Stochastic Model of the Histidine Kinase Switch in the *Caulobacter* Cell Cycle

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***Short Abstract* — The morphological change of *Caulobacter crescentus* from swarmer to stalked cell is a result of elaborate regulations. The two histidine kinase PleC and CckA controls the physiology development and the cell cycle development. Here we present a stochastic model that reveals the states of the histidine kinase at different cell stage. With the simulation result, we believe the kinase form of PleC in the swarmer pole is essential for the cell cycle development.**

***Keywords* — *Cauoubacter* cell cycle, histidine kinase, stochastic simulation.**

I. Introduction

The asymmetric division of *Caulobacter* requires elaborate regulations that control the chromosome segregation, polar differentiation and regulator localization [1]. Experiments have identified CtrA as one of the master transcription regulators in the *Caulobacter* cell cycle [2]. In swarmer cells the CtrA response regulator binds to the chromosome origin of replication and inhibits the initiation of chromosome replication. During the swarmer-to-stalk transition the active CtrA~p, gets dephosphorylated and degraded, and the cell initiates the chromosome replication.

In the physiology level, the flagella pole development in *Caulobacter* is controlled by the response regulator DivK, with the histidine kinase DivJ and PleC [3]. The freely diffusing DivK is phosphorylated by DivJ kinase, localized at the stalked pole and dephosphorylated by PleC phosphatase at the flagella pole [4]. After cytokinesis, the activities of PleC and DivJ are physically separates. As a consequence, DivK~p level drops dramatically in the swarmer cell, and permits flagella development. In addition, DivK~p is as an allosteric regulator that turns the PleC phosphatase into the kinase form, which phosphorylates DivK in return.

Furthermore, the DivK~p pole indirectly inactivates the CtrA through a non-canonical histidine kinase DivL [4]. In the swarmer to stalk cell transition, the DivK~p binds to DivL and inhibits CckA kinase activity, which in turn inactivates CtrA. In this abstract we present our stochastic simulation on the reaction-diffusion model for the DivJ-DivK-PleC and DivL-CckA-CtrA regulation network.

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II. Mathematical Model

Our stochastic model is built based on the bistable switch model [5] in coordinate with the gene localization and mRNA. To demonstrate the spatiotemporal localization of regulator species, we deliberately enforce the localization of the regulatory species as model events. In the swarmer cell, PleC is localized to the old pole. At 30min, swarmer-to-stalk transition begins and DivJ is forced to the old pole. At 50min, PleC is cleared from the old pole and reappeared in the new pole at 90min. At 120min, cell is divided into two pre-division cells. Figure 1 shows the spatiotemporal population evolution of PleC kinase and CtrAp in the stochastic simulation. Our model reveals that PleC in the new pole stays in the kinase form and sequesters DivKp from binding to DivL. Hence, in the swarmer pole, CtrA is phosphorylated and active.

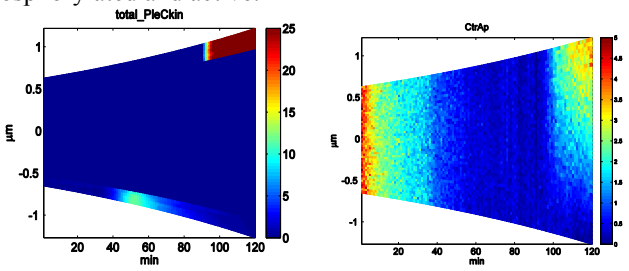

Figure 1: The spatiotemporal population of PleC kinase (left) and CtrAp (right), the plotted population is calculated from the average of 500 stochastic runs.

III. Conclusion

We developed a stochastic model for the regulatory network in the Caulobacter cell cycle. Our model favors the explanation that PleC in the swarmer pole stays in the kinase form and sequesters DivKp from binding to DivL. Hence, CtrA in the swarmer pole is active and inhibits the initiation of chromosome replication.

References

[1] S. Li, P. Brazhnik, B. Sobral, and J. J. Tyson. (2009) *PLoS Comput Biol,* **5**(8): e1000463.

[2] J. Collier and L. Shapiro (2007). *Current Opinion in Biotechnology*, **18**(4):333 - 340.

[3] K. C. Quon, B. Yang, I. J. Domian, L. Shapiro, and G. T. Marczynski (1998). *PNAS*, **95**(1): 120-125

[4] R. T. Wheeler and L. Shapiro., (1999) *Molecular Cell*, **4**(5): 683-694

[5] K. Subramanian, M. R. Paul, and J. J. Tyson. (2013) *PLoS Comput Biol*, **9**(9): e1003221.