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Dynamics of synthetic genetic repressilators with phase-repulsive coupling

Oscillatory processes have been discovered in various biological contexts. Circadian clock [1], biochemical oscillations [2] and cell cycle [3] are the well-known examples.

Recently, there were constructed genetic networks exhibiting a specific type of dynamical behavior [4, 5, 6]. A prominent example of synthetic genetic circuit is the repressilator constructed of three transcription factors inhibiting each other in cyclic way. The obvious output of such interaction is oscillations in protein concentrations [4].

Synthetic genetic circuits are organized simpler than natural ones and can evince important details of dynamical properties of the latter.

Given that cells interact with each other it would be of particular interest to investigate dynamics of such integrated population. Quorum sensing is the coupling mechanism found in many bacteria and utilizes a small molecule, autoinducer, which diffuses through cell membrane and activates some target gene [7].

Two theoretical schemes of the repressilator with the quorum sensing coupling mechanism were proposed earlier: phase-attractive [8] and phase-repulsive [9]. The latter one utilizes a negative feedback loop in the autoinducer production module in addition to the average negative feedback loop of the repressilator core. The following system of dimensionless equations describes the behavior of coupled repressilators with phase-repulsive coupling [9]:

$$\begin{aligned}
\frac{\mathrm{da_i}}{\mathrm{dt}} &= -a_i + \frac{\alpha}{1+C_i^n}; & \frac{\mathrm{dA_i}}{\mathrm{dt}} &= -\beta(A_i - a_i) \\
\frac{\mathrm{db_i}}{\mathrm{dt}} &= -b_i + \frac{\alpha}{1+A_i^n}; & \frac{\mathrm{dB_i}}{\mathrm{dt}} &= -\beta(B_i - b_i) \\
\frac{\mathrm{dc_i}}{\mathrm{dt}} &= -c_i + \frac{\alpha}{1+B_i^n} + \kappa\frac{S_i}{1+S_i}; & \frac{\mathrm{dC_i}}{\mathrm{dt}} &= -\beta(C_i - c_i)
\end{aligned}$$

$$\frac{\mathrm{dS_i}}{\mathrm{dt}} = -k_{s0}S_i + k_{s1}B_i - \eta(S_i - Q\bar{S})$$

The uppercase letters A_i, B_i and C_i denote protein concentrations, while lowercase a_i, b_i and c_i are proportional to the concentrations of mRNA corresponding to those proteins, S_i denotes AI concentration, where i is a cell index. $\bar{S} = \dfrac{1}{N}\sum\limits_{i=1}^{N} S_i$, where N is the total number of cells. α is a maximal transcription rate. n is Hill coefficient or cooperativity. Q is proportional to population density. β is the ratio between mRNA and protein lifetimes.

We have investigated dynamics of synthetic genetic oscillators — repressilators — coupled through autoinducer diffusion in phase-repulsive manner. We have examined emergence of periodic regimes, stable inhomogeneous steady states depending on the main systems' parameters: coupling strength and maximal transcription rate. However, these regimes were shown to exist in [9].

It has been found that the autoinducer production module added to the isolated repressilator causes the limit cycle to disappear through infinite period bifurcation for sufficiently large transcription rate (α). We have found hysteresis of limit cycle and stable steady state, the size of which is determined by ratio between mRNA and protein lifetimes.

Two coupled oscillators system demonstrates stable anti-phase oscillations which can become a chaotic regime through invariant torus emergence, that was investigated in [10], or via Feigenbaum period doubling bifurcation cascade [11], which is alternative way to chaos found by us in the system.

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