Strong fluctuations and cycling in biological systems

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Outline:

Length scales in biology

Predator-prey cycles

folklore of predator-prey cycles
some numerical simulations leading to…
some theory leading to … a new simple mechanism
relation to the SI model

Biochemical oscillations

self-regulation of gene expression
glycolysis

Strong fluctuations in extinction and population cycles

Collaborators:
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Former Graduate Students:
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Undergraduate Students:
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Environmental Biology, *NSF*
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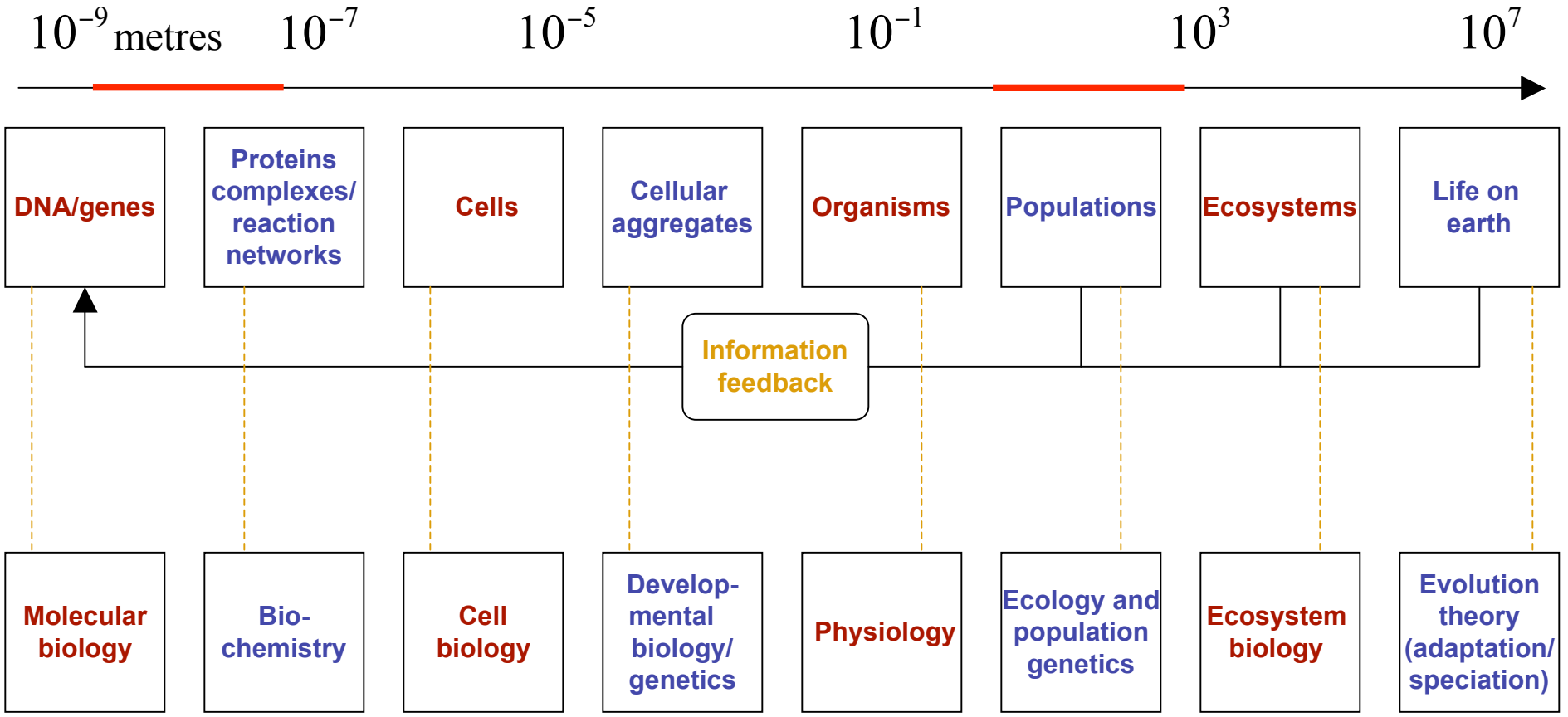
NIGMS, *NIH*

Relevant publications

Predator-prey cycles from resonant amplification of demographic stochasticity
*A. J. McKane and T. J. Newman, Physical Review Letters **94**, 218102 (2005).*

Amplified biochemical oscillations in cellular systems
A. J. McKane, J. D. Nagy, T. J. Newman, and M. O. Stefanini,
Journal of Statistical Physics, to appear October 2007 (published JSP online)

Length scales in biology



Textbook description of cycles using population-based models (PBM)

Lotka-Volterra system

$$\dot{V} = rV - \mu V - bPV$$
$$\dot{P} = b'PV - \mu' P$$

V – prey density
P – predator density

Neutral cycles which depend on initial conditions – thus not biologically robust

+ logistic growth of prey

$$\dot{V} = rV(1 - \alpha V) - \mu V - bPV$$
$$\dot{P} = b'PV - \mu' P$$

Cycles disappear – replaced by damped oscillations to constant steady-state

+ predator satiation (non-linear functional response)

$$\dot{V} = rV(1 - \alpha V) - \mu V - bPV/(1 + \beta V)$$
$$\dot{P} = b'PV/(1 + \beta V) - \mu' P$$

Cycles reappear – as "limit cycles"

But cycles are so much more intuitive than this! What's missing?

Other mechanisms for cycling

e.g. environmental forcing, spatial coupling, new nonlinear interactions

Nisbet and Gurney (1982), Aparicio and Solari (2001),
Bjornstad and Grenfell (2001), Pascual, Mazzega, and Levin (2001)

An individual-based model (IBM)

It's hard to think clearly in terms of continuous densities – let's go back to a more fundamental description in terms of individuals:

Three types of "objects": prey (V), predators (P), and empty spaces (E)

Constraint: total number of objects is fixed at *N*

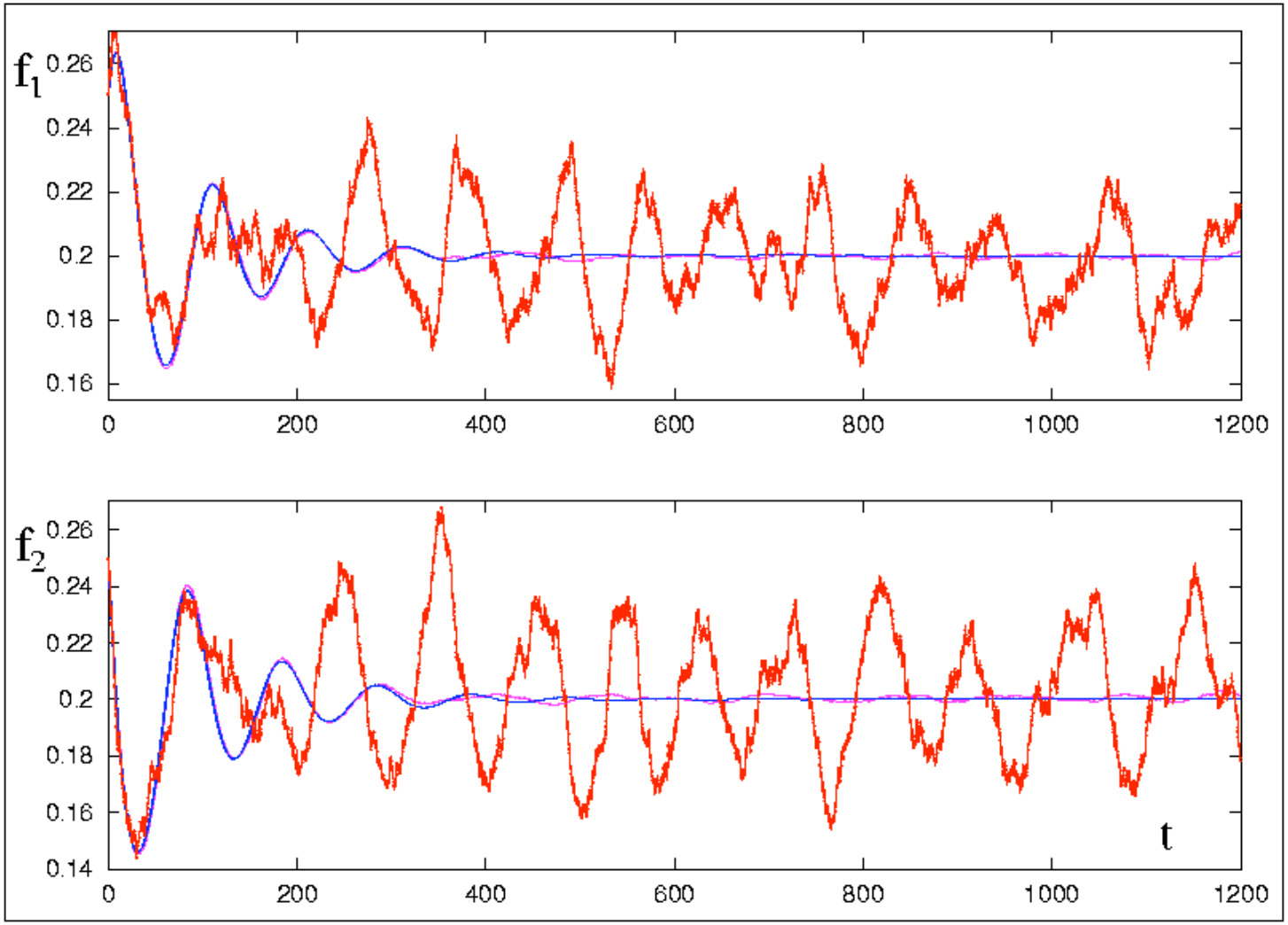
Interactions:

prey birth	$V + E \rightarrow V + V$
prey death (not due to predation)	$V \rightarrow E$
predation	$P + V \rightarrow P + E$ or $P + V \rightarrow P + P$
predator death	$P \rightarrow E$

Implement as a stochastic process on a computer … and compare with mean-field theory – which is the LV equation with logistic prey reproduction

Simulation results from the IBM

f_1=P – number density of predators, f_2=V – number density of prey



Blue – solution of LV equation, Purple – average over replicates

Red – one single replicate (N=3200)

Observations are striking, but not new

The observation of large cycles in IBMs of predator-prey (or host-pathogen) systems has been previously reported – the authors were perplexed, since the IBM should behave, for large populations, in accordance with the PBM.

e.g. Renshaw (1991), Rai and Singh (2000)

Bartlett (1960) commented on the possibility that noise could induce cycles in disease models (SIR), but did not uncover the mechanism.

Fluctuations about the steady-stated are amplified (or resonated)

We construct a mathematical description of the system using the language of master equations.

The fundamental object is *Q(m,n,t)* – the probability that at time *t* there are *m* prey and *n* predators.

From the master equation one can derive mean-field equations of motion for the average number densities of predators and prey – these are identical to the LV equations.

One can then take fluctuations into account for large *N* by expanding around mean field theory via

$$m/N = V + x/\sqrt{N}\ , \qquad n/N = P + y/\sqrt{N}$$

↔ **van Kampen expansion**

(for large *N* the fluctuations will have an amplitude of *1/√N).*

Naively, these fluctuations will be negligible for large *N* – but they're not!

The equations for *x* and *y* have the form

$$\dot{x} = ax + by + \text{noise}$$
$$\dot{y} = cx + dy + \text{noise}$$

where *a, b, c, d* and the noise terms are known functions of the death/birth/predation rates.
(note – noise terms are correlated)

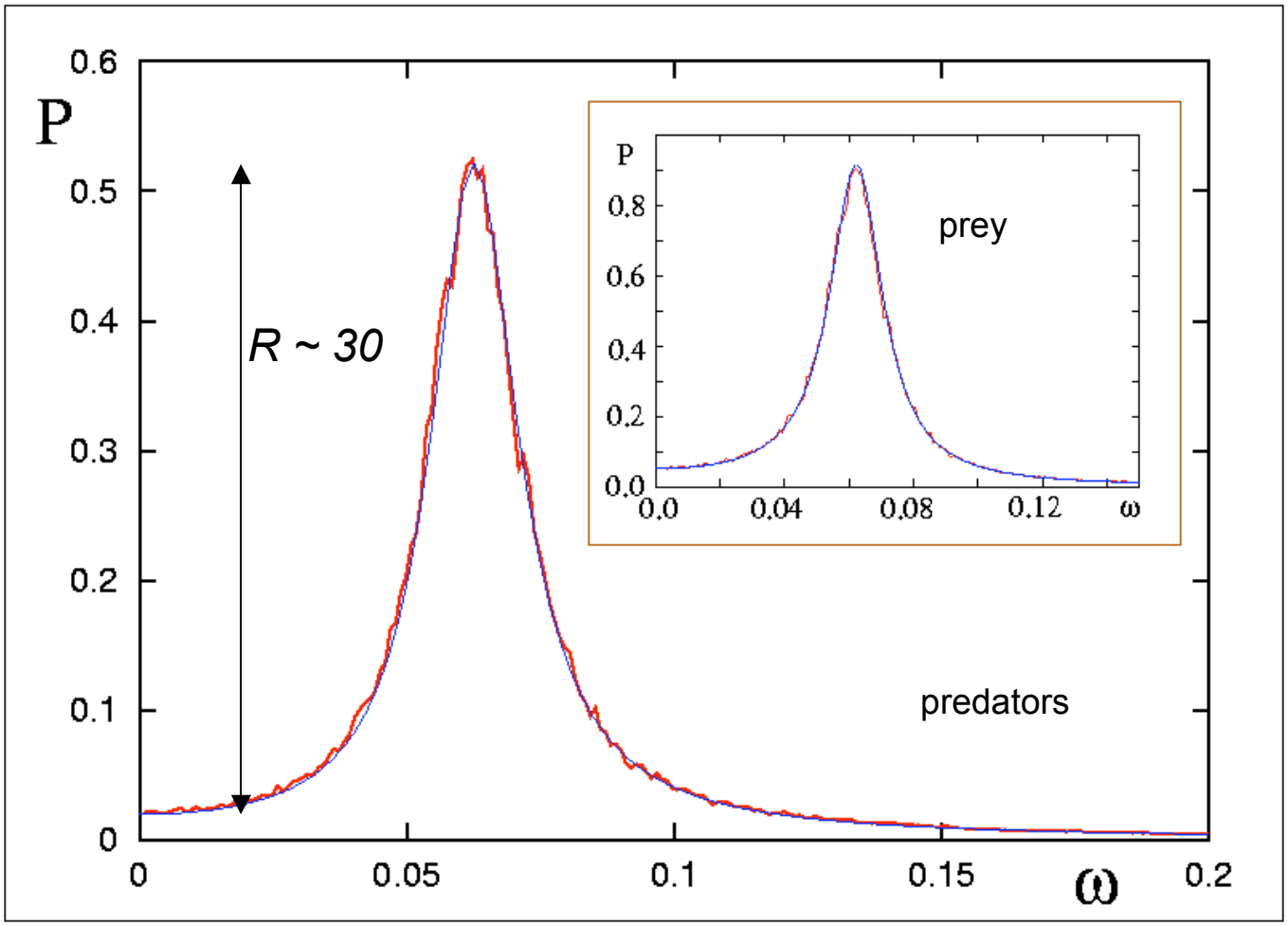
(cf – Chubynsky's Moscow-Kiev Bus paradigm).

Eliminating y we find an equation for *x* of the form $\ddot{x} + \gamma\dot{x} + \omega_0^{\,2}x = \text{noise}$

This is exactly analogous to a damped pendulum with a random forcing – the pendulum will oscillate at (almost) natural frequency ω_0, since the noise has a flat frequency spectrum – i.e. the noise will automatically resonate the pendulum.

Oscillation amplitude scales as ***R/√N*** *, where R is resonant enhancement at* ω_0

Power spectra



The power spectrum shows a resonant peak at a frequency equal to the cycle frequency.
Blue line – theory, red line – simulation

Results directly map to SI disease dynamics

The Volterra predator-prey model is essentially identical to the classic SI model of disease dynamics, and so all of our results carry across:

Three types of "objects": susceptibles (S), infecteds (I), and empty spaces (E)

Constraint: total number of objects is fixed at *N*

Interactions:

susceptible birth	$S + E \rightarrow S + S$
susceptible death (not due to infection)	$S \rightarrow E$
infection	$I + S \rightarrow I + I$
infected death	$I \rightarrow E$

These interaction rules are identical to the simplest predator-prey system:

prey ↔ susceptible, predator ↔ infected

Some details on the mathematics

$$\frac{dP(\boldsymbol{n},t)}{dt} = \sum_{\boldsymbol{n}'}\left[W(\boldsymbol{n}\,|\,\boldsymbol{n}')P(\boldsymbol{n}',t) - W(\boldsymbol{n}'\,|\,\boldsymbol{n})P(\boldsymbol{n},t)\right]$$

$$n_i = N\varphi_i + \sqrt{N}\,x_i, \qquad P(\boldsymbol{n},t) = \Pi(\boldsymbol{x},t)$$

van Kampen expansion

zeroth order

$$\frac{d\varphi_i}{dt} = F_i(\boldsymbol{\varphi})$$

$$\varphi_i(t) = \varphi_i^{SS} + \delta\varphi_i(t)$$

$$\frac{d\delta\boldsymbol{\varphi}}{\delta\tau} = \underline{\boldsymbol{A}}\,\delta\boldsymbol{\varphi}$$

Interested in cases where eigenvalues of A are complex with negative real parts - i.e. damped transient oscillations

first order

$$\partial_t\Pi = -\partial_i x_j A_{i,j}\Pi + \tfrac{1}{2}\partial_i\partial_j B_{i,j}\Pi$$

↓ FP → SDE

$$\dot{x}_i = A_{i,j}x_j + \xi_i$$

$$\left\langle \xi_i(t)\xi_i(t')\right\rangle = B_{i,j}\delta(t-t')$$

↓ solve exactly for power spectra etc

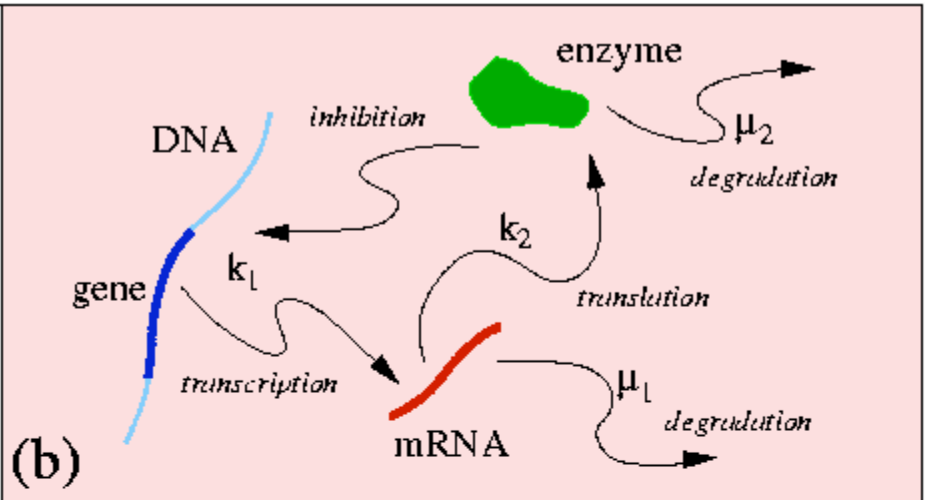
$$P_i(\omega) = \left\langle |\,\tilde{x}_i(\omega)\,|^2\right\rangle$$

Biochemical oscillations

Self regulation of gene expression

$$M \xrightarrow{\mu_1} \emptyset$$
$$P \xrightarrow{\mu_2} \emptyset$$
$$\emptyset \xrightarrow{k_1} M$$
$$M \xrightarrow{k_2} M + P$$
$$k_1 = k_0 \exp(-\lambda[P])$$

(a)

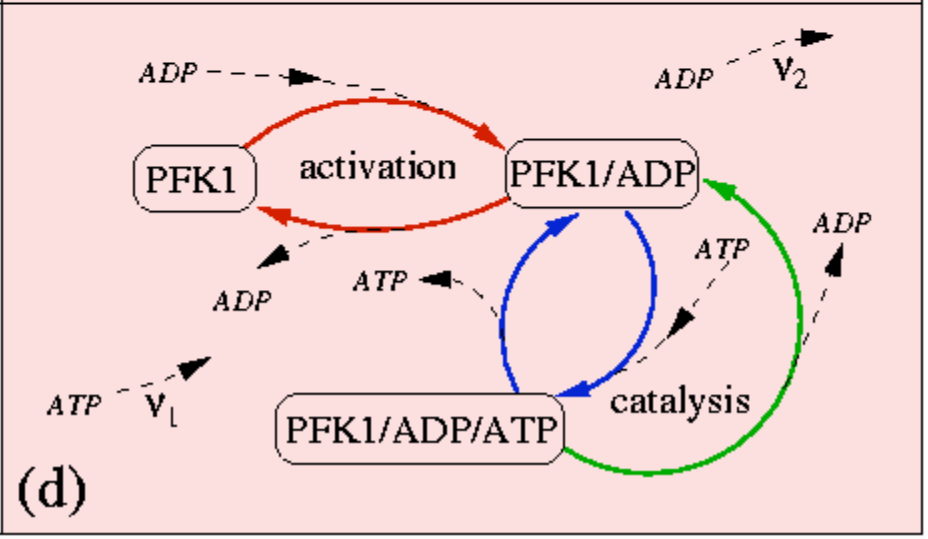


(b)

Key step in glycolysis

$$\text{bath} \xrightarrow{\nu_1} ATP$$
$$ADP \xrightarrow{\nu_2} \text{bath}$$
$$ATP + PFK1/ADP \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} PFK1/ADP/ATP$$
$$PFK1/ADP/ATP \xrightarrow{k_2} ADP + PFK1/ADP$$
$$ADP + PFK1 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} PFK1/ADP$$

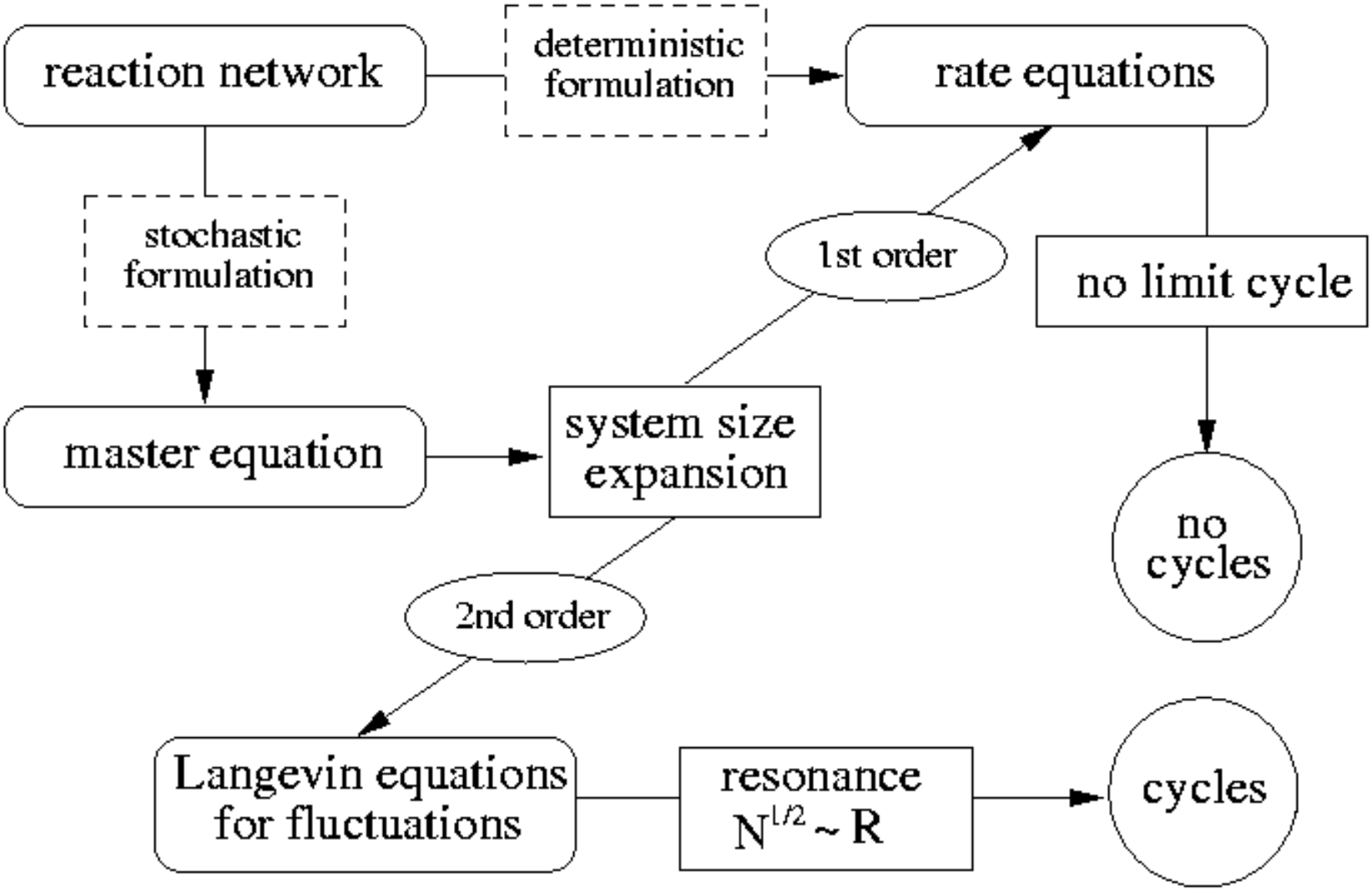
(c)



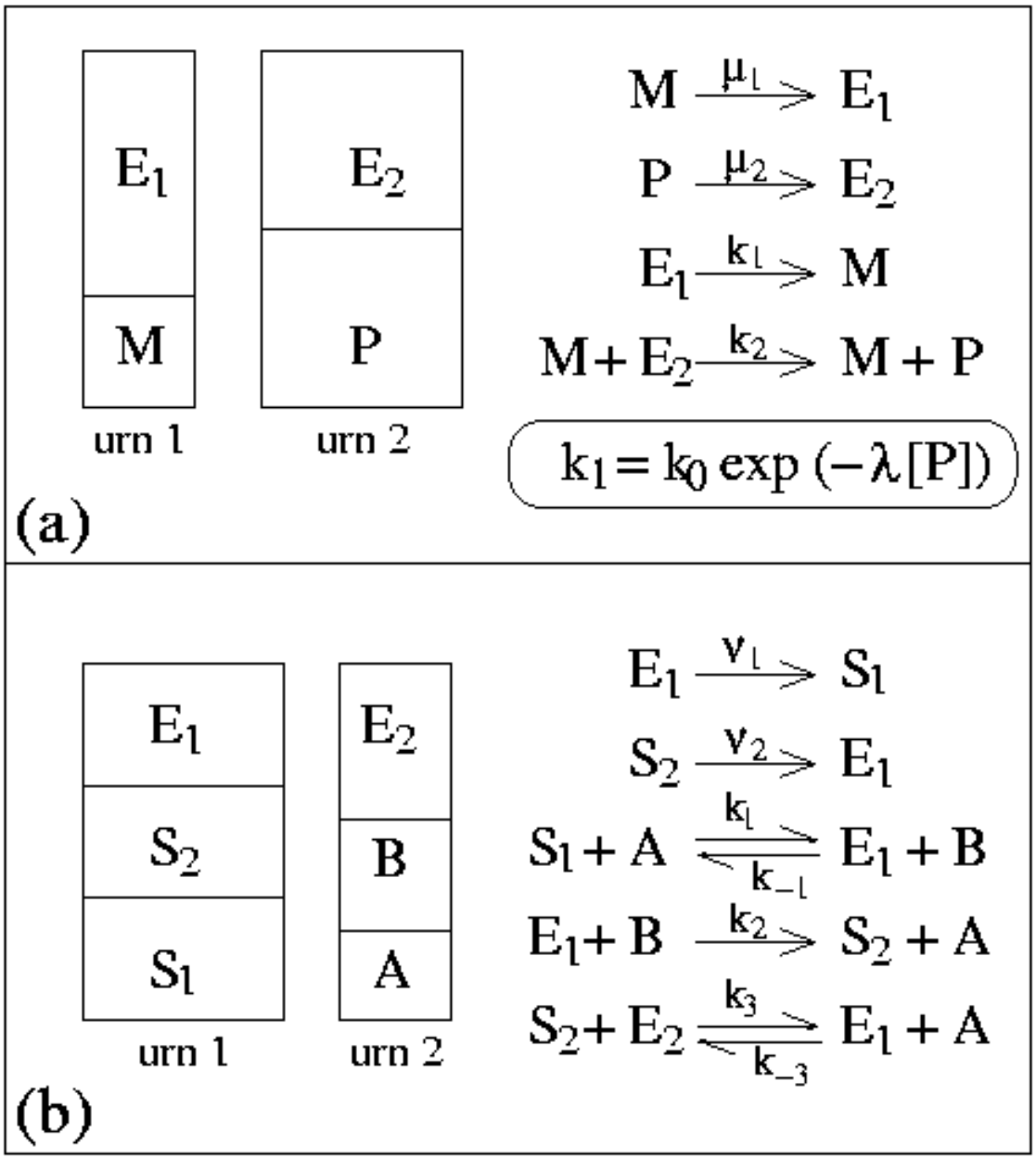
(d)

The mean field equations (i.e. chemical rate equations) for each of these reaction networks have no sustained cycling behavior for any combination of parameter values – they are "thoroughly boring."

Calculational strategy



“Bath model” representation of reactions

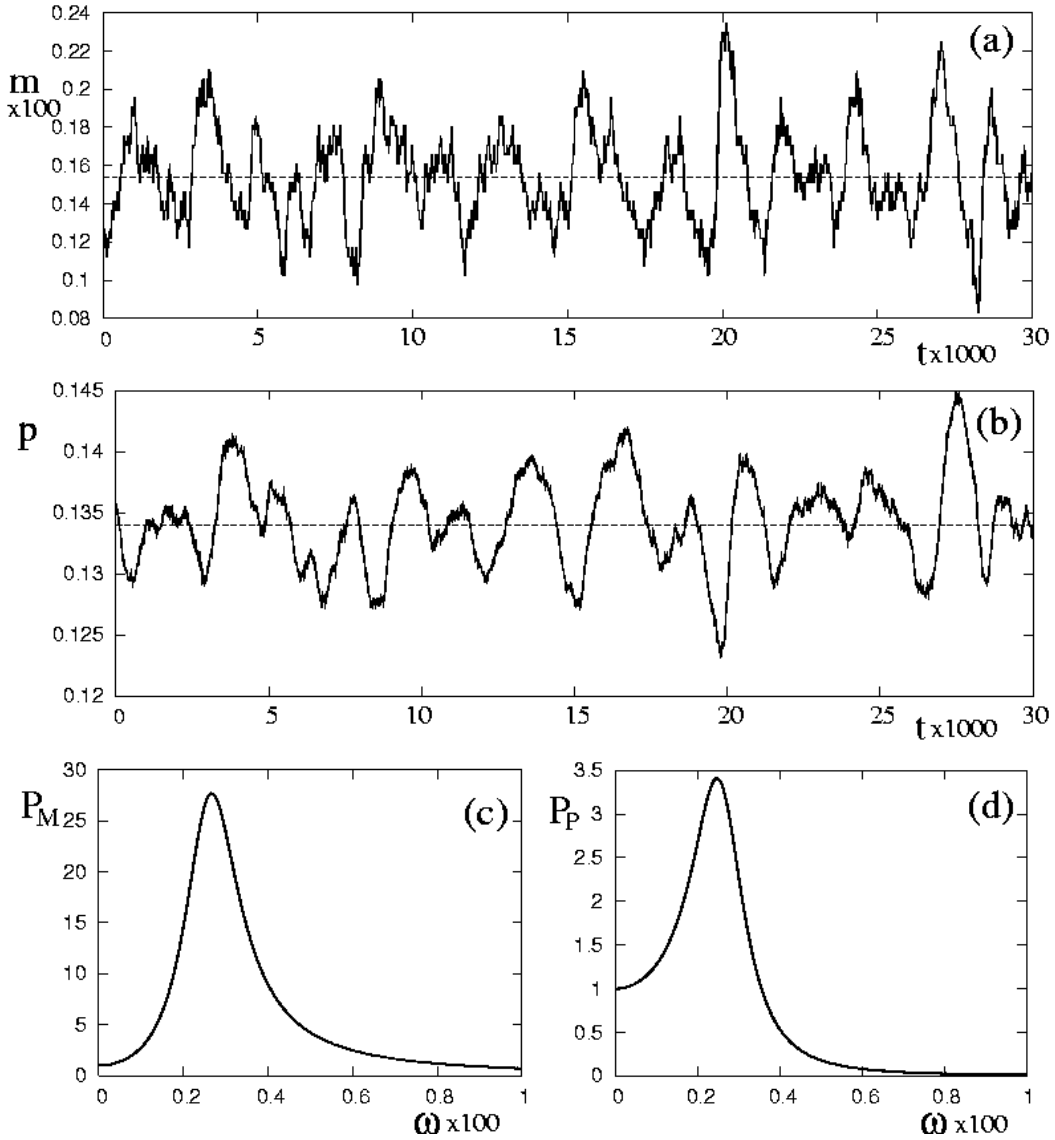


M – mRNA
P – protein

S_1 – ATP
S_2 – ADP
A – PFK/ADP
B – PFK/ADP/ATP

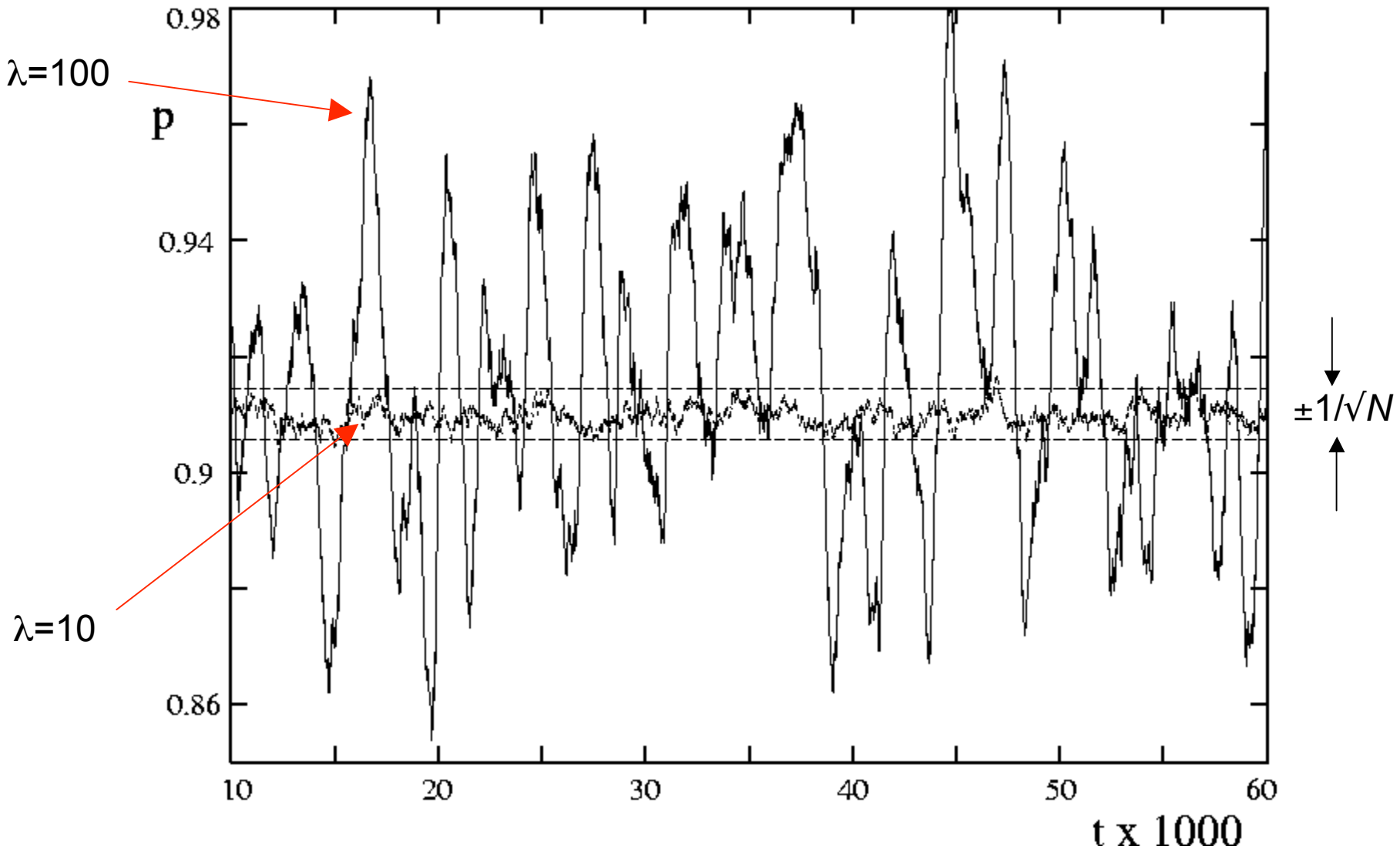
mRNA-protein feedback

N ~ 20,000



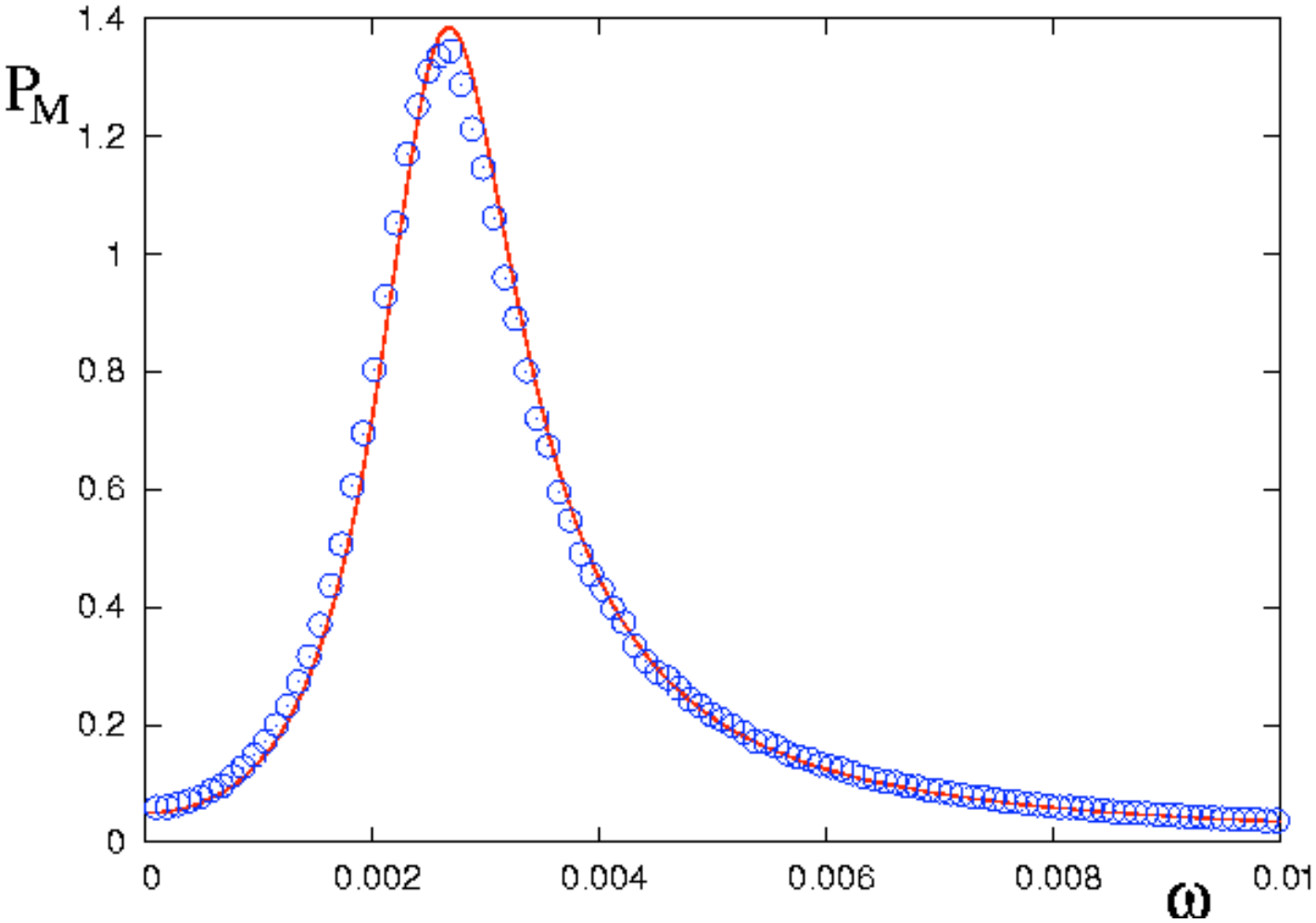
mRNA-protein feedback

Explicit demonstration of amplified size of oscillations



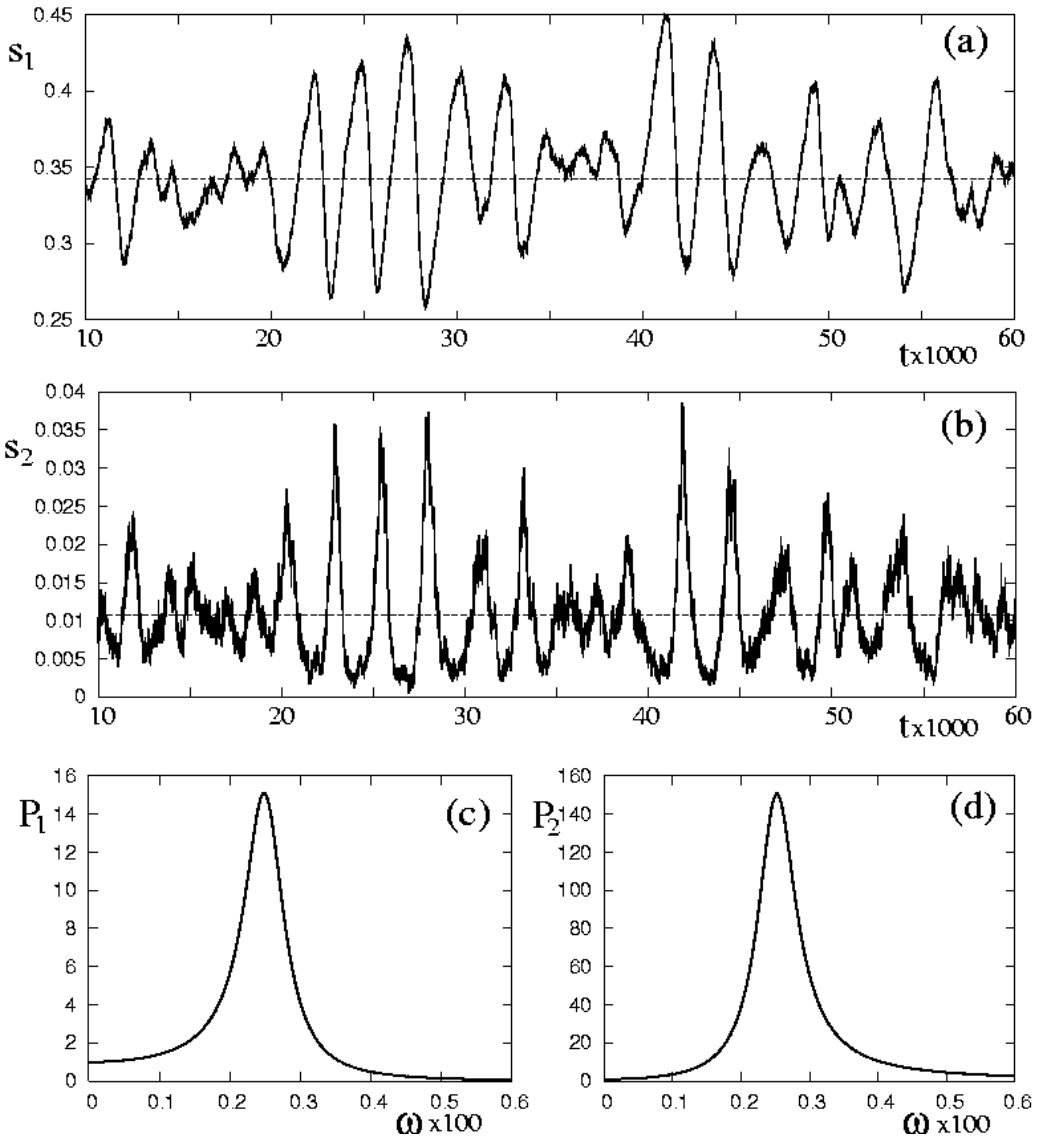
mRNA-protein feedback

Power spectrum for mRNA concentration – theory and simulation



Selkov's model of glycolysis

N ~ 4,000



R ~ 150

Summary

We have presented a new mechanism for oscillations in populations of small to intermediate size.

The essential criterion is that the mean-field (or infinite population) dynamics exhibit damped oscillations (at a frequency ω_0).

In a finite population, stochastic events, such as birth, death, or infection, in the form of white internal noise will automatically resonate the system at the frequency ω_0 and produce large sustained oscillations.

The amplitude of the oscillations scales as $R/\sqrt{N}$

R – enhanced resonance factor (exactly calculable using vK expansion)

N – number of individual "agents" in population

We have discussed this mechanism in the context of

predator-prey systems

the closely related SI disease system

biochemical oscillations (self-regulation of gene expression, and glycolysis)

This mechanism is very general

there are many further applications in biology, and other areas

Is this effect known or named?

"Stochastic resonance" would be a perfect name for this effect, but this term is already in wide-spread use for a different effect:

external periodic signal applied to a non-linear system, and then a resonant periodic output being obtained using optimized noise level

The term "coherence resonance" was introduced in the late '90's to describe
i) periodic output of an excitable system in the subcritical region of a Hopf bifurcation, which is induced by internal noise
ii) noise-enhanced temporal periodicity of a bursting signal

the term has also attracted more widespread usage
the term "self-induced stochastic resonance" has also been used to describe similar phenomena

The effect described here occurs in systems which have no bifurcation points. These systems are "boring" from a deterministic viewpoint, as they have no sustained oscillatory behavior throughout their parameter space.

The mechanism for noise-induced oscillations is extremely simple and can be analyzed exactly using the van Kampen expansion.