



Systems biology

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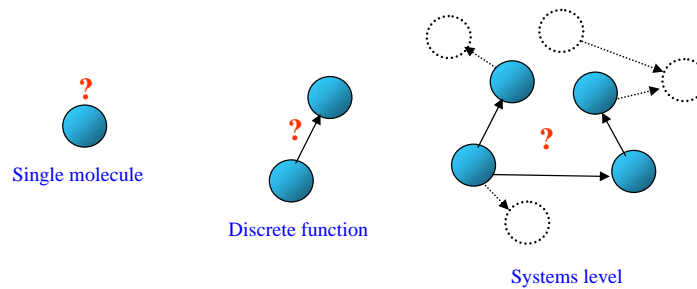
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systems biology... a philosophy

"Systems biology...is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programmes, but different....It means changing our philosophy, in the full sense of the term"

Denis Noble



Data are the precursor to any model. The minimal basis of a cellular network model is a list of the molecular players and a list of the 'influences' of one set of players on another



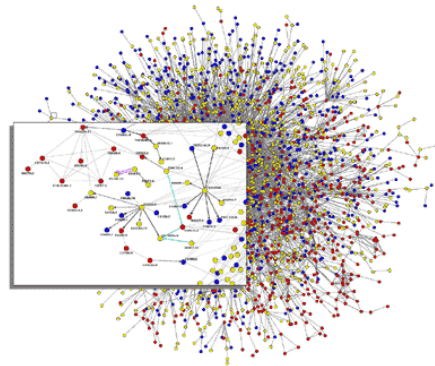
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Gathering data at a systems level

As high-throughput experimental approaches became available there was a push towards the collection of data at a systems level.



Many protein interactions are absolutely essential. However, it remains unclear which fraction of interactions are really necessary on a global scale.

C. Elegans interactome. Marc Vidal's lab, 2004



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Towards a more GLOBAL FUNCTIONAL approach

As more data high-throughput data becomes available there is a shift towards global functional approaches, where we look at

Issues arising when analyzing high-throughput data:

- Size
- High-dimensionality
- Different units of measure

The paradigm is to look at large complex datasets without losing focus on the details. Computational approaches can help us solve this paradigm.

This requires :

- Structure the data in usable (common) formats
- Define what data is required for functional assessments, design computational approaches to process and analyze data at a systems level.



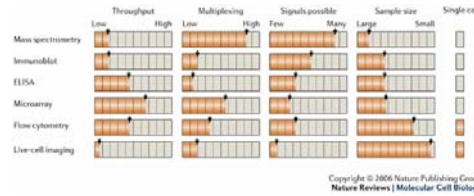
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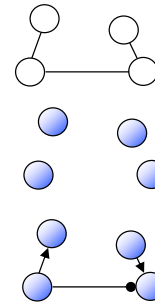
Gathering experimental data

Different data, different information:



When gathering experimental data we face three possible scenarios:

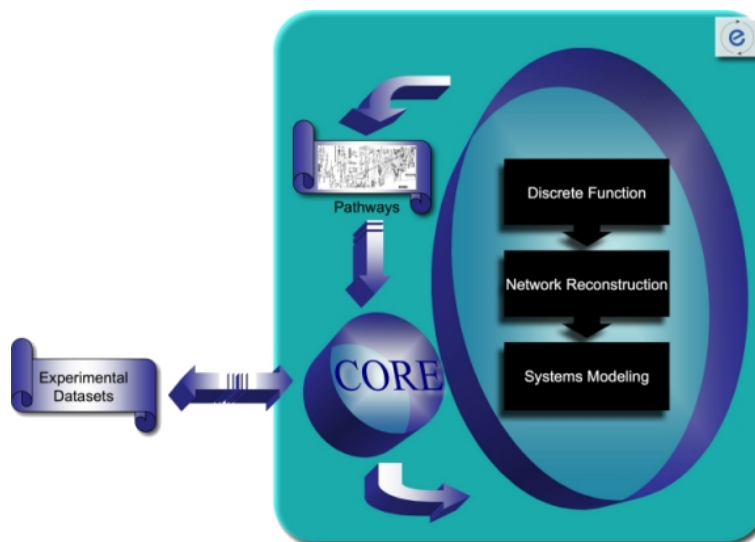
- **Connectivity without Activity** (eg. yeast two-hybrid)
- **Activity without connectivity** (eg. microarray)
- **Activity and connectivity** (rare,...pathway inference)



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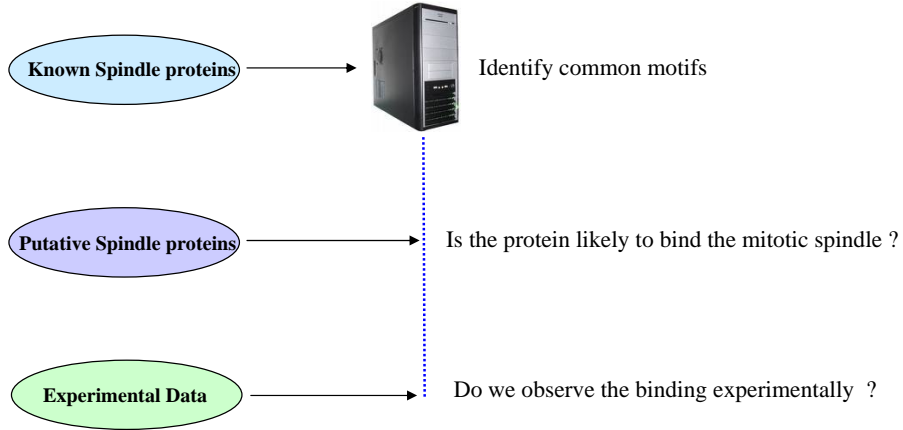




Discrete Function Prediction

A considerable amount of knowledge can be gained from analyzing individual protein sequences or protein families in the absence of detailed knowledge of what the precise interactions between these proteins are. We term this "discrete function prediction".

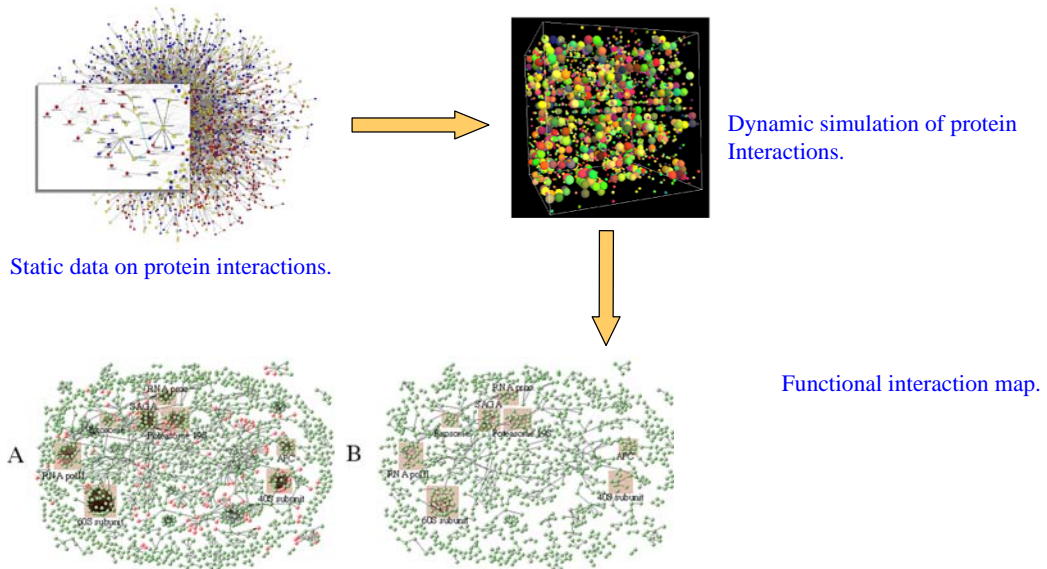
An example using the Mitotic spindle protein complexes



Brunak S. Lab, DTU
Orengo C. Lab, UCL



Discrete Function Prediction



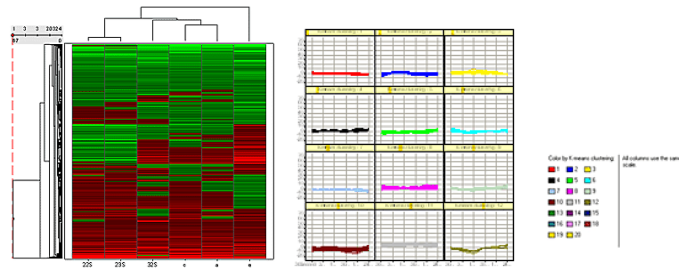
Bernaschi M., BMC Bioinformatics. 2007

Network Reconstruction

Describes the “reverse engineering” of a network, where the relation between, entities is derived from the experimental measurements.

An example using Microarray data:

- Direct analysis (e.g. Clustering)



- Indirect analysis (e.g. Promoter analysis)



Bayesian network reconstruction using microarrays

Bayesian network

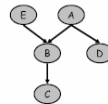
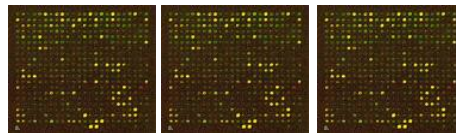


Figure 2.1: An example of a simple Bayesian network structure. This network structure implies several conditional independence statements: $(A \perp E)$, $(B \perp D | A, E)$, $(C \perp A, D, E | B)$, $(D \perp B, C, E | A)$, and $(E \perp A, D)$. The joint distribution has the product form $P(A, B, C, D, E) = P(A)P(E)P(B|A, E)P(C|B)P(D|A)$

Microarray series

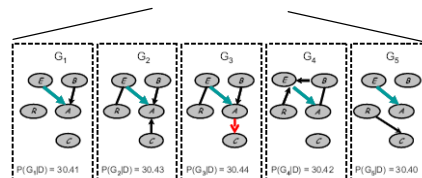


Time or treatment

Probe profiles



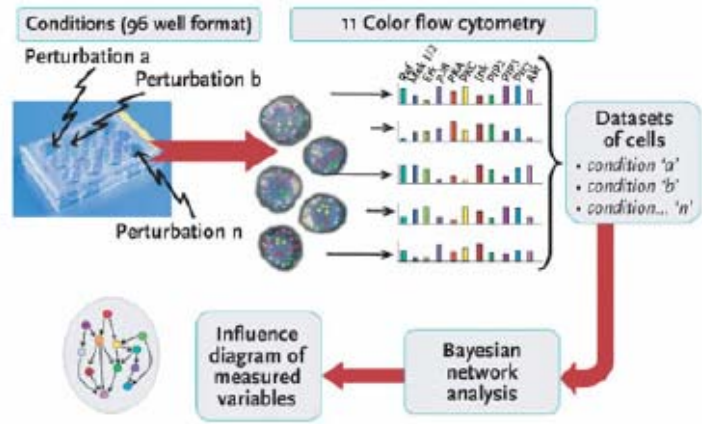
Possible solutions



Modified from the Thesis of Dana Pe'er 2003
<http://arep.med.harvard.edu/~dpeer/thesis/thesis.pdf>



Network reconstruction by inference



K. Sachs, Science 308 (5721): 523-529

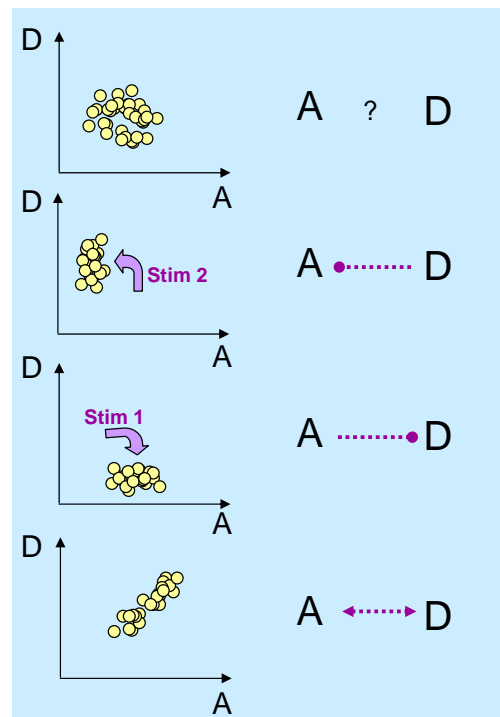
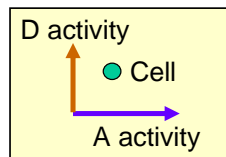
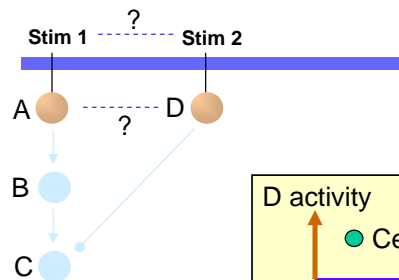
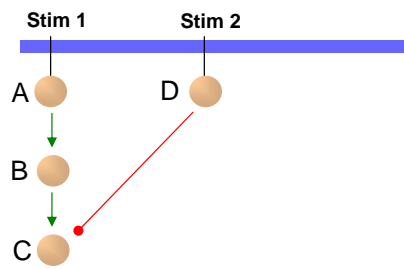


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Pathway inference

• Is there a relationship between two measured parameters (A and D)

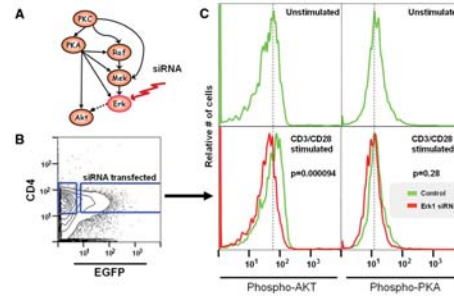
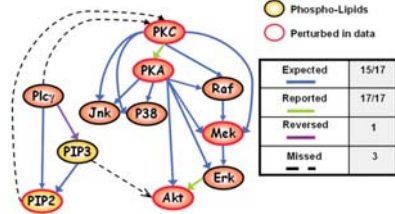


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Assessing inferred pathways

A Model inference result



- (A) The model predicts that an intervention on Erk will affect Akt, but not PKA.
- (B) To test the predicted relationships, Erk1 and Erk2 were inhibited using siRNA in cells stimulated with antibody to CD3 (anti-CD3) and anti-CD28.
- (C) Amounts of Akt (+GFP) phosphorylation in transfected CD4+ cells were assessed
- (D) When Erk expression is inhibited, phosphorylated Akt is reduced to amounts similar to those in unstimulated cells, confirming our prediction ($P = 0.000094$). PKA is unaffected ($P = 0.28$).

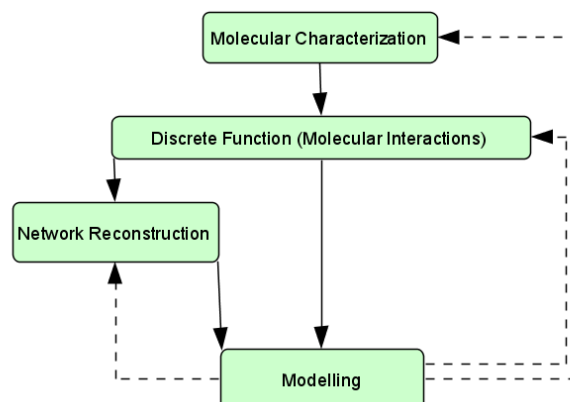
K. Sachs, Science 308 (5721): 523-529



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Network modeling uses and contributes to all systems biology approaches



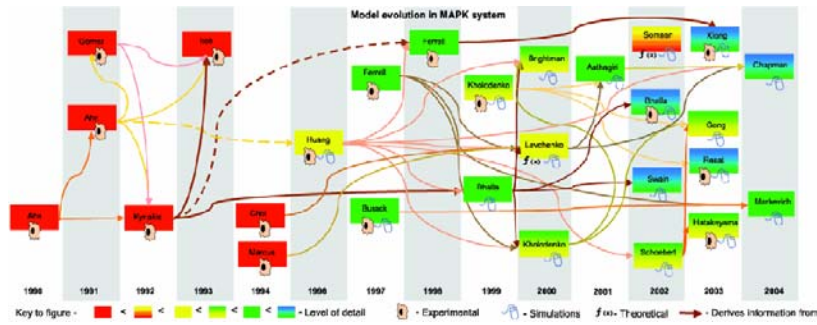
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Network Models

Network models constitute a “knowledge snapshots” of an event. The information from the model can then be used to perform simulations and derive predictions to drive further experiments.

Models evolve as the knowledge progresses and new experimental/ computational approaches are developed.



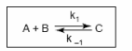
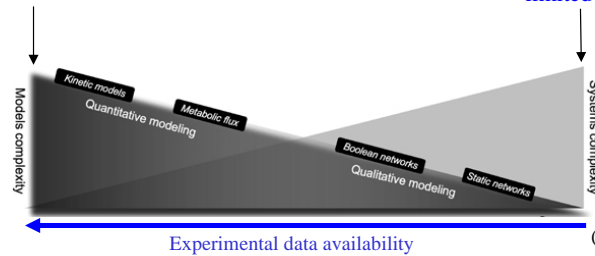
Le Novère N., <http://www.ebi.ac.uk/biomodels/>

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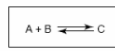
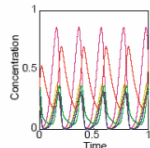
Different data, different modeling approaches

Small networks, well described activity

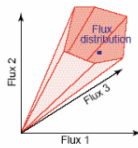
Large networks, limited described activity



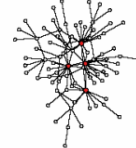
Dynamic models
Stoichiometry
Kinetic parameters



Static models
Stoichiometry
No parameters



Static models
No stoichiometry
No parameters



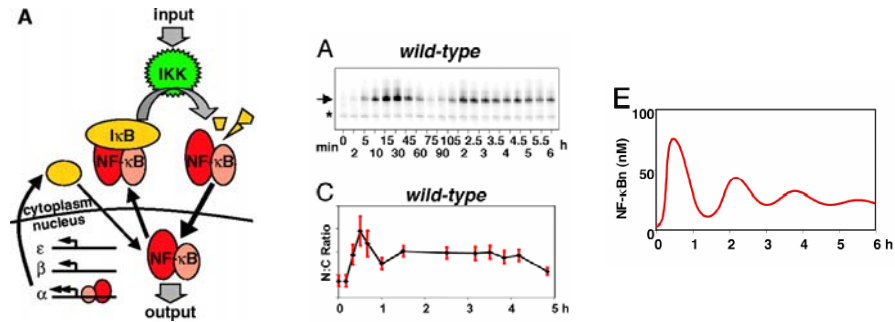
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Kinetic models (ODE)

Systems where the reaction kinetics are known, can be described, numerically using a set of ordinary differential equations (ODEs).

Generally the equations are derived by fitting experimental data. They describe how a component behaves in time, by taking into account how the component is influenced by all the other components in the network.

Since the models use kinetic data, the results are expressed in concentrations over time.



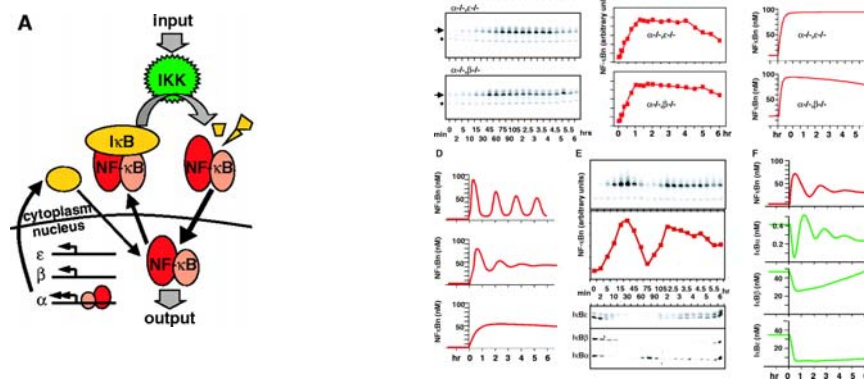
Kearns, JCB 2006



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Modeling the NF κ B pathway



- A) Analysis of NF-Bn by EMSAs
- B) Quantification
- C) Model-fitting
- D) Model testing with different I κ B transcription rates
- E) Biochemical analysis of NF κ B
- F) Verification of the computational model for wild-type cells.



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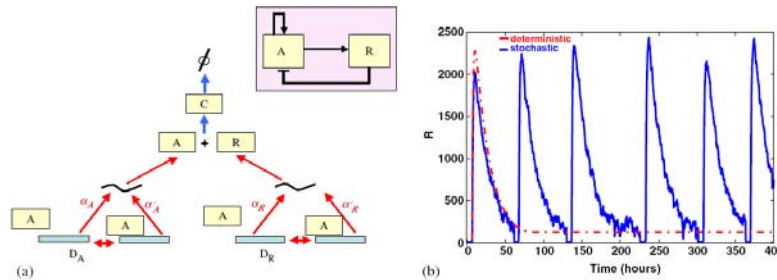




Stochastic models

Similar to ODE models, but a stochastic value is added in the equations to take into account the non-deterministic nature of Biochemical reactions (e.g. spatial distributions)

The result of these equations describe the concentration of a component but also a range of its possible values.



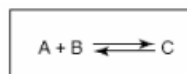
Vilar J., PNAS 2002



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Flux Modelling



Basic ideas

- **model variables** = the **metabolic fluxes** of the set of biochemical reactions
- **constraint-based** approach: initially, the fluxes can take any real value, the application of **constraints** reduces the possible flux distributions
- analyses **explore** the flux distributions fulfilling the constraints

General hypotheses imposed as constraints:

1. metabolism operates at **steady-state**
2. some reactions are **irreversible**
3. fluxes are bound to a maximal value

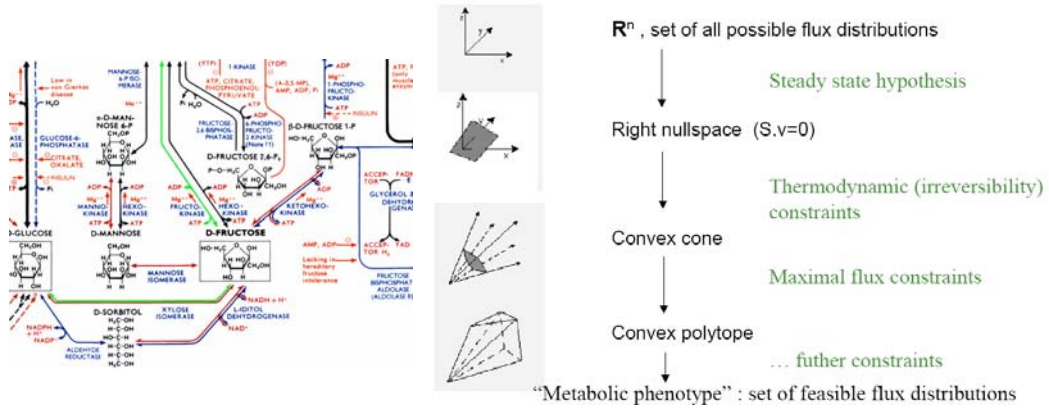


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Building a flux state-space

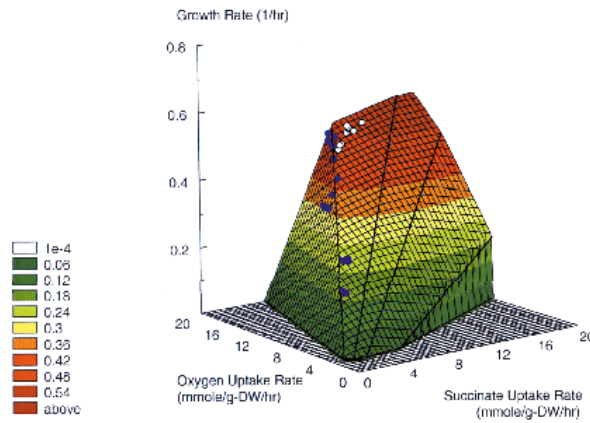


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Example of Flux modeling

Biomass production in E-Coli, with succinate



Edwards et al, Nature 2001



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Standardized Qualitative Dynamic Modeling

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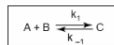
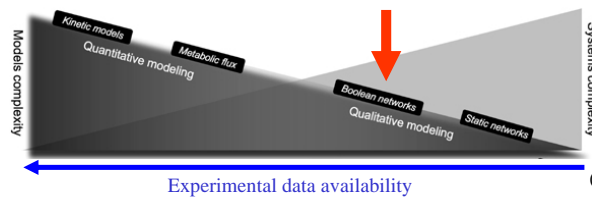
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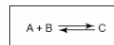
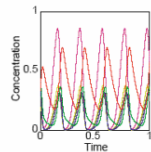
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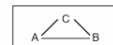
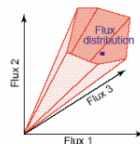
Standardized Qualitative Dynamic Modelling



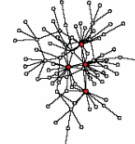
Dynamic models
Stoichiometry
Kinetic parameters



Static models
Stoichiometry
No parameters



Static models
No stoichiometry
No parameters



- Addresses the simulation of “larger” networks from a qualitative standpoint

- Based on topological rather than quantitative data



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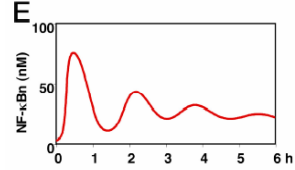
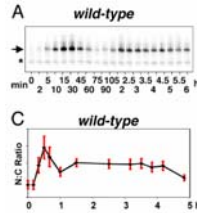
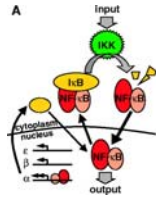


The topology provides useful information

Quantitative approach

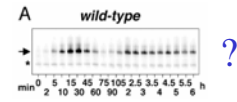
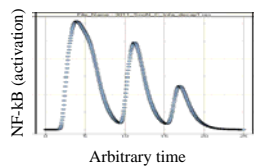
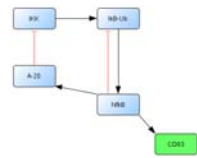
- Design model topology
- Perform experiment
- Measure level of the components
- Describe the reaction mathematically
- Make predictions

Published ODE model
Kearns JCB 2006



Standardized Qualitative modeling (Boolean)

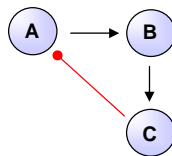
- Design model topology
- Perform simulations
- Perform experiment to verify model or compare against existing literature
- Make predictions



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The components of a Boolean model



NODES:

- Represent “functions” rather than specific molecular entities (i.e. Node A could be a phosphorylated protein, an RNA molecule, or a molecular complex)
- Each node can exist in two states (active|inactive), mapping to “a” molecular change in the state of the node

EDGES:

- Represent causal relationship rather than an interaction, and can represent a non-direct relationship (will explain this further on)
- Each edge expresses either (activation|inhibition) relationship between nodes



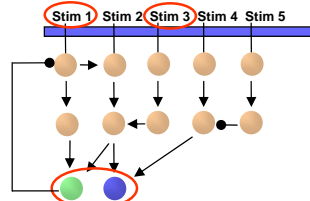
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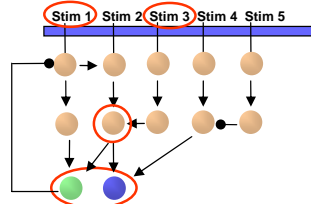


What questions does qualitative modeling try to answer

- What is the general behavior of the network upon different stimuli



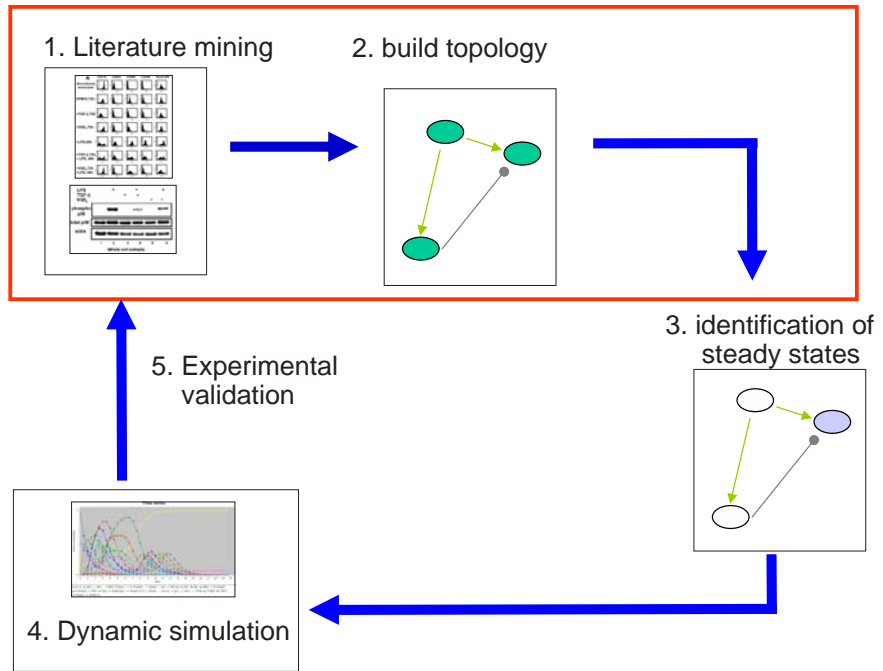
- What is the role of a component / relationship within a network



Small-Print : Some of the answers you will not get

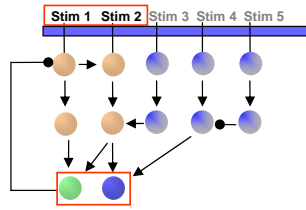
- What the activation of a node means in molecular terms (unless specified in the model)
- The amount of activated / inhibited component
- The timing of the events in a real scale

Modeling workflow



building the model

- Define a start and end point in your model. Networks can be large and interconnected, you can easily be side-tracked. Remember the question are you trying to answer.



i.e. Q: what is the role of I-Smad and R-Smad in the regulation of TGFβ

- Gather information to build a blue-print skeleton model. Have other people collected in formations on this pathway

Some model repositories:

Reactome (www.reactome.org)
 BioModels (www.ebi.ac.uk/biomodels)
 CellDesigner models (www.systems-biology.org/cd/models.html)
 KEGG (www.genome.jp/kegg)
 Panther (www.pantherdb.org)
 Biocarta (www.biocarta.com)
 NetPath (www.netpath.org)



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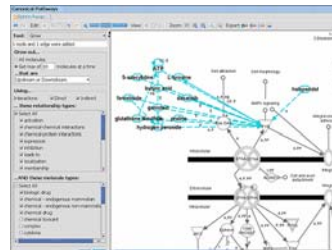
Find information on gene connectivity

- Start with text mining tools to get a good overview

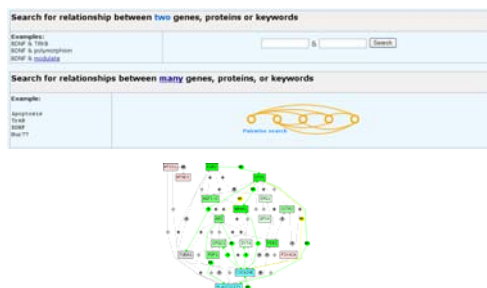
INTACT (<http://www.ebi.ac.uk/intact>)



Ingenuity (www.ingenuity.co) [not free]



Chilibot (www.chilibot.net)



Ihop (www.ihop-net.org)



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Tips for expanding the model

- Read the articles, extract information from figures, use discussion as a trampoline to other articles.
- Number of papers on a subject is usually a good meter for the confidence on a particular relationship.
- For each paper annotate the relationship described. Use a reference manager. Annotate the references on the model.
- The model will never be complete, focus on the question you are trying to answer.
- The model should be as close as possible to the the organism, cell type and event that you are modeling. Canonical models might not reflect your experimental setup, resulting in a wrong set of predictions.

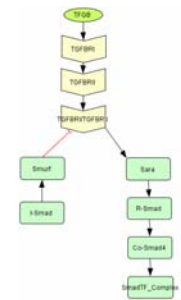
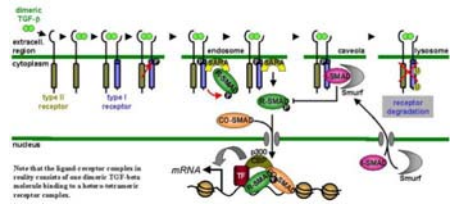


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From databases to Boolean models

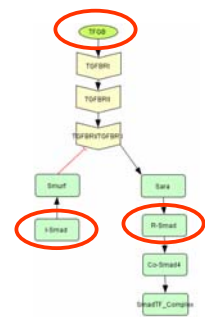
- Re-build the model by extracting information on the sequence of events



CellDesigner.org

- Ease of use
- Activation / Inhibition edges
- Possibility to download models from repositories
- Position tags
- Annotation fields

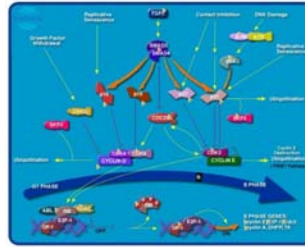
- If necessary complete the model with the nodes of interest to answer your question both from a model and an experimental point of view.



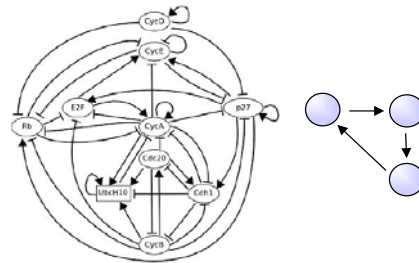
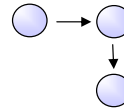
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Most cellular pathways contain feed-back loops



Mammalian Cell cycle
(BioCarta)



Mammalian Cell cycle
(A. Faure' et al., Bioinf. 2006)



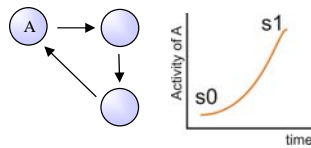
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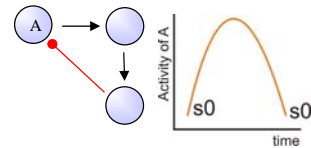
Feed-back loops induce steady states

Feedback loops, are defined as circular chains of interactions, such that each element of a circuit influences its own future level of activation

Positive feed-back



Negative feed-back



Mathematical: Multiple stationary states

Transitory states, oscillations

Biological: Differentiation

Homeostasis

A “Steady State” corresponds to a stable configuration of the network.
Steady states constitute the basis of our simulation approach (!),
and therefore need to be included during the model building

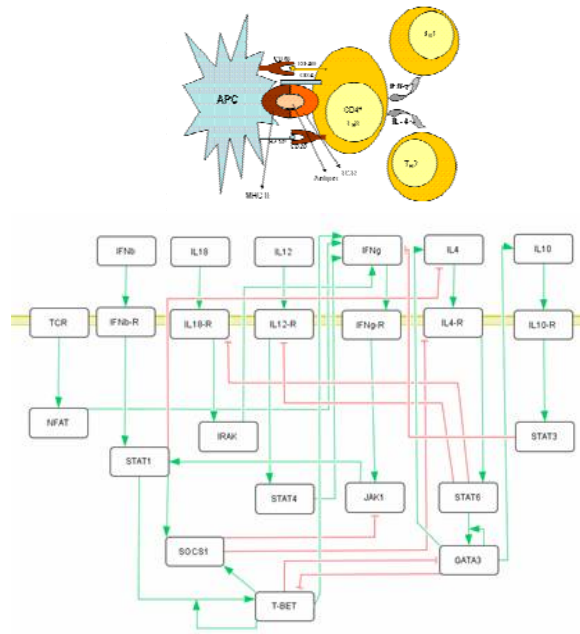


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Example of steady-states using the THelper network

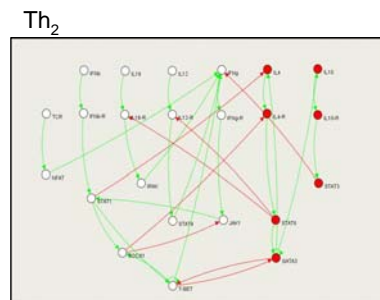
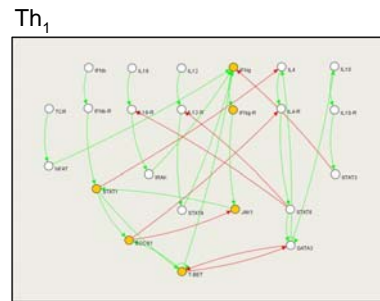
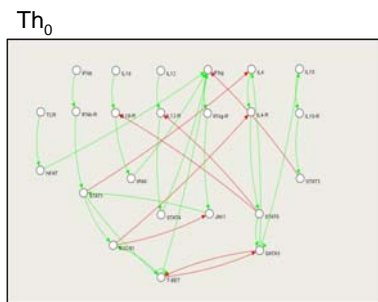
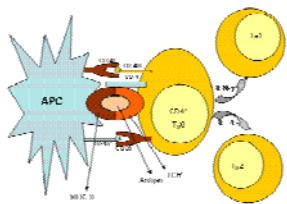


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Th0 Th1 and Th2 states

2^3 possible states = 8388608

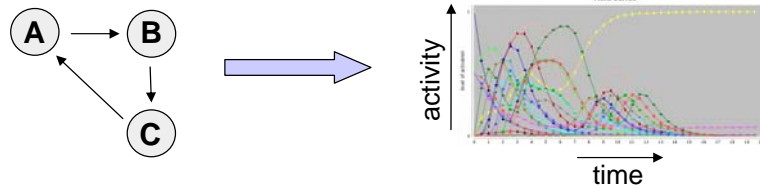


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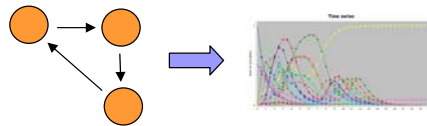


Steady-states as initial conditions for dynamic simulations



- How do we set the initial status of the network ?

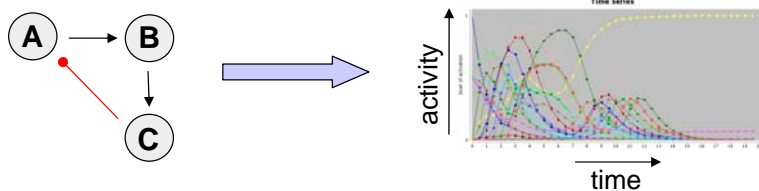
Use the predicted steady-states



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Moving from static to dynamic simulations



$$\frac{dx_i}{dt} = \frac{-e^{0.5h} + e^{-h(\omega_i - 0.5)}}{(1 - e^{0.5h})(1 + e^{-h(\omega_i - 0.5)})} \gamma_i x_i$$

Parameters assigned by the topology

- Strength of activators and inhibitors

Reaction-specific parameters

- Decay
- Steepness of reaction



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