Generalized Structural Kinetic Modeling

From Chinese Dynasties to Photosynthesis

Thilo Gross

MPI für Physik komplexer Systeme

Thanks

Wolfgang Ebenhöh

Ulrike Feudel

Bernd Blasius

Ralf Steuer

Dirk Stiefs

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Bringing cartoons to life

Gene Regulation

Simulation is not a good approach:

It requires much information

It is fundamentally inefficient

The Dynastic Cycle

$$\begin{aligned} \dot{f} &= \alpha_f(p - \beta c - (1-\beta)\ell) \\ \dot{b} &= \alpha_b(c - \gamma l - (1-\gamma)m) \\ \dot{r} &= \alpha_r(c - e) \end{aligned}$$

We have defined the scale parameters

$\alpha_f = \frac{P^*}{F^*}$ inverse life expectancy of farmers

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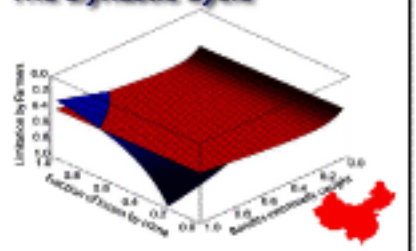
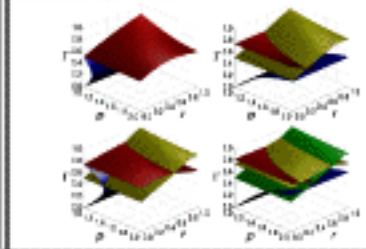
The Dynastic Cycle

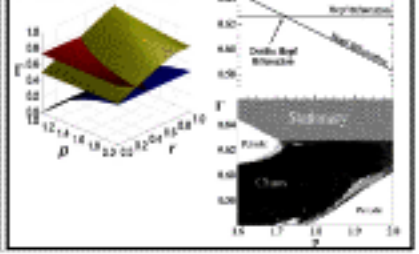


Generalized Structural Kinetic Modeling

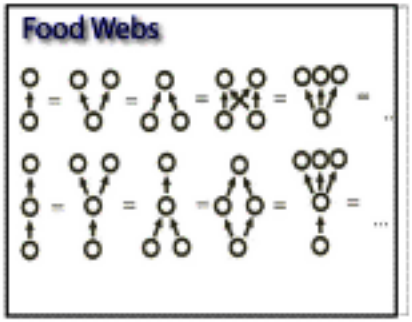
Food Chains



Food Chains



Food Webs



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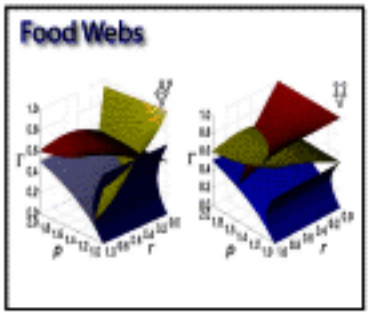
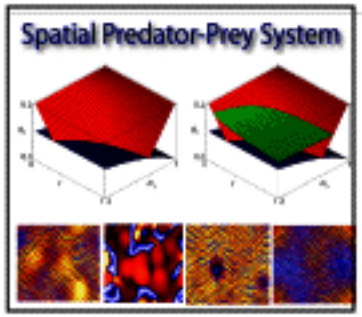
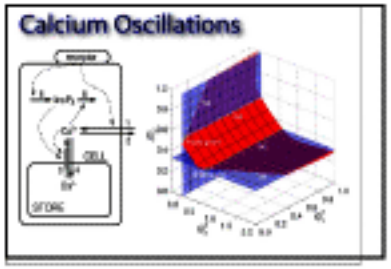


Spatial Predator-Prey System

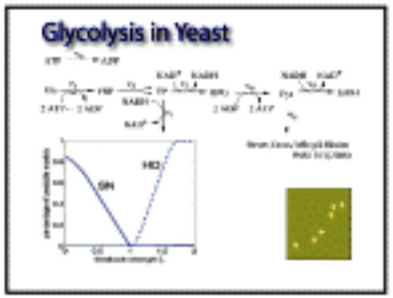


Thilo Gross
MPI PKS, Dresden

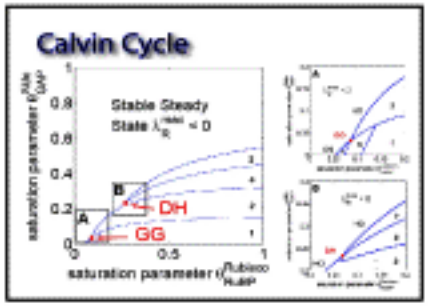
Calcium Oscillations



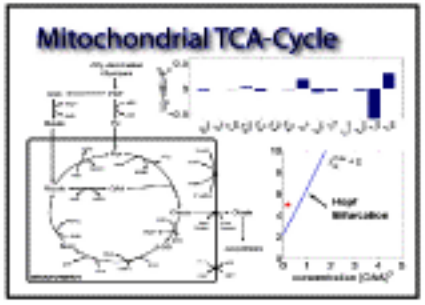
Glycolysis in Yeast



Calvin Cycle



Mitochondrial TCA-Cycle



Summary

Some (non trivial) insights can be extracted from very general models:

Important parameters Local bifurcations

Certain features of global dynamics

Interesting parameter regions

GSK Modeling should be used for screening large classes of plausible models before detailed modeling is attempted.

Bringing cartoons to life

NATURE|Vol 445|22 February 2007

ESSAY

Putting the pieces together

Bringing cartoons to life

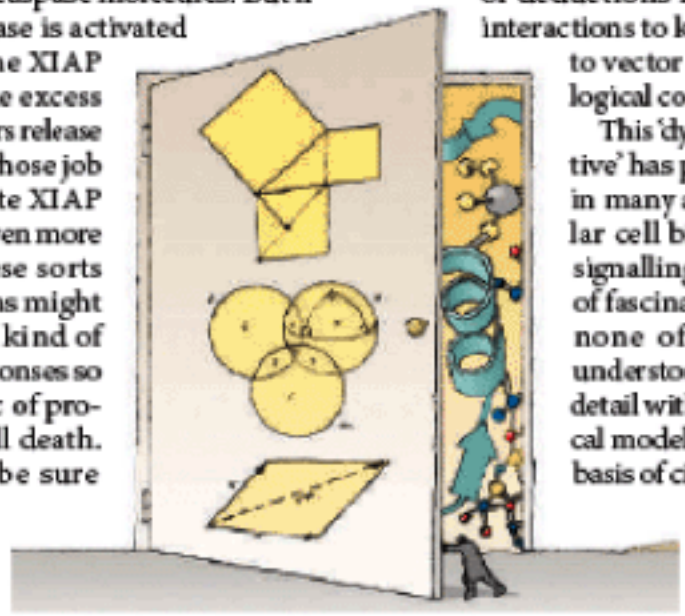
To understand cells as dynamic systems, mathematical tools are needed to fill the gap between molecular interactions and physiological consequences.

John J. Tyson

Open any issue of *Nature* and you will find a diagram illustrating the molecular interactions purported to underlie some behaviour of a living cell. The accompanying text explains how the link between molecules and behaviour is thought to be made. For the simplest connections, such stories may be convincing, but as the mechanisms become more complex, intuitive explanations become more error prone and harder to believe.

A better way to build bridges from molecular biology to cell physiology is to recognize that a network of interacting genes and proteins is a dynamic system evolving in space and time according to fundamental laws of reaction, diffusion and transport. These laws govern how a regulatory network, confronted by any set of stimuli, determines the appropriate response of a cell. This information-processing system can be described in precise mathematical terms, and the resulting equations can be analysed and

possibilities in the programmed-cell-death network. For instance, small amounts of caspase in the cell are neutralized by binding to an inhibitory protein XIAP — whose function is to prevent accidental firing of the suicide pathway by inadvertent activation of a few caspase molecules. But if enough caspase is activated to saturate the XIAP pool, then the excess caspase triggers release of a protein whose job is to eliminate XIAP and free up even more caspase. These sorts of interactions might generate the kind of dynamic responses so characteristic of programmed cell death. But can we be sure our intuition is correct? Under what conditions is the off state stable to small signals but

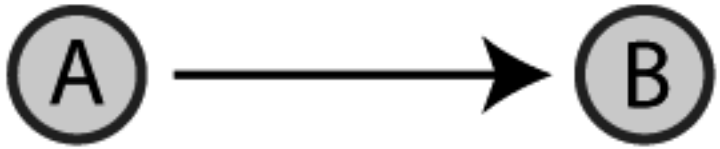


I. KAPUSTA/IMAGES.COM

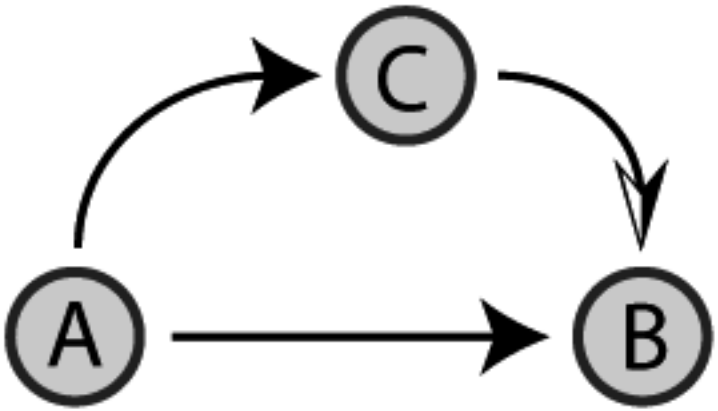
notions; for example, 'bifurcation points' correspond to thresholds. Bifurcation analysis is a powerful tool for deducing qualitative dynamical features of complex reaction networks. In this fashion, dynamical systems theory forges a rigorous chain of deductions from molecular interactions to kinetic equations to vector fields to physiological consequences.

This 'dynamical perspective' has proven its merits in many areas of molecular cell biology. Calcium signalling shows a variety of fascinating behaviours, none of which can be understood in quantitative detail without mathematical models. The molecular basis of circadian rhythms is another area in which mathematical modelling is essential to understanding such physiologically

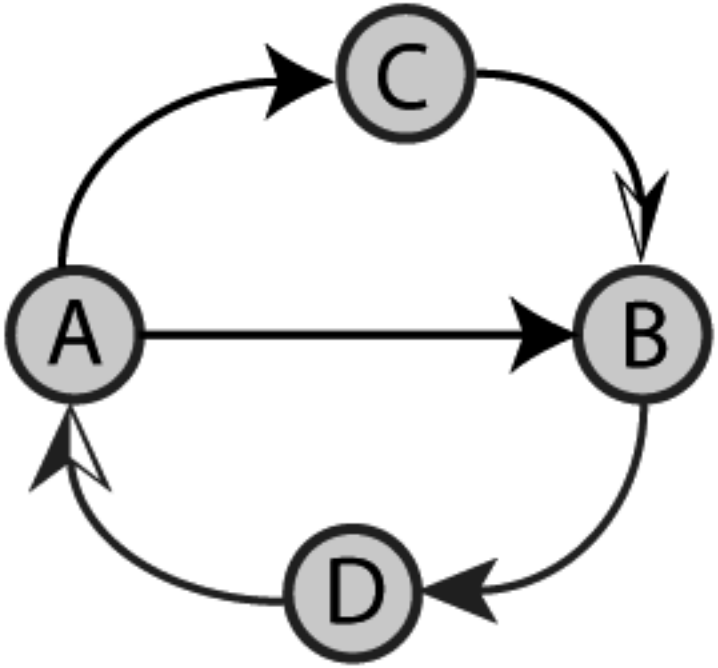
Cartoons



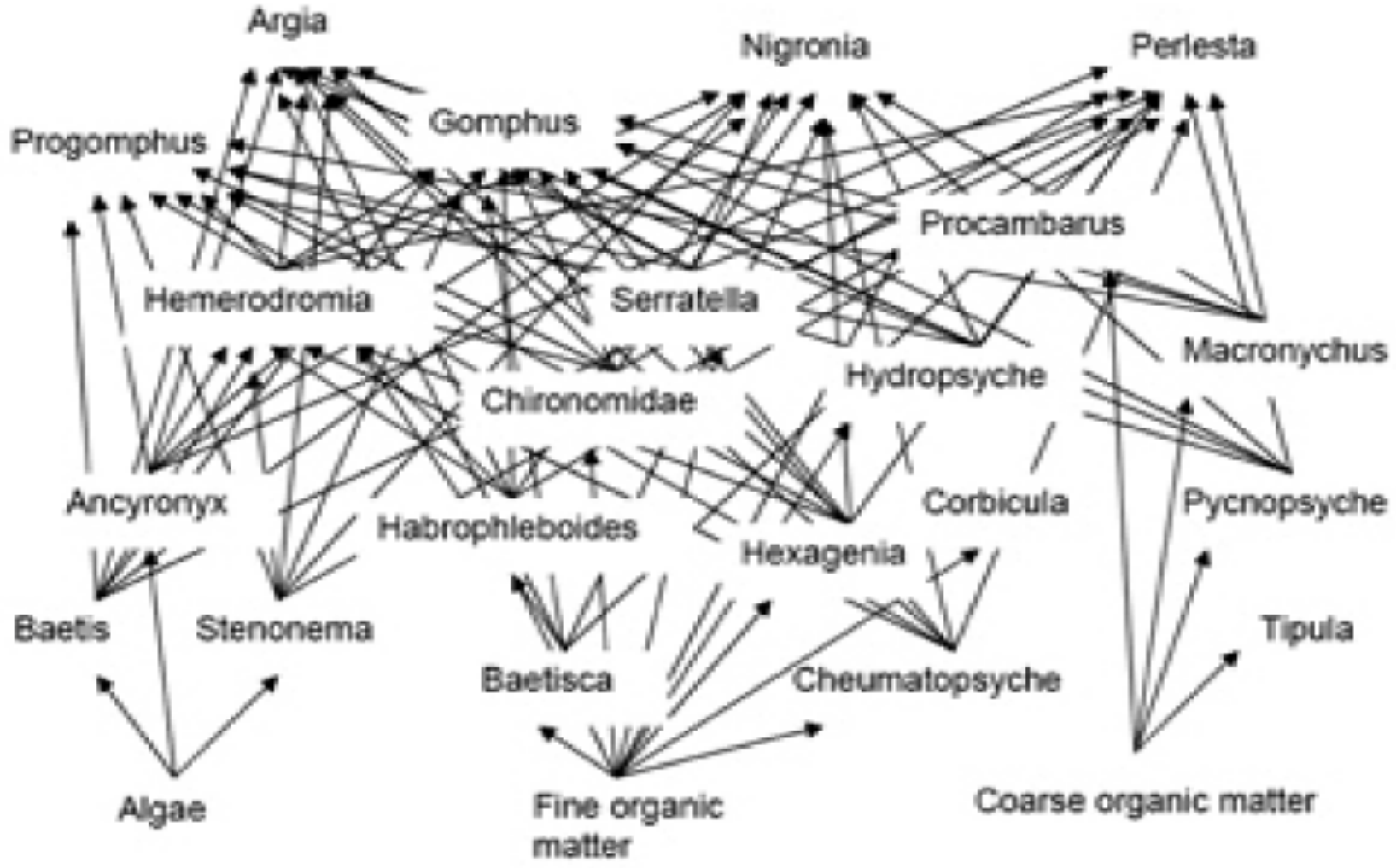
Cartoons



Cartoons

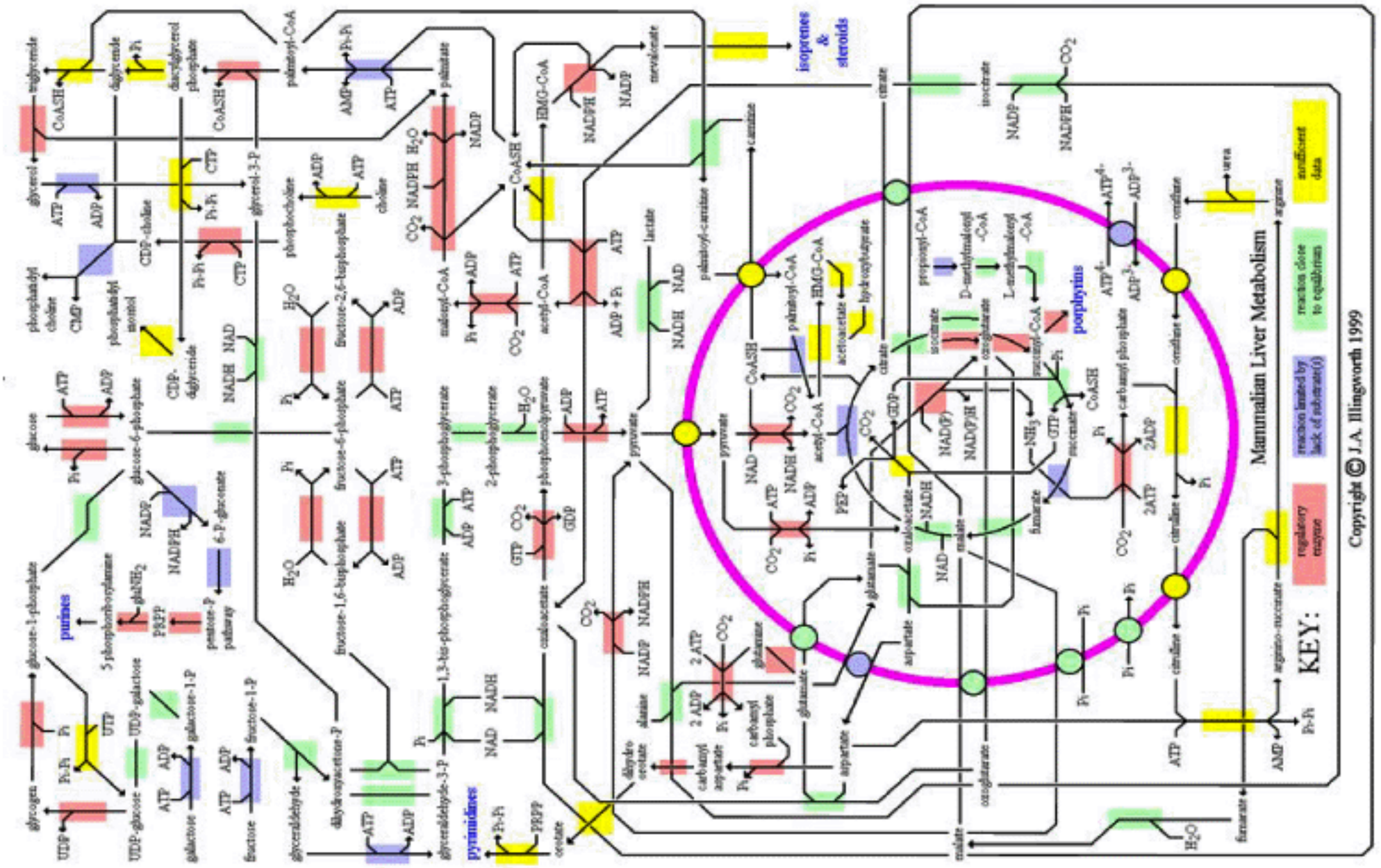


Urban Food Web



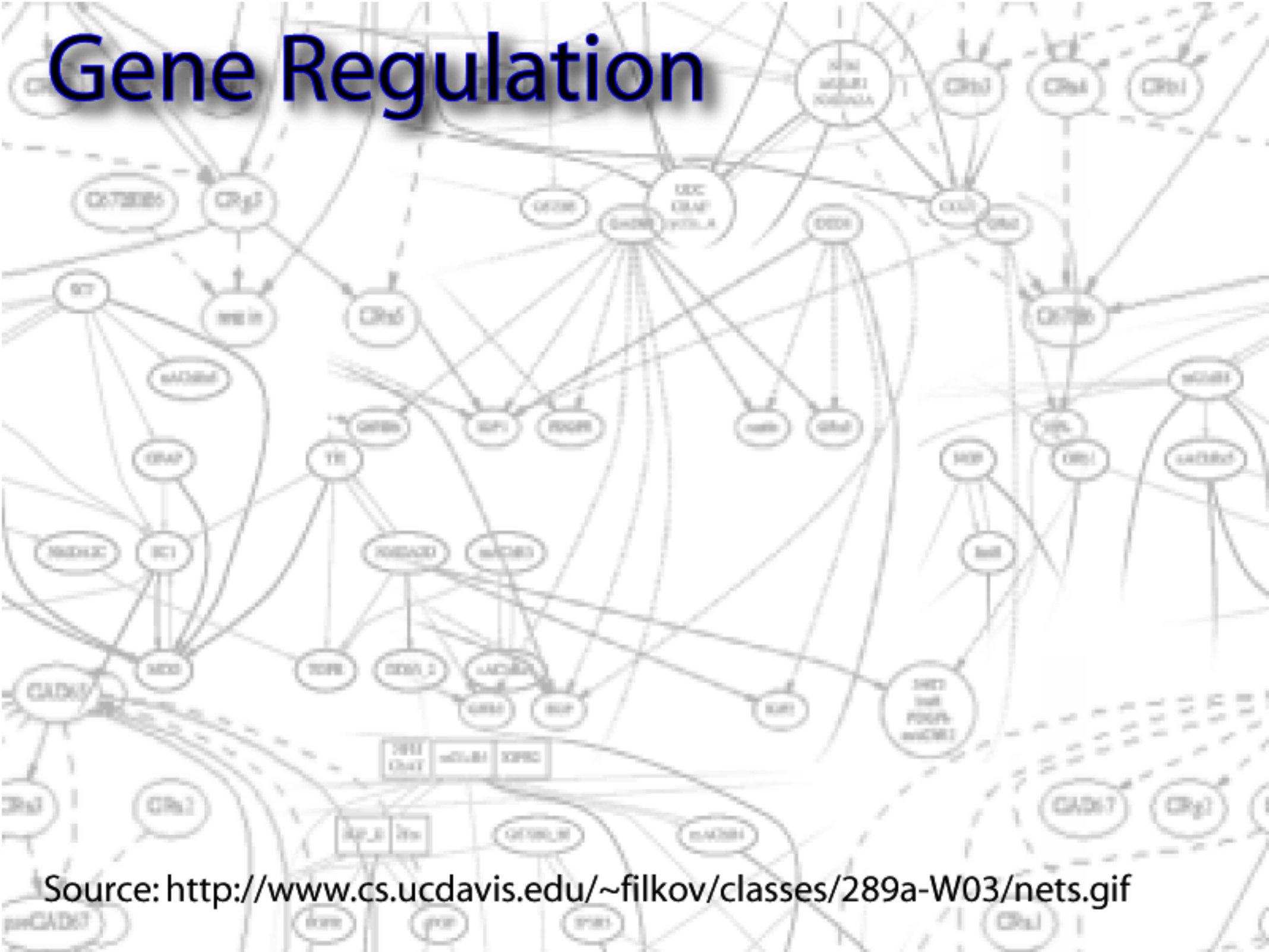
Source:
http://esapubs.org/bulletin/backissues/087-4/web_images_oct/urban/urban_foodwebs_3.jpg

Alcohol Metabolism



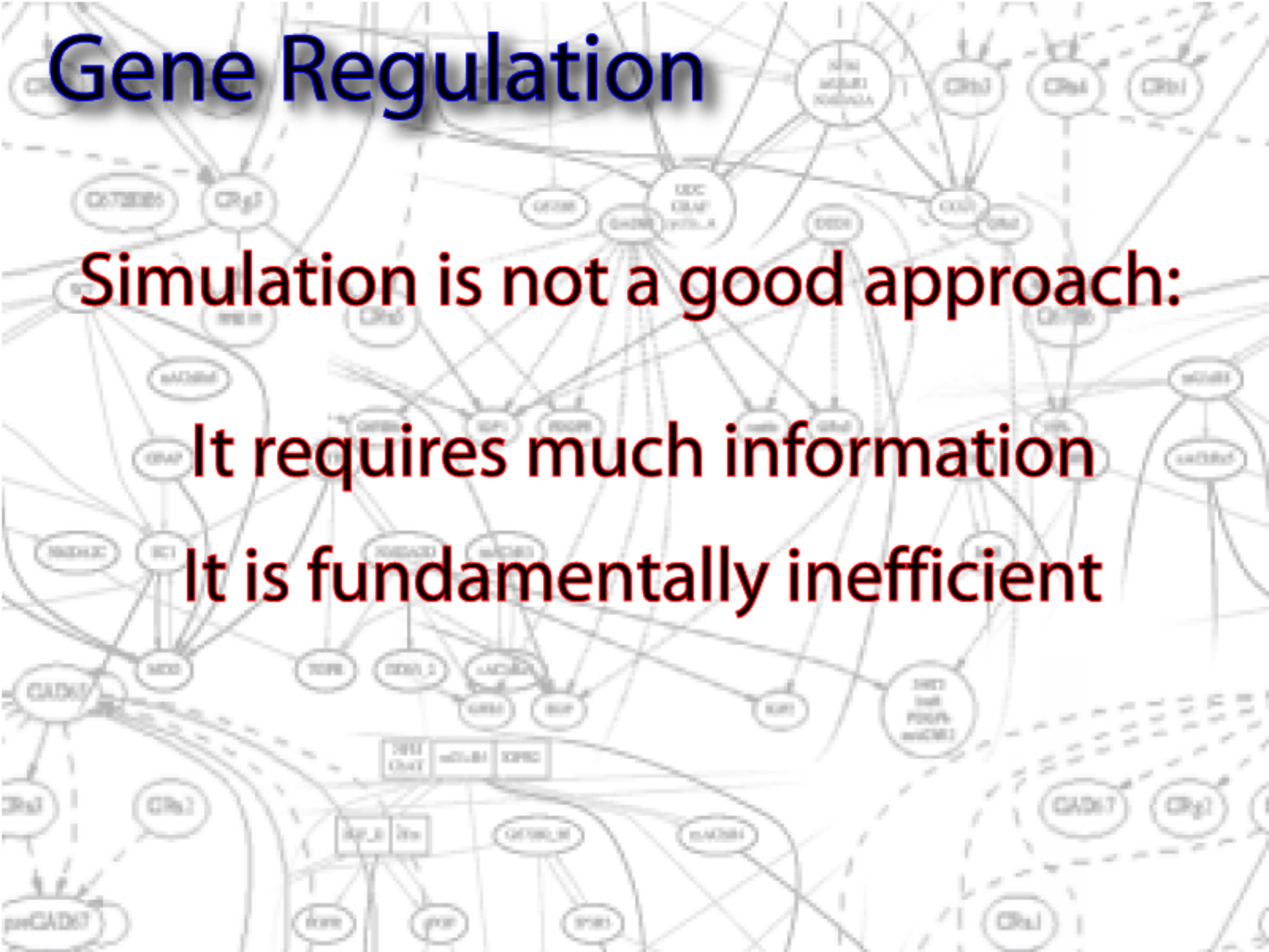
http://www.cptc.ctc.edu/library/Bio%20118%20Lecture%20Notes%20Rev%200105_files/image191.jpg

Gene Regulation



Source: http://www.cs.ucdavis.edu/~filkov/classes/289a-W03/nets.gif

Gene Regulation



Simulation is not a good approach:

It requires much information

It is fundamentally inefficient

Conventional Models

Input:

Network topology
Specific functional forms of interactions

Output:

Mainly: Trajectories
Steady States
Stability
Bifurcations

Generalized Models

Input:

Network topology

Parameters describing the steady states

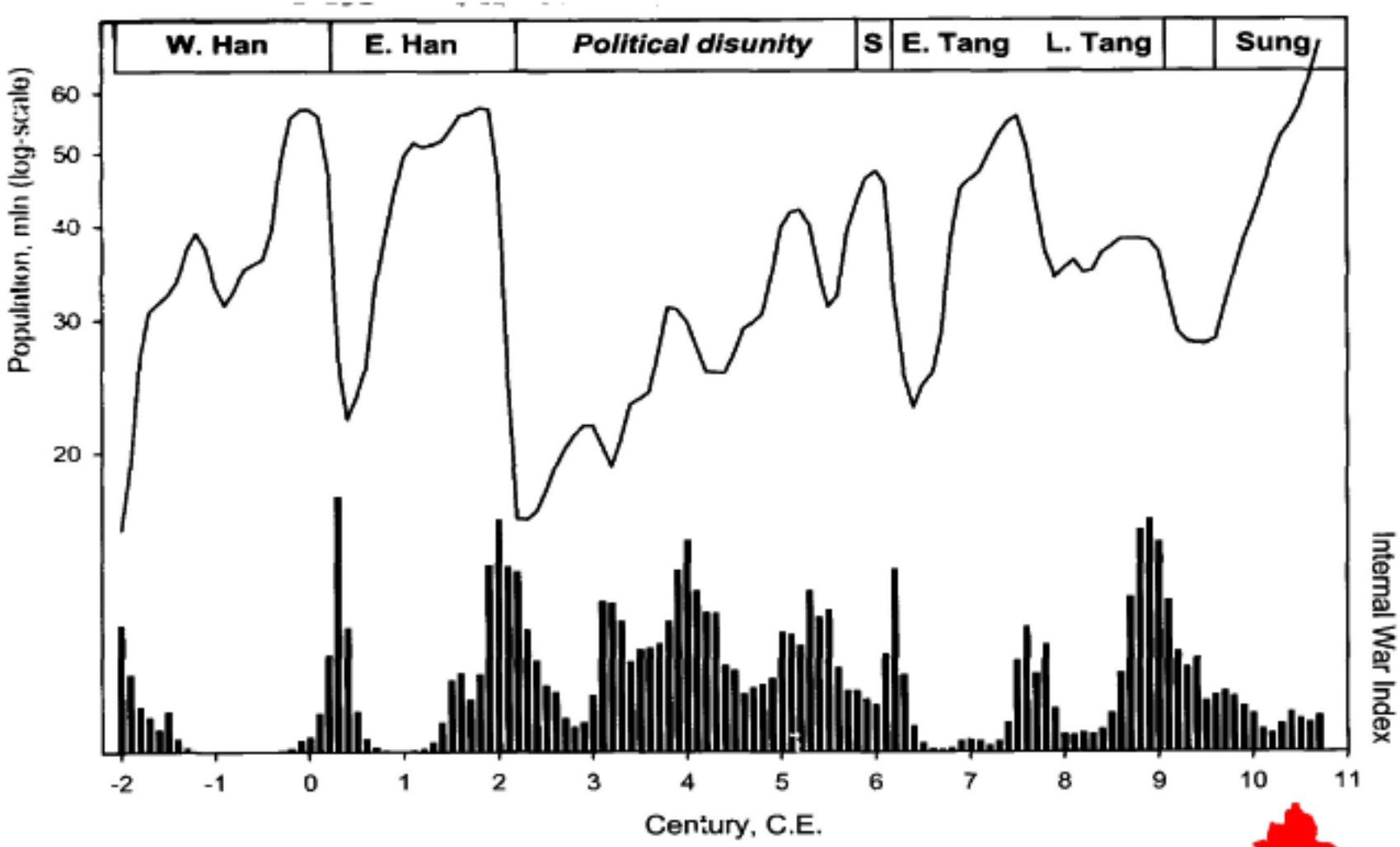
Output:

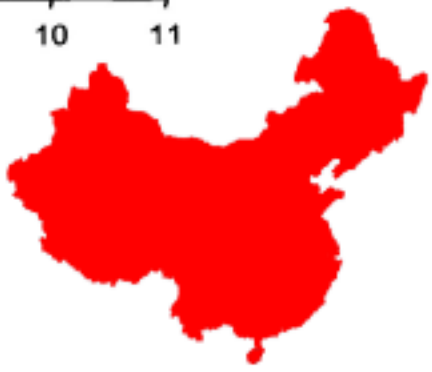
Local stability of steady states

Local Bifurcations

Some insights on global dyamics

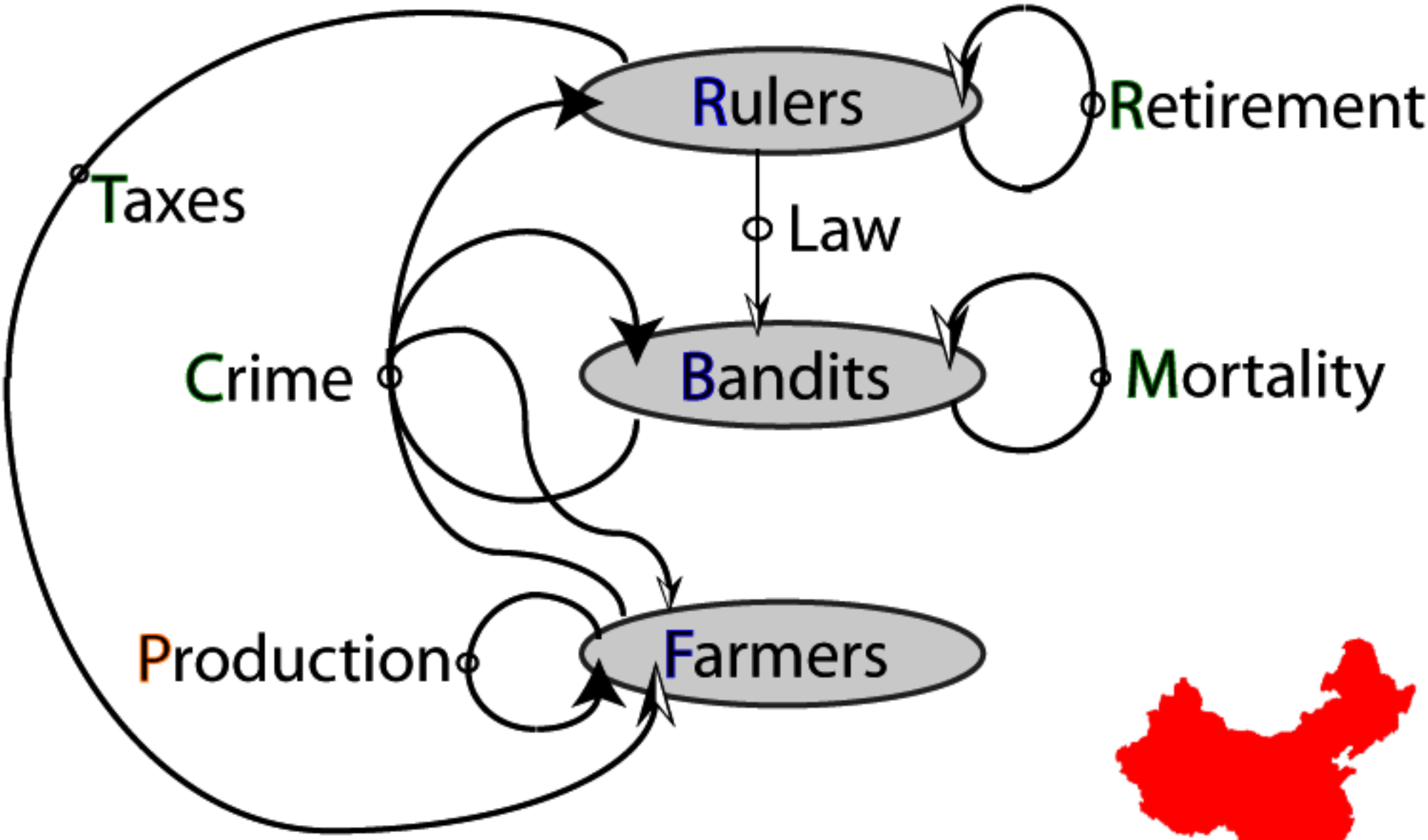
The Dynastic Cycle





Peter Turchin: *Historical Dynamics, 2003*

The Dynastic Cycle



Chu and Lee, *J. Pop. Econ* (1994)

The Dynastic Cycle

$$\begin{aligned}
\dot{F} &= P(F) - C(F,B) - T(F,R) \\
\dot{B} &= C(F,B) - L(R,B) - M(B) \\
\dot{R} &= C(F,B) - E(R)
\end{aligned}$$

A generalized model of the dynastic cycle

The Dynastic Cycle

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\end{aligned}$$

Assume that there is a steady state, then we can define

$$f := \frac{F}{F^*}, \quad p(f) := \frac{P(F)}{P(F^*)}, \quad \ldots$$

The Dynastic Cycle

$$\dot{f} = \frac{P^*}{F^*}p(f) - \frac{C^*}{F^*}c(f,b) - \frac{T^*}{F^*}t(f,r)$$

$$\dot{b} = \frac{C^*}{B^*}c(f,b) - \frac{L^*}{B^*}l(r,b) - \frac{M^*}{B^*}m(b)$$

$$\dot{r} = \frac{C^*}{R^*}c(f,b) - \frac{E^*}{R^*}e(r)$$

Assume that there is a steady state, then we can define

$$f := \frac{F}{F^*}, \quad p(f) := \frac{P(F)}{P(F^*)}, \ \ldots$$

The Dynastic Cycle

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\begin{aligned}
\dot{f} &= \alpha_{\mathrm{f}}(p - \beta c - (1-\beta)t) \\
\dot{b} &= \alpha_{\mathrm{b}}(c - \gamma l - (1-\gamma)m) \\
\dot{r} &= \alpha_{\mathrm{r}}(c - e)
\end{aligned}
$$

We have defined the scale parameters

$\alpha_{\mathrm{f}} = \dfrac{P^*}{F^*}$ inverse life expectancy of farmers

$\gamma = \dfrac{1}{\alpha_{\mathrm{b}}} \dfrac{L^*}{B^*}$ fraction of bandits that get eventually caught

The Dynastic Cycle

Suppose we knew a steady state ...

...what do we need to know to decide if it is stable?

The Dynastic Cycle

Suppose we knew a steady state ...

...what do we need to know to decide if it is stable?

Scale Parameters

Life expectancy of farmers, bandits and rulers?

What fraction of bandits is eventually caught?

What fraction of the farmer's losses is caused by crime?

The Dynastic Cycle

Suppose we knew a steady state ...

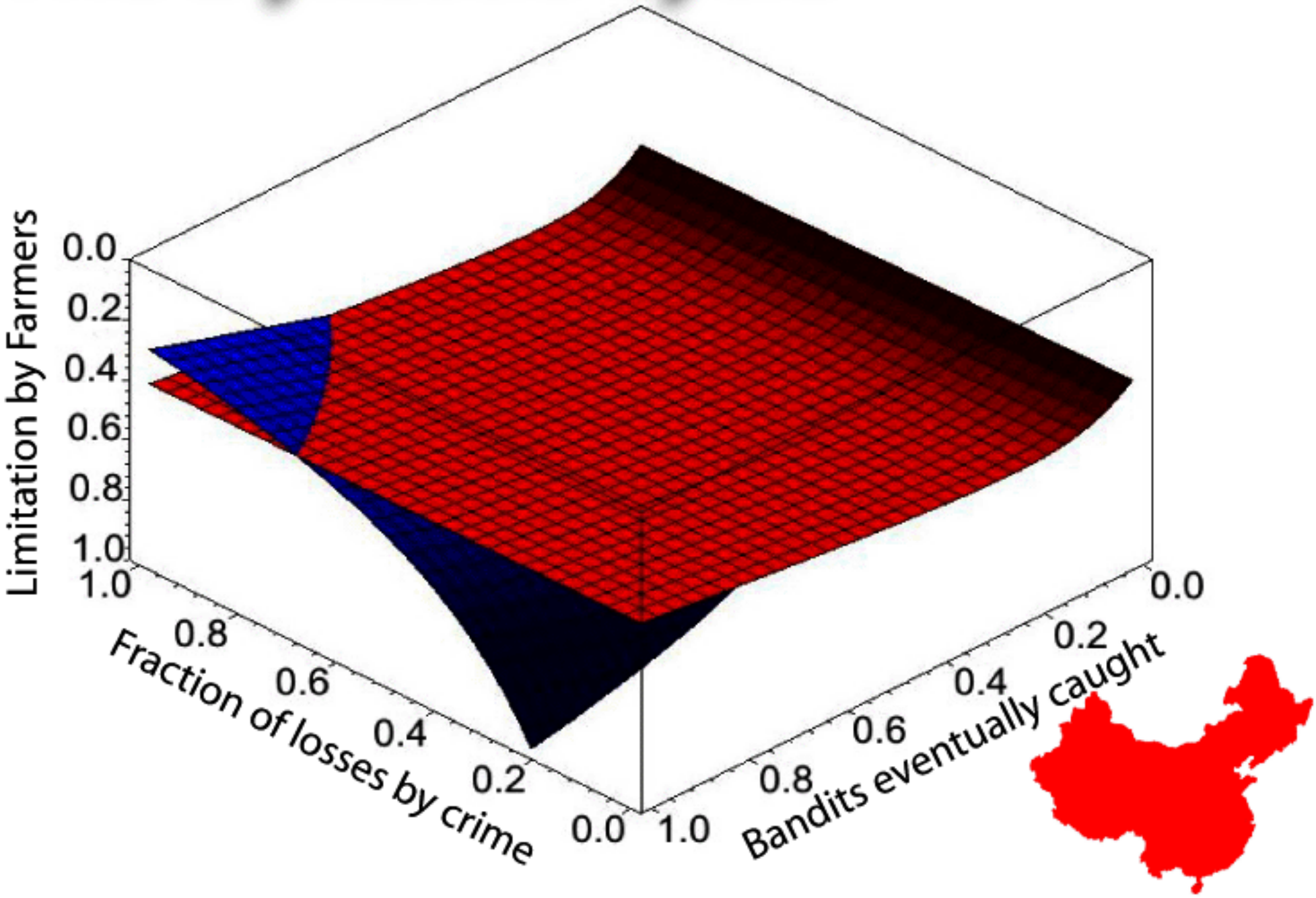
... what do we need to know to decide if it is stable?

Exponent Parameters

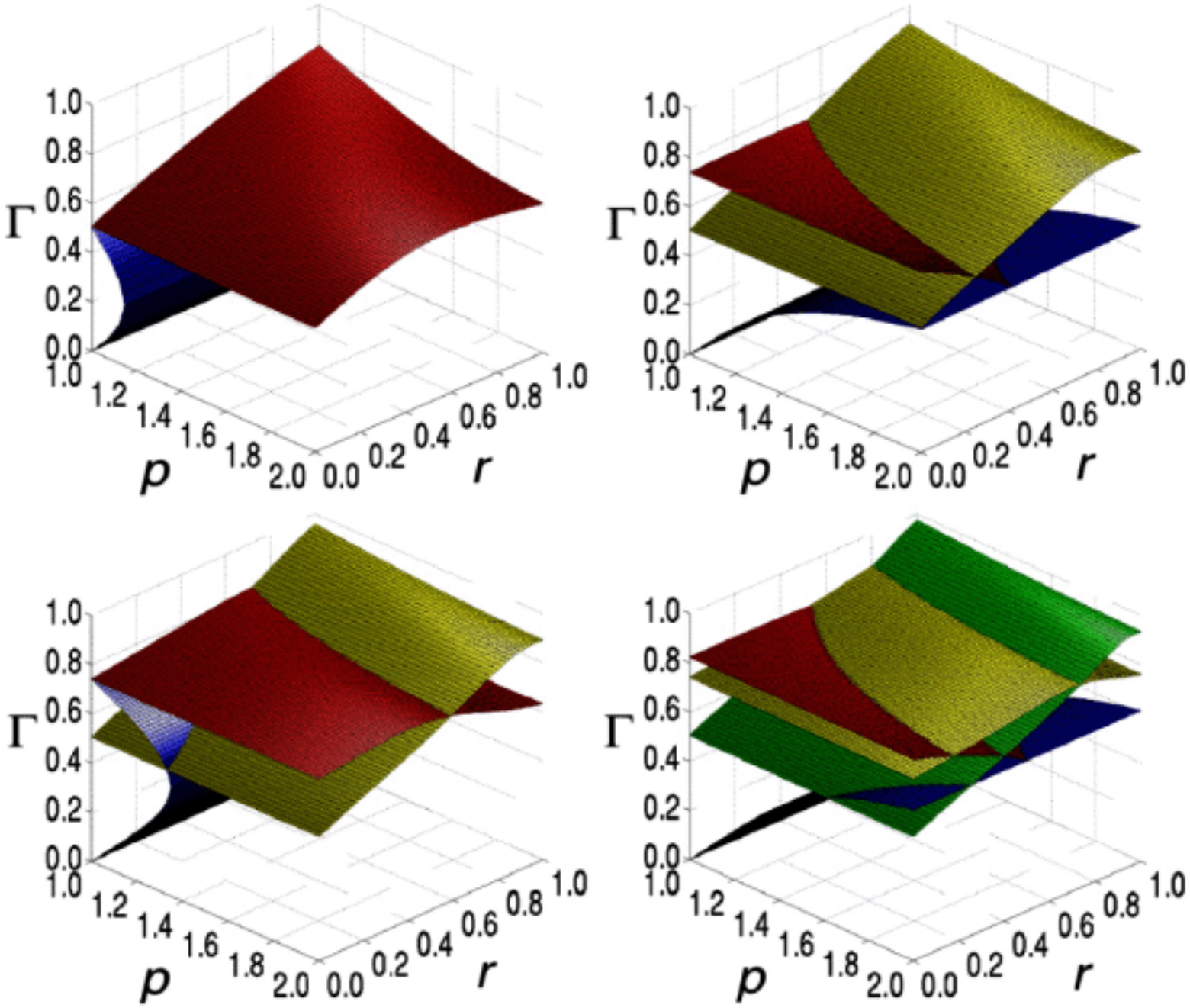
How strongly is production limited by the number of farmers?

= How much productive land is still available?

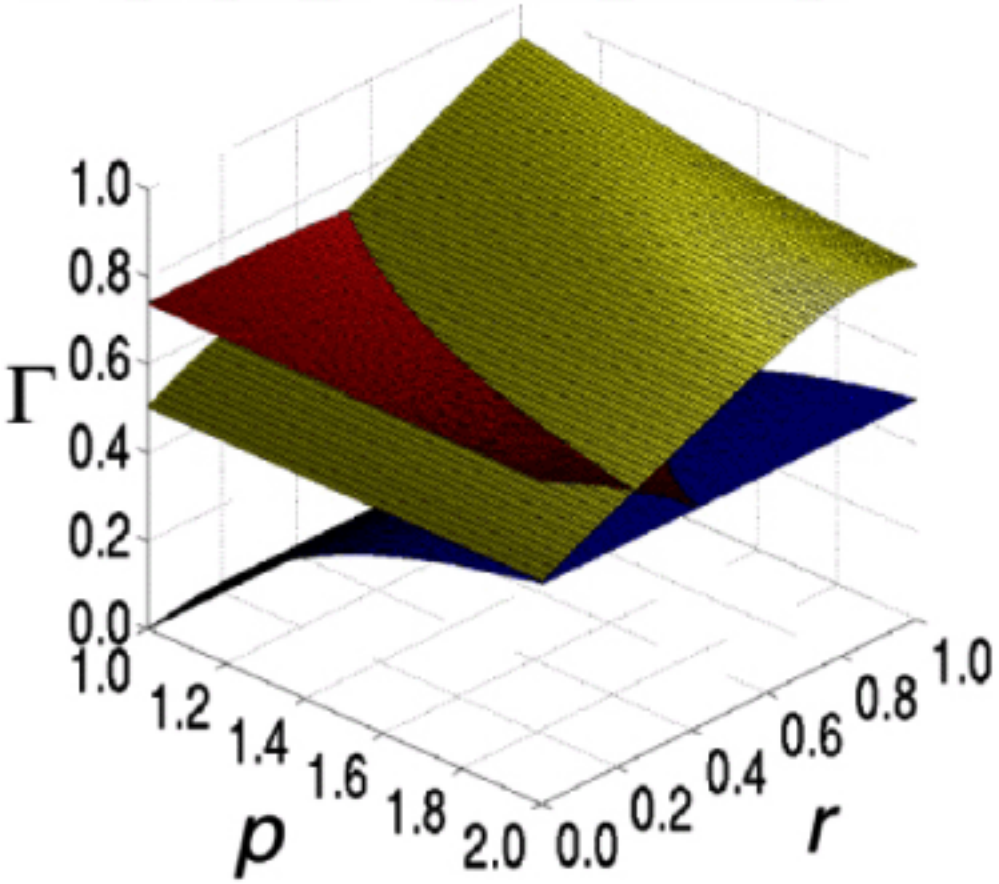
The Dynastic Cycle



Food Chains



Food Chains


Γ
1.0
0.8
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0.4
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0.0
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1.2
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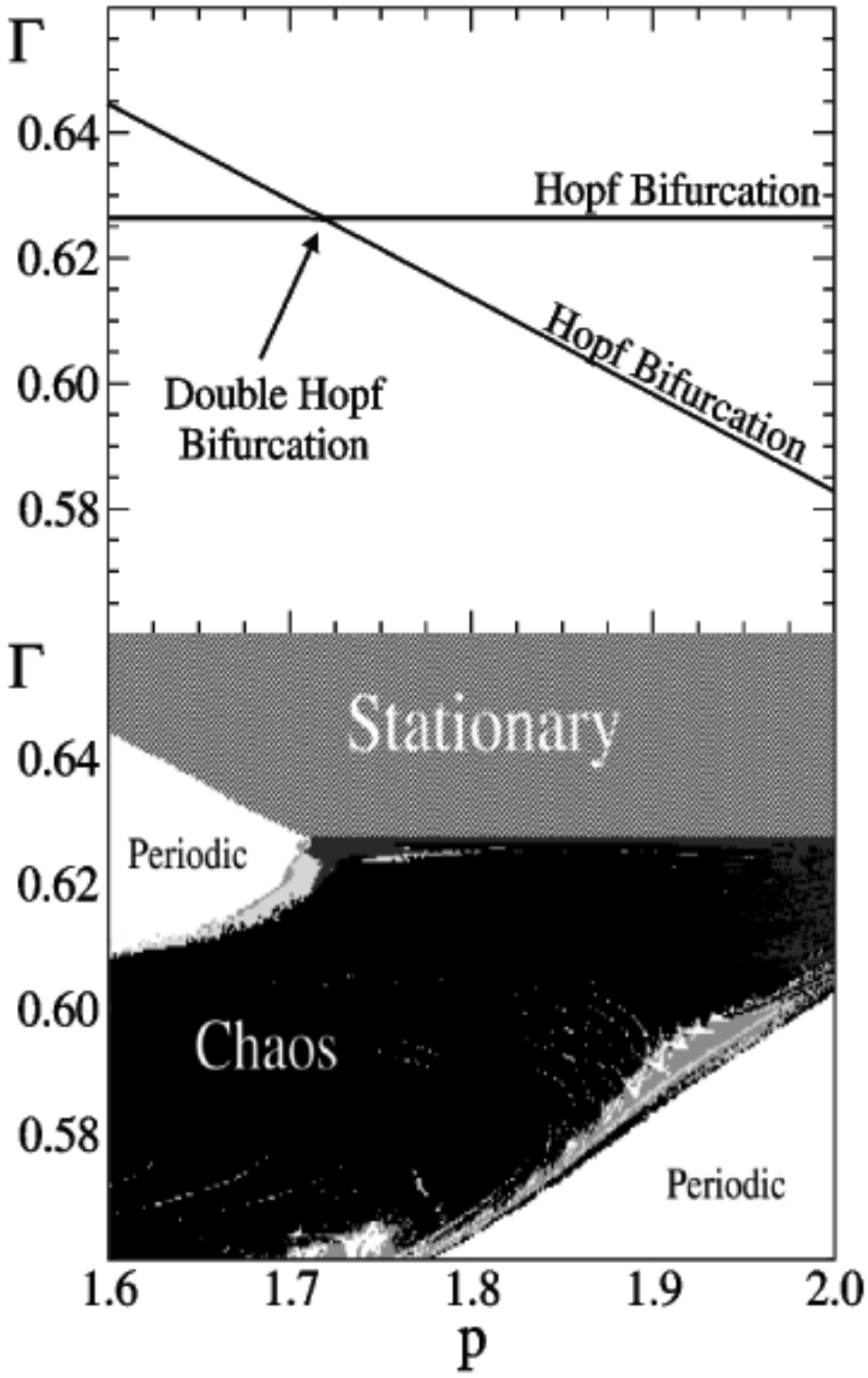
Γ
0.64
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0.58
Hopf Bifurcation
Hopf Bifurcation
Double Hopf
Bifurcation
Γ
0.64
0.62
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Stationary
Periodic
Chaos
Periodic
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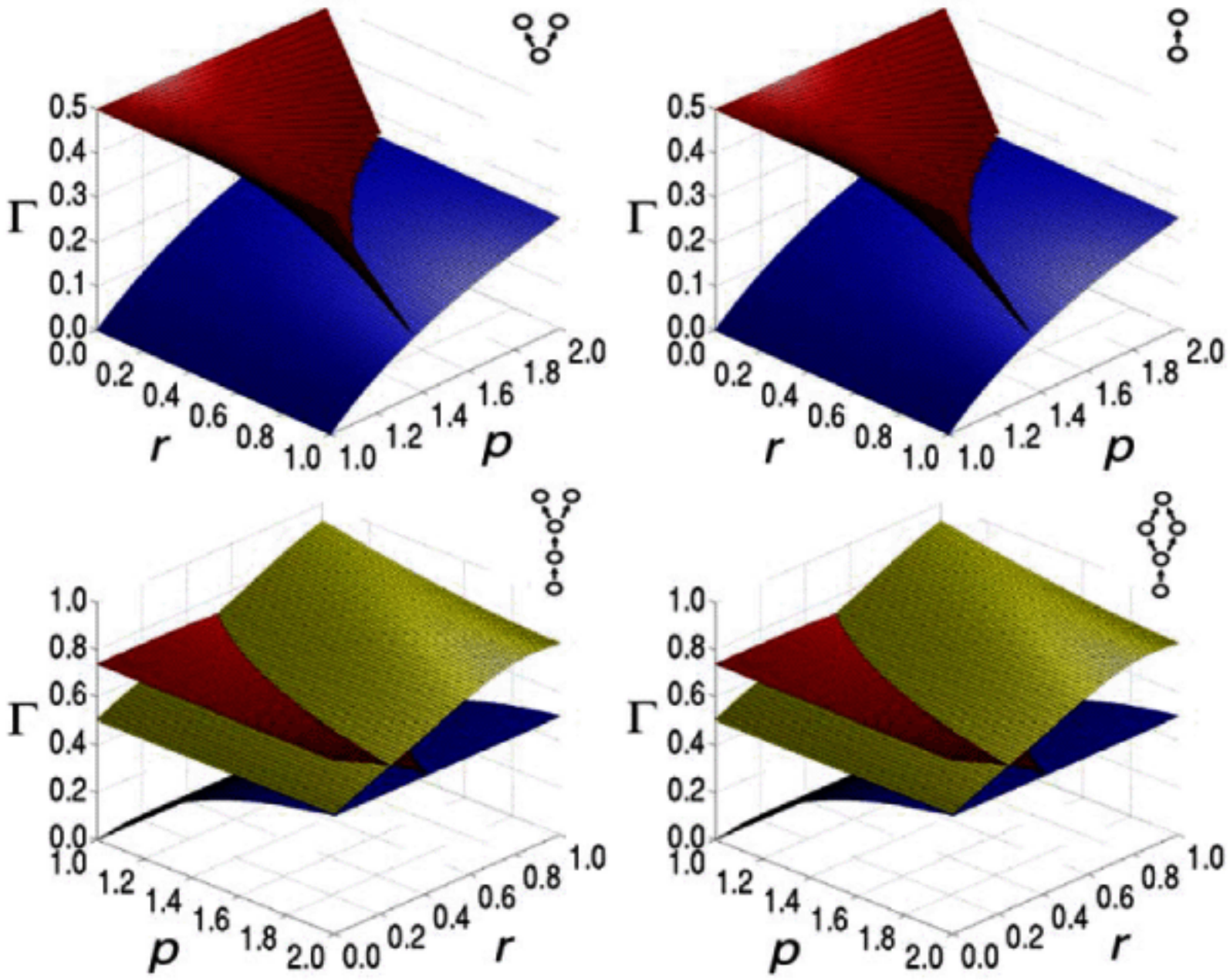
1.7
1.8
1.9
2.0
p

Food Webs



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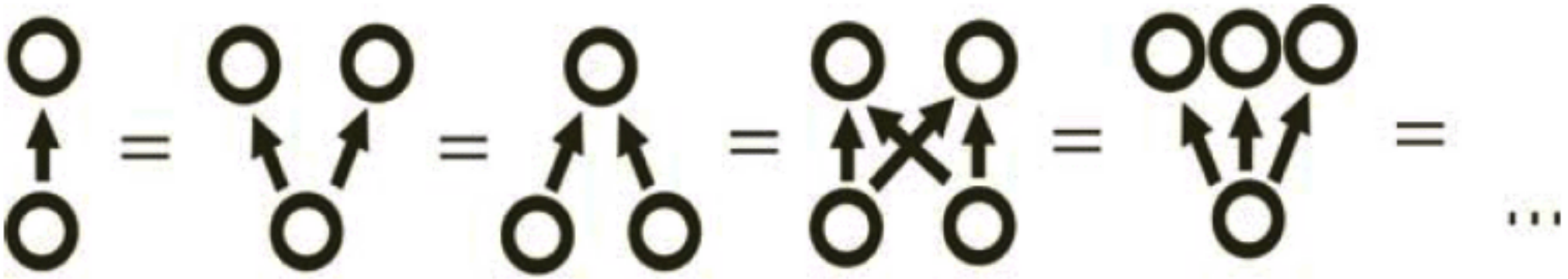

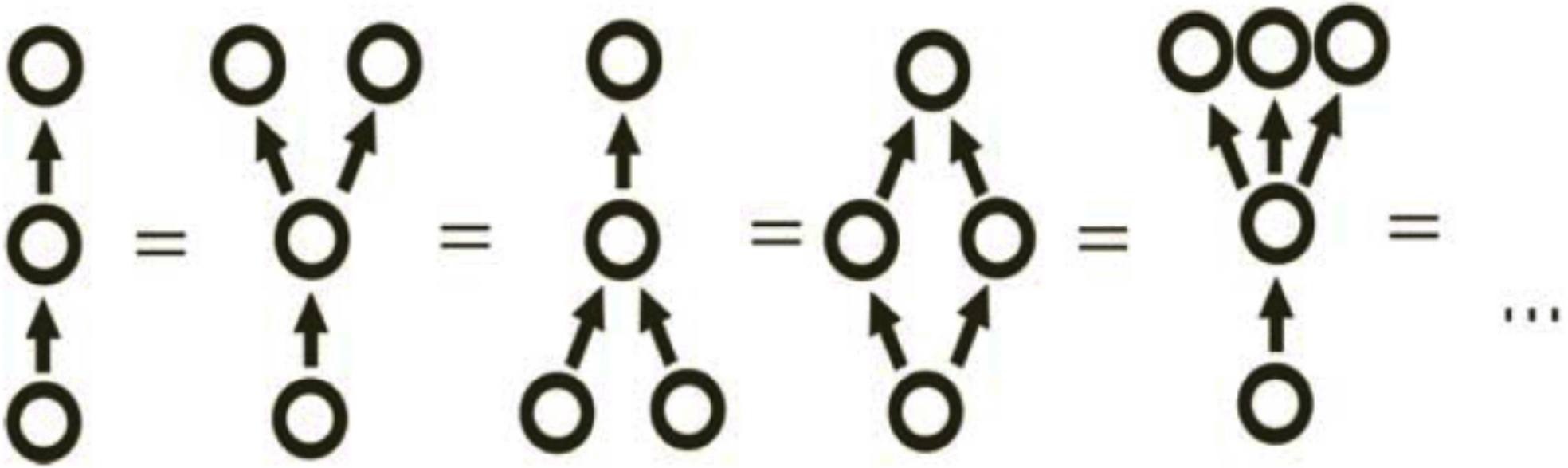

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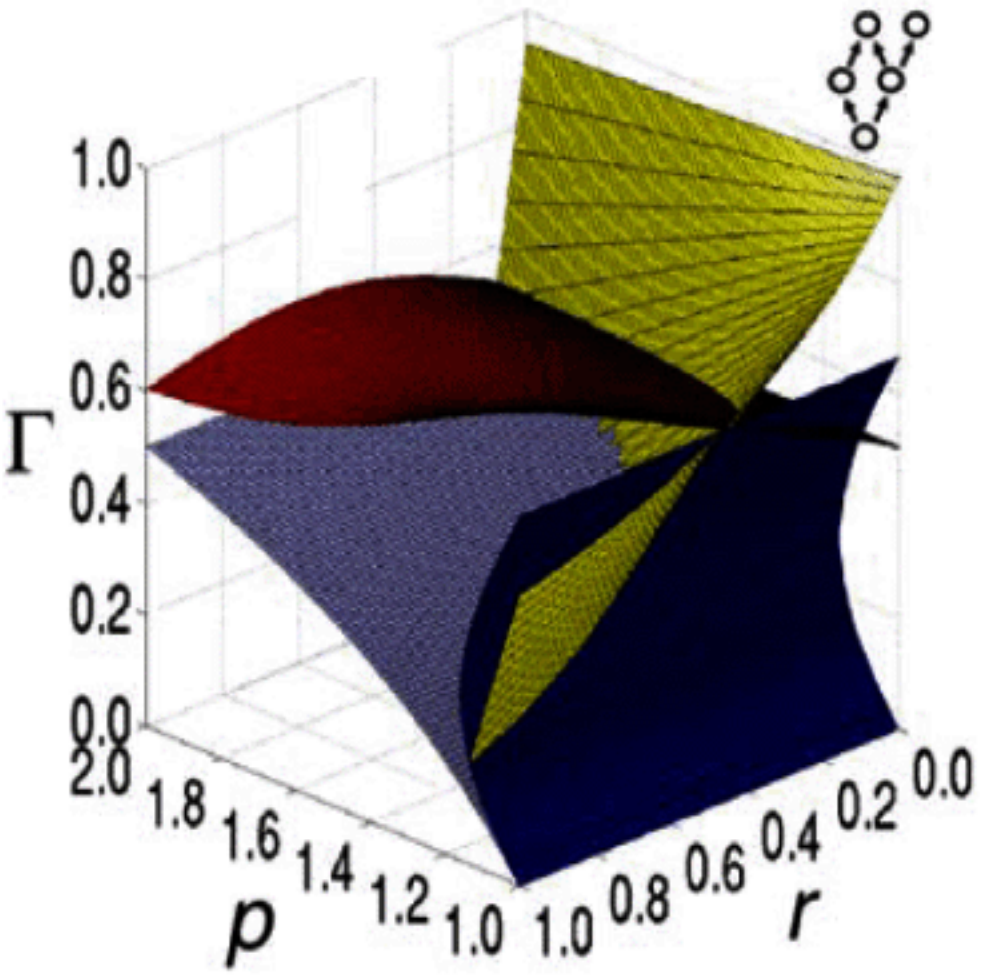
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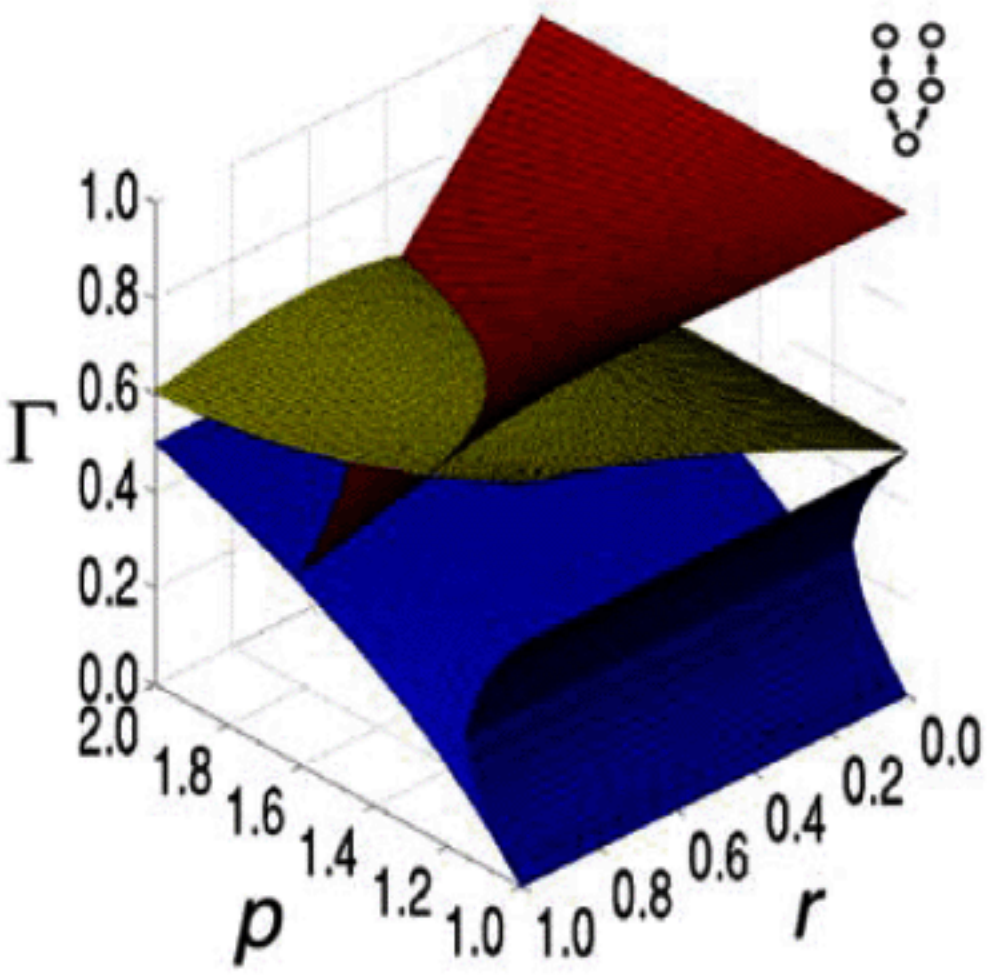
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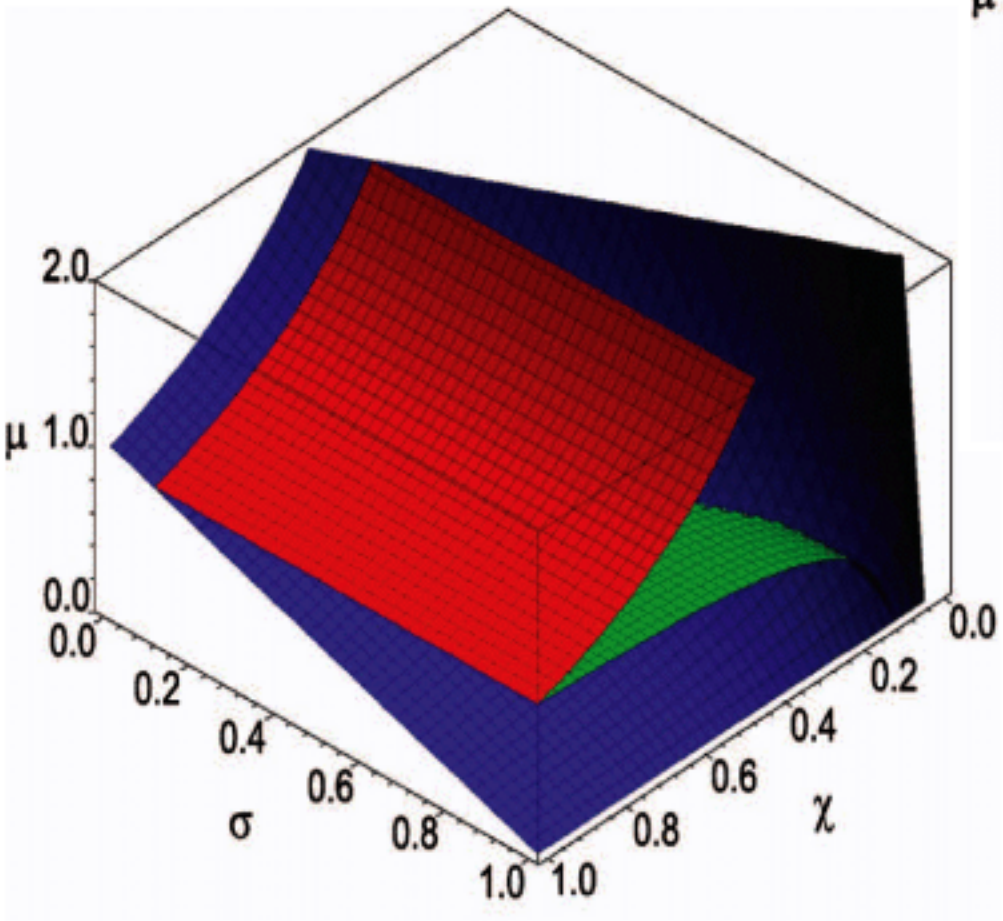
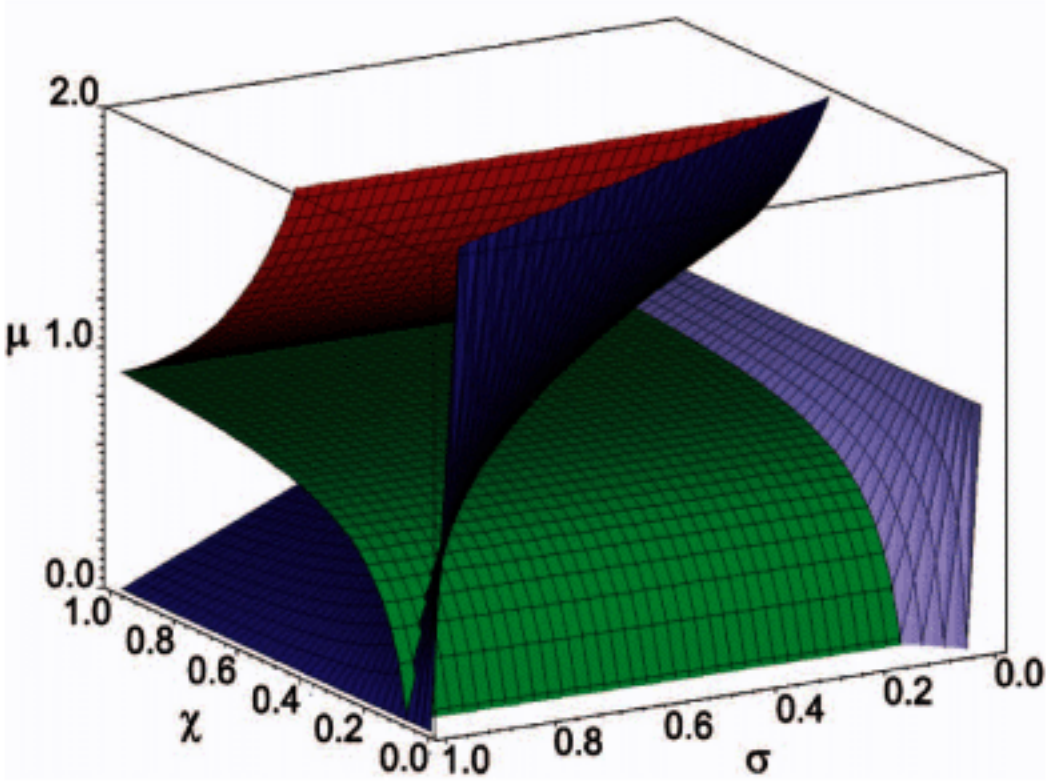
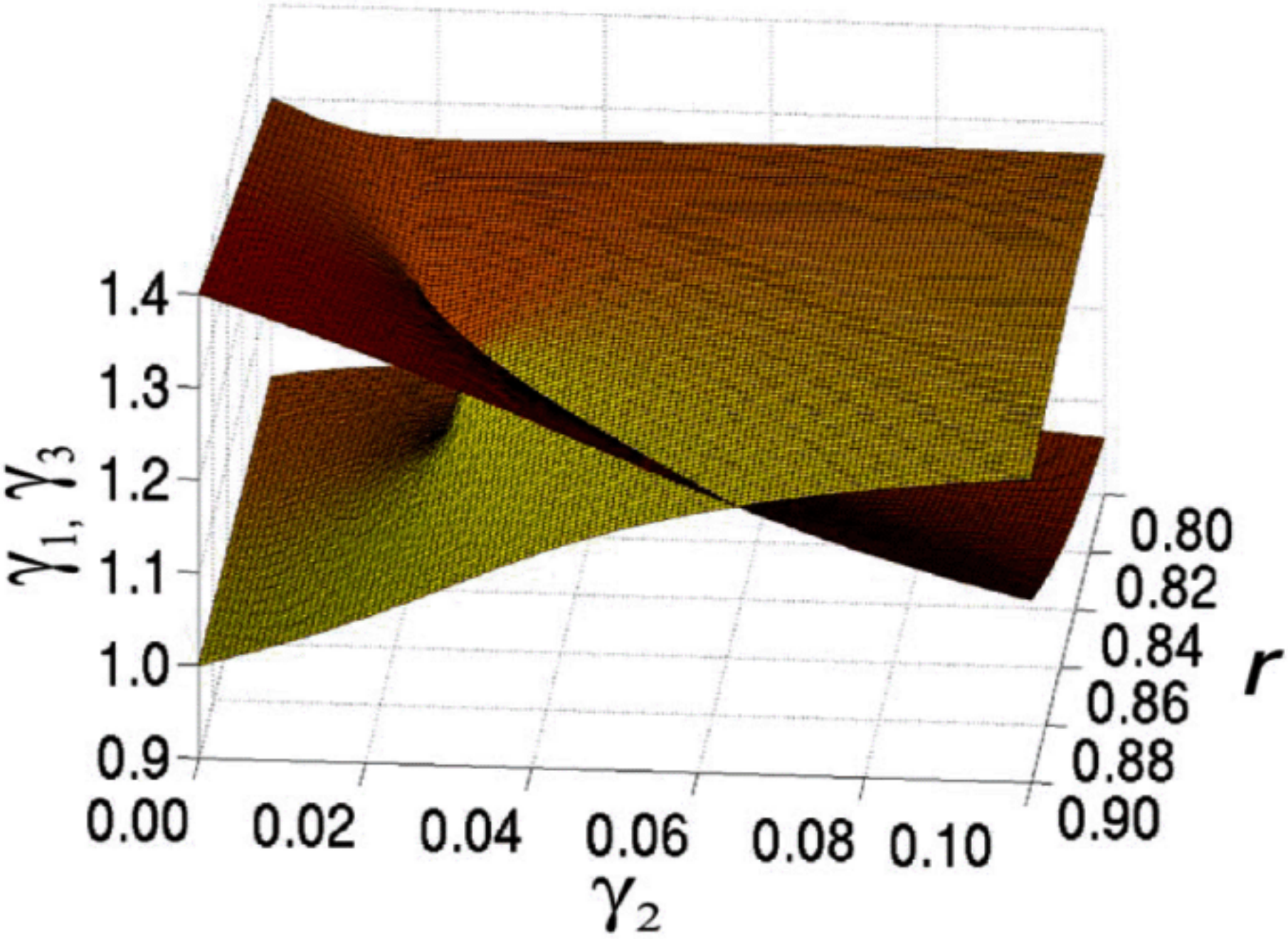
Codimension 4 in Lasers





Whitney Umbrella



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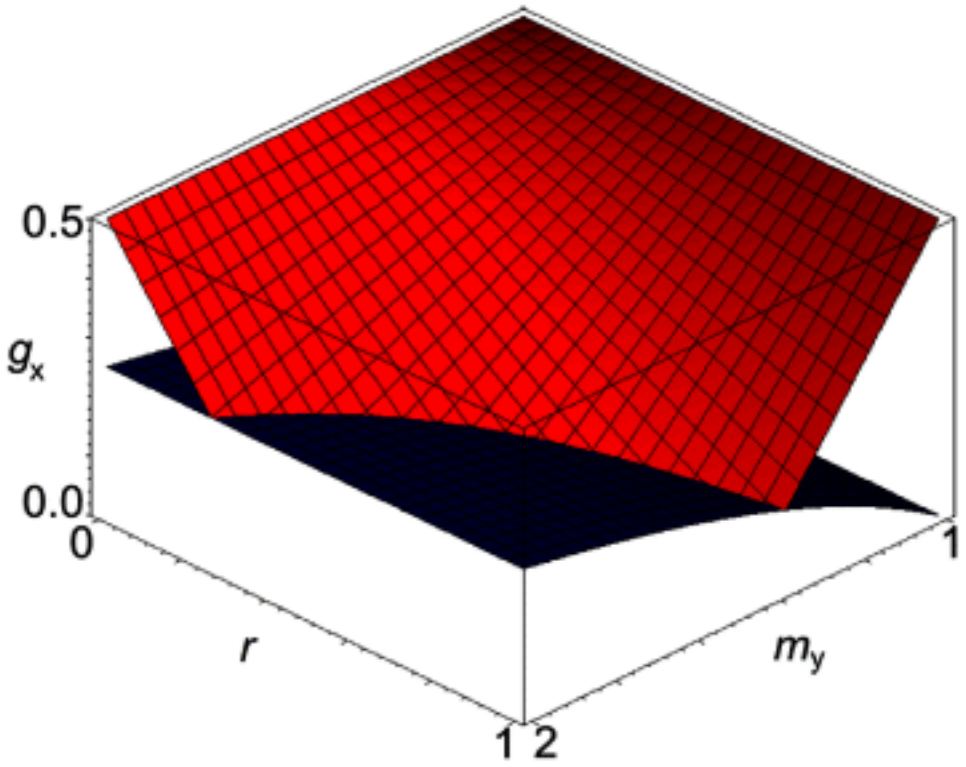
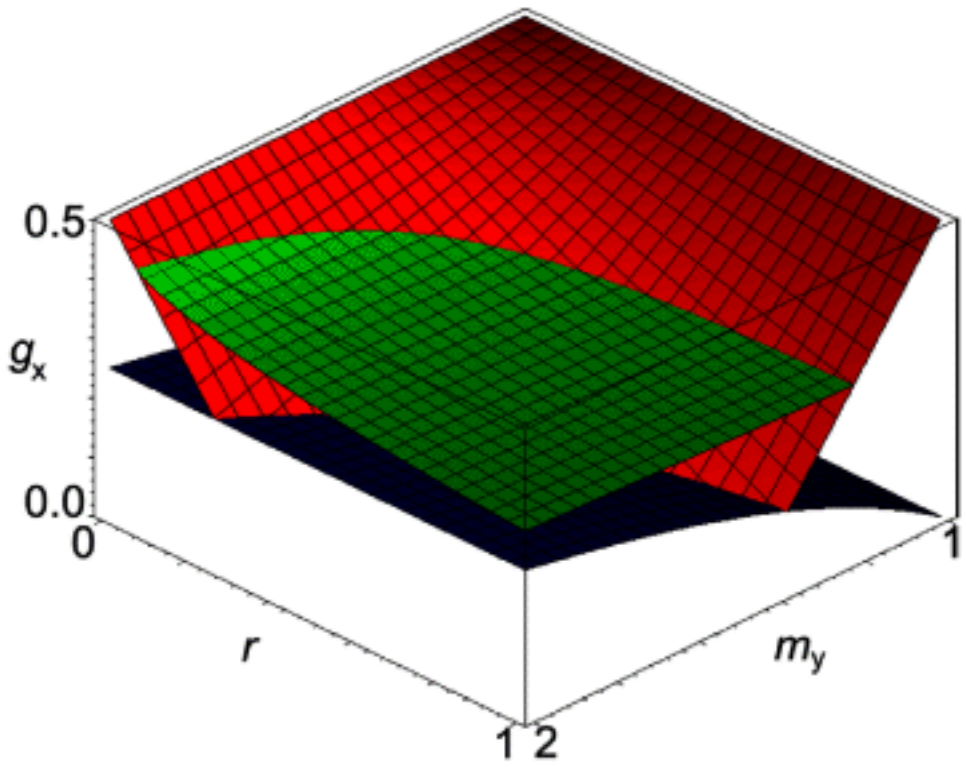
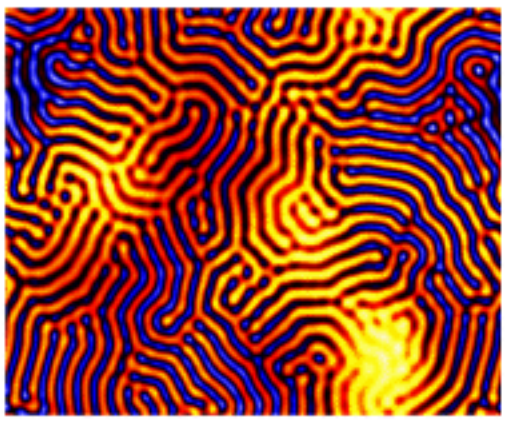
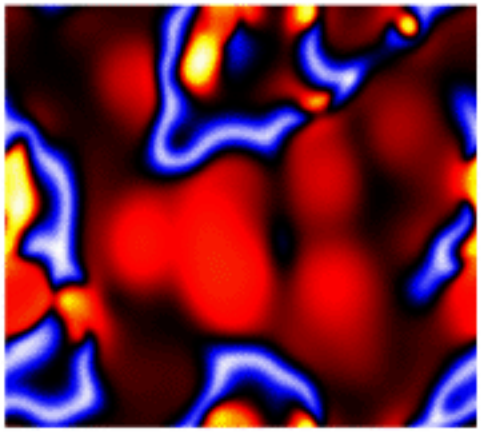
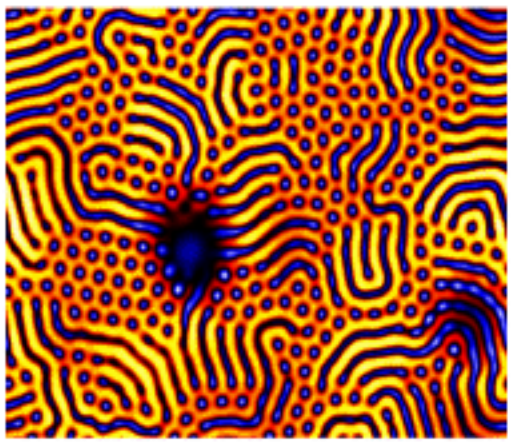
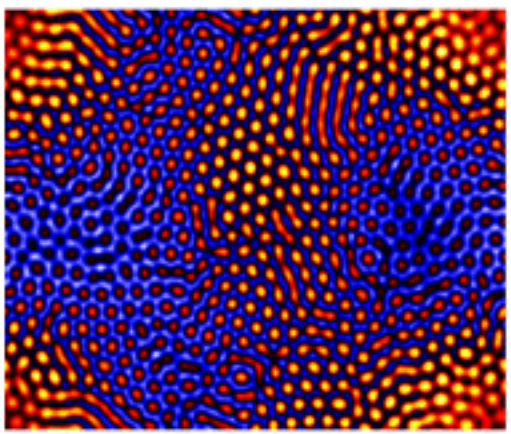




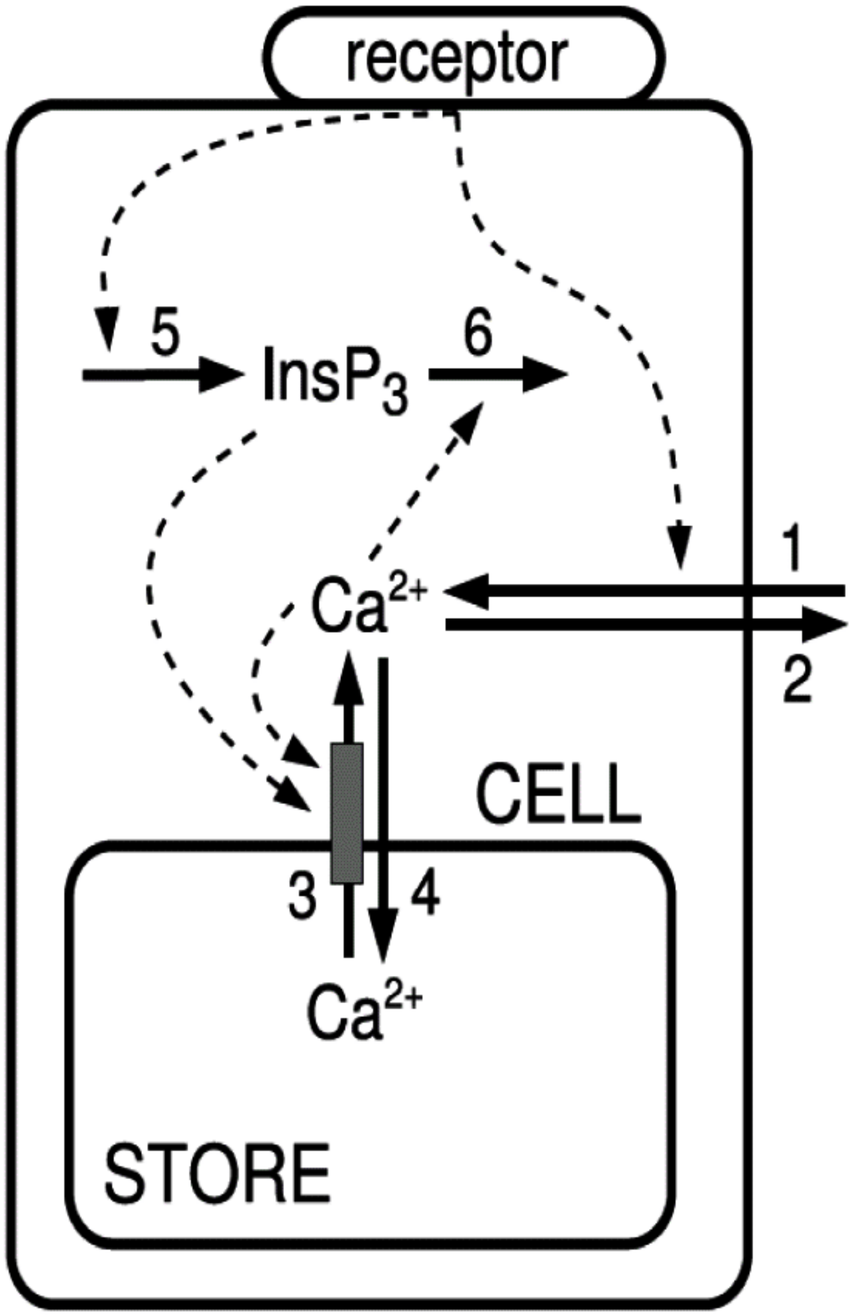


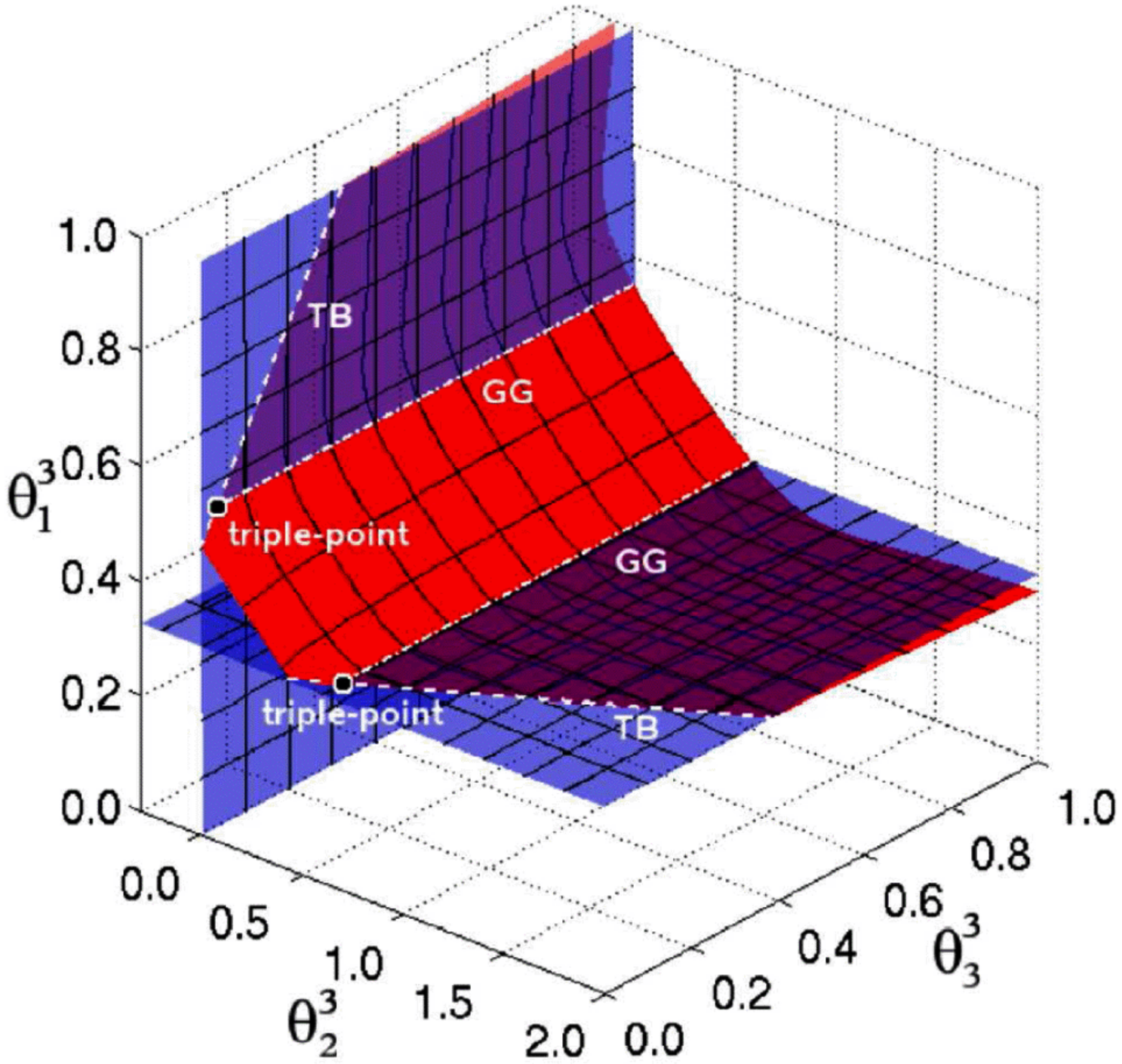




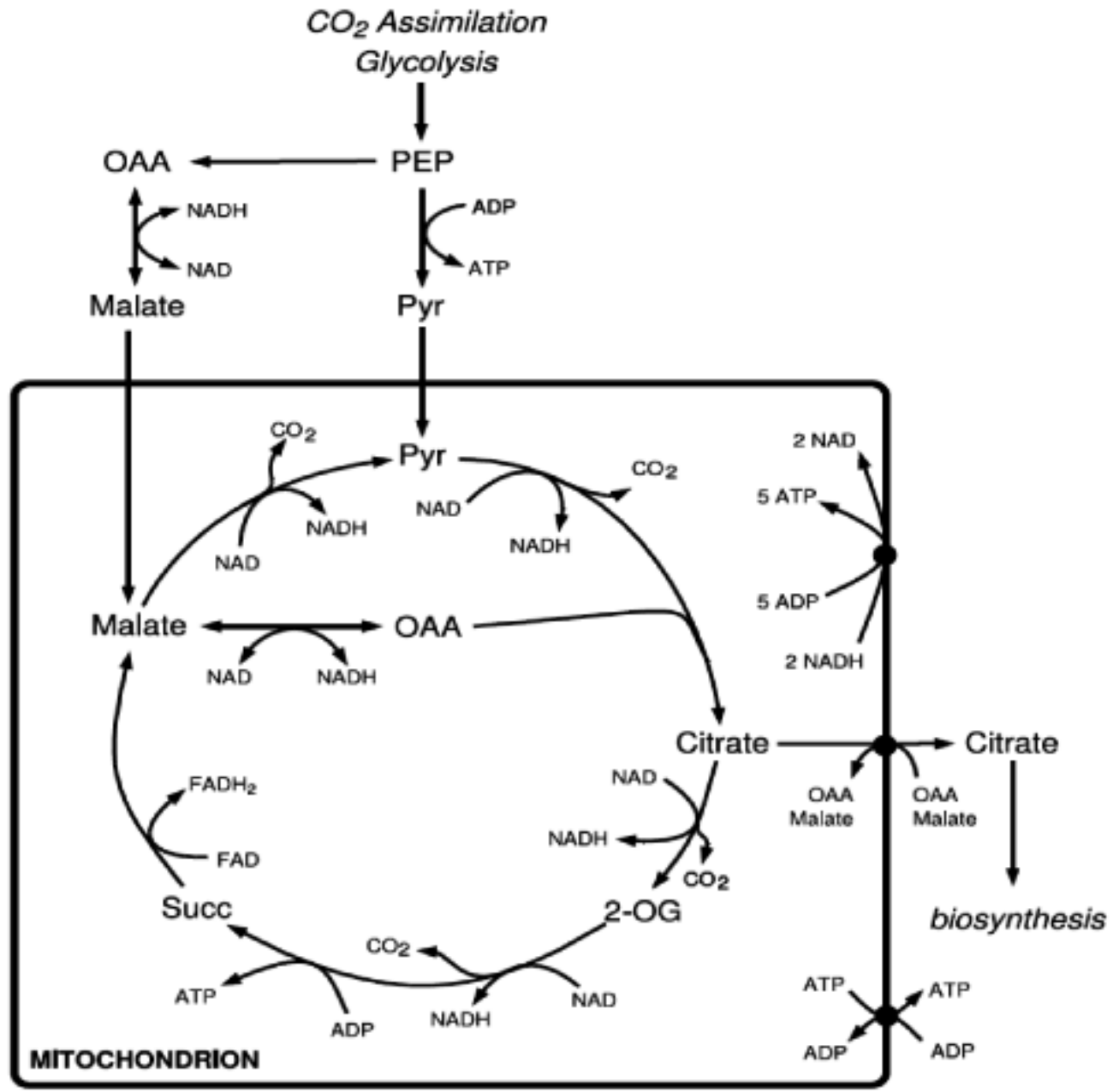


Calcium Oscillations

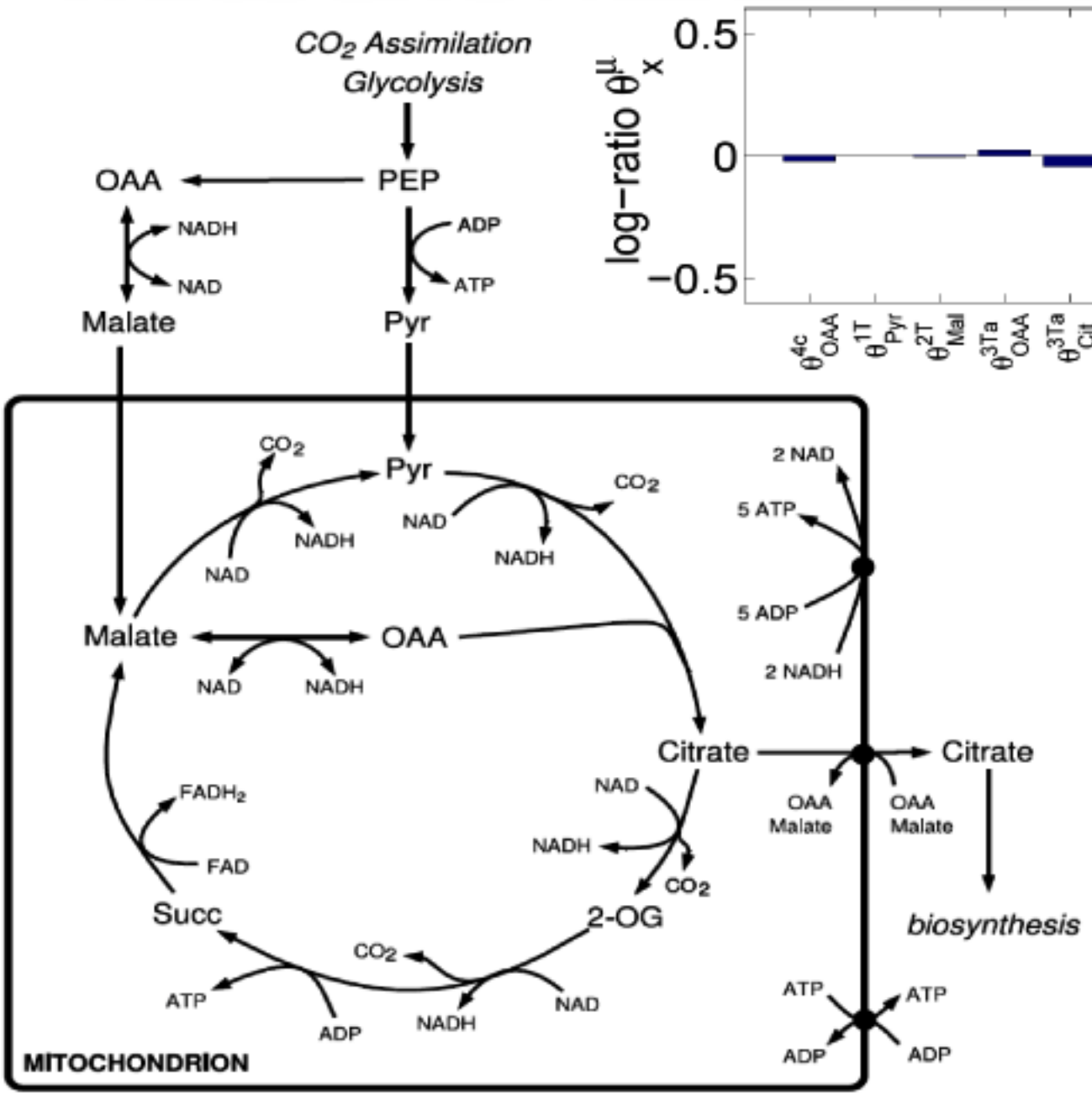


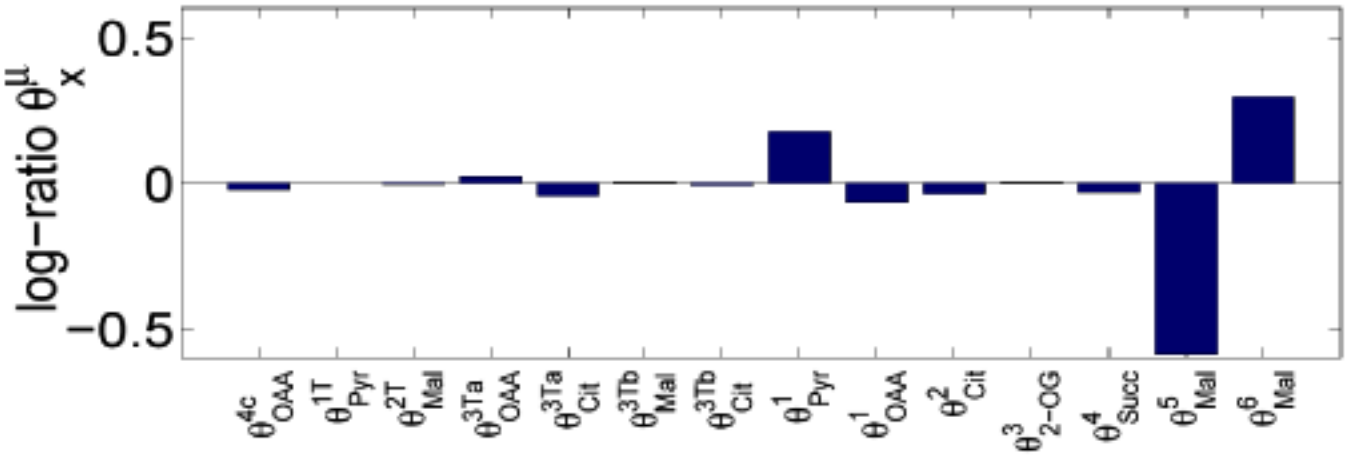


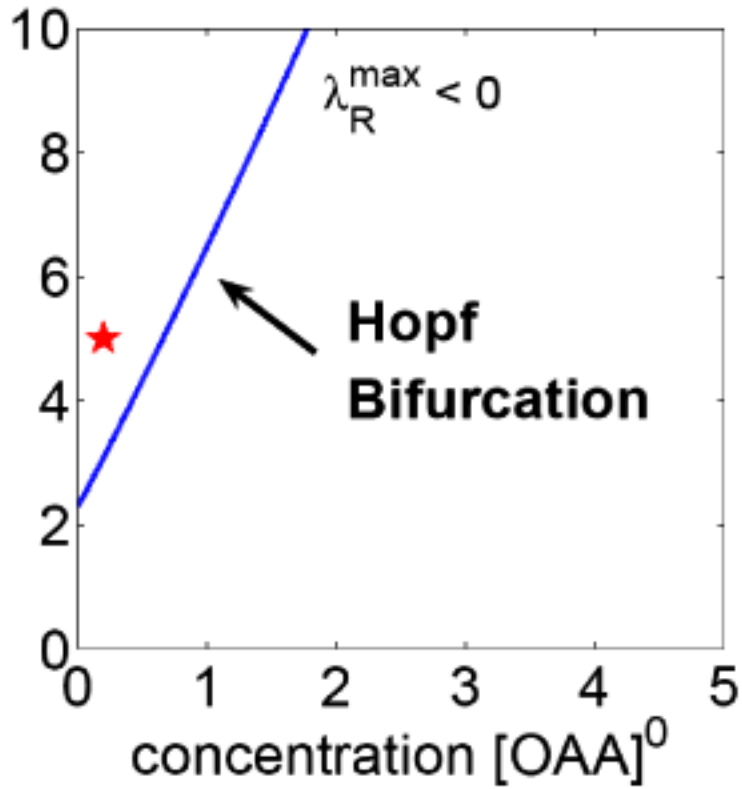
Mitochondrial TCA-Cycle



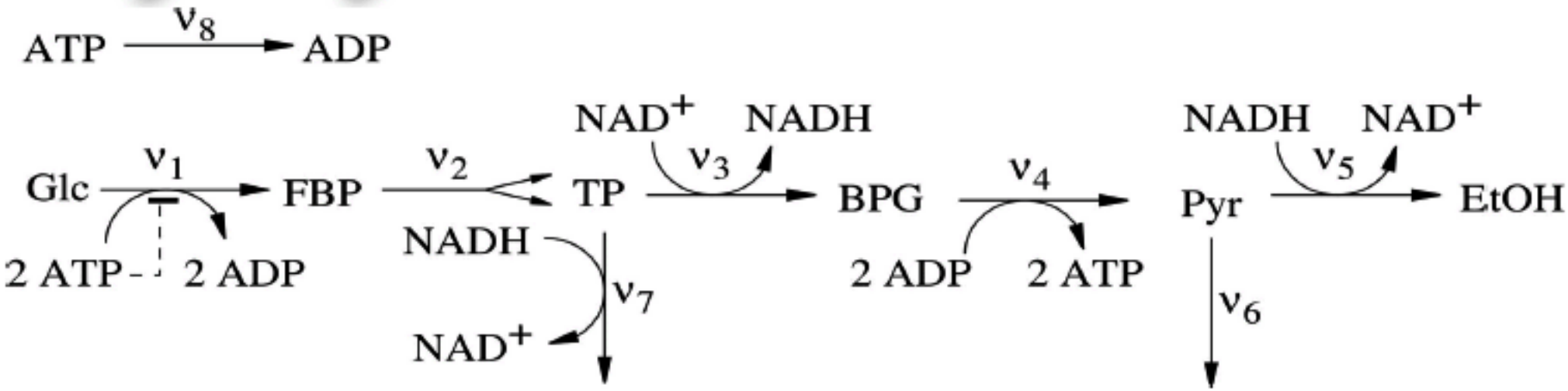
Mitochondrial TCA-Cycle



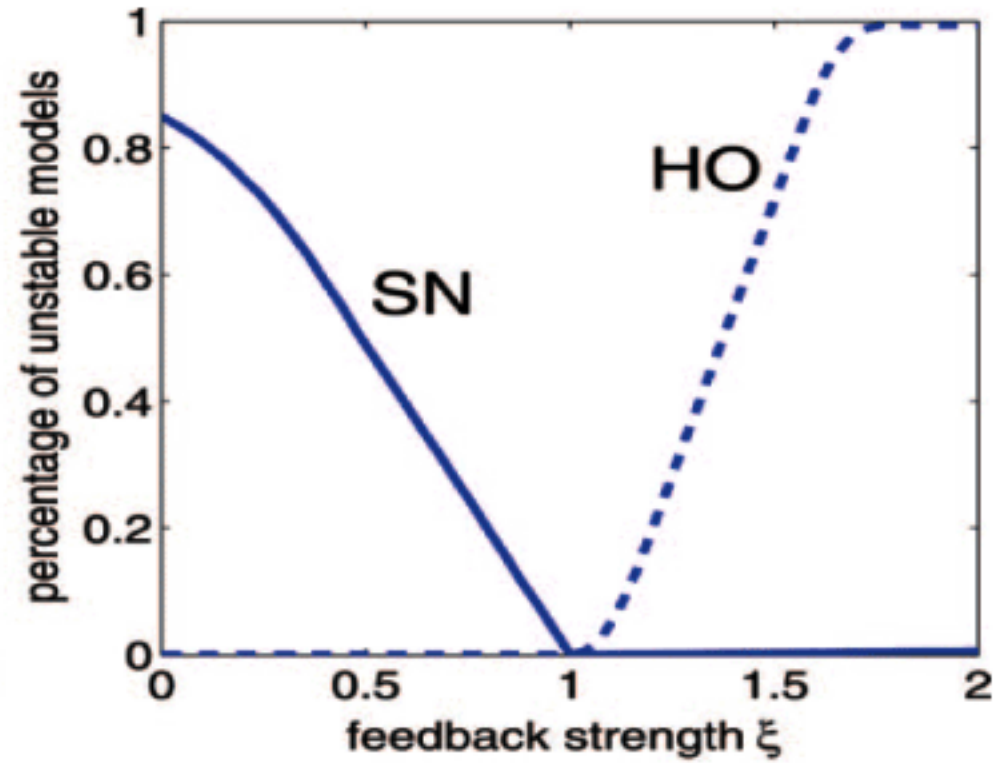




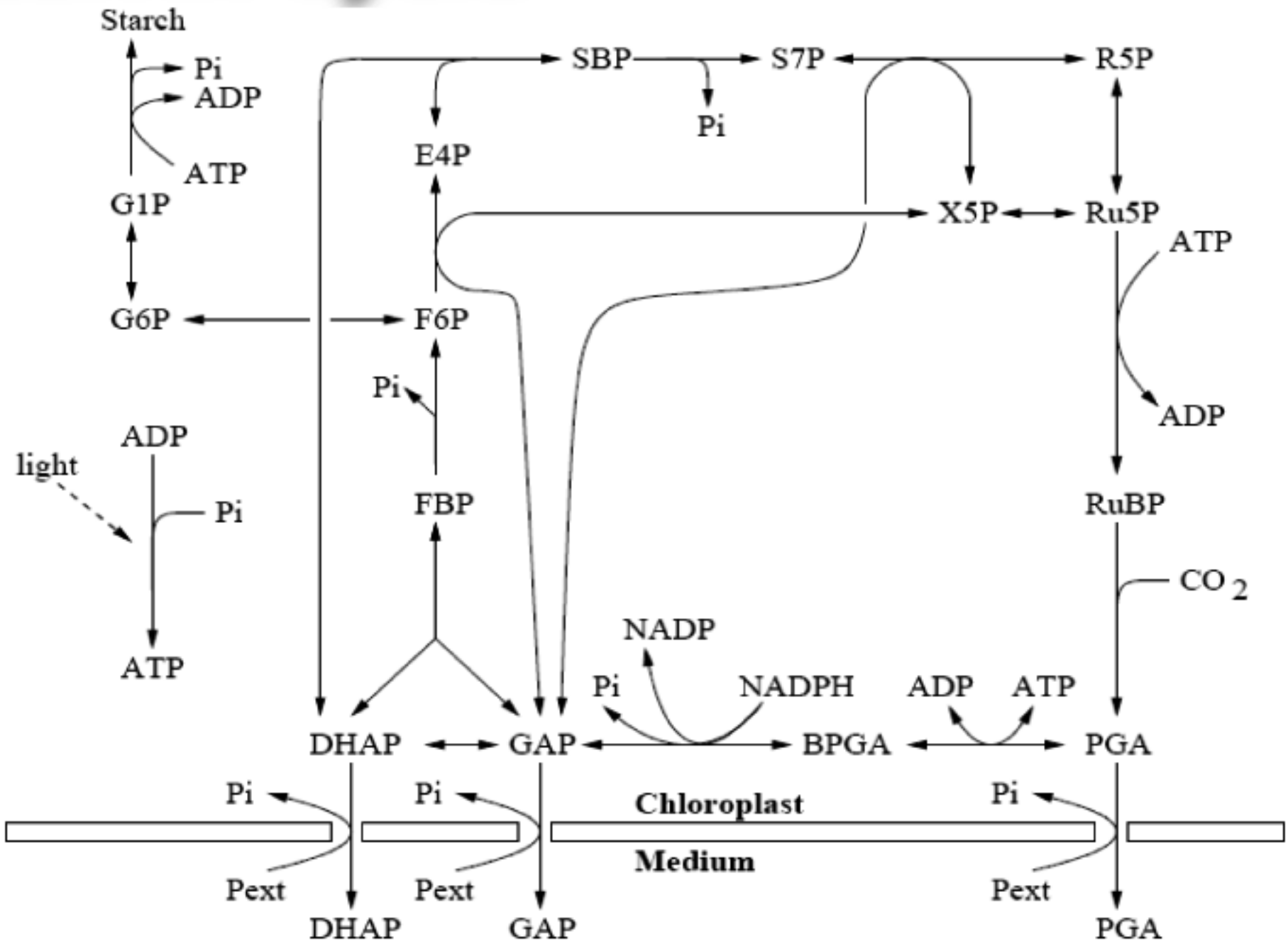
Glycolysis in Yeast



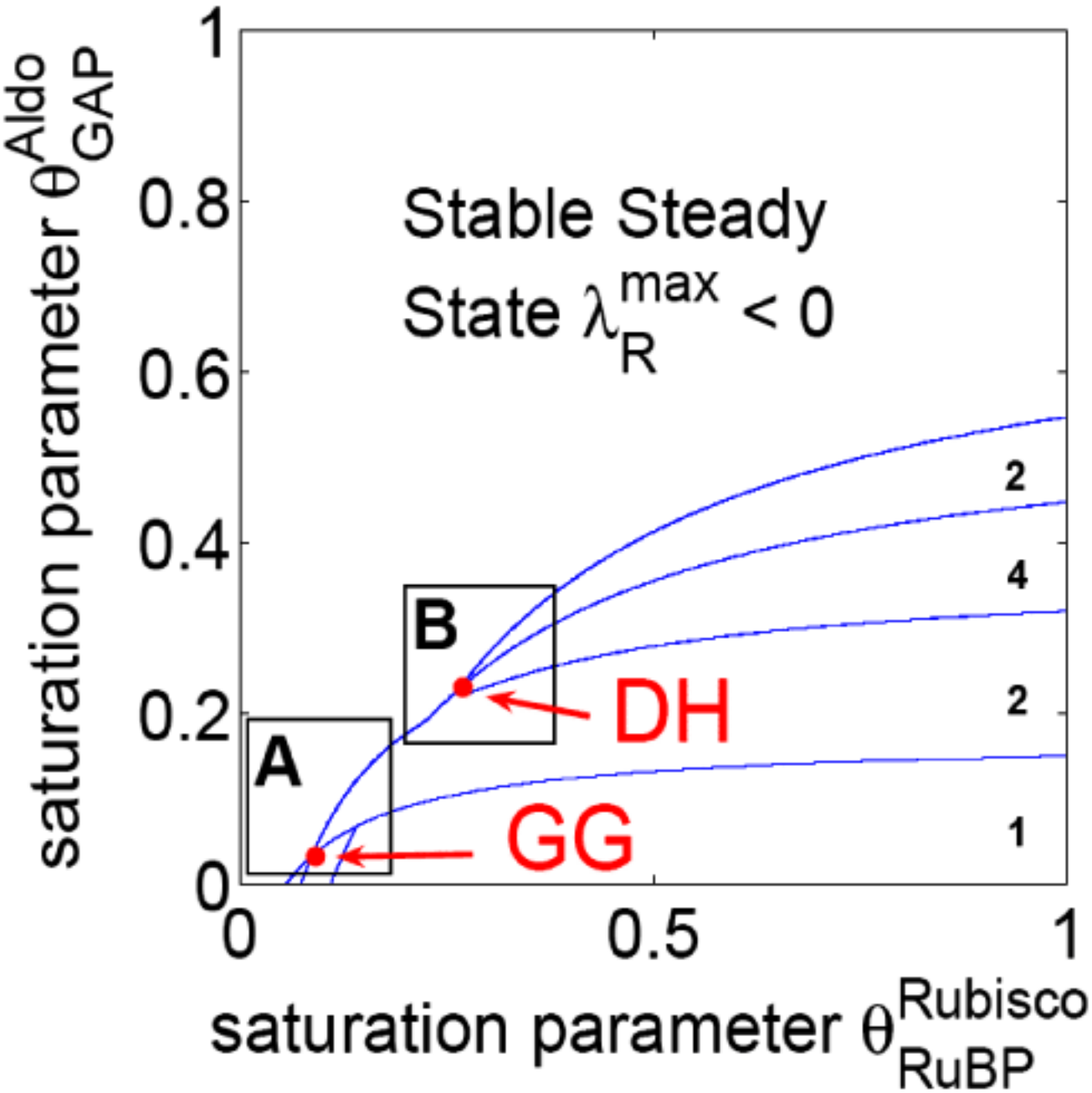
Steuer, Gross, Selbig & Blasius
PNAS 103 (2006)

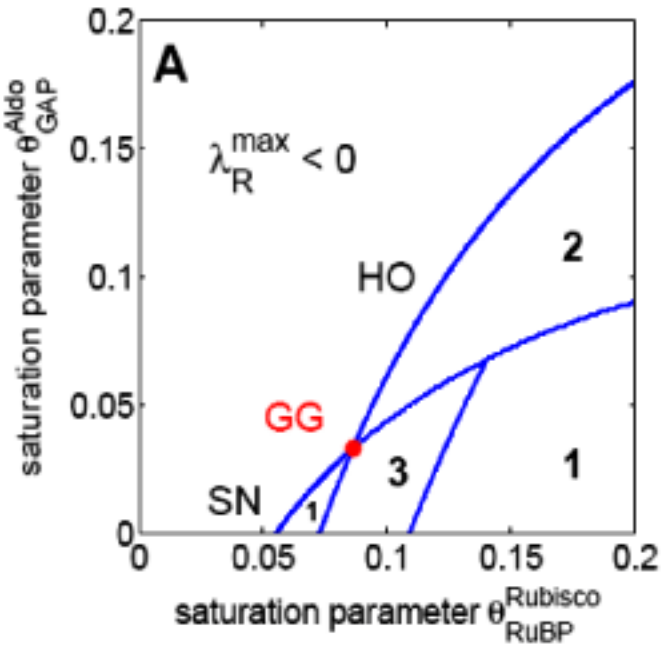


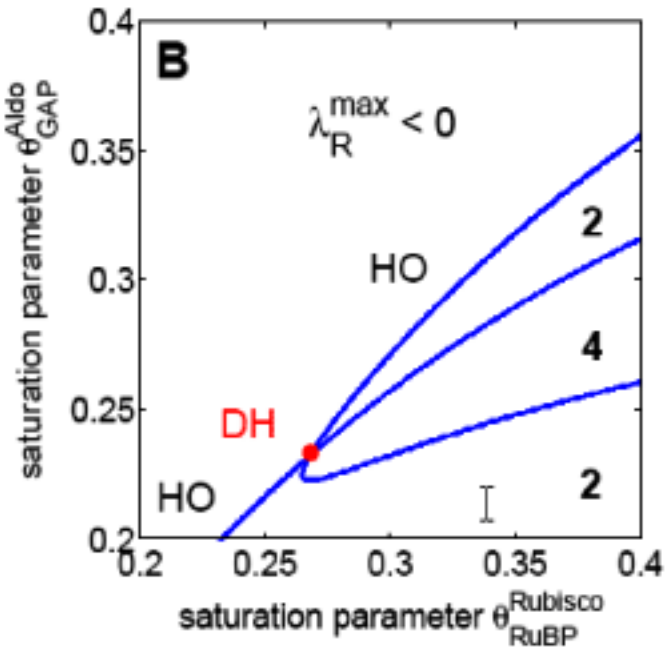
Calvin Cycle



Calvin Cycle







Summary

Some (non trivial) insights can be extracted from very general models:

Important parameters Local bifurcations

Certain features of global dynamics

Interesting parameter regions

GSK Modeling should be used for screening large classes of plausible models before detailed modeling is attempted.