Temporal dynamics in cell cycle entry

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***Short Abstract* — The cell's transition from quiescence proliferation is a highly variable process. Over the last four decades, two lines of apparently contradictory, phenomenological models have been proposed to account for such temporal variability. These include the transition probability (TP) model, the growth control (GC) model, and their variaants . The growth control model was later proposed as an alternative explanation for the restriction point, which we recently demonstrated as being controlled by a bistable Rb-E2F switch. Here, through a combination of modeling and experiments, we show that these different models essentially reflect different aspects of the temporal dynamics in cell cycle entry.**

I. Introduction

CELL-TO-CELL variability in the transition from the quiescent to the proliferative state is a well-known phenomenon [1]. In a given population of proliferating cells, such variation leads to partitioning of the cell population into subpopulations at different cell cycle phases. This phenomenon is observed even in a population of isogenic cells that were synchronized by serum starvation. Upon serum stimulation, the serum-starved (quiescent) population of cells reenters the cell cycle and undergoes the G1/S transition, but the rate at which cells reenter the cell cycle is variable among different types [2,3], and can be modulated by external conditions [4].

To account for the variable transition timing in cell cycle progression, two lines of models have been proposed: transition probability (TP) model [4-7] and growth control (GC) model [8-10]. The TP models attribute the temporal variability to random state transitions through different phases of the cell cycle. Despite excellent fit to experimental data, a major criticism against the TP model is lack of mechanistic explanation for the random transition. The alternative GC model proposes that the observed temporal variability arises from growth rate heterogeneity within a cell population, rather than random state transitions. Remarkably, this line of models has been able to provide equally good fit to various experimental data.

There has been active debate between these two lines of thinking since initial proposition of the TP model [7]. While never resolved, the debate gradually faded since the concept of the restriction point was proposed [11], which we have shown to be controlled by a bistable Rb-E2F switch [12]. Interestingly, the GC model has recently been proposed as an alternative explanation for the concept of the R-point[10].

II. Summary of Results and Conclusion

In this work, we show that these seemingly contradictory views reflect different aspects of the same underlying temporal dynamics in cell cycle entry, as has been speculated [13]. Specifically, we focus on the analysis of temporal activation of E2F by both stochastic modeling and experiments. We show that our stochastic model predictions demonstrate excellent fit to our experimental data under various serum conditions and nodal perturbations. In parallel, we provide unique sets of parameters for the TP and GC models to describe E2F activation patterns, demonstrating that E2F activation dynamics can be accurately recast into the framework of the TP model and the GC model. While the phenomenological models lack direct mechanistic insights into the underlying dynamics, we show that there is a quantitative mapping between these models and the mechanistic model. As such they can potentially serve as concise, quantitative phenotypes of the cell physiology.

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References

1. Pardee AB, Dubrow R, Hamlin JL, Kletzien RF (1978) Animal-Cell Cycle. Annual Review of Biochemistry 47: 715-750.
2. Zetterberg A, Larsson O (1985) Kinetic-Analysis of Regulatory Events in G1 Leading to Proliferation or Quiescence of Swiss 3t3 Cells. Proceedings of the National Academy of Sciences of the United States of America 82: 5365-5369.
3. Zetterberg A, Larsson O, Wiman KG (1995) What Is the Restriction Point. Current Opinion in Cell Biology 7: 835-842.
4. Shields R, Smith JA (1977) Cells Regulate Their Proliferation through Alterations in Transition-Probability. Journal of Cellular Physiology 91: 345-355.
5. Shields R (1978) Further Evidence for a Random Transition in Cell-Cycle. Nature 273: 755-758.
6. Brooks RF, Bennett DC, Smith JA (1980) Mammalian-Cell Cycles Need 2 Random Transitions. Cell 19: 493-504.
7. Smith JA, Martin L (1973) Do Cells Cycle. Proceedings of the National Academy of Sciences of the United States of America 70: 1263-1267.
8. Castor LN (1980) A G1 Rate Model Accounts for Cell-Cycle Kinetics Attributed to Transition-Probability. Nature 287: 857-859.
9. Cooper S (1987) On G0 and Cell-Cycle Controls. Bioessays 7: 220-222.
10. Cooper S (2003) Reappraisal of serum starvation, the restriction point, G0, and G1 phase arrest points. Faseb Journal 17: 333-340.
11. Pardee AB (1974) A restriction point for control of normal animal cell proliferation. Proceedings of the National Academy of Sciences of the United States of America 71: 1286-1290.
12. Yao G, Lee TJ, Mori S, Nevins JR, You LC (2008) A bistable Rb-E2F switch underlies the restriction point. Nature Cell Biology 10: 476-U255.
13. Nurse P (1980) Cell cycle control - both deterministic and probabilistic? Nature 286: 9-10.