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Cooperative Stability Renders Protein Complex Formation more Robust and Controllable

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Abstract

Protein complexes are the fundamental units of many biological functions. Despite their many advantages, one major adverse impact of protein complexes is accumulations of unassembled subunits that may disrupt other processes or exert cytotoxic effects. Synthesis of excess subunits can be inhibited via negative feedback control or they can be degraded more efficiently than assembled subunits, with this latter being termed cooperative stability. Whereas controlled synthesis of complex subunits has been investigated extensively, how cooperative stability acts in complex formation remains largely unexplored. To fill this knowledge gap, we have built quantitative models of heteromeric complexes with or without cooperative stability and compared their behaviors in the presence of synthesis rate variations. A system displaying cooperative stability is robust against synthesis rate variations as it retains high dimer/monomer ratios across a broad range of parameter configurations. Moreover, cooperative stability can alleviate the constraint of limited supply of a given subunit and makes complex abundance more responsive to unilateral upregulation of another subunit. We also conducted an in-silico experiment to comprehensively characterize and compare four types of circuits that incorporate combinations of negative feedback control and cooperative stability in terms of eight systems characteristics pertaining to optimality, robustness and controllability. Intriguingly, though individual circuits prevailed for distinct characteristics, the system with cooperative stability alone achieved the most balanced performance across all characteristics. Our study provides theoretical justification for the contribution of cooperative stability to natural biological systems and represents a guideline for designing synthetic complex formation systems with desirable characteristics.

Keywords:
Protein Complex; Cooperative Stability; Protein Degradation; Optimality; Robustness; Controllability.