Linear robustness analysis of non-linear biomolecular networks with kinetic perturbations

Steffen Waldherr and Frank Allgöwer

Institute for Systems Theory and Automatic Control
Universität Stuttgart

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Robustness analysis

Informal definition of robustness

Robustness is a property that allows a system to maintain its function in the presence of internal and external perturbations.

H. Kitano, 2004

<table>
<thead>
<tr>
<th>System / Model: $\dot{x} = Sv(x)$</th>
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<tbody>
<tr>
<td>$x \in \mathbb{R}^n$: amounts of signalling molecules</td>
</tr>
<tr>
<td>$v(x) \in \mathbb{R}^m$: reaction rates</td>
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<tr>
<td>$S \in \mathbb{R}^{n \times m}$: stoichiometric matrix</td>
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- **Perturbations**: kinetic perturbations (changes in reaction kinetics $v$)
- **Function**: Qualitative dynamical behaviour (stability, oscillations, ...)
Formal robustness measures

- Non-robust perturbation = any deviation from the nominal point for which the system **looses functionality**
- Robustness measure = **smallest** norm of non-robust perturbations
Why robustness analysis?

Robustness analysis for model evaluation
- Biological systems are robust $\leftrightarrow$ models should be robust!
- Find parts of the system which need to be modelled carefully
- Evaluate effects of uncertainty on model predictions

Robustness analysis for system understanding
- Understand mechanisms which confer robustness to biological systems
- Detect fragile points, e.g. for medical intervention
- Guide system design in bioengineering and synthetic biology
Outline

1. Theory of kinetic perturbations
2. Robustness analysis with kinetic perturbations
3. Adaptation with kinetic perturbations
Outline

1. Theory of kinetic perturbations
   - Definition of kinetic perturbations
   - Mapping kinetic perturbations to parameter variations

2. Robustness analysis with kinetic perturbations

3. Adaptation with kinetic perturbations
Kinetic perturbations – the basic idea

Kinetic perturbations = reaction rate perturbations

- nominal rates $v(x)$ to perturbed rates $\tilde{v}(x)$
- nominal model $\dot{x} = Sv(x)$ to perturbed model $\dot{x} = S\tilde{v}(x)$
- Consider nominal steady state $x_0$: $Sv(x_0) = 0$
- Kinetic perturbation, if $\tilde{v}(x_0) = v(x_0)$

- Reaction rates in steady state unperturbed, but reaction rate slopes may vary:

\[ \nu(x) \]
\[ \tilde{\nu}(x), \text{ increased slope} \]
\[ \nu(x) = 0.7x \]
\[ \tilde{\nu}(x), \text{ reduced slope} \]
\[ x_0 = 1 \]
Formal definition of kinetic perturbations

Definition

The network \( \dot{x} = S\tilde{v}(x) \) is said to be a \textit{kinetic perturbation} of the nominal network \( \dot{x} = Sv(x) \) at \( x_0 \in \mathbb{R}^n \) with \( Sv(x_0) = 0 \), if \( \tilde{v}(x_0) = v(x_0) =: v_0 \).

- Consider the reaction rate Jacobian \( V = \frac{\partial v}{\partial x} \)
- For the perturbed network, we have

\[
\tilde{V}(x_0) = \frac{\partial \tilde{v}}{\partial x}(x_0) = V(x_0) + \bar{\Delta}
\]

- Local effects of the kinetic perturbation are determined by \( \bar{\Delta} \)
  - Scaled perturbation \( \Delta_{i\ell} = \frac{x_{0,i\ell}}{v_{0,i}} \bar{\Delta}_{i\ell} \)
  - \( \|\Delta\| \) is a measure for the perturbation size

- Steady state concentration \( x_0 \) and flux \( v_0 \) are unperturbed
- Steady state reaction slopes \( V(x_0) \) are perturbed by \( \bar{\Delta} \)
Mapping kinetic perturbations to parameter changes

- Considering generalised mass action (GMA) networks
- GMA reaction rate: \( v_i(x) = k_i \prod_{\ell=1}^{n} x_\ell^{\alpha_{i\ell}} \)
  - \( \alpha_{i\ell} > 0 \): \( x_\ell \) is a substrate for / activates \( v_i \)
  - \( \alpha_{i\ell} < 0 \): \( x_\ell \) inhibits \( v_i \)
- Non-integer kinetic orders \( \alpha_{i\ell} \)
  - Effect of constrained diffusion (fractal reaction kinetics)
  - Result of model simplifications (as in S-systems, Savageau et al.)
- Perturbed reaction rate \( \tilde{v}_i(x) = \tilde{k}_i \prod_{\ell=1}^{n} x_\ell^{\tilde{\alpha}_{i\ell}} \)

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<th>Parameter change</th>
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<td>( \frac{\partial \tilde{v}<em>i}{\partial x</em>\ell} = \frac{\partial v_i}{\partial x_\ell} + \frac{v_{0,i}}{x_{0,\ell}} \Delta_{i\ell} )</td>
<td>( \tilde{\alpha}<em>{i\ell} = \alpha</em>{i\ell} + \Delta_{i\ell} )</td>
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<tr>
<td>( \tilde{k}<em>i = k_i \prod</em>{\ell=1}^{n} x_{0,\ell}^{-\Delta_{i\ell}} )</td>
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Biochemical interpretation of kinetic perturbations

Are kinetic perturbations biochemically plausible?

Yes, because kinetic perturbations map to parameter variations in reasonable model classes for intracellular networks such as

- GMA networks
- enzymatic networks (Michaelis-Menten or Hill reaction kinetics)
- genetic networks (sigmoidal activation & inhibition functions)

Biochemical interpretation

- Positive $\Delta_{i\ell}$: more cooperativity in reaction $i$ with respect to species $\ell$
- Negative $\Delta_{i\ell}$: increase saturation in reaction $i$ with respect to species $\ell$
Outline

1. Theory of kinetic perturbations

2. Robustness analysis with kinetic perturbations
   - Kinetic perturbations affect dynamical properties
   - Robustness analysis via the structured singular value
   - Example: Oscillations in the MAPK cascade

3. Adaptation with kinetic perturbations
Inducing bifurcations by kinetic perturbations

Example “network”

\[ v_1 = \frac{kx^2}{1 + Mx^2} \]
\[ \dot{x} = v_1 - v_2 \]
\[ v_2 = x \]

\[ \frac{\partial v_1}{\partial x} (1) = \frac{\partial v_1}{\partial x} (1) + \bar{\Delta} \]

\[ \bar{\Delta} = 0 : x_0 \text{ stable} \]
\[ \bar{\Delta} = \bar{\Delta}^* : \text{ transcritical bifurcation at } x_0 \]
\[ \bar{\Delta} > \bar{\Delta}^* : x_0 \text{ unstable} \]

Loss of bistability by a kinetic perturbation
Inducing bifurcations by kinetic perturbations

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Loss of bistability by a kinetic perturbation
### Robustness with respect to kinetic perturbations

**Perturbed Jacobian**

\[
\tilde{A}(\Delta) = A + S(\text{diag } v_0)\Delta(\text{diag } x_0)^{-1}
\]

**Robustness radius for kinetic perturbations**

- Robustness measure = size of smallest perturbation such that \( \tilde{A}(\Delta) \) has an eigenvalue on the imaginary axis

\[
\psi = \inf \{ \|\Delta\| \mid \det(j\omega I - \tilde{A}(\Delta)) = 0 \}
\]

- Can be formulated as structured singular value (\( \mu \)) problem with

\[
G(j\omega) = (\text{diag } x_0)^{-1}(j\omega I - A)^{-1}S(\text{diag } v_0)
\]

Result:

\[
\psi = \left( \sup_{\omega} \mu_{\Delta} G(j\omega) \right)^{-1}
\]

Robustness problem can be solved with standard \( \mu \) analysis tools.
Robustness radius for scalar perturbations

- Perturbation of a single interaction: Species $\ell$ on reaction $i$

$$\bar{\Delta} = \begin{pmatrix} 0 \\ \vdots \\ 1 \\ \vdots \\ 0 \end{pmatrix} \bar{\Delta}_{i\ell}(0 \ldots 1 \ldots 0) = e_i \bar{\Delta}_{i\ell} e^T_\ell$$

- Perturbed Jacobian $\tilde{A}(\Delta_{i\ell}) = A + S e_i v_0,i \Delta_{i\ell} x^{-1}_0,\ell e^T_\ell$

Robustness radius

$$\psi = \{ |\Delta_{i\ell}| | \det(j \omega I - \tilde{A}(\Delta_{i\ell})) = 0 \}$$

$$= \left( \sup_{\omega \in \mathcal{R}(G_{\ell i})} |G_{\ell i}(j \omega)| \right)^{-1}$$

- $\mu-$problem with $G_{\ell i}(j \omega) = e^T_\ell x^{-1}_0,\ell (j \omega I - A)^{-1} S v_0,i e_i$

- Explicit formula for the robustness radius
- Allows to detect fragile interactions in the network
Robustness analysis in the vector case

- Perturbation of several interactions either
  - from one species \( \ell \) to several reactions \( E_i \nu \) or
  - from several species \( E_\ell \chi \) to one reaction \( i \).
  \[
  \bar{\Delta} = E_i \bar{\Delta}_{i \ell} e^T_\ell
  \]

- Perturbed Jacobian \( \tilde{A}(\Delta_{i\ell}) = A + SE_i \text{diag}(E_i \nu_0)\Delta_{i\ell} x_{0,\ell}^{-1} e^T_\ell \)

Robustness analysis in the vector case

- Results depend on the norm that is chosen:
  - 1-norm or \( \infty \)-norm: robustness radius from a linear program
  - 2-norm: explicit formula for robustness radius

- Also requires to compute a supremum over \( \omega \).

- Non-robust perturbation is the solution of an affine equation \( M\bar{\Delta} = b \).
The MAPK cascade

Huang & Ferrell 1996

Medium scale network with 22 species and 30 (irreversible) reactions

Where to perturb this network in order to get oscillations?
Single interaction analysis of the MAPK cascade

- Checking all 660 network interactions for a scalar kinetic perturbation to induce oscillations
- Found 8 fragile interactions ($|\Delta^*| < 1$), e.g.:
  - Negative feedback from MAPKpp to MAPKK phosphorylation
  - Positive feedback from MAPKpp to catalysis of MAPK / MAPKKpp complex
  - Saturated catalysis of MAPKpp / Phosphatase complex
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![Diagram of the MAPK cascade]

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Effect of a kinetic perturbation on the dynamics

\[ P_{\text{MAPK}}(P) \xrightarrow{v_{30}} \text{MAPK}(P) + \text{K-P'ase} \]

Critical perturbation \( \Delta^* = -0.76 \)

Robustness analysis with kinetic perturbations, S. Waldherr
Effect of a kinetic perturbation on the dynamics

Critical perturbation $\Delta^* = -0.76$

Robustness analysis with kinetic perturbations, S. Waldherr
Effect of a kinetic perturbation on the dynamics

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Robustness analysis with kinetic perturbations, S. Waldherr
Outline

1. Theory of kinetic perturbations
2. Robustness analysis with kinetic perturbations
3. Adaptation with kinetic perturbations
   - Properties of biomolecular adaptation
   - Achieving adaptation with kinetic perturbations
   - Example: Adaptation in the MAPK cascade
1. Adaptation
A dynamical system \( u \mapsto y \) is said to adapt, if persistent changes in \( u \) do lead to transient, but not persistent changes in \( y \).

Local adaptation = consider only infinitesimally small changes in \( u \)

2. Local adaptation without transient response
The system \( u \mapsto y \) is said to perfectly adapt locally at \((u_0, y_0)\), if

\[
\lim_{u_s \to 0} \lim_{t \to \infty} \left( y(t, u_0 + u_s h(t)) - y_0 \right) \div u_s = 0.
\]
Adaptation and robustness

Adaptation to a slowly changing perturbation

= Robustness of steady state concentration to this perturbation

Slowly changing perturbations in biology

- Protein amounts due to stochastic gene expression
- Environmental conditions such as light, temperature, or nutrient availability
Conditions for adaptation

1. Linear approximation at steady state

\[
\dot{x} = Ax + Bu
\]
\[
y = Cx,
\]
with:
\[
A = S \frac{\partial v}{\partial x}(x_0, u_0)
\]
\[
B = S \frac{\partial v}{\partial u}(x_0, u_0)
\]

2. Transformation to frequency domain

\[
dy(s) = C(sI - A)^{-1}Bu(s) = G(s)du(s).
\]

3. Necessary and sufficient condition for local adaptation

By the final value theorem of the Laplace transformation:

local adaptation \iff \ G(0) = 0 \quad A \text{ invertible} \iff \det \begin{pmatrix} A & B \\ C & 0 \end{pmatrix} = 0

Last condition is affected by kinetic perturbations!
Achieving adaptation with kinetic perturbations

Effect of kinetic perturbation on adaptation condition

- Perturbation of Jacobian due to a kinetic perturbation $\ell \rightarrow i$:
  \[
  \tilde{A} = A + S e_{i} v_{0,i} \Delta_{i\ell}(x_{0,\ell})^{-1} e_{\ell}^{T}
  \]

- Adaptation as goal:
  \[
  \det \begin{pmatrix} \tilde{A} & B \\ C & 0 \end{pmatrix} = \det \begin{pmatrix} A + S e_{i} v_{0,i} \Delta_{i\ell}(x_{0,\ell})^{-1} e_{\ell}^{T} & B \\ C & 0 \end{pmatrix} = 0.
  \]

Compute a critical kinetic perturbation

\[
\Delta^{*}_{i\ell} = (-e_{j}^{T} M_{out} M_{0}^{-1} M_{in} e_{\ell})^{-1} \frac{x_{0,\ell}}{v_{0,i}}
\]

with
\[
M_{0} = \begin{pmatrix} A & B \\ C & 0 \end{pmatrix}, \quad M_{in} = \begin{pmatrix} I \\ 0 \end{pmatrix} S, \quad M_{out} = \begin{pmatrix} I & 0 \end{pmatrix}
\]
Example: Adaptation in the MAPK cascade

Goal: achieve adaptation of nuclear MAPKpp

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Huang-Ferrell MAPK cascade model as before

- Added an input by controlling E1 production

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Result of analysis with kinetic perturbations

- No adaptation with transient response possible through kinetic perturbations
- Network lacks a feedback or feedforward loop
Adaptation in an extended MAPK cascade model

Model feedback extension

- Added a protein genetically regulated by MAPK
- Feedback by formation of inhibitory complex

Candidate interactions for adaptation

Found five candidate interactions in newly added feedback loop for adaptation via kinetic perturbations.
Adaptation achieved even for large stimulus changes.
Non-linear dynamics depend on which interaction is targeted.
Conclusions

**Kinetic perturbations**
- Perturbation class suited for biochemical network analysis
- Kinetic perturbations = reaction rate slope changes at steady state
- Biochemically plausible for GMA / enzymatic / genetic networks

**Robustness analysis with kinetic perturbations**
- Efficient robustness analysis via $\mu$–analysis methods
- Results indicate fragile network interactions
- Non-robust perturbations are explicitly computed

**Adaptation with kinetic perturbations**
- Find network modifications to achieve perfect local adaptation
- Steady state is kept unperturbed intrinsically
- Adaptation even to large stimulus changes in many cases