Modeling biochemical signal transduction in heterogeneous cell populations

Steffen Waldherr, Jan Hasenauer, and Frank Allgöwer

Institute for Systems Theory and Automatic Control
Universität Stuttgart

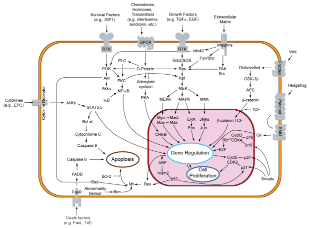
August 28, 2011

The big picture

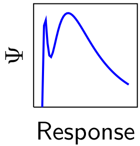
Common Stimulus

0.5 μM

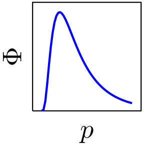
Intracellular signal transduction



Heterogeneous response



Cellular heterogeneity



Main points

Heterogeneous cellular properties lead to a heterogeneous response from a common stimulus

- Heterogeneity formulated in terms of probability densities
- May not be a simple density, nonparametric description needed

Response of non-interacting heterogeneous populations is **linear**!

- Linear is easy
- Makes analysis algorithms computationally efficient

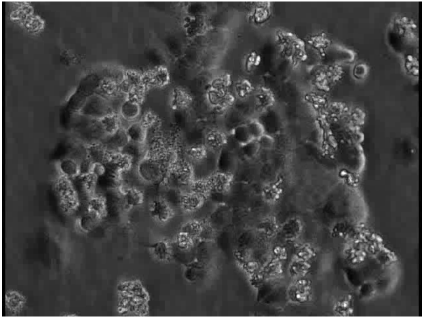
Outline

1. Examples of heterogeneity in cellular signaling
2. Construction of heterogeneous signaling models
3. Simulation and analysis of heterogeneous signaling models

Outline

1. Examples of heterogeneity in cellular signaling
2. Construction of heterogeneous signaling models
3. Simulation and analysis of heterogeneous signaling models

Apoptosis death time distributions



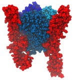
Institute for Cell Biology and Immunology,
Universität Stuttgart

Observations

- Cells in a clonal population die at different times
- Some cells survive completely
- Heterogeneity in protein amounts of caspases and death receptors observed

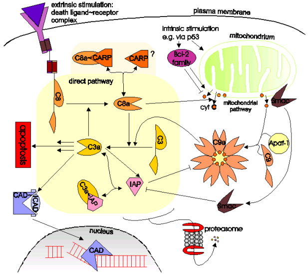
Heterogeneous apoptotic signaling

Apoptotic stimulus

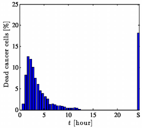


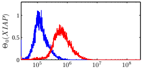
10 ng/ml TNF

Cell death signalling



Death time distribution





Heterogeneous caspase & receptor amounts

Outline

1. Examples of heterogeneity in cellular signaling
2. Construction of heterogeneous signaling models
3. Simulation and analysis of heterogeneous signaling models

The intracellular signaling model

- Single cell mathematical model as starting point:

$$\dot{x} = Sv(x, p), \qquad x(0) = x_0$$

- **Assumption:** Pathway components x and structure S, $v(\cdot, \cdot)$ are the same for all cells, but parameters p and initial state x_0 may be different.
- Ensemble model for N cells indexed i, $i = 1, \ldots, N$:

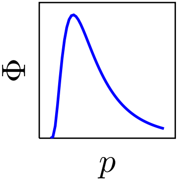
$$\dot{x}^{(i)} = Sv(x^{(i)}, p^{(i)}), \qquad x^{(i)}(0) = x_0^{(i)}$$

Key assumptions / simplifications

- Heterogeneity only in parameters and initial conditions
- No interactions among cells

Formulating the cellular heterogeneity

- Probability density function Φ for parameter values



- For any given cell i: $p^{(i)} \sim \Phi$
- $\Phi(p)$ is also the number density of cells in the population with parameter p

Ensemble model for cell population

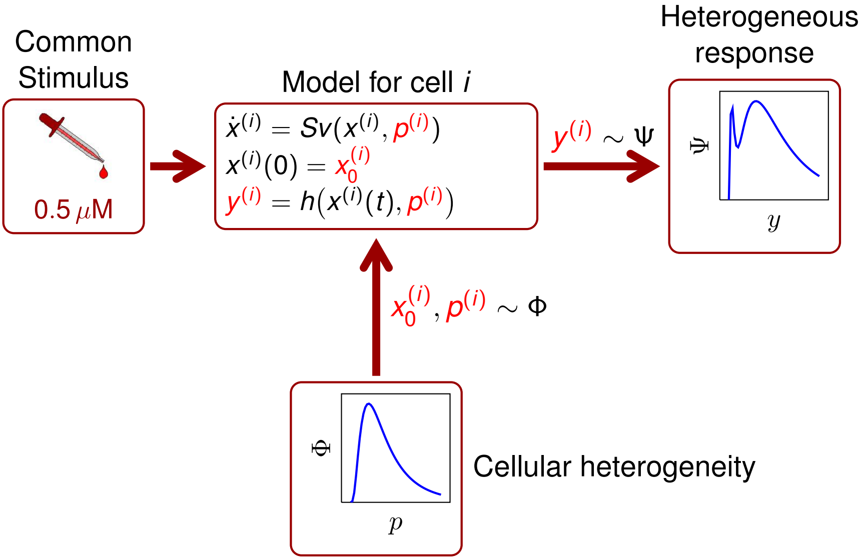
$$\dot{x}^{(i)} = Sv(x^{(i)}, p^{(i)}), \qquad x^{(i)}(0) = x_0^{(i)}$$

$$\mathrm{Prob}(p^{(i)} \in \mathcal{P}, x_0^{(i)} \in \mathcal{X}) = \int_{\mathcal{P}\times\mathcal{X}} \Phi(x,p)dpdx$$

The response distribution

- Response of individual cell $y^{(i)}$ is a function of the state trajectory:
$$y^{(i)} = h\big(x^{(i)}(t, p^{(i)}, x_0^{(i)}), p^{(i)}\big)$$
- Examples:
  - One concentration at time t_k: $y = x_j(t_k)$
  - Time point at which a threshold is crossed: $y = \inf\{t : x_j(t) \geq 0.5 x_k(0)\}$
- Response heterogeneity can be described by a probability density function $\Psi(y)$:
$$\mathrm{Prob}(y^{(i)} \in \mathcal{Y}) = \int_{\mathcal{Y}} \Psi(y) dy$$
- $\Psi(y)$ is also the number density of cells with response y.

Model for heterogeneous populations



Common Stimulus

0.5 μM

Model for cell *i*

$$\dot{x}^{(i)} = Sv(x^{(i)}, p^{(i)})$$

$$x^{(i)}(0) = x_0^{(i)}$$

$$y^{(i)} = h\big(x^{(i)}(t), p^{(i)}\big)$$

$y^{(i)} \sim \Psi$

Heterogeneous response

$x_0^{(i)}, p^{(i)} \sim \Phi$

Cellular heterogeneity

Linearity of heterogeneous populations

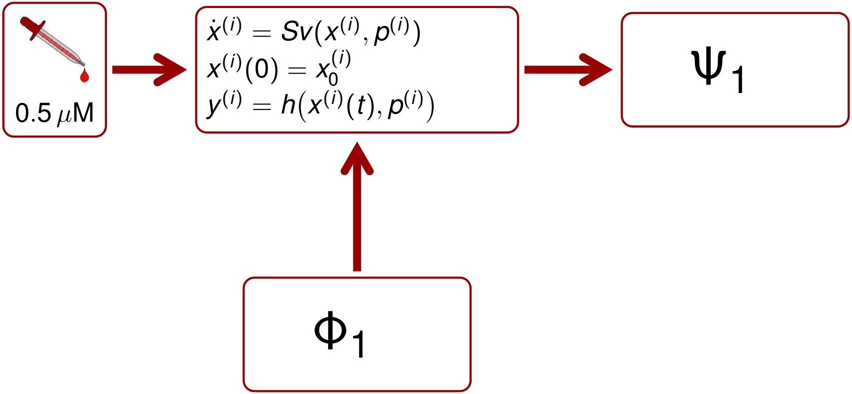
Linearity

$$F(a+b) = F(a) + F(b)$$

Linearity of heterogeneous populations

Linearity

$$F(a+b)=F(a)+F(b)$$



0.5 μM

$$\dot{x}^{(i)} = Sv(x^{(i)}, p^{(i)})$$
$$x^{(i)}(0) = x_0^{(i)}$$
$$y^{(i)} = h\big(x^{(i)}(t), p^{(i)}\big)$$

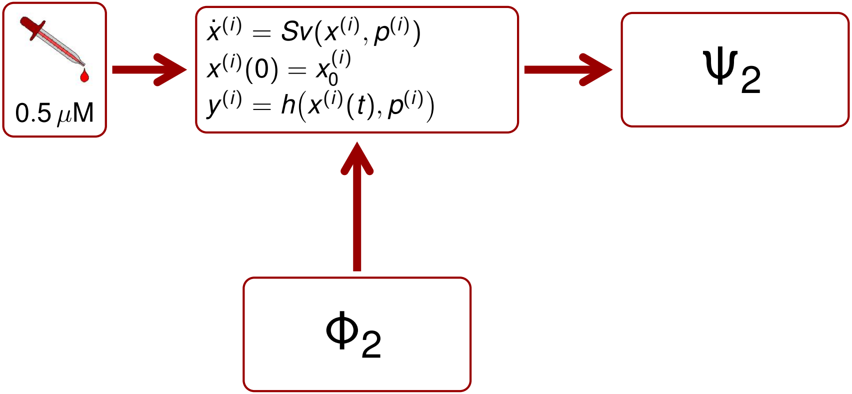
Ψ_1

Φ_1

Linearity of heterogeneous populations

Linearity

$$F(a+b) = F(a) + F(b)$$



0.5 μM

$$\dot{x}^{(i)} = Sv(x^{(i)}, p^{(i)})$$
$$x^{(i)}(0) = x_0^{(i)}$$
$$y^{(i)} = h\big(x^{(i)}(t), p^{(i)}\big)$$

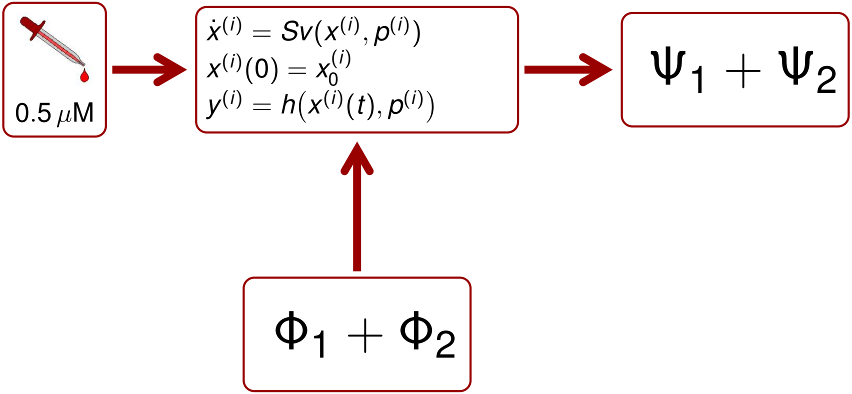
Ψ_2

Φ_2

Linearity of heterogeneous populations

Linearity

$$F(a+b) = F(a) + F(b)$$



0.5 μM

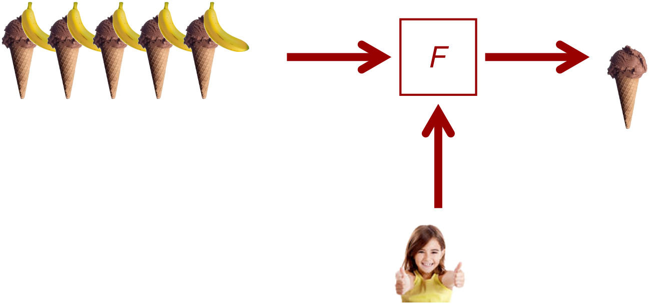
$$\begin{aligned} \dot{x}^{(i)} &= Sv(x^{(i)}, p^{(i)}) \\ x^{(i)}(0) &= x_0^{(i)} \\ y^{(i)} &= h\left(x^{(i)}(t), p^{(i)}\right) \end{aligned}$$

$$\Psi_1 + \Psi_2$$

$$\Phi_1 + \Phi_2$$

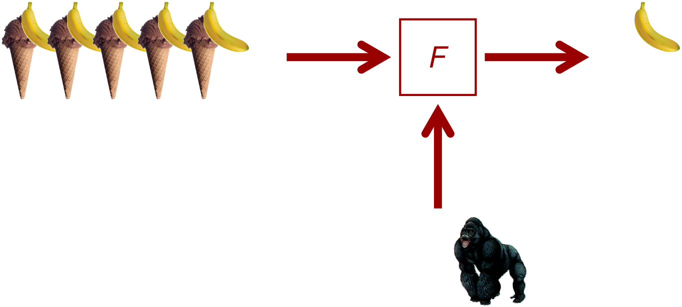
On linearity

- Reminder: No interactions among cells!



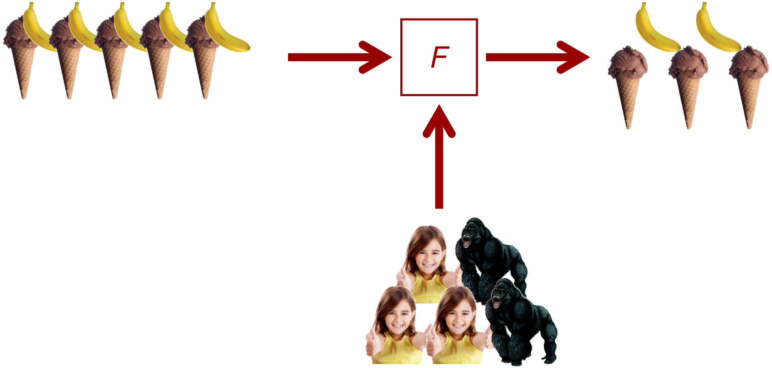
On linearity

- Reminder: No interactions among cells!



On linearity

- Reminder: No interactions among cells!



$F(3 \times$  $+ 2 \times$  $) = 3 \times$  $+ 2 \times$ 

Formulation as partial differential equation – state density function

Modeling approach

- Probability density function Θ for extended state (= concentrations + parameters)

$$\mathrm{Prob}(x(t) \in \mathcal{X}, p \in \mathcal{P}) = \int_{\mathcal{X}\times\mathcal{P}} \Theta(t, x, p)dxdp$$

Resulting equation

- Fokker-Planck equation with a drift term only

$$\frac{\partial\Theta(t, x, p)}{\partial t} = -\mathrm{div}_{(x,p)}(Sv(x, p)\Theta(t, x, p))$$

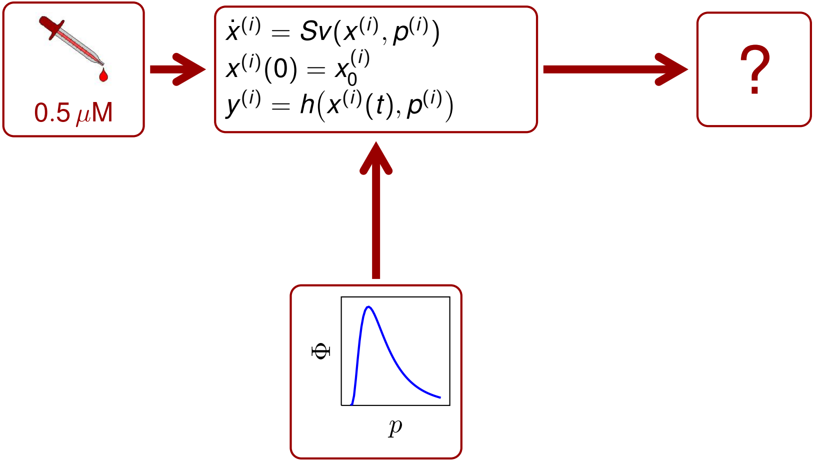
- Initial condition

$$\Theta(0, x, p) = \Phi(x, p)$$

Outline

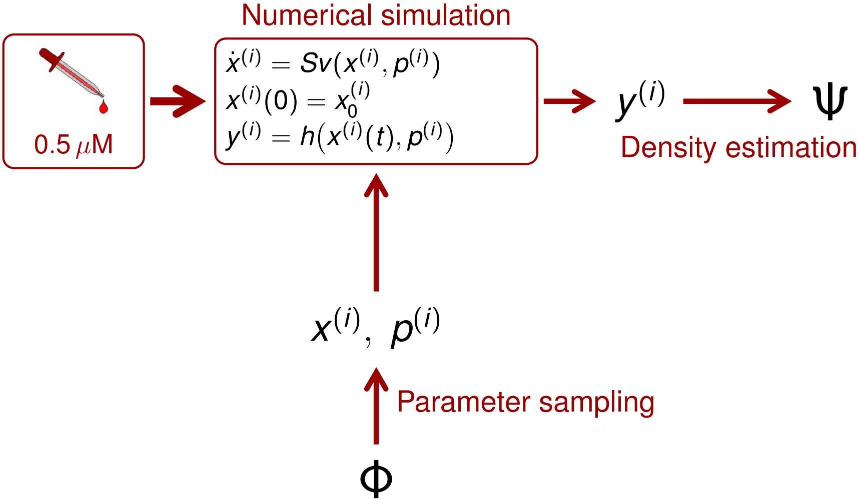
1. Examples of heterogeneity in cellular signaling
2. Construction of heterogeneous signaling models
3. Simulation and analysis of heterogeneous signaling models

Simulating heterogeneous cell populations



$$\dot{x}^{(i)} = Sv(x^{(i)}, p^{(i)})$$
$$x^{(i)}(0) = x_0^{(i)}$$
$$y^{(i)} = h\big(x^{(i)}(t), p^{(i)}\big)$$

Simulating heterogeneous cell populations



Numerical simulation

0.5 μM

$$\dot{x}^{(i)} = Sv(x^{(i)}, p^{(i)})$$
$$x^{(i)}(0) = x_0^{(i)}$$
$$y^{(i)} = h\big(x^{(i)}(t), p^{(i)}\big)$$

$$y^{(i)} \longrightarrow \Psi$$

Density estimation

$$x^{(i)},\ p^{(i)}$$

Parameter sampling

$$\Phi$$

Density estimation of the response distribution

- Histogram

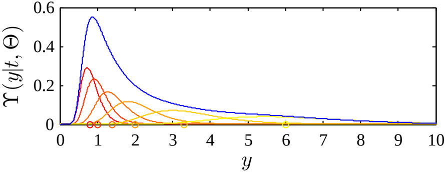
$$\Psi(y) = \frac{1}{N(y_{k+1} - y_k)} \#\{i : y_k \leq y^{(i)} \leq y_{k+1}\}$$

- Naive estimator (“Sliding histogram”):

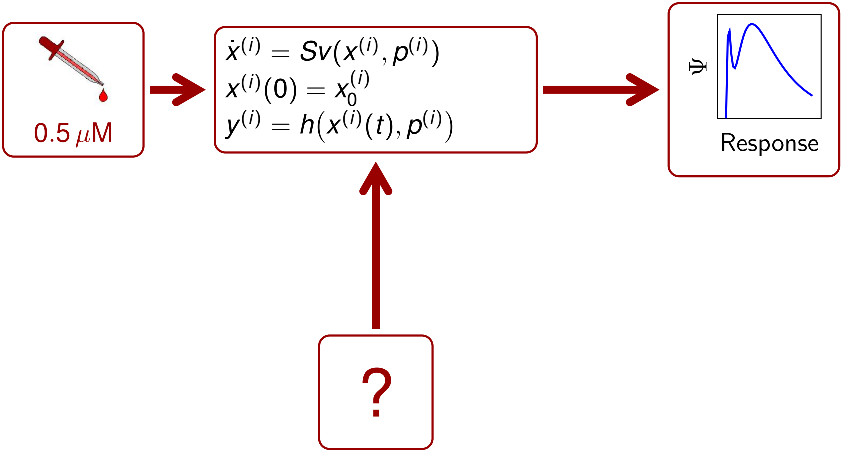
$$\Psi(y) = \frac{1}{Nh} \#\{i : y - \frac{h}{2} \leq y^{(i)} \leq y + \frac{h}{2}\}$$

- Kernel density estimator:

$$\Psi(y) = \frac{1}{N} \sum_{i=1}^{N} \mathcal{K}_{y^{(i)}}(y)$$



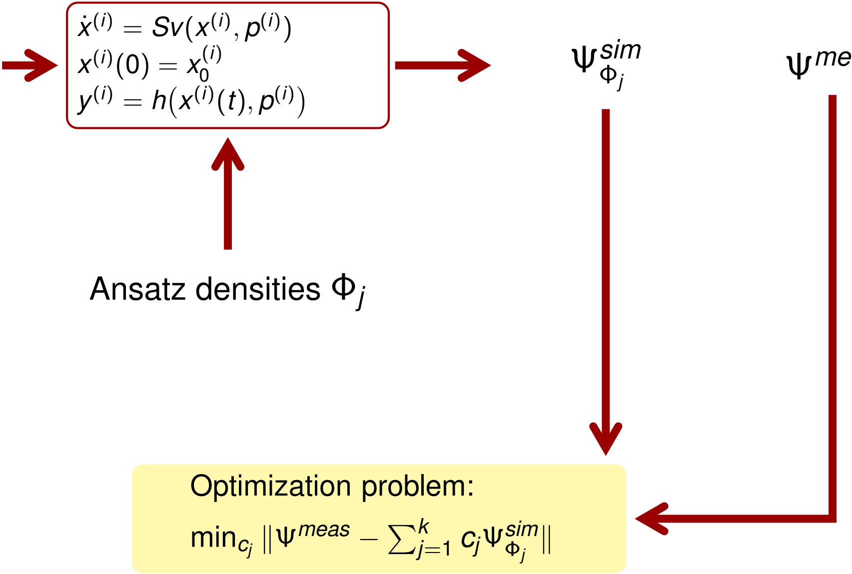
Parameter estimation from population snapshot data



0.5 μM

$$\dot{x}^{(i)} = Sv(x^{(i)}, p^{(i)})$$
$$x^{(i)}(0) = x_0^{(i)}$$
$$y^{(i)} = h\big(x^{(i)}(t), p^{(i)}\big)$$

Optimizing over the cellular heterogeneity



$$\dot{x}^{(i)} = Sv(x^{(i)}, p^{(i)})$$
$$x^{(i)}(0) = x_0^{(i)}$$
$$y^{(i)} = h\big(x^{(i)}(t), p^{(i)}\big)$$

$\Psi_{\Phi_j}^{sim}$

Ψ^{meas}

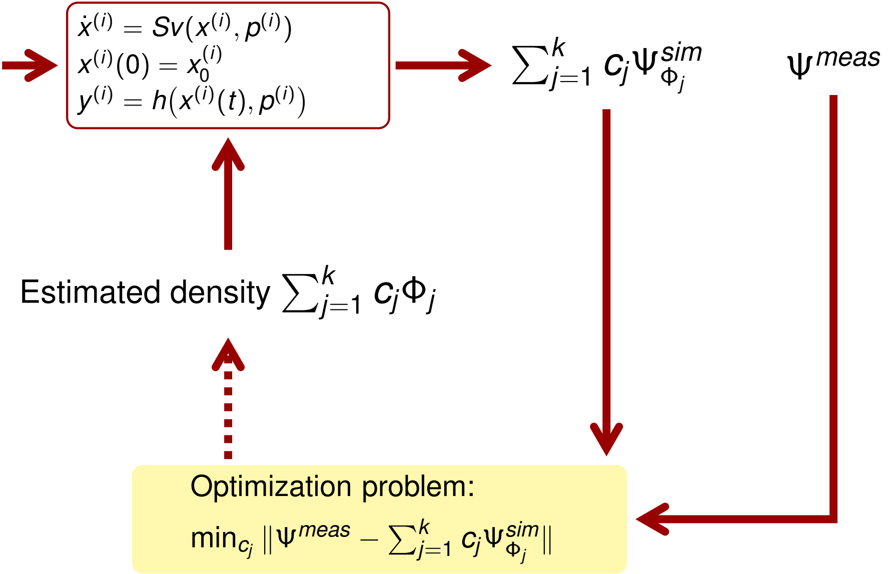
Ansatz densities Φ_j

Optimization problem:

$\min_{c_j} \|\Psi^{meas} - \sum_{j=1}^{k} c_j \Psi_{\Phi_j}^{sim}\|$

BMC Bioinformatics 12:125 (2011)

Optimizing over the cellular heterogeneity



$$\dot{x}^{(i)} = Sv(x^{(i)}, p^{(i)})$$
$$x^{(i)}(0) = x_0^{(i)}$$
$$y^{(i)} = h\big(x^{(i)}(t), p^{(i)}\big)$$

$\sum_{j=1}^{k} c_j \Psi_{\Phi_j}^{sim}$

Ψ^{meas}

Estimated density $\sum_{j=1}^{k} c_j \Phi_j$

Optimization problem:

$\min_{c_j} \|\Psi^{meas} - \sum_{j=1}^{k} c_j \Psi_{\Phi_j}^{sim}\|$

BMC Bioinformatics 12:125 (2011)

Wrap-up

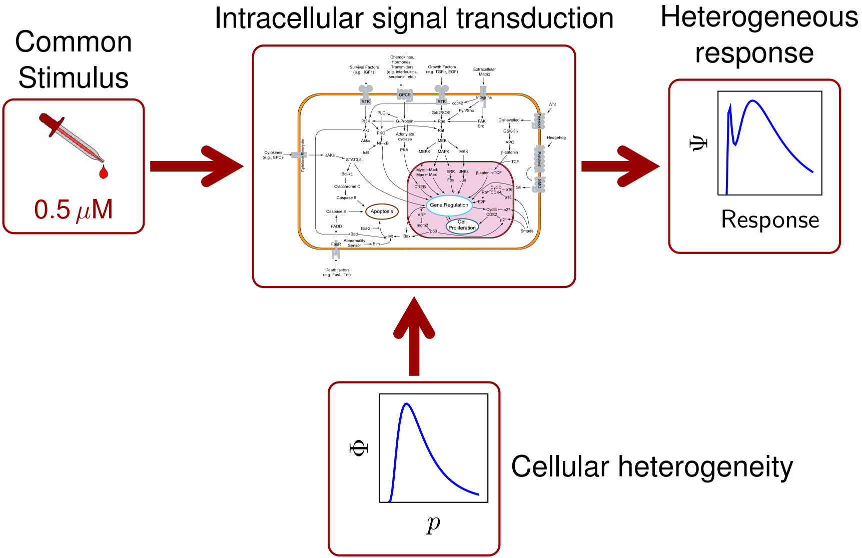
Heterogeneous cellular properties lead to a heterogeneous response from a common stimulus

- Heterogeneity formulated in terms of probability distributions
- Simulation by parameter sampling and density estimation

Response of non-interacting heterogeneous populations is **linear**!

- Makes repeated simulations computationally cheap
- Optimizing for measured response distribution, ...?

The big picture (again)



Common Stimulus

0.5 μM

Intracellular signal transduction

Heterogeneous response

Cellular heterogeneity