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Research paper

How to couple identical ring oscillators to get quasiperiodicity, extended chaos, multistability, and the loss of symmetry

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ABSTRACT

We study the dynamical regimes demonstrated by a pair of identical 3-element ring oscillators (reduced version of synthetic 3-gene genetic Repressilator) coupled using the design of the 'quorum sensing (QS)' process natural for interbacterial communications. In this work QS is implemented as an additional network incorporating elements of the ring as both the source and the activation target of the fast diffusion QS signal. This version of indirect nonlinear coupling, in cooperation with the reasonable extension of the parameters which control properties of the isolated oscillators, exhibits the formation of a very rich array of attractors. Using a parameter-space defined by the individual oscillator amplitude and the coupling strength, we found the extended area of parameter-space where the identical oscillators demonstrate quasiperiodicity, which evolves to chaos via the period doubling of either resonant limit cycles or complex antiphase symmetric limit cycles with five winding numbers. The symmetric chaos extends over large parameter areas up to its loss of stability, followed by a system transition to an unexpected mode: an asymmetric limit cycle with a winding number of 1:2. In turn, after long evolution across the parameter-space, this cycle demonstrates a period doubling cascade which restores the symmetry of dynamics by formation of symmetric chaos, which nevertheless preserves the memory of the asymmetric limit cycles in the form of stochastic alternating "polarization" of the time series. All stable attractors coexist with some others, forming remarkable and complex multistability including the coexistence of torus and limit cycles, chaos and regular attractors, symmetric and asymmetric regimes. We traced the paths and bifurcations leading to all areas of chaos, and presented a detailed map of all transformations of the dynamics.

1. Introduction

Coupled oscillators are the most frequently used model to study such collective phenomena as synchronization [1], wave generation, multistability [2] etc. in all fields of fundamental science and its applications. Coupling can quench oscillations by either suppressing all oscillators to the same fixed point (amplitude death) or by creating an inhomogeneous stable steady-state (oscillation death, see [3] for review) which shares the phase space with other oscillatory regimes. There are

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many designs of coupling initiated by studies of real systems: starting from the old classic observations of pulse-coupled fireflies, direct scalar or vector reagents exchange between chemical reactors, electric and/or synaptic interactions between neurons, up to very recent investigations of combined coupling between chemical oscillators [4], half-center oscillator configurations constituted by two bursters [5], and plant interactions [6], which attempt to explain biennial rhythm in fruit production. Nonlocal connections between oscillators can lead to the formation of chimeras (coexistence of coherent and incoherent clusters) in homogeneous populations, even of very different natures: phase oscillators [7,8], chemical oscillators [9], metronome ensemble [10], see [11] for review. However, chimera death is also determined by the particular coupling mechanism [12].

During the last decade new experimental objects – synthetic genetic oscillators – have attracted great attention [see e.g. reviews: [13,14] as a new tool for probing the mechanisms of gene expression regulation and as a possible instrument for genetic therapy. We explore the ring-type oscillator which is a well-known circuit in physics and applied technology [e.g. review [15]], and became very popular in synthetic biology after 2000 under the name of "Repressilator" [16] due to its actual assembly and insertion into the bacterial cell E.coli. The Repressilator consists of three genes whose protein products (A, B, C) repress the transcriptions of each other unidirectionally in a cyclic way (..A–┫ B–┫ C–┫ A..). Recently this circuit has been improved upon [17,18], "making it an exceptional precise biological clock" [19]. The electronic analog of the Repressilator was presented in [20,21]. The cooperativity of transcription repression, which is the core process of the Repressilator, is typically described by the Hill function $\sim\boldsymbol{\alpha}/(1+\mathbf{x}^{\mathbf{n}})$ where $\mathbf{x}$ is repressor abundance. The dynamics of coupled Repressilators is very sensitive to the value of $\mathbf{n}$ which controls the steepness of repression and $\boldsymbol{\alpha}$ which determines the amplitude of the isolated Repressilator**.**

The effectiveness of a genetic oscillator such as the Repressilator depends on how they can function collectively, thereby requiring a coupling method. An almost obvious suggestion was to use the natural bacterial quorum sensing (QS) mechanism, used for cell-cell communication in bacterial populations [22,23], as the instrument to synchronize genetic oscillators located in different cells. The core of QS is the production of small molecules (autoinducer) which can, first, easily diffuse across the cell membrane and external medium and, second, work to activate/repress transcription of an intended target gene. By manipulating the positions of the gene providing the autoinducer production and QS-sensitive promoters controlling the transcription of other genes in the genetic circuits, one can obtain different coupling types and, as a result, different sets of collective modes in populations of synthetic genetic oscillators. If the autoinducer is not only a signal molecule but also works as an integral participant of the oscillator then its diffusion provides the direct coupling which supports, for example, the wave propagation in bacterial populations [24].

Alternatively, QS may be implemented in a genetic oscillator as an additional element not required for the generation of the auto-oscillations. In this case the coupling may be described as indirect because its activity is mediated by the complex chain: production of autoinducer, its diffusion and binding with the promoter of the target gene. Such coupling is typically nonlinear because of bimolecular interaction of autoinducer and target instead of the linear intercellular diffusion of similar variables in direct coupling. This coupling method has been explored in model simulations of QS-coupled relaxation oscillators [25,26] and repressilators [27], and its ability to synchronize the in-phase regime for detuned populations was demonstrated. Further work [28] has demonstrated that the model [27] may exhibit more complex collective regimes if the ranges of key parameters are reasonably extended. Later, in-phase synchronization of coupled Repressilators in the presence of noise was demonstrated [29]**.** More complex and flexible dynamics, which better corresponds to biological diversity, have been demonstrated in [30,31].

In this work we couple two Repressilators via the scheme of quorum sensing, as suggested in [32,33]. In this version of coupling it is important that the production of signal molecules is associated with the gene which is located inside the Repressilator ring upstream with respect to the target gene, which accepts the impact of autoinducer. This means that this coupling should be classified as "conjugate", because in the ordinary differential equation (ODE) system (1) (see the next section), the production of the autoinducer and its effect on the target gene are controlled by the equations for different repressors. Intercellular communication is realized by the simple diffusion of autoinducer but the coupling as a whole is more complex since it cannot be reduced to the well-studied diffusion-controlled ODE**.** Such a coupling seems quite acceptable for real genetic networks and nevertheless may be constructed in artificial networks of a different nature.

Recently [34] we have demonstrated by numerical and electronic simulations that two coupled identical Repressilators show the development of very flexible dynamics if the $\mathbf{n}$ increases up to $\mathbf{n}=4$. We found spatially homogeneous and inhomogeneous types of chaos over large areas of the coupling strength ($\mathbf{Q}$) as well as the set of periodic windows which contains inhomogeneous limit cycles partially synchronized with i: j winding number, e.g. $i=1,2,\ldots,\ j=i+1$ despite the identical nature of the oscillators.

Our main goal here is to trace the routes from self-organized quasiperiodicity to the unusual collective regimes, including homogeneous (spatial symmetric) chaotic regimes and inhomogeneous (spatial asymmetric) limit cycles. We present the detailed map of isolated and overlapping regimes over a large plane of the key parameters $\mathbf{Q}$ (coupling strength) and $\boldsymbol{\alpha}$ (oscillator strength) for other parameters fixed. To present the results in a foreseeable form, we restrict the ratio $\boldsymbol{\alpha}$-max / $\boldsymbol{\alpha}$-min to 25, based on a reasonable scatter of the corresponding experimental data on the difference between weak and strong promoters [35,36].

It is known that in the model [33] the anti-phase (**AP**) limit cycle, which is the single stable attractor under small coupling strength, loses stability via torus bifurcation if the coupling strength increases. This torus-bifurcation boundary between the AP limit cycle and stable self-organized quasiperiodicity delineates a very large region in the $\mathbf{Q}$-$\boldsymbol{\alpha}$ plane inside