Topological structures enhance the presence of dynamical regimes in synthetic networks

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Genetic and protein networks, through their underlying dynamical behavior, characterize structural and functional cellular processes, and are thus regarded as "driving forces" of all living systems. Understanding the rhythm generation mechanisms that emerge from such complex networks has benefited in recent years by synthetic approaches, through which simpler network modules (e.g., switches and oscillators) have been built. In this manner, a significant attention to date has been focused on the dynamical behavior of these isolated synthetic circuits, and the occurrence of unifying rhythms in systems of globally coupled genetic units. In contrast to this, we address here the question: Could topologically distinct structures enhance the presence of various dynamical regimes in synthetic networks? We show that an intercellular mechanism, engineered to operate on a local scale, will inevitably lead to multirhythmicity, and to the appearance of several coexisting (complex) dynamical regimes, if certain preconditions regarding the dynamical structure of the synthetic circuits are met. Moreover, we discuss the importance of regime enhancement in synthetic structures in terms of memory storage and computation capabilities. © *2010 American Institute of Physics*. [doi:10.1063/1.3515200]

The understanding of the primary rhythm generation mechanisms in biological networks in general is a necessary precondition to characterize system's structures and elementary design principles. Recently, synthetic biology has offered a "concept of reduced complexity," analyzing the dynamical characteristics of genetic and metabolic networks in terms of single building blocks (synthetic switches and oscillators), which are further combined to display complex cooperative behavior. In accordance with this concept, we address here the question whether topologically distinct structures will enhance the presence of dynamical regimes in synthetic networks. We show that an autoinducer-mediated intercellular signaling mechanism organized in local manner inevitably leads to the formation of complex dynamical structures. Additionally, we discuss the importance of regime enhancement in synthetic circuits in terms of memory storage and computation capabilities.

I. INTRODUCTION

Cellular populations exhibit complex collective behavior. Their dynamics is generally determined by the underlying genetic or metabolic networks, where the distinct genes or metabolites communicate with each other through different means, e.g., chemically. Thus, understanding the primary rhythm generation mechanisms would lead to valuable information characterizing system's structures and elementary design principles. Recently, the study of complex biological networks has profited from the notion of reduced complexity which synthetic biology offers. In particular, the design of artificial genetic units resembling submodules of natural circuitry (e.g., switches[1–3] and oscillators[4–7]) offers the opportunity to study specific cellular functions and signaling pathways for which limitations occur in the natural environment. On the other hand, the construction of bacterial strains that exhibit programmed behavior offers a novel, engineering-driven approach in biological research, which focuses on larger-scale changes of existing cellular architectures and on the construction of elaborate synthetic systems for the solemn goal to improve or regulate the given biological properties. The fulfillment of these tasks in turn imposes new challenges on the current synthetic biology research, requiring substantially new design principles and improved understanding of the cellular environment. Thus, it is necessary to design and investigate large-scale systems, allowing the synthetic units to communicate with each other. This requirement is an absolute requisite to ensure an appropriate and global cellular response to external signals in both cases: (i) construction of synthetic networks as a means to exploit the design principles of natural genetic networks and (ii) design of synthetic circuits to serve as a control mechanism for gene expression, protein function, or metabolism in cellular populations.

Recently, the possibility to use the quorum-sensing mechanism in order to investigate global synchronization in synthetic genetic networks has been reported for deterministic[8–10] as well as for noise-driven[11] genetic oscillators. It is important to point out that these circuits are globally coupled through small molecules of autoinducer (AI) diffusing between cells. This intercellular signaling mechanism, if governed by the slow time scale in the system,[12]

organizes the coupling through the slow recovery variable. The result is a coupling mechanism with phase-repulsive properties, mainly known as inhibitory coupling. We have shown in our previous investigations[13,14] that multistability and multirhythmicity are inherently present in genetic networks characterized with global, inhibitory coupling. In particular, we have shown that multirhythmicity is a result evoked by interactions (with phase-repulsive inhibitory properties) of globally coupled identical biological oscillators with relaxation dynamics. Moreover, the presence of global coupling between the oscillators resulted also in clustering, as a main manifestation of multistability.

The ability of genetic units to produce different dynamical regimes which also coexist is significant from various perspectives. First, multirhythmicity and the coexistence of several attractors for natural genetic networks imply a substantially improved adaptability: if one of the regimes becomes unprofitable for cell functioning, the genetic unit can easily switch to some other coexistent regime. Second, the presence of multistability and multirhythmicity in synthetic genetic circuits is an important phenomenon from an engineering perspective, since both offer an intriguing potential for numerous biotechnological applications (biosensors, programming genetic units, etc.). It has been reported, e.g., that multistability is a main mechanism for memory storage and temporal pattern recognition.[15]

It is a well known fact, however, that chains (rings) of locally coupled identical oscillators, in contrast to the globally coupled scenario, undergo complicated bifurcation transitions, including the coexistence of multiple periodic orbits with different frequencies and amplitudes, spatial patterns, and modulation instabilities.[16–18] Moreover, ensembles of (uni)bidirectionally coupled oscillators with a ring topology play an important role in the information processing in neuroscience and medicine, e.g., such networks are involved in the generation of stable periodic motor commands by central pattern generation of the nervous system controlling rhythmic regulation in animals.[19]

Thus, in contrast to the previous investigations, where only global communication mechanisms were considered, we elaborate here the possibility of rhythm enhancement if the synthetic system is characterized with diffusive, local coupling architectures. We propose for this purpose a modified synthetic design where the oscillators are coupled diffusively in a local manner. Using detailed bifurcation[20] and numerical analysis, we discuss the underlying mechanisms which give rise to novel collective phenomena and explore its possibilities for information processing and memory storage.

II. MODEL EQUATIONS

The model considered here is a modification of a hysteresis-based relaxation genetic oscillator coupled by a quorum-sensing mechanism proposed in Ref. 12. In particular, the oscillator is constructed by combining two engineered gene network components, a toggle switch,[1] and an intercell communication system.[21,22] The synthesis of both repressor proteins constituting the toggle switch is mutually exclusive, providing bistability. The intercellular signaling 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.

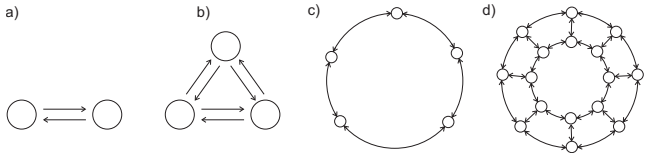

FIG. 1. Schematic representations of the investigated systems. (a) $N=2$, (b) $N=3$, (c) $N=5$, and (d) $N=16$ locally coupled oscillators.

In contrast to the original model, where oscillators in separate cells communicate with each other in a global manner, here we define a synthetic design where local communication is established (see Fig. 1). In the most general case, each of the oscillators communicates only with the neighboring synthetic unit(s). The time evolution of the elements in the system is governed by the dimensionless equations (see Ref. 12 for details),

$$\frac{du_i}{dt} = \alpha_1 f(v_i) - u_i + \alpha_3 h(w_i),$$

$$\frac{dv_i}{dt} = \alpha_2 g(u_i) - v_i, \tag{1}$$

$$\frac{dw_i}{dt} = \varepsilon(\alpha_4 g(u_i) - w_i) + 2d(w_{i+1} + w_{i-1} - 2w_i),$$

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, and w_i represents the concentration of AI molecules which diffuse through the cell membrane. The dimensionless parameters α_1 and α_2 regulate the operation of the repressor in the toggle switch, α_3 is the activation due to the AI, and α_4 is the repressing of the AI. The coupling coefficient in the system is given by d and depends 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.

III. DYNAMICAL CHARACTERISTICS OF LOCALLY COUPLED OSCILLATORS

Contemporary models of synthetic networks consist of oscillators, globally coupled with AI exchange,[8,9] exhibiting mainly in-phase oscillatory behavior. Additionally, the existence of inhomogeneous steady state (IHSS) has been reported.[12–14,23] Moreover, in our previous investigations, we have determined the underlying mechanisms leading to the appearance of multiple dynamical regimes and clustering.[13,14] In particular, we have defined that a necessary condition for multistability and multirhythmicity in synthetic genetic networks is the presence of inhibitory diffusive coupling with phase-repulsive properties. In contrast to these, we report here that the observed rhythmicity in synthetic

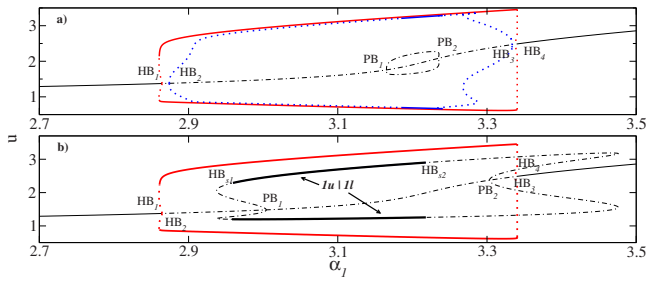

FIG. 2. (Color online) Bifurcation diagram obtained by variation of α_1 to illustrate the (a) oscillatory and (b) OD regimes. Parameters: $\varepsilon=0.01$, $\alpha_2=5$, $\alpha_3=1$, $\alpha_4=4$, $\beta=\eta=\gamma=2$, and $d=0.001$ (a), $d=0.005$ (b). Here and in the following charts, thin solid lines denote a stable steady state, thick solid lines denote a stable OD regime, and dashed-dotted lines denote an unstable steady state. The limit cycles are given in gray, with solid lines denoting stable, and dotted lines denoting unstable limit cycles.

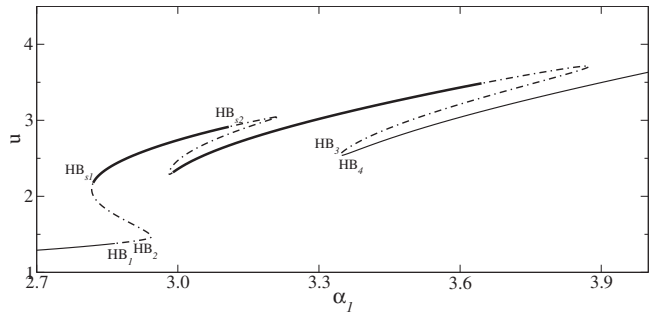

FIG. 3. Different distributions of the oscillators between the clusters: the left stable branch displays a $1l|2u$ distribution, whereas the $2l|1u$ distribution is stable in the right part of the branch. $N=3$ and $d=0.005$. Other parameters as in Fig. 2.

networks can be enhanced if coupling mechanisms with local characteristics are defined. We discuss here two main phenomena: the existence of different possible modes of organized collective behavior manifested via constant protein concentrations and a complex dynamical behavior obtained for coupled ring structures. Moreover, we show and characterize a specific feature of identical genetic oscillators locally coupled on a ring: the manifestation of an inhomogeneous steady state in a multiple cluster distribution. This is not standard and previously not reported for genetic networks. Additionally, we compare and discuss the differences in the dynamical structure of locally and globally coupled systems in terms of biotechnological applications. It is important to note here that our results, although obtained for relatively small networks ($N=2$, 3, 5, and 16 oscillators), could be further generalized for large-scale systems.

A. Identification of characteristic dynamical regimes via bifurcation analysis

The dynamical structure of the minimal case of $N=2$ locally coupled oscillators [Fig. 1(a)] does not differ from the corresponding globally coupled example. This is, of course, expected, since both coupling mechanisms have identical characteristics in the restricted case of two coupled units. Thus, the bifurcation analysis in this case shows the presence of both in-phase and antiphase oscillations (the second being present for low coupling values), which in turn depend on the diffusion properties of the membrane. Both periodic branches, as shown in Fig. 2(a), are marked with Hopf bifurcations (HBs), showing a clear coexistence of these oscillatory regimes. The behavior of the system is however changed when the coupling coefficient (d) is increased. In particular, for $d_{\text{crit}}=0.003$, stable inhomogeneous steady state emerges in the system.

The IHSS [also called oscillation death (OD)], as in the case of globally coupled oscillators, is a result of symmetry breaking of the steady state in the system through a pitchfork bifurcation [PB in Fig. 2(b)].[24–26] This means that the unstable homogeneous steady state splits into two additional branches which gain stability through Hopf bifurcations, denoted as HB_{s1} (HB_{s2}) in Fig. 2(b). We note here that in the minimal case of $N=2$ locally coupled oscillators, the OD phenomenon is manifested as a two cluster distribution (identical to the global coupling scenario[12–14]). The oscillators populate the two clusters and remain in a steady state, i.e., producing constant protein levels in the cell. The distribution of the oscillators between these two stable clusters, however, depends on the number of oscillators composing the system. In the minimal case presented here, there is only one possible distribution: one of the oscillators populates the lower stable cluster, whereas the second one populates the upper stable cluster, a situation which we denote as $1l|1u$ [Fig. 2(b)]. The minimal extension of this system [$N=3$ identical oscillators, as in Fig. 1(b)], on the other hand, allows two different distributions $1l|2u$ and $2l|1u$. Both of them are stable in a given α_1 interval range, as shown in Fig. 3. We note here that we introduced a slight heterogeneity between the distinct oscillators in the system ($<0.1\%$) in order to obtain the complete bifurcation chart, as shown in Fig. 3. Therefore, only the upper bifurcation branch is shown.

In the most general case, for N synthetic oscillators, locally coupled in a diffusive manner, $N-1$ different distributions of the oscillators between the two clusters are possible, each characterized with a shift in the protein production level (we have identified and characterized the identical system's properties in the case of globally coupled oscillators as well[13]).

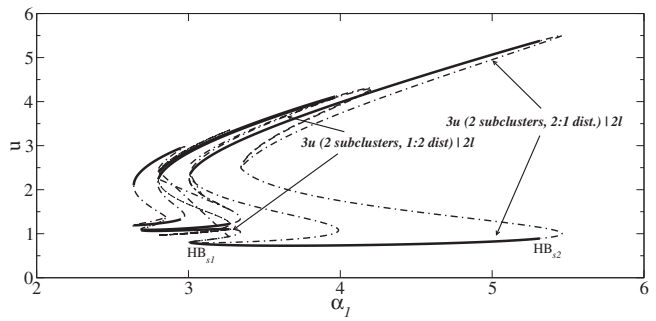

FIG. 4. Different cluster distributions for $N=5$ oscillators locally coupled, as shown in Fig. 1(c). $d=0.05$ and other parameters as in Fig. 2.

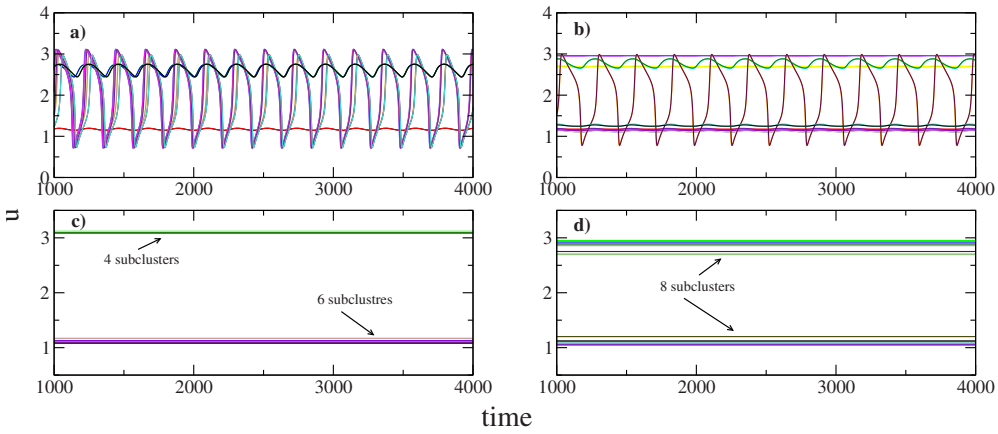

FIG. 5. (Color online) Complex dynamical structures for $N=16$ oscillators (coupling mechanism as shown in Fig. 1). (a) $\alpha_1^{\text{ring-I}}=\alpha_1^{\text{ring-II}}=3.1$, $d^{\text{ring-I}}=d^{\text{ring-II}}=d_c=0.003$; (b) $\alpha_1^{\text{ring-I}}=3.1$, $\alpha_1^{\text{ring-II}}=2.97$, $d^{\text{ring-I}}=0.0042$, $d^{\text{ring-II}}=0.047$, $d_c=0.001$; (c) $\alpha_1^{\text{ring-I}}=\alpha_1^{\text{ring-II}}=3.1$, $d^{\text{ring-I}}=d^{\text{ring-II}}=d_c=0.0047$; (d) $\alpha_1^{\text{ring-I}}=3.1$, $\alpha_1^{\text{ring-II}}=2.97$, $d^{\text{ring-I}}=0.0042$, $d^{\text{ring-II}}=0.047$, $d_c=0.005$. Other parameters as in Fig. 2.

B. Characterizing enhanced number of dynamical regimes

1. Formation of steady state clusters

In contrast to the contemporary examples of globally coupled synthetic oscillators, the local structure imposed on the intercellular signaling mechanism here enables the presence of enhanced number of various dynamical regimes for increased size of the system. In what follows, we discuss in particular the OD case. The investigation of synthetic networks where oscillation death occurs is important, since OD provides stable heterogeneity in a homogeneous medium. This could further imply possible mechanisms characterizing cell differentiation, usually associated with the existence of distinct attractors in genetic regulatory networks.[27,28]

In systems characterized with local signaling mechanisms, due to the spatial organization of the cells and the diffusive properties of the local, phase-repulsive coupling, OD is manifested via complex dynamical structures. Hence, in addition to the standard two cluster decomposition, a different cooperative behavior of the oscillators is possible. The lower (upper) level (or both) is now constituted of several subclusters, characterized with different protein expression levels. In the case of $N=5$ identical oscillators [Fig. 1(c)], the occurrence of OD in a form of a three-cluster decomposition is possible, with different distributions of the oscillators between the stable attractors (Fig. 4) (stable with respect to small perturbations).

Thus, we can state that the local topological structures, compared to the globally coupled scenarios, contribute to an enhanced number of possible dynamical regimes in the synthetic network. It is important to note here that due to the design principles of the particular circuits, cells are localized in space, and thus controllable (in terms of expressed protein concentrations). Additionally, it is a well accepted fact that OD is considered as an extension of Turing's mechanism[29] in oscillatory media, although the phase space is generally shared with a limit cycle. Namely, OD as a stable inhomogeneous steady state resembles Turing's dissipative structures, only without space variables. In a sense, instead of the spatial Turing's structure, in OD, a set of clusters is present. However, both phenomena are intrinsically related to fast diffusion of the slow variable. Taking in mind that this behavior has been correlated and interpreted as a type of dynamical differentiation and considered as a background of morphogenesis, one could speculate that enhanced rhythmicity, which is obtained via intercellular signaling mechanisms characterized with local properties, plays a crucial role in these processes. Moreover, the characteristics of OD as manifested in the locally coupled structures (multiple stable distinct steady state levels) are main mechanisms for memory storage and temporal pattern recognition (e.g., registration, storage, and information processing). One could envision a new synthetic design based on the currently investigated network properties in order to construct small synthetic units to serve as efficient memory devices, offering enhanced storage capabilities (depending on the number of subclusters present) in contrast to the contemporary memory devices.

2. Complex dynamical structures

The modes of organized collective behavior in structures of locally coupled synthetic units (oscillators) are multiplied for increased system sizes. The complexity of the corresponding dynamical regimes is manifested with the formation of multiple (sub)clusters, which could be observed even for a slight increase of the size of the system. In particular, we investigate a dynamical scenario where two rings of phase-repulsively coupled synthetic oscillators (each ring containing $N=8$ identical oscillators) are additionally coupled through the corresponding ring elements [e.g., the first oscillator of the outer ring is coupled to the corresponding oscillator in the inner ring, etc., as shown in Fig. 1(d)]. The numerical analysis we have performed shows a significant enhancement of the possible dynamical regimes, characterized with distinct different properties. We investigated two different scenarios: (i) both rings are identical, and the coupling strength between the rings (d_c) is equal to the coupling strength inside the distinct rings ($d^{\text{ring-I}}=d^{\text{ring-II}}=d_c$), (ii) oscillators are identical within a single ring, but characterized with different α_1 values in separate rings ($\alpha_1^{\text{ring-I}}=\alpha_1^{\text{ring-II}}$). Moreover, the coupling strengths in this case differ as well, such that $d^{\text{ring-I}}\neq d^{\text{ring-II}}\neq d_c$.

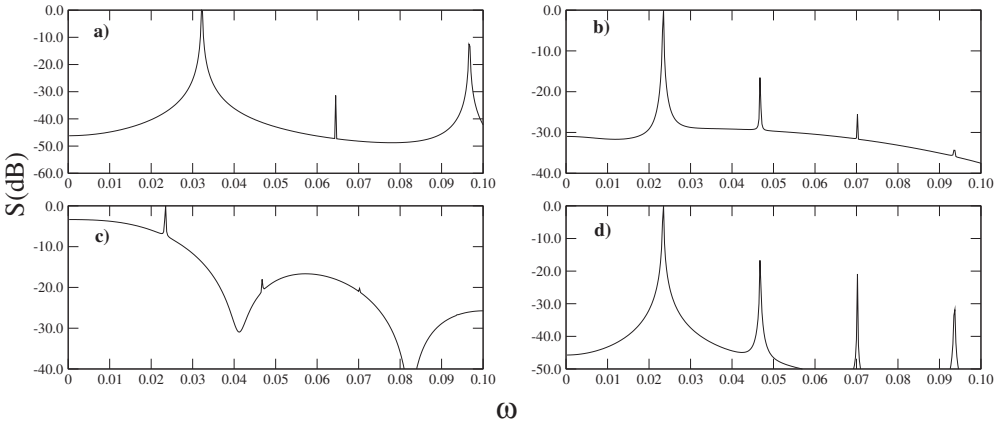

FIG. 6. Power spectra for (a) the case of $N=16$ identical, globally coupled oscillators. [(b)–(d)] Power spectra for three from a locally coupled structure of $N=16$ identical relaxators [as shown in Fig. 1(d)]. Other parameters as in Fig. 2.

The number of complex dynamical structures is significantly increased, as the number of oscillators, and the possible coupling scenarios increase. Therefore, a complete characterization of the dynamical behavior is impossible to perform for larger systems. We can however generalize that under small and intermediate coupling, different complex oscillatory solutions could be observed [an example is given in Fig. 5(a)]. These structures are characterized with multiple cluster distributions, described with phase and/or amplitude changes. Despite these, the dynamical picture of the system is enhanced with mixed complex solutions, where some of the oscillators are located in the stable OD regimes, whereas others perform oscillatory behavior with various amplitude values [Fig. 5(b)]. If the coupling intensity is slightly increased, various manifestations of the OD regime are possible [4:6 subcluster distributions, as shown in Fig. 5(c), or an OD manifestation where both the upper and the lower levels are defined via 8 subclusters, Fig. 5(d)].

The enhanced presence of complex modes of organized collective behavior in the case of locally coupled structures in contrast to their globally coupled counterexamples can be further determined by the gradual changes in the corresponding power spectra, as shown in Fig. 6.

IV. DISCUSSION

The presence of multistability and multirhythmicity in synthetic biological circuits is an important phenomenon from an engineering perspective, since both offer an intriguing potential for numerous biotechnological applications. We have shown in this paper that specific topological structures, characterized with AI-mediated inhibitory coupling with local properties, inevitably lead to an enhanced presence of various dynamical regimes in synthetic genetic networks. Thus, the results presented here are significantly different from the corresponding characteristics of globally coupled synthetic systems. We underline in particular the nonstandard manifestation of OD, where separate stable clusters are additionally characterized with the formation of subclusters. Moreover, we have identified a possibility for different oscillator distributions between separate (sub)clusters, which in turn leads to multiple stable attractors and complex dynamical structures in systems of identical oscillators, locally coupled on a ring.

Recent advances in the so-called rolled-up nanotechnology have led to the realization of the idea to use bioanalytic microsystems for spatial and temporal control of single cells.[30] In particular, biological components could be integrated into single rolled-up tubes, which are processed in parallel with high throughput and excellent reproducibility. This new type of highly integrative lab-on-a-tube technology thus provides the possibility to confine precise number of single cells equipped with the corresponding synthetic circuits in distinct nanotubes. Such spatial configuration of the cells will then allow the AI molecules to diffuse only between neighboring cells, in which manner, the local coupling characteristics will be fulfilled.

Therefore, one could envision and assume that the ability of genetic circuits to display a rich multistable behavior opens the possibility for the construction of new-era computational and memory storage devices, based on genetic and DNA-computing. Additionally, it is important to mention that the results reported here represent only partially the richness of the dynamical structures obtained in a synthetic network, if local coupling mechanisms characterize its design. One could further speculate that the genetic networks profit from the elaborated enhanced rhythmicity: increasing the multistability and multirhythmicity in a given network enhances the fitness of the cellular population under environmental changes and optimizes network's functionality. However, the complexity of the dynamical features observed in these cases requires additional investigations, opening simultaneously numerous questions, e.g., the characterization of dynamical scenarios where multiple, globally coupled cellular populations communicate with each other in a "local manner."

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