MPIDS Seminar

MAX-PLANCK-GESELLSCHAFT

Genetic and dynamic stabilization of microbial populations for synthetic biology

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Many multicellular substrates exhibit emergent dynamics which are essential for their proper function. I study how the collective dynamics of these cell populations or tissues arise from the coupling of physical and biological processes across organizational levels. The goal of my research is to extract fundamental theoretical principles that provide a deepened understanding and can be exploited for medical and biotechnological applications. Here, I present recent findings which address two challenges for synthetic biology, or, more specifically: instabilities that threaten the long-term viability of engineered functionality in microbial populations.

Firstly, programming cells with additional behavior by introducing artificial gene regulatory networks increases the demand for cellular resources and therefore likely reduces their growth rate. At the population level, this creates evolutionary pressure towards deactivation or impairment of the engineered function. We show that the impact of this severe genetic instability can be limited by periodic reductions in population size [1]. By suppressing beneficial mutations, undesired evolutionary adaptation is slowed down, extending the average lifetime of the desired function. We derive quantitative estimates for the suppression factor using two different analytical approximations to cover the full range of possible population dynamics and selective advantages. In addition to synthetic biology, these results can also be applied more broadly to correctly design and interpret experimental and directed evolution studies.

A second, dynamic, instability occurs when multiple microbial strains are placed in the same finite environment to construct synthetic ecologies for more complex tasks: In the long run, the fastest-growing cell type will displace less competitive strains, disrupting any synergistic function. We theoretically explore gene regulatory networks which employ quorum sensing based on diffusible signaling molecules to autonomously limit population growth. We show that a range of different population dynamics from steady states to oscillations can be achieved, consistent with experimental observations in controlled microfluidic environments. Equipping two strains with orthogonal quorum-sensing systems, such synthetic population control can stabilize a co-culture of two strains, increasing robustness to differences in growth rates [2]. Depending on the individual parameters and cross-talk between the quorum-sensing systems, we find distinct multi-strain dynamics that could be useful for a variety of applications.

References:
[1] P. Bittihn, J. Hasty, L. S. Tsimring, Physical Review Letters **118**, 028102 (2017)
[2] S. R. Scott, M. O. Din, P. Bittihn, L. Xiong, L. S. Tsimring, J. Hasty, Nature Microbiology **2**, 17083 (2017)

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