Control of synchronization in inhibitory coupled genetic oscillators

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Abstract

The cellular function is regulated at the level of gene expression. Due to the complexity of underlying processes the study of gene expression dynamics is possible only with synthetic genetic networks, which include limited numbers of interacting genes. Especially interesting that such synthetic genetic networks allow studying of quorum-sensing or interaction between cells to understand the mechanisms of clustering, synchronization and cell differentiation. In this study the nonlinear dynamics of an ensemble of genetic relaxators have been simulated under the influence of noise, intrinsically present on many stages of gene expression. Numerically it was shown and explained that the control of population size, coupling strength and intensity of fluctuations can effectively change the dynamics of the system. These results should help in design of artificial genetic chips or in understanding of natural and very complex genetic networks.

Brief biography

I have obtained PhD in Physics & Mathematics in 1998 at Moscow State University (Russia) and Habilitation at Potsdam University (Germany) in 2003. In 2004 I was working as a lecturer at Exeter University (UK). From 2005 I lead the VW-project in Potsdam. I apply ideas and methodology of nonlinear dynamics and statistical physics to the investigation and modeling of complex biological systems, in particular on the intercellular level. My current investigations include the study of the proteasome function (protein degradation) and research of genetic networks (i.e. protein synthesis).

Description of the work

An important goal of bioengineering is the design and construction of integrated genetic circuits that are capable of performing elaborate functions in a cellular context. For instance, nanorobots can be created by encoding a synthetic gene into DNA, coupling in the necessary way, and downloading it into a cell. To achieve that goal understanding genetic networks is important. For this aim, the investigation of gene dynamics is indispensable, that is now possible only with synthetic genetic circuits, which consist of a limited number of genes that are designed to operate relatively isolated from the rest of the cellular machinery. Even on this level the dynamics of interacting genes

can be very complex because there exists interaction between cells, called as quorum sensing, and because all biomolecular processes of gene expression are intrinsically stochastic. Additionally, the cell colony can grow, and hence the number of interacting circuits is always increased.

The goal of this project was to investigate how quorum sensing, stochasticity and population size may influence and control the dynamical regimes of coupled synthetic genetic oscillators. Recent experimental progress in designing of oscillating genetic networks, e.g. a ring oscillator [1] or a relaxator [2], has opened the gate for quantitative analysis or modeling of more complex genetic circuits. In this project I have investigated the model of coupled synthetic relaxators, recently suggested in [3]. The relaxator oscillators coupled via quorum sensing proposed in [3] are constructed by combining two synthetic gene networks, one of which is a toggle switch [4], in which two genes mutually repress each other and operate in a bistable regime. The second network is based on the dynamics of an autoinducer (AI) which drives the toggle switch and provides an intercell communication. These networks have been experimentally realized in *Escheria coli* and *Vibrio fischeri*. The scheme of this genetic network is presented in Fig.1.

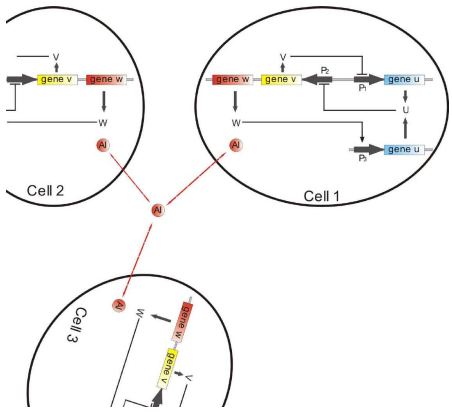

Figure 1: Scheme of coupled genetic relaxators. The genetic network inside each cell is coupled with another cell by a diffusion of small autoinducer molecules, which influence the gene expression.

Significance and Potential Relevance

Synthetic genetic networks represent a basic step towards logical cellular control, whereby biological processes could be monitored and manipulated at the DNA level. From the construction of simple genetic relaxators one can envision the design of devices and genetic software capable of performing elaborate functions in living cells. The resulting cell can then be used for *in vivo* biosensing, synthesizing complex biomaterials, executing programmed cell death, or

interfacing with microelectronic circuits by transducing biochemical events to and from electronics. The results obtained here with extensive numerical simulations have shown how we can control dynamics regimes in a population of coupled genetic relaxators and, in this way, program the necessary functions.

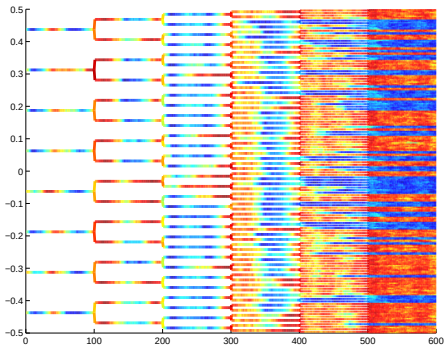

Figure 2: Example of cell tree visualization. The cell population is growing along the time line (x-axis). The protein concentration inside each cell is encoded with a color, from blue (low concentration) to red (high concentration). It is clearly seen that genetic oscillators undergo oscillation death and are clusterized, because at the right we can only see blue and red colors, but not the colors in between.

Methodologies applied and resources used

Each genetic relaxator is described by a system of three first order stochastic differential equations (SDE). One more equation is necessary to describe the dynamics of intercellular media. Since, the population of many coupled relaxators have been studied, simultaneous simulation of many SDE have been used. Sometimes, to check the population size effects and related with that reduction of stochasticity the simulation of up to 300,000 differential equations with noise was necessary. For this research the usage of high-performance computing was of absolute importance. I have used facilities and help of personnel of CESCA-CEPBA computer centre in Barcelona (Kadesh computer). Such massive and extensive simulations have been impossible without support of the HPC-EUROPA project.

After simulation the time series obtained have been analyzed using methods of nonlinear dynamics. Additionally, for the visualization of the dynamics the cell growth trees have been used.The example of such cell tree, that illustrate clustering, is shown in Fig.2. On this tree the concentration of the protein is encoded with a color bar.

Results, presentations and publications

I have numerically studied the effect of noise, quorum sensing, and population size in an ensemble of genetic relaxation oscillators. It was shown that naturally occurring noise can be exploited in a way to control the dynamics of the system, switching the system between synchronous oscillations and the regime of oscillation death, and oscillation suppression. These results allow controlling the dynamics by variation of the noise intensity. This control is qualitatively different fo different values of quorum sensing strength, because strong coupling in this system leads to the regime of oscillation death, i.e. clusterization, what means biologically the cell differentiation. Interestingly the intermediate noise leads not to randomness but to the improved periodicity of genetic oscillations. This features can be probably used in the construction of genetic clocks. Finally the system size effects have been investigated. It was shown that the dynamics of the system is sufficiently affected by the variation of population size. The results obtained could be used in bioengineering or in the study of natural genetic networks.

These results have been presented as follows:

1. Seminar talk "Noise-induced Effects in Complex Biosystems", Barcelona-Terrassa, Spain, 16.06.2005.

2. Poster, "Control of gene expression in ensemble of genetic oscillators", International Seminar & Workshop on Nonlinear Dynamics in Biophysics, Dresden, Germany, June 27-July 1, 2005.

These results are summarized and will be submitted at the end of January 2006 in two papers:

1. A. Zaikin, A. Koseska, J. García-Ojalvo, and J. Kurths, "Quorum sensing and cell growth induce programmed diversity in noisy genetic oscilla tors", (title is tentative, in preparation).

2. A. Koseska, A. Zaikin, J. García-Ojalvo, and J. Kurths, "Noise, Quorum Sensing and Population Size Controlled Oscillations in Relaxator Genet ic Oscillators", (title is tentative, in preparation).

Acknowledgments

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