Model selection in gene regulation and prediction of oscillations

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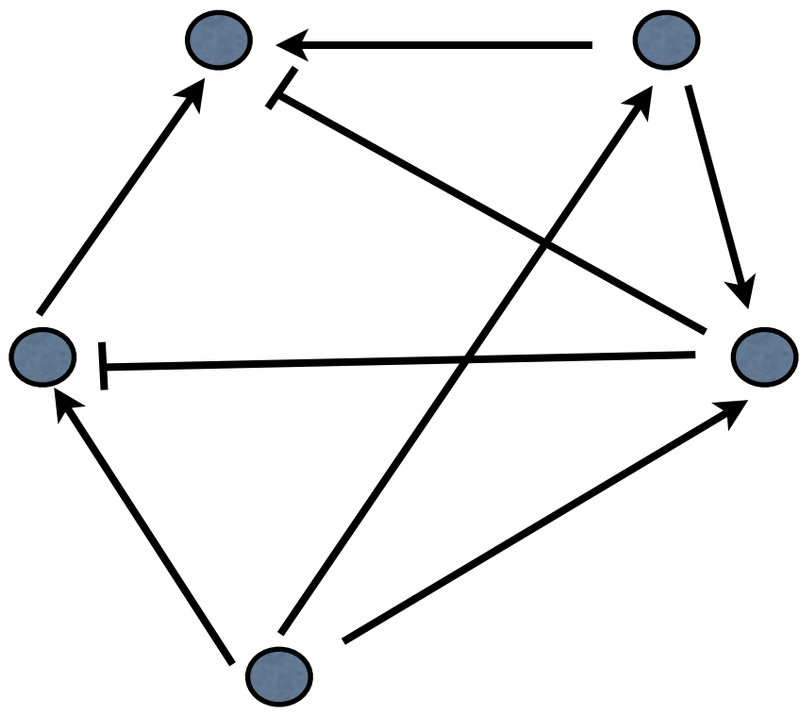
Main Question

- Neuroscience has a fundamental equation: Hodgkin-Huxley
- Cellular/gene processes modeling does not have such an equation.
- Selection of ad-hoc models, nonlinearities.
- Conclusions are often worded in general terms: adding positive feedback to a negative feedback circuit makes it more robust; negative feedback oscillator is less robust than slow-fast oscillator.
- Can we justify making model-independent conclusions based on analysis of particular models?

Robustness with respect to network structure perturbation

- Robustness in broader sense, not just parameters and non-linearities.
- A particular problem: Given a network, do we only model proteins, or include both proteins and mRNA?
- Adding delay?

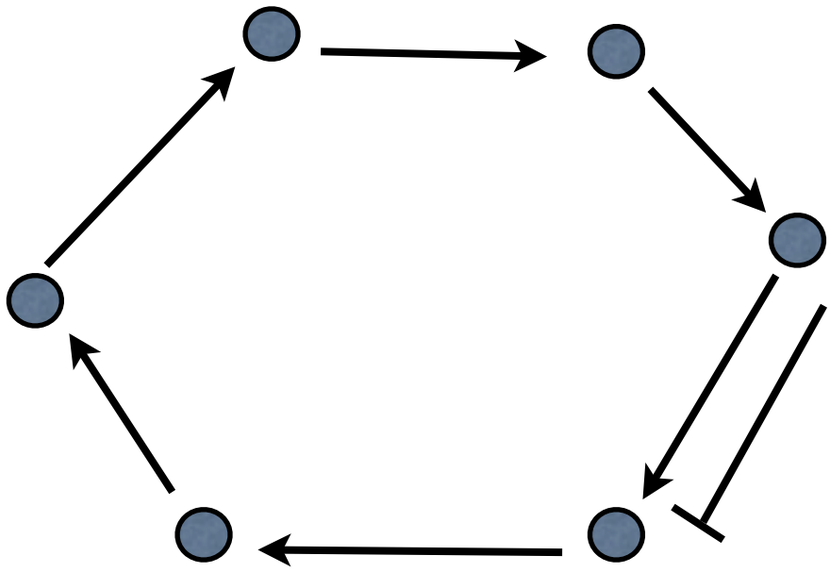


Test case: prediction of stability of equilibria

- Simple feedback loop
- General case
- Numerical simulation of the "Composite regulatory oscillator" of Yang et. al. 2009

Simple negative feedback loop

$$\begin{aligned} \dot{x}_1 &= -d_1 x_1 - a_1 f_1(x_n) \\ \dot{x}_i &= -d_i x_i + a_i f_i(x_{i-1}),\ i = 2, \ldots, n \end{aligned} \qquad \begin{aligned} \frac{df_i}{dx_{i-1}} &= 1 \text{ for all } i \\ d_i, a_i &> 0 \end{aligned}$$



Theorem. (Othmer, Arcak-Sontag)
Equilibrium 0 is stable, if

$$\frac{a_1 a_2 \ldots, a_n}{d_1 d_2 \ldots d_n} < \frac{1}{(\cos(\pi/n))^n}.$$

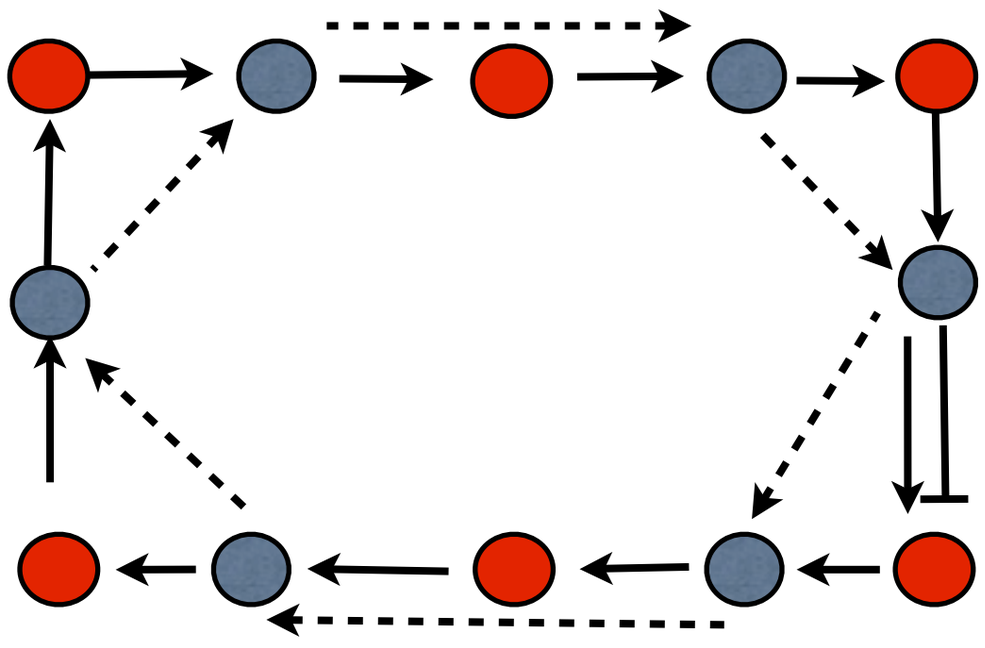
This condition is necessary, when

$$d_1 = d_2 = \ldots d_n$$

Simple feedback loop with mRNA

$$
\begin{aligned}
\dot{y}_1 &= -b_1 y_1 + \delta a_1 f_1(x_n) \\
\dot{x}_1 &= -d_1 x_1 + c_1 y_1 \\
\dot{y}_i &= -b_i y_i + a_i f_i(x_{i-1})\ i = 2, \ldots, n \\
\dot{x}_i &= -d_i x_i + c_i y_i,\ i = 2, \ldots, n.
\end{aligned}
$$

y=mRNA
x=protein



Theorem. (Othmer, Arcak-Sontag)
Equilibrium 0 is stable, if

$$\frac{c_1 \ldots c_n}{b_1 \ldots b_n} \frac{a_1 a_2 \ldots, a_n}{d_1 d_2 \ldots d_n} < \frac{1}{(\cos(\pi/2n))^{2n}}.$$

Relationship between big and small systems

If $\frac{c_1 \dots c_n}{b_1 \dots b_n} \geq 1$ then stability in the large system implies the stability in the small system.

"Longer loops are less stable"

Proof:

$$\frac{a_1 a_2 \dots a_n}{d_1 d_2 \dots d_n} \leq \frac{c_1 \dots c_n}{b_1 \dots b_n} \frac{a_1 a_2 \dots, a_n}{d_1 d_2 \dots d_n} < \frac{1}{(\cos(\pi/2n))^{2n}} < \frac{1}{(\cos(\pi/n))^n}$$

If production rate of proteins c_i too small the implication does not hold.

General case

Two linear systems:

Protein only $\dot{x} = Ax - Dx$ (Small)

protein and mRNA

$$\begin{aligned} \dot{x} &= Cy - Dx \\ \dot{y} &= Ax - By, \end{aligned}$$ (Large)

B, C, D are diagonal matrices

A is mRNA production and has all combinatorial control in it

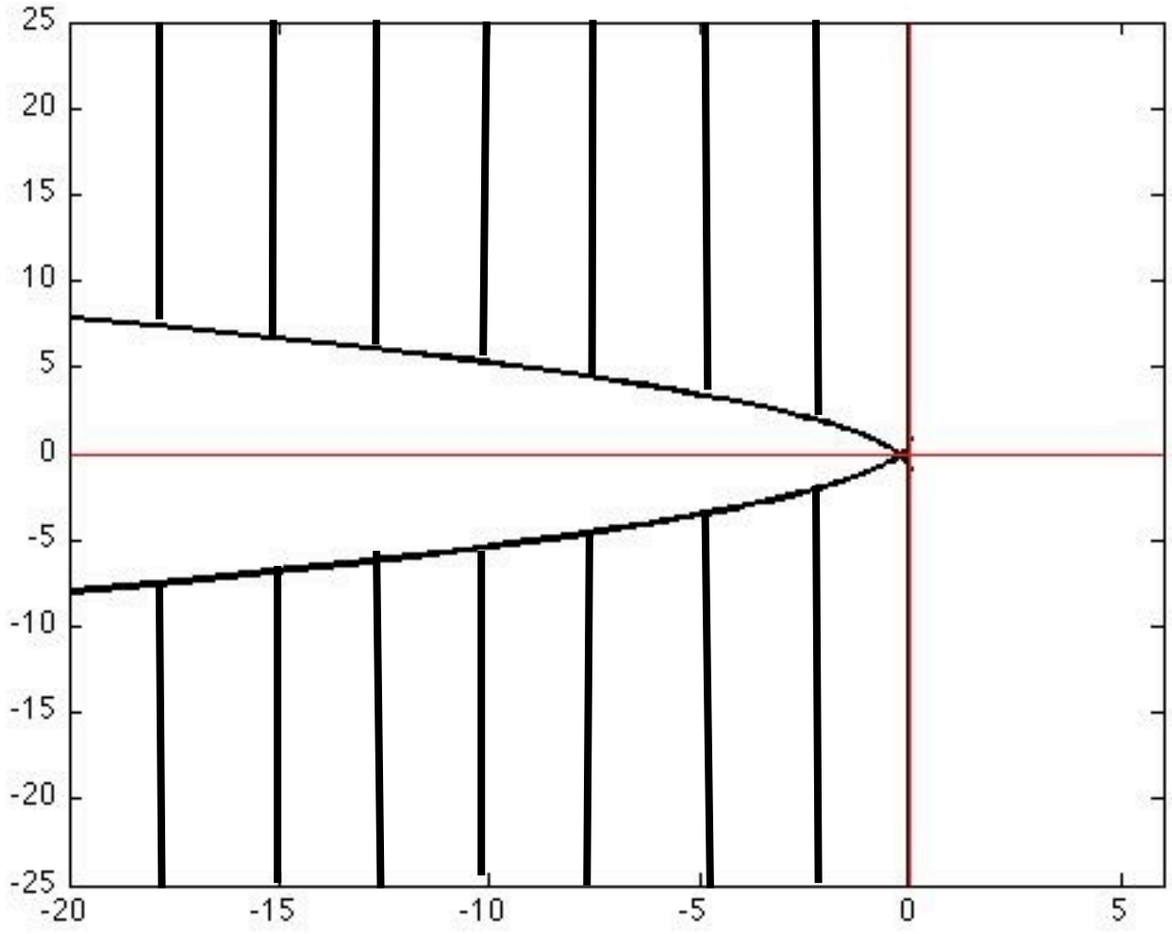
Is there a correspondence between eigenvalues of small and large system?

Small system is more stable

Simplify: Assume $B = bI, C = cI, D = dI,$ where I is the identity matrix

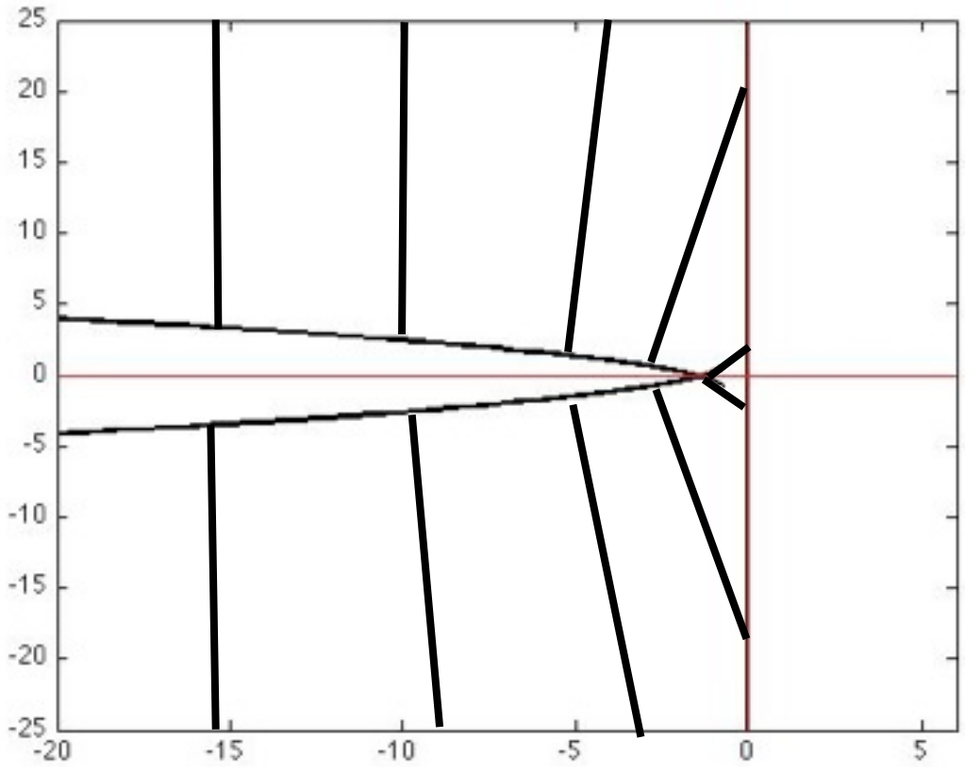
$$b = d = c = 1$$

Any eigenvalue for the small system in the black region will yield an unstable eigenvalue of the large region.

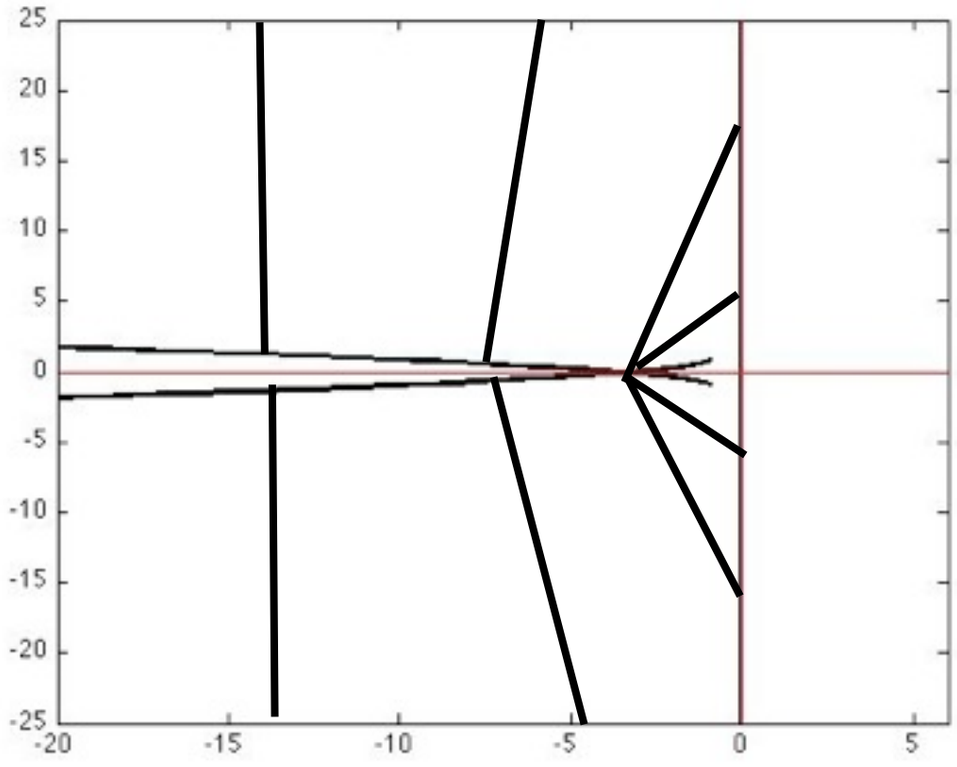


Larger translation rate yields more instability

$b = d = 1, c = 3$



$b = d = 1, c = 10$



Instability region meets real axis in $d(\frac{b}{c} - 1) < x < 0$ Nonempty when $\frac{c}{b} > 1$

Case study: Kuznetzov oscillator

I. Hysteresis based relaxation oscillators:
difficult to synchronize but support a pattern formation
perhaps more robust to noise
II. repressilator (cyclic feedback) oscillators:
easier to synchronize, no pattern formation.

Yang, Lee, Kuznetzov (2009):combine two types of oscillators in one model

$\epsilon = \text{ small}, \alpha_2 = O(1)$

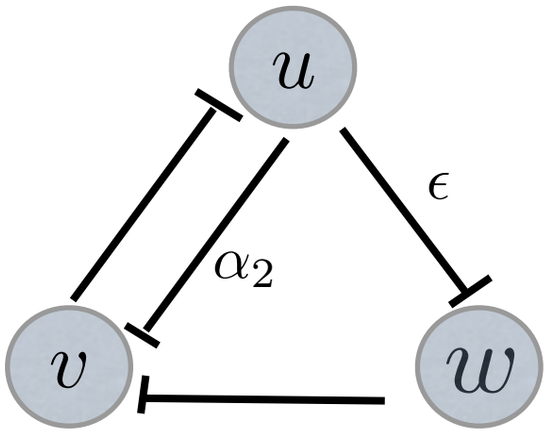
relaxation oscillator

$\epsilon = O(1), \alpha_2 = \text{ small}$

repressilator (cyclic feedback system)

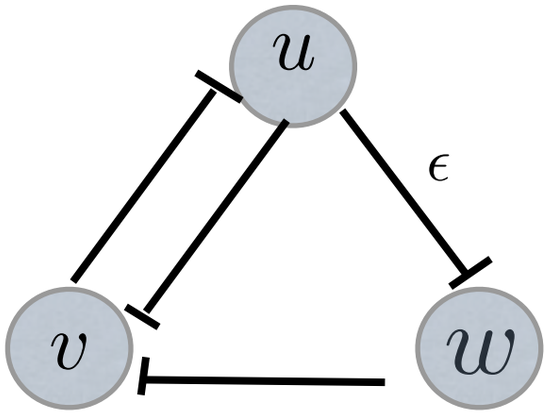
$$\begin{aligned} \dot{u} &= \frac{\alpha_1}{1+v^n} - u \\ \dot{v} &= \frac{\alpha_1}{1+w^n} + \frac{\alpha_2}{1+u^n} - v \\ \dot{w} &= \epsilon(\frac{\alpha_1}{1+u^n} - w) \end{aligned}$$

Two oscillators



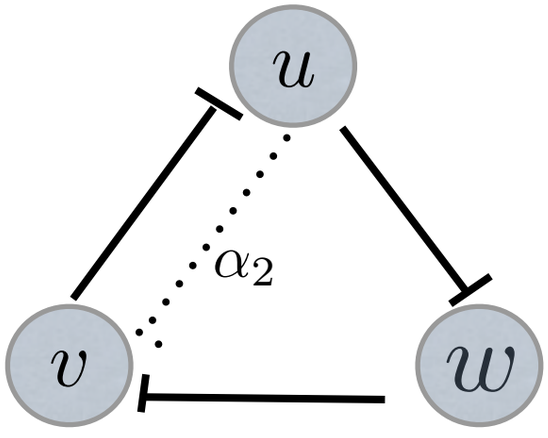
u,v proteins, w small signaling molecule

$$\begin{aligned} \dot{u} &= \frac{\alpha_1}{1+v^n} - u \\ \dot{v} &= \frac{\alpha_1}{1+w^n} + \frac{\alpha_2}{1+u^n} - v \\ \dot{w} &= \epsilon\left(\frac{\alpha_1}{1+u^n} - w\right) \end{aligned}$$



Relaxation: Bistability in u-v network and small ϵ

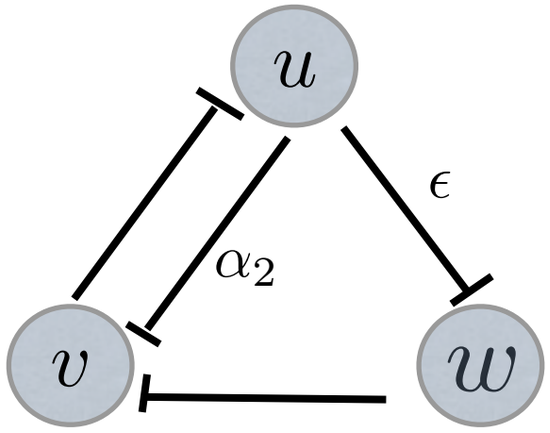
$$\epsilon = \text{ small}, \alpha_2 = O(1)$$



Repressilator: three negative feedbacks

$$\epsilon = O(1), \alpha_2 = \text{ small}$$

Observations



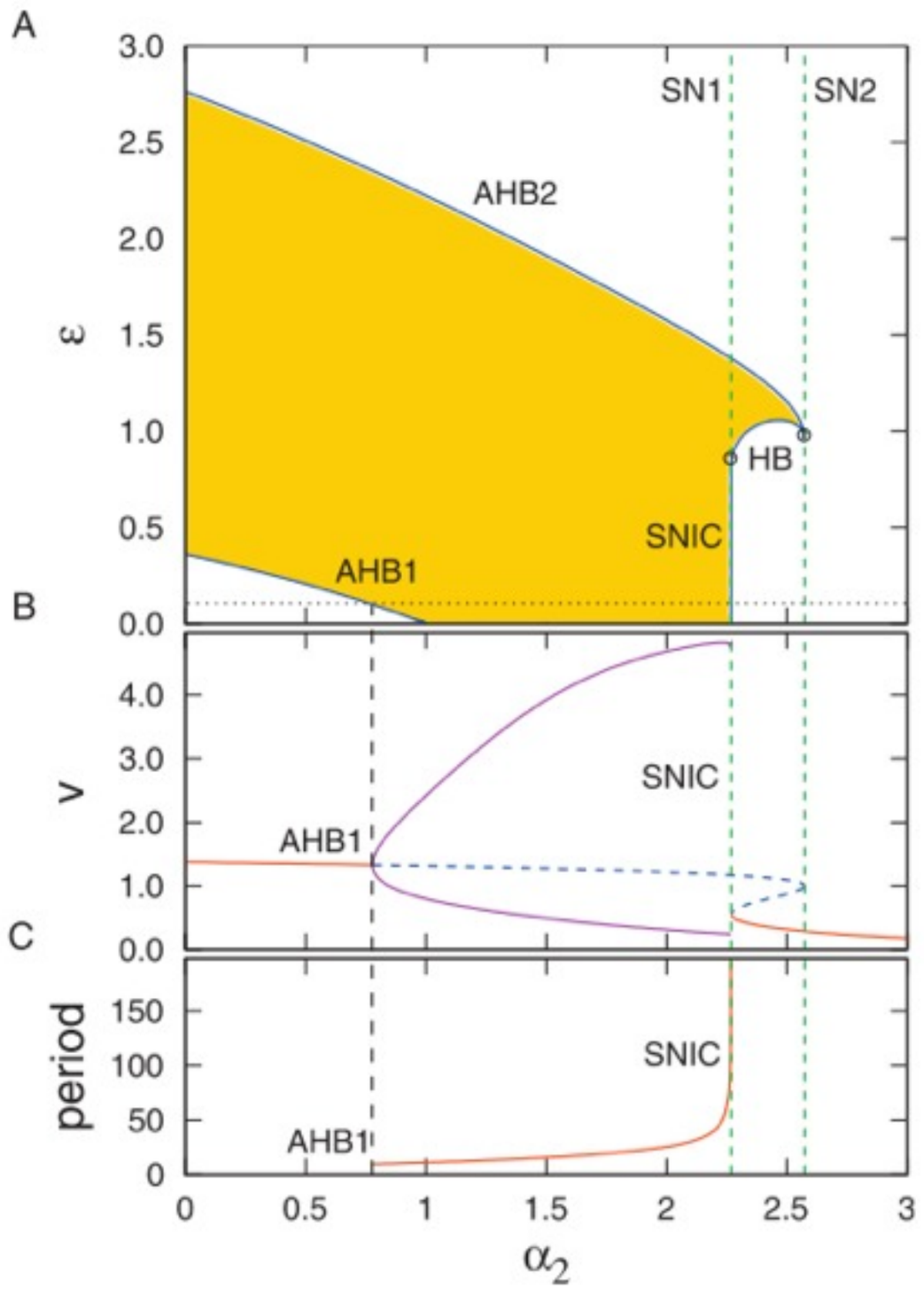
- No oscillations for small α_2, ϵ

- for small α_2 oscillations limited by Hopf bifurcations

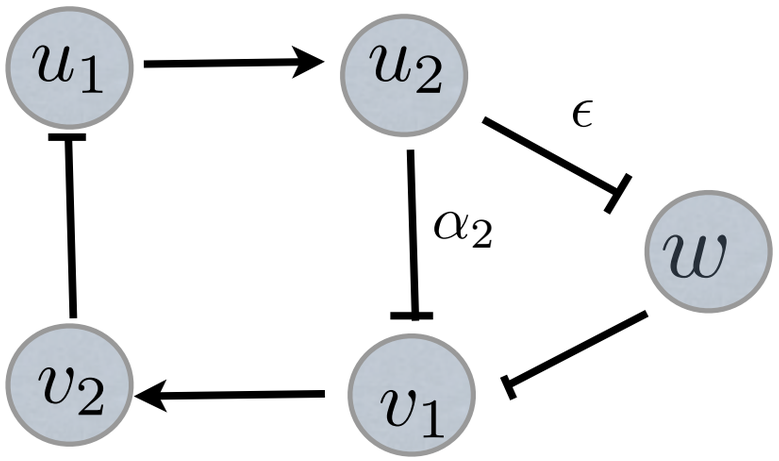
- for small ϵ oscillations limited by saddle-node on invariant circle.

- no oscillations for large ϵ

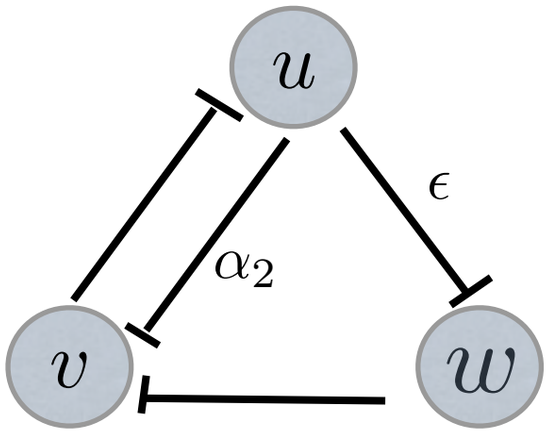
- Are these conclusions persistent, or model dependent?



Extended model with mRNA



$$
\begin{aligned}
\dot{u_1} &= \frac{\alpha_1}{1+v_2^n} - u_1 \\
\dot{u_2} &= u_1 - u_2 \\
\dot{v_1} &= \frac{\alpha_1}{1+w^n} + \frac{\alpha_2}{1+u_2^n} - v_1 \\
\dot{v_2} &= v_1 - v_2 \\
\dot{w} &= \epsilon(\frac{\alpha_1}{1+u_2^n} - w)
\end{aligned}
$$



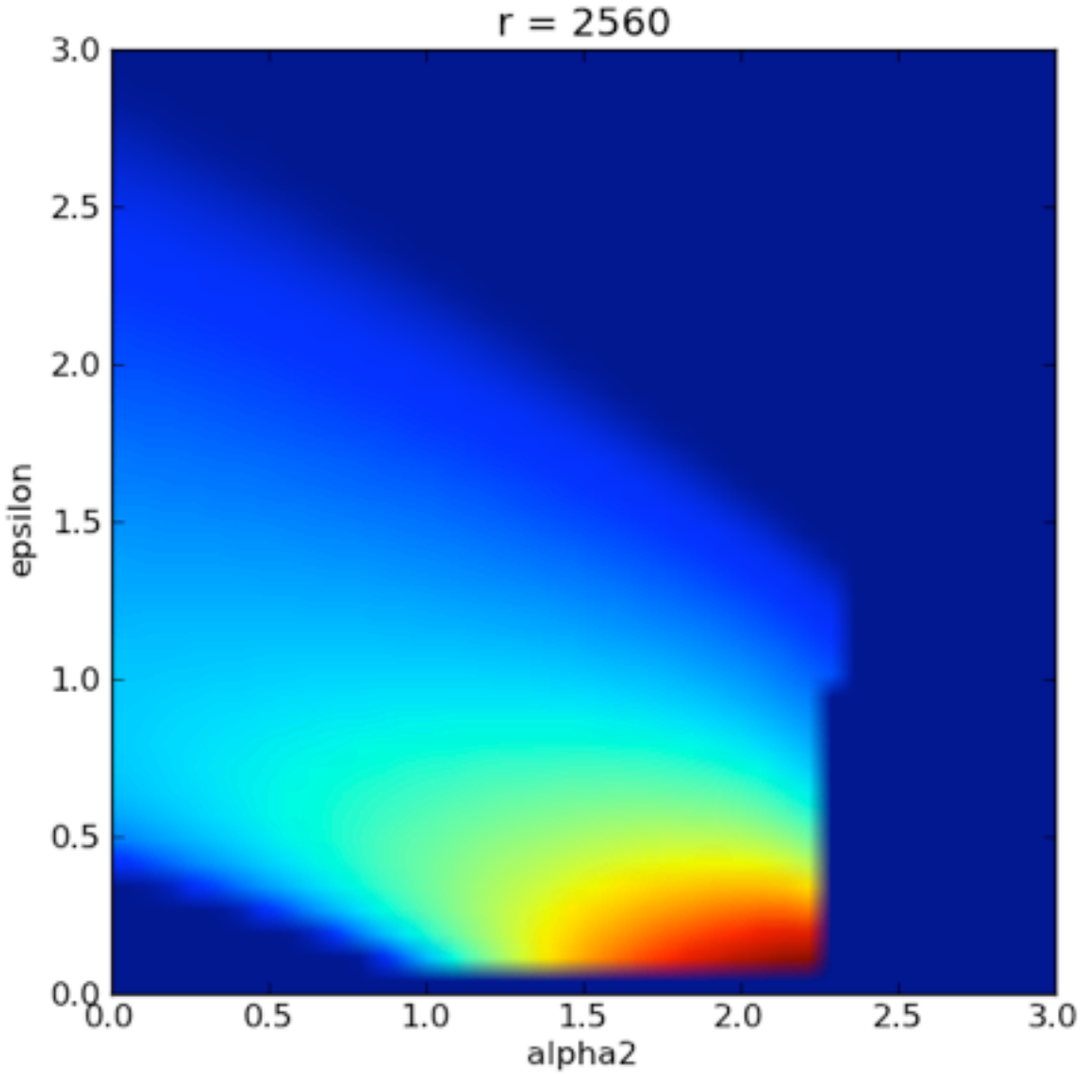
Protein only model

Same equilibria structure for both models.
Structure of periodic orbits?

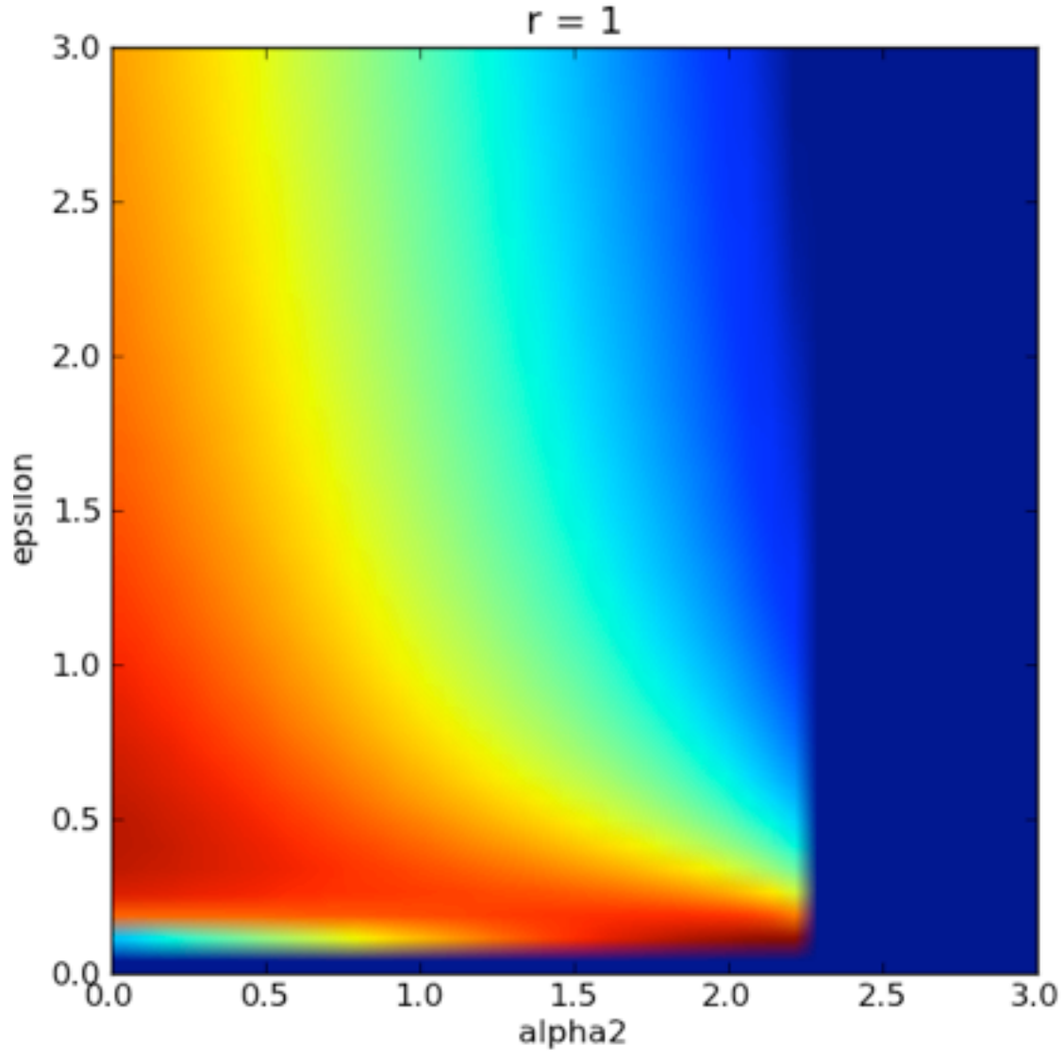
Numerical integration in parameter space

Heat map: amplitude of the periodic solution for two models

protein model

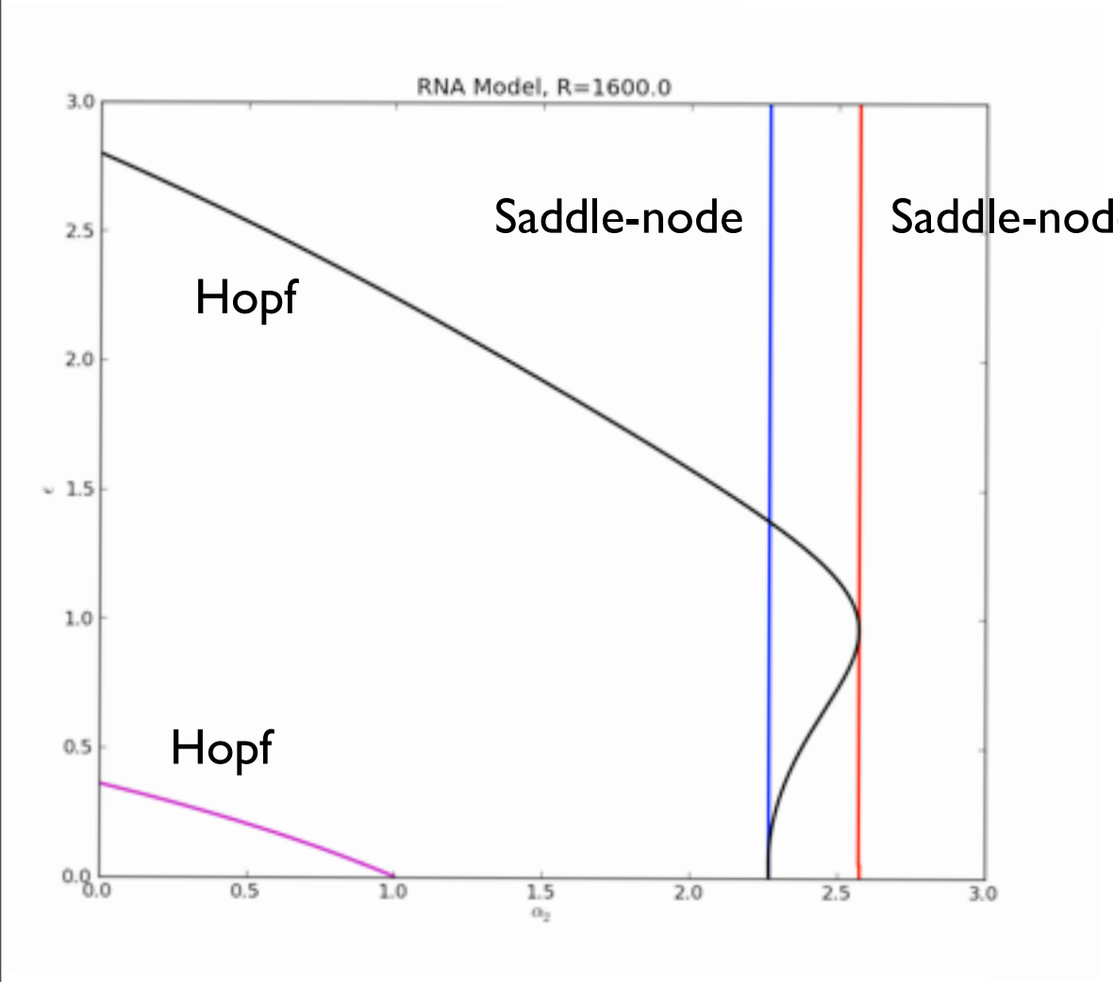


protein and mRNA model

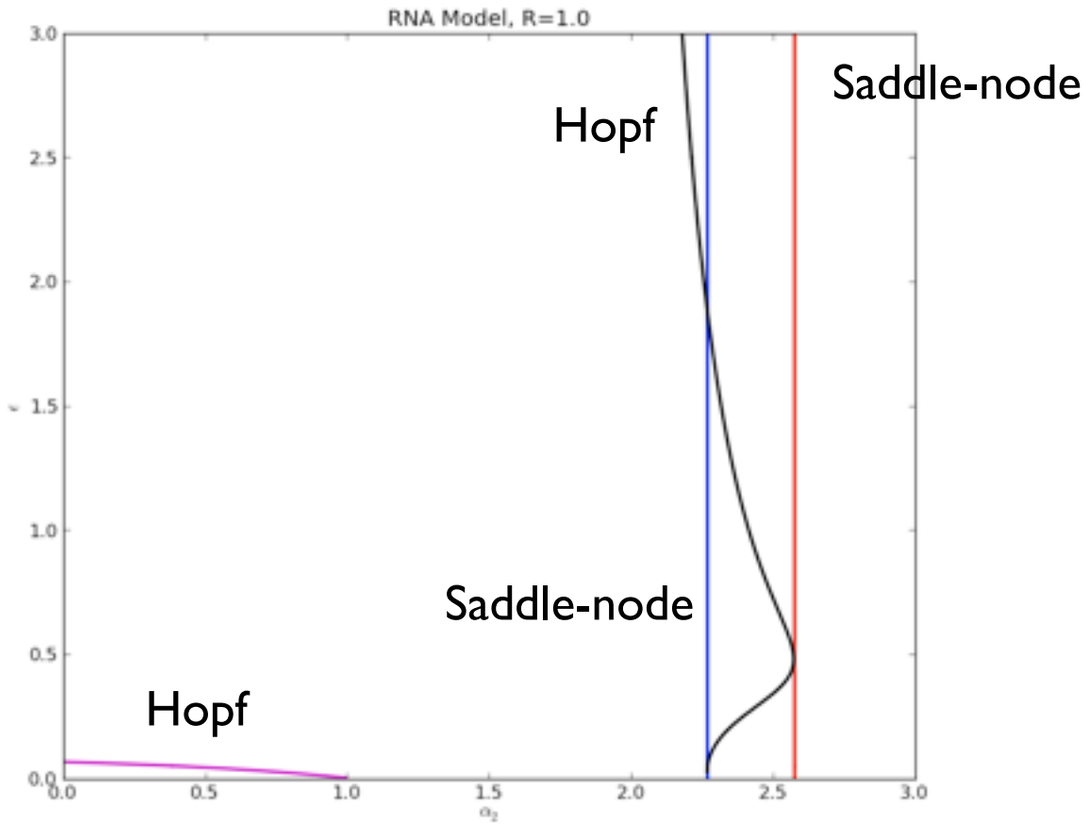


Bifurcation diagrams

Protein model



Protein and mRNA model



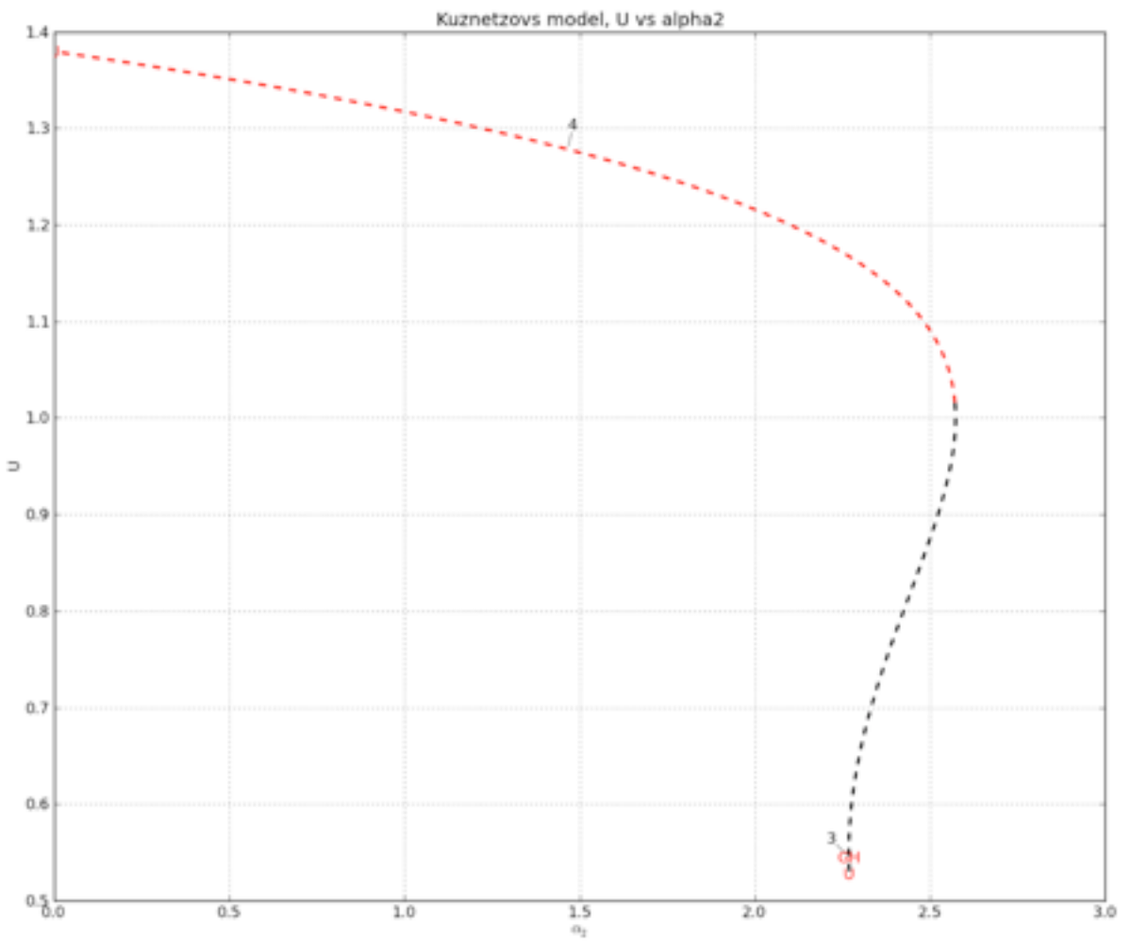
Qualitative or quantitative differences?

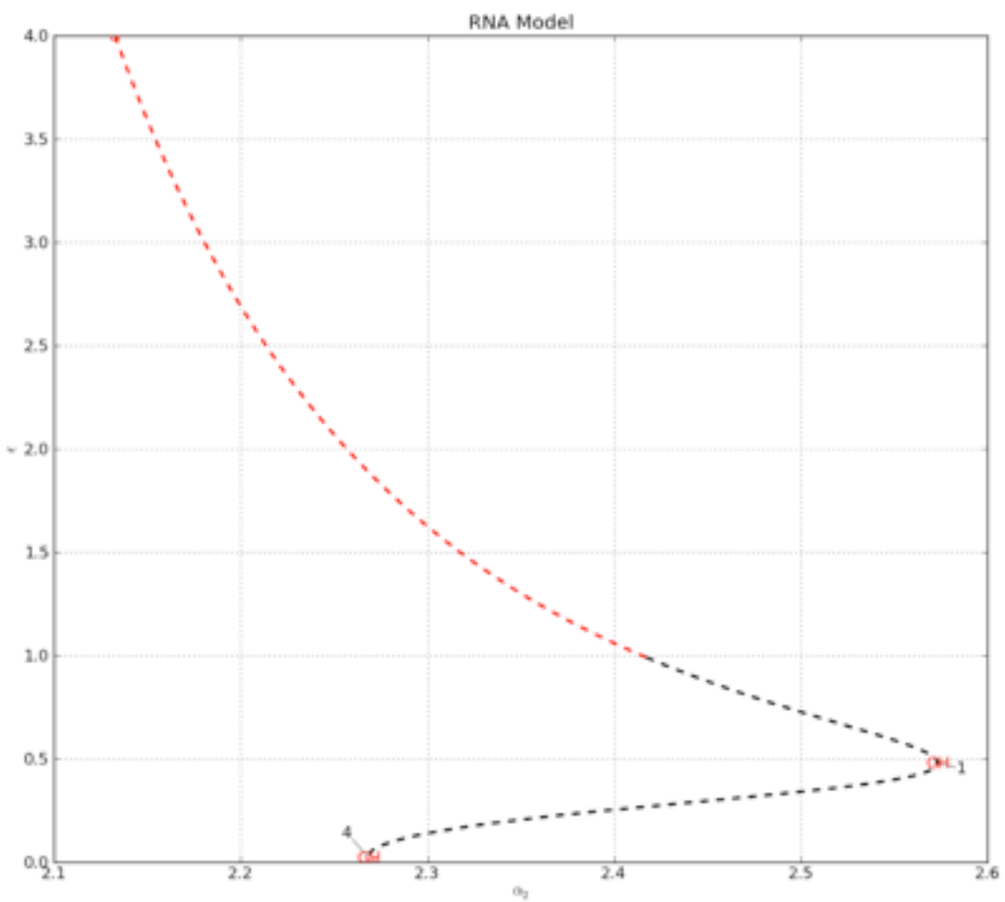
Qualitative difference!

Protein model

Protein and mRNA model

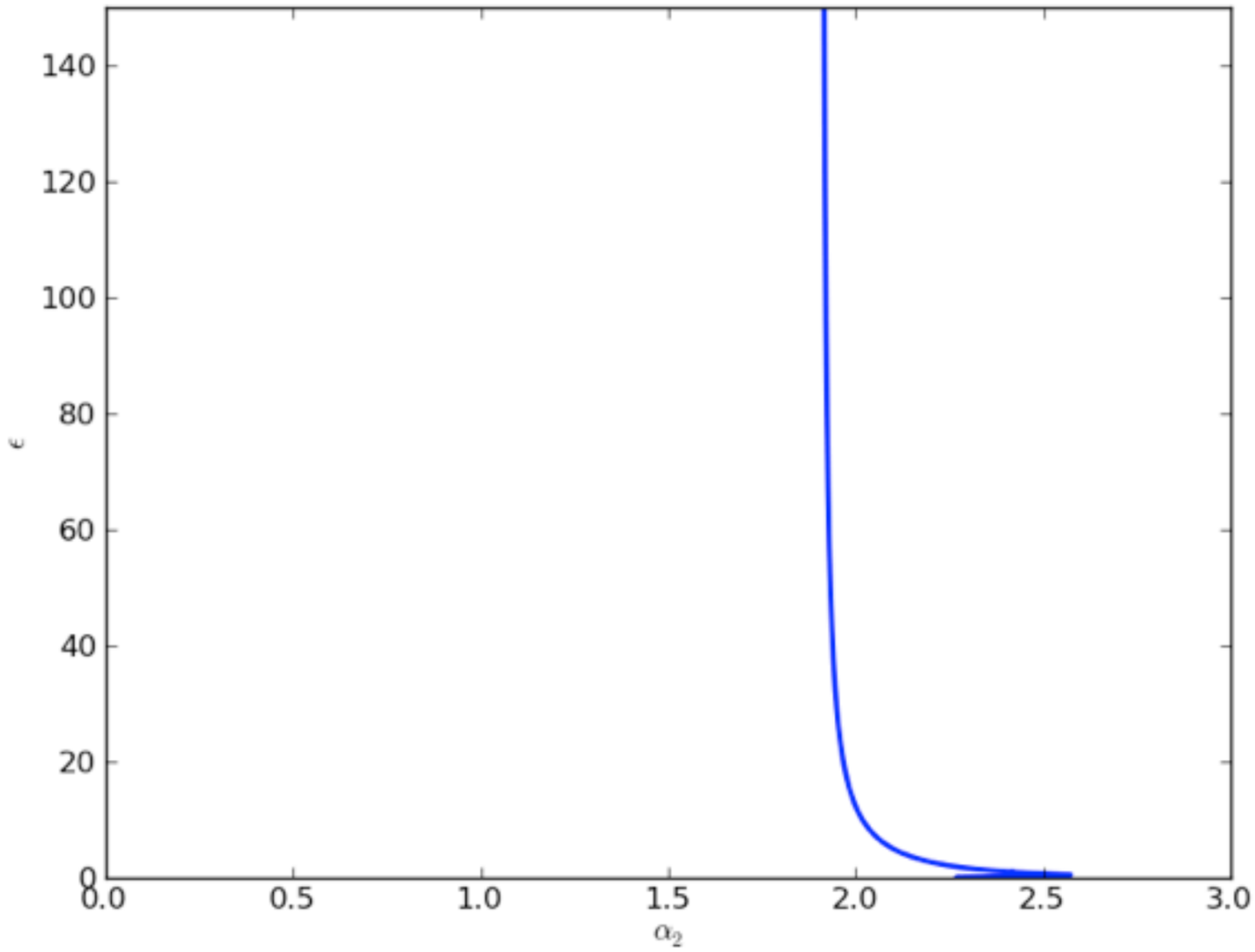
Top Hopf curve:





Oscillations for all ϵ at small α_2

Top Hopf curve
has a vertical asymptote



Bifurcation diagrams quantitatively and qualitatively different

- Significant differences for large epsilon
- Region of no oscillation for small ϵ, α_2 much smaller
- Boundaries of bifurcation region different - implication for length of the periodic orbit

- Broader question: How do we make conclusions from models that are model independent?

Conclusions

- How do we make responsibly model-independent conclusions from models?
- Is it even possible?
- Analyzed particular dilemma: do we use protein only, or protein and mRNA models for a given network.
- For cyclic feedback systems longer system less stable (assumption - sufficiently strong translation rates)
- General problem: adding mRNA can destabilize the system
- Particular problem repressilator & relaxation oscillator. Conclusions different for different models.

Thanks

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