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Fitness Effects of Network Non-Linearity Induced by Gene Expression Noise[1] CHRISTIAN RAY, The University of Texas M.D. Anderson Cancer Center, TIM COOPER, University of Houston, GABOR BALAZSI, The University of Texas M.D. Anderson Cancer Center — In the non-equilibrium dynamics of growing microbial cells, metabolic enzymes can create non-linearities in metabolite concentration because of non-linear degradation (utilization): an enzyme can saturate in the process of metabolite utilization. Increasing metabolite production past the saturation point then results in an ultrasensitive metabolite response. If the production rate of a metabolite depends on a second enzyme or other protein-mediated process, uncorrelated gene expression noise can thus cause transient metabolite concentration bursts. Such bursts are physiologically unnecessary and may represent a source of selection against the ultrasensitive switch, especially if the fluctuating metabolic intermediate is toxic. Selection may therefore favor correlated gene expression fluctuations for enzymes in the same pathway, such as by same-operon membership in bacteria. Using a modified experimental *lac* operon system, we are undertaking a combined theoretical-experimental approach to demonstrate that (*i*) the *lac* operon has an implicit ultrasensitive switch that we predict is avoided by gene expression correlations induced by same-operon membership; (*ii*) bacterial growth rates are sensitive to crossing the ultrasensitive threshold. Our results suggest that correlations in intrinsic gene expression noise are exploited by evolution to ameliorate the detrimental effects of nonlinearities in metabolite concentrations.

Christian Ray
The University of Texas M.D. Anderson Cancer Center

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