Introduction to Modular Response Analysis

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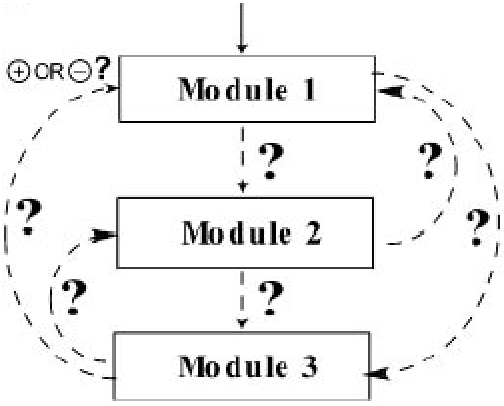
Modular Response Analysis

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

Quantifying module interactions

Let us consider the evolution of module i :

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

At steady-state of module i :

$$f_i(\mathbf{x}, \mathbf{p}) = 0$$

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

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

expresses the sensitivity of module i to other modules j.

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:

$$\begin{cases} r_{ij} := \dfrac{x_j}{X_i}\dfrac{\partial X_i}{\partial x_j} = \left(\dfrac{\partial \ln X_i}{\partial \ln x_j}\right)_{\text{module } i \text{ at steady-state}} & \text{if } i \neq j \\ r_{ii} := -1 & \end{cases}$$

These coefficients reflect the regulatory interactions between the modules.

Quantifying module interactions

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

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 :

$$R_{i,p_j} := \left(\frac{d \ln X_i}{dp_j} \right)_{\text{entire system at steady-state}}$$

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 $i = j$

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

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

Inferring the regulatory structure

$$\mathbf{r} \cdot \mathbf{R_p} + diag\left(\mathbf{r_p}\right) = 0$$

$$\text{where } r_{p_i} = \left(\frac{\partial \ln X_i}{\partial p_i} \right)_{\text{module } i \text{ at steady-state}}$$

$$\mathbf{r} = -diag\left(\mathbf{r_p}\right) \cdot \mathbf{R_p}^{-1}$$

Note that $\mathbf{R_p}$ is nonsingular

if $\frac{\partial \mathbf{f}}{\partial \mathbf{p}}$ and Jacobian $\frac{\partial \mathbf{f}}{\partial \mathbf{x}}$ are nonsingular

Inferring the regulatory structure

$$\mathbf{r} = -diag\left(\mathbf{r_p}\right) \cdot \mathbf{R_p}^{-1}$$

whose diagonal terms are

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

therefore

$$diag\left(\mathbf{r_p}\right) = \left[diag\left(\mathbf{R_p}^{-1}\right)\right]^{-1}$$

Inferring the regulatory structure

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

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

The matrix $\mathbf{r}$ provides the regulatory structure of the system. It is a normalized inverse of $\mathbf{R_p}$

Because these relationships derive from $\dot{x}_i = f_i(\mathbf{x}, \mathbf{p}) = 0$ 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

Sontag (2008) *Essays Biochem.* 45:161-176

Another way to posit the problem is to note that each row $\mathbf{r}_i$ of the regulation matrix is orthogonal to n-1 response vectors

$$\mathbf{R}_{p_j} \quad (j \neq i)$$

As a consequence in the absence of noise $\mathbf{r}_i$ is uniquely defined as normal to the hyperplane generated by $\left(\mathbf{R}_{p_j}\right)$

Introducing noise / redundancy in the data

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

However in the presence of noise $\left(\mathbf{R}_{p_j}\right)$ 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 $\left(\mathbf{R}_{p_j}\right)$

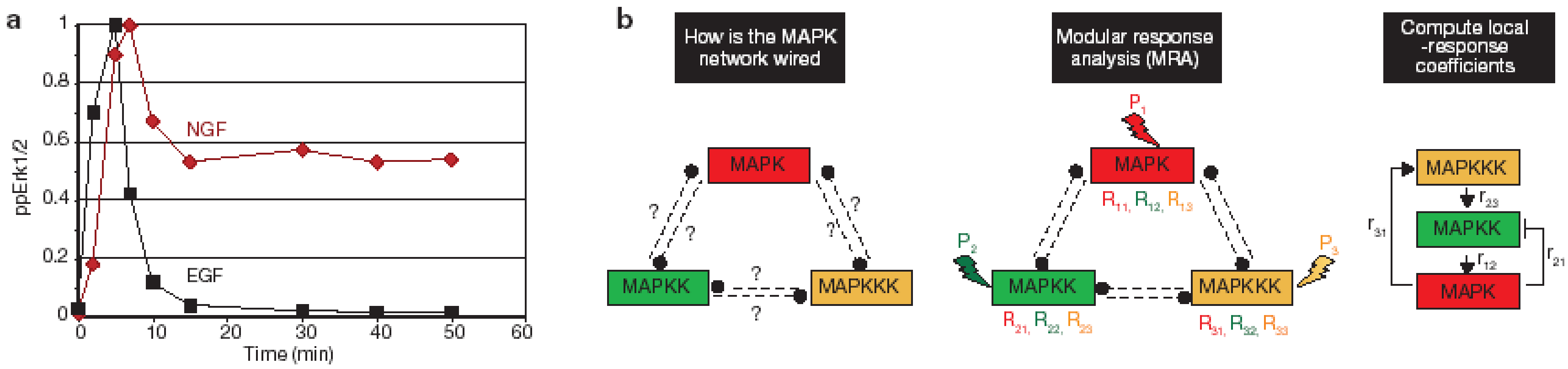
This in turn determines the most likely $\mathbf{r}_i$
It is colinear with the left singular vector associated with the smallest singular value.

This procedure is akin to total least squares regression.

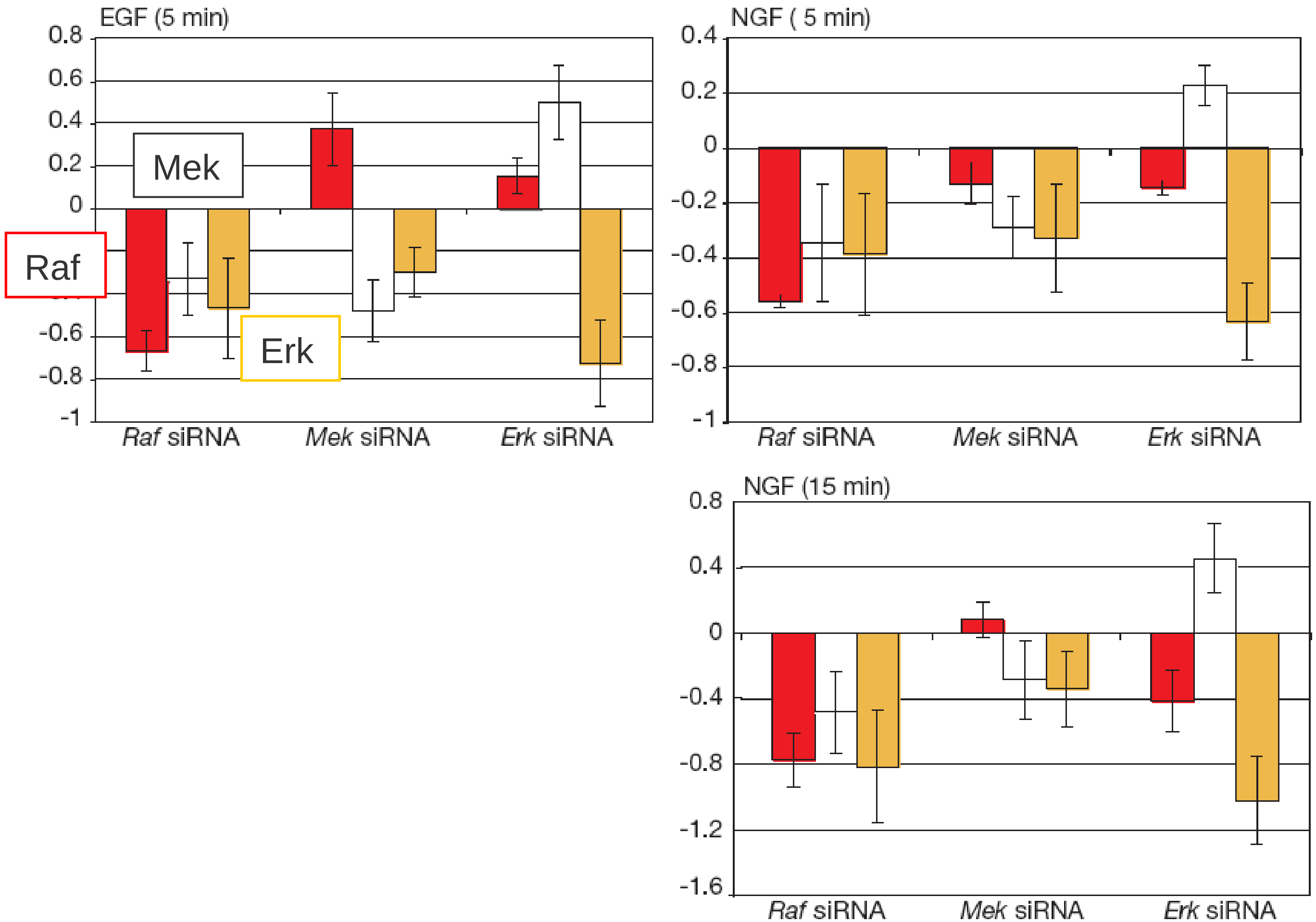
Example of MRA success

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

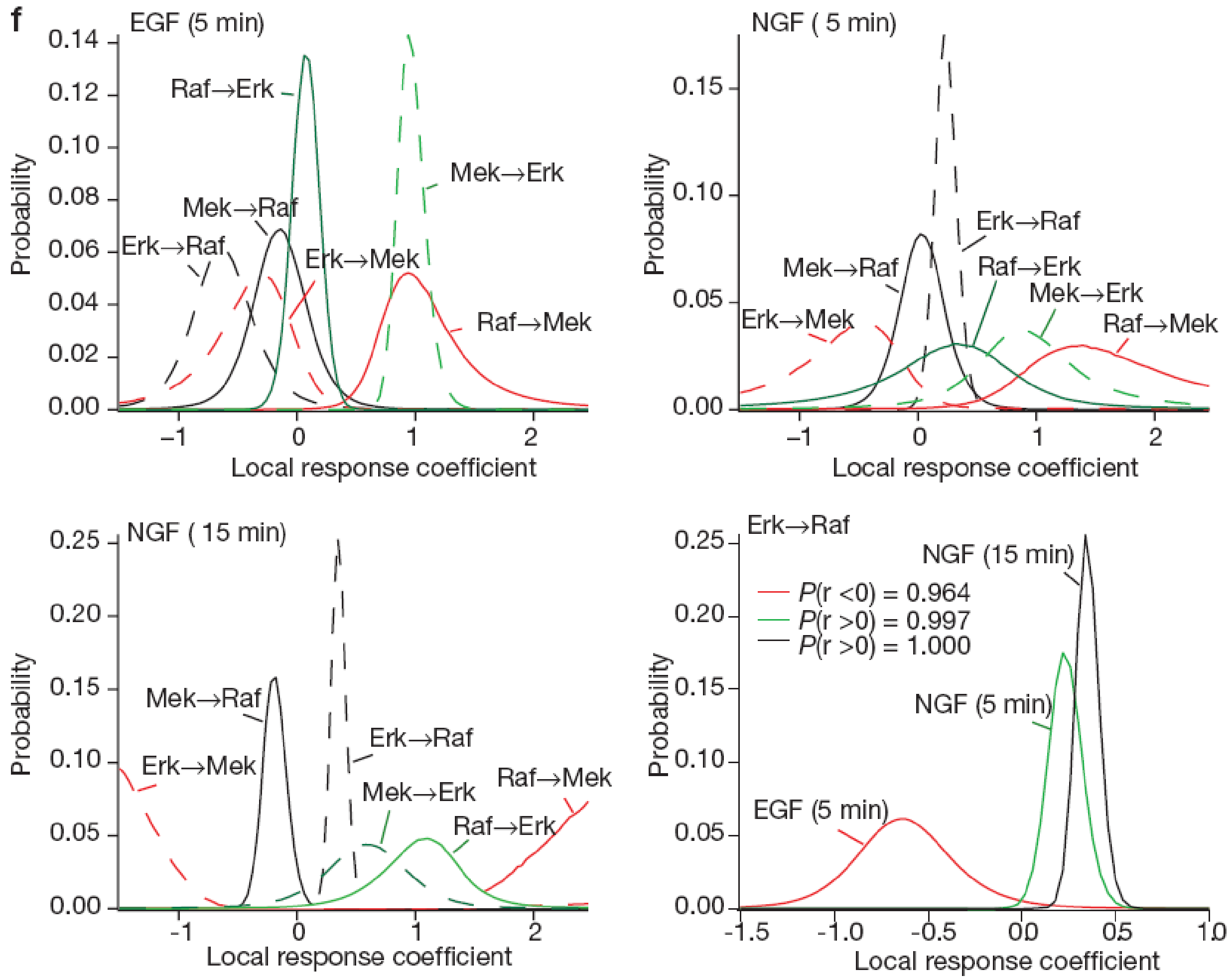
Santos *et al.* (2007) *Nature Cell Biol*. 9:324-330



Global responses

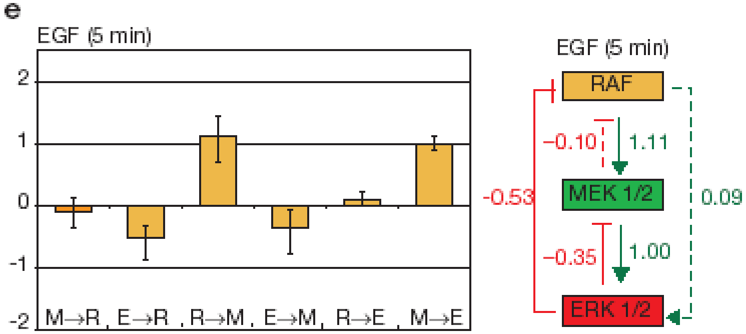


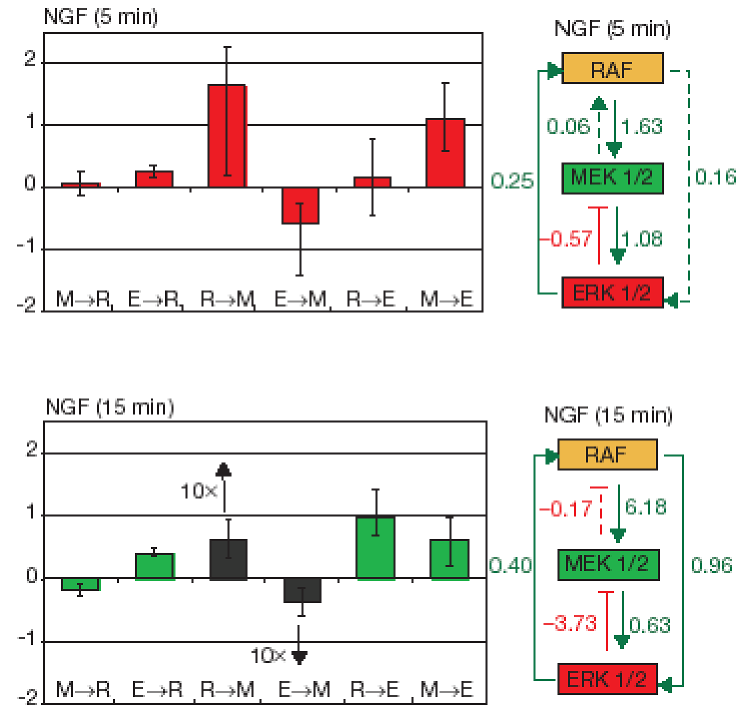
Local responses



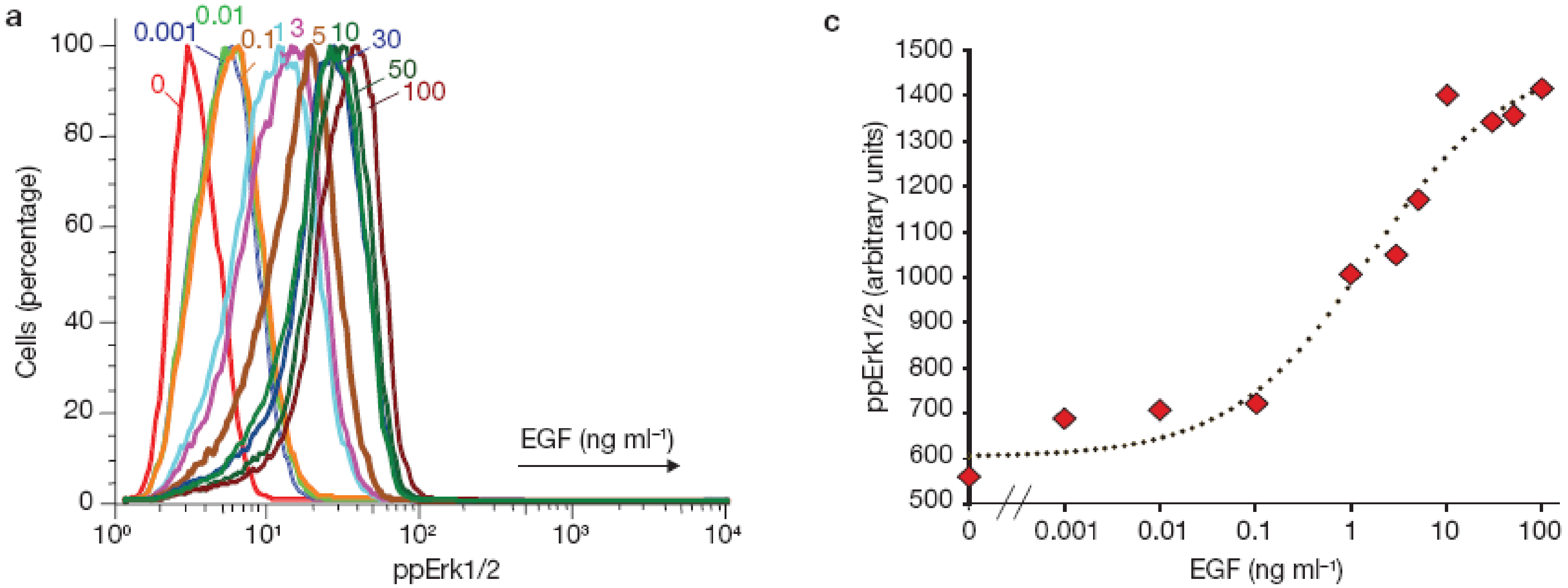
MAPK regulatory structure

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



Bimodal response to NGF