Systems Biology of the JAK-STAT signalling pathway of the Epo-Receptor

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Outline

- **Systems Biology**
- **JAK-STAT pathway of the Epo receptor**
- **A dynamical model for JAK-STAT pathway**
- **Observing the unobservable**
- *In silico* **biology: Predicting a new experiment**
- **Infering systems' properties**

Enlarging Physics, Math, Engineering

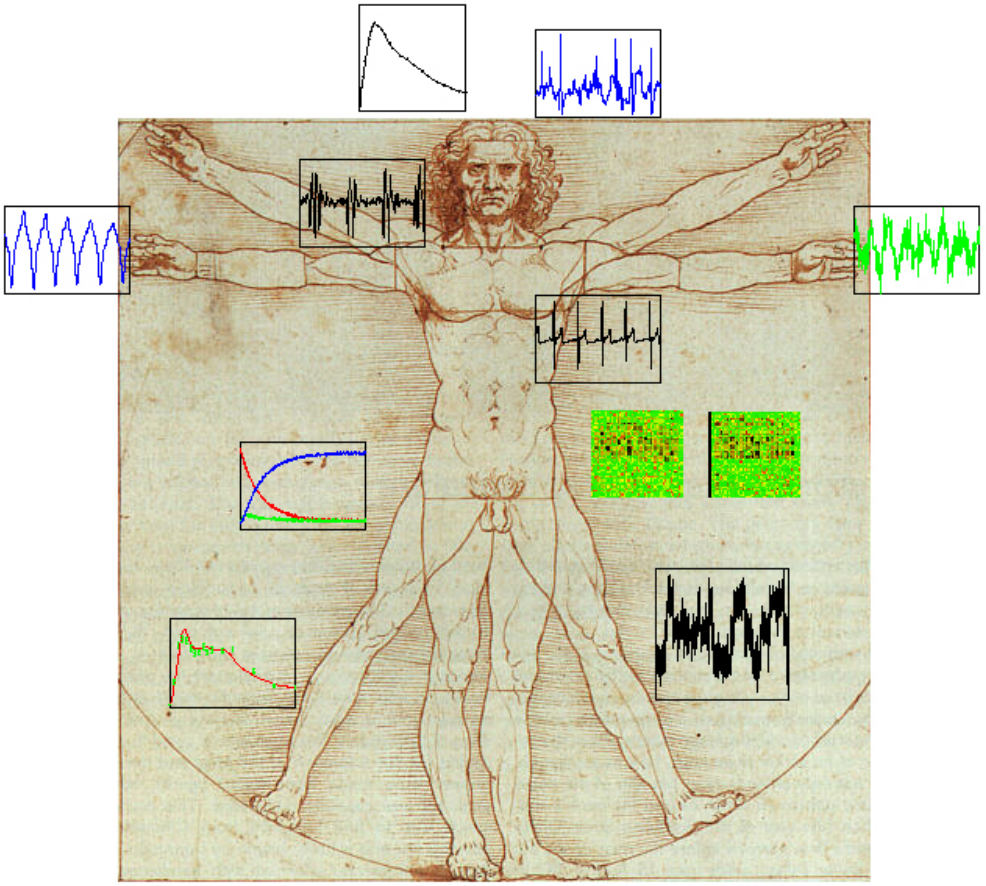
- **Since Newton:**

  Mathematization of inanimate nature

- **21st century:**

  Additionally: Mathematization of animate nature

Man : A Dynamical System



Diseases caused or expressed by malfunction of dynamical processes

Two Directions in Systems Biology

- **Putting all the omics together**

  Top-down, so far: large scale, qualitative, static

- **Understanding biomedical networks by data-based mathematical modelling of their dynamical behavior**

  Bottom-up, so far: small scale, quantitative, dynamic

  Both approaches will converge to: large scale, quantitative, dynamic

  Common ground: Investigating networks

Direction II in Systems Biology

Understanding biomedical systems by data-based mathematical modelling of their dynamical behavior

From components and structure to behavior of networks

Why Mathematical Modelling in BioMed?

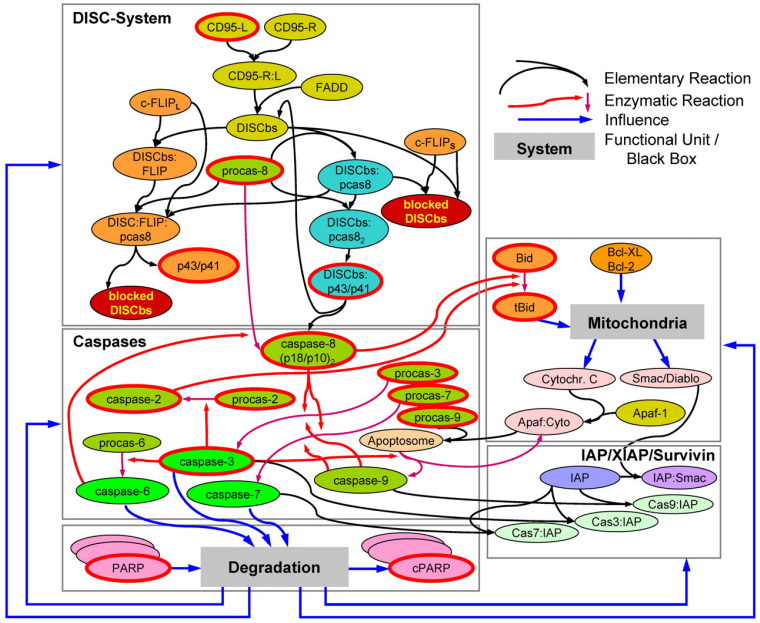
- Make assumptions explicit
- Understand essential properties, failing models
- Condense information, handle complexity
- Understand role of dynamical processes, e.g. feed-back
- Impossible experiments become possible
- Prediction and control
- Understand what is known
- Discover general principles
- "You don't understand it until you can model it"

Why Modelling in Cell Biology?

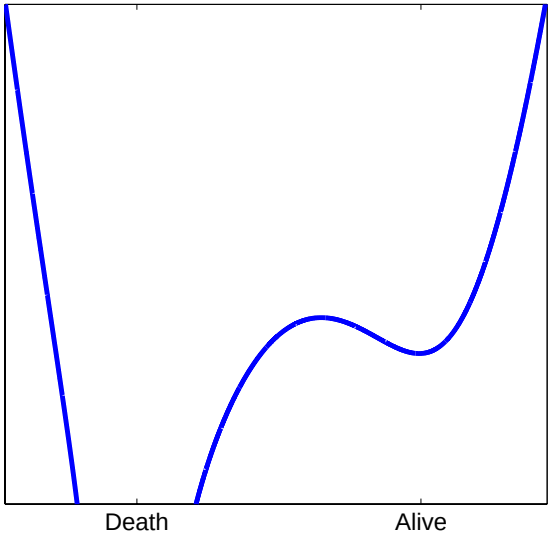
- **Basic Research**
  - **Genomes are sequenced, but ...**
  - **... function determined by regulation**
  - **Regulation = Interaction & Dynamics**
  - **Function: Property of dynamic network**
  - **"Systems Biology"**
- **Application**
  - **Drug development takes 10 years and 1 bn $/€**
  - **Reduce effort by understanding systems**

Examples of Networks I: Apoptosis

Pathway cartoon



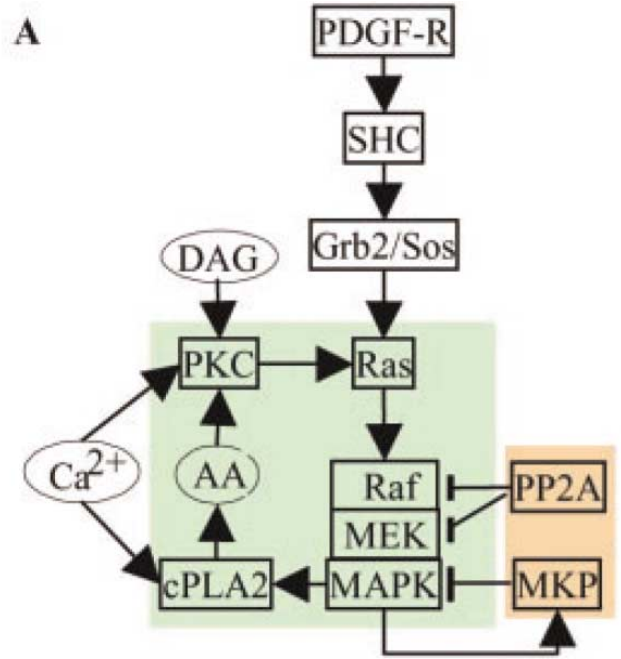
System's behavior



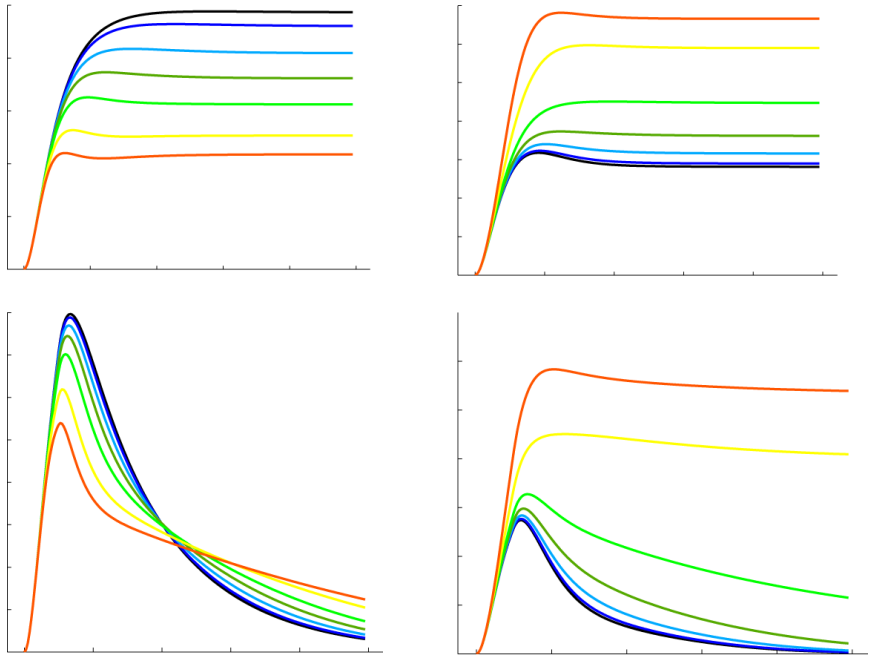
Threshold behavior, one-way bistable

Examples of Networks II: MAP Kinase

Pathway cartoon

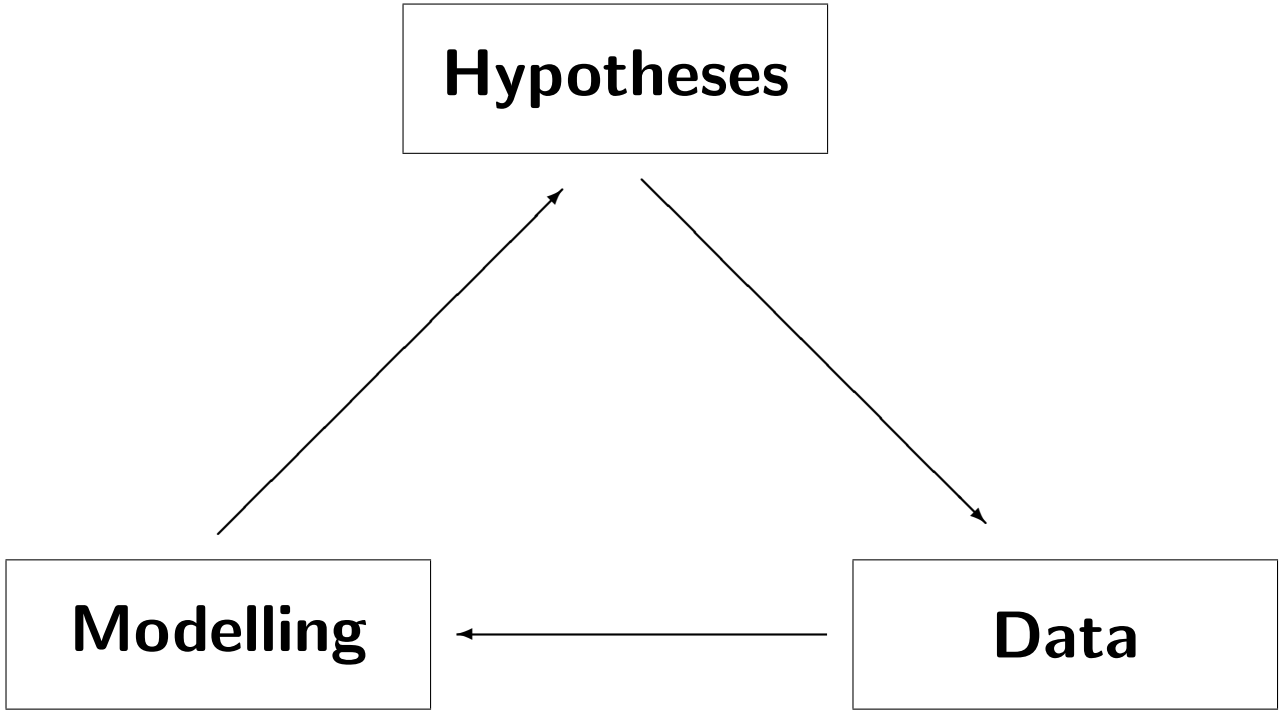


System's behavior



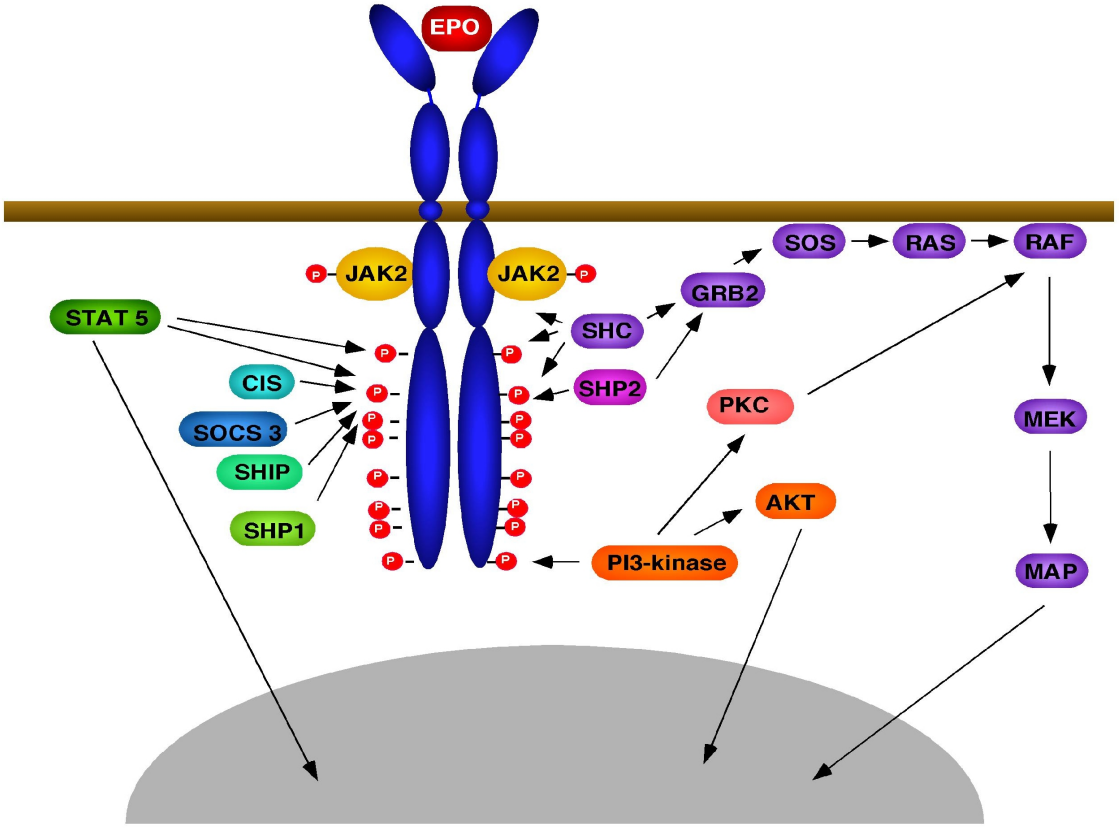
Time scales/parameters important

The Systems Biology Cycle: A Process



Make the cycle happen: Wet/dry couple projects

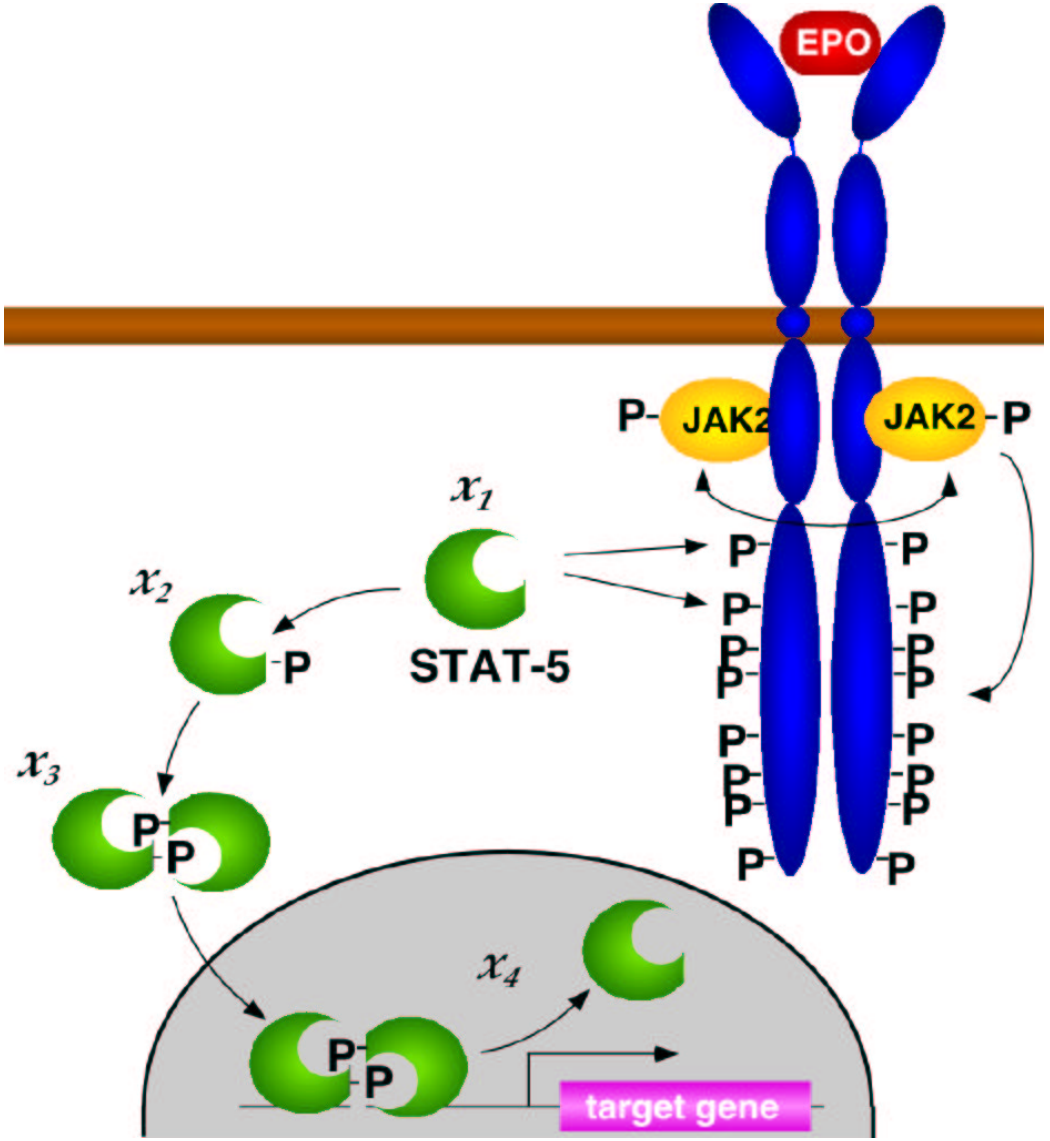
Signal transduction through the Erythropoietin receptor (EpoR)



In collaboration with Prof. Ursula Klingmüller

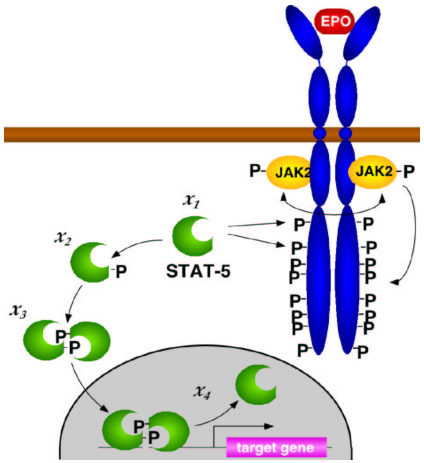
German Cancer Research Centre, Heidelberg

JAK – STAT Pathway



From the Cartoon to Mathematical Equations

$$
\begin{aligned}
\dot{x}_1 &= -k_1 x_1 \mathrm{EpoR_A} \\
\dot{x}_2 &= k_1 x_1 \mathrm{EpoR_A} - k_2 x_2^2 \\
\dot{x}_3 &= \frac{1}{2} k_2 x_2^2 - k_3 x_3 \\
\dot{x}_4 &= k_3 x_3
\end{aligned}
$$



Measurements

- $\mathbf{y_1(t)}$: **Phosphorylated STAT-5 in the cytoplasm**

$$\mathbf{y_1(t) = x_2(t) + 2\,x_3(t)}$$

- $\mathbf{y_2(t)}$: **All STAT-5 in the cytoplasm**

$$\mathbf{y_2(t) = x_1(t) + x_2(t) + 2\,x_3(t)}$$

- $\mathbf{y_3(t)}$: **Activation of the Epo receptor**

$$\mathbf{y_3(t) = EpoR_A(t)}$$

Simulation vs. Data-Based Modeling I

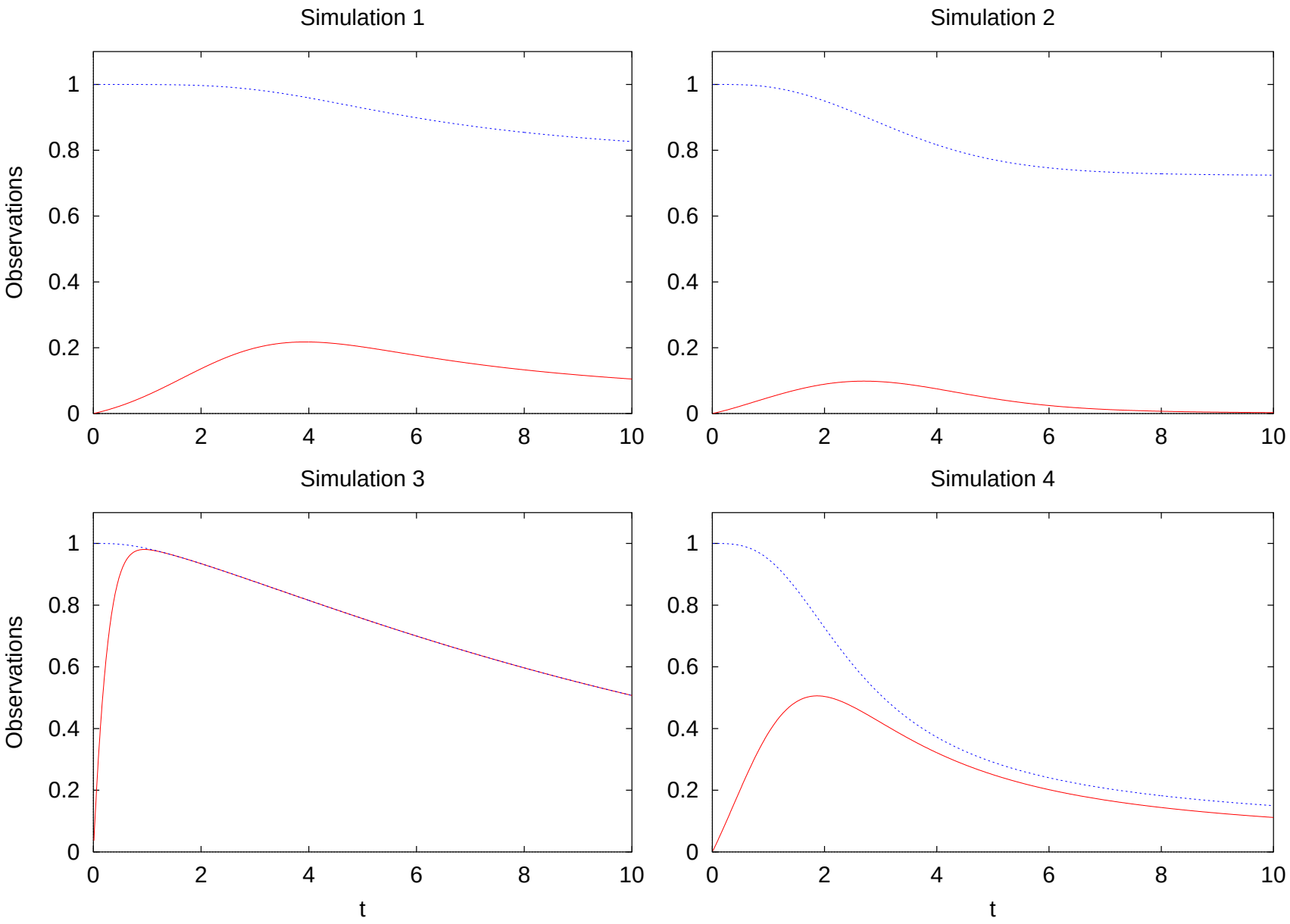
Model comprises:

- **Structure of the equations (the cartoon)**
- **Values of the parameters**

Simulation:

- **Structure from pathway cartoon**
- **Parameters from**
  - **Independent measurements**
  - **Literature**
  - **Educated guesses**

Simulations



Simulation vs. Data-Based Modeling II

Simulation dilemma:

If discrepancies between experiment and model

- **Wrong structure or wrong parameters ?**

Data-based modeling:

- **Structure from pathway cartoon**
- **Parameters estimated from data**

If discrepancies:

Think about the cartoon ! Learn biology !

Parameter Estimation in Nonlinear Partially Observed Noisy Dynamical Systems

Dynamics:

$$\dot{\vec{x}} = \vec{f}(\vec{x}, \vec{k})$$

Observation:

$$\vec{y}(t_i) = \vec{g}(\vec{x}(t_i), \vec{k}) + \vec{\epsilon}(t_i), \quad \vec{\epsilon}(t_i) \sim N(0, \Sigma_i)$$

Log-Likelihood:

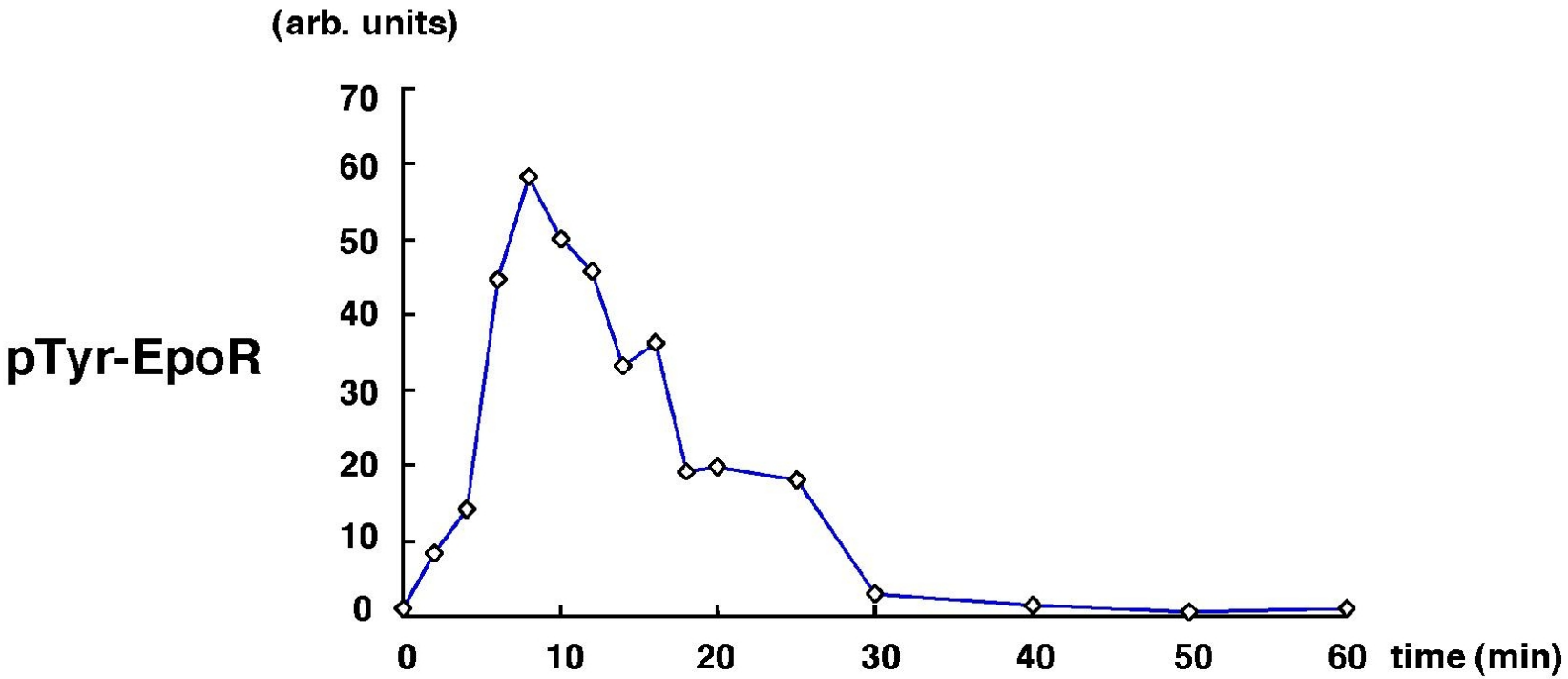
$$E = \chi^2(\vec{k}, \vec{x}(t_0)) = \sum_{i=1}^{N} \sum_{j=1}^{M} \left(\frac{(y_j^D(t_i) - g_j(\vec{x}(t_i; \vec{k}, \vec{x}(t_0))}{\sigma_{i\,j}} \right)^2$$

A lot of Math and Physics ...

- Numerics to solve differential equations
- Optimisation theory
- Statistics
- Theory of Dynamical Systems
- ...

The Data

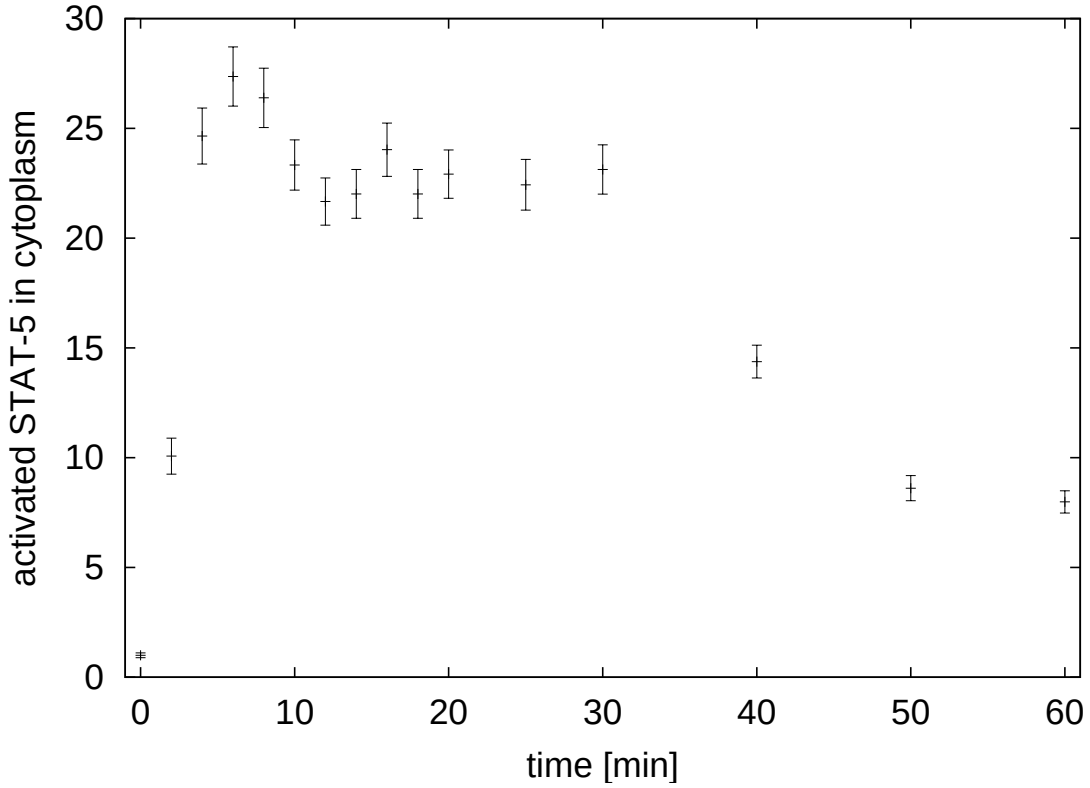
Activation of the Epo receptor :



Maximum at 8 min

The Data

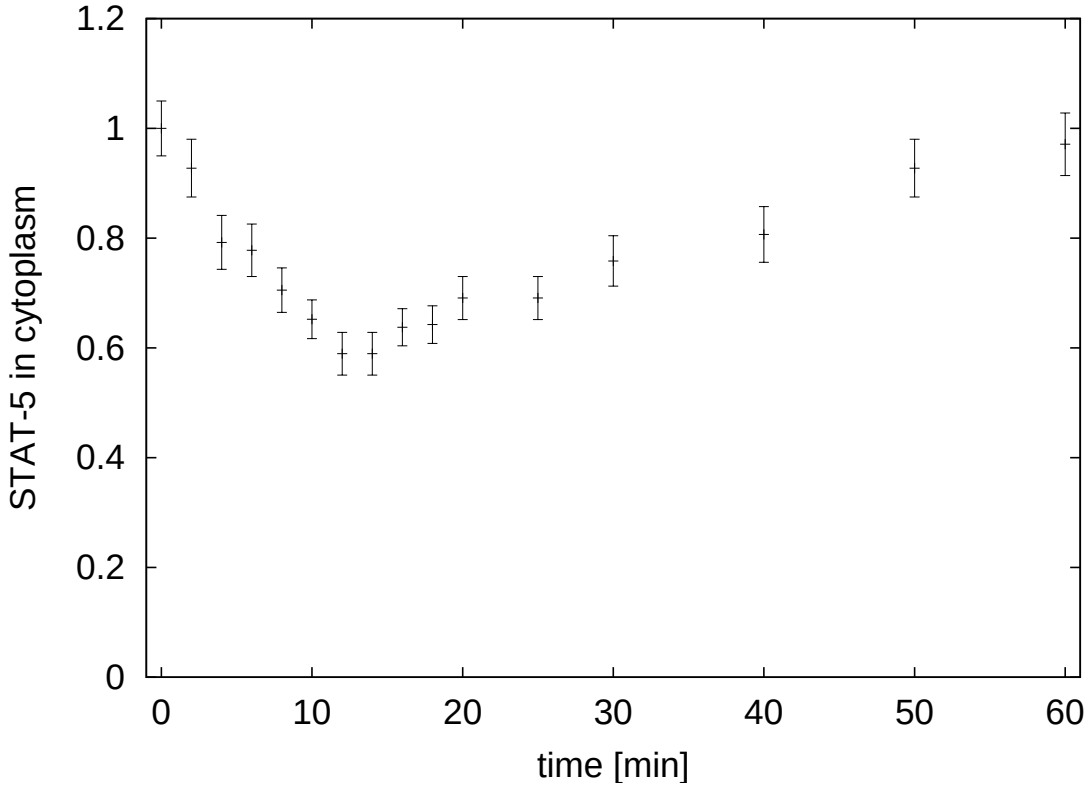
Phosphorylated STAT-5 in cytoplasm :



Plateau from 10 to 30 min

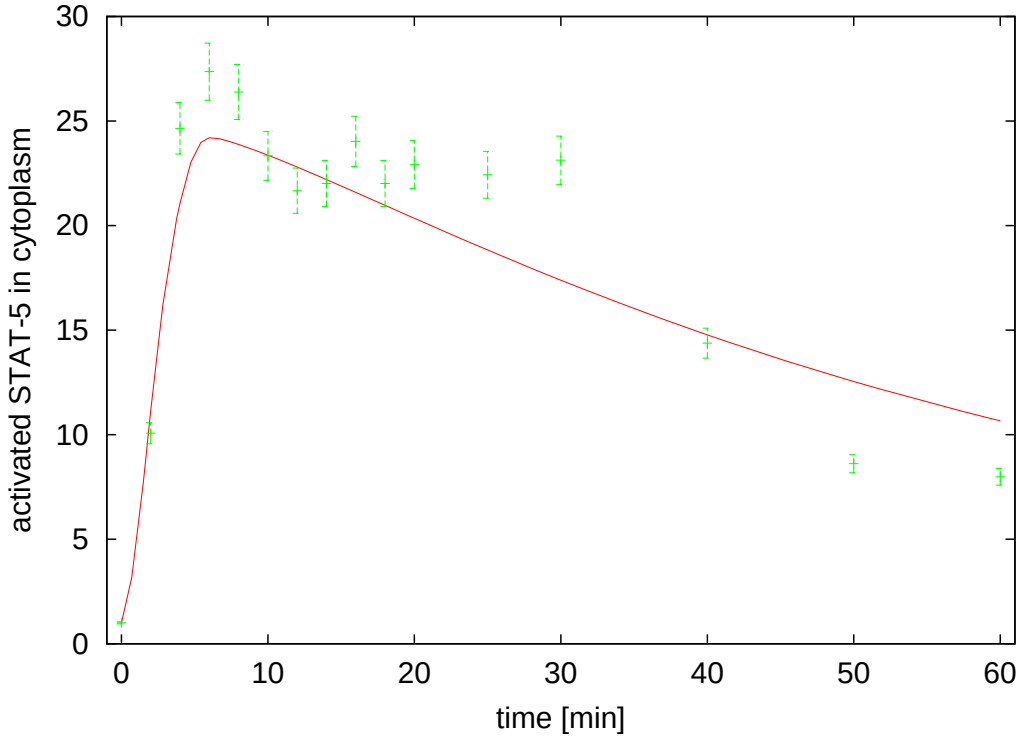
The Data

All STAT-5 in cytoplasm :



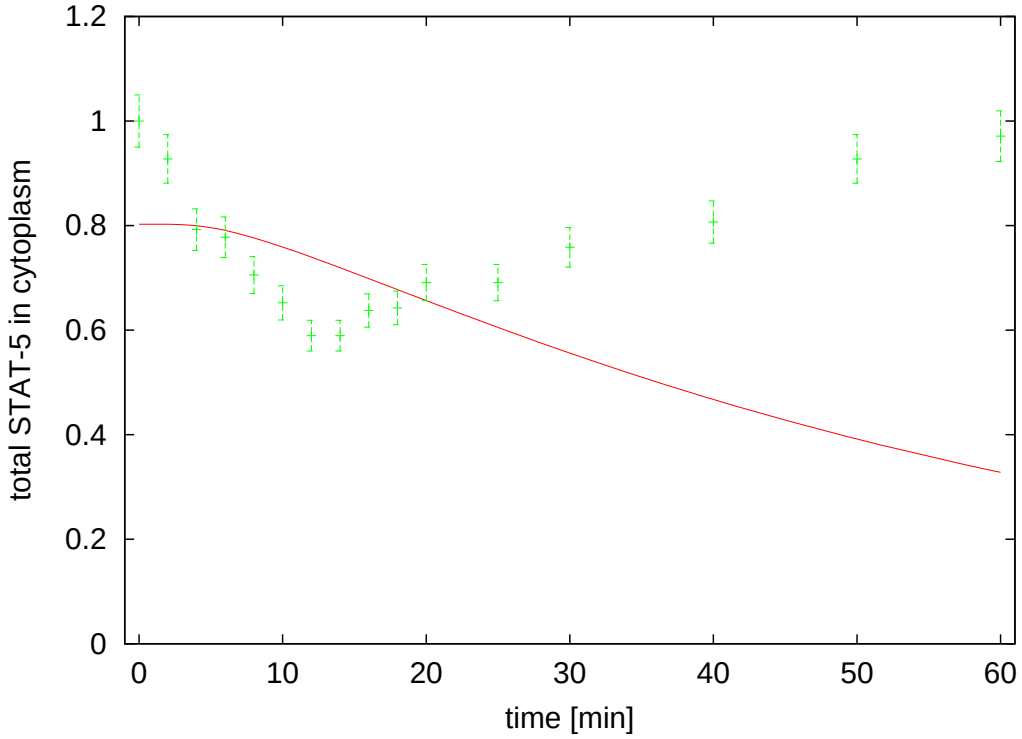
First Results

Phosphorylated STAT-5 in cytoplasm :

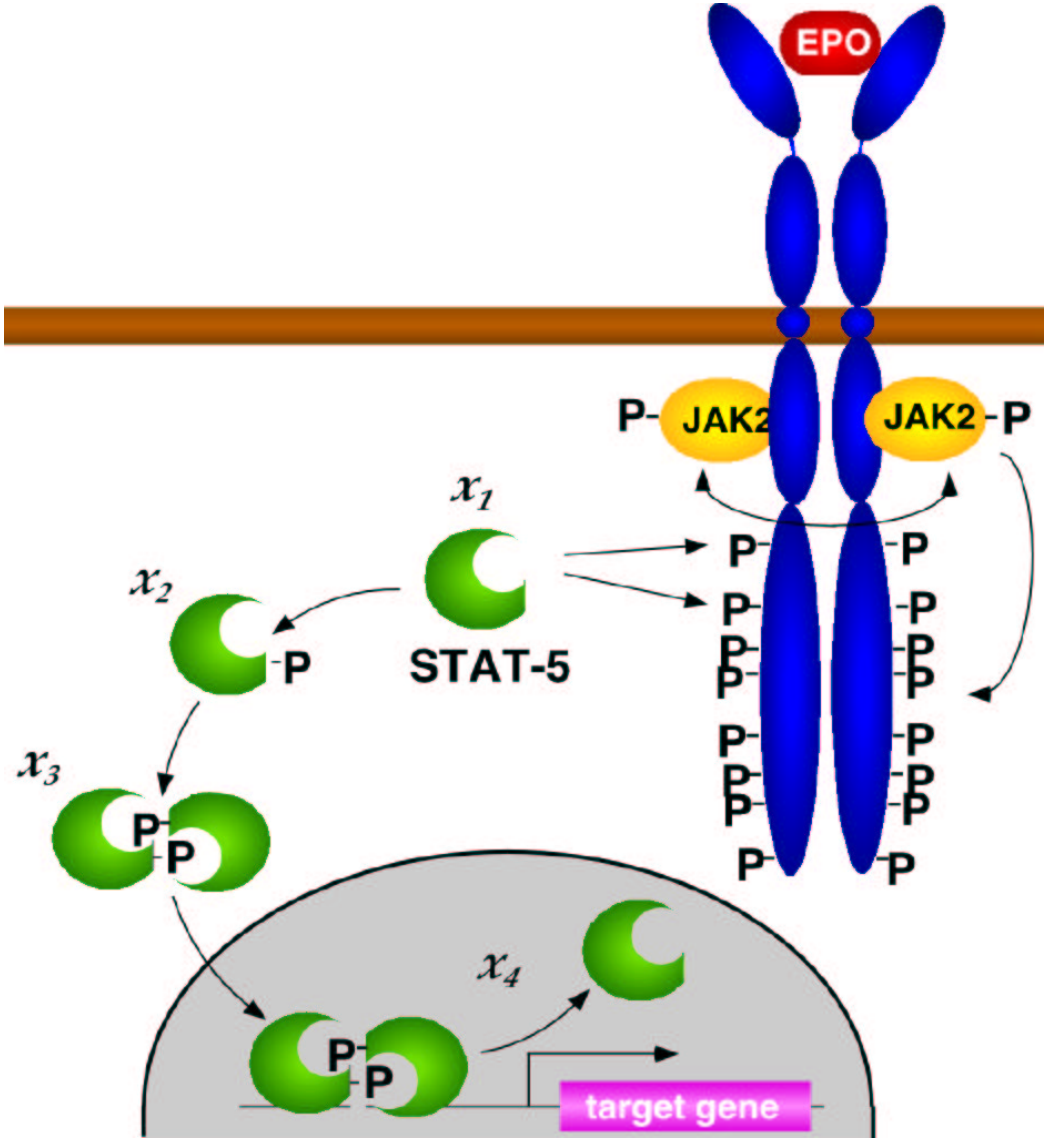


First Results

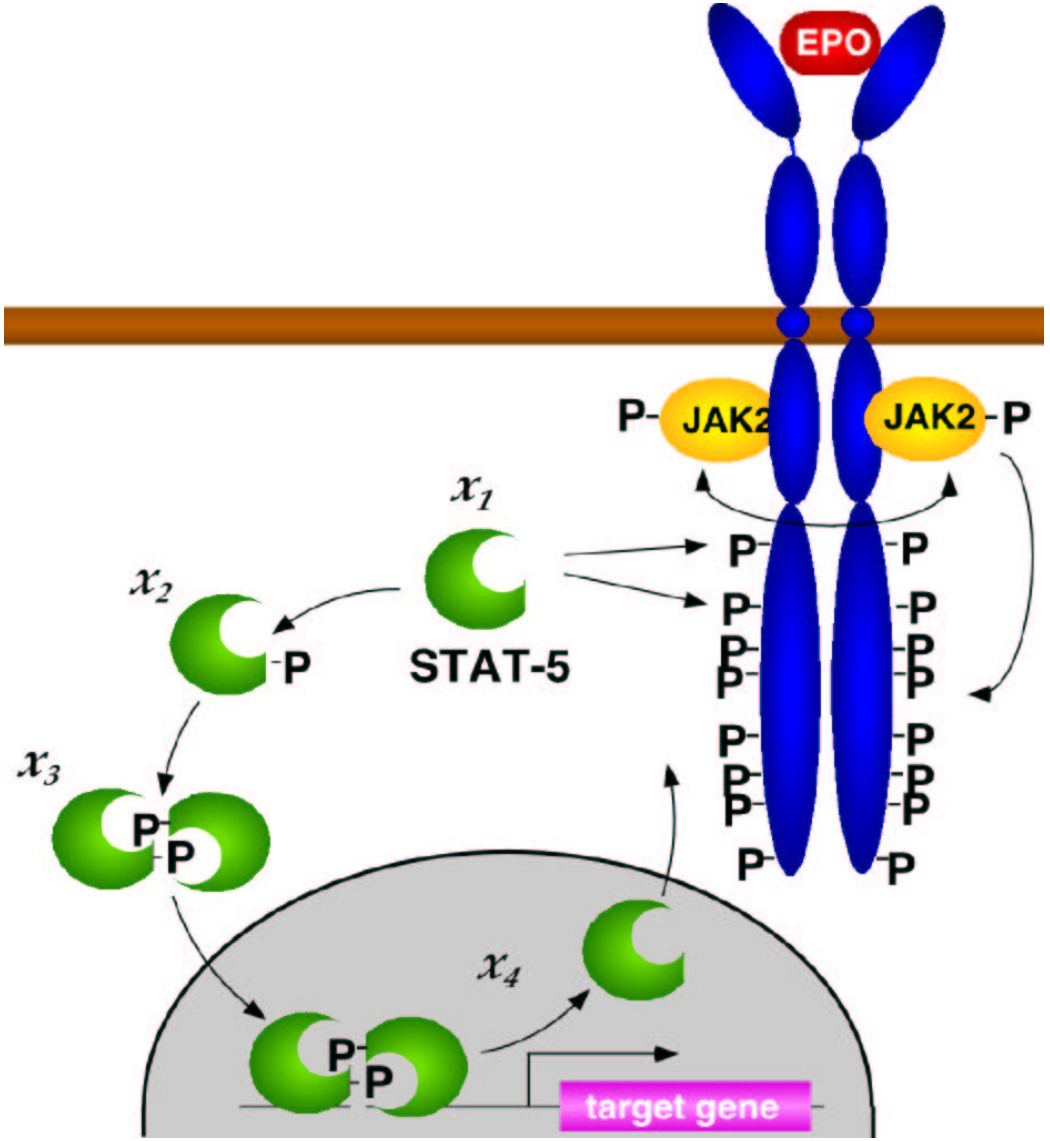
All STAT-5 in cytoplasm :



JAK – STAT Pathway



Model Extension

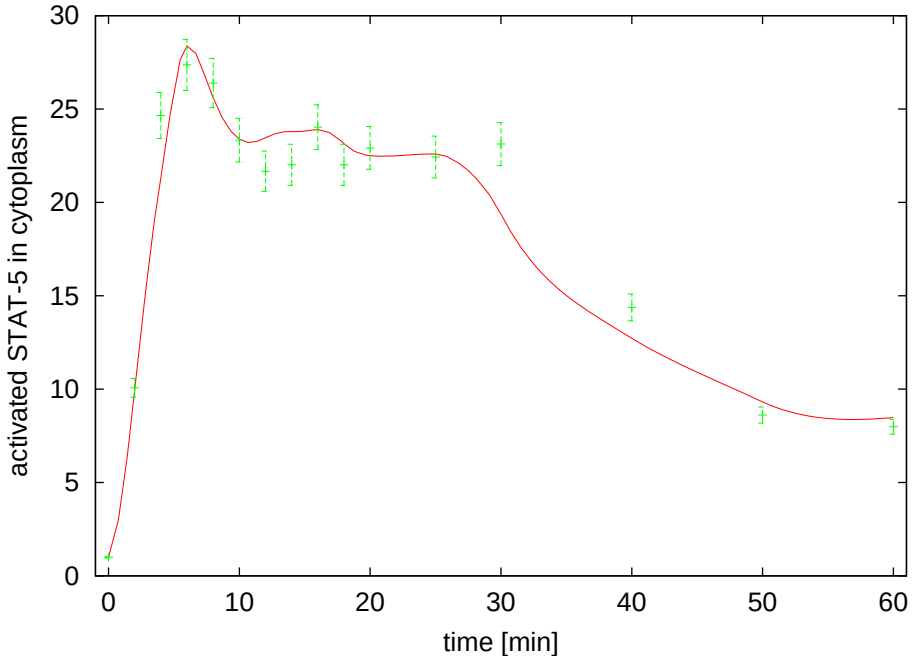


Second Try

$$
\begin{aligned}
\dot{x}_1 &= 2k_4 x_3^{\tau} - k_1 x_1 \mathrm{EpoR_A} \\
\dot{x}_2 &= k_1 x_1 \mathrm{EpoR_A} - k_2 x_2^2 \\
\dot{x}_3 &= \frac{1}{2} k_2 x_2^2 - k_3 x_3 \\
\dot{x}_4 &= k_3 x_3 - k_4 x_3^{\tau}
\end{aligned}
$$

Results

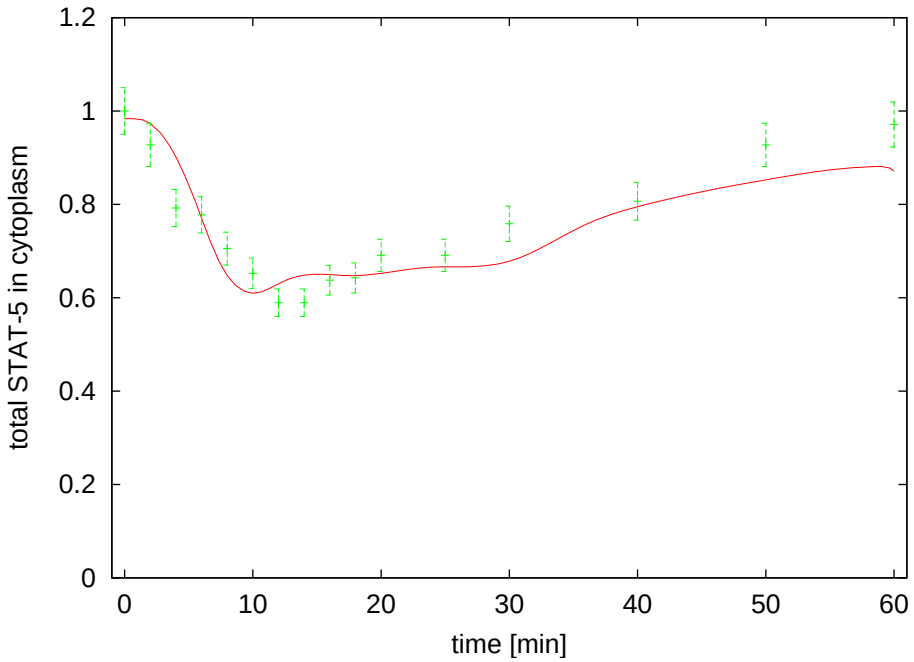
Phosphorylated STAT-5 in cytoplasm :



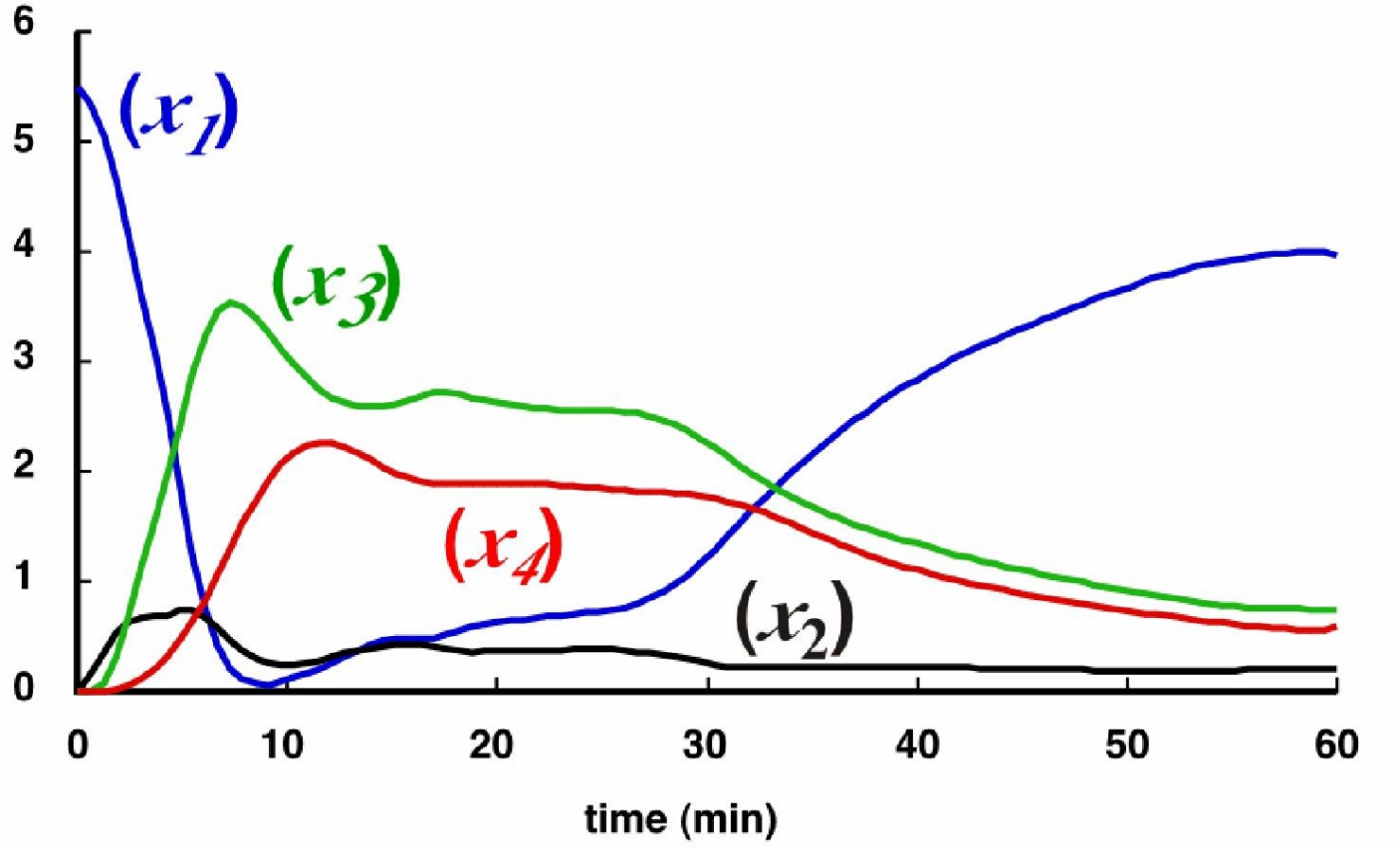
Sojourn time in nucleus $\tau \approx$ 6 min

Results

All STAT-5 in cytoplasm :



Observing the Unobservable: Individual Players



In silico Biology: Impossible Experiments

"What happens if ... ?" Investigations

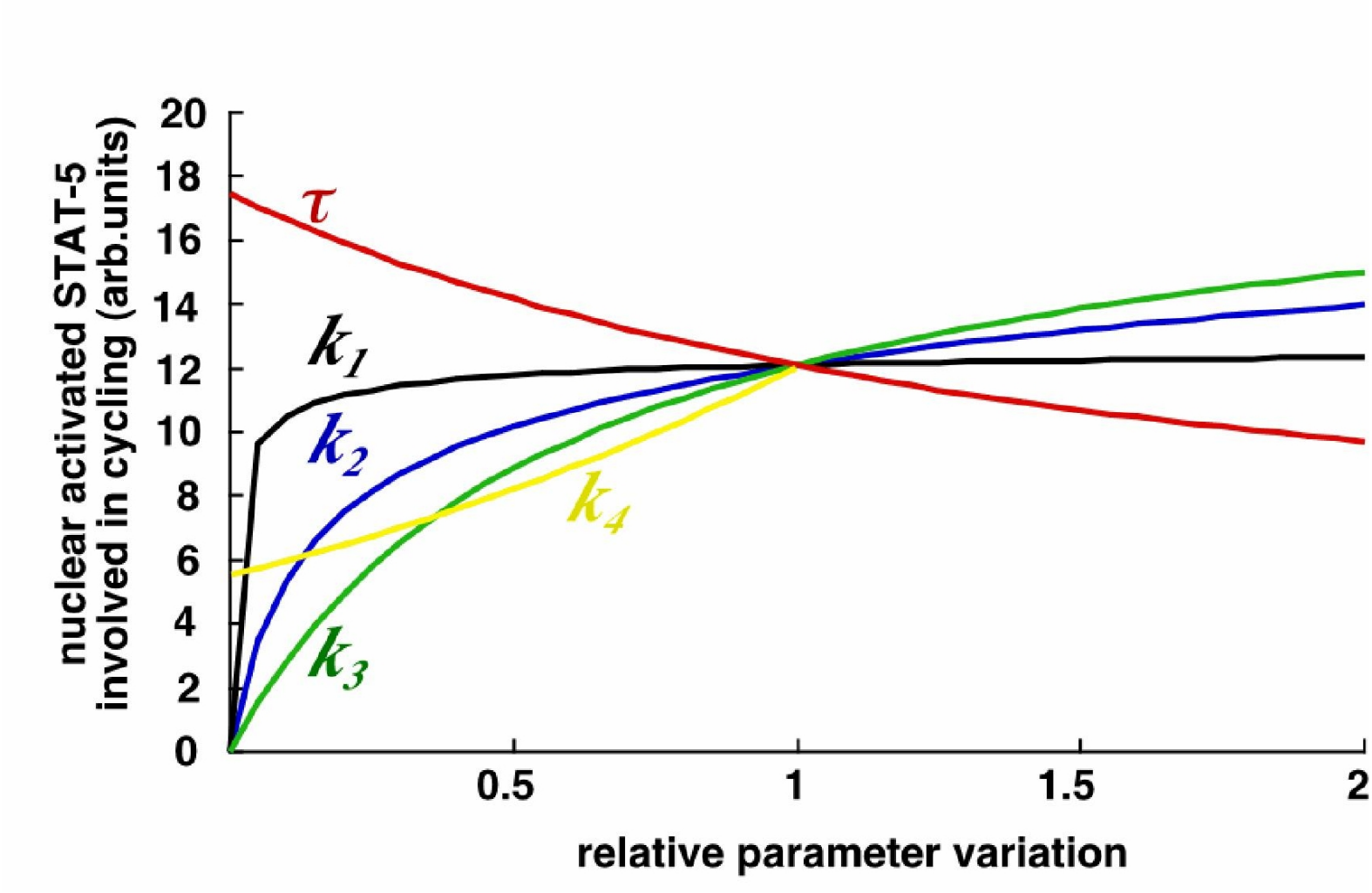
Sensitivity analysis:

- **Change parameters in the model**
- **Calculate the transcriptional yield**

Perspective:

Identification of potential targets for medical intervention

Sensitivity Analysis



Prediction of New Experiment

- **Result of sensitivity analysis:**

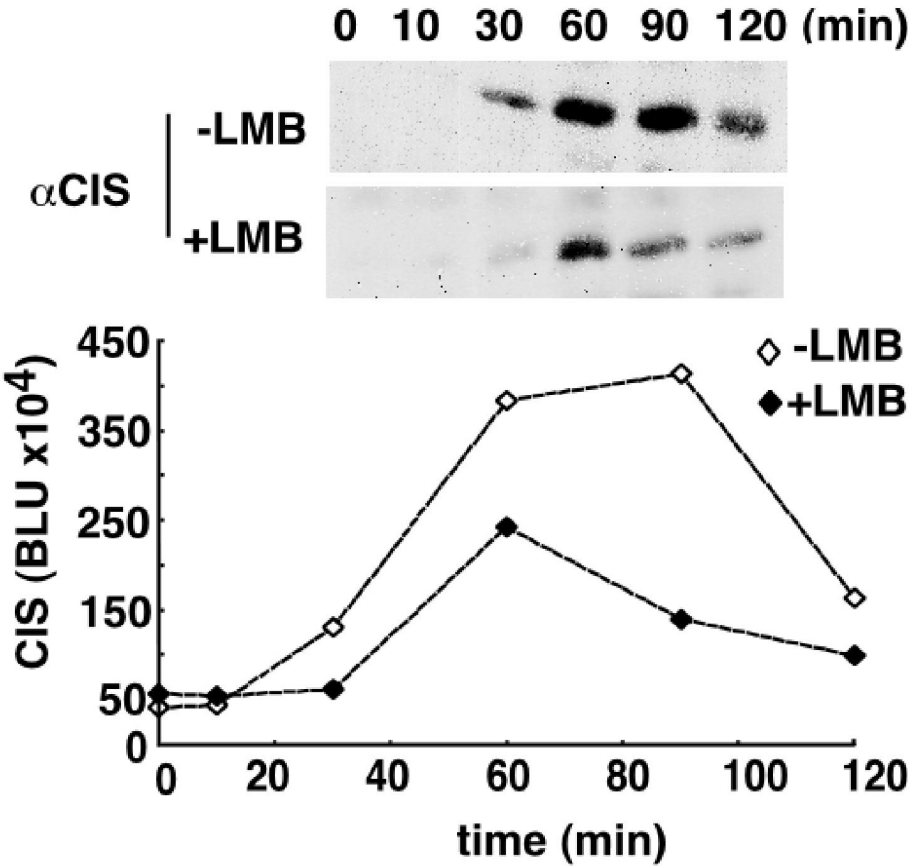
  Transcriptional yield is most sensitive to nuclear shuttling parameters.

- **Setting nuclear export to zero**

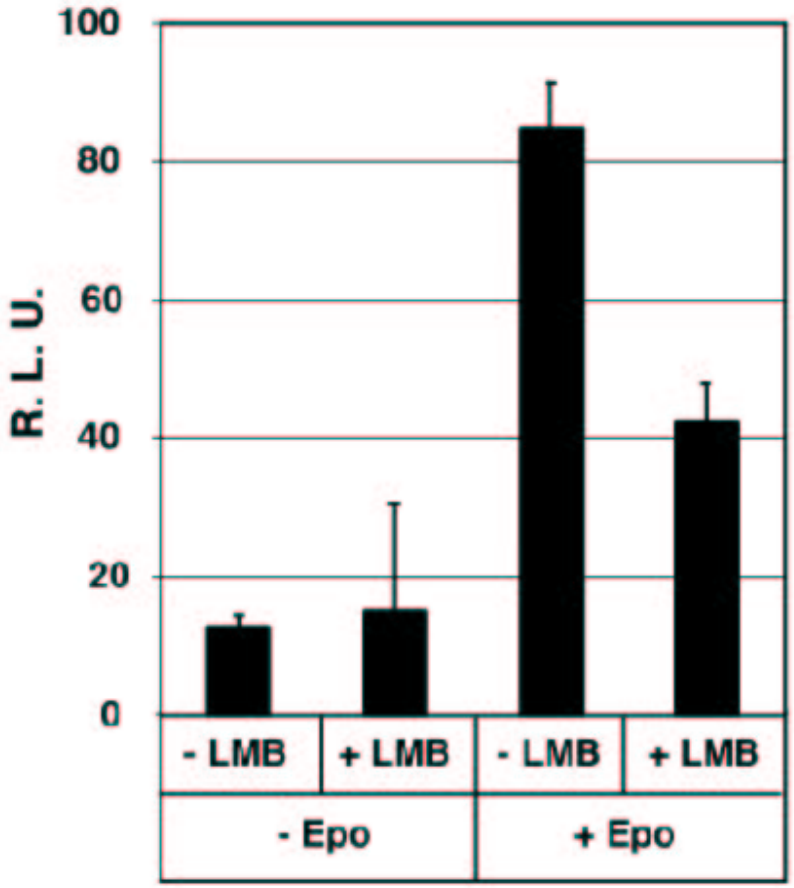
  $\Longrightarrow$ **Only one cycle : Only 50 % efficiency**

- **Blocking nuclear export by Leptomycin B confirms prediction.**

Experimental Confirmation of Prediction



Experimental Confirmation of Prediction



Why Cycling ?

- **Optimal use of limited pool of STAT-5**
- **Continuous monitoring of receptor activity :**

Systems' property: "Remote Sensor"

Swameye et al. Proc. Natl. Acad. Sci. 100, 2003, 1028-1033

"All models are wrong ..."

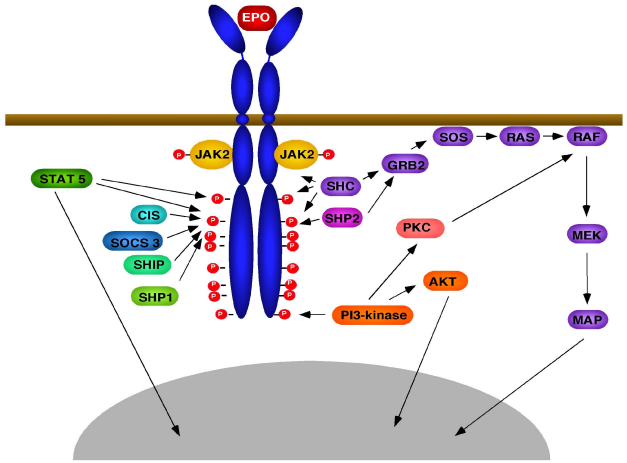
- No scaffolding for receptor–STAT-5 interaction, 200 eqs.
- Spatial effects, ODE vs. PDE
- Stochastic effects
- Data averaged over 10^6 cells

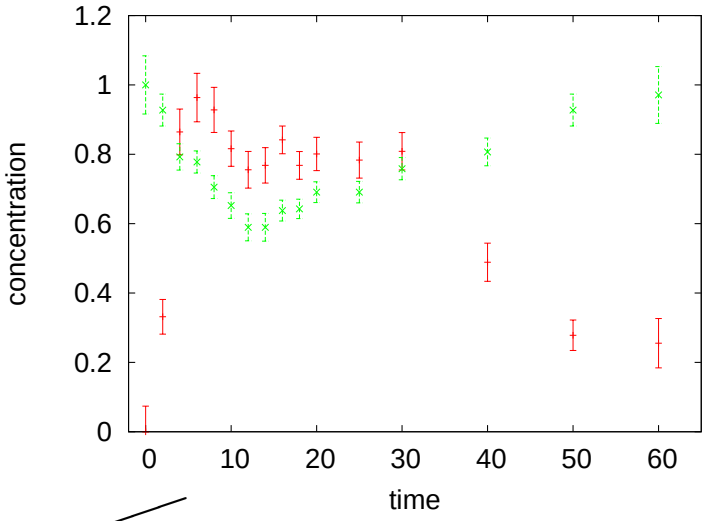
"... but some are useful"

- Capture the main effects, neglect the rest
- Make testable prediction
- Deliver insights

Art of mathematical modeling: Making wise errors

Signal transduction through the Erythropoietin receptor (EpoR)





$$\dot{\vec{x}} = \vec{f}(\vec{x}, \vec{k})$$

In silico **biology**

Test the prior knowledge

Understanding systems' properties

Identification of potential drug targets