复旦大学数学科学学院

数学综合报告会

报告题目：**Synthetic Approaches to Waddington Landscape and Pattern Formation**

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摘要： The process of cell fate determination has been depicted intuitively as cells travelling and resting on a rugged landscape, which has been probed by various theoretical studies. However, few stud-ies have experimentally demonstrated how underlying gene regulatory networks shape the land-scape and hence orchestrate cellular decision-making in the presence of both signal and noise. We tested different topologies and verified a synthetic gene circuit with mutual inhibition and auto-activations to be quadrastable, which enables direct study of quadruple cell fate determination on an engineered landscape. We show that cells indeed gravitate towards local minima and signal inductions dictate cell fates through modulating the shape of the multistable landscape. Experi-ments, guided by model predictions, reveal that sequential inductions generate distinct cell fates by changing landscape in sequence and hence navigating cells to different final states. We then further expanded this quadrastable gene network to couple gene expression regulation (reaction) with quorum sensing (diffusion) to guide bacteria colonies to form self-regulated paterns. Reaction-diffusion (RD) has long been proposed as one major mechanism underlying biological pattern formation. However, it remains elusive how such mechanism functions in a multicellular context, largely due to the lack of suitable model systems to probe operations of RD quantitatively in vivo. Using our engineered circuits, we show that bacteria cells follow instructions from gene circuits to form repetitive alternating ring patterns. An experimentally verified mathematical model confirms that a RD based travelling wave generates observed ring patterns. Single cell time lapse imaging further reveals that such pattern-formation is robust against randomness of initial cellular states. Powered by our synthetic biology setup, we test alternative designs of gene networks and show that gene networks enriched with feedback and therefore high likelihood of multistability are foundations of RD based biological pattern formation.

Our work provides a synthetic biology framework to approach cell fate determination and suggests a landscape-based explanation of fixed induction sequences for targeted differentiation. In addi-tion, these results verified close connections between gene network topology and resulting RD driven pattern formation, offering an engineering approach to help understand biological development.

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