Stochastic fluctuations in metabolic pathways

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Reference

- Erel Levine and Terence Hwa. *Stochastic fluctuations in metabolic pathways*. PNAS May 29, 2007, 104(22):9225-9229.

Random fluctuations in organisms

- Because of the limited number of molecules for typical molecular species in microbial cells, random fluctuations in molecular networks are common place and may play important roles in vital cellular processes.
  - Pattern formation and collective dynamics
  - Cell-to-cell variability
  - Implications on cellular regulation
  - Phenotypic diversity
  - ……

Noise propagation

- The stochastic expression of individual genes at both the translational and transcriptional levels.
- Noise propagation in the context of small, ultra-sensitive genetic circuits: where noise at a circuit node (i.e., a gene) was shown to either attenuate or amplify output noise in the steady state.
- Several key questions that arise from these studies of genetic noise include

  i whether stochastic gene expression could further propagate into signaling and metabolic networks through fluctuations in the levels of key proteins controlling those circuits;

  ii whether noise propagation also occurs in those circuits.

- An analytic approach to characterize the probability distribution for all nodes of a class of molecular networks in the steady state.
- Apply the method to analyze fluctuations and their correlations in metabolite concentrations for various core motifs of the metabolic network.

Individual Nodes

- Reaction from substrate S to product P catalyzed by Enzyme E is

$$S + E \underset{k_-}{\overset{k_+}{\rightleftarrows}} SE \xrightarrow{k_2} P + E$$

- The macroscopic flux *c* leaded by Michaelis-menten model is

$$c = v_{\max} \frac{[S]}{[S] + K_M}$$

- where $v_{\max} = k_2[E]$ and $K_M = \frac{k_- + k_2}{k_+} \simeq \frac{k_-}{k_+}$ for $k_\pm \gg k_2$.

Individual Nodes (cont'd)

- The probability of having N_{SE} complexes given *m* substrate molecules and N_E enzymes is

$$p\left(N_{SE} \mid m, N_E\right) = \frac{K^{-N_{SE}}}{Z_{m,N_E}} \frac{m!N_E!}{N_{SE}!\left(m-N_{SE}\right)!\left(N_E-N_{SE}\right)!}$$

- for $N_{SE} < N_E$ and *m*. Here $K^{-1} = Vk_+/k_-$ is the Boltzmann factor associated with the formation of an *SE* complex. Then the turnover rate

$$w_m = \frac{k_2}{V\sum N_{SE} \cdot p\left(N_{SE} \mid m, N_E\right)} = v_{\max} \frac{m}{m+\left(K+N_E-1\right)} + O\left(K^{-3}\right)$$

- where $v_{\max} = k_2 N_E/V$. And $w_m = v_{\max} m/\left(m+K\right)$ for single enzyme.

Probability Distribution of a Single Node

- Consider the influx of substrate molecules to be a Poisson process with rate *c.*
- To find the probability of having *m* substrate molecules, the Master equation for probability $\pi(m)$ of finding *m* substrate molecules at the steady state is written as

$$\frac{d}{dt}\pi(m) = \left[c(a-1) + (\hat{a}-1)w_m\right]\pi(m)$$

$$= c\left[\pi(m-1) - \pi(m)\right] + \left[w_{m+1}\pi(m+1) - w_m\pi(m)\right]$$

- Here they defined lowering and raising operators $ah(n) = h(n-1)$ and $\hat{a}h(n) = h(n+1)$ for any function $h(n)$.

Probability Distribution of a Single Node

- The solution of this steady state equation is of the form

$$\pi(m) \sim c^m \Big/ \prod_{k=1}^{m} w_k$$

- Then

$$\pi(m) = \begin{pmatrix} m + K + (N_E - 1) \\ m \end{pmatrix} (1 - z)^{K + N_{E_z m}} \, , z = c/v_{\max}$$

Flux balance on the node

- The condition that the incoming flux equals the outgoing flux is written as

$$c = \langle w_m \rangle = v_{\max} \frac{s}{s + (K + N_E)}$$

  which is microscopic flux of the reaction.

- Compare to the macroscopic flux leaded by Michaelis-menten model

$$c = v_{\max} \frac{[S]}{[S] + K_M}$$

Noise Index

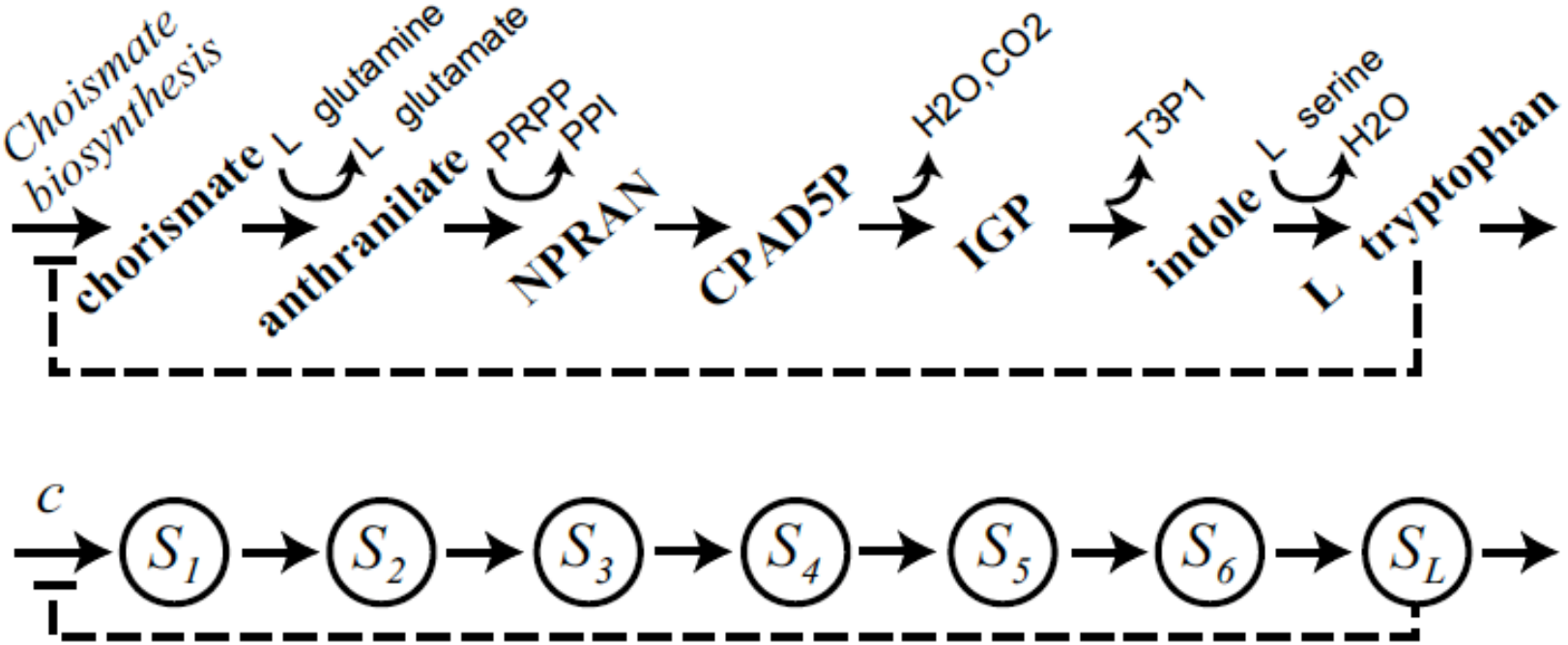
- Define noise index to characterize the variation of substrate concentration in the steady state as

$$\eta_S^2 \equiv \frac{\sigma_s^2}{s^2} = \frac{v_{\max}}{c\left(K + N_E\right)}$$

- which decreases with the average occupancy *s* as expected.
- It is bound from below by $1/\sqrt{K + N_E}$, which can easily be several percent.
- Generally, large noise is obtained when the reaction is catalyzed by a small number of high-affinity enzymes (i.e., for low *K* and N_E).

Linear Pathways

- Tryptophan biosynthesis pathway in *E. coli* and model for a directed pathway.



Independence of number of molecules

- Master equation for the joint probability function $\pi = \pi(m_1, m_2, \ldots m_L)$ of linear pathway

$$\frac{d}{dt}\pi = \left[c(a_1 - 1) + \sum_{i=1}^{L-1} (\hat{a}_i a_{i+1} - 1) w_{m_i}^{(i)} + (\hat{a}_L - 1) w_{m_L}^{(L)} \right] \pi$$

- To solve the steady-state equation by plugging a solution of the form

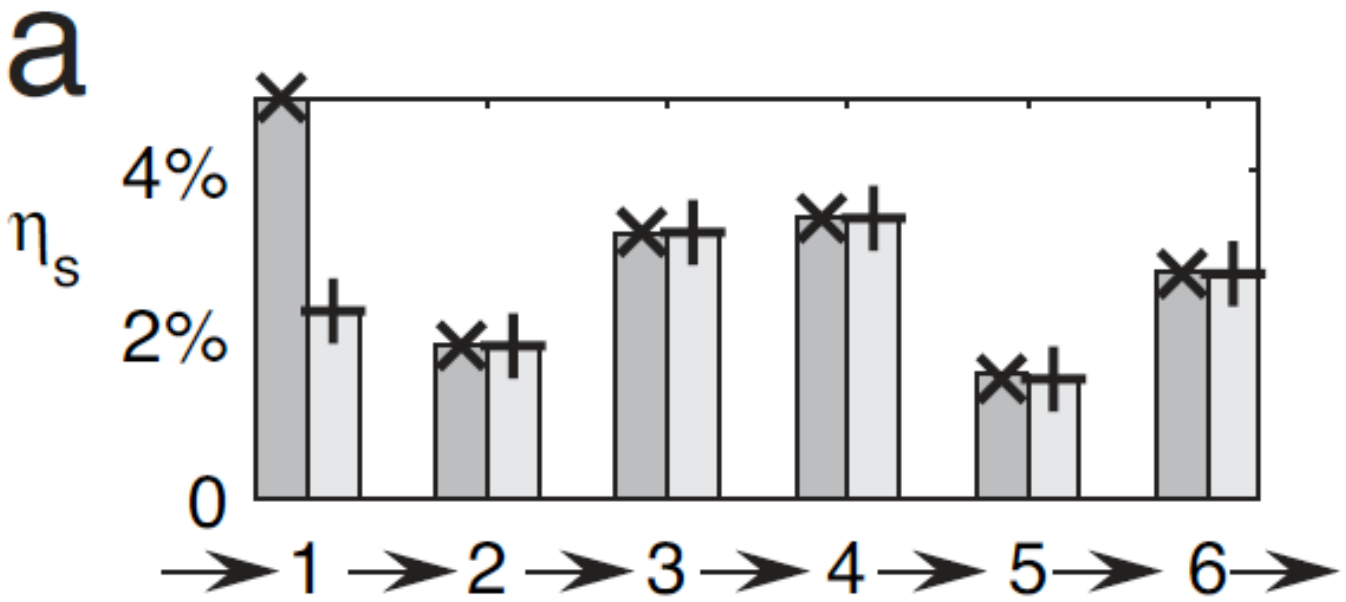
$$\pi(m_1, m_2, \ldots m_L) = \prod g_i(m_i)$$

- One can find that in fact

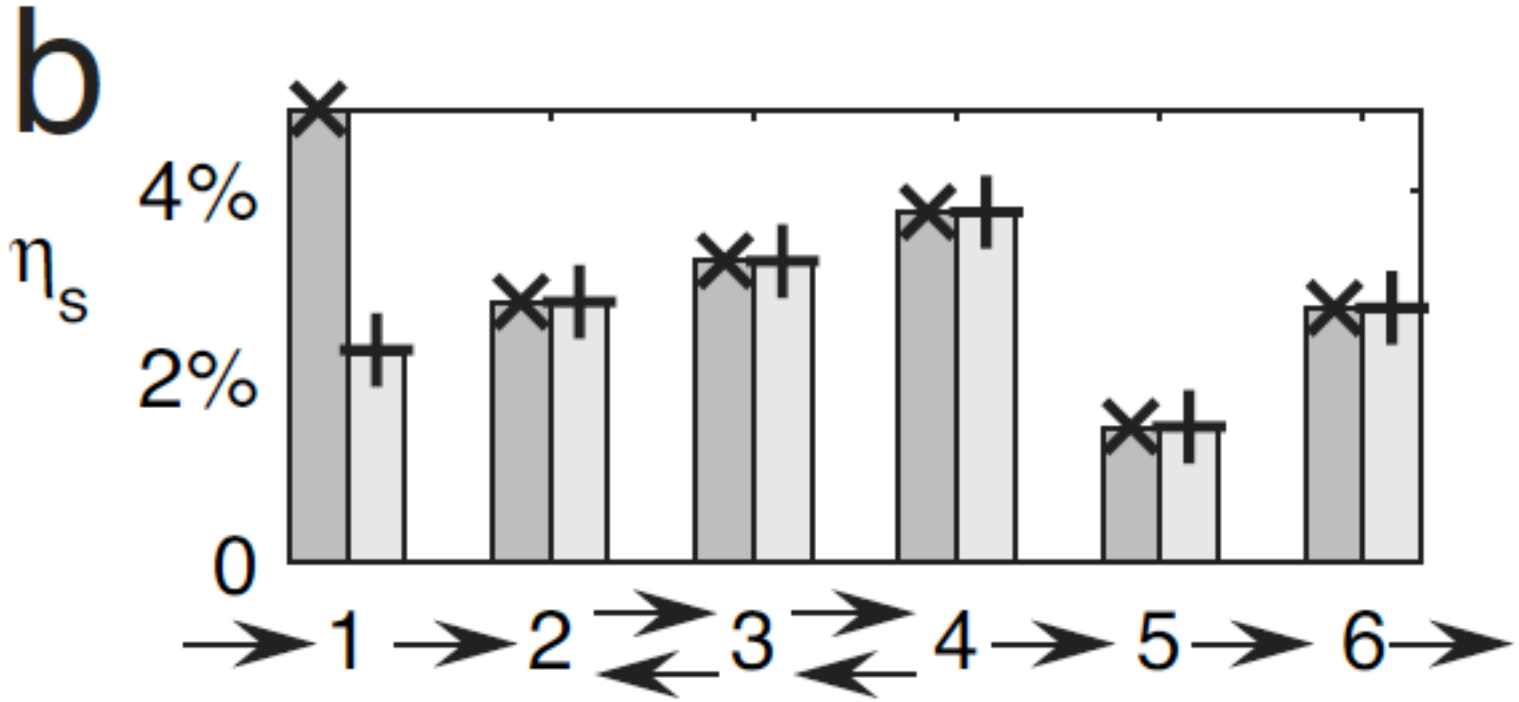
$$g_i(m_i) = \pi_i(m_i)$$

Directed Pathways

- Monte Carlo simulations (bars) are compared with the analytic prediction (symbols) obtained by assuming decorrelation for different nodes of the pathways.
- Dark gray: $v_1 = 1.1c$ -> Light gray: $v_1 = 5c$.



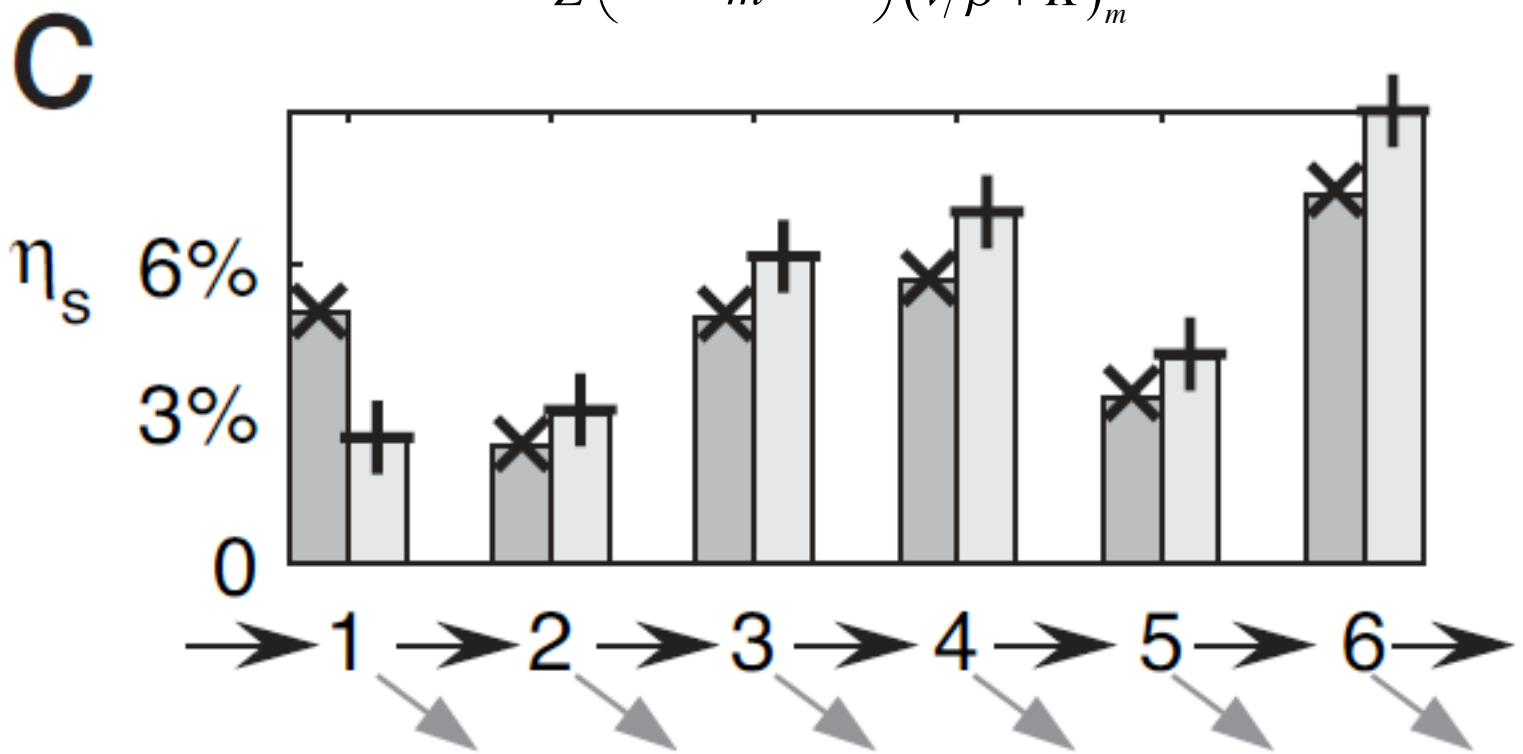
Reversible Reactions



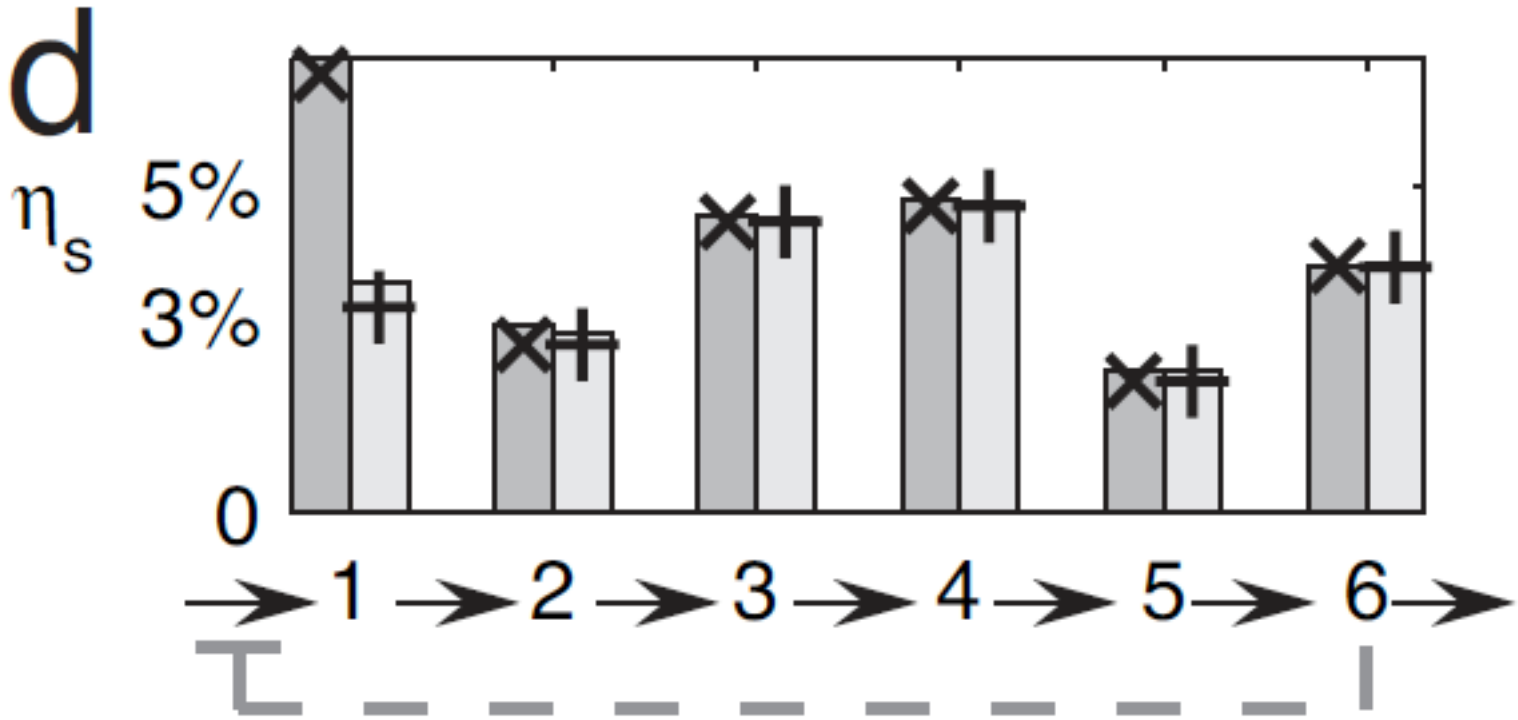
Dilution of Intermediates

- Linear degradation $u_m = \beta m$, where $\beta = \ln(2)$.

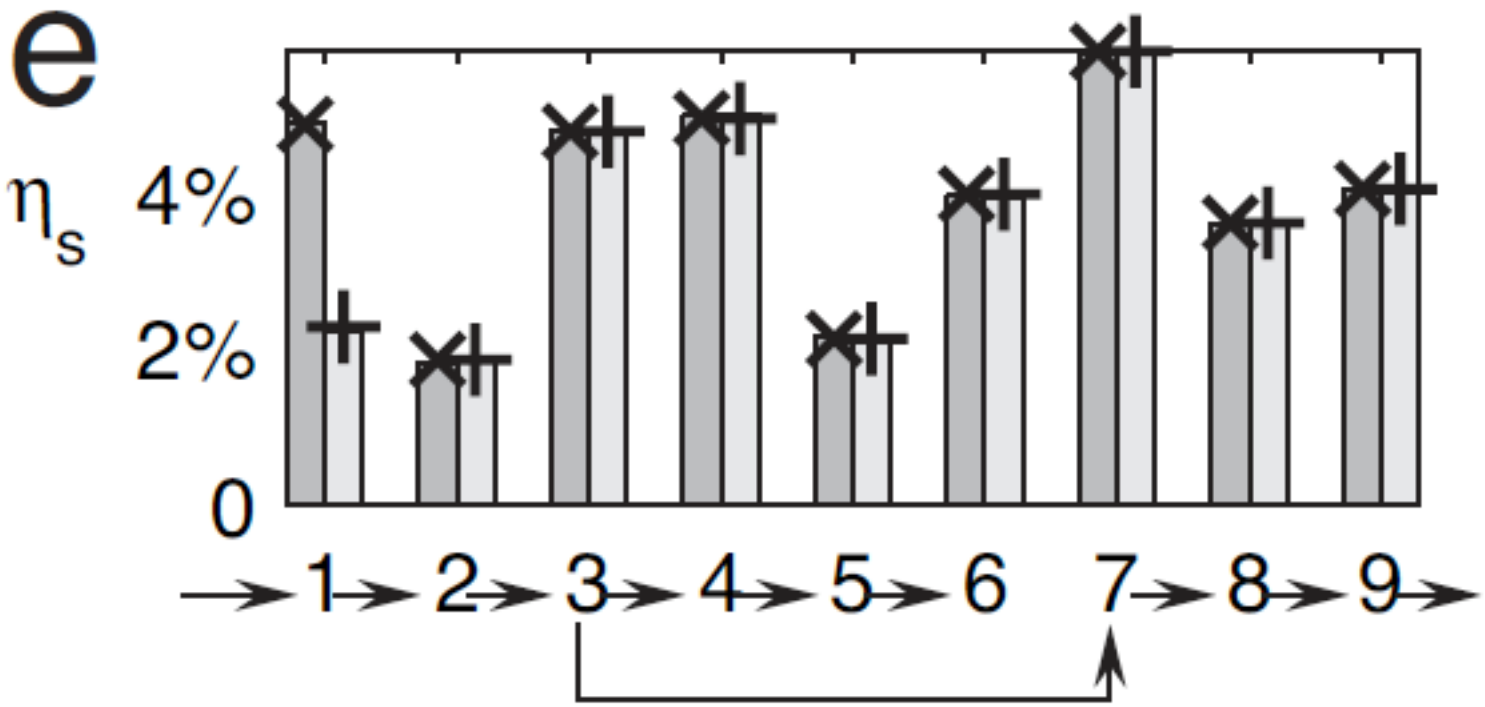
$$\pi(m) = \frac{1}{Z}\binom{m+K-1}{m}\frac{(c_0/\beta)^m}{(v/\beta+K)_m}$$



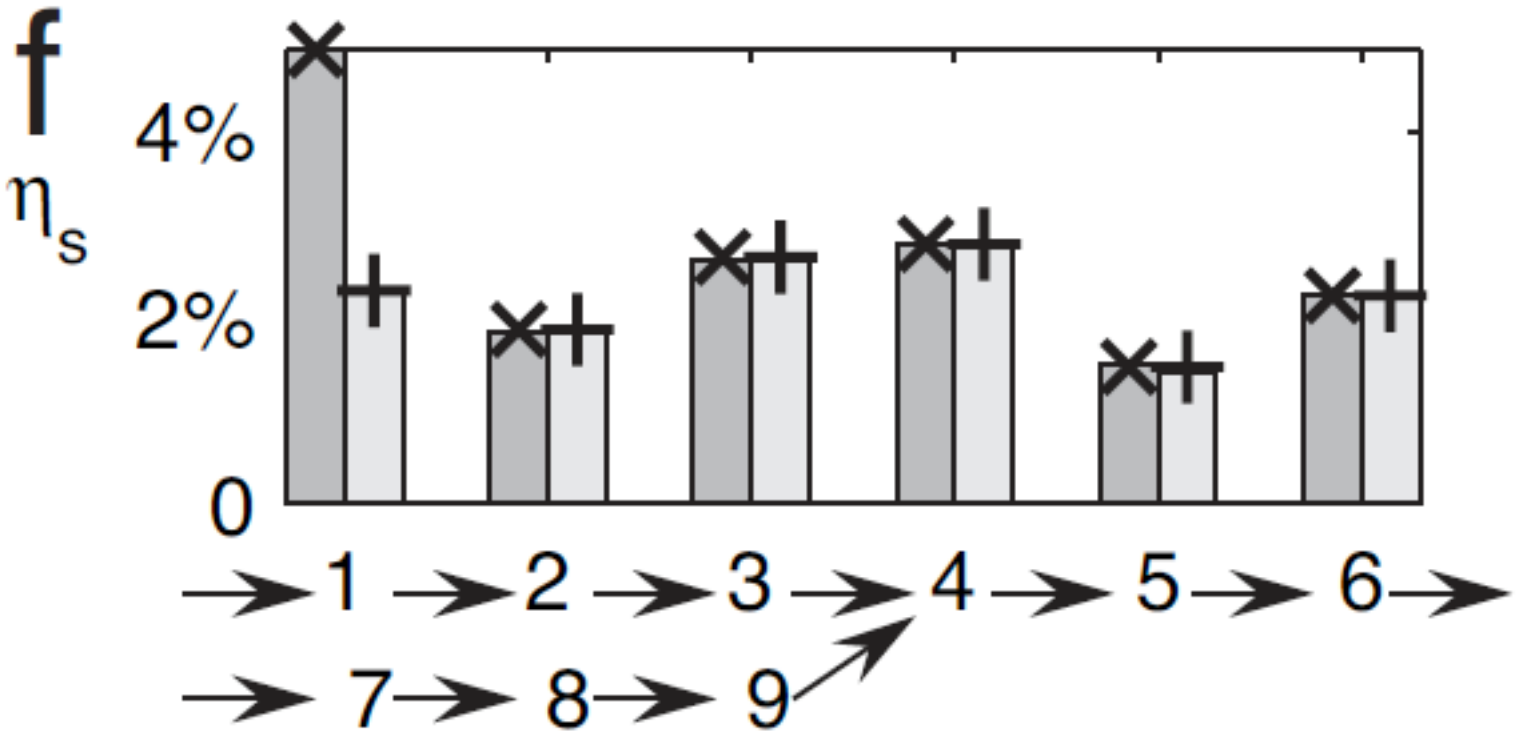
End-Product Inhibition



Diverging Pathways



Converging pathways



Discussion

- This work characterized stochastic fluctuations of metabolites for dominant simple motifs of the metabolic network in the steady state.
- The intermediate metabolites in a linear pathway, the key motif of the biochemical network, are statistically independent.
- The main conclusion, that the steady-state fluctuations in each metabolite do not depend on the fluctuations in other upstream metabolites, is qualitatively different from conclusions obtained for gene networks in recent studies, e.g., the “noise addition rule” and its extension to cases where the signals and the processing units interact.
- But as well as generalized mass-transport models, this work suggested that statistical independence goes well beyond the Poisson case.

Discussion (cont'd)

- The absence of noise propagation for a large part of the metabolic network allows intermediate metabolites to be shared freely by multiple reactions in multiple pathways, without the need of installing elaborate control mechanisms.
- The work suggests that in many cases, steady state fluctuations do not bear information about the pathway structure.