Cell cycle regulation in the budding yeast

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Introduction

The cell cycle is the sequence of events by which a growing cell duplicates all its components and then divides into two daughter cells so that they can repeat the process.

The cell cycle usually divided into 4 phases, G1, S, G2 and M. Where G1 and G2 are gaps in which cell prepares materials for the next coming phases. During S phase, cell duplicates their genetic materials and they will be separated into two daughter cells in M phase. In fact, S, G2 and M phases in budding yeast are regarded as only one phase called S/M phase in budding yeast because it’s hard to distinguish them clearly. And budding yeast cell division is asymmetric by which the mother cell divides into a small “daughter” cell and a large “mother” cell.

Consider the small “daughter” cell in G1 phase (Fig. 1). The small cell grows up until meet the G1 checkpoint (Is the cell is big enough? Is DNA undamaged? If yes), the cell executes START. A bud emerges and keeps growing; the cell starts DNA synthesis; the spindle pole duplicates and mitosis commences. At the M checkpoint chromosome must be properly aligned on mitotic spindle and DNA synthesis is complete. If yes, the cell processes through anaphase, telophase and cell separation.

In the budding yeast, a single CDK, Cdc28, which is in conjunction with two families of cyclins: Cln1-3 and Clb1-6, control the major cell cycle events. Cln1/Cdc28 and
Cln2/Cdc28 play major roles in budding and spindle pole body duplication. Cln3/Cdc28 seems to govern the size at which newborn cells execute START. Clb5/Cdc28 and Clb6/Cdc28 are essential for timely DNA replication. Clb3/Cdc28 and Clb4/Cdc28 seem to assist in DNA replication and spindle formation. Clb1/Cdc28 and Clb2/Cdc28 are necessary for proper completion of mitosis. Based on that, a protein-protein wire-diagram interaction network (Fig.2) was constructed and it was cast into a set of ordinary differential equations, 11 dynamic variables, with numbers of kinetic parameters ([Chen et al. MBC 2000, table 1 and 2]). This mathematical model is an intensive model that explains correctly wild type phenotype as well as many mutant phenotypes by doing simulation.

![Protein-protein interaction network](image1)

*The protein-protein interaction network. CDK Cdc28 is not present because it is in excess (assumption). This network can be read from left to right.*

![Phase trajectory of wild type](image2)

*Phase trajectory of wild type*

However, by doing simulation does not give out the underlying mechanism that controls cell cycle. Doing bifurcation analysis reveals not only the underlying mechanism but also the mechanism that controls the START and FINISH transitions. Further more, the bifurcation analysis turns out several interesting issues, is the temporal behavior transient of not? What is the abnormality at START and FINISH transitions, the
dynamical organization of cell cycle? … Those issues are very like dynamic road map (fig. 4).

The dynamic road map. There are many “roads” that the system can moves along but it gets to the same destination.

The core of cell cycle

There are two major and important events in budding yeast cell cycle, they are G1/S transition, START, by which the activities of cyclin dependent kinases (CDK) rise up abruptly causing budding, DNA synthesis and drive the cell into M phase, and exiting M phase, FINISH, by which the activities of a cyclin dependent kinase drop down dramatically causing separation of genetic materials (DNA) into two daughter cells then dividing a cell into two cells completely.

To generate those behaviors, CDK activities rising up abruptly and CDK activities dropping down dramatically, the best way is introduce a positive feedback loop for the former and a negative feedback loop for the later one.
The abrupt increasing occurs via a saddle node. As the Mass increase up to a critical value, CLB5 jump from a low value to high value.

The negative feedback loop makes oscillation. Firstly, Clb2 rise up then IEP and Cdc20 follow up later on. When Cdc20 rise up it down regulate Clb2 to decay. Clb2 decay causing IEP and Cdc20 decay, therefore Clb2 rise up again to make oscillations.

In the mathematical model, the positive feedback loop MASS MBF Clb5 MBF causes the abruptly rising up of Clb5 activities, then Clb2 rise up as consequence, since its inhibitor, Sic1, is down regulated by rising up Clb5.

And the dropping down dramatically of Clb2 activities is caused by two negative feedback loops, Clb2 IEP Cdc20 Clb2. See figure 4 for more detail.

**Bifurcation analysis**

By taking the mass of cell as a controlling parameter, and varying mass, we found bifurcation diagram for the wild type budding yeast cell cycle. Base on that, the budding yeast cell cycle is characterized by two kinds of solutions, steady state and oscillatory state.
The lower steady state corresponds to G1 state, where the activities of Clb5 cyclin are not fluctuating in time.

The oscillatory state corresponds S/M state, where the increasing of Clb5 activity executes START, the increasing of Clb2 activity causes spindle formation (M phase) and the decreasing of Clb2 activity drives the cell division (FINISH).

It turns out that the cell cycle is a switch-like that if cyclins’ activities are low, it OFF, otherwise, it is ON. Those transitions come up from positive and negative feedback loops as show in fig 4 (A)-(B) and (C). In addition, the START transition is driven by cell size mean while the FINISH transition is driven by dynamics.

Discussion

The cell cycle is a switch-like. The cell size is a driven force to turn it on via a positive feedback loop and the dynamics turns it off via negative feedback loops. Under bifurcation analysis, the underlying mechanism of controlling of cell cycle, switch-like mechanism between two phases G1 and S/M, the mechanism of START and FINISH transition, changing dynamical properties of solutions, were discovered.

The whole cell cycle is characterized by two states, a steady state, in which the activities of Clb5 proteins are very low and unchanged, and a stable oscillatory state, in which the activities of Clb5 proteins are varying, increasing of Clb5 activity causes DNA
replication, increasing of Clb2 activity causes the formation of spindle (M phase) and Clb2 activity decreasing causes the cell division, fig.5.

The bifurcation analysis is a useful mathematical tool that helps us understand more clearly about not only the cell cycle but also the dynamic systems described by ODEs. Especially, it’s useful for biologists, who carry out experiments

References