifestations of the oscillation quenching are known: amplitude and OD phenomena.

Generally, amplitude death (AD) refers to a situation where oscillations are suppressed when individual oscillators are coupled, and return to a steady state of the system instead. Thus, AD results in a *homogeneous* steady state (HSS). There are three main mechanisms that lead to AD phenomena: (i) large mismatches between the oscillator's frequencies result in oscillation suppression,[6,7] (ii) the existence of a time delay in the coupling,[8–12] and (iii) AD can also occur in systems of identical oscillators, but only when they are coupled through dissimilar (or conjugate) variables.[13] AD phenomenon in general has attracted much attention in the investigations of complex dynamical systems, since this particular type of oscillation quenching arises in various examples in physical, biological, and chemical systems, or social sciences, etc. The investigations of AD phenomenon, therefore, range from experimental[14] to various theoretical research,[15,16] etc.

The second manifestation of oscillation quenching—the OD phenomenon, has a significantly different background of occurrence compared to AD. Namely, OD is a result of breaking the system's symmetry through a pitchfork bifurcation (PB) whereby the HSS splits, giving rise to two additional branches, which further gain stability through Hopf bifurcations (HBs). This idea, pioneered by Turing in Ref. 17, was mathematically formulated by Prigogine and Lefever[18] for two identical Brusselators coupled in a diffusionlike manner: their interactions can break symmetry, which leads to a stable *inhomogeneous* steady state (IHSS). Furthermore, it has been shown theoretically that OD is model independent, persisting for large parametric regions in several models of diffusively coupled chemical[19] or biological oscillators.[20] Experimental results reported by Dolnik and Marek[21] show the extinction of oscillations in chemical reactors coupled by mutual mass exchange. Later, Crowley and Epstein[2] demonstrated for two coupled, slightly nonidentical chemical oscillators that the basis for OD is a specific, vector-type coupling, namely, coupling via a slow recovery variable. Recently, OD was also found in a model of globally coupled synthetic genetic relaxators which interact via diffusion of signaling molecules, produced by a protein with slow kinetics.[22] It is important to note that OD in the investigated systems is always accompanied (coexists) in parameter space with stable synchronous oscillations.[2,23,24]

However, OD (in contrast to AD) has been poorly investigated in populations of globally coupled oscillators. On the other hand, the OD phenomenon provides a very important research topic because it produces heterogeneity in a homogeneous oscillating medium. Moreover, this kind of behavior has been correlated and interpreted as a type of dynamical differentiation in biological systems. This view was already initiated by Turing[17] in his investigations of IHSSs in reaction-diffusion systems, and has been further extended by Kaneko,[25] who proposed clustering in coupled map dynamics as a physical background of biological differentiation. Furthermore, in the limits of this approach, it was recently shown[26] that cell differentiation is a result of bifurcation of cell states via intercellular interactions, while the population regulation could be seen through a self-consistent determination of the bifurcation parameter through cell-cell interactions.

In our previous work[27] we have investigated the behavior of globally coupled genetic relaxation oscillators in the presence of small detuning and have shown 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 OD. This result is substantially different from previous findings on oscillation quenching, where for homogeneous populations, the coexistence of OD and limit cycle oscillations is always present. We have also pointed out the fact that this phenomenon is intrinsically related to fast diffusion of the slow variable, a model structure typical for relaxation oscillators. We have therefore hypothesized that the phenomenon of oscillation death dominance (ODD) is rather general and model independent, e.g., ODD could be observed for different models of coupled synthetic genetic networks, chemical and biochemical systems, or other models where a global intensive inhibitor diffusion takes place.

To support this statement, we perform here an extensive analysis of various systems (biological, chemical, synthetic, etc.), which differ in their phase portrait structure as well as coupling mechanisms. By means of bifurcation analysis (using the XPPAUT package[28]), carried out initially on minimal systems of two coupled units, we show that ODD is characteristic for systems with significantly different dynamics and does not depend on the coupling characteristics as long as the general criterion, fast diffusion of the slow variable, is met. Moreover, we investigate and characterize the manifestation of ODD in populations (results being valid for the case of N coupled oscillators, in general), where more complex dynamical structures exist due to clustering of the oscillators.

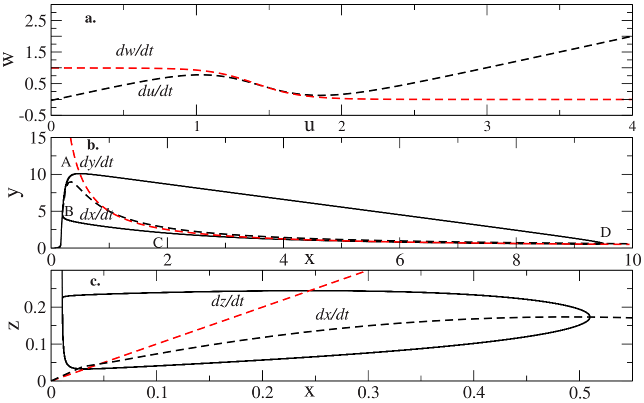

FIG. 1. (Color online) Model overview: (a) characteristic N-shaped nullcline (synthetic genetic oscillator model); (b) nullcline representation (dashed lines) in a triangle limit cycle (Brusselator model); (c) specific structure of the Oregonator model (dashed lines represent the nullclines). The axes notation corresponds to the systems' nomenclature in this manuscript.

II. ODD EFFECT IS INDEPENDENT OF THE SYSTEM'S STRUCTURE: MODEL OVERVIEW

The background of OD, as already mentioned, is fast diffusion of the inhibitor in reaction diffusion systems. There exist various models in the literature for which this type of diffusion is quite natural and for which, in the presence of small detuning, the effect of ODD holds true. Thus, in order to demonstrate the generality of the effect of ODD, we investigate here its manifestation in several models which differ in their dynamics and coupling mechanisms: on the one hand, we investigate several representations of systems characterized with an N-shaped nullcline [see Fig. 1(a)] (e.g., synthetic genetic, membrane or calcium oscillators), and on the other hand, we show the existence of ODD for oscillators with significantly different phase space realizations. The phase portraits of these systems are either triangle [Fig. 1(b)] as in the widely investigated model of the Brusselators, or have a specific structure, as in the model of coupled Belousov–Zhabotinskii (BZ) oscillators, the coupled Oregonators [Fig. 1(c)]. In Secs. II A and II B we discuss in details the dynamics and structure of each model type separately.

A. Representation of oscillators with N-shaped nullclines

The positioning of the nullclines in each system determines its dynamical behavior. In general, in dynamical system with one N-shaped nullcline and a second nullcline represented as a line intersecting the first one [Fig. 1(a)], an occurrence of alternatively slow and fast "relaxation" oscillations is generated over a wide range of parameter intervals. Thus, a general characteristic of these oscillators is the presence of multiple time scales in the system. Although extensively used in electrical engineering and physics, they have become also a modeling tool for many biological and chemical processes. Here, we use a synthetic genetic oscillator,[22] a membrane oscillator,[29] and a model characterizing calcium (Ca^{2+}) oscillations in the pancreatic β-cells[20] as representative examples. We investigate further the presence of ODD in the minimal model of two coupled units, and characterize its dependence on the coupling type and the detuning present in the systems.

1. Model of synthetic genetic relaxation oscillators

In the past several years, collective rhythms of regulatory genetic networks have been a subject of considerable interest, especially because of the fact that the advancement of molecular biology techniques has enabled observations of the dynamics of regulatory networks via engineered synthetic genetic circuits in laboratories. Therefore, several theoretical[22,30–33] and experimental models[34,35] of distinct synthetic oscillators or populations have been proposed and realized. The main means of coupling in the constructed systems has been realized via a transmembrane diffusion of a signaling molecule, called autoinducer (AI), into the extracellular medium. It has been also shown that a particular realization of an AI mediated coupling in these systems can lead to the appearance of OD,[22,24,31] only if the AI is generated by the slow variable, in contrast to the relaxation model,[33] where the production of AI is regulated via the fast variable, and thus, OD does not occur in the system. Generally, the oscillators engaged in OD in synthetic genetic networks are distributed between two clusters, while each being in a stable steady state. This corresponds to two different but constant protein concentration levels.[22,24,31] The presence of OD in synthetic circuits is important on the one hand, since it can be interpreted as a promising tool for cell function regulation: it provides a stable variability of protein concentration. On the other hand, OD can be viewed as an additional mechanism for genetic switching based on interacting limit cycles, a mechanism substantially different from a standard genetic toggle switch.[36]

The model considered here consists of hysteresis-based relaxation genetic oscillators coupled by a quorum-sensing mechanism proposed in Ref. 22. Namely, the oscillator is constructed by combining two engineered gene network components, a toggle switch,[36] and an intercell communication system, which have been previously implemented experimentally in *Escherichia coli*[37] and *Vibrio fischeri*.[38] The synthesis of both repressor proteins, constituting the toggle switch, is regulated in such a way that the expression of the two genes is mutually exclusive, providing for bistability. The second network component is based on the dynamics of the AI, which, on the one hand, drives the toggle switch through the hysteresis loop, and on the other hand provides intercellular communication via diffusion through the cell membrane.

The time evolution of the elements in the system is governed by the dimensionless equations (see Ref. 22 for details),

$$\begin{aligned}\frac{du_i}{dt} &= \alpha_1^{(i)} f(v_i) - u_i + \alpha_3 h(w_i),\\ \frac{dv_i}{dt} &= \alpha_2 g(u_i) - v_i,\\ \frac{dw_i}{dt} &= \varepsilon(\alpha_4 g(u_i) - w_i) + 2d(w_e - w_i),\\ \frac{dw_e}{dt} &= \frac{d_e}{N}\sum_{i=1}^{N}(w_i - w_e),\end{aligned} \tag{1}$$

where N is the total number of cells (oscillators), u_i and v_i represent the proteins of which the toggle switch is made in the ith cell, w_i and w_e are the intra- and extracellular AI concentrations, respectively. The dimensionless parameters $\alpha_1^{(i)}$ and α_2 regulate the operation of the repressor in the toggle switch, α_3—the activation due to the AI, and α_4—the repressing of the AI. 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 the model (established for $\varepsilon \ll 1$) allows the system to produce relaxation oscillations which emerge via a HB.

In our previous work[27] we have assumed that the detuning between different cells is achieved with variability in the α_1 parameter values, thus defining $d_{ij}=\alpha_1^{(i)}/\alpha_1^{(j)}$ as a detuning measure between the cells. The suggestion for introducing the variability in α_1 is realistic from an experimental point of view, because this parameter is affected by the plasmid copy number, which, in turn, is changing during the cell proliferation. We have observed that under strong coupling via the slow variable, the detuning can eliminate standard oscillatory solutions for a system of $N=2$ coupled synthetic units in a large region of the parameter space, providing ODD [Fig. 2(b)], in contrast to the case of identical elements [Fig. 2(a)], where a clear coexistence of OD and a full amplitude oscillatory regime is observed. Note that even for slightly detuned parameter values, the HSS corresponding to cells being identical "splits" in slightly IHSSs with different concentration values. Thus, in Fig. 2(b), and later throughout the manuscript, the analysis is preformed following the dynamical changes of the system through the upper level branch of the slightly IHSS. This result was characterized in detail for different coupling and detuning values in Ref. 27.

However, almost all biological processes, especially those that occur on a genetic level, are noisy in general. Thus, many regulatory parameters differ when comparing separate cells. Moreover, even in a well-controlled experimental setup, it is often very difficult to pinpoint in which parameter specifically variations occur. Therefore, it will be of general interest to investigate additionally the cumulative effect of many parameter mismatches on ODD. In particular, this could be achieved by introducing heterogeneity in several parameters which influence the dynamics of single genes, the coupling values, and the index of time scale separation. Allowing such situations to occur (e.g., variability

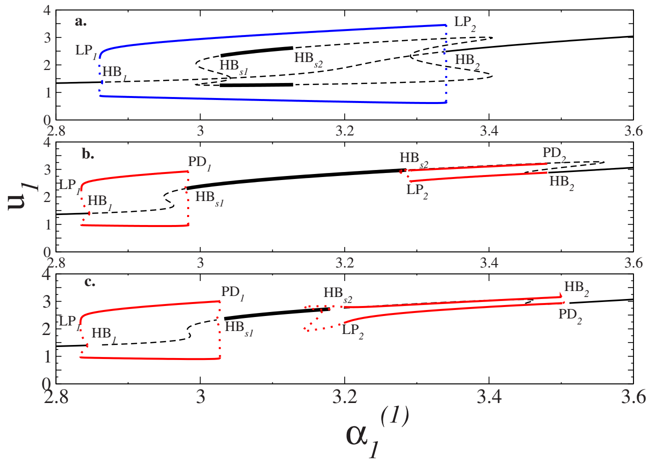

FIG. 2. (Color online) Manifestation of OD and ODD in a system of coupled synthetic oscillators [Eq. (1)]. (a) Coexistence of OD and limit cycle oscillations for identical elements—$d_{ij}=1$, $d=0.006$; (b) ODD for $d_{ij}=0.97$ and $d=0.008$; (c) ODD under a cumulative effect of parameter mismatches in $\alpha_1^{(i)}$, ε, and d. Other parameters: $\alpha_2=5.0$, $\alpha_3=1.0$, $\alpha_4=4.0$, $\varepsilon=0.01$, $d_e=1$, and $N=2$. Here and in the following charts, solid lines denote stable steady and oscillatory solutions, whereas dotted and dashed lines refer to unstable steady/oscillatory solutions. Thick solid black lines denote stable OD (IHSS), and thin solid black lines denote stable HSS. The limit cycles represent in-phase solutions (blue lines online) in (a) and Figs. 3–5 and 6(a), quasi-in-phase solutions [blue lines online in Figs. 5(b), 5(c), and 6(b)], asymmetric regimes [red lines online in Figs. 2(b), 2(c), 3, 4(b), 6(b), and 7], and inhomogeneous limit cycles (red lines online) in Figs. 5(a)–5(c) and 8(b). LP represents limit point, PD a period doubling, and PB a pitchfork bifurcation. A detailed description of all dynamical solutions of the system of coupled synthetic oscillators is given in Ref. 27.

present also in d and ε) lowers the initial detuning threshold (in α_1) necessary for the realization of ODD; an example of a cumulative detuning effect on ODD is shown in Fig. 2(c). Thus, the mismatches present in various parameters in the system most probably increase the possibility for ODD and enlarge the parameter interval where this effect could be observed. This situation in a certain way accounts for the robustness of ODD, allowing for a wide window of possibilities and experimental manipulations where this particular type of oscillation quenching could be observed and investigated. Additionally, ODD is also observed when d_e is varied, preserving its existence even when the diffusion of the AI in the extracellular medium is not very fast (results not shown here).

2. The membrane model

In this section we consider the interactions of another strong relaxation oscillator generating a limit cycle due to the N-shaped nullclines. In particular, we investigate a model used to describe the kinetics of lipid peroxidation in a cell membrane, which in the 1970s was also interpreted as a model for the cell cycle of mammalian cells.[29,39] The phase portrait of this model is in general very similar to the structure of the synthetic genetic oscillator discussed previously. However, due to the biological relevance, a different coupling type, namely, local coupling via the slow variable, seems more appropriate here.

The reduced dimensionless form for two coupled oscillators may be then written as

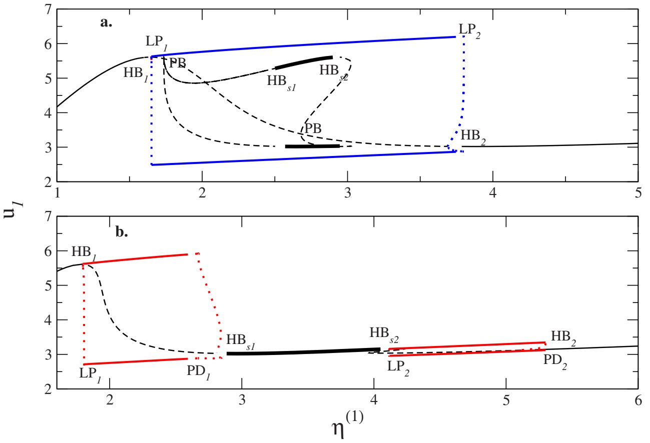

FIG. 3. (Color online) (a) Coexistence of OD and in-phase oscillations for two identical membrane oscillators [Eq. (2)], $d_{ij}=1.0$, $d=0.5$; (b) ODD for $d_{ij}=0.7$, $d=0.5$. Other parameters: $\gamma=0.5$, $\delta=0.15$, and $\varepsilon=0.05$. Due to the proximity to the bifurcation point, the bifurcation branch is not completely closed.

$$\frac{dx_i}{dt}=\frac{1}{\varepsilon}\left(k+0.5x_iy_i-x_i^2-\frac{1.5\gamma x_i}{x_i+\delta}\right),$$

$$\frac{dy_i}{dt}=\eta^{(i)}-1.5x_iy_i-dy_i-\frac{0.5\gamma x_i}{x_i+\delta}+d(y_{i+1}-y_i). \tag{2}$$

The parameter ε controls the stiffness of the oscillators and could vary between 0.1 and 0.01, and d denotes the coupling strength. These equations are derived from a realistic set of chemical equations, but for our purpose here, we will omit all physicochemical details and consider this system as a paradigmatic model for an oscillator of relaxation type. For identical oscillators and any value of the coupling coefficient for which OD is present in the system, there is a clear coexistence of the OD regime with the full amplitude oscillatory regimes [Fig. 3(a)]. However, a slight divergence introduced in the η parameter ($d_{ij}=\eta^{(i)}/\eta^{(j)}$) values assures for a complete removal of the oscillatory solutions from the middle of the parameter interval [Fig. 3(b)].

The occurrence of ODD is linked to the interdependency of the coupling strength and the detuning present in the system. This characteristic is general and valid for all systems where ODD is observed. As discussed in Ref. 27, ODD emerges 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 coupling strength d. In general, if a smaller variability between the cells is present, then a larger coupling coefficient is necessary in order to observe ODD, and vice versa, if the cells differ significantly between each other, then even small coupling values will produce ODD in the system.

As we have shown so far, the occurrence and the stability of ODD do not depend directly on the coupling characteristics of the system. As long as diffusive coupling via the slow variable is assured, ODD can be observed independently of the organization of the coupling—ODD exists in various systems for which different coupling mechanisms (local or global) are "natural" in the distinct cases.

3. Ca-metabolism in insulin-secreting pancreatic β-cells

An important control center in glucose homeostasis is the insulin-secreting pancreatic β-cell, localized in the islets of Langerhans. Insulin secretion is a complex multicellular process, which relies on the interaction between β-cells within an islet as well as on the interactions between islets in the pancreas. Under normal conditions, glucose stimulation evokes well-synchronized oscillations of the cytosolic Ca^{2+} concentration ($[\mathrm{Ca}^{2+}]_i$) in the β-cells in an islet, which in turn triggers pulses of insulin secretion.[40,41] It has been suggested that a disturbance in the Ca^{2+} oscillations could contribute to the irregularity of insulin oscillations in diabetes patients. Therefore, it is of outmost interest to investigate and characterize the mechanism underlying the coordination and the metabolic coupling in pancreatic β-cells. However, the extent of the metabolic coupling and its influence on islet cell coordination is unclear.[42] In Ref. 20, for e.g., the effect of intracellular Ca diffusion has been analyzed using a Morris–Lecar-like β-cell model.[43] It was shown that surprisingly, the diffusion of calcium through gap junctions, if too strong, can have a desynchronizing effect by promoting OD, from which it was concluded that Ca gap-junctional diffusion does not make an important contribution to the normal function of pancreatic islets of Langerhans. Since the Ca oscillation model can be classified as another representative of relaxation oscillators with an N-shaped nullcline, we extend our investigations here to the possibility for ODD in this case as well, and examine the necessary conditions under which the production of constant Ca concentrations dominates in the system.

The particular model is explained in detail in Ref. 20. For the purpose of our investigations we introduce, however, a reduced form of the model, which is sufficient to characterize the occurrence of ODD with the following representation:

$$\frac{dV_i}{dt} = \frac{1}{C_m}(I_{\mathrm{app}} - I_{i_K} - I_{i_{K(\mathrm{ATP})}} - I_{i_{C_a}} - I_{i_{K(C_a)}} - I_{i_c}),$$

$$\frac{c_i}{dt} = f_{\mathrm{cyt}}(-\alpha I_{i_{C_a}}(V_i) - k^{(i)}_{\mathrm{PMCA}} c_i + g_{c,C_a}(c_j - c_i)), \tag{3}$$

where V represents the membrane potential, and c accounts for the cytosolic calcium concentration, $[\mathrm{Ca}^{2+}]_i$. The parameter $k^{(i)}_{\mathrm{PMCA}}$ denotes the plasma membrane C_a^{2+} ATPase pump rate, and in the case of two coupled cells, for which we are performing the bifurcation analysis here, we define the divergence as $d_{ij} = k^{(i)}_{\mathrm{PMCA}} / k^{(j)}_{\mathrm{PMCA}}$. Other variables have the same notation and values as in Ref. 20. Although similar investigations of coupled nonidentical cells were performed in Ref. 20, the authors there have used a strong heterogeneity (divergence of order 0.2) and very high coupling coefficients ($g_{c,C_a} \sim 0.5$), which resulted in a large parameter interval where OD is stable. Moreover, for such coupling values, there is a coexistence of OD, the HSS of the system, and stable oscillations. In contrast to this, we investigate here the dynamical behavior of coupled β-cells in the region of moderate coupling ($g_{c,C_a} \sim 0.035$), and a parameter mismatch not greater than 4% in their k_{PMCA} values, which fulfills the condition that the symmetry of the system is being broken and OD has been observed. Under these relations, a clear coexistence of OD and in-phase oscillations is present in the case of identical elements [Fig. 4(a)], whereas for the current choice of parameters (4% divergence between individual cells), a partial ODD can be established [Fig. 4(b)], removing the stable oscillatory solutions from the middle of the parameter interval.

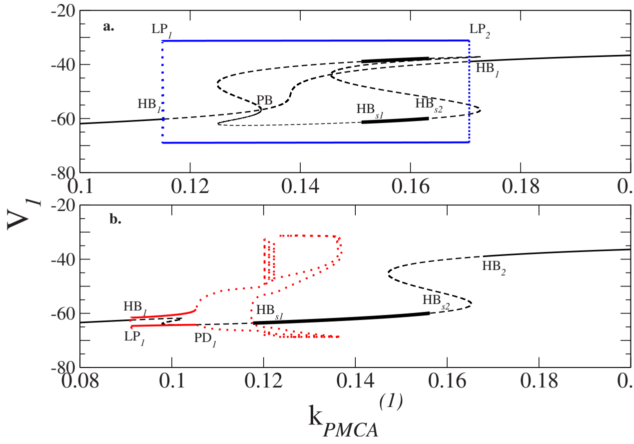

FIG. 4. (Color online) Manifestation of (a) coexistence of OD and limit cycle oscillations for a system of $N=2$ coupled identical Morris–Lecar-like β-cells [Eq. (3)], where $d_{ij}=1.0$ and $g_{c,C_a}=0.035$; (b) ODD for divergence $d_{ij}=1.3$ and $g_{c,C_a}=0.035$. Other parameters as in Ref. 20.

B. Representation of oscillators with model-specific phase portraits

In this section we investigate conditions necessary for the emergence of ODD in systems which differ in their dynamical structure from the previously investigated oscillators with N-shaped nullclines. In particular, we consider two chemical models, the well-known Brusselator model and a model describing BZ reaction using a simplified Oregonator model. Although no general subclassification of these models exists, both systems are characterized with specific phase portraits. In general, the Brusselator has a particular triangle phase portrait [Fig. 1(b)] with three distinct times (or rates) on the cycle: $T_{\mathrm{slow}}(T_{AB})$ being the time of a phase point motion on the slow (left) part of the x-nullcline, the time of jump to the y-nullcline is denoted as $T_{\mathrm{fast}}(T_{BC}, T_{DA})$, and $T_{\mathrm{moderate}}(T_{CD})$ characterizes the time of motion of the phase point on the y-nullcline. The relaxation of the oscillators is defined as $T_{\mathrm{slow}}/(T_{\mathrm{fast}}+T_{\mathrm{moderate}})$. On the other hand, the Oregonator model has a more specific structure of the phase portrait, marked by the coexistence of the HSS and IHSS. In contrast to the models describing the oscillators with an N-shaped nullcline which contain the parameter ε in an explicit form, the stiffness in these two models is controlled by the kinetic parameters. In what follows, we analyze in detail the conditions necessary for the appearance of OD and ODD separately in both systems.

1. Model of two diffusively coupled Brusselators

The Brusselator is an autocatalytic model involving two intermediates. It illustrates how the fundamental laws of thermodynamics and chemical kinetics as applied to open systems far from equilibrium can give rise to self-organizing behavior and dissipative structures in the form of temporal oscillations and spatial pattern formation. In the simplest form, the Brusselator model includes two coupled variables representing the concentrations of the intermediate products. Thus, the classical model for two identical Brusselators with vector coupling (via y) through a semipermeable membrane is described by

$$\frac{dx_i}{dt} = A^{(i)} - (B+1)x_i + x_i^2 y_i, \qquad \frac{dy_i}{dt} = Bx_i - x_i^2 y_i + d(y_j - y_i). \tag{4}$$

The coupling as given here is not the most customary one, since we disregard coupling through activatory variables, but it is the limiting case of the general asymmetrical coupling. Although this representation of the model does not exactly correspond to a specific chemical reaction, it is useful for investigations because it is paradigmatic and it has permitted to obtain a lot of analytical results which could be further generalized. Moreover, steady states and oscillatory regimes for coupled Brusselators were investigated in details,[19,23,44–47] but for identical elements. It has also been observed that coupling the Brusselators via the inhibitory y-variables contributes to an easier detection of OD for coupling greater than a predefined value, $d_{\text{crit}} > 0.309$, even for soft oscillators. Moreover, the region of OD is more pronounced in the (B,D) parameter plane for $A=1$. We will therefore continue to use this parameter plane for OD description, but investigate its dependence on the divergence introduced in the A values of separate elements $(d_{ij}=A^{(i)}/A^{(j)})$. However, we note that the results obtained below are not sensitive to this choice of A values.

Using a linear stability analysis in the case of identical elements, $d_{ij}=1$, it can be easily estimated that the HSS looses its stability through a HB for $B > A^2+1$ (i.e., $B_{\text{crit}}=2$, for $A=1$, which will be used in this work), where a limit cycle is created. Thus, a clear coexistence of OD and in-phase oscillations [emerging from HB_1 in Fig. 5(a)] is observed. Moreover, the oscillators easily demonstrate a spatially inhomogeneous limit cycle (IHLC) [emerging from HB_{s2} in Fig. 5(a)], born via a HB of the IHSS and provides high frequency oscillations with amplitudes very sensitive to coupling values.

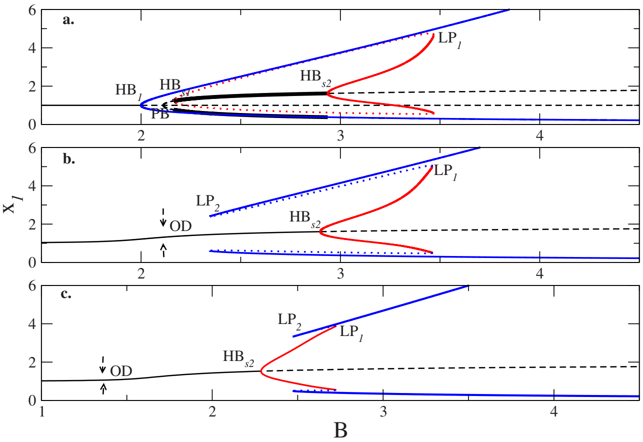

FIG. 5. (Color online) (a) OD realization for two identical Brusselators [Eq. (4)] ($d_{ij}=1$ and $d=0.45$), (b) ODD for two nonidentical Brusselators with $d_{ij}=0.97$ and $d=0.45$, and (c) ODD manifestation for $d_{ij}=0.97$ and $d=1.4$.

In contrast to the case of identical Brusselators [Fig. 5(a)], the bifurcation structure is qualitatively different when a slight diversity is introduced in the system. A specific property of the bifurcation diagram in this case is the absence of a gap between OD and the stable HSS (the HSS and the IHSS here are not separated with an unstable steady state). Therefore, we mark the "left" OD limit $B > A^2/2D+1$ (a detailed analysis of the system is given in Ref. 23) with additional arrows in the bifurcation continuation, whereas the "right" boundary of OD is characterized with a HB [Fig. 5(b)]. Apart from this, the parameter B has no upper limit and the amplitude of oscillations is increased for larger B values, making the oscillators very stiff. Although a nonstandard situation, OD "pushes" the oscillatory solutions [IHLC (emerging from HB_{s2} in Fig. 5) and quasi-in-phase regime (emerging from LP_2 in Fig. 5(b))] to the side, thus establishing dominance over a given parameter interval in this case as well.

Due to the condition $B > A^2/2D+1$, for larger coupling values, the left OD limit is pushed further to smaller B values [see Fig. 5(c), where $B_{\text{crit}} \approx 1.36$ for $d=1.45$]. Again, the HSS and the IHSS are not separated with an unstable steady state. Thus, the oscillatory solutions could be created only through a HB marking the right stability end of the OD solution. This means that the oscillatory regimes are shifted to higher B values, and the detuning [$d_{ij}=0.97$ in Fig. 5(c)] abolishes completely the oscillatory solutions in a large part of the parameter plane, replacing them with OD, and establishing a clear dominance of the OD regime (ODD).

2. Belousov–Zhabotinskii oscillators—system of coupled Oregonators

Coupled chemical oscillators are key components of many naturally occurring but also constructed systems, and have been therefore in the center of scientific research for a long time. One of the most frequently used models to investigate the dynamics of chemical systems is the model constructed from two, nearly identical BZ oscillators, physically coupled by mass transfer. One manifestation of such a system is given through a three-variable Oregonator model used in Ref. 2 to elucidate how the chemistry of the system generates the various behavior (such as OD, in-phase and antiphase oscillations) observed in experiments. We are interested whether this experimentally realized system manifests ODD, taking in mind the selective roles of the activatory and inhibitory variable exchanges which are difficult to separate in experiments.

For the purpose of our investigations, we use the Oregonator model in the most simplified, two-dimensional form,

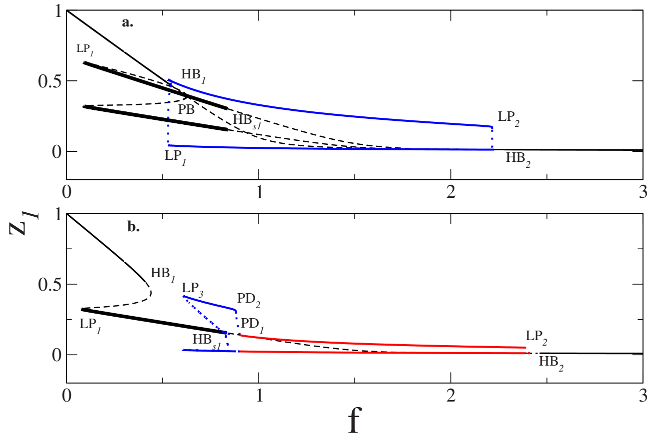

FIG. 6. (Color online) Characterization of (a) OD for $N=2$ coupled identical Oregonators ($d_{ij}=1.0$, $d=1.0$) and (b) effect of ODD for nonidentical Oregonators [Eq. (5)] ($d_{ij}=1.2$, $d=1.0$). Other parameters: $\varepsilon=0.05$, $q=0.005$.

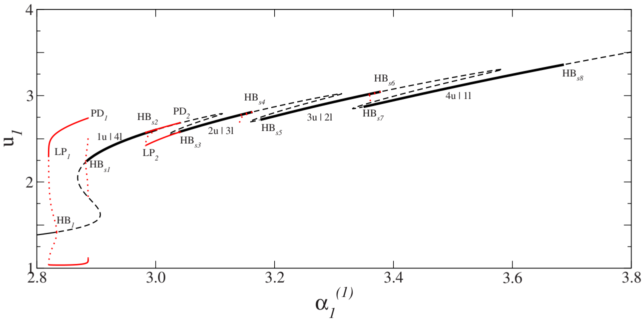

FIG. 7. (Color online) Different stable cluster distributions for $N=5$ coupled oscillators (the bifurcation branch for one oscillator is plotted). From left to right: one oscillator located in the "(u)pper" OD cluster, four in the "(l)ower" one—$1u|4l$ distribution, $2u|3l$, $3u|2l$, and $4u|1l$ distributions. The oscillatory solutions—asymmetric oscillations are pushed between the stable distributions establishing ODD. $d=0.008$ and $d_{ij}=0.97$. Other parameters as in Fig. 2.

$$\frac{dx_i}{dt}=\frac{1}{\varepsilon}\left(x_i(1-x_i)-f^{(i)}z_i\frac{(x_i-q)}{q+x_i}\right),$$
$$\frac{dz_i}{dt}=x_i-z_i+d(z_j-z_i). \tag{5}$$

Here, ε and q are kinetic parameters related to the reagent reaction rates, as well as f, through which we define the divergence in the system as $d_{ij}=f^{(i)}/f^{(j)}$. x and z are proportional to the concentration of HB_rO_2 and metal ions.[2]

In the case of identical elements, the bifurcation diagram is a nonstandard one compared to the systems with an N-shaped nullcline. Here, in a large part of the parameter interval, there is a coexistence of OD with a HSS of the system, and an additional coexistence with the in-phase oscillations [see Fig. 6(a)]. However, for a slight divergence in the f values, dominance of OD is established, although a partial coexistence of the IHSS with the full amplitude oscillatory solutions still exists [see Fig. 6(b)]. For increased diversity between the coupled Oregonators in the system, the ODD will be complete (charts not shown here).

III. EMERGENCE OF OSCILLATION DEATH DOMINANCE IS INDEPENDENT ON THE SIZE OF THE SYSTEM

Diffusive local or global coupling in systems consisted of many oscillators can have an important effect on both, local dynamics and pattern formation (the second being recently related to clustering[26]). Dynamical differentiation, or clustering, on the other hand, has been observed in chemical systems, e.g., in globally coupled chaotic and periodic metal electrodissolutions.[48,49] Additionally, in our recent work, we have investigated the effect of OD and its contribution to cooperative differentiation in multicellular populations,[50] where we have shown that populations display richer dynamical behavior, and the effect of clustering has to be considered when analyzing OD. Therefore, in this section we study the effects that the size of the system has on the emergence of ODD, separately for a system characterized with an N-shaped nullcline (the model of synthetic relaxation oscillators), and a system with different dynamical characterization, the Brusselator.

A. Coupled synthetic genetic relaxation oscillators

In the generalized case of N coupled oscillators ($N>2$), the dynamics of the system becomes more complex due to the possibility for cluster formation. As we have previously reported,[24] in the deterministic case of N coupled oscillators, there exist $N-1$ different distributions of the oscillators between two stable clusters through which OD is manifested. Each of the separate cluster distributions here is characterized with slightly different protein concentration levels, distinguishing the $N-1$ clusters from each other. Furthermore, in the case of nonidentical elements, grouping of the oscillators between the "upper" and "lower" clusters in OD is still present, although due to the detuning 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 in the range $[\alpha_1^{(1)}\pm 10\%]$, as discussed in Ref. 27). Again, $N-1$ different distributions of oscillators between the two "cluster groupings" are possible with different stable cluster distributions in distinct parameter intervals (e.g., for $N=5$ given in Fig. 7). ODD is established in the given parameter regions, "pushing" the oscillatory solutions between the stable OD distribution branches. Although the number of cluster distributions increases with N, the qualitative behavior of the system does not change. Thus, the effect of ODD can be generalized to large populations, as shown for a system of five coupled oscillators here. Moreover, the accuracy of ODD in a system with $N>2$ coupled nonidentical oscillators was reconfirmed by extensive numerical simulations (results not reported here). The same generalization of ODD holds true for all previously investigated systems characterized with an N-shaped nullcline as well.

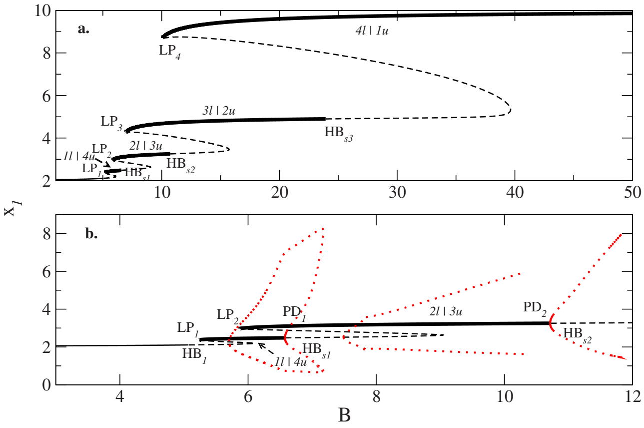

FIG. 8. (Color online) (a) OD cluster groupings in the case of $N=5$ coupled Brusselators. (b) Dominance of the OD solution over the oscillatory regimes (stable regions are plotted with solid and unstable with dotted lines). Parameters: $d=0.6$ and $d_{ij}=0.99$.

B. Manifestation of ODD for *N* coupled Brusselators

As we have already discussed, the dynamical structure of the Brusselator model differs in general from systems characterized by an N-shaped nullcline, and a characteristic, nonstandard manifestation of ODD is observed [Fig. 5(b)]. For these reasons, we investigate the influence of the system size on the emergence of ODD in a system of five coupled Brusselators, generalizing it further for N coupled oscillators. Similar to the previous case of the synthetic system, there exist $N-1$ different distributions of the oscillators between the two "cluster groupings" through which OD is manifested in the case of diffusively coupled Brusselators as well. These distributions correspond to a separation of the oscillators in the lower and the upper level of OD [e.g., $1l|4u$, $2l|3u$, etc., as shown in Fig. 8(a)]. The bifurcation analysis here is performed only on the upper branch of the IHSS. Thus, we present here only that part of the diagrams necessary for the current discussion. These $N-1$ cluster distributions are stable in distinct parameter intervals. However, due to their specific structure, namely, the coexistence of separate stable branches, the oscillatory solutions are not strictly "pushed" between the stable OD branches (Fig. 8(b) shows a zoomed region for $B \in [1,12]$), where the partial coexistence of OD and limit cycle solutions, as well as between different OD distributions, is clearly shown. Thus, complete ODD is not established in this system, since there are small parameter regions where the oscillatory and the OD solutions coexist. In the major region of the parameter interval where stable OD branches are created, however, the oscillatory solutions are unstable, thus leaving the ODD as the unique solution in these parameter intervals [Fig. 8(b)].

Since the effect of ODD is sustained when the number of oscillators in the system increases, we can generalize it and show that ODD is preserved over the oscillatory solutions in a wide parameter interval ranges and holds true for the case of N coupled oscillators.

IV. DISCUSSION

In this work we have devoted special attention to the emergence of OD phenomena, particularly analyzing the conditions under which a dominance of this OD can be established. As already shown in Ref. 27 in the limits of a specific genetic model, coupling in the presence of detuning provides ODD, eliminating the periodic regimes from the same parameter interval in the phase diagram. In that context, we have demonstrated first of all that the observation of ODD requires significantly smaller parameter mismatches in the genetic oscillators if several parameters are detuned. Next, we have generalized here the conditions under which ODD occurs in various systems which differ in their dynamical characteristics.

On one hand, ODD is manifested for systems with a relaxation type of oscillations, a specific property of systems characterized with an N-shaped nullcline, such as genetic, calcium, and membrane oscillators, whereas on the other hand, ODD can also be observed for oscillators with a model-specific phase portrait, e.g., a triangle phase portrait (the Brusselators), or have a specific structure of coexistence of HSS and IHSS (the Oregonator model). Moreover, we have investigated the dependence of ODD on the coupling characteristics and showed that in systems where a fast diffusion of the inhibitor in reaction diffusion systems has been met, as those which are analyzed here, in the presence of detuning, the emergence of ODD is generic for local as well as for global coupling. Thus, we can generalize, at least for these two large groups of models, that ODD is independent of the model structure, as well as of the model details and the coupling type: the OD regime does not compete any longer with the full amplitude periodic regimes in the phase space, establishing its clear dominance in the phase plane. Additionally, the size of the system does not influence the emergence of ODD. In the case of N coupled oscillators ($N>2$), although the dynamics of the system becomes more complicated due to the clustering that occurs, the OD regime pushes the oscillatory solutions to the side, establishing again a clear dominance over the remaining dynamical regimes.

OD is the manifestation of an inhomogeneous stable steady state in homogeneous media. Since the initial work by Turing in this field, a lot of attention has been paid to the mechanisms which lead to the occurrence of IHSSs, but for a stationary medium in which the point element is in a steady state. Thus, OD may be considered as an extension of Turing's mechanism in oscillatory media, although the phase space is shared with a limit cycle. Additionally, ODD, which we discuss here and which is observed for reasonable and natural values of parameter detuning, enlarges the robustness of the Turing structures in oscillatory media. Taking in mind that such structures are considered as a background of morphogenesis and differentiation, we can speculate that ODD not only extends the applicability of Turing's idea, but also provides an additional parameter, the value of detuning, which can control the transitions between steady and oscillating states in developing, in particular, biological systems.

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