Introduction to Modular Response Analysis

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Modular Response Analysis

Untangling the wires: A strategy to trace functional interactions in signaling and gene networks

Kholodenko et al. (2002), PNAS 99:12481-12486

Inverse engineering problem:
given observable steady-state responses of the whole system to perturbations, deduce internal interactions
Underlying assumptions

- Each module reaches a steady-state that is stable on its own
- Each module $i$ communicates with other modules through only one molecular species $x_i$ (this assumption can be relaxed)
- There are module-specific parameters that can be acted upon experimentally

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Quantifying module interactions

Let us consider the evolution of module $i$:

$$\dot{x}_i = f_i(x, p)$$

At steady-state of module $i$:

$$f_i(x, p) = 0$$

$$\frac{\partial f_i}{\partial x_i} \frac{\partial x_i}{\partial x_j} + \frac{\partial f_i}{\partial x_j} = 0$$

$$\frac{\partial x_i}{\partial x_j} = -\left(\frac{\partial f_i}{\partial x_j}\right) / \left(\frac{\partial f_i}{\partial x_i}\right)$$

expresses the sensitivity of module $i$ to other modules.
Quantifying module interactions

One defines local response coefficients reflecting how module $i$ at steady-state responds to changes in the output of module $j$ with other modules unchanged:

$$
\begin{align*}
    r_{ij} &= \left( \frac{\partial \ln x_i}{\partial \ln x_j} \right)_{\text{module } i \text{ at steady-state}} \quad \text{if } i \neq j \\
    r_{ii} &= -1
\end{align*}
$$

These coefficients reflect the regulatory interactions between the modules.

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Quantifying module interactions

One defines *local response coefficients* reflecting how module \( i \) at steady-state responds to changes in the output of module \( j \), with other modules unchanged, under the assumption that each module communicates with other modules through only one species \( x_j \):

\[
\begin{aligned}
    r_{ij} &= \left( \frac{\partial \ln x_i}{\partial \ln x_j} \right)_{\text{module } i \text{ at steady-state}} \\
    r_{ii} &= -1
\end{aligned}
\]

However they are *not directly observable* in the entire system because of interactions with other modules.

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Quantifying the global system response

Global response coefficients express the observable response in module $i$ when the entire system relaxes to a new steady-state in response to a perturbation $p_j$ specific of module $j$:

$$R_{i,p_j} = \frac{d \ln x_i}{dp_j}$$
Decomposing the system response

The response of module $i$ is the sum of all responses mediated by modules $k$ and of the direct effect of the perturbation when $i = j$

$$R_{i,p_j} = \sum_{k \neq i} r_{ik} R_{k,p_j} \quad \text{for} \quad i \neq j$$

$$R_{i,p_i} = \sum_{k \neq i} r_{ik} R_{k,p_i} + \left( \frac{\partial \ln x_i}{\partial p_i} \right)_{\text{module } i \text{ at steady-state}}$$
Inferring the regulatory structure

\[ r \cdot R_p + \text{diag}(r_p) = 0 \]

where \( r_{pi} = \left( \frac{\partial \ln x_i}{\partial p_i} \right) \)

module \( i \) at steady-state

\[ r = -\text{diag}(r_p) \cdot R_p^{-1} \]

Note that \( R_p \) is nonsingular

if \( \frac{\partial f}{\partial p} \) and Jacobian \( \frac{\partial f}{\partial x} \) are nonsingular
Inferring the regulatory structure

\[ r = -\text{diag}(r_p) \cdot R_p^{-1} \]

whose diagonal terms are

\[ -1 = -r_{p_i} \left( R_p^{-1} \right)_{ii} \]

therefore

\[ \text{diag}(r_p) = \left[ \text{diag}(R_p^{-1}) \right]^{-1} \]
Inferring the regulatory structure

We can therefore derive an explicit relationship to calculate the local response matrix $r$ from the global response matrix $R_p$:

$$r = -[\text{diag}(R_p^{-1})]^{-1} \cdot R_p^{-1}$$

The matrix $r$ provides the regulatory structure of the system. It is the normalized inverse of $R_p$.

Because these relationships derive from $\dot{x}_i = f_i(x, p) = 0$ they can also be generalized to extremal responses, not only to steady-state responses.
Introducing noise / redundancy in the data

Andrec et al. (2005), J. Theoret. Biol. 232:427-441

Another way to posit the problem is to note that each row $r_i$ of the regulation matrix is orthogonal to $n-1$ response vectors $R_{pj}$ ($j \neq i$).

As a consequence in the absence of noise $r_i$ is uniquely defined as normal to the hyperplane generated by $\left( R_{pj} \right)$.
Introducing noise / redundancy in the data

In the absence of noise adding more data would leave unchanged \( \text{rank}(\mathbf{R}_{p_j}) = n - 1 \)

However in the presence of noise \( (\mathbf{R}_{p_j}) \) will have full rank \( n \) because the noise is full rank.

One then uses SVD to reduce its rank to \( n-1 \) in order to delineate the most likely hyperplane supporting \( (\mathbf{R}_{p_j}) \)

This in turn determines the most likely \( r_i \)

It is colinear with the left singular vector associated with the smallest singular value.

This procedure is akin to total least squares regression.
Example of MRA success

Growth factor-induced MAPK network topology shapes Erk response determining PC-12 cell fate


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Global responses

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Local responses

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Different responses of the MAPK cascade to EGF and NGF are accompanied by a different feed-back pattern. The positive loop generates a bistable behaviour in the presence of NGF.
Unimodal response to EGF

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Bimodal response to NGF

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