Criticality and Adaptivity in Enzymatic Networks

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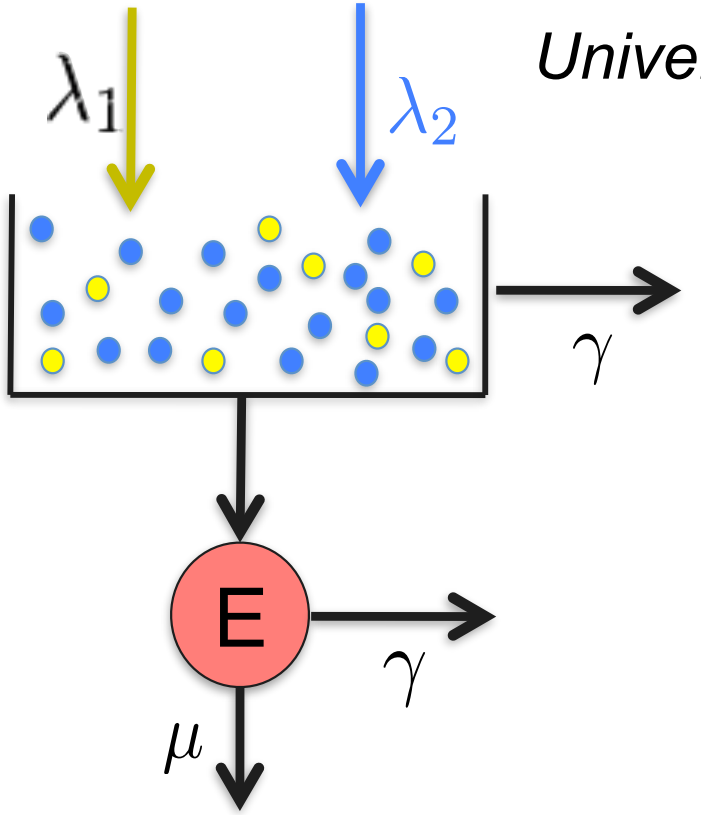

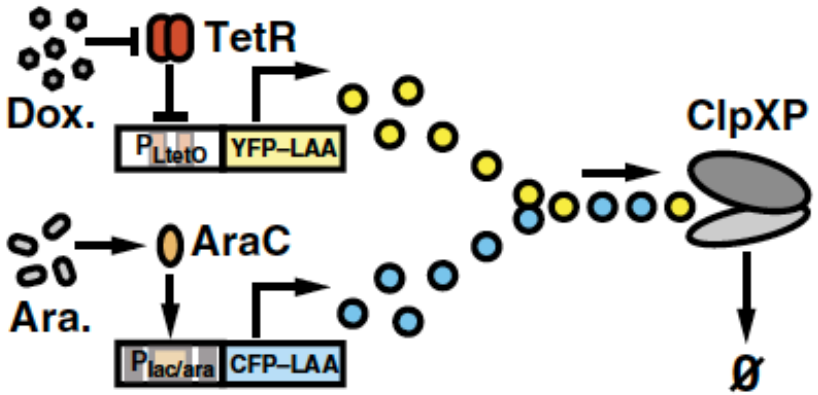

UCSD

BCI

Acknowledgements

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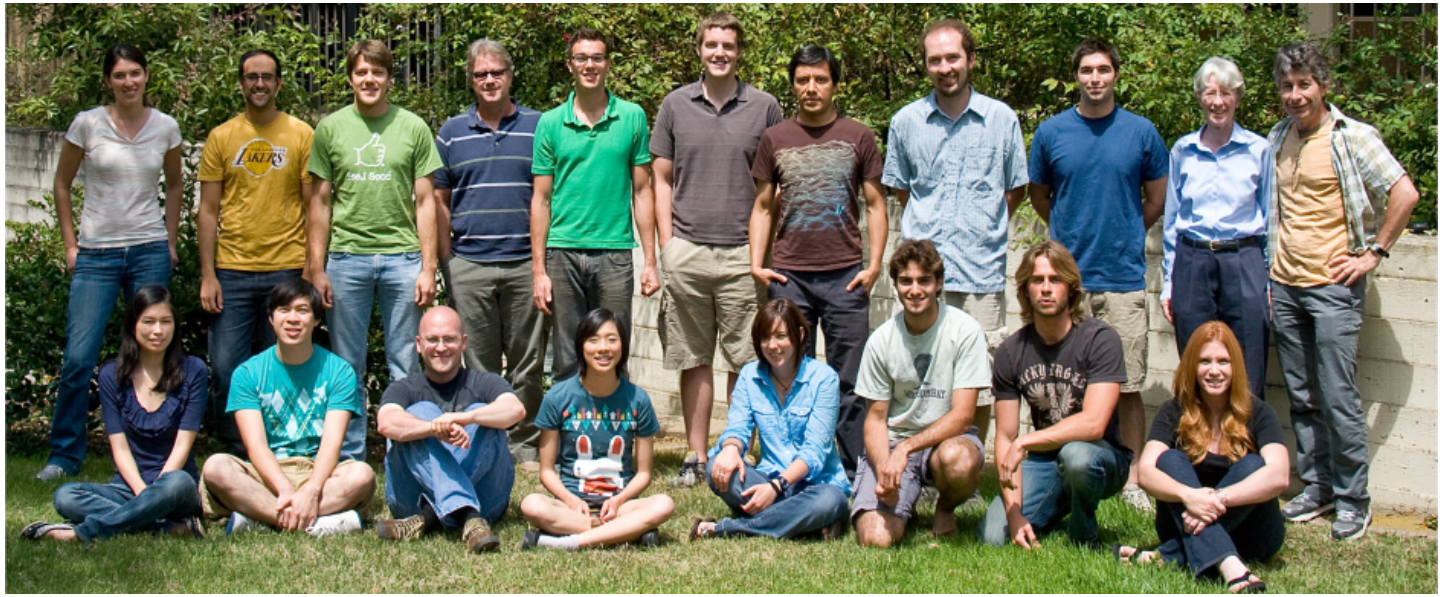
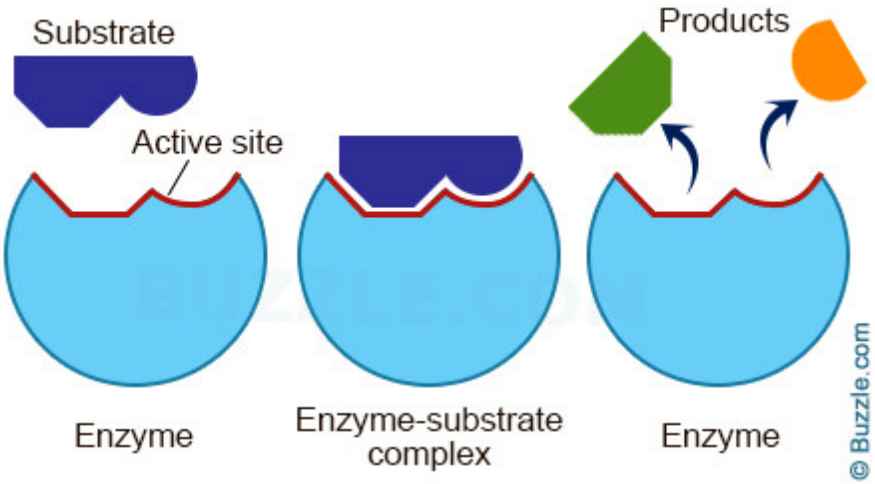


- Thanks to NSF and NIH for funding

Enzymes

- Large biological molecules that act as catalysts for complex biochemical reactions in living organisms



$$S + E \underset{\eta^-}{\overset{\eta^+}{\rightleftharpoons}} [SE] \xrightarrow{\mu} E + P$$

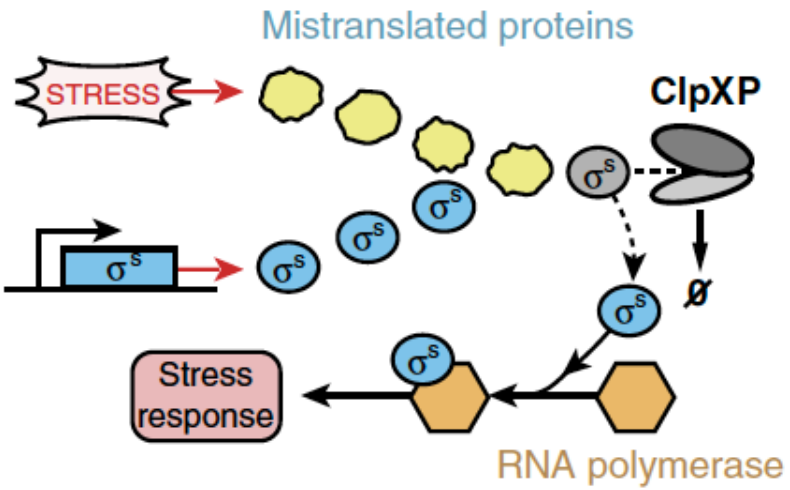
- Deterministic model: Michaelis-Menten equation

$$\frac{d[P]}{dt} = \frac{\mu[E]_0[S]}{K + [S]}, \qquad K = \frac{\eta^-}{\eta^+}$$

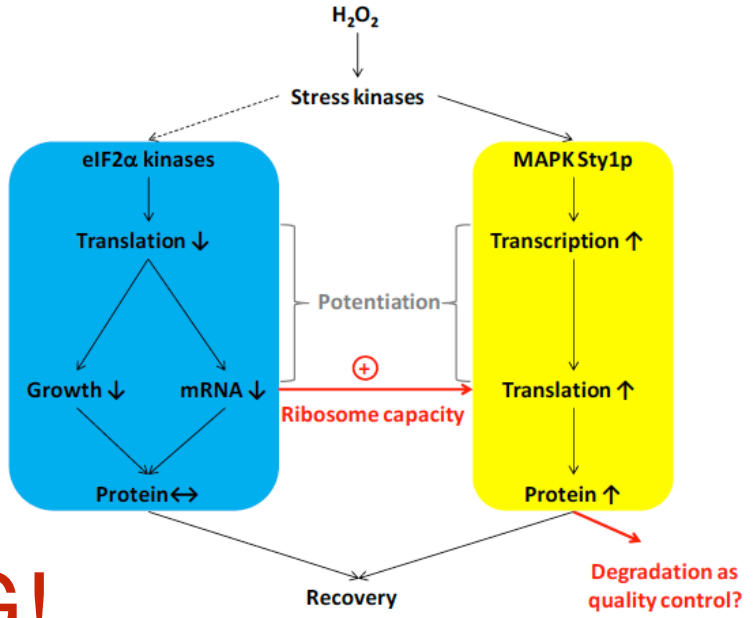
- Here: stochastic model, limited #enzymes, shared

Bottlenecks in Enzymatic Processing

Competitive enzymatic degradation in *E. Coli*:

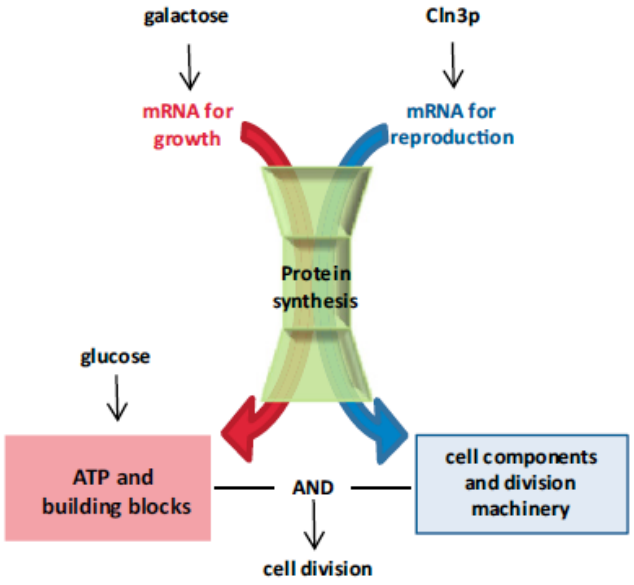


Oxidative stress response in *S. pombe*:

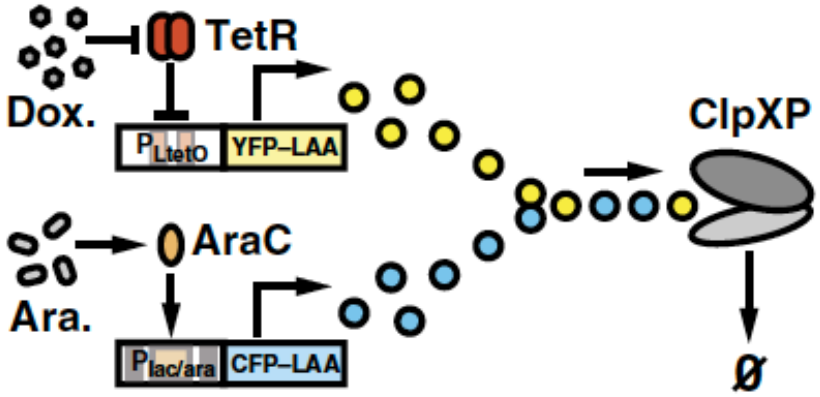


QUEUEING!

Translational crosstalk:



Synthetic shared degradation model



Connection to Queueing

- Queueing theory traditionally has used stochastic models to understand congestion effects in man-made systems in engineering and business where the processing resources are limited
- Queueing theory useful for formulating, analysing and interpreting models
- Two interesting regimes

Two Regimes in Queueing

Underloaded

No queue for iPad mini in London, Nov 2, 2012
Photo by Rik Henderson

Service rate > arrival rate

Queues are short

Little competition

Overloaded

Photo by Ilze Ziedins

Service rate < arrival rate

Queues are long

Strong competition

Two Regimes in Queueing

Underloaded

No queue for iPad mini in London, Nov 2, 2012
Photo by Rik Henderson

Service rate > arrival rate

Queues are short

Overloaded

Photo by Ilze Ziedins

Service rate < arrival rate

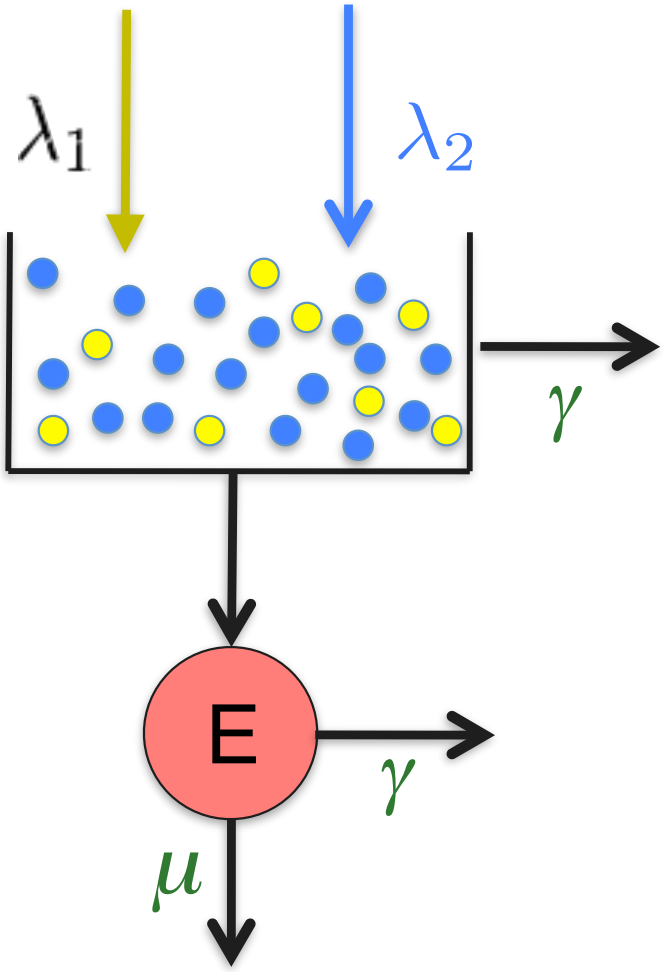
Queues are long

Balance: service rate = arrival rate

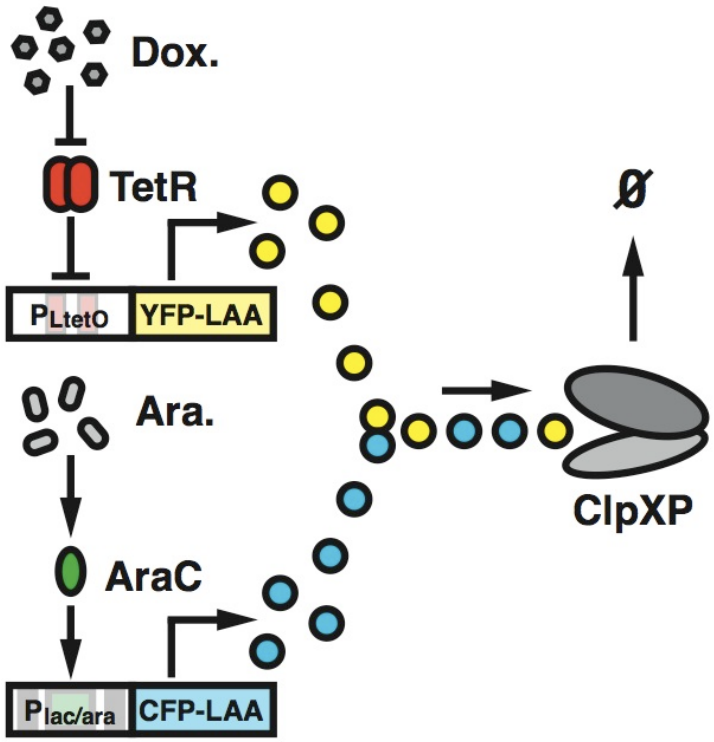
Outline

- Competition for common downstream (degradation) enzyme
- Adaptive enzymatic processing
- Enzymatic networks with shared resources

Competition for Enzymatic Processing



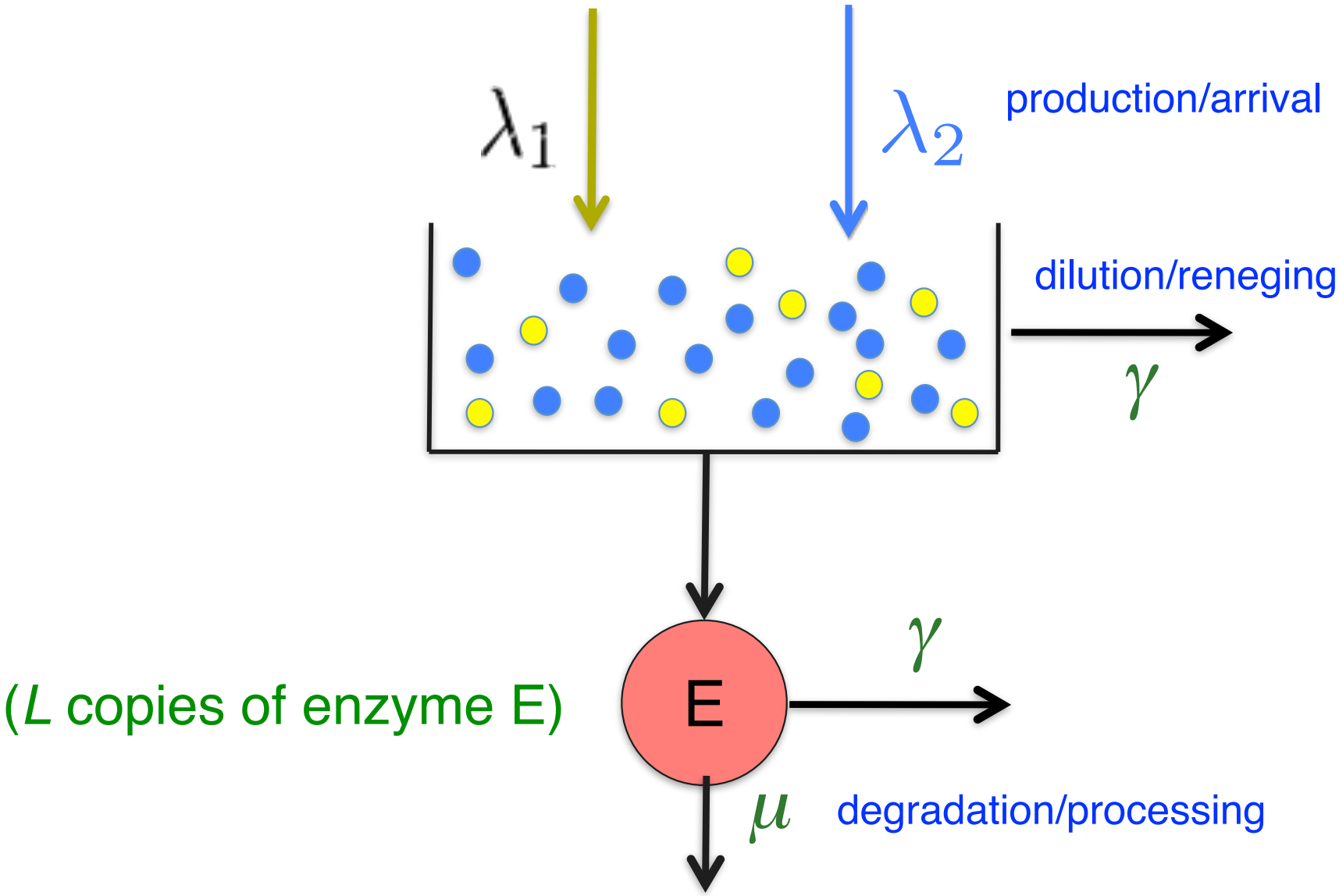
Theory



Experiment

Competition for Degradation

- Two uncoupled proteins X_1 and X_2 are processed downstream by a common enzyme E



Stochastic Model

Biochemical reaction network: protein species X_1, X_2

$$\varnothing \xrightarrow{\lambda_i} X_i \qquad \text{(production)}$$

$$X_i + E \xrightarrow{\eta} X_i E \qquad \text{(binding of enzyme)}$$

$$X_i E \xrightarrow{\mu} E \qquad \text{(degradation)}$$

$$X_i E \xrightarrow{\gamma} E, \qquad X_i \xrightarrow{\gamma} \varnothing \quad \text{(dilution)}$$

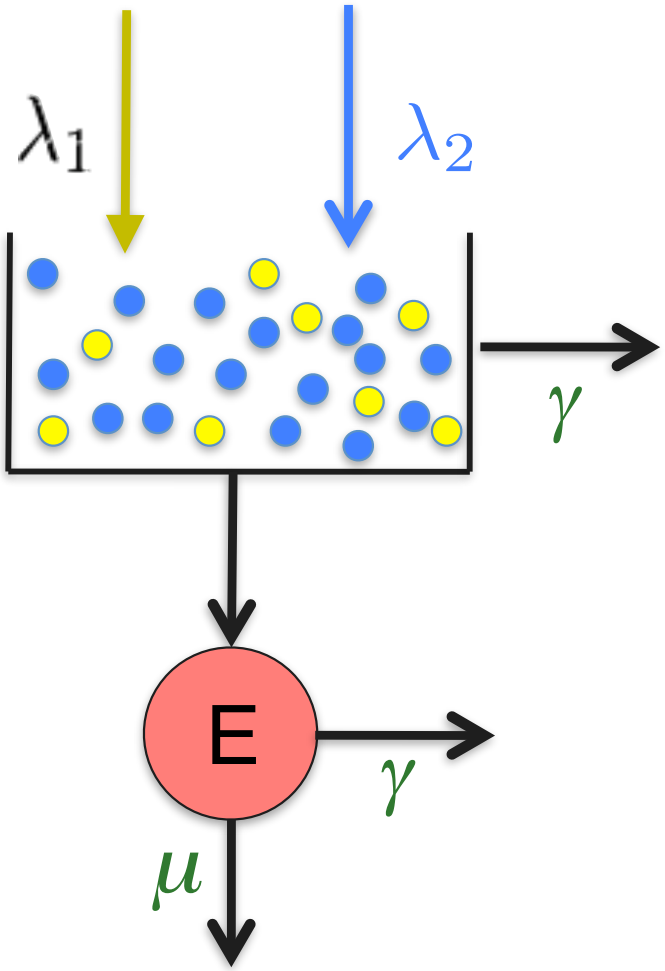
Assume: exponential reaction times and binding is instantaneous

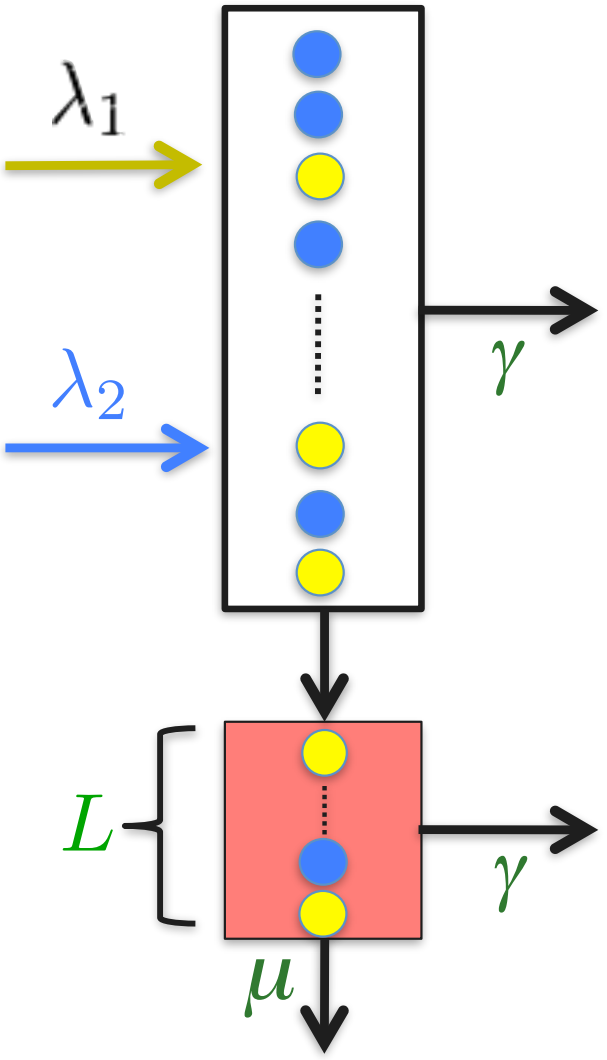
Key stochastic processes (*i=1,2*):

$Q_i(t)$ = total number of molecules of species i in the system at time t (includes free molecules and those being degraded)

$N(t)$ = total number of protein molecules in system at time t

Multiclass Queue: Processing in Random Order + Reneging





$$\text{Total service rate} = \phi(n) = min(n, L)\mu + n\gamma$$

n = total number of protein molecules in system

Steady-State Distribution (Quasireversible Queue)

Markovian state descriptor: ordered list of the types in the queue (incl. those being processed)

Theorem (Kelly): There is a unique steady-state distribution for the "list" Markov process. The associated steady-state distribution for the total number of molecules in the system, *N*, is:

$$P(N=n) = c\frac{\Lambda^n}{\prod_{\ell=1}^{n}\phi(\ell)}$$

and conditioned on *N=n*, the stationary distribution for the molecular count process *Q* is a binomial distribution with parameters $(n; p_1, p_2)$:

$$P(Q=(q_1,q_2)) = P(N=n)\frac{n!}{q_1!q_2!}p_1^{q_1}p_2^{q_2}$$

$$\Lambda = \sum_i \lambda_i \qquad p_i = \frac{\lambda_i}{\Lambda}$$

Moments:

$$
\begin{aligned}
E[Q_i] &= p_i E[N] \\
E[Q_i^2] &= p_i(1-p_i)E[N] + p_i^2 E[N^2] \\
Var(Q_i) &= p_i^2(Var(N) - E[N]) + p_i E[N] \\
E[Q_i Q_j] &= p_i p_j (E[N^2] - E[N]) \quad \text{for } j \neq i
\end{aligned}
$$

Correlation:

$$r_{ij} = \frac{E[Q_i Q_j] - E[Q_i]E[Q_j]}{\sqrt{Var(Q_i)Var(Q_j)}}$$

$$r_{ij} = \frac{F-1}{\sqrt{(F-1+1/p_i)(F-1+1/p_j)}} \qquad j \neq i$$

$$F = \frac{Var(N)}{E[N]}$$

Fano factor - can be computed exactly

Moments for *N*

- Distribution: $P(N=n) = c\dfrac{\Lambda^n}{\prod_{\ell=1}^{n}\phi(\ell)}$

  where

$$\Lambda = \sum_i \lambda_i \qquad\qquad \phi(n) = \min(n, L)\mu + n\gamma$$

- Normalizing constant *c*:

$$c^{-1} = \sum_{n=0}^{L-1} \frac{\zeta^n}{n!} + \frac{\zeta^L}{L!} M(1, \beta+1, \delta)$$

$$M(x,y,z) = \sum_{n=0}^{\infty} \frac{(x)_n z^n}{(y)_n n!}$$

confluent hypergeometric function

$$\zeta = \frac{\Lambda}{\mu+\gamma}, \quad \beta = \frac{L\mu}{\gamma} + L, \quad \delta = \frac{\Lambda}{\gamma}$$

- Moment generating function:

$$E[e^{uN}] = c\left(\sum_{n=0}^{L-1} \frac{(e^u\zeta)^n}{n!} + \frac{(e^u\zeta)^L}{L!} M(1, \beta+1, e^u\delta)\right)$$

Moments and Correlations for Q (L=1)

$$
\begin{aligned}
E[Q_i] &= \frac{p_i \delta M(2, \beta+1, \delta)}{\beta M(1, \beta, \delta)}, \\
Var(Q_i) &= \frac{2p_i^2 \delta^2 M(3, \beta+2, \delta)}{\beta(\beta+1) M(1, \beta, \delta)} - \left(\frac{p_i \delta M(2, \beta+1, \delta)}{\beta M(1, \beta, \delta)} \right)^2 + \frac{p_i \delta M(2, \beta+1, \delta)}{\beta M(1, \beta, \delta)}, \\
r_{ij} &= \frac{h(\beta, \delta)}{(h(\beta, \delta) + p_i^{-1})^{1/2} (h(\beta, \delta) + p_j^{-1})^{1/2}},
\end{aligned}
$$

$\beta = (\mu/\gamma) + 1$, $\delta = \Lambda/\gamma$, $\Lambda = \sum_{i=1}^{m} \lambda_i$,

$$
f(\beta, \delta) = \frac{2\delta M(3, \beta+2, \delta)}{\beta+1} - \frac{\delta (M(2, \beta+1, \delta))^2}{\beta M(1, \beta, \delta)},
$$

$$
g(\beta, \delta) = M(2, \beta+1, \delta), \qquad h(\beta, \delta) = \frac{f(\beta, \delta)}{g(\beta, \delta)},
$$

Zero Dilution Limit for L=1

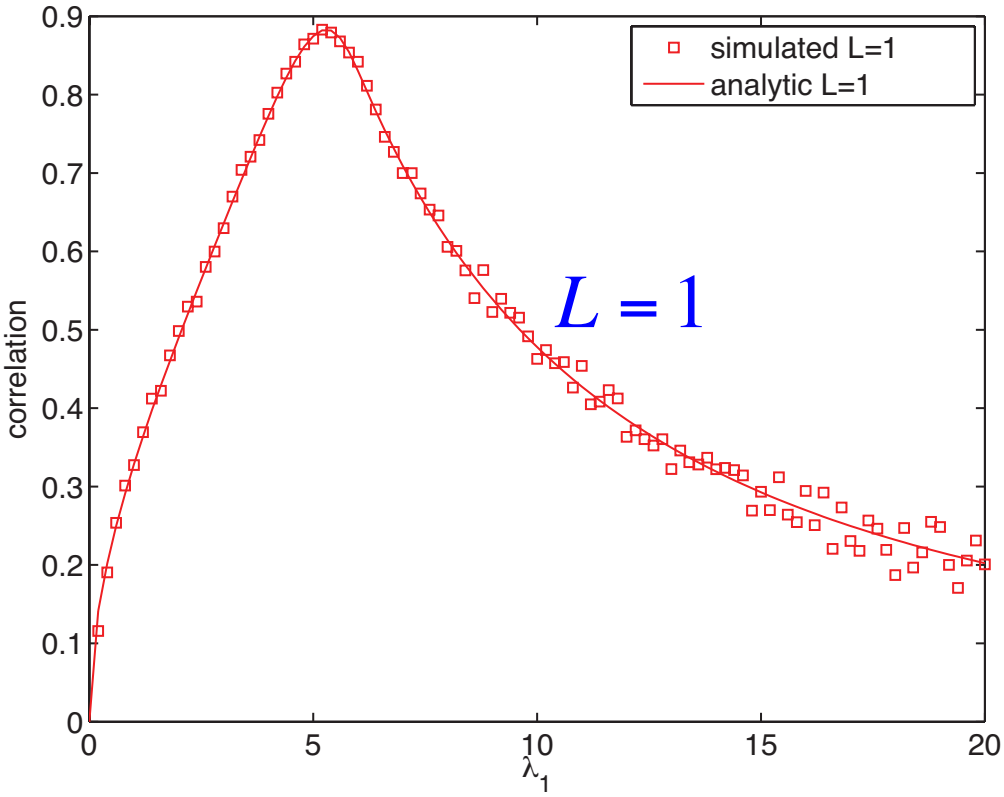
- For $\gamma \to 0$ and $\rho = \Lambda / \mu < 1$

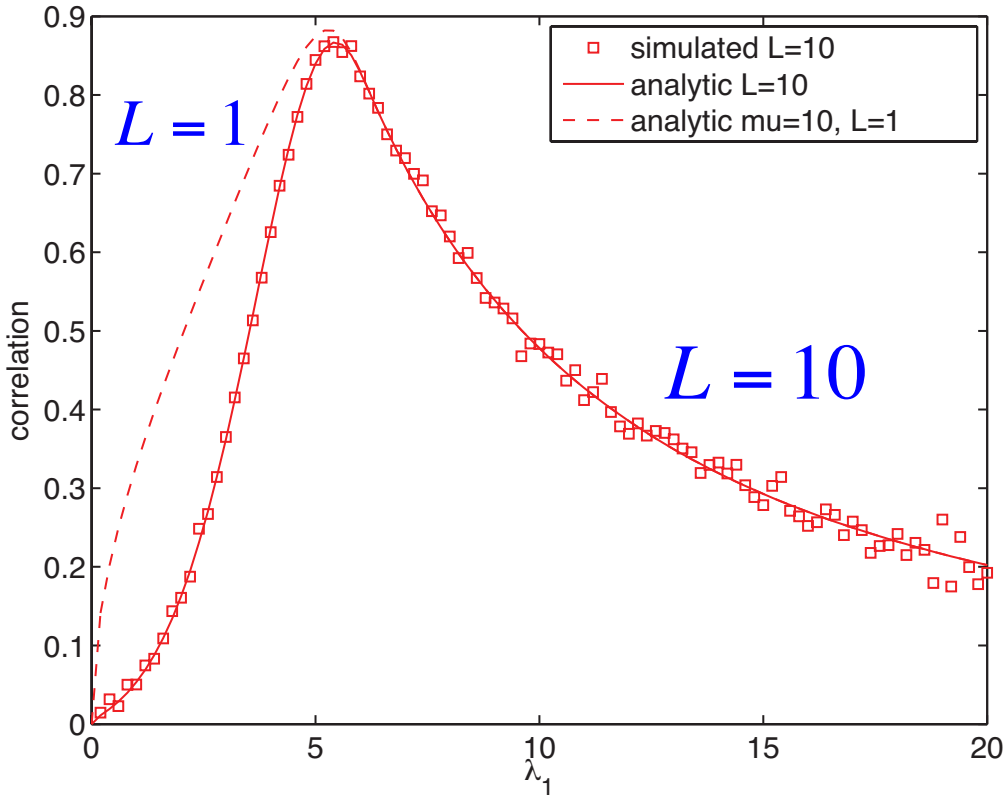
$$r_{ij} = \frac{1}{\left(1+\frac{1}{p_i}\left(\frac{1}{\rho}-1\right)\right)^{\frac{1}{2}}\left(1+\frac{1}{p_j}\left(\frac{1}{\rho}-1\right)\right)^{\frac{1}{2}}}$$

Here $p_i = \lambda_i / \Lambda$, $p_j = \lambda_j / \Lambda$

Correlation Resonance (non-zero dilution)

- Correlation as a function of λ_1



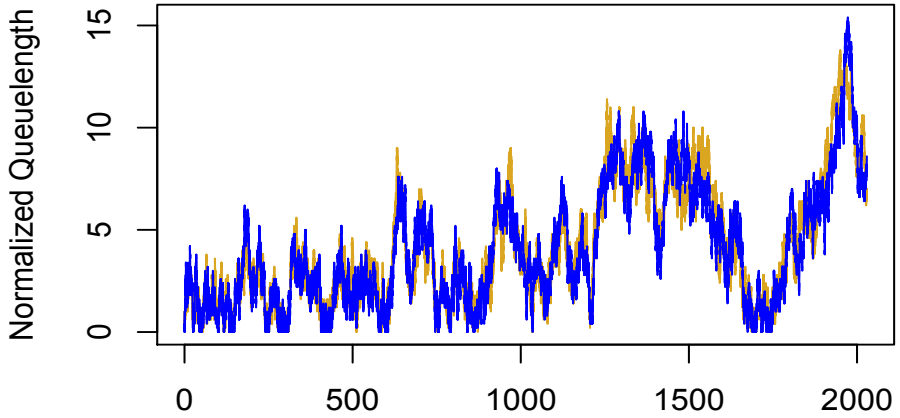


Simulation parameters:

$$\lambda_2 = 5 \quad \mu L = 10 \quad \gamma = .01 \quad \eta = 10^8$$

Dynamics (Stochastic Simulations, L=1)

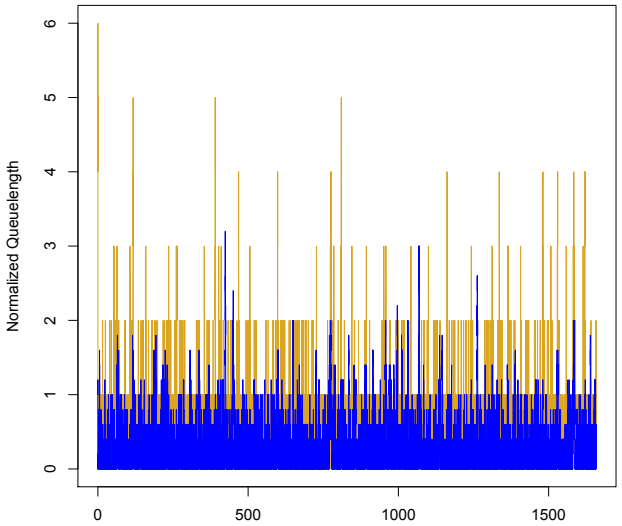
Balanced



$\lambda_2 = 5,\ \lambda_1 = 5$

$\mu = 10$

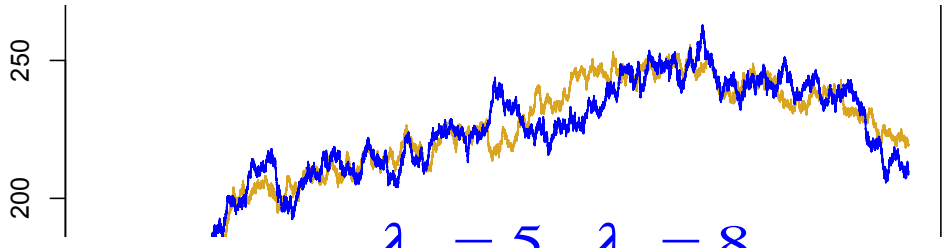
Underloaded



$\lambda_2 = 5,\ \lambda_1 = 1$

$\mu = 10$

Overloaded (with small reneging)



$\lambda_2 = 5,\ \lambda_1 = 8$

$\mu = 10$

R Simulation code: Ruibo Ma

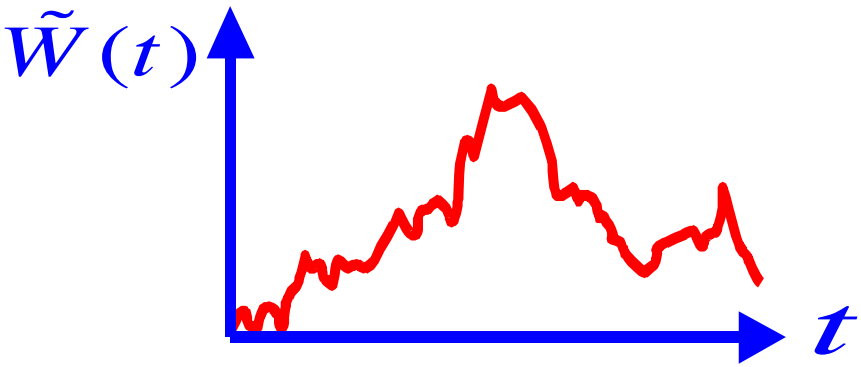
Theorem (at balance: $\rho \triangleq \frac{\lambda_1 + \lambda_2}{\mu} = 1, \ \gamma = 0$)

Let $\hat{Q}_i^r(t) = \frac{Q_i(r^2 t)}{r}, \ i = 1,2$ (diffusion scaling)

As $r \to \infty$,

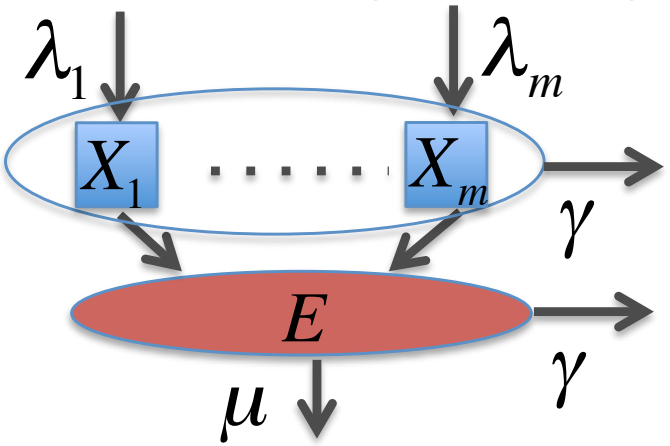
$\hat{Q}_i^r(\bullet) \to \lambda_i \tilde{W}(\bullet), \ \ i = 1,2$ (convergence in distribn)

where $\tilde{W}$ is a one-dimensional reflecting Brownian motion.



Generalizations

- Finitely many types of proteins $X_1, \ldots, X_m$



$$\varnothing \xrightarrow{\lambda_i} X_i \qquad \text{(production)}$$

$$X_i + E \xrightarrow{\eta} X_i E \qquad \text{(binding of enzyme)}$$

$$X_i E \xrightarrow{\mu} E \qquad \text{(degradation)}$$

$$X_i E \xrightarrow{\gamma} E, \qquad X_i \xrightarrow{\gamma} \varnothing \qquad \text{(dilution)}$$

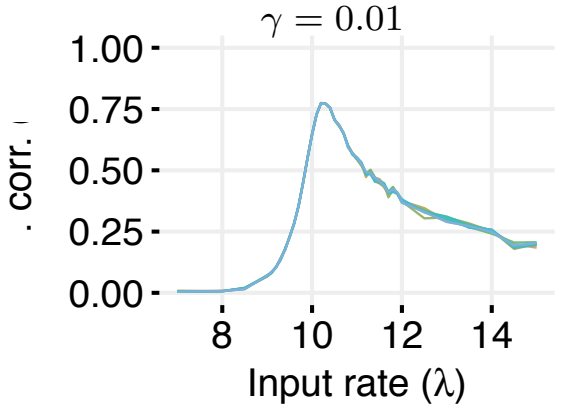
Steady-state multivariate distribution factorizes:

$$P(Q = (q_1, \ldots, q_m)) = P(N = n) \frac{n!}{q_1! \ldots q_m!} p_1^{q_1} \ldots p_m^{q_m}$$

$$P(N = n) = c \frac{\Lambda^n}{\prod_{\ell=1}^{n} \phi(\ell)}, \qquad \phi(\ell) = \mu \min(\ell, L) + \ell\gamma$$

$$r_{ij} = \frac{F - 1}{\sqrt{(F - 1 + 1/p_i)(F - 1 + 1/p_j)}}, \qquad i \neq j,$$

F – Fano factor for N

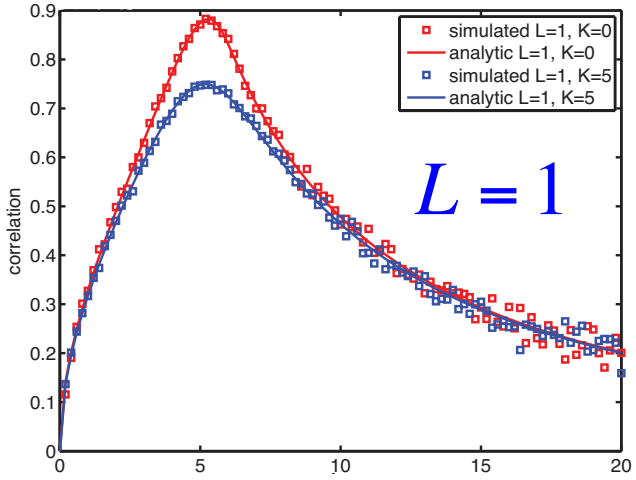


$m = 8$, $\lambda_i = \lambda \ \forall i$, $L = 80$, $\mu = 1$

Correlation resonance near balance

Generalizations

- Reversible binding $X_i + E \underset{\eta^-}{\overset{\eta^+}{\rightleftharpoons}} X_i E$

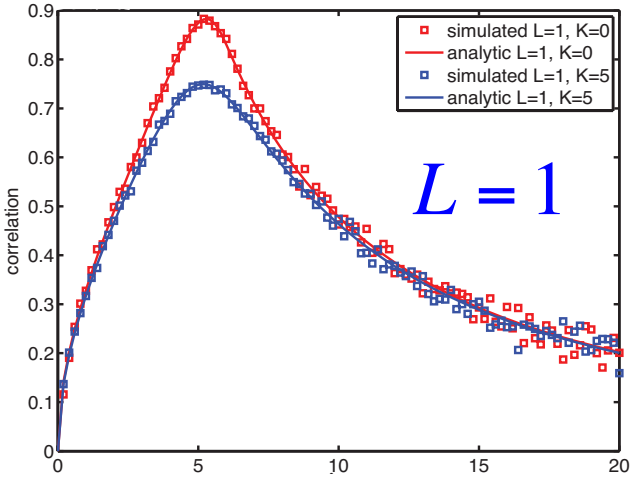


$$m = 2 \quad \lambda_2 = 5 \quad \mu = 10 \quad \gamma = .01$$

$$\eta^+ = 10^8 (K = 0) \quad \eta^- = 1000 (K > 0) \quad K = \eta^- / \eta^+$$

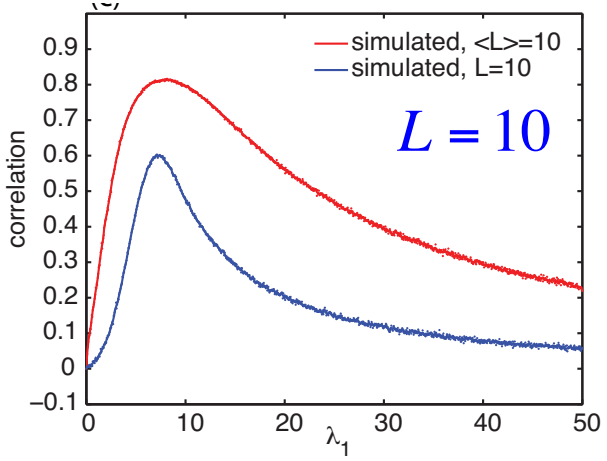
Generalizations

- Reversible binding $X_i + E \underset{\eta^-}{\overset{\eta^+}{\rightleftharpoons}} X_i E$



$$m = 2 \quad \lambda_2 = 5 \quad \mu = 10 \quad \gamma = .01$$
$$\eta^+ = 10^8 (K = 0) \quad \eta^- = 1000 (K > 0) \quad K = \eta^- / \eta^+$$

- Fluctuating enzymes $\varnothing \xrightarrow{\nu} E, \quad E \xrightarrow{\gamma} \varnothing, \quad X_i E \xrightarrow{\gamma} \emptyset$



$$m = 2 \quad \lambda_2 = 5 \quad \mu = 1 \quad \gamma = .1 \quad \nu = 1$$
$$\eta^+ = 200 \quad \eta^- = 1000$$

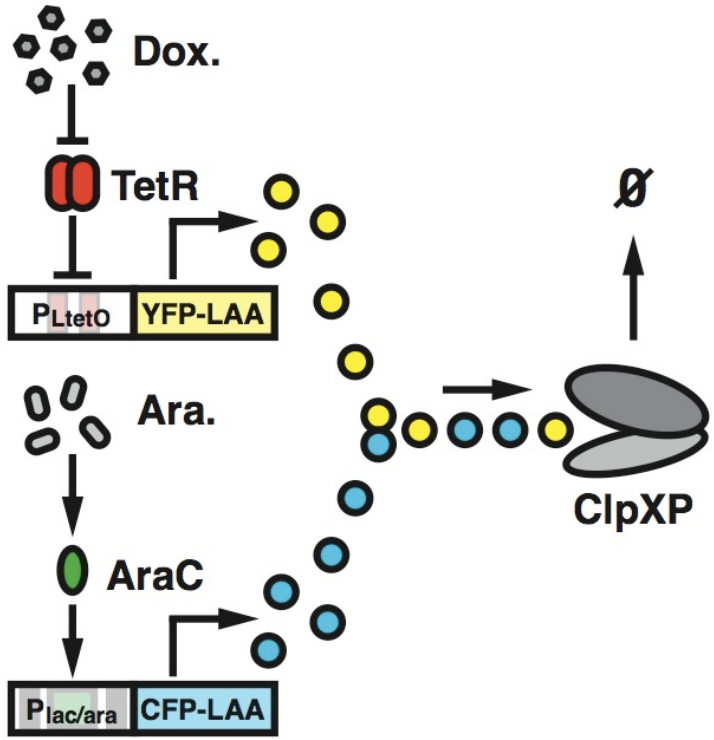
Experiment

Queueing in a Synthetic Gene Network

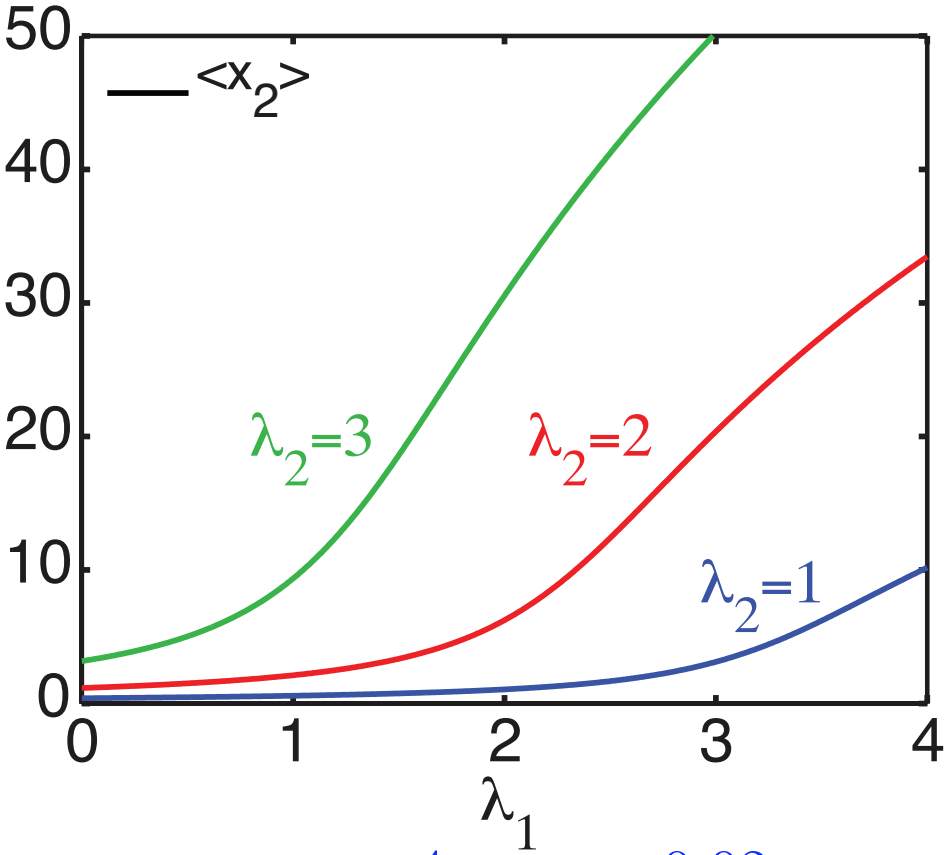
- Two independently synthesized fluorescent proteins: YFP and CFP in *E Coli*
- ClpXP protease degrades LAA tagged proteins

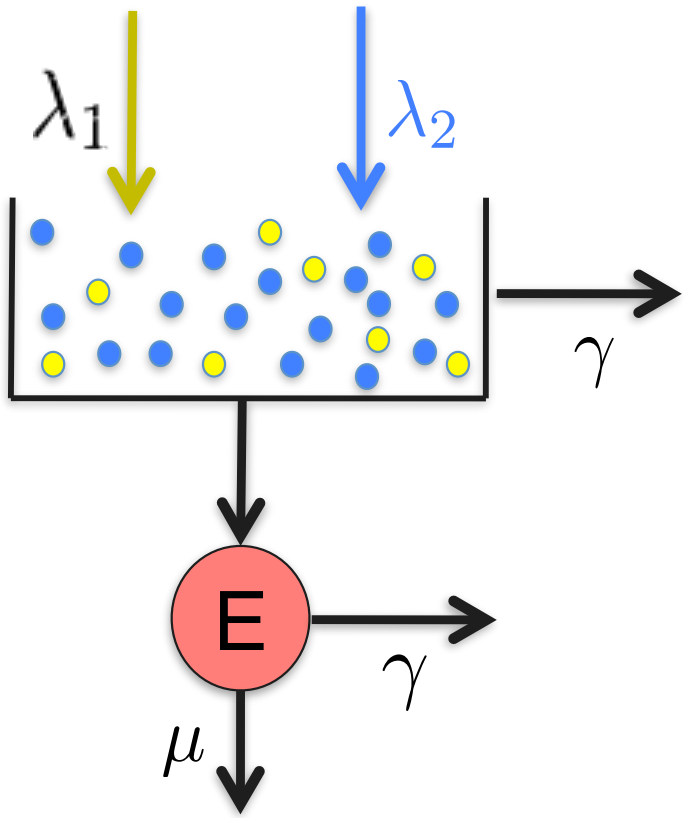
- Tet promoter driving YFP
  - Repressible by TetR
  - Tunable by Doxycycline

- Lac/Ara promoter driving CFP
  - Activated by AraC
  - Tunable by Arabinose



Effect of Coupling on Mean:





$\mu = 4 \quad \gamma = 0.02$

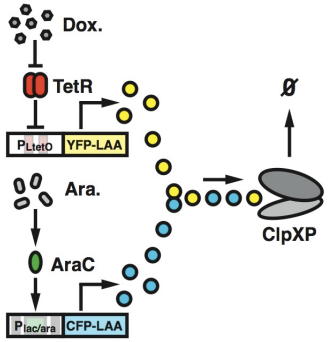
$L = 1 \quad K = 0.2$

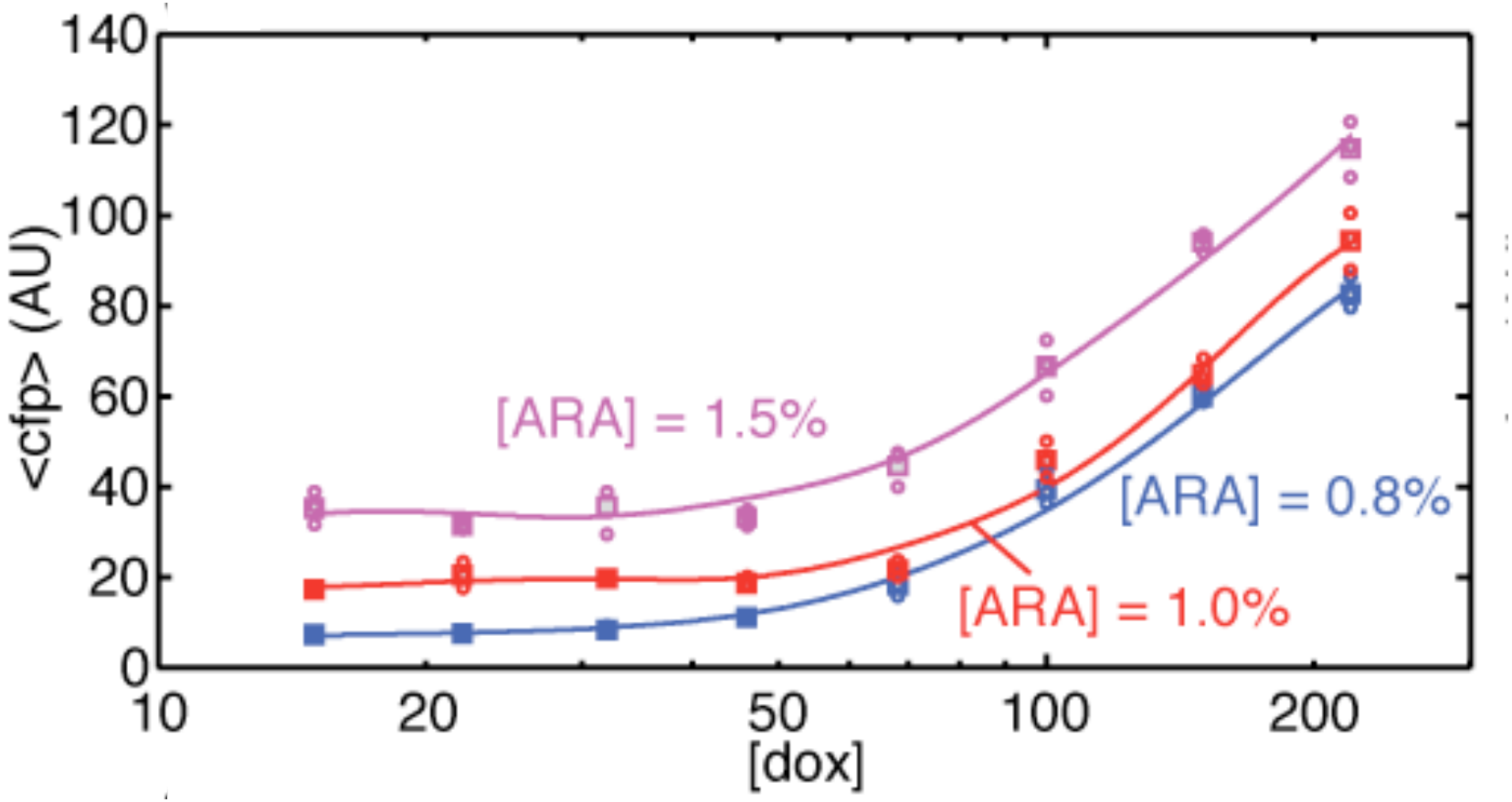
As λ_1 increases, means both X_1 and X_2 increase rapidly at the "balance" point, where

$$\lambda_1 + \lambda_2 = \mu$$

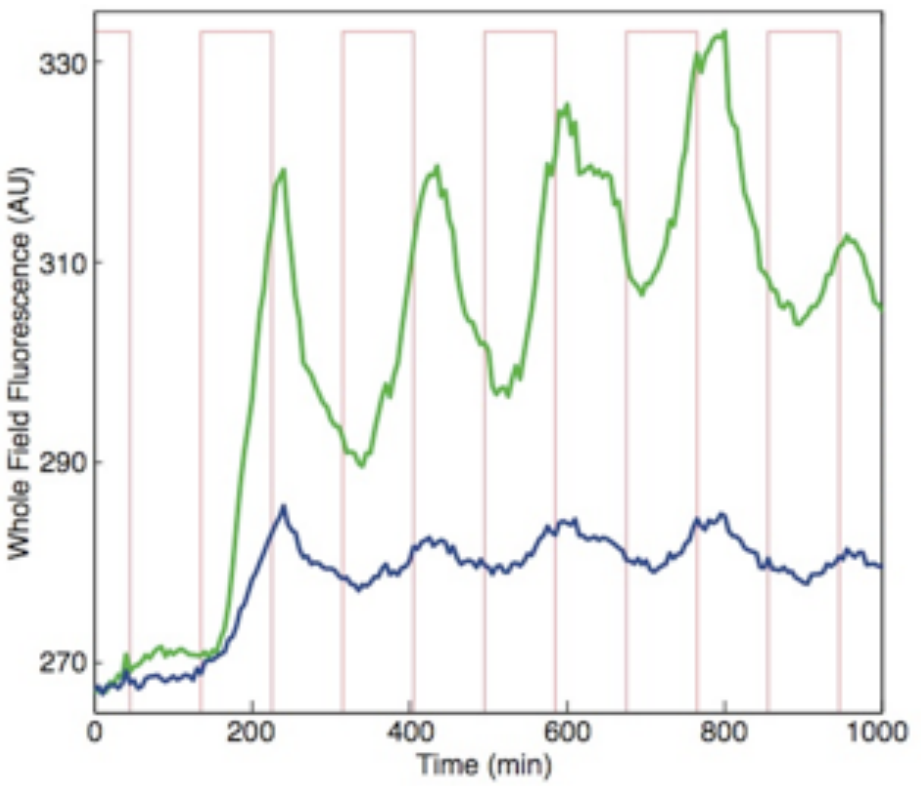
Effect of Coupling on Mean:

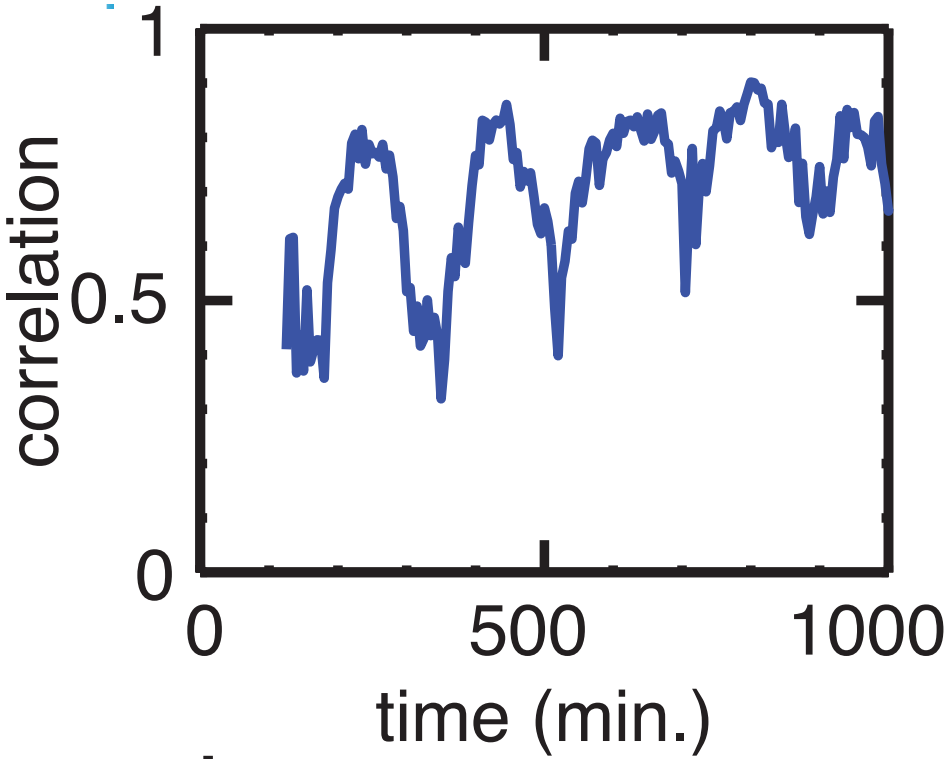
Experiment: modulated doxycycline





Dynamic Modulation





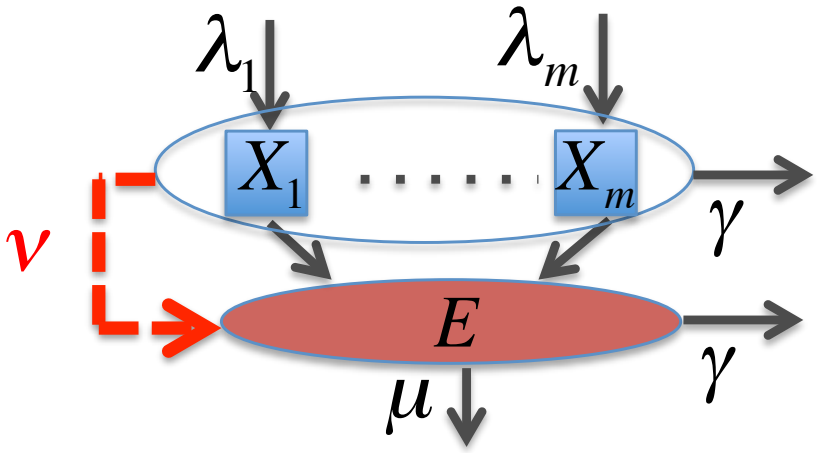
Red trace: periodic influx of doxycycline

Green trace: response in level of YFP

Blue trace: response in level of CFP due to coupled degradation

Adaptive Enzymatic Processing (Theory)

Stochastic Model with Adaptation



$$\varnothing \xrightarrow{\lambda_i} X_i, \quad \varnothing \xrightarrow{\nu} E,$$

$$X_i + E \underset{\eta^-}{\overset{\eta^+}{\rightleftharpoons}} X_i E \xrightarrow{\mu} E,$$

$$X_i E \xrightarrow{\gamma} \varnothing, \quad X_i \xrightarrow{\gamma} \varnothing, \quad E \xrightarrow{\gamma} \varnothing.$$

$$\nu(Q) = \alpha N = \alpha \sum_{i=1}^{m} Q_i$$

If enzymes are underloaded - make less
If enzymes are overloaded - make more

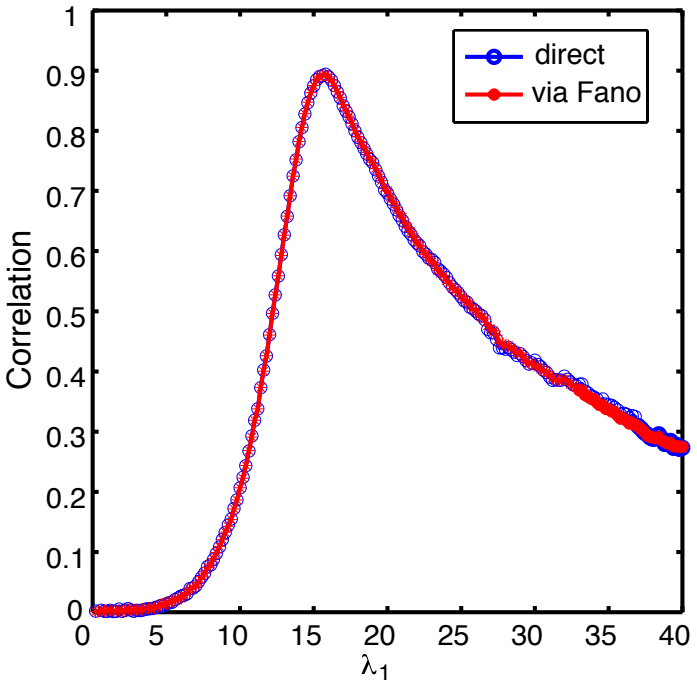
Steady-State Distribution

Steady-state multivariate distribution factorizes and can express the steady-state correlations in terms of Fano factor *F* for *N:*

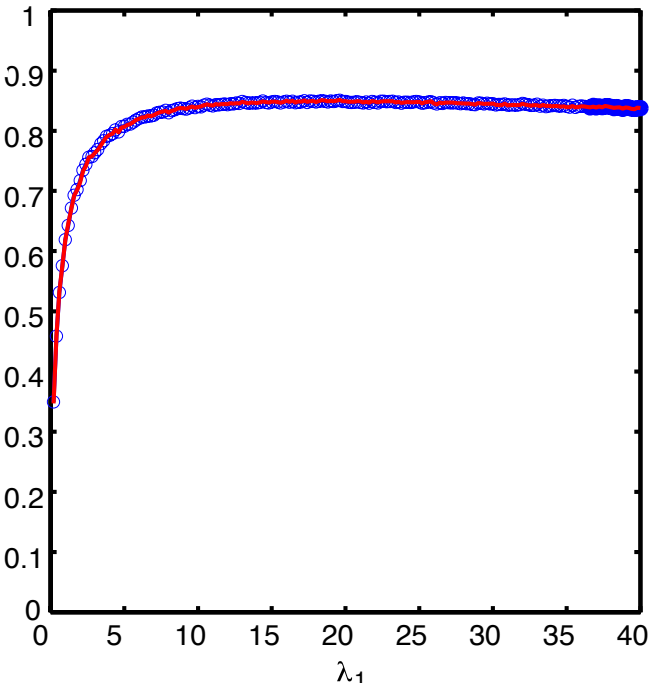
$$r_{ij} = \frac{F-1}{\sqrt{(F-1+1/p_i)(F-1+1/p_j)}}, \quad i \neq j,$$

For instant irreversible binding, *(N,L)* is a two-dimensional birth-death process.

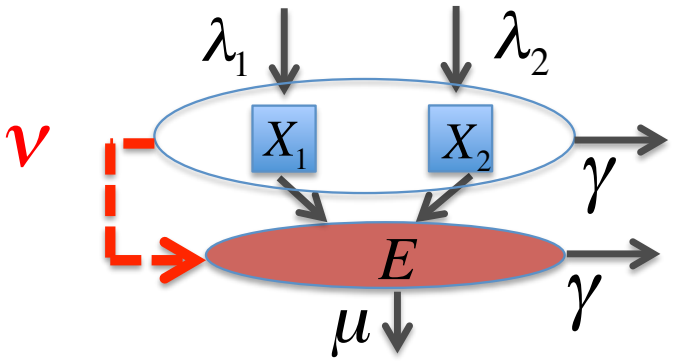
Correlation vs. λ_1 (with slow adaptation)



fixed *L*=25



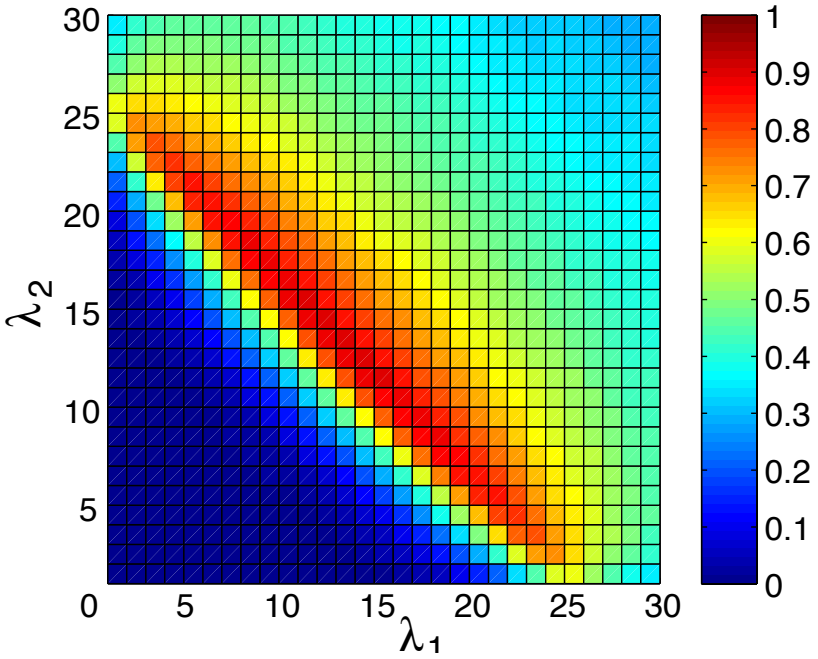
adaptive *L*



$m = 2,\ \lambda_2 = 10,\ \mu = 1$

$\gamma = .01,\ \nu = .01N$

Correlation for variable λ_1, λ_2



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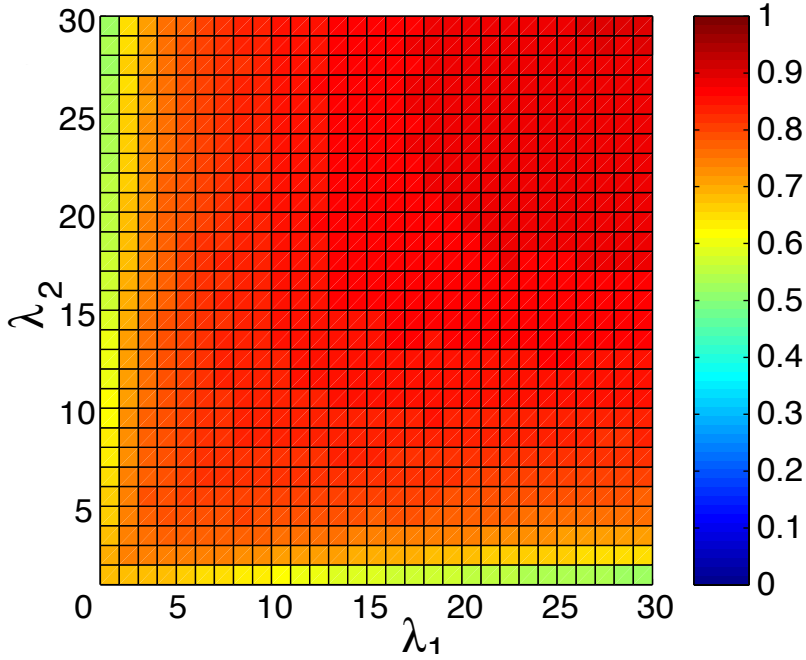
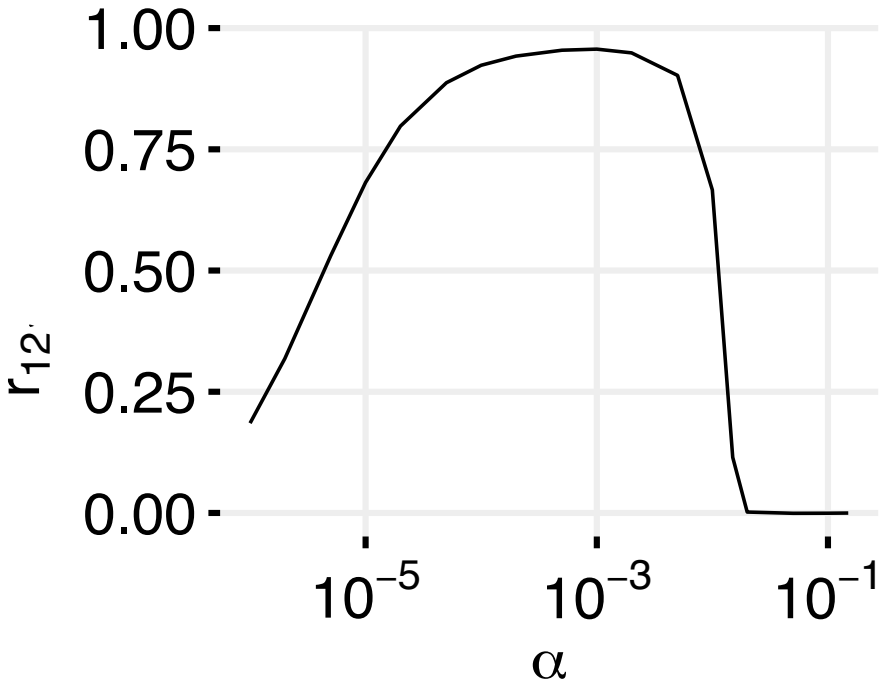


adaptive *L*

$$m = 2,\ \mu = 1$$

$$\gamma = .01,\ \nu = .01N$$

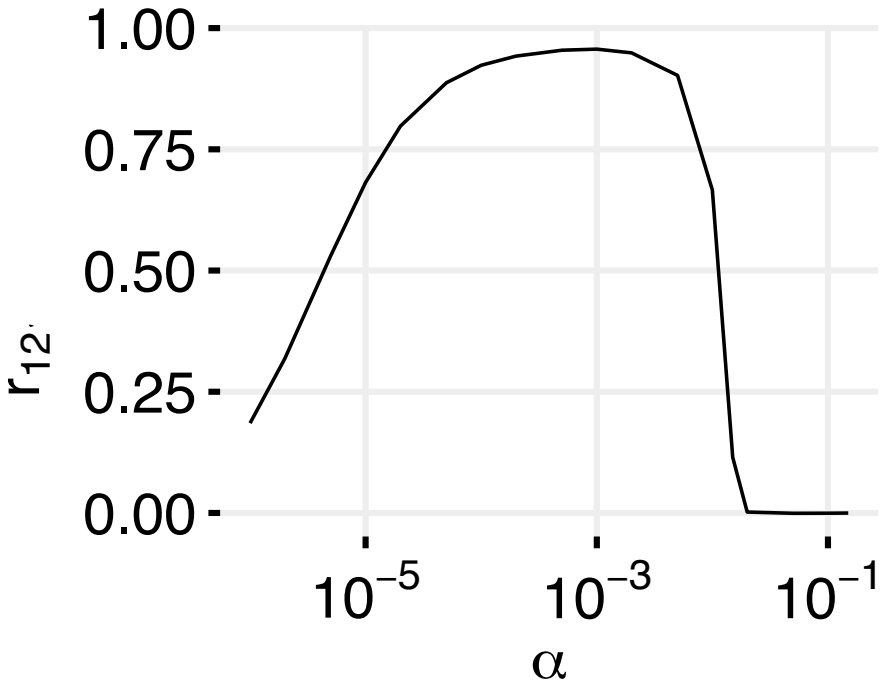
Effect of α

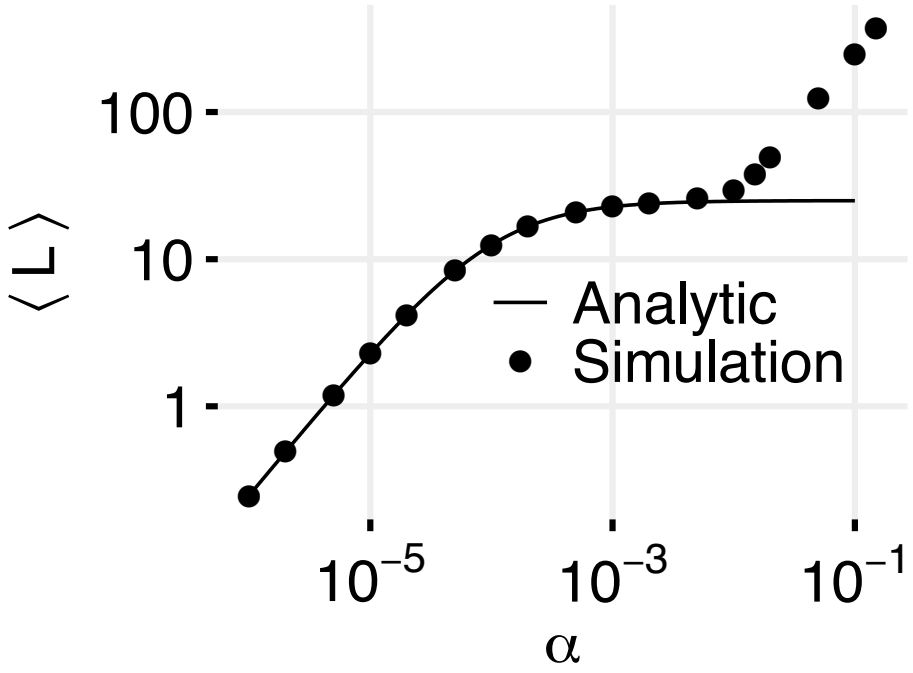


$$m = 2,\ \nu = \alpha N,\ \lambda_1 = 10,\ \lambda_2 = 15,\ \mu = 1,\ \gamma = .01$$

$$\frac{\gamma^2}{\mu} \leq \alpha \leq \gamma$$

Effect of α



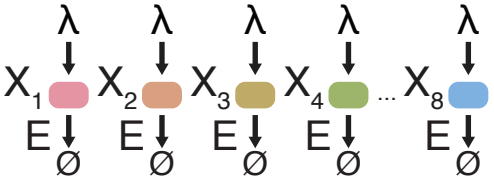


$$m = 2,\ \nu = \alpha N,\ \lambda_1 = 10,\ \lambda_2 = 15,\ \mu = 1,\ \gamma = .01$$

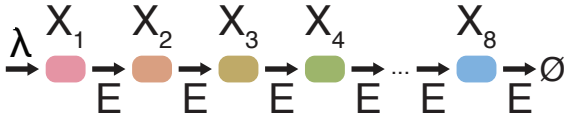
$$\frac{\gamma^2}{\mu} \leq \alpha \leq \gamma$$

Enzymatic Networks with Shared Resources

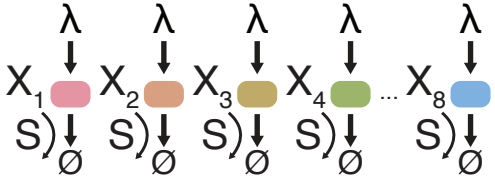
parallel network with shared enzyme

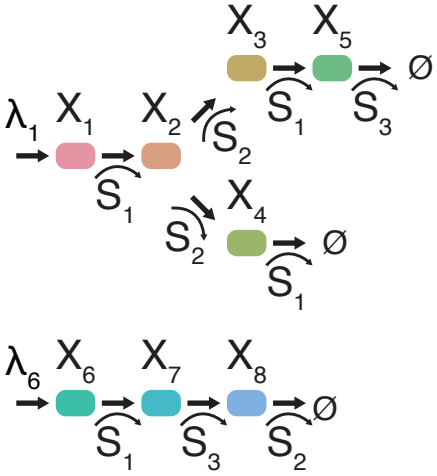


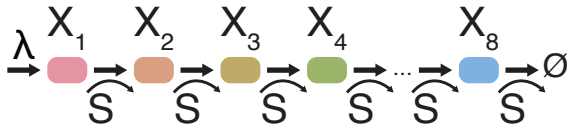
serial network with shared enzyme



networks with shared cofactor







Conclusions

- Shared processing resources produce correlated behavior in enzymatic networks
- By mapping stochastic enzymatic models to multiclass quasireversible queues, we obtained explicit formulas for steady-state multi-variate distributions and correlations
- Correlations have a strong peak near balance point
- Slow adaptation of enzymatic resources leads to high correlations in broad regions of parameter space
- Theoretical predictions agree with experimental results for a two-component synthetic gene network

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THANK YOU