Dynamics of synthetic genetic networks

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Introduction

How do varieties arise?

The control of the protein

The protein structure is encoded in the genes.

The central dogma of biology: DNA $\rightarrow$ RNA $\rightarrow$ protein

The gene regulation

promoter: contact region of the DNA for the RNA polymerase

transcription factor proteins: affect directly or indirectly the

rate of transcription

Difficulties for the modeling

- natural genetic networks are huge
- structure not completely resolved
- interaction dynamics often unknown

→ reduce complexity
→ synthetic genetic networks

Synthetic genetic networks

- artificial genetic modules
- consist of a limited number of genes
- designed to operate isolated from the rest of the cellular machinery
- test system for special functions of natural gene networks
- greatly reduced complexity of natural networks
The toggle switch

- two repressors and two constitutive promoters
- mutual inhibition
- basic module of bistability - memory

The repressilator

- a network of three transcriptional repressors that inhibit one another in a cyclic way
- synthetic genetic clock
The repressilator

• a network of three transcriptional repressors that inhibit one another in a cyclic way
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The repressilator with quorum sensing

Objectives

- oscillation death as a mechanism of cell differentiation
- repressive coupling between the cells
- separate time scales in the dynamics
- more nonlinear behaviour

Suggested modifications

- put the auto inducer under control of protein TetR
- consider different mRNA / protein ratio $\beta$ for each pair
- increase the Hill coefficient $n$ to recent experimental values

The modified repressilator with quorum sensing


The modified repressilator

\[
\begin{align*}
\dot{a}_i &= -a_i + \frac{\alpha}{1 + C_i^n} \\
\dot{b}_i &= -b_i + \frac{\alpha}{1 + A_i^n} \\
\dot{c}_i &= -c_i + \frac{\alpha}{1 + B_i^n} + \kappa \frac{S_i}{1 + S_i} \\
\dot{A}_i &= \beta_a (a_i - A_i) \\
\dot{B}_i &= \beta_b (b_i - B_i) \\
\dot{C}_i &= \beta_c (c_i - C_i) \\
\dot{S}_i &= -k_{s0} S_i + k_{s1} B_i - \eta (S_i - Q \bar{S})
\end{align*}
\]
The coupling $Q$ as the bifurcation parameter

$$Q = \frac{\sigma AN/V_{ext}}{k_{se} + \sigma AN/V_{ext}}$$

- $Q$ is proportional to the cell density
- external cell volume controllable in chemostat experiment by fixed cell number
- $Q$ varies in the range $[0, 1]$

The effect of the modifications

slow-fast dynamics due to the modification

intracellular repression
Repressive ↔ reinforcing coupling

Reinforcing

Repressive
The stable dynamic regimes

oscillatory

inhomogen limit cycle

clustering

single fixed point
Multistability by varying cell density

- Clustering
- Inhomogeneous limit cycle
- Oscillatory
- Single fixed point
The bifurcation analysis in the minimal system of two cells oscillation death and single fixed point
Inhomogeneous limit cycle and oscillation death
The anti-phase oscillations
The comparison

![Graph showing the comparison of different regimes.

The x-axis represents the parameter Q, ranging from 0 to 0.7.

The y-axis on the left represents the number of regimes, ranging from 10 to 1000.

The y-axis on the right represents the parameter $a_1$, ranging from 1 to 1000.

The graph shows different regimes:
- Oscillatory regimes are represented by a green region.
- Single fixed point regimes are represented by a blue region.

The regions are labeled IHLC and IHSS.

The graph illustrates the transition between different regimes as Q varies.
The system size effect

The artificial differentiation (IHLC, IHSS) becomes more likely in large ensembles.

The system size influences the position of IHLC and IHSS.
Conclusion

- Synthetic genetic networks are perfect test systems
- The repressive cell-to-cell communication enables very rich dynamics including multistability and clustering
- The oscillation death could be a mechanism of artificial cell differentiation
- Design of artificial genetic chips with desired functions
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