Periodic oscillations without Hurwitz

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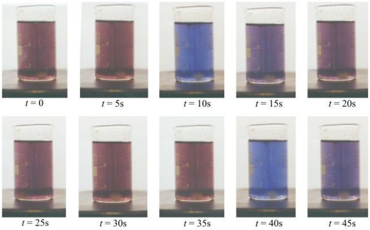
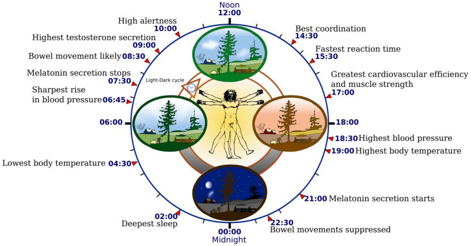
DFG Deutsche Forschungsgemeinschaft

UNIVERSITÄT LEIPZIG

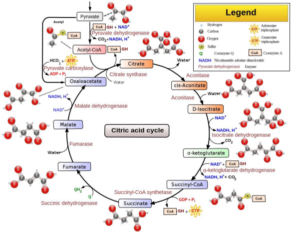
Motivation



$t = 0$
$t = 5s$
$t = 10s$
$t = 15s$
$t = 20s$
$t = 25s$
$t = 30s$
$t = 35s$
$t = 40s$
$t = 45s$



Noon
12:00
High alertness
10:00
Highest testosterone secretion
09:00
Bowel movement likely 08:30
Melatonin secretion stops
07:30
Sharpest rise
in blood pressure 06:45
06:00
Lowest body temperature 04:30
02:00
Deepest sleep
00:00
Midnight
22:30
Bowel movements suppressed
21:00 Melatonin secretion starts
19:00 Highest body temperature
18:30 Highest blood pressure
18:00
Greatest cardiovascular efficiency
and muscle strength
17:00
Fastest reaction time
15:30
Best coordination
14:30
Light-Dark cycle



Legend
Pyruvate
Pyruvate dehydrogenase
Acetyl-CoA
Pyruvate carboxylase
Oxaloacetate
Citrate
Citrate synthase
Aconitase
cis-Aconitate
D-Isocitrate
Isocitrate dehydrogenase
α-ketoglutarate
α-ketoglutarate dehydrogenase
Succinyl-CoA
Succinyl-CoA synthetase
Succinate
Succinic dehydrogenase
Fumarate
Fumarase
Malate
Malate dehydrogenase
Citric acid cycle
Water

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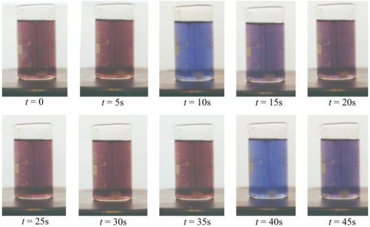

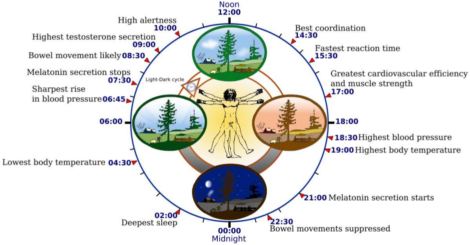

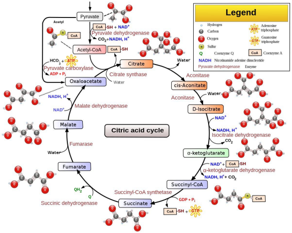

Q1: Is stability needed? (damped oscillations)

A standard route: Hurwitz computation

$$p(\lambda) = a_0\lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n$$

$$H = \begin{pmatrix} a_1 & a_3 & a_5 & \dots & \dots & \dots & 0 & 0 & 0 \\ a_0 & a_2 & a_4 & & & & \vdots & \vdots & \vdots \\ 0 & a_1 & a_3 & & & & \vdots & \vdots & \vdots \\ \vdots & a_0 & a_2 & \ddots & & & 0 & \vdots & \vdots \\ \vdots & 0 & a_1 & & \ddots & & a_n & \vdots & \vdots \\ \vdots & \vdots & a_0 & & & \ddots & a_{n-1} & 0 & \vdots \\ \vdots & \vdots & 0 & & & & a_{n-2} & a_n & \vdots \\ \vdots & \vdots & \vdots & & & & a_{n-3} & a_{n-1} & 0 \\ 0 & 0 & 0 & \dots & \dots & \dots & a_{n-4} & a_{n-2} & a_n \end{pmatrix}.$$

Hurwitz computation for purely imaginary eigenvalues $\Rightarrow$
good candidate for **local Hopf bifurcation** (non-resonant, simple, transverse).

Global Hopf bifurcation I

There are also ‘easier’ results for periodic orbits than local Hopf!

GLOBAL HOPF BIFURCATION FROM A MULTIPLE EIGENVALUE*

SHUI-NEE CHOW
Michigan State University, East Lansing, MI 48824

JOHN MALLET-PARET
Brown University, Providence, RI 02912

and

JAMES A. YORKE
University of Maryland, College Park, MD 20742, U.S.A.

Theorem (Chow, Mallet-Paret, Yorke ’78)

An isolated Hopf point with any net-change of stability implies nonstationary periodic solutions.

Hopf point: non-hyperbolic equilibrium with invertible Jacobian.
Net-change: the hyperbolic spectrum changes through the Hopf point.

No parity/resonance/transversality checking! Moreover, one gets here a ‘global’ continuum (‘snakes’ tbc). However, stability is not given.

Pros and cons of Hurwitz

Pros:

1. Characterization of the spectral problem (theory!)
2. Identification of the bifurcation point for Hopf bifurcation

Pros and cons of Hurwitz

SIAM REVIEW
Vol. 10, No. 1, January, 1968

BIGRADIENTS AND THE PROBLEM OF ROUTH AND HURWITZ*

A. S. HOUSEHOLDER†

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Pros:

1. Characterization of the spectral problem (theory!)
2. Identification of the bifurcation point for Hopf bifurcation

Cons:

1. Computational complexity (doomed for not-small networks)
2. Lack of biochemical insights (black box)
3. Local result, stability not (yet) addressed (numerical simulations)

Alternative routes

1. **Zero-eigenvalue bifurcations** (Takens-Bogdanov)
   Problem:
   Takens-Bogdanov (double zero) $\Rightarrow$ Hopf (purely imaginary), but $\not\Leftarrow$
2. **Poincare-Bendixson**
   Problem:
   either dim 2 or very special structure (monotone cyclic feedback systems)
3. **Inheritance** (perturbation arguments)
   Problem:
   Algorithm and/or reaction rates.
4. **Global methods** (intermediate value theorem)

Alternative routes

The Poincaré–Bendixson Theorem for Monotone Cyclic Feedback Systems

John Mallet-Paret[1] and Hal L. Smith[2]

Stable Periodic Solutions for the Hypercycle System

J. Hofbauer,[1] J. Mallet-Paret,[2] and H. L. Smith[3]

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Inheritance of oscillation in chemical reaction networks

Murad Banaji[a,*]

[a]*Middlesex University, London, Department of Design Engineering and mathematics, The Burroughs, London NW4 4BT, UK.*

P^--matrices, D-stability

Definition (P^--matrices, or Hicksian)

A matrix A is a P^- matrix if any k principal minor of A is of sign $(-1)^k$.
(P_0^- indicates the closure)

Definition (D-stability)

A matrix A is D-stable if AD is stable for any positive diagonal matrix D.

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Proposition

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Sketch of proof: D-stability requires A to be P_0^- matrix, thus A is not D-stable. Change of stability along a parametrization $[A\,\mathrm{Id}, AD]$ implies at least one point with eigenvalue of zero-real part (intermediate value theorem). Binet:

$$\det AD = \det A \det D \neq 0,$$

No zero-eigenvalues, thus purely imaginary.

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Corollary (from Fisher & Fuller 1958)

If a matrix A is an unstable P^- matrix, then there exists a positive diagonal matrix $\bar{D}$ such that $A\bar{D}$ has purely imaginary eigenvalues.

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Sketch: Fisher& Fuller proved that if a matrix A is a P^- matrix, then there exists a positive diagonal matrix $\bar{D}$ such that $A\bar{D}$ has all negative real eigenvalues.

Linear Algebra?

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I think of steady-state Jacobians of reaction networks in form

$$Jac = AD$$

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Q2: Is Linear Algebra alone able to provide classic local Hopf bifurcation?

Global Hopf bifurcation II

An index for global Hopf bifurcation in parabolic systems*)

By *Bernold Fiedler* at Heidelberg

Theorem (Fiedler, '85)

$$\dot{x} = f(x, \lambda), \quad f \text{ analytic}$$

Assume $\bar{x}(\lambda)$ *an analytic parametrization of a family of steady states for* $\lambda \in [a, b]$ *with the following conditions:*

1. *the Jacobian of* $\bar{x}(\lambda)$ *is invertible for all* λ
2. *the Jacobian of* $\bar{x}(a)$ *has different hyperbolic spectrum than* $\bar{x}(b)$.

Then there are nonstationary periodic solution.

Proof relates to the [Chow, Mallet-Paret, Yorke] result.

Analyticity is used to handle 'continua' of Hopf points.

Two reference examples

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Stable but not P_0^- negative diagonal stoichiometric sub-matrix

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$$\begin{array}{rcl} A & \underset{1}{\rightarrow} & B + C \\ B & \underset{2}{\rightarrow} & C \\ C + D & \underset{3}{\rightarrow} & A \\ D & \underset{4}{\rightarrow} & 2B \end{array}$$

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

stable ev: $($-0.34 \pm 0.56i - 1, -2.32$)$

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$$
\begin{aligned}
A &\underset{1}{\to} B + C \\
B &\underset{2}{\to} C \\
C + D &\underset{3}{\to} A \\
D &\underset{4}{\to} 2B
\end{aligned}
$$

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

stable ev: (-0.34 $\pm$ $0.56i - 1$, -2.32)

$$
SD = \begin{pmatrix} -1 & 0 & 1 & 0 \\ 1 & -1 & 0 & 2 \\ 1 & 0 & -1 & 0 \\ 0 & 0 & -1 & -1 \end{pmatrix} \begin{pmatrix} d_1 & 0 & 0 & 0 \\ 0 & d_1 & 0 & 0 \\ 0 & 0 & d_3 & 0 \\ 0 & 0 & 0 & d_4 \end{pmatrix}
$$

For $d_4 \to 0$, $SD \approx \begin{pmatrix} -1 & 0 & 1 & 0 \\ 1 & -1 & 0 & 0 \\ 1 & 1 & -1 & 0 \\ 0 & 0 & -1 & 0 \end{pmatrix}$, with ev $(-1.66 \pm 0.56i, 0.32, 0)$

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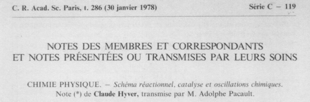
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NOTES DES MEMBRES ET CORRESPONDANTS
ET NOTES PRÉSENTÉES OU TRANSMISES PAR LEURS SOINS

CHIMIE PHYSIQUE. — *Schéma réactionnel, catalyse et oscillations chimiques.*
Note (*) de **Claude Hyver**, transmise par M. Adolphe Pacault.

$$\mathbf{2}A_1 + B \underset{9}{\to} \ldots$$

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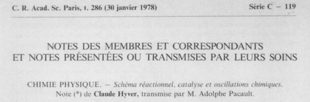
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ev: $(-2, -1, -1.9 \pm 0.7i, -1.2 \pm 1.1i, -0.4 \pm 1i, \mathbf{0.1} \pm \mathbf{0.4i})$ ...we need length!

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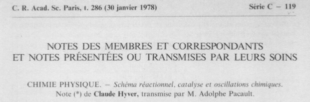
$$A_1 \underset{1}{\to} A_2 \underset{2}{\to} A_3 \underset{3}{\to} A_4 \underset{4}{\to} A_5 \underset{5}{\to} A_6 \underset{6}{\to} A_7 \underset{7}{\to} A_8 \underset{8}{\to} B + C$$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It is a unstable P^- matrix!

First easy case: parameter-rich kinetics

Definition (V, Stadler '24)

A kinetic model $r(x, p)$ is *parameter-rich* if **any** value $r'_{jm} > 0$ of the nonzero partial derivative

$$\frac{\partial r_j}{\partial x_m} \neq 0 \quad \text{if } m \text{ is reactant to } j$$

is attainable at **any** steady-state value $\bar{x}$, for a proper choice of p.

Examples: Michaelis-Menten, Generalized Mass Action, Hill kinetics (NOT mass action)

Theorem (V, '23)

If a network endowed with parameter-rich kinetics contains a negative-diagonal stoichiometric matrix U such that either

1. *U is a stable matrix but not a P_0^- matrix, or*
2. *U is an unstable P^- matrix*

then there are parameter choices for purely-imaginary eigenvalues.

First example 'worked-out' in Parameter-rich kinetics

$$A \underset{1}{\rightarrow} B + C \qquad D \underset{5}{\rightarrow} 2B$$

$$B \underset{2}{\rightarrow} C \qquad D + E \underset{6}{\rightarrow} 2E$$

$$C + D \underset{3}{\rightarrow} A \qquad E \underset{7}{\rightarrow}$$

$$C \underset{4}{\rightarrow} E \qquad \underset{F_D}{\rightarrow} D$$

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

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$$Jac = \begin{pmatrix} -r'_{1A} & 0 & r'_{3C} & r'_{3D} & 0 \\ r'_{1A} & -r'_{2B} & 0 & 2r'_{5D} & 0 \\ r'_{1A} & r'_{2B} & -r'_{3C} - r'_{4C} & -r'_{3D} & 0 \\ 0 & 0 & -r'_{3C} & -r'_{3D} - r'_{5D} - r'_{6D} & -r'_{6E} \\ 0 & 0 & r'_{4C} & r'_{6D} & r'_{6E} - r'_{7E} \end{pmatrix}$$

RESCALE:

$$r'_{3D} = r'_{4C} = r'_{5D} = r'_{6D} = r'_{6E} = r'_{7E} \approx \varepsilon$$

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RESCALE:

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at $\varepsilon = 0$ spectrum approximated by

$$\begin{pmatrix} -1 & 0 & 1 & 0 \\ 1 & -1 & 0 & 2 \\ 1 & 1 & -1 & 0 \\ 0 & 0 & -1 & -1 \end{pmatrix} \begin{pmatrix} r'_{1A} & 0 & 0 & 0 \\ 0 & r'_{2B} & 0 & 0 \\ 0 & 0 & r'_{3C} & 0 \\ 0 & 0 & 0 & r'_{5D} \end{pmatrix}$$

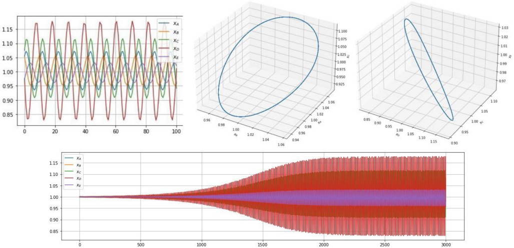
regular perturbation argument yields purely imaginary eigenvalues for the full system

First example ‘worked-out’ in Parameter-rich kinetics

Stable periodic orbits for the Michaelis-Menten system!

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

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



Mass Action

Also mass action has a Jacobian that can be expressed as AD!
(e.g. Clarke's Stoichiometric Network Analysis)

The core observation is:

$$\begin{cases} r_j(x) = k_j x^n \\ r_j'(x) = n k_j x^{n-1} = n k x^{n-1} \frac{x}{x} = n \mathrm{r}_j(x) \frac{1}{x} \end{cases}$$

At steady state, linear constraints

$$S\mathrm{r}(\bar{x}) = Sv = 0$$

and thus Jacobian

$$Jac = B(v)\,\mathrm{diag}(1/\bar{x}).$$

Mass Action

Jacobian:

$$Jac = B(v)\,\mathrm{diag}(1/\bar{x})$$

Theorem (V, '24)

If a mass action system has a flux vector v such that either

1. *$B(v)$ is a stable matrix but not a P_0^- matrix, or*
2. *$B(v)$ is an unstable P^- matrix*

then there are parameter choices for purely-imaginary eigenvalues and consequent nonstationary periodic solutions.

NOTE: $B(v)$ is fully determined by the stoichiometry of the system.

Q3: Can we get simple sufficient stoichiometric patterns?

Janos' example 'worked-out' in mass action

$$\underset{\mathbf{F}}{\to} A_1 \underset{1}{\to} A_2 \underset{2}{\to} A_3 \underset{3}{\to} A_4 \underset{4}{\to} A_5 \underset{5}{\to} A_6 \underset{6}{\to} A_7 \underset{7}{\to} A_8 \underset{8}{\to} B + C$$

$$2A_1 + B \underset{9}{\to} \ldots$$

$$2A_1 + C \underset{10}{\to} \ldots$$

Equilibria constraints:

$$Sv = 0 \quad \Leftrightarrow \quad v = k(5, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1)$$

$$Jac(x) = S\,\mathrm{diag}(v)K^T\,\mathrm{diag}\,1/\bar{x} = SS^{-T}\,\mathrm{diag}\,1/\bar{x}$$

Janos' example 'worked-out' in mass action

$$\underset{\mathbf{F}}{\rightarrow} A_1 \underset{1}{\rightarrow} A_2 \underset{2}{\rightarrow} A_3 \underset{3}{\rightarrow} A_4 \underset{4}{\rightarrow} A_5 \underset{5}{\rightarrow} A_6 \underset{6}{\rightarrow} A_7 \underset{7}{\rightarrow} A_8 \underset{8}{\rightarrow} B + C$$

$$2A_1 + B \underset{9}{\rightarrow} \ldots$$

$$2A_1 + C \underset{10}{\rightarrow} \ldots$$

$$Jac(x) = B(v)\,\mathrm{diag}\,1/\bar{x} = S\,\mathrm{diag}(v)K^T\,\mathrm{diag}\,1/\bar{x} = SS^{-T}\,\mathrm{diag}\,1/\bar{x}$$

$$= \begin{pmatrix} -9 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -2 & -2 \\ 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 \\ -2 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 \\ -2 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & -1 \end{pmatrix} \mathrm{diag}\,1/\bar{x}$$

eigenvalues of $B(v)$:

$$(-9.9, -1, -0.5 \pm 0.8i, -1, 3 \pm 0.9i, -1.7 \pm 0.3i, +\mathbf{0}, \mathbf{005} \pm \mathbf{0.3i})$$

Unstable P^- matrix $\Rightarrow$ periodic orbits!

A second criterion: fully-open systems, any type of kinetics

Theorem (V' 24)

Consider any fully-open reaction network system

$$\dot{x} = g(x) := F + f(x) - Dx.$$

The following statements are equivalent:

1. *the system admits a Hopf bifurcation;*
2. *the system admits an unstable steady state with complex-conjugated eigenvalues λ_1, λ_2 with positive-real part*

$$\Re(\lambda_1) = \Re(\lambda_2) = p > 0$$

and no other real eigenvalue $\lambda_i = p$.

Sketch of proof:

1. $\bar{x}$ s.t. $f(\bar{x}) = 0$.
2. choose $D(\beta) = \beta\,\mathrm{Id}$, $F(\beta) = \beta\,\mathrm{Id}\,\bar{x}$
3. $g(\bar{x}, \beta) = 0$ for all β, but shift in spectrum.

Grazie per l'attenzione!