Criticality and Adaptivity in Enzymatic Networks

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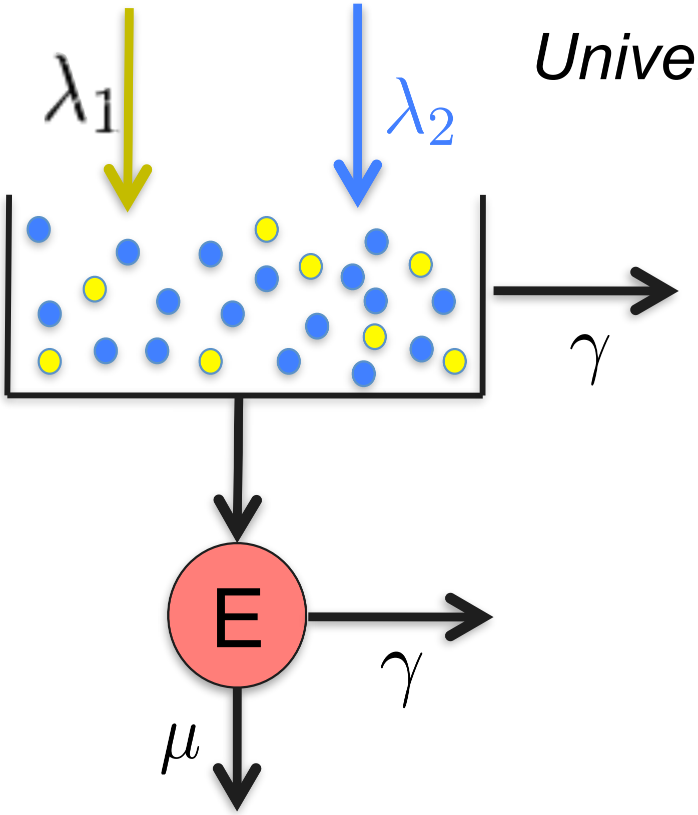

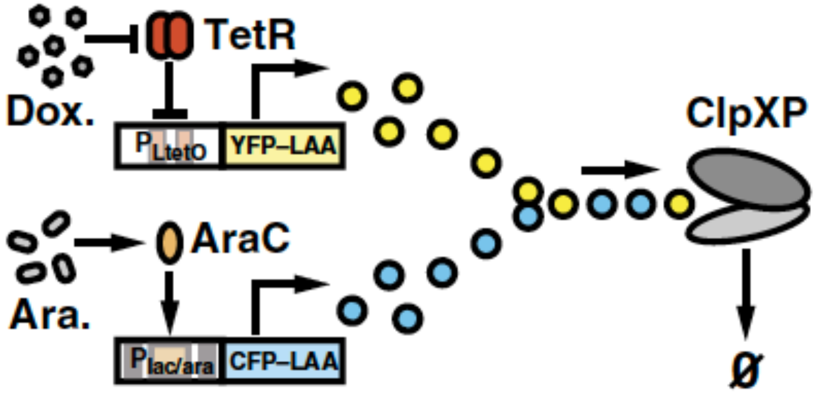

Acknowledgements

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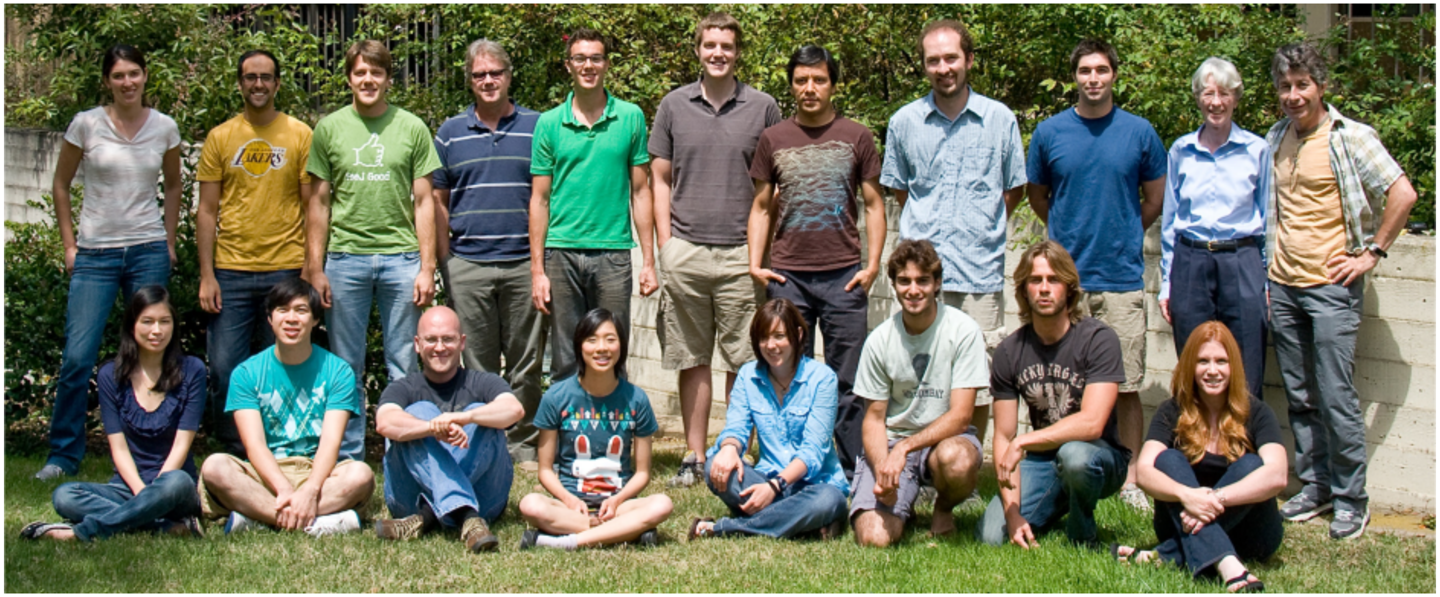
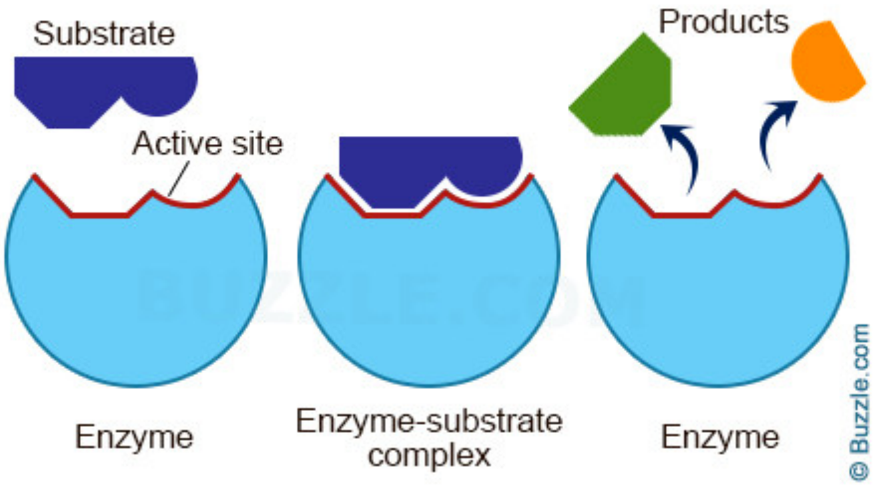
- members of the UCSD Systems Biodynamics Lab



- Thanks to NSF and NIH for funding

Enzymes

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



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

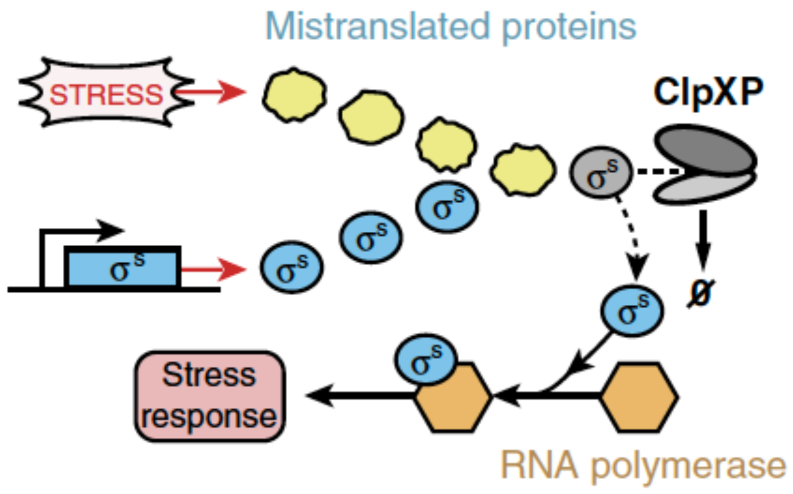
- Deterministic model: Michaelis-Menten equation

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

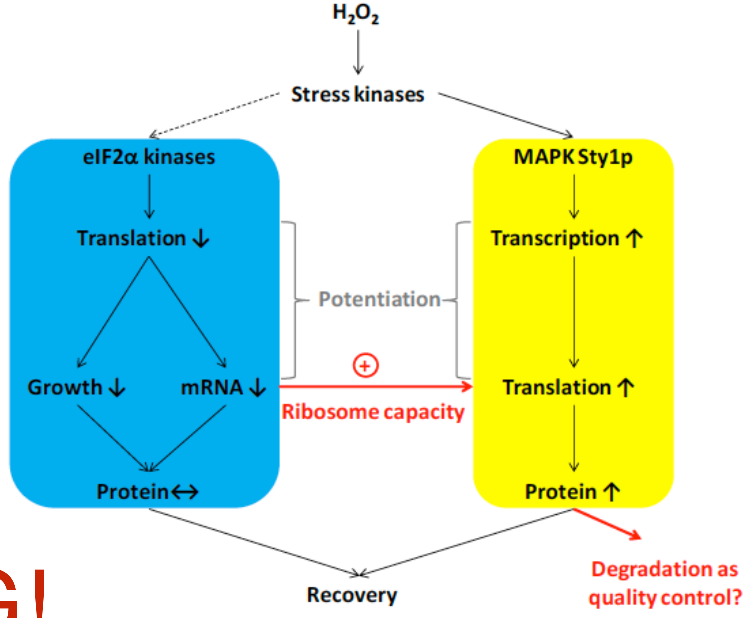
- Here: stochastic model, limited #enzymes, shared

Bottlenecks in Enzymatic Processing

Competitive enzymatic degradation in *E. Coli*:

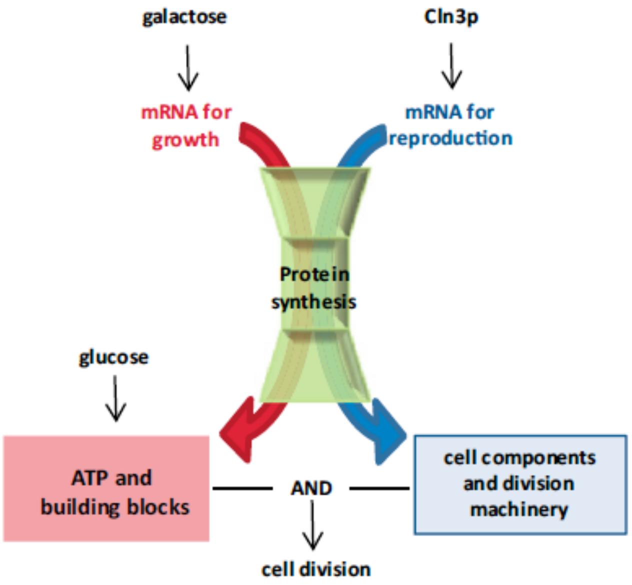


Oxidative stress response in *S. pombe*:

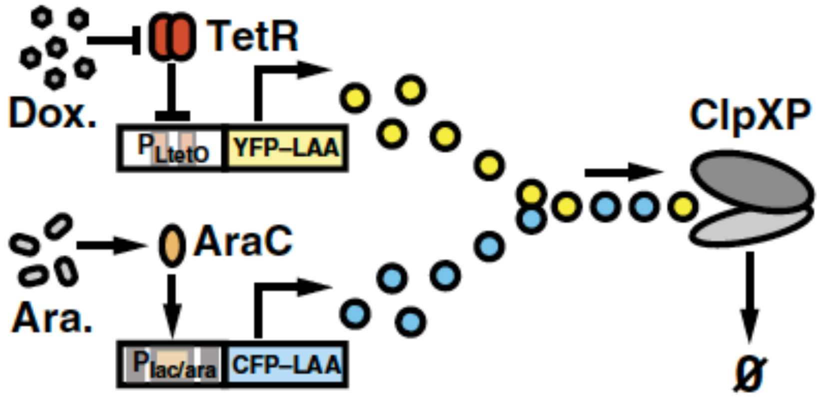


QUEUEING!

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

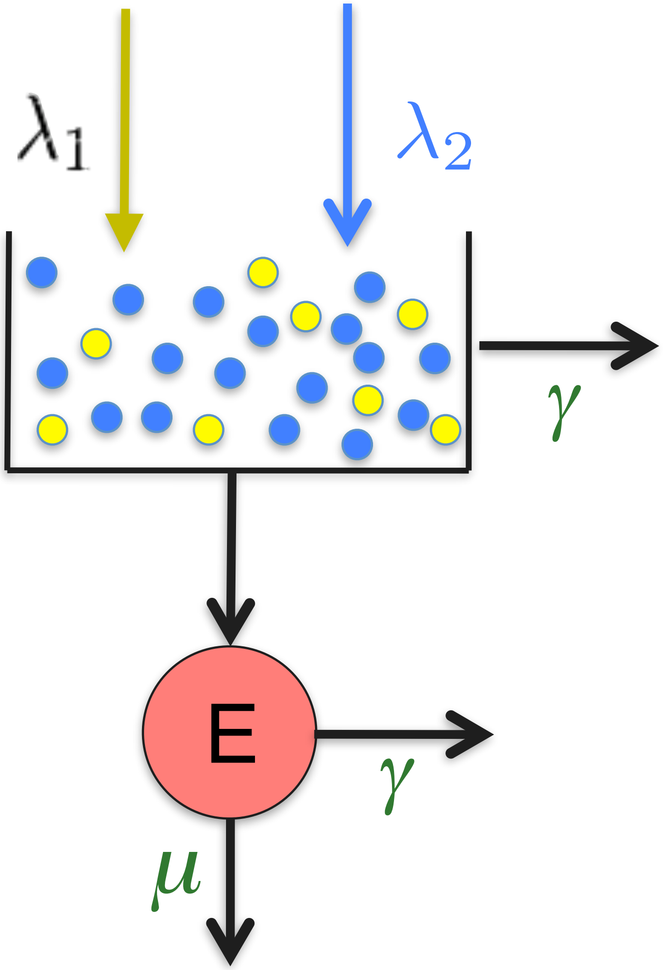
Outline

- Competition for common downstream (degradation) enzyme

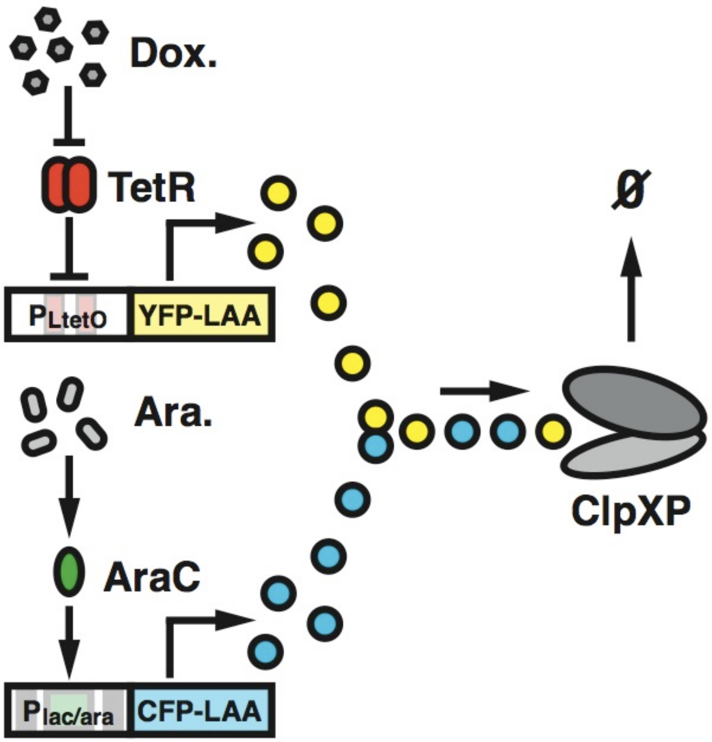
- Adaptive enzymatic processing

- Enzymatic networks with shared resources

Competition for Enzymatic Processing



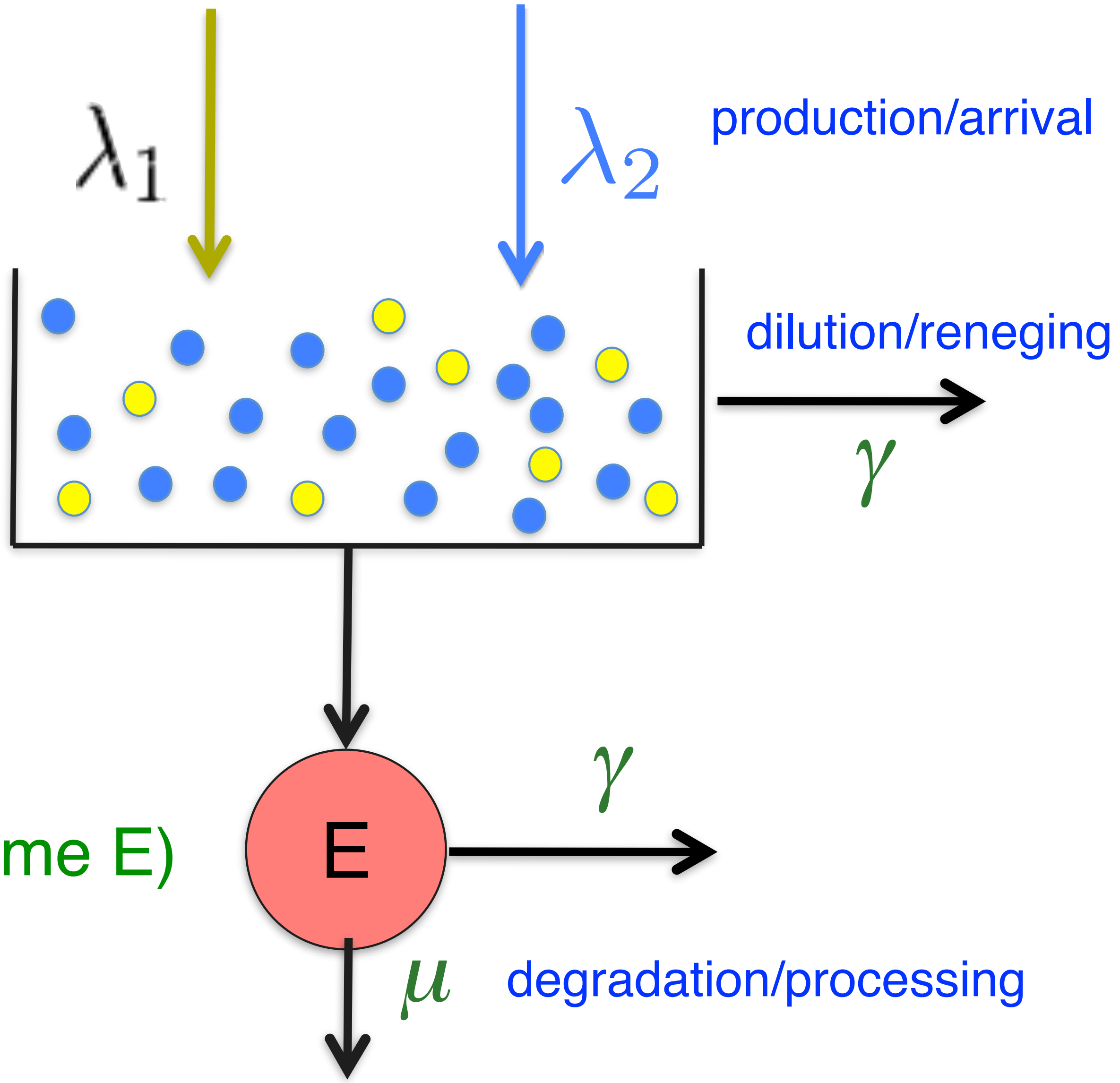
Theory



Experiment

Competition for Degradation

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



(*L* copies of enzyme E)

Stochastic Model

Biochemical reaction network: protein species X_1, X_2

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

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

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

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

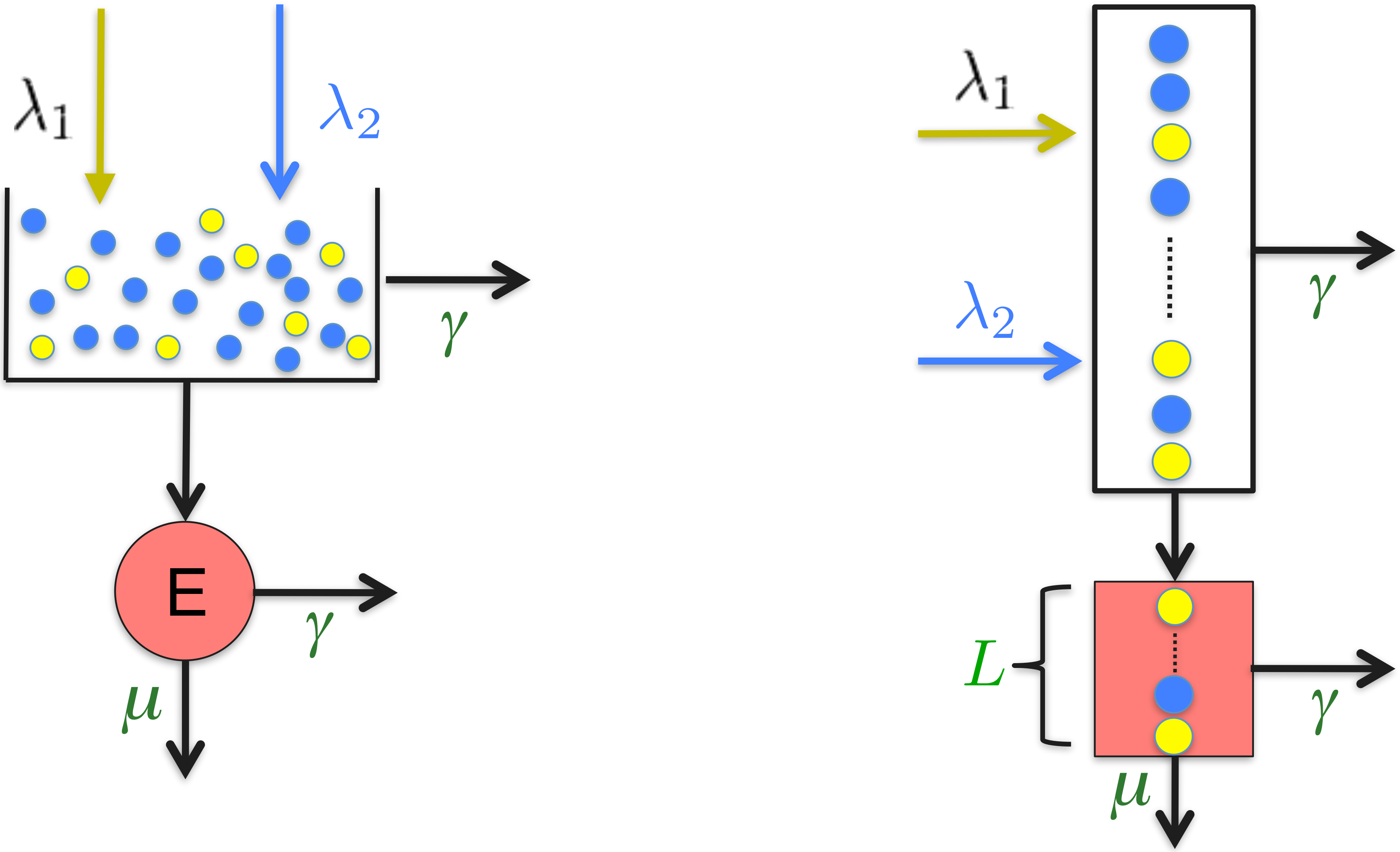
Assume: exponential reaction times and binding is instantaneous

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

$$\begin{aligned} Q_i(t) \quad &= \quad \text{total number of molecules of species } i \text{ in the system at time t} \\ &\quad\quad \text{(includes free molecules and those being degraded)} \end{aligned}$$

$$N(t) = \text{total number of protein molecules in system at time t}$$

Multiclass Queue: Processing in Random Order + Reneging



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

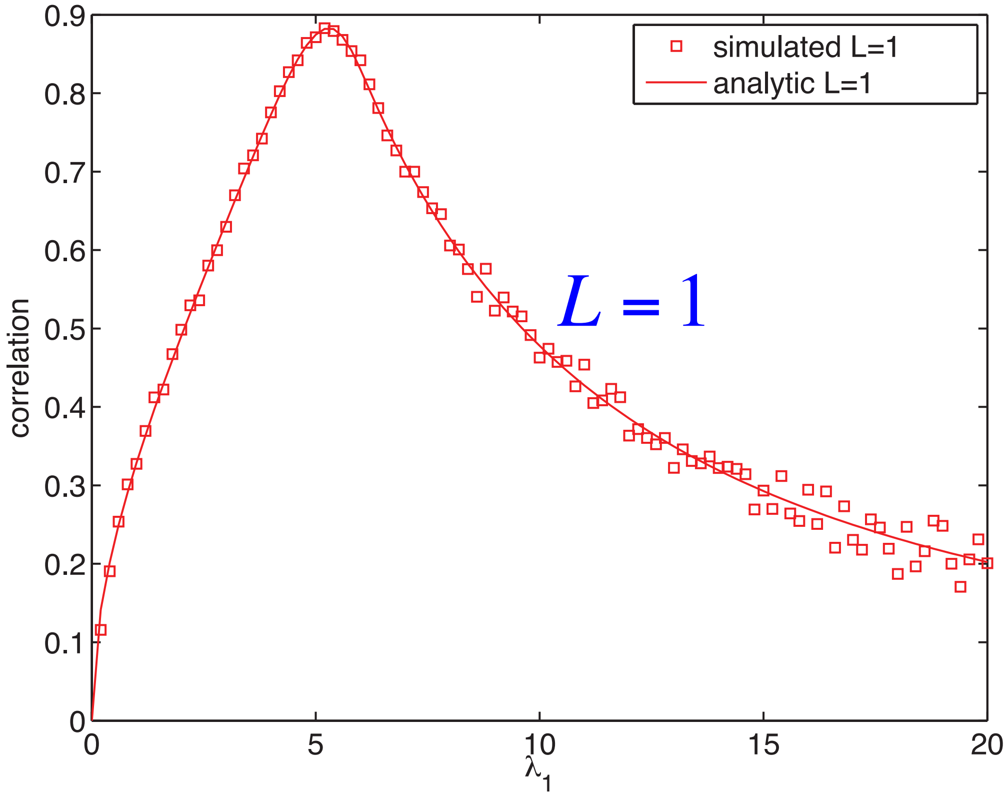
- For $\gamma \to 0$ and $\rho = \Lambda / \mu < 1$

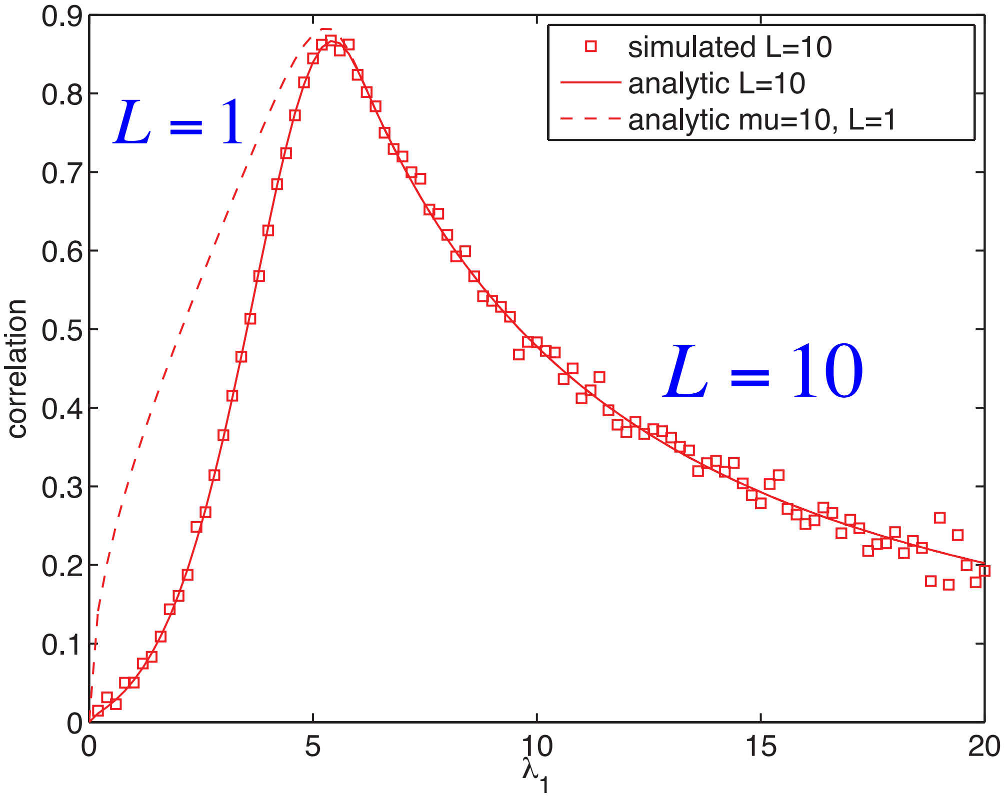
$$r_{ij} = \frac{1}{\left(1 + \frac{1}{p_i}\left(\frac{1}{\rho} - 1\right)\right)^{\frac{1}{2}} \left(1 + \frac{1}{p_j}\left(\frac{1}{\rho} - 1\right)\right)^{\frac{1}{2}}}$$

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

Correlation Resonance (non-zero dilution)

- Correlation as a function of λ_1



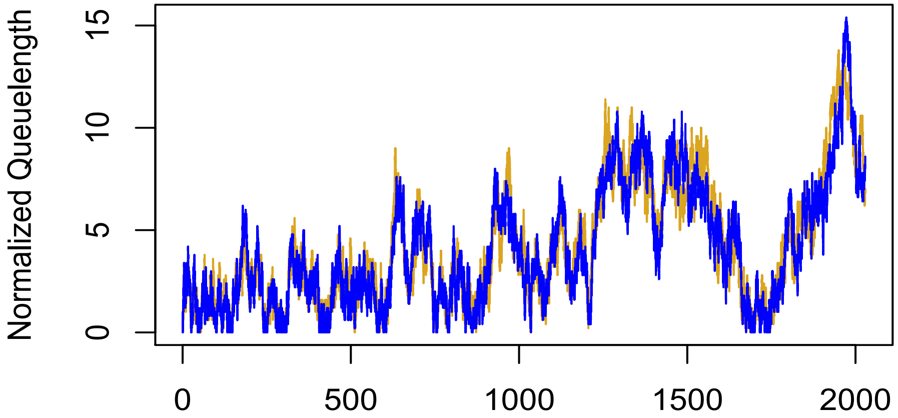


Simulation parameters:

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

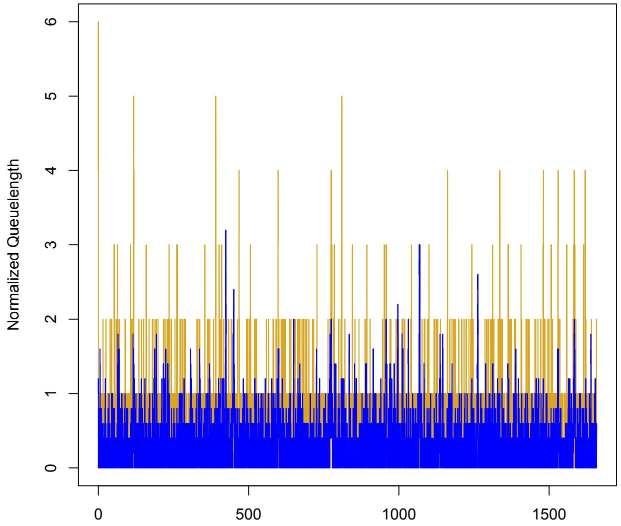
Dynamics (Stochastic Simulations, *L*=1)

Balanced



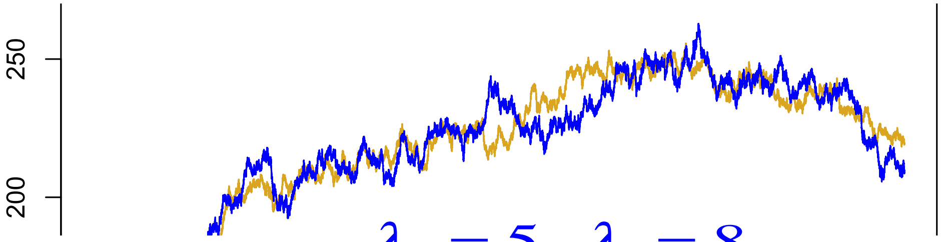
$$\lambda_2 = 5,\ \lambda_1 = 5$$
$$\mu = 10$$

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

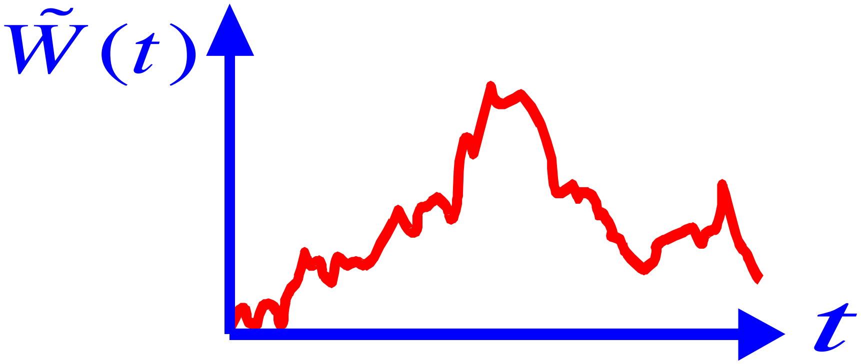
Theorem (at balance: $\rho \triangleq \frac{\lambda_1 + \lambda_2}{\mu} = 1, \;\; \gamma = 0$)

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

As $r \to \infty$,

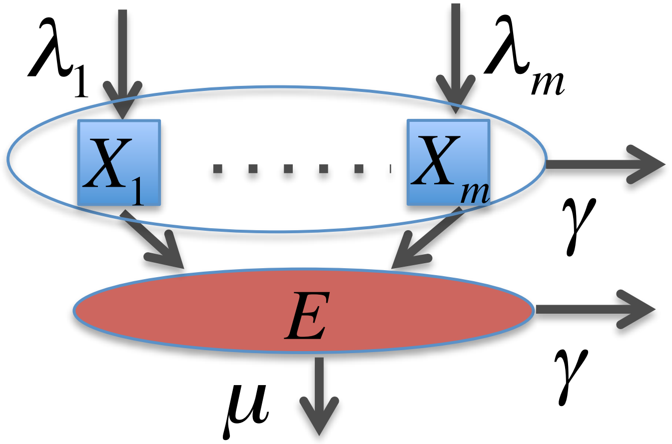
$\hat{Q}_i^r(\bullet) \to \lambda_i \tilde{W}(\bullet), \;\; i = 1,2$ (convergence in distribn)

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



Generalizations

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



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

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

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

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

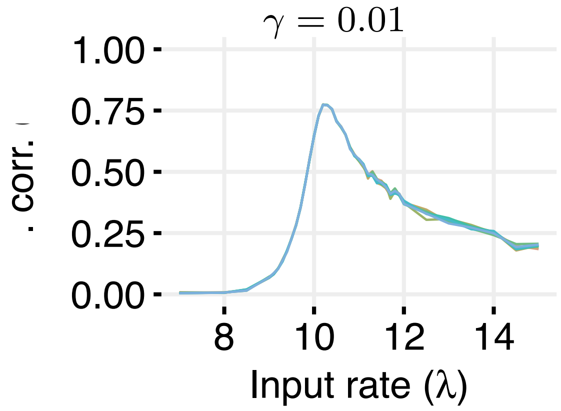
Steady-state multivariate distribution factorizes:

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

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

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

F – Fano factor for N

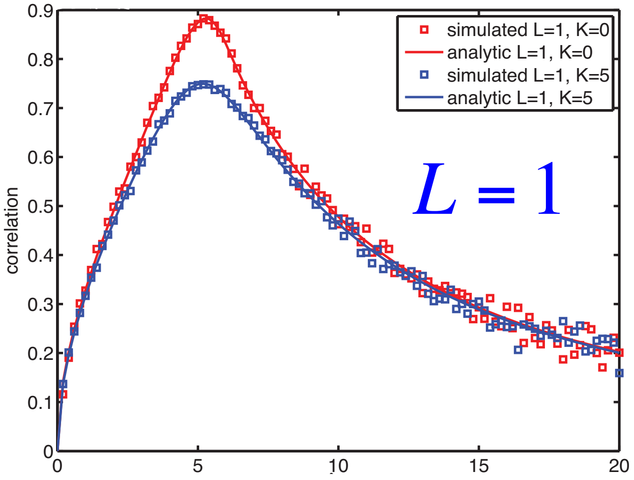


$m = 8,\ \lambda_i = \lambda\ \forall i,\ L = 80,\ \mu = 1$

Correlation resonance near balance

Generalizations

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

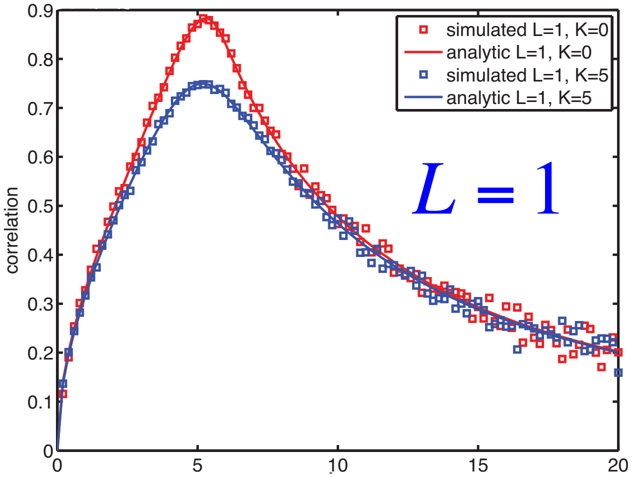


$$m = 2 \quad \lambda_2 = 5 \quad \mu = 10 \quad \gamma = .01$$

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

Generalizations

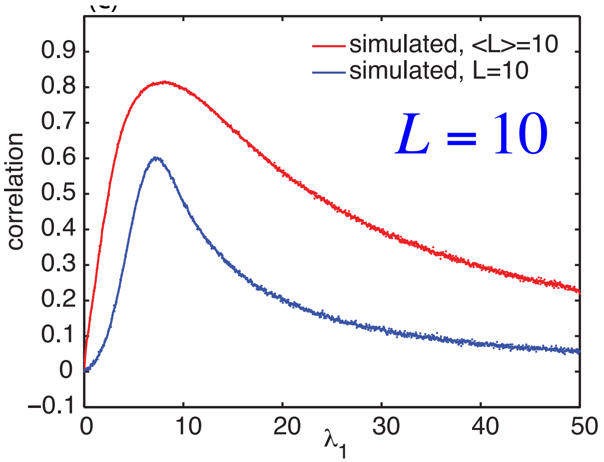
- Reversible binding $X_i + E \underset{\eta^-}{\overset{\eta^+}{\rightleftharpoons}} X_iE$



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

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

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



$$m = 2 \quad \lambda_2 = 5 \quad \mu = 1 \quad \gamma = .1 \quad \nu = 1$$

$$\eta^+ = 200 \quad \eta^- = 1000$$

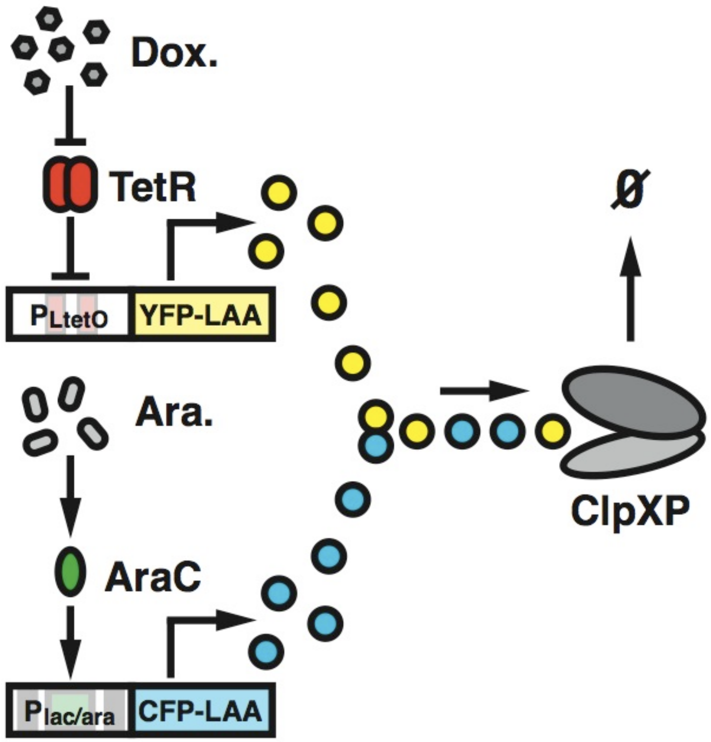
Experiment

Queueing in a Synthetic Gene Network

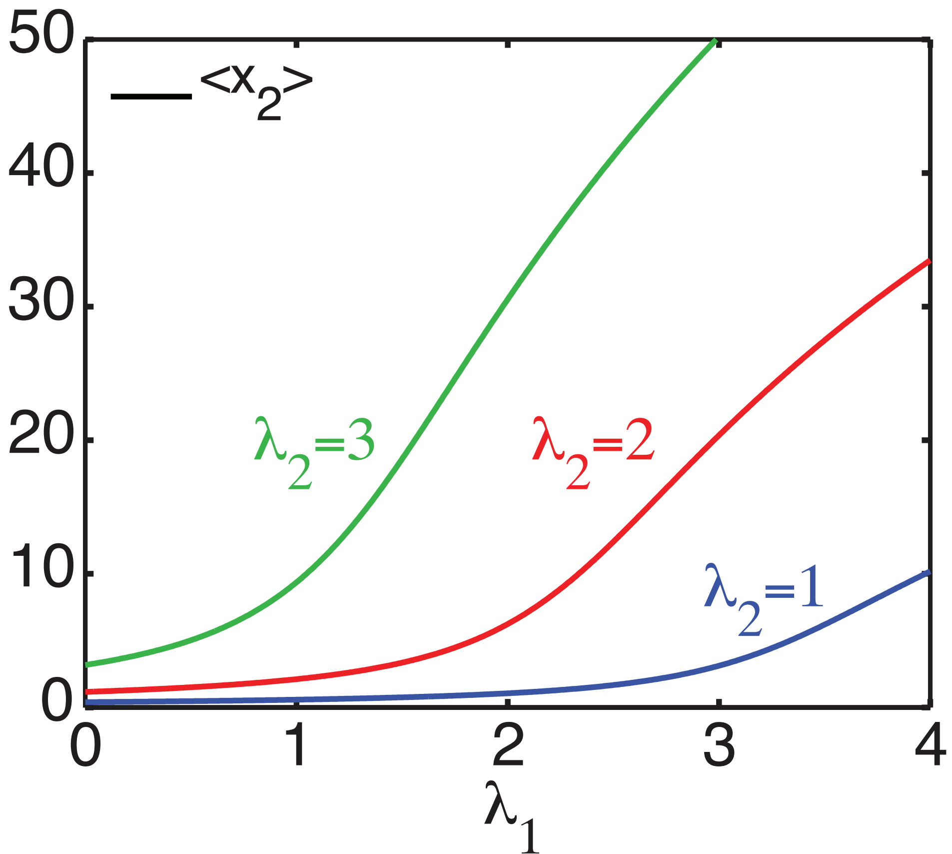
- Two independently synthesized fluorescent proteins: YFP and CFP in *E Coli*
- ClpXP protease degrades LAA tagged proteins

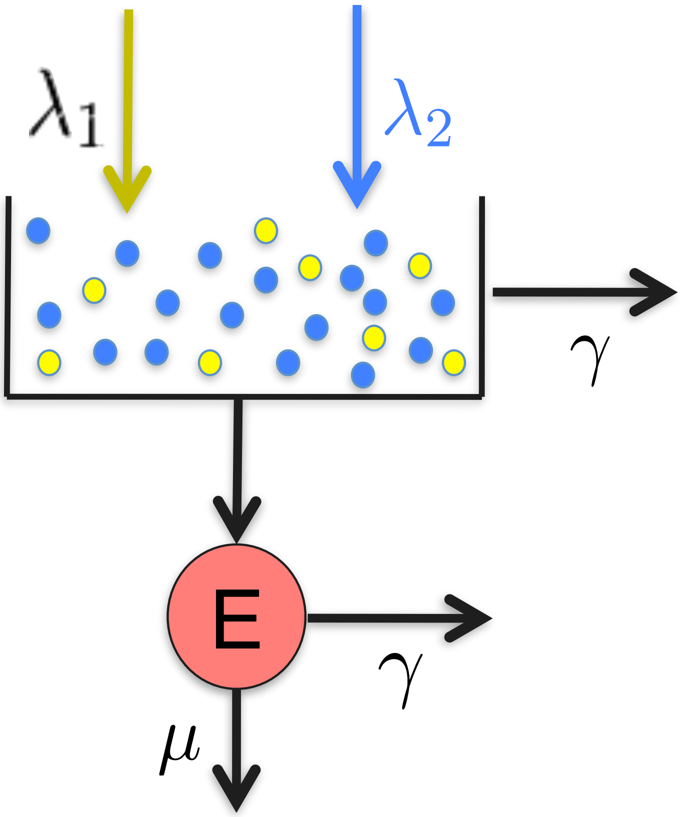
- Tet promoter driving YFP
  - Repressible by TetR
  - Tunable by Doxycycline

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



Effect of Coupling on Mean:





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

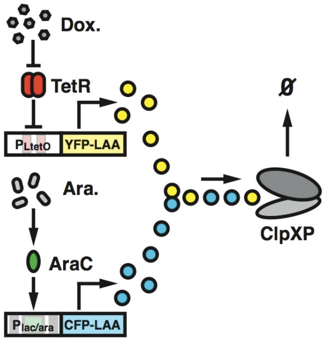
$L = 1$ $K = 0.2$

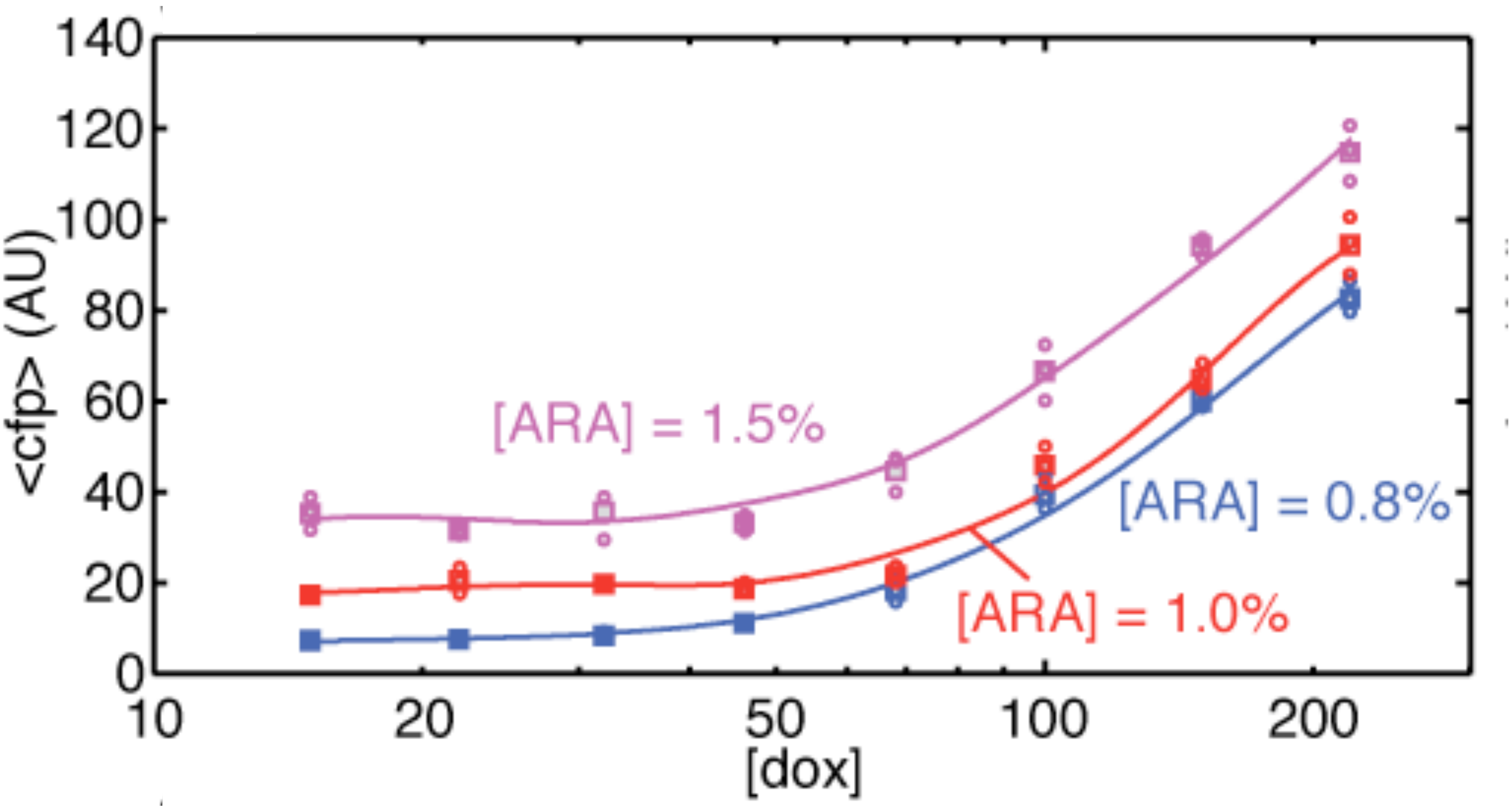
As λ_1 increases, means both X_1 and X_2 increase rapidly at the “balance” point, where

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

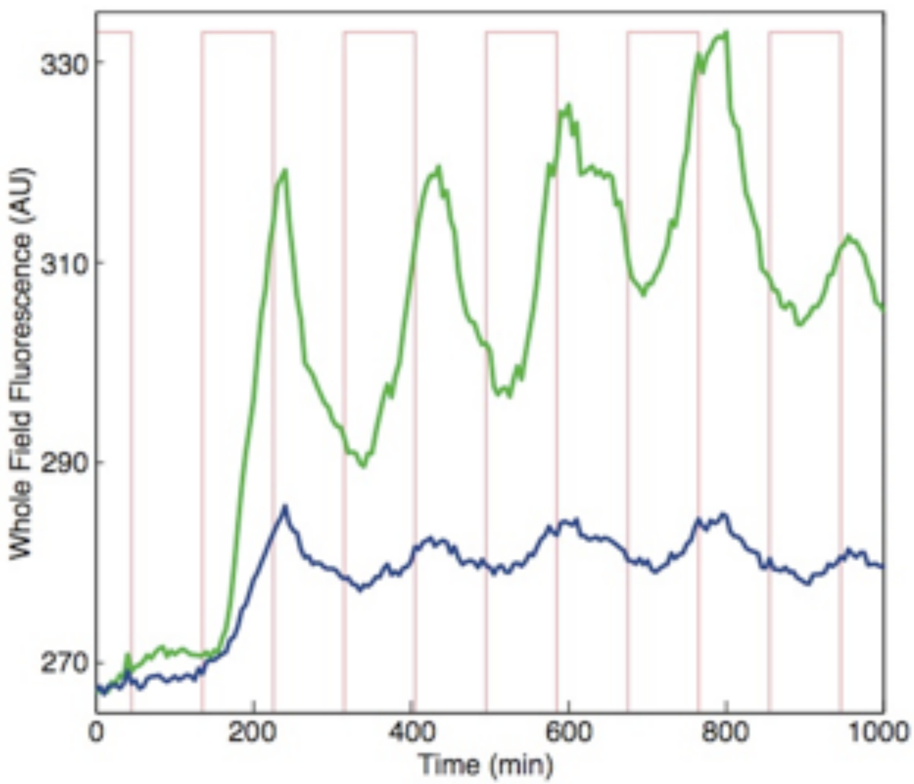
Effect of Coupling on Mean:

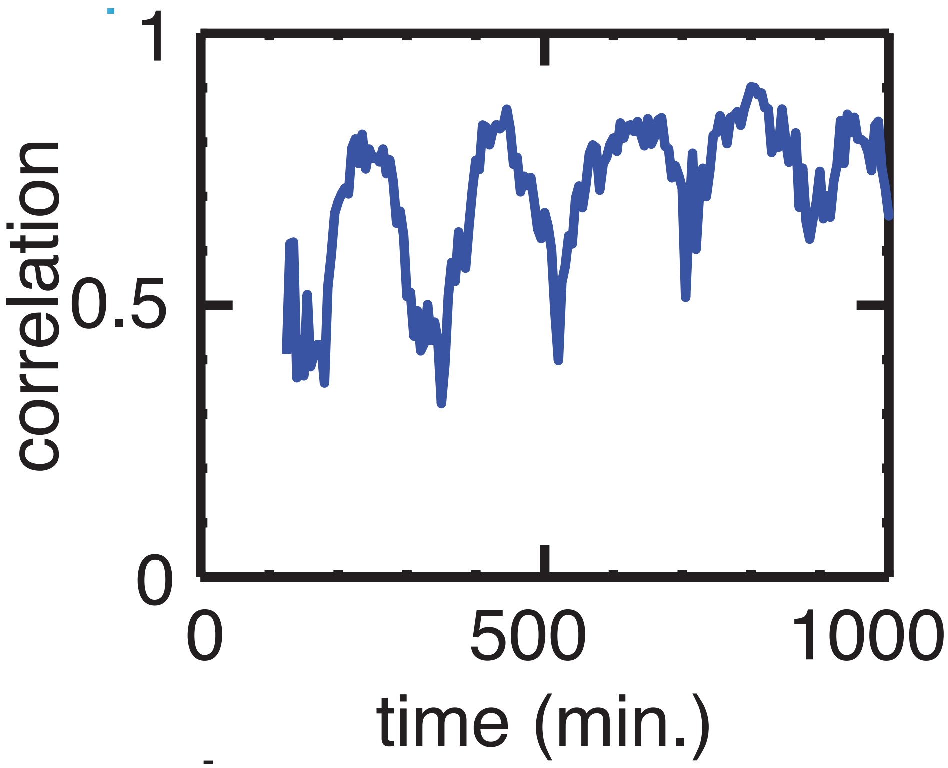
Experiment: modulated doxycycline





Dynamic Modulation





Red trace: periodic influx of doxycycline

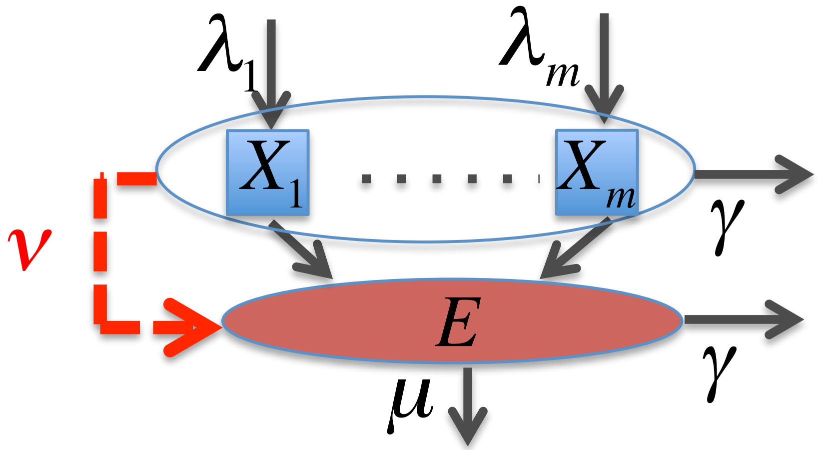
Green trace: response in level of YFP

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

Adaptive Enzymatic Processing

(Theory)

Stochastic Model with Adaptation



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

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

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

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

If enzymes are underloaded - make less

If enzymes are overloaded - make more

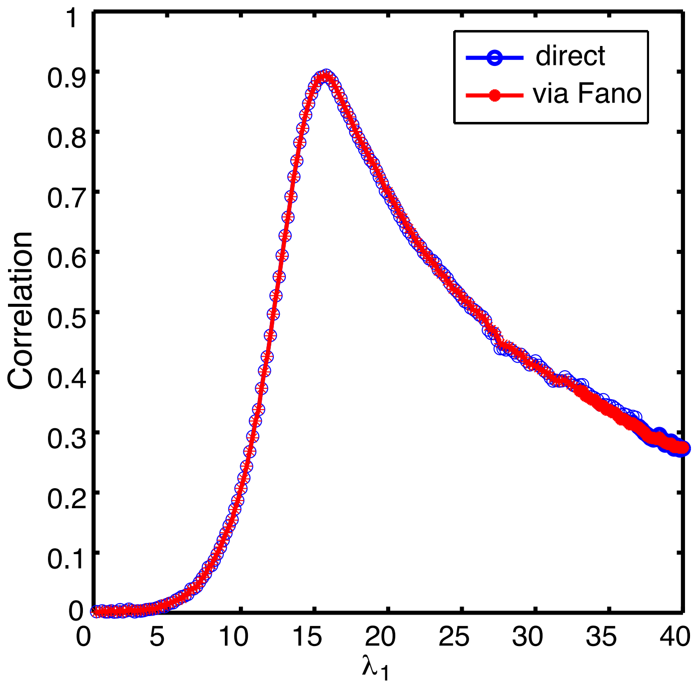
Steady-State Distribution

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

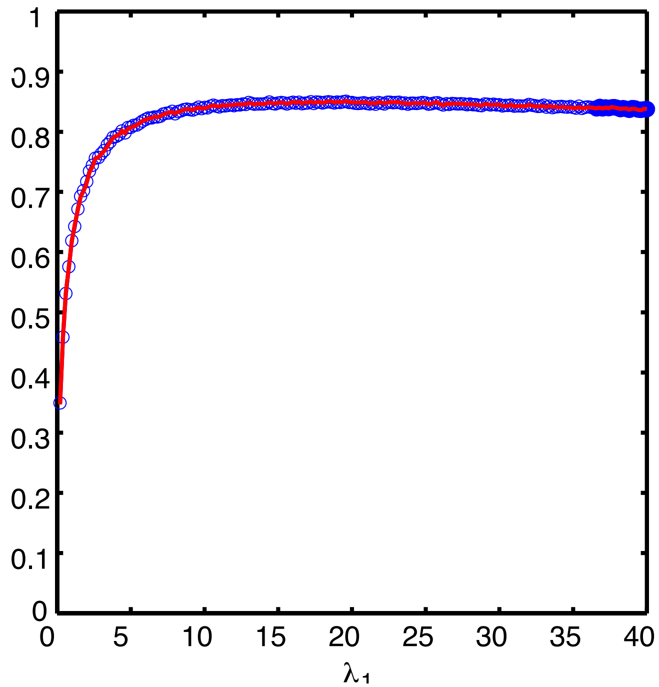
$$r_{ij} = \frac{F-1}{\sqrt{(F-1+1/p_i)(F-1+1/p_j)}}, \quad i \neq j,$$

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

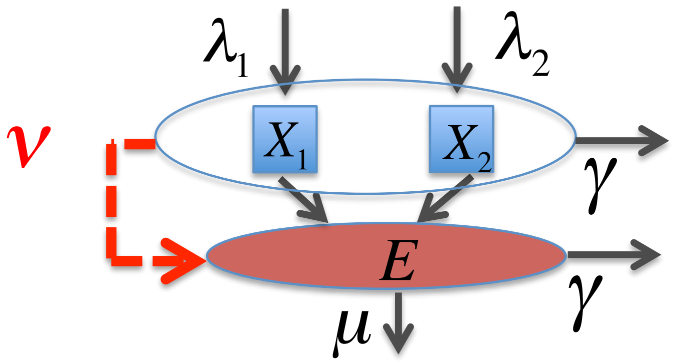
Correlation vs. λ_1 (with slow adaptation)



fixed *L*=25



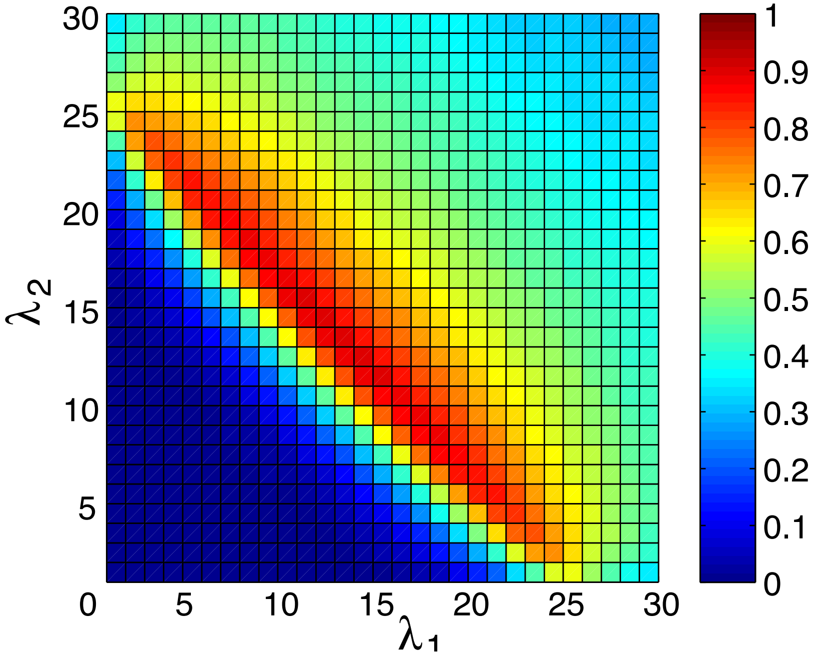
adaptive *L*



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

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

Correlation for variable λ_1, λ_2



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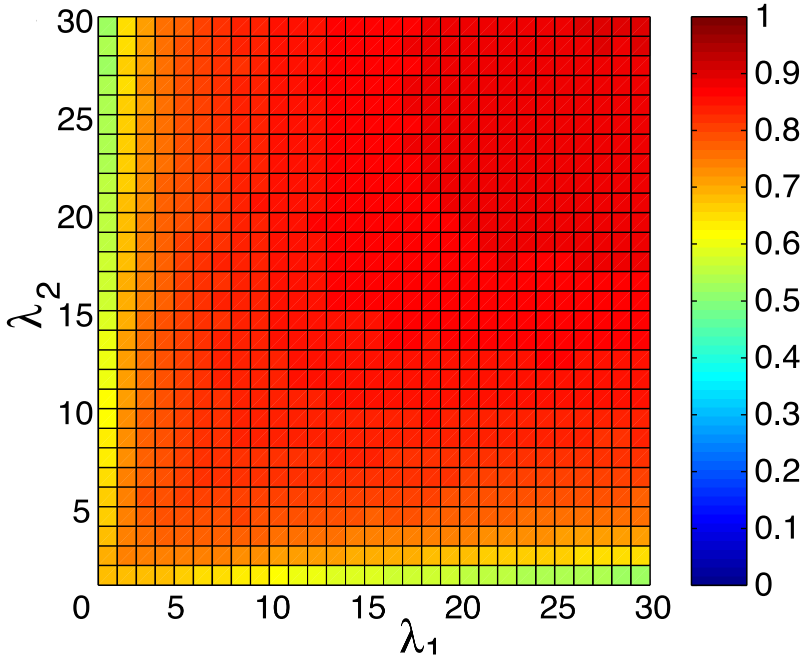
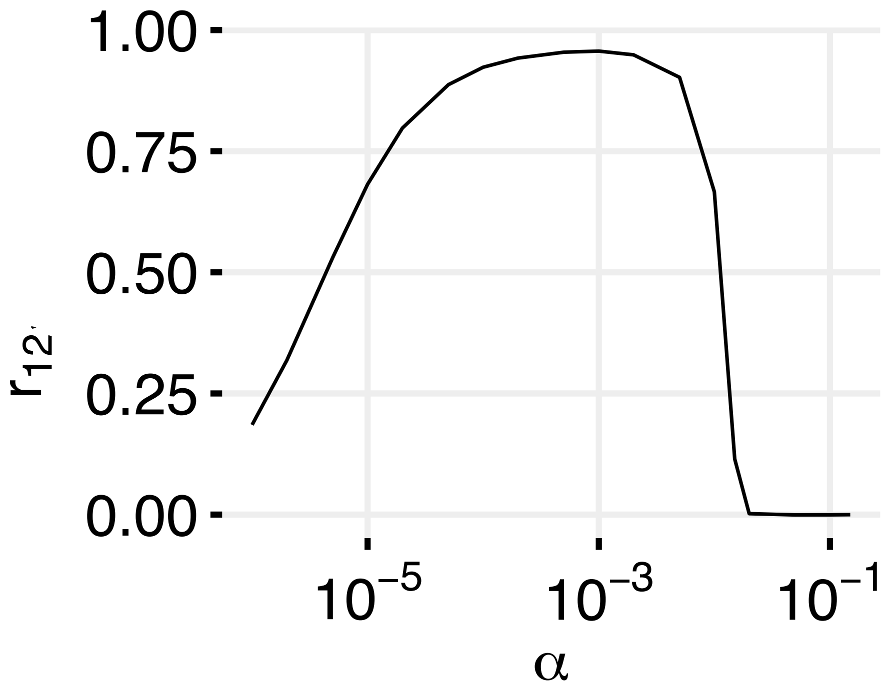


adaptive *L*

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

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

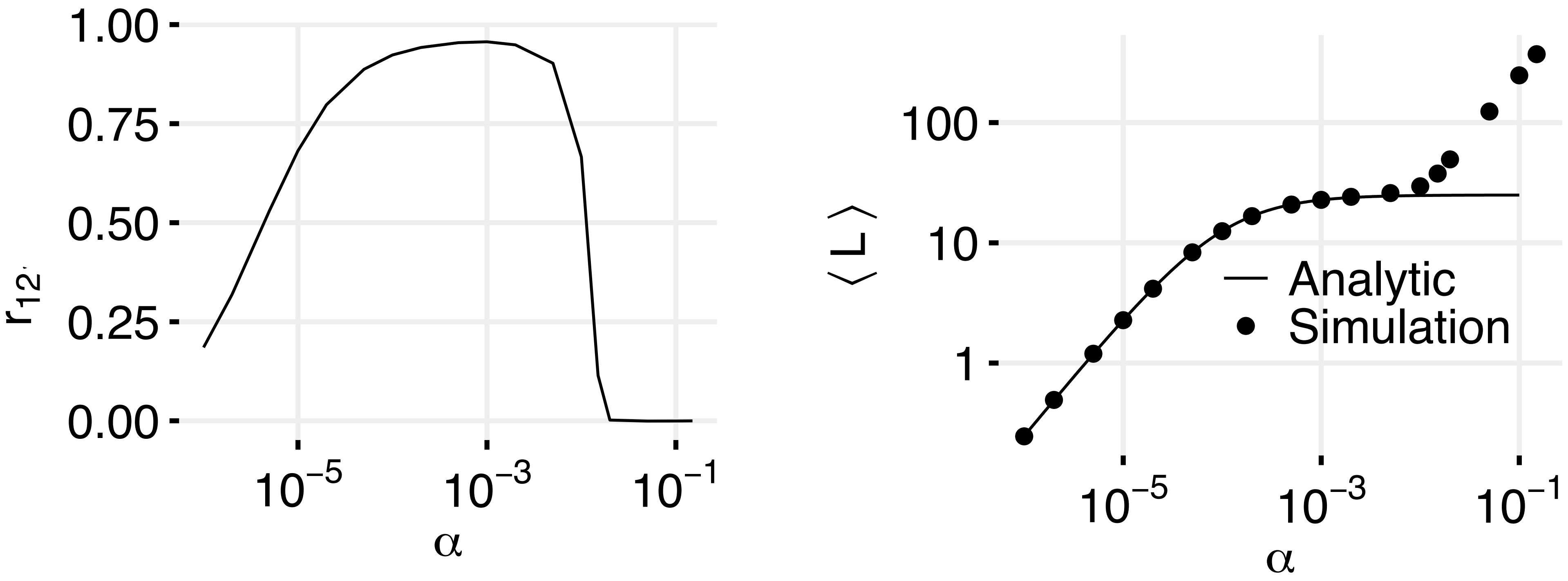
Effect of α



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

$$\gamma^2 / \mu = \alpha \le \gamma$$

Effect of α

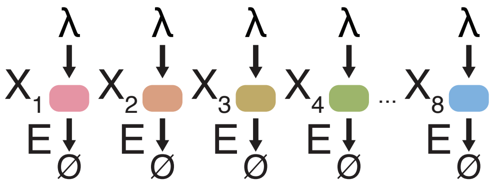


$$m = 2,\ \nu = \alpha N,\ \lambda_1 = 10,\ \lambda_2 = 15,\ \mu = 1,\ \gamma = .01$$

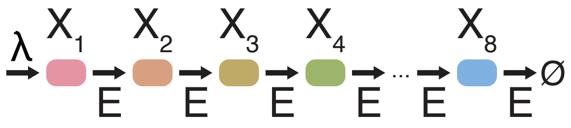
$$\gamma^2 / \mu = \alpha \le \gamma$$

Enzymatic Networks with Shared Resources

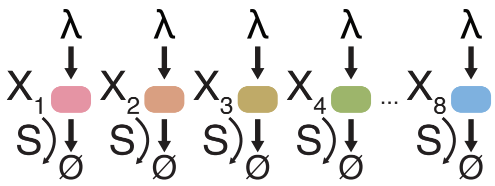
parallel network with shared enzyme

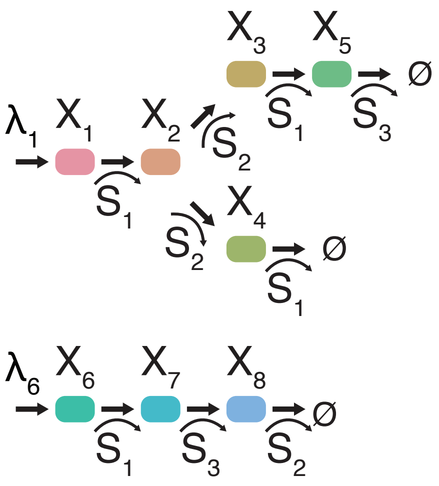


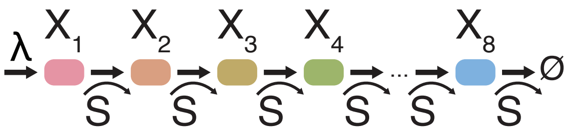
serial network with shared enzyme



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

References

Correlation Resonance Generated by Coupled Enzymatic Processing, W. H. Mather, N. A. Cookson, J. Hasty, L. S. Tsimring and R. J. Williams, Biophysical Journal, 99, 3172-3181.

Queueing up for enzymatic processing: correlated signaling through coupled degradation, N. A. Cookson, W. H. Mather, T. Danino, O. Mondragon-Palomino, R. J. Williams, L. S. Tsimring and J. Hasty, Molecular Systems Biology 7:561.

Factorized time-dependent distributions for certain multiclass queueing networks and an application to enzymatic processing networks, W. H. Mather, J. Hasty, L. S. Tsimring, and R. J. Williams, Queueing Systems 1-16.

Criticality and Adaptivity in Enzymatic Networks, P. J. Steiner, R. J. Williams, J. Hasty, and L. S. Tsimring, Biophysical J., Vol. 111, 1078-1087.

THANK YOU