Epigenetic Chromatin Silencing

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Our research concerns epigenetic aspect of cellular differentiation. The role of histone modifications and organization of DNA into heterochromatin and euchromatin regions in eukaryotic gene regulation is well recognized. We study a model of chromatin silencing in budding yeast. We analyze the phase space of the system and study the conditions under which it becomes bistable, allowing for different (activated vs. silenced) epigenetic states. Our model helps us to understand the phenotype of some mutants. We are also performing experiment and analyzing single cell gene expression data to verify qualitative features of our model.

I. Introduction

One of interesting questions in developmental biology is how, in a multicellular organism, there are multiple heritable cell types without changes to the genetic information. One aspect of this question is related to the maintaining of a particular cell fate, once it is achieved. Such heritable locking of different cells into different fates without irreversible change in genetic information is called epigenetic phenomenon. Apart from its key role in developmental biology, epigenetic effects are of great importance in certain diseases such as cancer [1]. Understanding the mechanism of epigenetic silencing is the key aspect of our study.

There are some similarities among various mechanisms suggested for silencing in different organisms [2]. Generally, it is believed that there is a nucleation center which starts silencing by recruiting silencing complex. Silencing complex, in turn, recruits a histone modifying enzyme. This enzyme causes modification of some of the lysine tails in the neighboring histones. This leads to binding of silencing complex to neighboring histones, which again, in turn, recruits further histone modifying enzymes. The silenced region propagates until it meets some boundary element or until the system reaches a stationary state.

Studying in budding yeast had a major contribution in understanding how chromatin silencing works [3]. The mechanism by which silencing nucleates and spreads in budding yeast is relatively well investigated [4]. In budding yeast, nucleosomes in silenced regions are bound by a group of proteins named as SIR complex. Also, acetyl group from certain lysines of histone tails are removed. Histone acetylation is normally associated with transcriptionally active regions.

II. Methods

We write down a mean field equation to describe the state of the system. We analyze the bifurcation diagram of the model, as a function of *alpha* (the acetylation rate), *gamma* (the rate of deacetylation of neighbors caused by the SIR complex) and *rho* (concentration of ambient SIR complex) leading to monostability and to bistability. We are interested in the dynamics of the boundary between two locally stable silenced and unsilenced regions.

We also formulate a stochastic version of our model. In the biology context, the discussion on the process of silencing is mostly focused on the case where the silencing propagation is initiated through a nucleation center. However, an important aspect which has not received much attention yet is the degree of the robustness of the system to spontaneous nucleation. We are analyzing the stability of solutions of our model to the noise and the switching between different states. It is very well a possibility that there is more to the control mechanism of epigenetic states and our theoretical considerations might shed some light on this aspect, for example, by suggesting specific signatures to look for in experimental studies.

We are also performing experiments on different mutants of yeast. Our goal is to sweep different points in the parameter space by changing concentration of certain chemicals which affect *gamma* and *alpha*. We analyze single cell gene expression data as the system goes through different parts of parameter space. We are looking to compare the experiment results with qualitative predictions of our model. We consider the case where there is a limited supply of SIR proteins. The resulting depletion effect gives rise to interesting counter-intuitive consequences.

III. Conclusion

Our model for chromatin silencing gives rise to different dynamical behaviors possible within the same molecular model and guides the formulation of more refined hypotheses that could be addressed experimentally. Our model helps us to understand the phenotype of some mutants. We are constructing a more refined model that incorporates the inheritance of structural organization of chromatin through cell divisions.

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References

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