From Reaction Networks to Information Flow

Using Modular Response Analysis to Track Information in Signalling Networks

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October 15, 2010

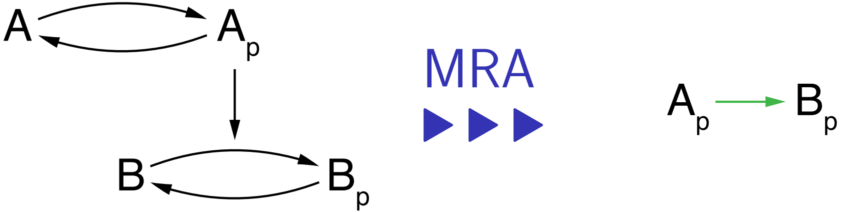
Reaction networks → information flow?

MRA

Oda and Kitano (2006)

Weinberg (2006)

Reaction networks → information flow?



The dynamic behaviour of a biochemical reaction system is determined by

$$\frac{d}{dt}\boldsymbol{c}(t) = \boldsymbol{N}\boldsymbol{v}(\boldsymbol{c}(t))$$

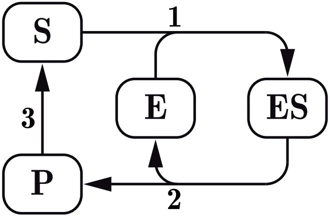
with

$\boldsymbol{c} \in \mathbb{R}^m$ concentration vector

$\boldsymbol{N} \in \mathbb{R}^{m \times n}$ stoichiometric matrix

$\boldsymbol{v} \in \mathbb{R}^n$ reaction rate vector.

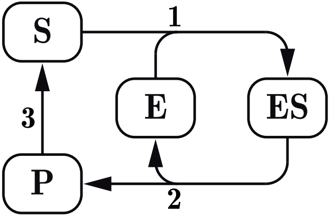
Example – System



$$\frac{d}{dt}\boldsymbol{c}(t) = \boldsymbol{N}\boldsymbol{v}(\boldsymbol{c}(t))$$

$$\frac{d}{dt}\begin{bmatrix} S(t) \\ E(t) \\ ES(t) \\ P(t) \end{bmatrix} = \begin{bmatrix} -1 & 0 & 1 \\ -1 & 1 & 0 \\ 1 & -1 & 0 \\ 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} k_{+1}ES(t) - k_{-1}E(t)S(t) \\ k_{+2}E(t)P(t) - k_{-2}ES(t) \\ k_{+3}S(t) - k_{-3}P(t) \end{bmatrix}$$

Example – System



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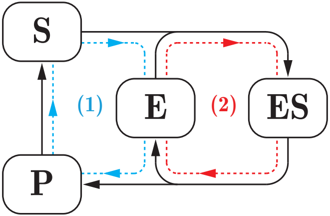
with

$$m_0 = 2$$

Conservation Analysis

If conservation relations exist,
one can separate $\boldsymbol{N}$ by

$$\boldsymbol{N} = \begin{bmatrix} \boldsymbol{N_R} \\ \boldsymbol{N_0} \end{bmatrix}$$



with

$\boldsymbol{N_R} \in \mathbb{R}^{m_0 \times n}$ linearly independent metabolites

$\boldsymbol{N_0} \in \mathbb{R}^{(m-m_0) \times n}$ linearly dependent metabolites

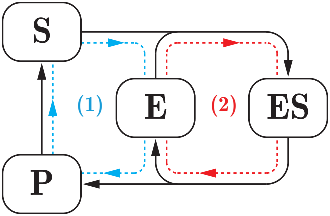
and

$$m_0 = rank(\boldsymbol{N}).$$

Conservation Analysis

From the separation it follows that

$$\boldsymbol{N} = \begin{bmatrix} \boldsymbol{I} \\ \boldsymbol{\Lambda_0} \end{bmatrix} \boldsymbol{N_R} = \boldsymbol{\Lambda} \boldsymbol{N_R}$$



from which the conservation relations can be determined as

$$\boldsymbol{\Gamma} = \begin{bmatrix} -\boldsymbol{\Lambda_0} & \boldsymbol{I} \end{bmatrix}$$

with

$\boldsymbol{\Lambda} \in \mathbb{R}^{m \times m_0}$ link matrix

$\boldsymbol{\Gamma} \in \mathbb{R}^{(m-m_0) \times m_0}$ conservation matrix.

Conservation Analysis

In practice, one has to solve $\boldsymbol{N^T}\boldsymbol{\Gamma^T} = 0$ which is getting numerically expensive with increasing system size.
Thus,

$$\boldsymbol{P}\boldsymbol{N^T}\boldsymbol{Q} = \boldsymbol{L}\boldsymbol{U}$$

where $\boldsymbol{U}$ is partitioned such that

$$\boldsymbol{U} = \begin{bmatrix} \boldsymbol{I} & \boldsymbol{M} \\ \boldsymbol{0} & \boldsymbol{0} \end{bmatrix}$$

from which $\boldsymbol{\Lambda}$, $\boldsymbol{N_R}$ and $\boldsymbol{\Gamma}$ follow to

$$\boldsymbol{\Lambda} = \begin{bmatrix} \boldsymbol{I} \\ \boldsymbol{M^T} \end{bmatrix}, \quad \boldsymbol{N_R} = \boldsymbol{\Lambda}^+\boldsymbol{N} \quad \text{and} \quad \boldsymbol{\Gamma} = \begin{bmatrix} -\boldsymbol{M}^T & \boldsymbol{I} \end{bmatrix},$$

respectively.

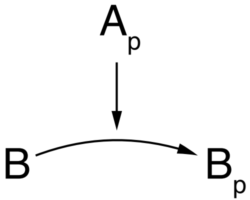
Modular Response Analysis

The unscaled elasticity coefficient matrix

$$\boldsymbol{\epsilon} = \left. \frac{\delta \boldsymbol{v}(\boldsymbol{c}(t))}{\delta \boldsymbol{c}(t)} \right|_{\bar{\boldsymbol{c}}}$$

gives the sensitivities of all local reaction rates to perturbations in all species concentrations. The dependencies among species are described by the (reduced) Jacobian matrix which is defined as

$$\begin{aligned} \boldsymbol{J} &= \boldsymbol{N}\boldsymbol{\epsilon} \\ \boldsymbol{J_R} &= \boldsymbol{N_R}\boldsymbol{\epsilon}\boldsymbol{\Lambda}. \end{aligned}$$



$$\epsilon^v_B > 0$$
$$\epsilon^v_{A_p} > 0$$
$$\epsilon^v_{B_p} < 0$$

Modular Response Analysis

After rescaling $\boldsymbol{\epsilon} \mapsto \tilde{\boldsymbol{\epsilon}}$ such that

$$\tilde{\boldsymbol{\epsilon}} = \boldsymbol{\epsilon} \frac{\boldsymbol{c}(t)}{\boldsymbol{v}(\boldsymbol{c}(t))}\bigg|_{\bar{\boldsymbol{c}}} \qquad \text{with} \qquad 0 < \tilde{\epsilon} < 1$$

the local and global response matrices follow to

$$\tilde{\boldsymbol{r}} = \boldsymbol{N_R} \tilde{\boldsymbol{\epsilon}} \boldsymbol{\Lambda}$$

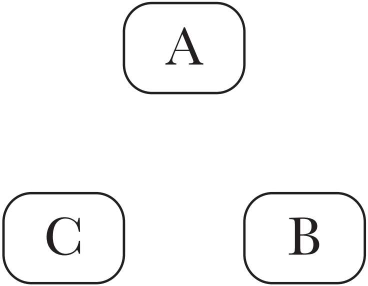
and

$$\tilde{\boldsymbol{R}} = \tilde{\boldsymbol{r}}^{-1},$$

respectively.

Modular Response Analysis – Example

$$\tilde{\boldsymbol{r}} = \begin{bmatrix} -1 & 2 & 0 \\ 0 & -1 & -3 \\ 1 & 0 & -1 \end{bmatrix}$$



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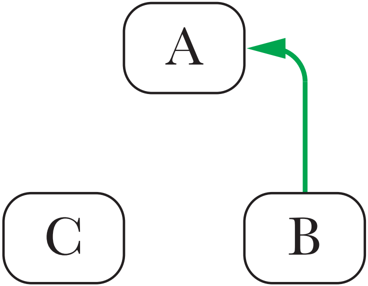

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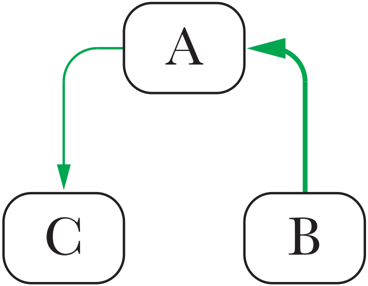
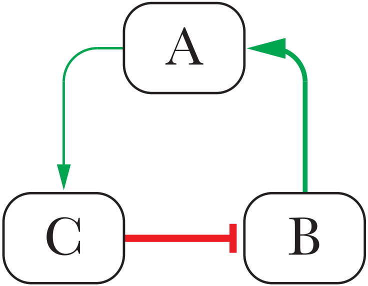


Modular Response Analysis – Example

$$\tilde{\boldsymbol{r}} = \begin{bmatrix} -1 & 2 & 0 \\ 0 & -1 & {\color{red}-3} \\ 1 & 0 & -1 \end{bmatrix}$$



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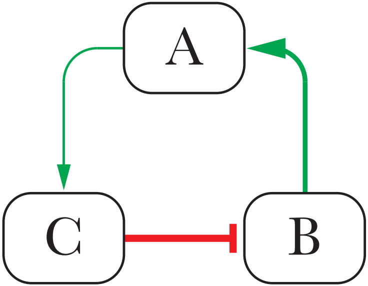

Modular Response Analysis

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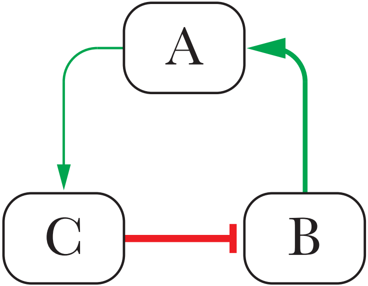


The influence between species in $\tilde{\boldsymbol{r}}$ and $\tilde{\boldsymbol{R}}$ can be categorised by

(k,l)-th entry < 0 inactivation of k by l

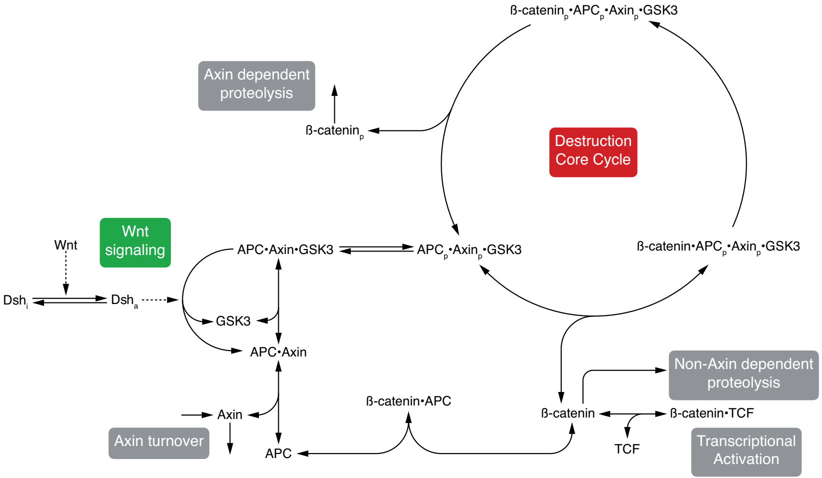
(k,l)-th entry > 0 activation of k by l

(k,l)-th entry $= 0$ no (direct) influence between k by l

with

$$k, l \in \{1, 2, ..., m_0\}$$

Wnt model

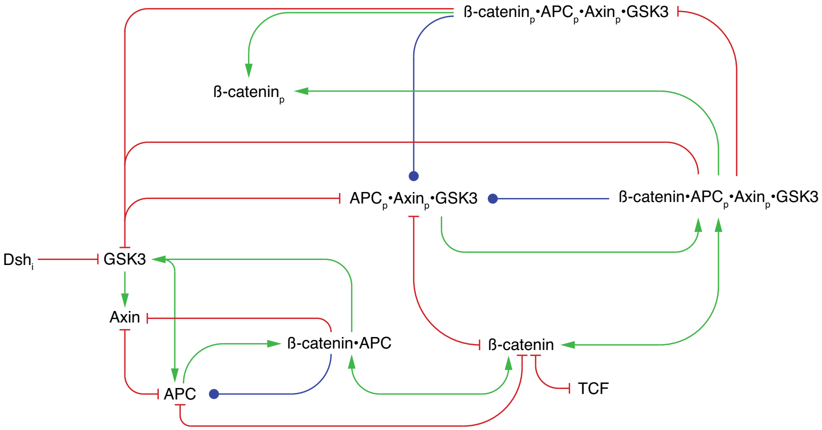


ß-catenin$_p$•APC$_p$•Axin$_p$•GSK3
Axin dependent proteolysis
ß-catenin$_p$
Destruction Core Cycle
Wnt
Wnt signaling
APC•Axin•GSK3
APC$_p$•Axin$_p$•GSK3
ß-catenin•APC$_p$•Axin$_p$•GSK3
Dsh$_i$
Dsh$_a$
GSK3
APC•Axin
Non-Axin dependent proteolysis
ß-catenin•APC
Axin
ß-catenin
ß-catenin•TCF
Axin turnover
APC
TCF
Transcriptional Activation

Elasticity sampling

1. calculate $\tilde{\boldsymbol{\epsilon}}$
2. store signs of $\tilde{\boldsymbol{\epsilon}} = \frac{\delta \boldsymbol{v}(\boldsymbol{c}(t))}{\delta \boldsymbol{c}(t)} \frac{\boldsymbol{c}(t)}{\boldsymbol{v}(\boldsymbol{c}(t))}$
3. sample $\mid \tilde{\epsilon} \mid$ randomly between 0 and 1
4. restore signs of $\tilde{\boldsymbol{\epsilon}}$
5. calculate $\tilde{\boldsymbol{r}}$ for each sample
6. observe sign changes between samples
7. plot

Local interactions of the reduced model



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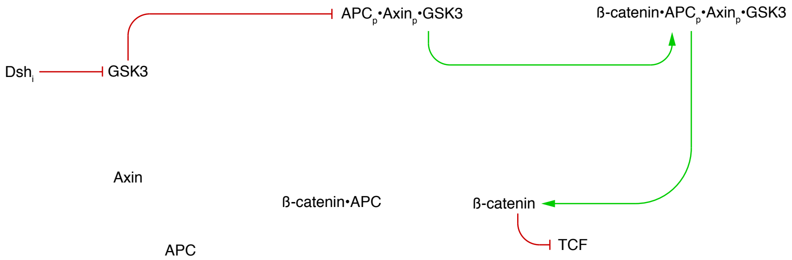
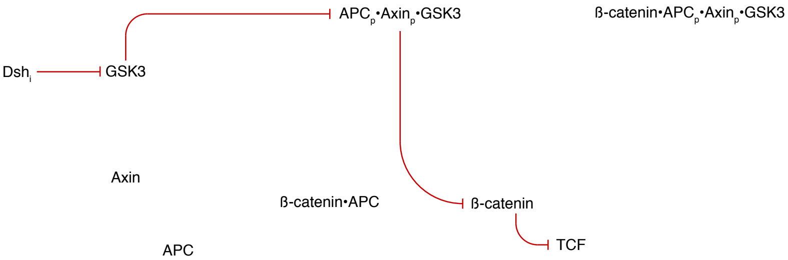


⇒ Input inhibits output

Local interactions of the reduced model



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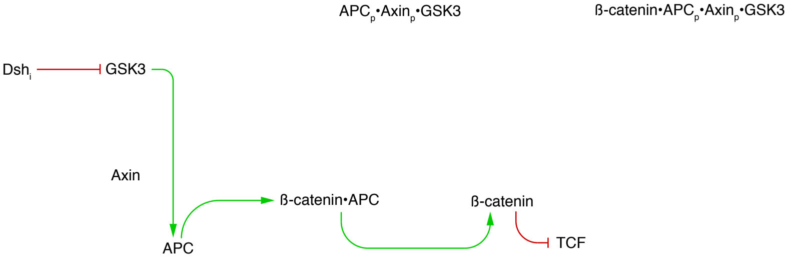

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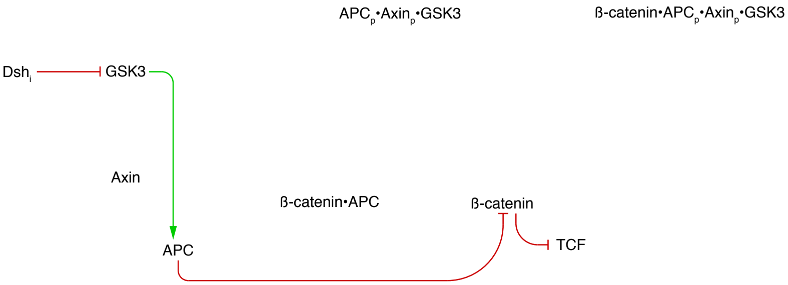

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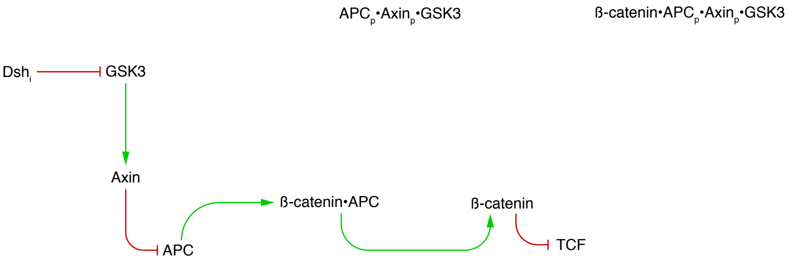

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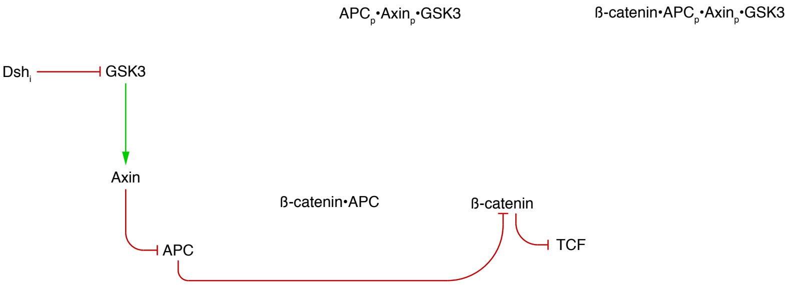

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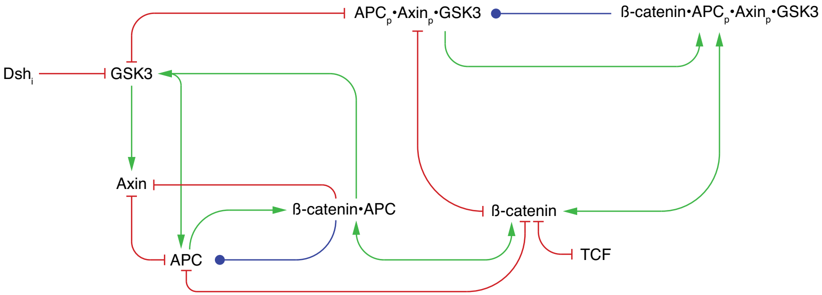


Effect of $\mathsf{Dsh_i}$ on TCF varies with the use of local interactions.
⇒ global interactions

$$\tilde{\boldsymbol{R}}_{(\mathsf{Dsh_i},\mathsf{TCF})} \leq 0$$

⇒ Wnt stimulus has no negative effect on transcription

Elasticity sampling applied to 4 models

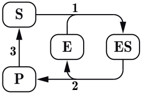


Figure: Example: 4 species, 3 reactions

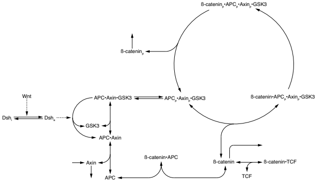


Figure: Wnt: 15 species, 17 reactions

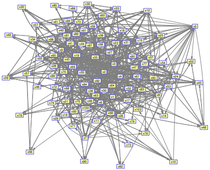
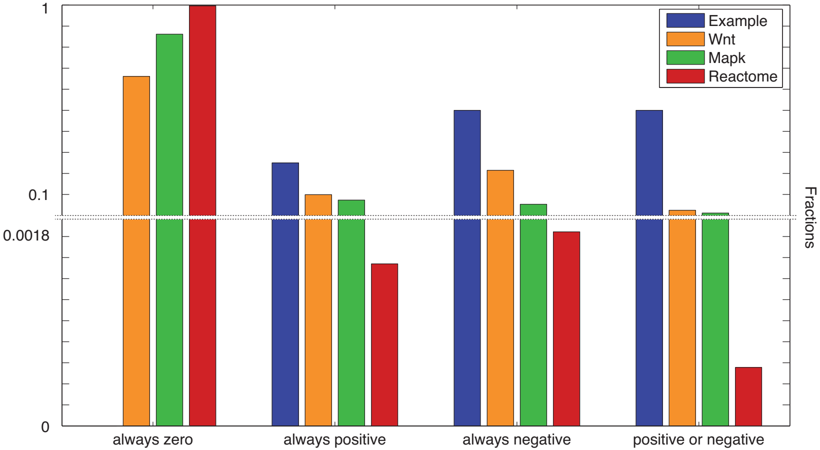


Figure: Schöberl: 97 species, 148 reactions

Figure: Reactome: 6232 species, 3652 reactions

Sign distribution after 1000 samples



Summary

Conservation and modular response analysis

- effective algorithm based on sparse matrix operations
- transform reaction networks to interaction networks

Sampling experiments

- large definiteness (99%) of interactions

Even without knowing the reaction network in detail, its information flow can be calculated.

Acknowledgements

Group of Systems Biology of Molecular Networks

- Nils Blüthgen
- Raphaela Fritsche
- Pawel Durek
- Anja Sieber
- Nadine Schmidt
- Franziska Witzel
- Bertram Klinger
- Jörn Schmiedel

Funding