Stoichiometric mechanisms for oscillations and multistability in reaction networks

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2½ preventive apologies

- MOST OF THE ARGUMENTS ARE IMPRECISE
- MOST OF THE ARGUMENTS ARE INCOMPLETE

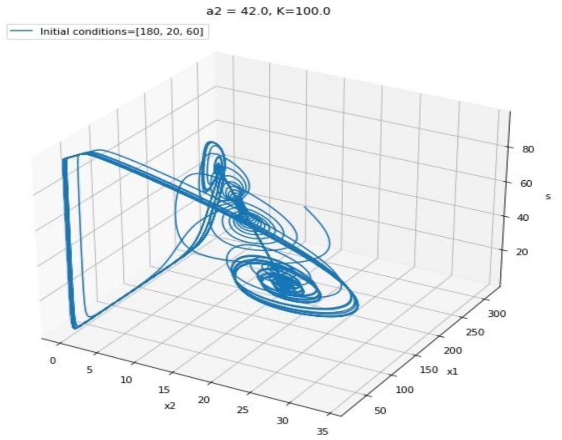
…the pictures are a bit random

Motivation:

FIND
UNIVERSAL STOICHIOMETRIC PATTERNS
FOR COMPLEX DYNAMICS

“UNIVERSAL” = VALID FOR ANY SIZE OF NETWORK

“COMPLEX DYNAMICS”= Multistability, Superlinear growth, Oscillations



MULTISTABILITY "=>" SUPERLINEAR GROWTH

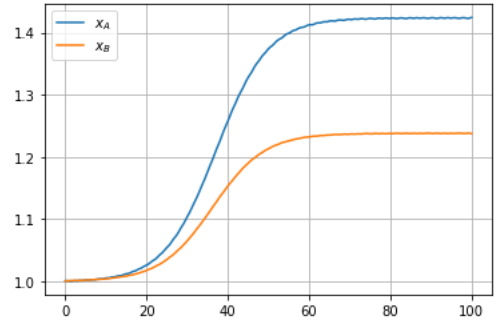
Ingredient: unstable manifold thoerem

Multistability =>

unstable steady state connected to stable steady state =>

Superlinear divergence from unstable steady state

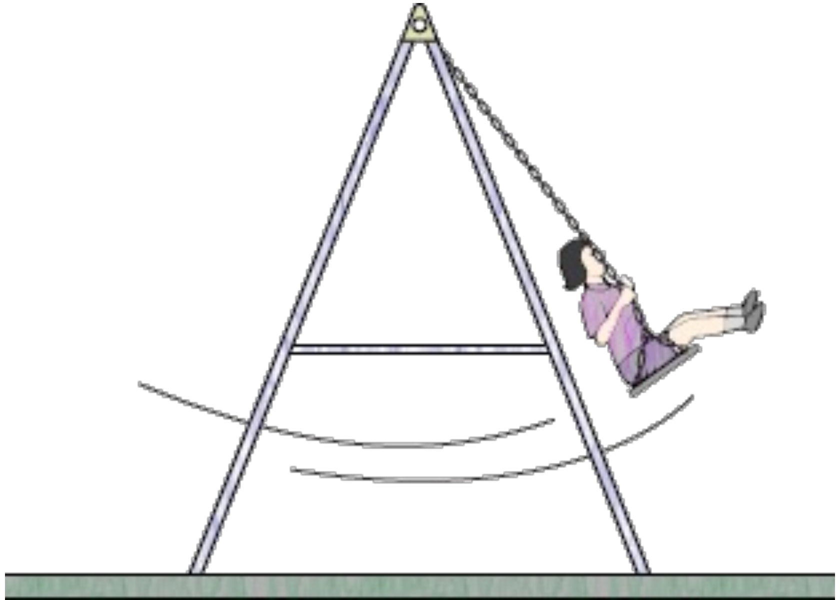
with sublinear convergence to the stable steady state =>

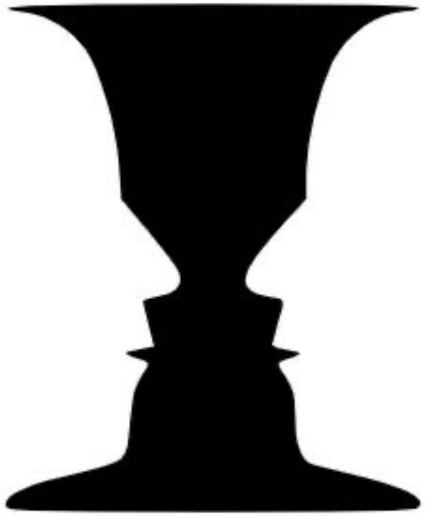


Two mechanisms

RECEIPT 1: Oscillations and Multistability

RECEIPT 2: Oscillations





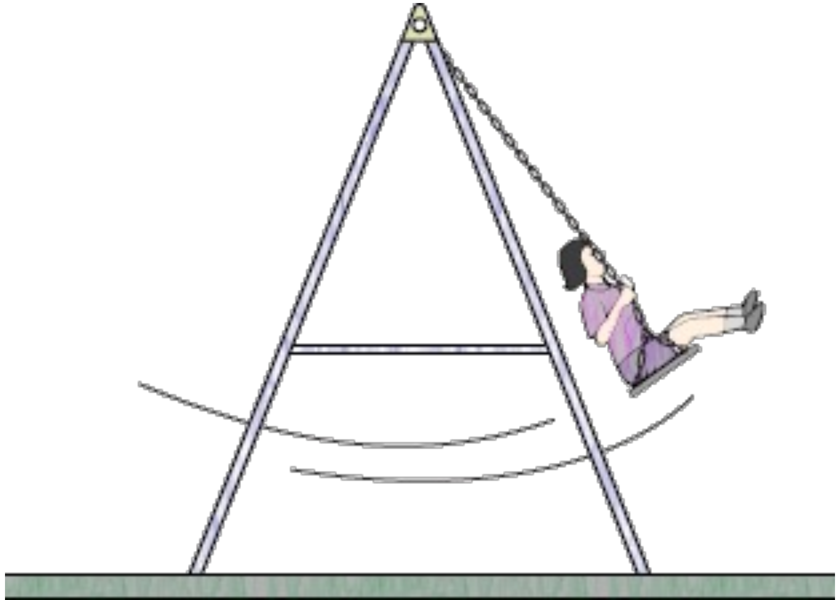
References (2023):

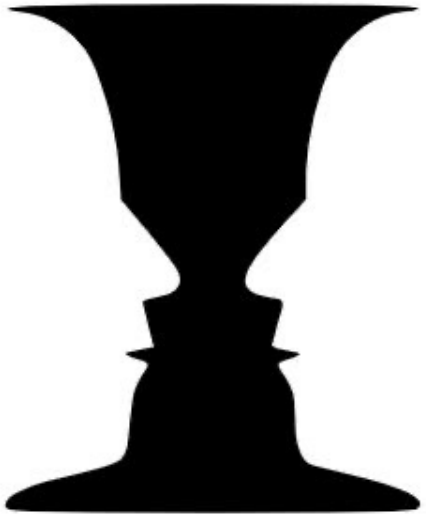
1. Symbolic Hunt …
2. [With Peter] Unstable Cores …

WARNING!
Multistability vs Multistationarity
Stable oscillations?

RECEIPT 1: Oscillations and Multistability

RECEIPT 2: Oscillations





References (2023):

1. Symbolic Hunt …
2. [With Peter] Unstable Cores …

RECEIPT 1 for Oscillations and Multistability

START WITH A SQUARE STOICHIOMETRIC SUBMATRIX
WITH NEGATIVE DIAGONAL AND DETERMINANT OF UNSTABLE SIGN

$$\begin{pmatrix} -1 & 0 & 1 \\ 1 & -1 & 0 \\ 1 & 1 & -1 \end{pmatrix}$$

"Determinant of unstable sign"=odd number of eigenvalues with positive real part

(unstable core)(unstable positive feedback)(autocatalytic core)

Eigenvalues: -1.66+0.56i, -1.66+0.56i, 0.32

Dichotomy

Is such unstable `positive-feedback' a principal submatrix
of a Hurwitz-stable stoichiometric submatrix
with negative diagonal?

Yes. OSCILLATIONS

No. MULTISTATIONARITY

Dichotomy. Yes. OSCILLATIONS

$$\begin{pmatrix} -1 & 0 & 1 & 0 \\ 1 & -1 & 0 & 2 \\ 1 & 1 & -1 & 0 \\ 0 & 0 & -1 & -1 \end{pmatrix}$$

Eigenvalues: -0.34+0.56i, -0.34-0.56i, -1, -2.32

Dichotomy. No. Multistationarity.

$$\begin{pmatrix} -1 & 0 & 1 & 0 & 0 & \dots & 0 \\ 1 & -1 & 0 & 0 & 0 & \dots & 0 \\ 1 & 1 & -1 & 0 & 0 & \dots & 0 \\ 0 & 0 & 0 & -1 & 0 & \dots & 0 \\ 0 & 0 & 0 & 0 & -1 & \dots & 0 \\ 0 & 0 & 0 & 0 & 0 & \dots & -1 \end{pmatrix}$$

Dichotomy. No. Multistationarity.

"Papers" generalization:

Maximal unstable
positive feedback
 +
stable steady-state
<=>
 multistationarity

Contents lists available at SciVerse ScienceDirect

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Concordant chemical reaction networks

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Some Results on Injectivity and Multistationarity in Chemical Reaction Networks

Authors: Murad Banaji and Casian Pantea | AUTHORS INFO & AFFILIATIONS

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Vol. 22, No. 3, pp. 1639–1672

Structural Conditions for Saddle-Node Bifurcations in Chemical Reaction Networks*

Nicola Vassena†

Example for receipt 1.

$$A \underset{1}{\rightarrow} B + C$$

$$B \underset{2}{\rightarrow} C$$

$$C + D \underset{3}{\rightarrow} A$$

$$C \underset{4}{\rightarrow} E$$

$$D \underset{5}{\rightarrow} 2B$$

$$D + E \underset{6}{\rightarrow} 2E$$

$$E \underset{7}{\rightarrow}$$

$$\underset{F_D}{\rightarrow} D$$

CONTAINS:

A -> B + C
B -> C
C+… -> A

Stoichiometrically our

$$\begin{pmatrix} -1 & 0 & 1 \\ 1 & -1 & 0 \\ 1 & 1 & -1 \end{pmatrix}$$

REFERENCE: “Symbolic Hunt…”
non autocatalytic version in “Unstable cores…” (with Peter)

Example for receipt 1: Oscillations

$$A \underset{1}{\rightarrow} B + C$$

$$B \underset{2}{\rightarrow} C$$

$$C + D \underset{3}{\rightarrow} A$$

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$$E \underset{7}{\rightarrow}$$

$$\underset{F_D}{\rightarrow} D$$

CONTAINS:

A -> B + C
B -> C
C+ D -> A
D -> 2B

Stoichiometrically our

$$\begin{pmatrix} -1 & 0 & 1 & 0 \\ 1 & -1 & 0 & 2 \\ 1 & 1 & -1 & 0 \\ 0 & 0 & -1 & -1 \end{pmatrix}$$

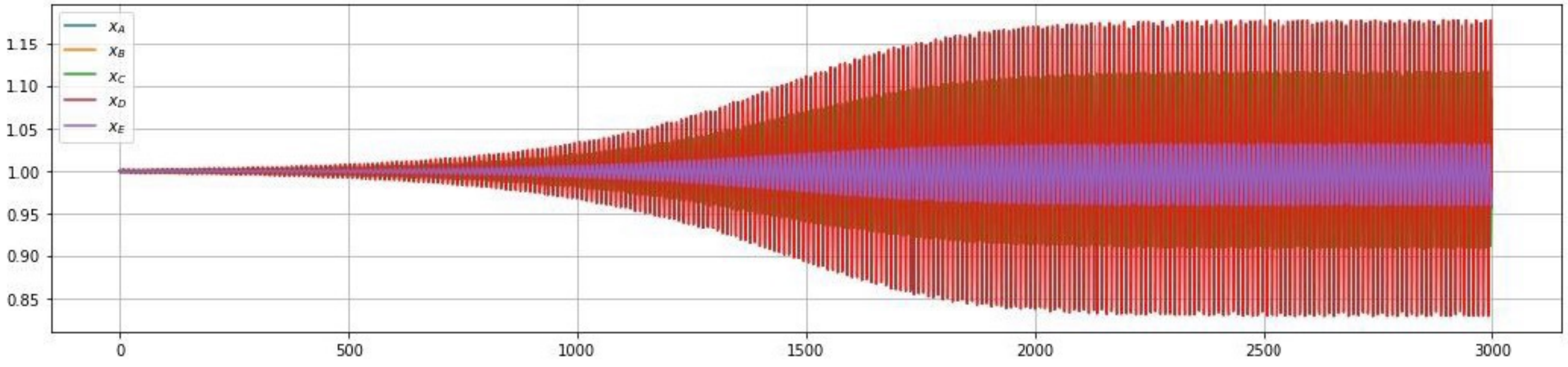
Example for receipt 1: Oscillations

$$A \xrightarrow[1]{} B + C$$
$$B \xrightarrow[2]{} C$$
$$C + D \xrightarrow[3]{} A$$
$$C \xrightarrow[4]{} E$$
$$D \xrightarrow[5]{} 2B$$
$$D + E \xrightarrow[6]{} 2E$$
$$E \xrightarrow[7]{}$$
$$\xrightarrow[F_D]{} D$$

$$\begin{cases} \dot{x}_A = -r_1(x_A) + r_3(x_C, x_D) \\ \dot{x}_B = r_1(x_A) - r_2(x_B) + 2r_5(x_D) \\ \dot{x}_C = r_1(x_A) + r_2(x_B) - r_3(x_C, x_D) - r_4(x_C) \\ \dot{x}_D = -r_3(x_C, x_D) - r_5(x_D) - r_6(x_D, x_E) + F_D \\ \dot{x}_E = r_4(x_C) + r_6(x_D, x_E) - r_7(x_E) \end{cases}$$

$$\begin{pmatrix} r_1(x_A) \\ r_2(x_B) \\ r_3(x_C, x_D) \\ r_4(x_C) \\ r_5(x_D) \\ r_6(x_D, x_E) \\ r_7(x_E) \\ F_D \end{pmatrix} = \begin{pmatrix} 2x_A \\ 8\frac{x_B}{1+x_B} \\ 8\frac{x_C x_D}{1+3x_D} \\ 64\frac{x_C}{1+15x_C} \\ 2\frac{x_D}{1+x_D} \\ 512\frac{x_D}{1+63x_D}\frac{x_E}{1+3x_E} \\ 72\frac{x_E}{1+11x_E} \\ 5 \end{pmatrix}$$

MICHAELIS-MENTEN KINETICS



Example for receipt 1: Oscillations

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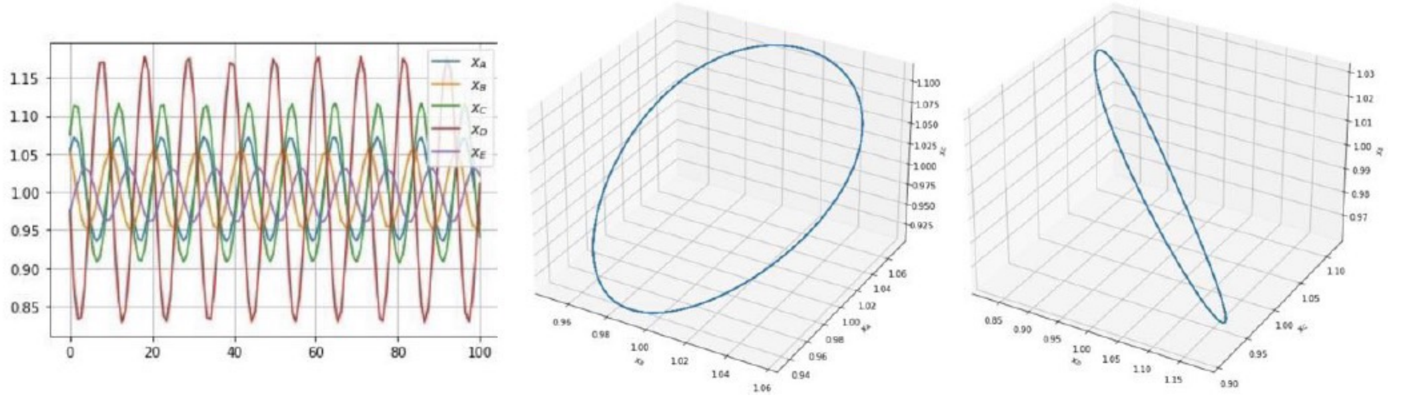
MICHAELIS-MENTEN KINETICS



Example for receipt 1: Multistationarity

$$A \underset{1}{\rightarrow} B + C$$

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$$E \underset{7}{\rightarrow}$$

$$\underset{F_D}{\rightarrow} D$$

CONTAINS:

A -> B + C
B -> C
C+ D -> A
D -> 2B
E+2D -> 2E
Stoichiometrically
maximal unstable positive feedback.

$$\det \begin{pmatrix} -1 & 0 & 1 & 0 & 0 \\ 1 & -1 & 0 & 2 & 0 \\ 1 & 1 & -1 & 0 & 0 \\ 0 & 0 & -1 & -1 & -1 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix} = 1$$

Example for receipt 1: Multistationarity

$$A \underset{1}{\rightarrow} B + C$$

$$B \underset{2}{\rightarrow} C$$

$$C + D \underset{3}{\rightarrow} A$$

$$C \underset{4}{\rightarrow} E$$

$$D \underset{5}{\rightarrow} 2B$$

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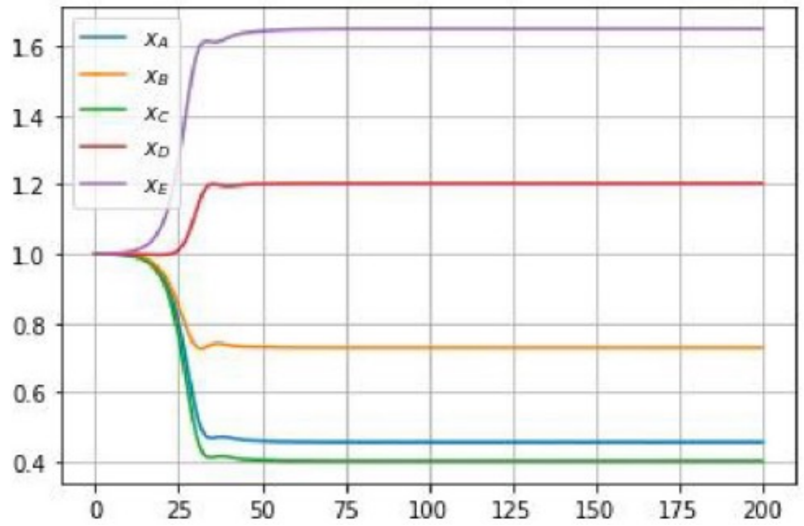
$$\begin{pmatrix} r_1(x_A) \\ r_2(x_B) \\ r_3(x_C, x_D) \\ r_4(x_C) \\ r_5(x_D) \\ r_6(x_D, x_E) \\ r_7(x_E) \\ F_D \end{pmatrix} = \begin{pmatrix} 4\frac{x_A}{1+x_A} \\ 16\frac{x_B}{1+3x_B} \\ 8\frac{x_C}{1+x_C}\frac{x_D}{1+x_D} \\ 64\frac{x_C}{1+15x_C} \\ x_D \\ 32\frac{x_D}{1+7x_D}\frac{x_E}{1+x_E} \\ 72\frac{x_E}{1+11x_E} \\ 5 \end{pmatrix}$$

MICHAELIS-MENTEN KINETICS

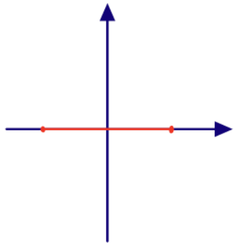
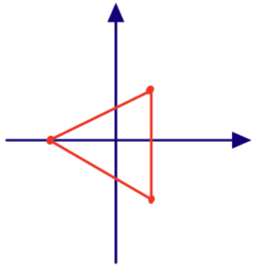
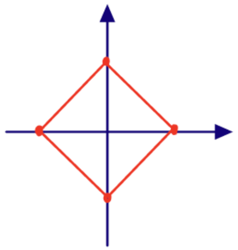
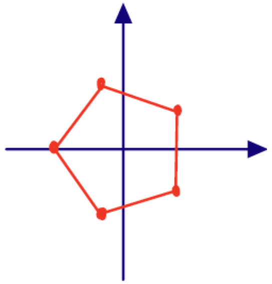


RECEIPT 2 for Oscillations

RECEIPT 2 for Oscillations

Negative-feedback cycles:

$$\begin{pmatrix} 0 & -1 \\ -1 & 0 \end{pmatrix} \begin{pmatrix} 0 & 0 & -1 \\ -1 & 0 & 0 \\ 0 & -1 & 0 \end{pmatrix} \begin{pmatrix} 0 & 0 & 0 & -1 \\ -1 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 \\ 0 & 0 & -1 & 0 \end{pmatrix} \begin{pmatrix} 0 & 0 & 0 & 0 & -1 \\ -1 & 0 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 \end{pmatrix}$$

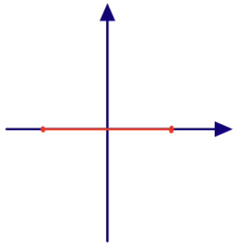
Look for even number of eigenvalues with positive real part (odd length!)

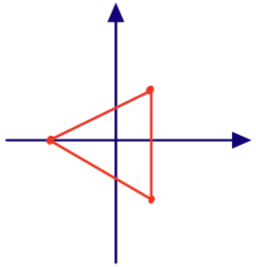
Possible network with such cycles (perhaps with degradations) oscillate

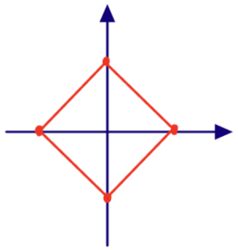
RECEIPT 2 for Oscillations

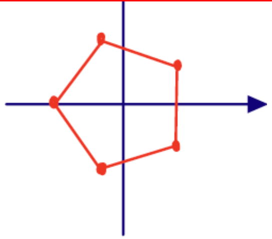
Negative-feedback cycles:

$$\begin{pmatrix} 0 & -1 \\ -1 & 0 \end{pmatrix} \begin{pmatrix} 0 & 0 & -1 \\ -1 & 0 & 0 \\ 0 & -1 & 0 \end{pmatrix} \begin{pmatrix} 0 & 0 & 0 & -1 \\ -1 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 \\ 0 & 0 & -1 & 0 \end{pmatrix} \begin{pmatrix} 0 & 0 & 0 & 0 & -1 \\ -1 & 0 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 \end{pmatrix}$$









Look for even number of eigenvalues with positive real part (odd length!)

Possible network with such cycles (perhaps with degradations) oscillate

Example for receipt 2: Oscillations

$$2A + B \underset{1}{\rightarrow} 2A + F$$

$$2B + C \underset{2}{\rightarrow} 2B + F$$

$$2C + D \underset{3}{\rightarrow} 2C + F$$

$$2D + E \underset{4}{\rightarrow} 2D + F$$

$$2E + A \underset{5}{\rightarrow} 2E + F$$

$$F \underset{6}{\rightarrow}$$

Example for receipt 2: Oscillations

$$2A + B \underset{1}{\rightarrow} 2A + F \qquad \underset{F_A}{\rightarrow} A$$

$$2B + C \underset{2}{\rightarrow} 2B + F \qquad \underset{F_B}{\rightarrow} B$$

$$2C + D \underset{3}{\rightarrow} 2C + F \qquad \underset{F_C}{\rightarrow} C$$

$$2D + E \underset{4}{\rightarrow} 2D + F \qquad \underset{F_D}{\rightarrow} D$$

$$2E + A \underset{5}{\rightarrow} 2E + F \qquad \underset{F_E}{\rightarrow} E$$

$$F \underset{6}{\rightarrow}$$

Example for receipt 2: Oscillations

$$2A + B \underset{1}{\rightarrow} 2A + F \qquad \underset{F_A}{\rightarrow} A$$

$$2B + C \underset{2}{\rightarrow} 2B + F \qquad \underset{F_B}{\rightarrow} B$$

$$2C + D \underset{3}{\rightarrow} 2C + F \qquad \underset{F_C}{\rightarrow} C$$

$$2D + E \underset{4}{\rightarrow} 2D + F \qquad \underset{F_D}{\rightarrow} D$$

$$2E + A \underset{5}{\rightarrow} 2E + F \qquad \underset{F_E}{\rightarrow} E$$

$$F \underset{6}{\rightarrow}$$

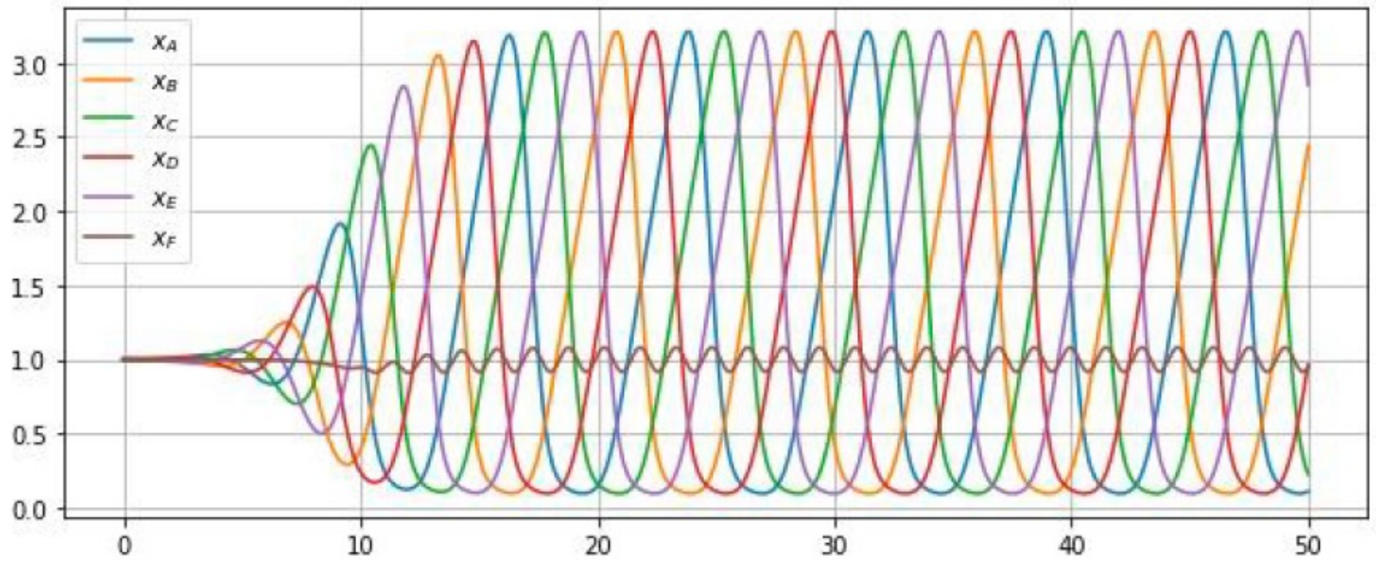
It contains negative feedback cycle:

$$\begin{pmatrix} 0 & 0 & 0 & 0 & -1 \\ -1 & 0 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 \end{pmatrix}$$

REFERENCE: "Unstable cores…" (with Peter)

Example for receipt 2: Oscillations

Mass Action System:

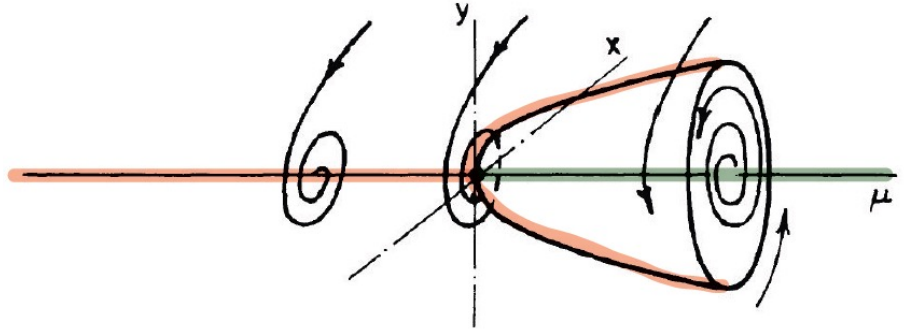


$$\begin{cases} \dot{x}_A = F_A - k_5 x_A x_E^2, \\ \dot{x}_B = F_B - k_1 x_A^2 x_B, \\ \dot{x}_C = F_C - k_2 x_B^2 x_C, \\ \dot{x}_D = F_D - k_3 x_C^2 x_D, \\ \dot{x}_E = F_E - k_4 x_D^2 x_E, \\ \dot{x}_F = k_5 x_A x_E^2 + k_1 x_A^2 x_B + k_2 x_B^2 x_C + k_3 x_C^2 x_D + k_4 x_D^2 x_E - k_6 x_F \end{cases}$$

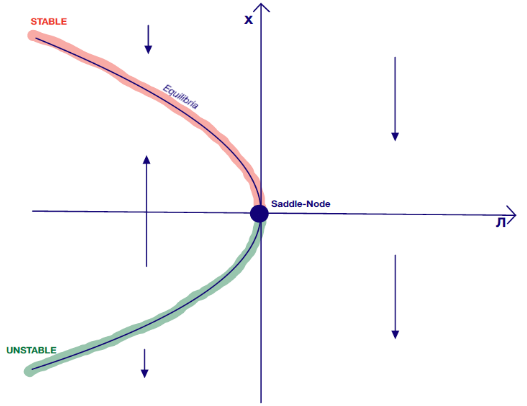
$$(k_1, k_2, k_3, k_4, k_5, k_6, F_A, F_B, F_C, F_D, F_E) = (1, 1, 1, 1, 1, 5, 1, 1, 1, 1, 1).$$

Tool: Bifurcation theory

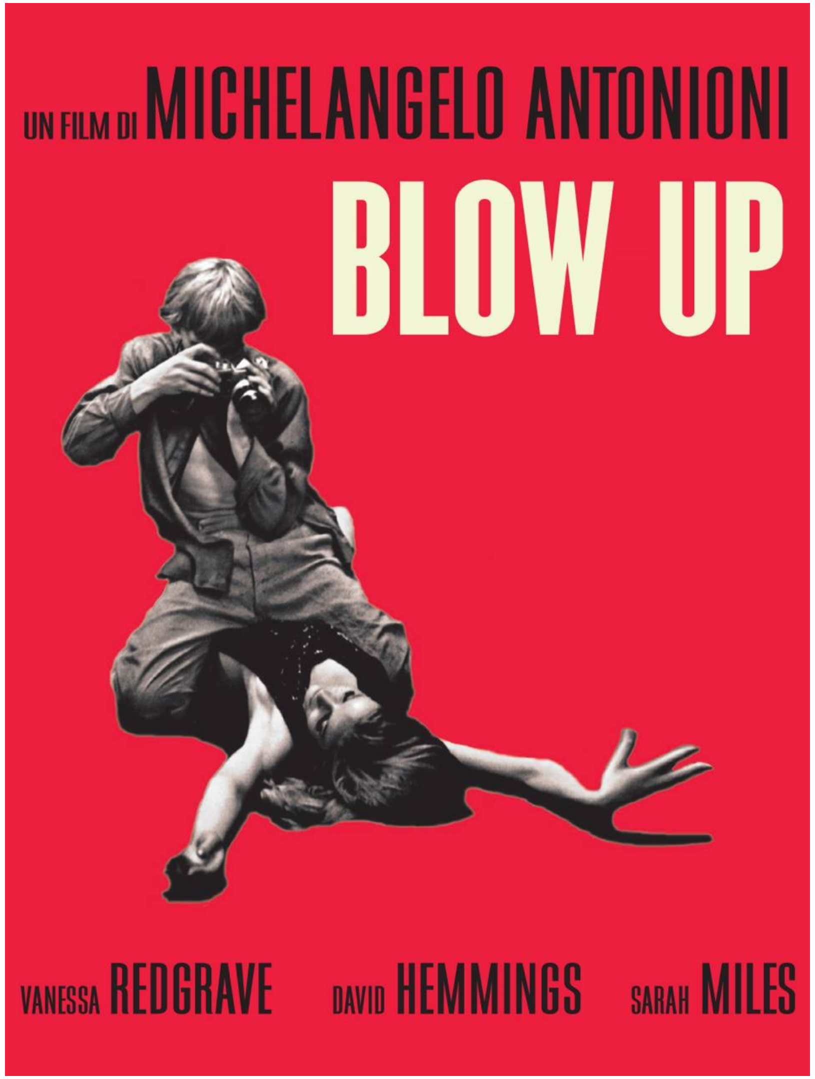
Hopf bifurcation for Oscillations



Saddle-node (at present) bifurcation for Multistationarity



How to make the small pattern dominant?



TUNE PARAMETERS!

Always possible with non-elementary kinetics
as Michaelis-Menten/Hill/Generalized Mass Action
("parameter-rich": see Definition with Peter)

More difficult with mass action!

GRAZIE PER L'ATTENZIONE!