

# Biological Design Doctoral Defense

## Multifaceted Effects of Resource Competition on Gene Expression and Noise

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### Abstract

A notable challenge when assembling synthetic gene circuits is that modularity often fails to function as intended. A crucial underlying reason for this modularity failure is the existence of competition for shared and limited gene expression resources. By designing a synthetic cascading bistable switches (Syn-CBS) circuit in a single strain with two coupled self-activation modules to achieve successive cell fate transitions, nonlinear resource competition within synthetic gene circuits is unveiled. However, in vivo it can be seen that the transition path was redirected with the activation of one switch always prevailing over that of the other, contradictory to coactivation theoretically expected. This behavior is a result of resource competition between genes and follows a ‘winner-takes-all’ rule, where the winner is determined by the relative connection strength between the two modules.

Despite investigation demonstrating that resource competition between gene modules can significantly alter circuit deterministic behaviors, how resource competition contributes to gene expression noise and how this noise can be controlled is still an open issue of fundamental importance in systems biology and biological physics. By utilizing a two-gene circuit, the effects of resource competition on protein expression noise levels can be closely studied. A surprising double-edged role is discovered: the competition for these resources decreases noise while the constraint on resource availability adds its own term of noise into the system, denoted “resource competitive” noise. Noise reduction effects are then studied using orthogonal resources. Results indicate that orthogonal resources are a good strategy for eliminating the contribution of resource competition to gene expression noise.

Noise propagation through a cascading circuit has been considered without resource competition. It has been noted that the noise from upstream genes can be transmitted downstream. However, resource competition’s effects on this cascading noise have yet to be studied. When studied, it is found that resource competition can induce stochastic state switching and perturb noise propagation. Orthogonal resources can remove some of the resource competitive behavior and allow for a system with less noise.



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