Autocatalysis and Unstable Cores in Parameter-Rich CRNs

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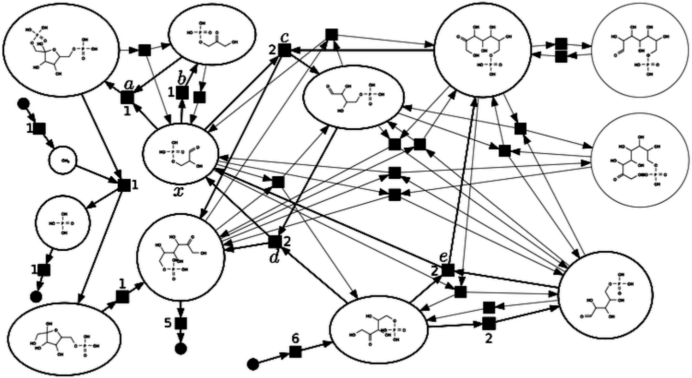
Large Bio-Chemical Reaction Networks



small part of the carbohydrate metabolism

- ○ vertices = chemical compounds (molecular types = labels)
- ■ hyperedges = chemical reactions

Some Notation

- chemical reaction:

$$s^j_{m_1} m_1 + \ldots + s^j_{m_{|M|}} m_{|M|} \quad \underset{j}{\to} \quad \tilde{s}^j_{m_1} m_1 + \ldots + \tilde{s}^j_{m_{|M|}} m_{|M|},$$

  stoichiometric coefficients s^j_m (educts) and $\tilde{s}^j_m$ (products)
- Assumption: no direct catalysts: $s^j_m \cdot \tilde{s}^j_m = 0$
- completely described by the stoichiometric matrix **S** with entries $S_{mj} = \tilde{s}^j_m - s^j_m$
- Concentrations x_m of species m
- Dynamics $\dot{x} = f(x) := Sr(x)$

Autocatalysis

Basic idea: There is a **net** reaction of the form

$$A + (X) \to 2A + (W)$$

where (X) and (W) is one more food or waste products.
There is not a single well-accepted definition.
The problem is trivial sums such as

$$X \to A \qquad \text{and} \qquad B + A \to C + A$$

that are not kinetically coupled but still yield $X + B + A \to 2A + C$
One would like to have a definition that depends ONLY on the structure of the network, not on the specific form of the kinetic model.

Kinetic model

We only require very general assumptions for a "sane" behavior of the reaction rates:
$r : \mathbb{R}^M_{\geq 0} \to \mathbb{R}^E$ is a *weakly monotonic kinetics* or *"monotone chemical function"* for a CRN with stoichiometric coefficients s^j_m if

(R1) $r_j(x) \geq 0$ for all $x \in \mathbb{R}^M_{\geq 0}$,

(R2) $r_j(x) > 0$ implies $x_m > 0$ for all m with $s^j_m > 0$,

(R3) $s^j_m = 0$ implies $\partial r_j / \partial x_m \equiv 0$,

(R4) if $x_k > 0$ for all $k \in M$ and $s^j_m > 0$ then $\partial r_j / \partial x_m > 0$.

For $\bar{x} \in \mathbb{R}^M_{\geq 0}$ we write $R_{jm}(\bar{x}) = \left. \frac{\partial r_j(x)}{\partial x_m} \right|_{x=\bar{x}}$.
The Jacobian of $\dot{x} = Sr(x)$ at $\bar{x}$ is $G(\bar{x}) = SR(\bar{x})$
Examples: mass actions kinetics, Michaelis-Menten kinects, Hill model, ...

Parameter-rich kinetic models

In general, the rate function $r(x)$ explicitly depends on the values of a vector of parameters p.

Definition

A kinetic rate model $r(x; p)$ is *parameter-rich* if, for every positive equilibrium, i.e., $Sr(\bar{x}) = 0$ and $\bar{x} > 0$, and every $|E| \times |M|$ matrix R with entries satisfying

- $R_{jm} > 0$ if $s^j_m > 0$ and
- $R_{jm} = 0$ if $s^j_m = 0$

there is a choice $\bar{p} = p(\bar{x}, R)$ such that

$$\frac{\partial r_j(x; \bar{p})}{\partial x_m}\Big|_{x=\bar{x}} = R_{jm}.$$

The two conditions on R derive directly from the axioms for weakly monotonic kinetic models.

Parameter-rich kinetic models

Why do we care?

In a parameter-rich kinetic model it is possible to

- fix the coordinates of an interior equilibrium $\bar{x}$ (if one exists for given S)
- and then choose parameters p such that $\bar{x}$ remains unchanged **and** the values of $R(\bar{x})$ can be chosen arbitrarily as long as they satisfy the sign conditions.

Therefore, we can construct sufficient conditions for instability of interior equilibria in CRNs, i.e., for CRNs to *admit instability*

Examples of parameter-rich models

- Michaelis-Menten kinetics

$$r_j(x) := a_j \prod_{m \in M} \left(\frac{x_m}{(1 + b^j_m x_m)} \right)^{s^j_m}$$

- Generalized Mass Action kinetics

$$r_j(x) := a_j \prod_{m \in M} x_m^{c^j_m}, \qquad \text{with } c^j_m \neq 0 \text{ if and only if } s^j_m \neq 0.$$

are parameter-rich kinetic models.
However, mass action kinetics is not parameter-rich.

The Goal

Find necessary and sufficient conditions on the stoichiometric matrix S such that there **exists** a choice of parameters $\mathbf{p}$ in a parameter-rich model for which the reaction networks shows dynamical instability.

- A parameter-rich CRN *admits instability* if there is choice of (non-zero) values in R such that $G = SR$ is Hurwitz-unstable

Child Selections

A *child selection* $\boldsymbol{\kappa} = (\kappa, E_\kappa, J)$ consists of a subset $\kappa \subseteq M$ of reactants, a choice E_κ of reactions and a bijection between reactants and reactions such that $m \in \kappa$ is a reactant of reaction $J(m) \in E_\kappa$.
A child selection therefore determines a square submatrix of S.

$$S[\boldsymbol{\kappa}]_{ml} := S[\kappa, E_\kappa]_{m,J(l)} = \tilde{s}_m^{J(l)} - s_m^{J(l)},$$

By construction the diagonal of $S[\boldsymbol{\kappa}]$ is negative since m is a reactant in reaction $J(l)$.
Is is not difficult to show that a child selection $\boldsymbol{\kappa}'$ is $S[\boldsymbol{\kappa}]$ coincides with a child selection in S. Thus the notion of a minimal child selection with some property is well defined: $\boldsymbol{\kappa}$ is minimmal w.r.t. some property $\mathbb{P}$ is there is no so smaller child selection $\boldsymbol{\kappa}'$ in $S[\boldsymbol{\kappa}]$.

Unstable cores

Theorem (Vassena 2023)

A parameter-rich CRN with stoichiometic matrix S admits instability if there is a child selection $\boldsymbol{\kappa}$ be a child selection such that $S[\boldsymbol{\kappa}]$ is Hurwitz-unstable.

Idea: choose all entries in R except $R_{m,J(m)}$ for $m \in \kappa$ to be $< \epsilon$. Then only the block in $G = SR$ belonging to $\boldsymbol{\kappa}$ has large entries $\gg \epsilon$, and thus eigenvalues of $S[\boldsymbol{\kappa}]R[\boldsymbol{\kappa}]$ are also eigenvalues of G (up to perturbations of order ϵ). Instability of $S[\boldsymbol{\kappa}]R[\boldsymbol{\kappa}]$ thus implies instability of G. The theorem is then obtained by setting $R[\boldsymbol{\kappa}] = I$.

Definition

An *unstable core* in S is a Hurwitz-unstable child selection for which no proper principle submatrix is unstable.

Every unstable core is an irreducible matrix.

D-unstable cores

Unstable cores are sufficient but not necessary for a CRN to admit instability

A matrix is D-unstable if there is a positive diagonal matrix D such that AD is Hurwitz-unstable.

Theorem

If S contains a D-unstable child selection then the CRN admits instability

A D-unstable core in S is a D-unstable matrix $S[\boldsymbol{\kappa}]$ for a child selection $\boldsymbol{\kappa}$ that does not contains a proper principal submatrix in D-unstable.

D-unstable cores

Proposition

Every unstable core (of S) contains a D-unstable core.

Conjecture

If S does not contain a D-unstable core than the CRN does not admit instability.

Positive and negative feedbacks

Definition

unstable-positive feedback is an unstable core satisfying $\operatorname{sign}\det S[\boldsymbol{\kappa}] = (-1)^{|\kappa|-1}$;
an *unstable-negative feedback* is an unstable core satisfying $\operatorname{sign}\det S[\boldsymbol{\kappa}] = (-1)^{|\kappa|}$.

Lemma

If $S[\boldsymbol{\kappa}]$ is an unstable-positive feedback then $G[\boldsymbol{\kappa}]$ is Hurwitz unstable for any choice of symbols in $R[\boldsymbol{\kappa}]$.

Unstable-positive Feedback

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

Unique unstable core

$$\begin{array}{c} \\ \mathrm{A} \\ \mathrm{B} \end{array} \begin{array}{c} \begin{array}{cc} 1 & 2 \end{array} \\ \begin{pmatrix} -1 & -2 \\ -1 & -1 \end{pmatrix} \end{array}$$

Multistationarity (one stable and one unstable fixed point)

Autocatalyic cores

Autocatalytic cores were introduced by *Nhge* a couple of years ago as minimal submatrices S' of S satisfying

(1) there is a positive vector v such that $S'v > 0$

(2) for every reaction column j there are entries m and $\tilde{m}$ that are reactants and products of j, resp.

Lemma

Nghe's autocatalyic cores are child selections in our sense.

At present the most useful definition of structural autocatalysis:
A CRN is (harbours) autocatalysis if it contains an autocatalytic core

Autocatalyic cores

A matrix A is a *Metzler matrix* if it has non-negative off-diagonal elements.

Theorem

A submatrix S is an autocatalytic core if (the column-reordered matrix) $S[\boldsymbol{\kappa}]$ is an unstable-postive feedback and a Metzler matrix.

- Unstable-negative feebacks are never autocatalytic.
- A network S is autocatalytic if and only if there is a child selection such $\boldsymbol{\kappa}$ such that $S[\boldsymbol{\kappa}]$ is a Hurwitz-unstable Metzler matrix.

Corollary

Every autocatalytic CRN admits instability

Unstable-positive Feedback

$$A + B \underset{1}{\rightarrow} C + E \qquad E \underset{5}{\rightarrow} \varnothing$$

$$B + C \underset{2}{\rightarrow} E \qquad \varnothing \underset{F_A}{\rightarrow} A$$

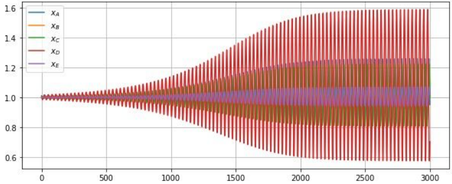
$$C + D \underset{3}{\rightarrow} A + E \qquad \varnothing \underset{F_B}{\rightarrow} B$$

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

Unique unstable core

$$\begin{array}{c} \\ A \\ B \\ C \end{array} \begin{array}{c} \begin{array}{ccc} 1 & 2 & 3 \end{array} \\ \begin{pmatrix} -1 & 0 & 1 \\ -1 & -1 & 0 \\ 1 & -1 & -1 \end{pmatrix} \end{array}$$

Not a Metzler matrix, not autocatalytic.
The associated parameter-rich system admits oscillations.



Oscillations with unstable-negative feedback

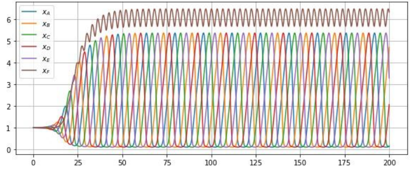
$$A + B \xrightarrow[1]{} A + F$$
$$B + C \xrightarrow[2]{} B + F$$
$$C + D \xrightarrow[3]{} C + F$$
$$D + E \xrightarrow[4]{} D + F$$
$$E + A \xrightarrow[5]{} E + F$$

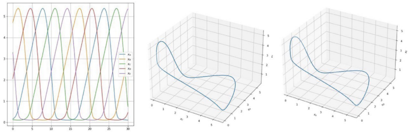
$$\varnothing \xrightarrow[F_A]{} A$$
$$\varnothing \xrightarrow[F_B]{} B$$
$$\varnothing \xrightarrow[F_C]{} C$$
$$\varnothing \xrightarrow[F_D]{} D$$
$$\varnothing \xrightarrow[F_E]{} E$$
$$F \xrightarrow[6]{} \varnothing$$

Unique unstable core

$$\begin{array}{c} \\ A \\ B \\ C \\ D \\ E \end{array} \begin{array}{c} \begin{array}{ccccc} 1 & 2 & 3 & 4 & 5 \end{array} \\ \begin{pmatrix} 0 & 0 & 0 & 0 & -1 \\ -1 & 0 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 \end{pmatrix} \end{array}$$

Unstable-negative feedback, hence non-autocatalytic.





In summary

- Parameter-rich kinetics is convenient device to explore the impact of network structure
- For chemists: instability and “interesting dynamical behaviour” is independent of autocatalysis
- Cores = minimal child selection with some interesting properties as “building blocks” of interesting behavior
- several open questions:
  - is a D-unstable core necessary for a network to admit instability
  - are there also cores e.g. for limit cycles [basically everything that can phrases in terms of sign matrices might work]
  - how does mass action kinetics fit into this:
    can one characterize unstable cores that do not admit instability under MAK?