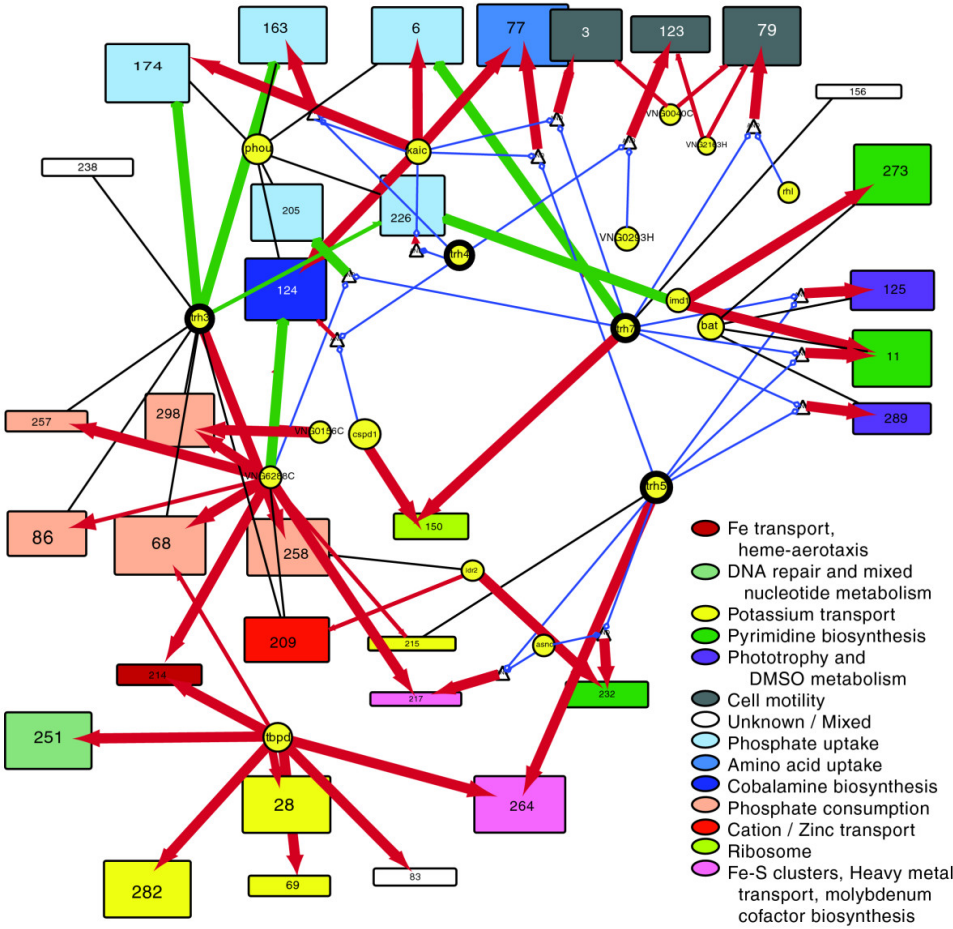
# Dynamics and Inference on Biological Networks




[Bonneau *et al.* 2006]

Sumeet Agarwal
(sumeet@iitd.ac.in)

# Outline

- Part I: Network Dynamics
  - What do we mean by ‘dynamics’?
  - Why study dynamics?
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  - Link with time series
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- Part II: Network Inference from Time Series Data
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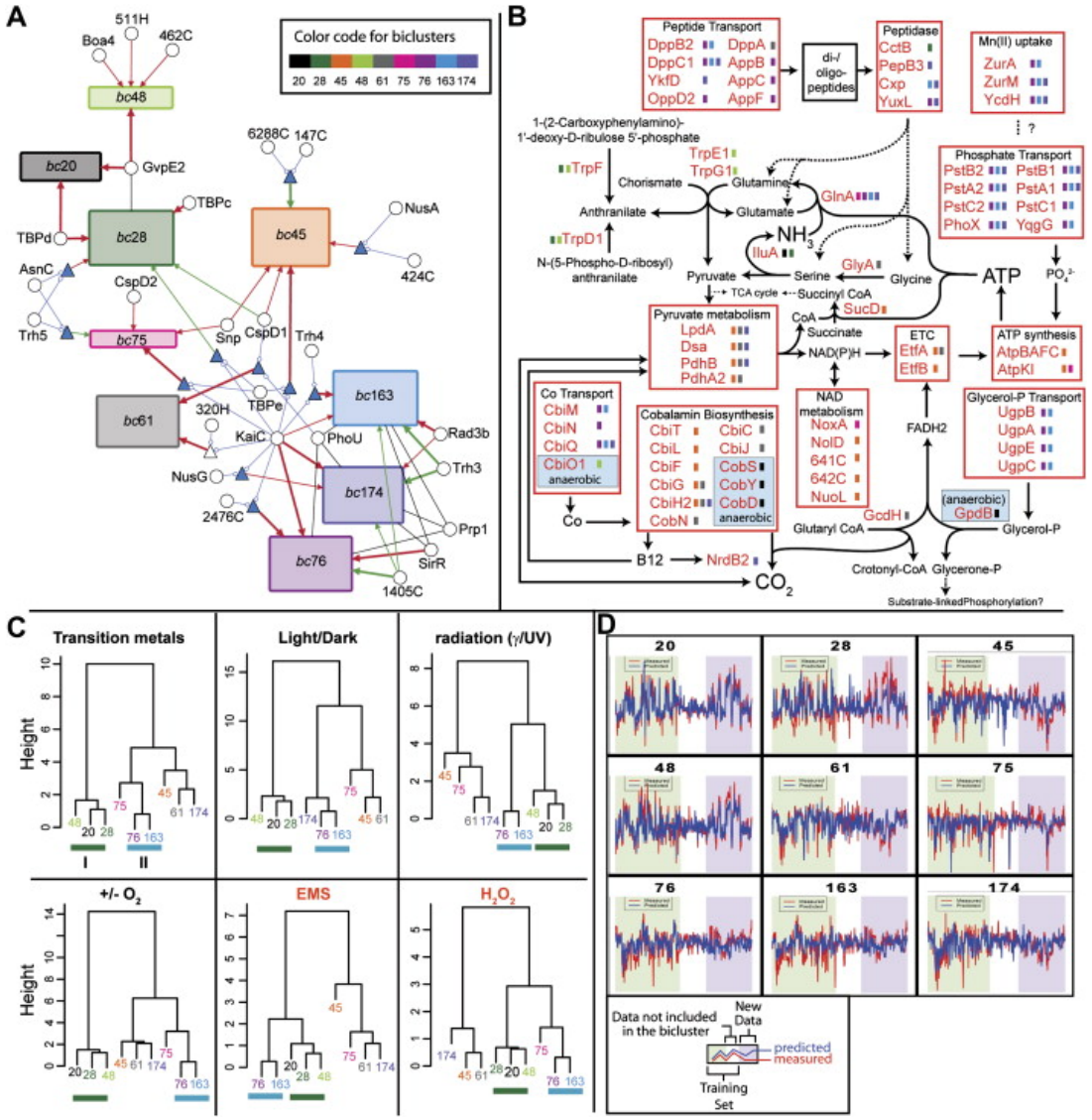
- Applications: Predictive Systems Biology

# What do we mean by ‘dynamics’?

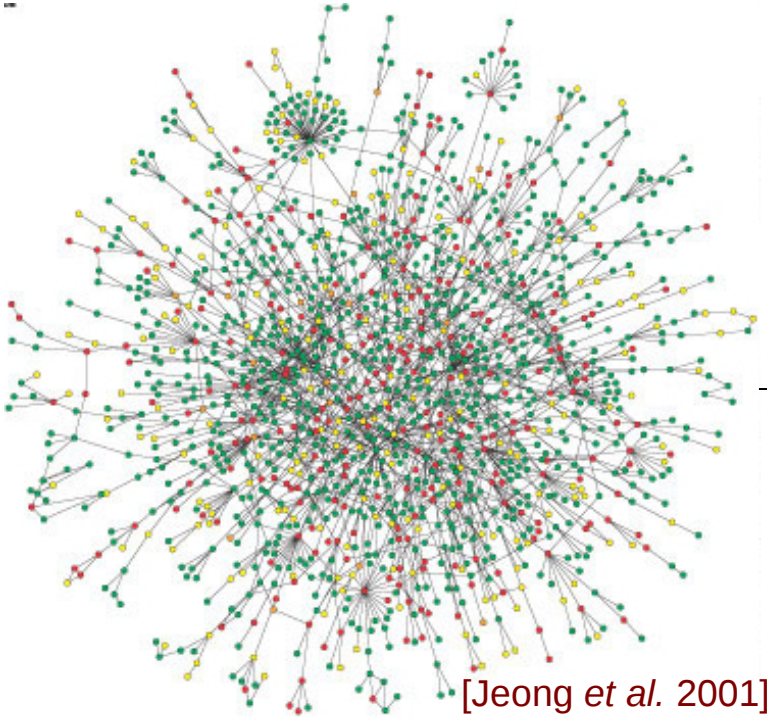
- Basically: things are changing with time
- For networks, each node may represent a time-varying quantity, such as gene expression levels
- Links may also change with time, or have a weight/strength dependent on the endpoints



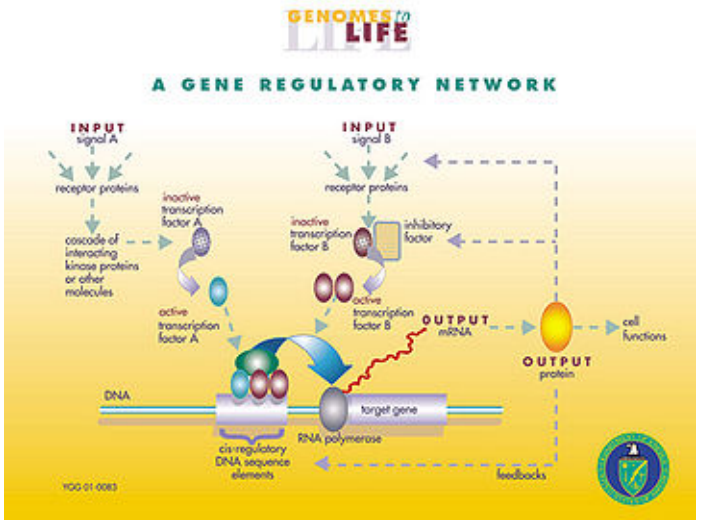

[Bonneau *et al.* 2007]

# Why study dynamics?

- Most networks/systems in the real world do change over time
- Studying dynamics tells us about certain properties of the system: both global (steady states, attractors) and local (causality)
- A model of dynamics can be used to make predictions about the future, and also about how the system responds to perturbation



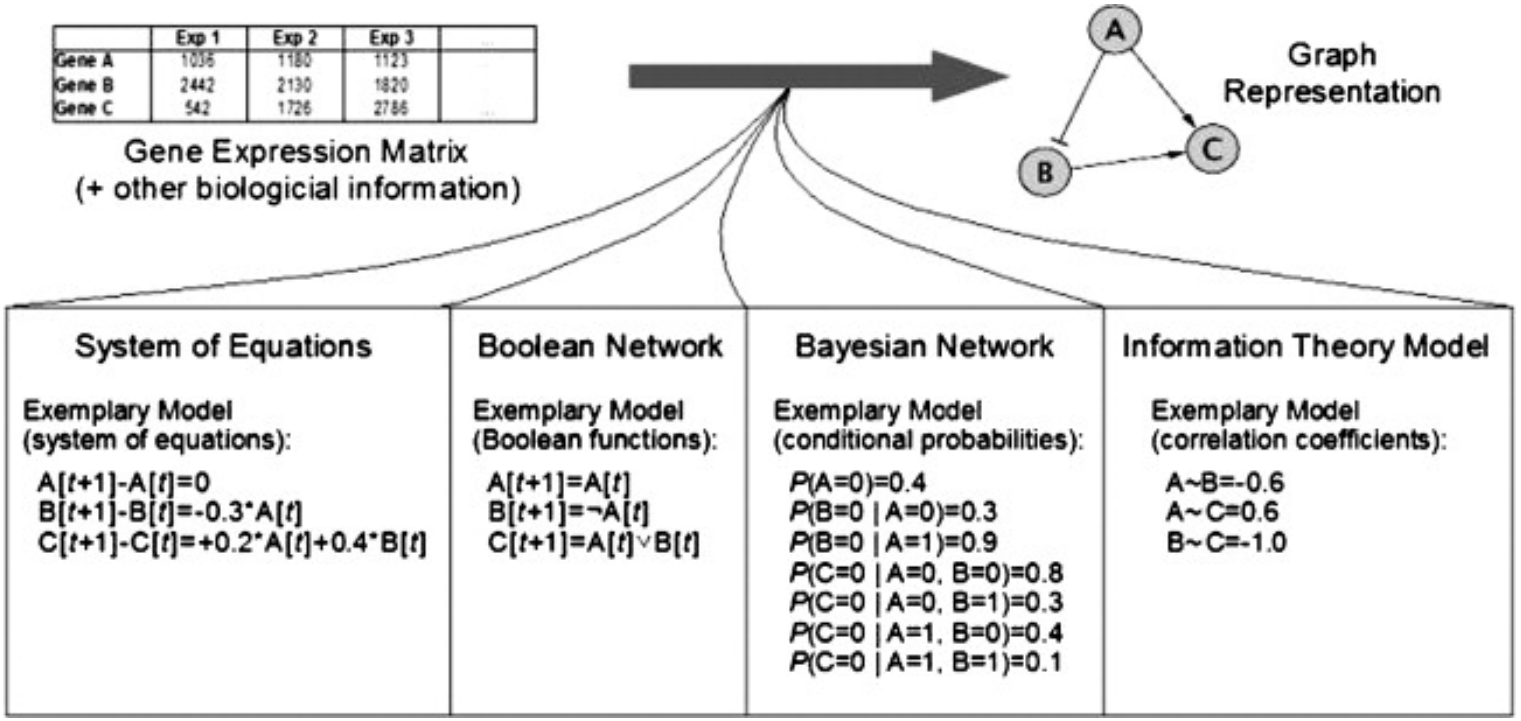
[Jeong *et al.* 2001]




[https://genomics.energy.gov]

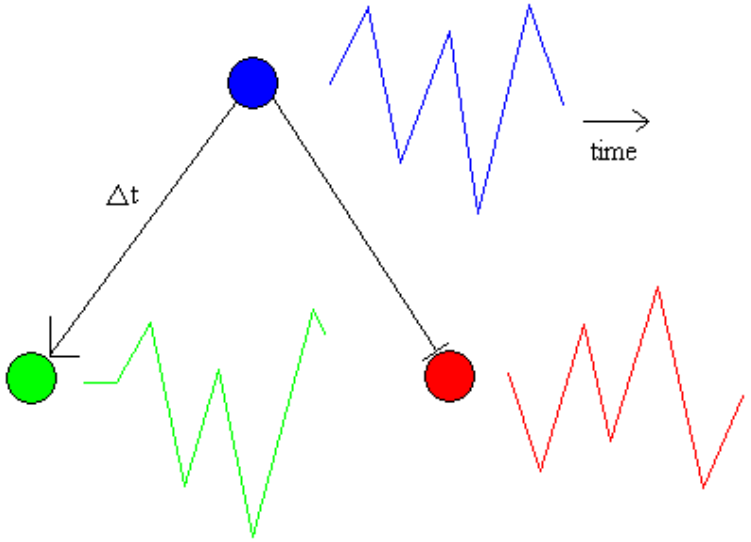
# Mathematical Representation

- The most preferred method, if feasible, is ordinary differential equations (ODEs), but for most large-scale systems we have to use appropriate simplifications for tractability




[Hecker *et al.* 2009]

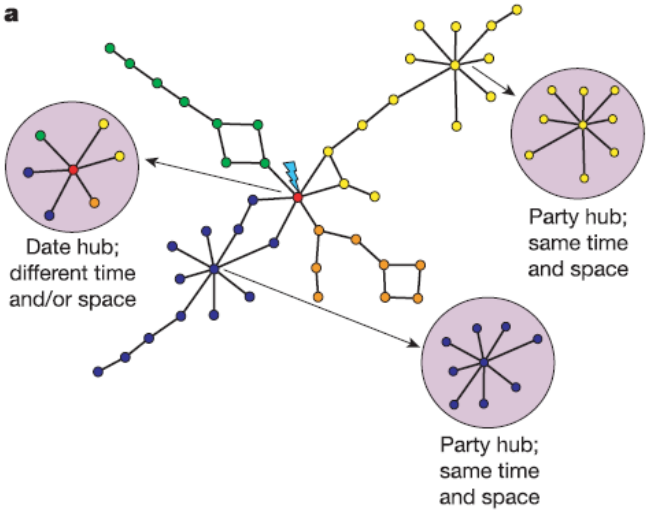
# Link with time series

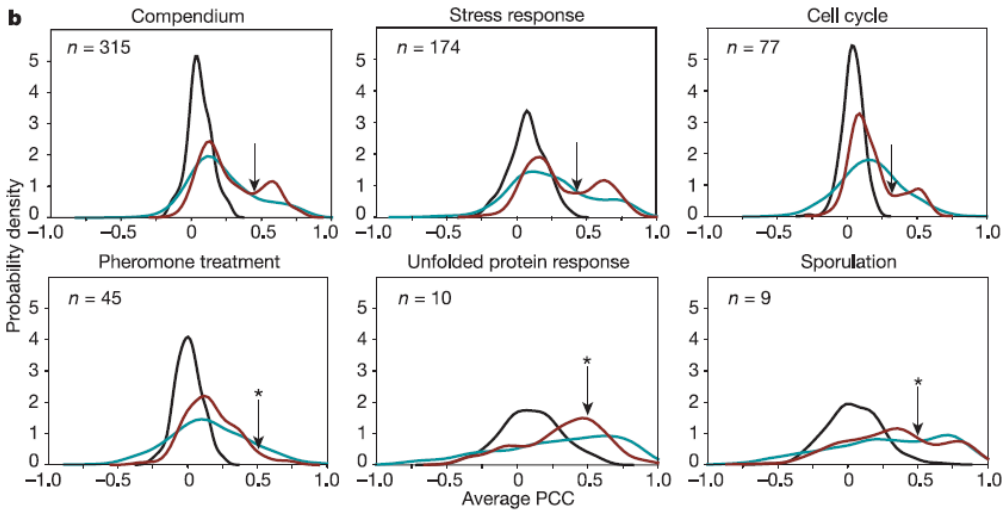



- The behaviour at each node can be described by a time series tracking an appropriate quantity (body weight, gene expression,...)
- In practice, raw observations are often in the form of time series data, which can be used (possibly combined with other information) to construct a plausible network
- Statistical techniques for time series (such as correlations) are widely used for this purpose---more on this later

# Example: date and party hubs

For a yeast protein-protein interaction network, hubs, defined as nodes with degree 5 or greater, were found to fall into two classes based on average co-expression with their interaction partners (Han *et al*. 2004):



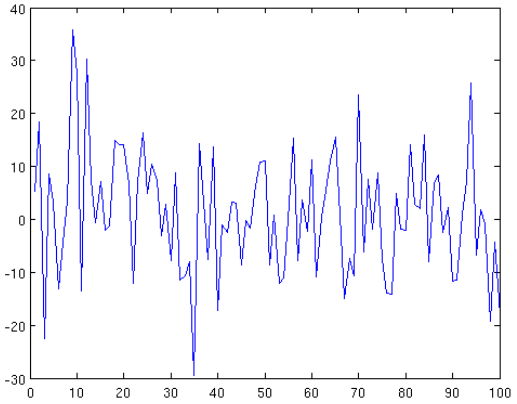




Date hubs were proposed to be high-level coordinators or linkers, whereas party hubs were thought to be local organisers for particular functional groups

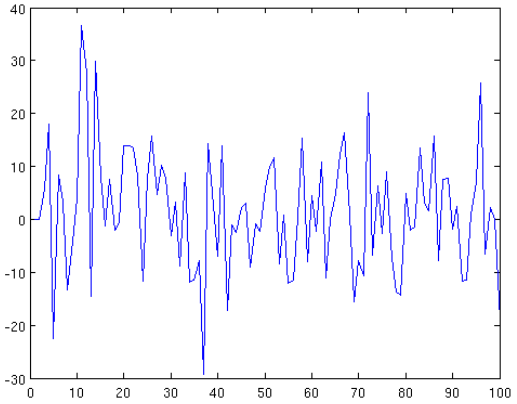
Intermission

# How to do Inference in Two Easy Steps

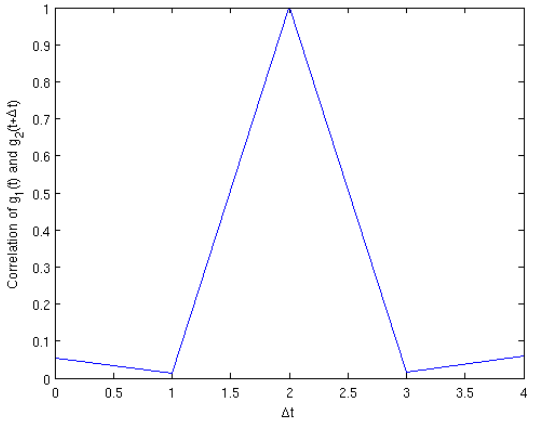
Gene 1

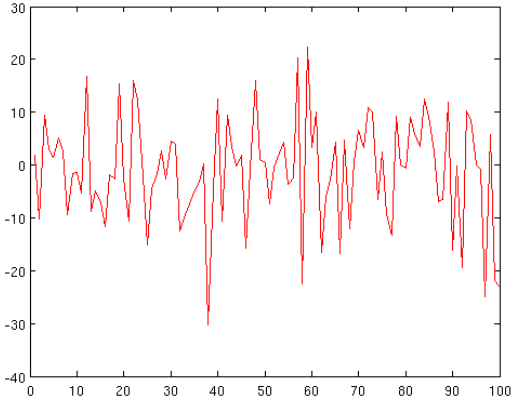


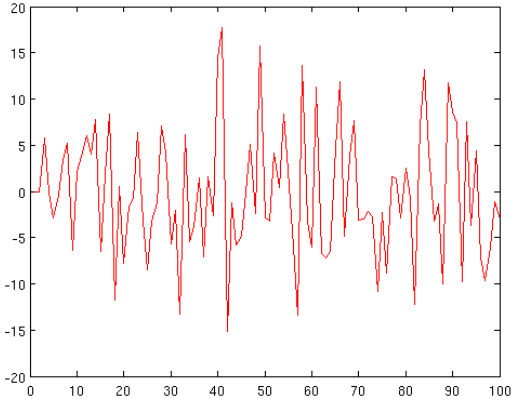
Gene 2

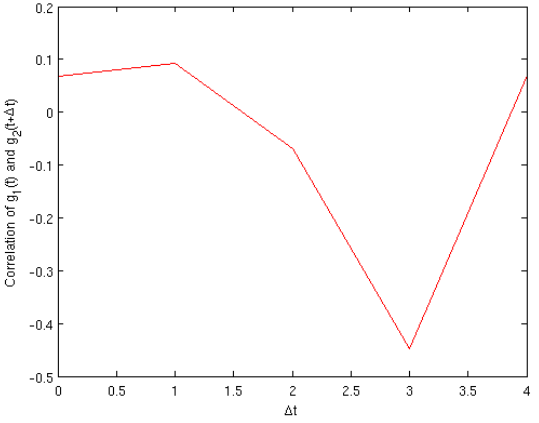


Cross-Correlograms



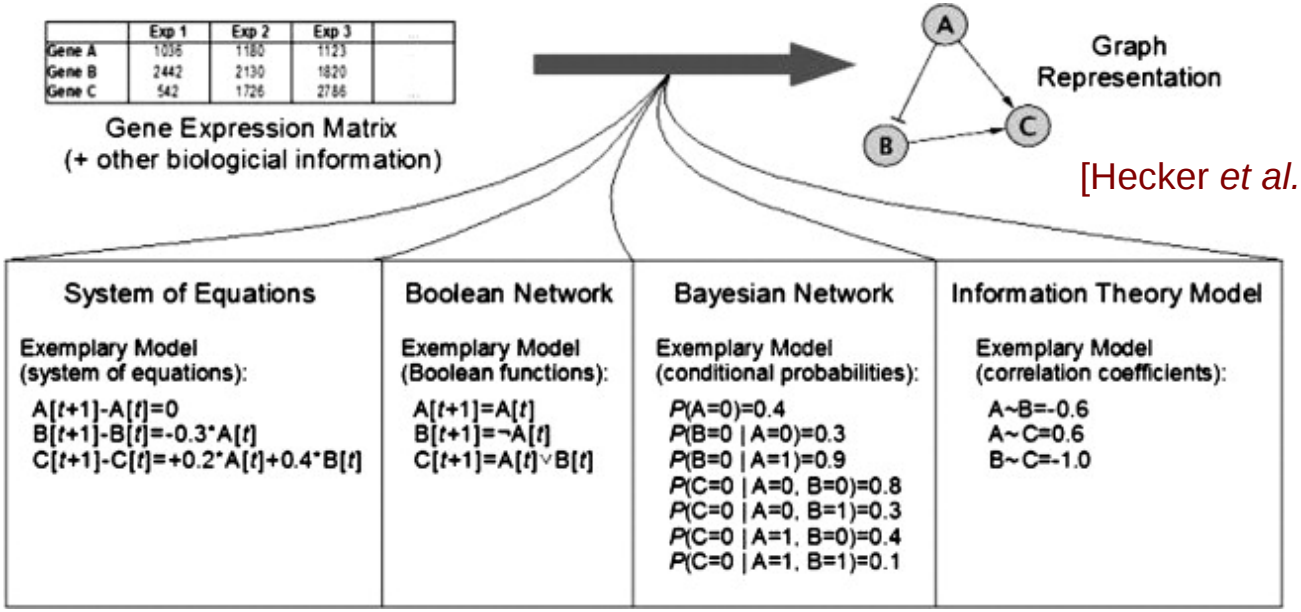





What can you infer about the relation between the two genes in each case?

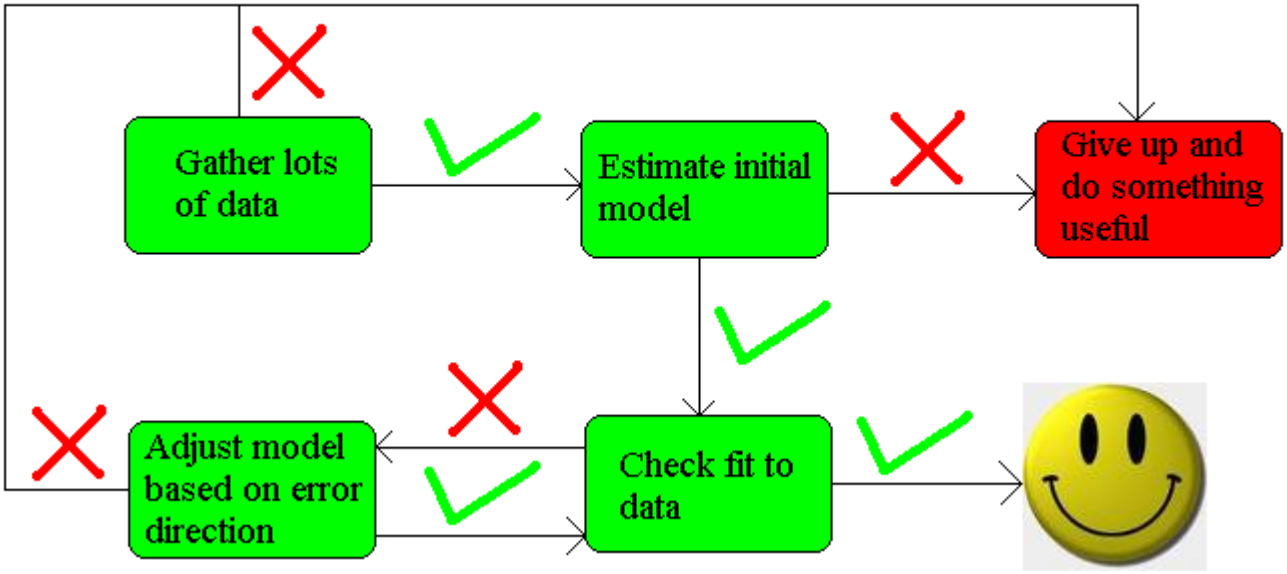
# Causality in networks

- Is a somewhat vexed philosophical notion; the classic 'correlation vs. causation' conundrum
- For our purposes, it just means we're trying to understand, at some given level (say proteins in a cell) whether changes in one entity lead to changes in another
- We can represent causal relationships in a network, and model them more precisely using a beautiful language called mathematics



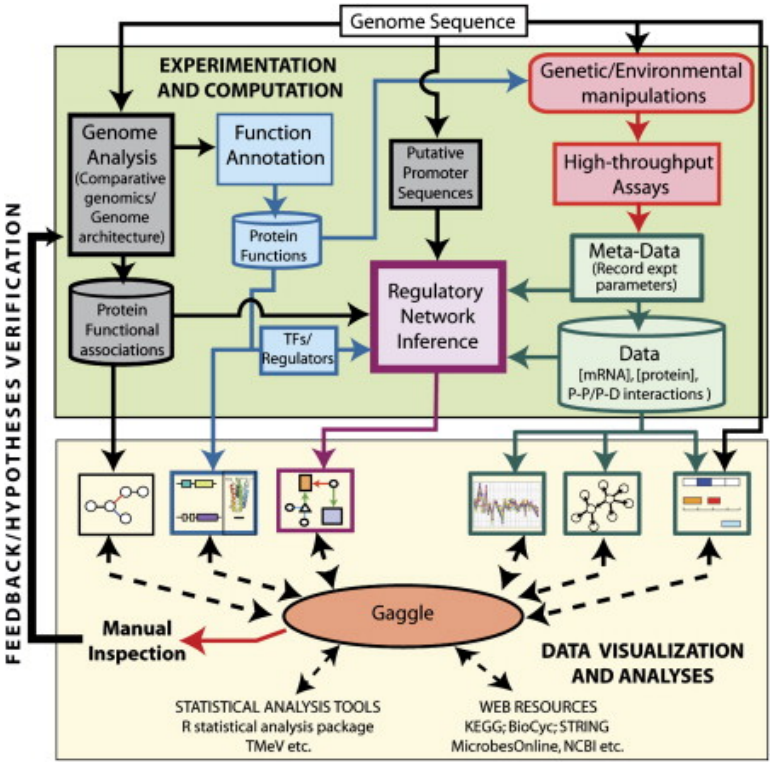
# Inference techniques

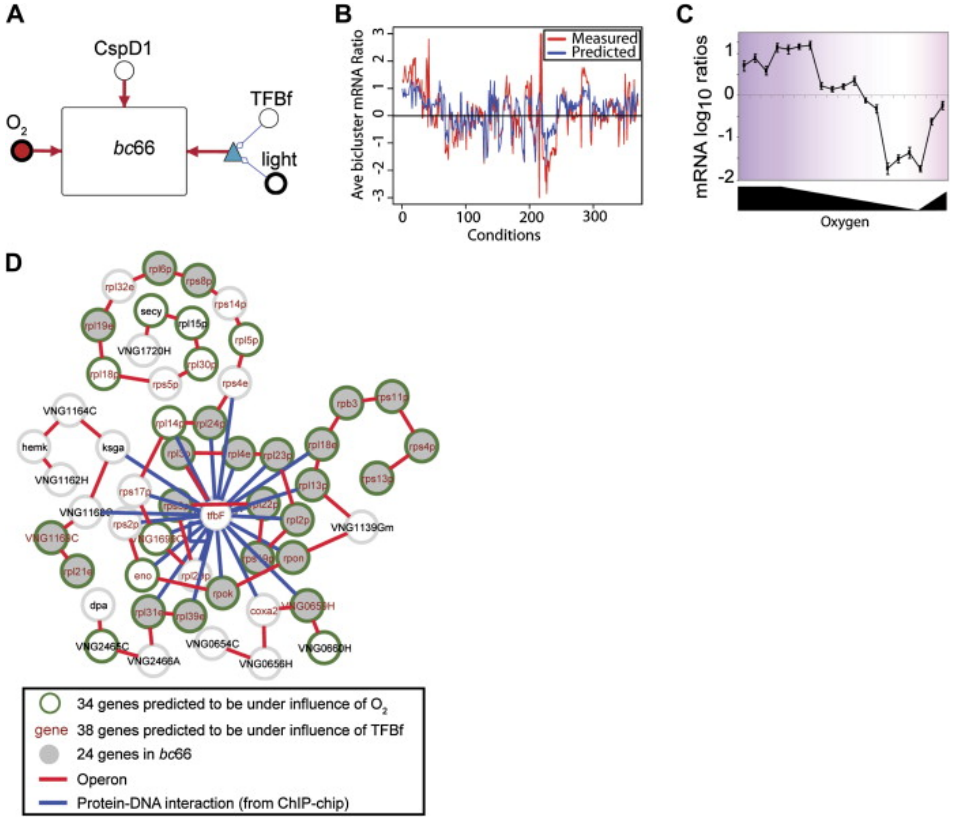
- We've already seen a simple example of how one might do this
- Two parts: inferring the network structure, and inferring the parameters or weights (which depend on the type of model used)
- Large number of techniques, but essential idea of all of them is to do statistical analysis of large quantities of experimental data
- Often involve iteration: infer a particular network, see how well it can reproduce your data, then attempt to adjust structure/parameters to improve this; stir and repeat until desired consistency is reached



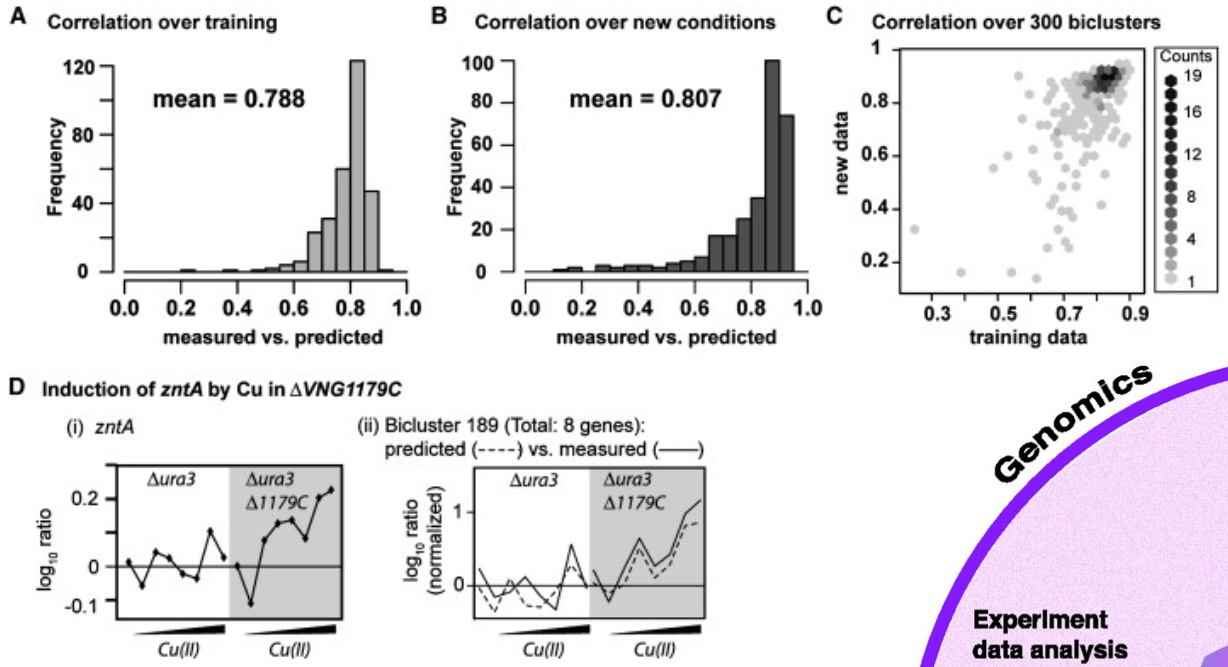
# Example: gene regulatory network for *H.salinarum*
(Bonneau *et al*. 2007)

For a novel, largely uncharacterised organism, using a large number of microarray experiments combined with homology and other information, a remarkably successful attempt at creating a network that explains the data



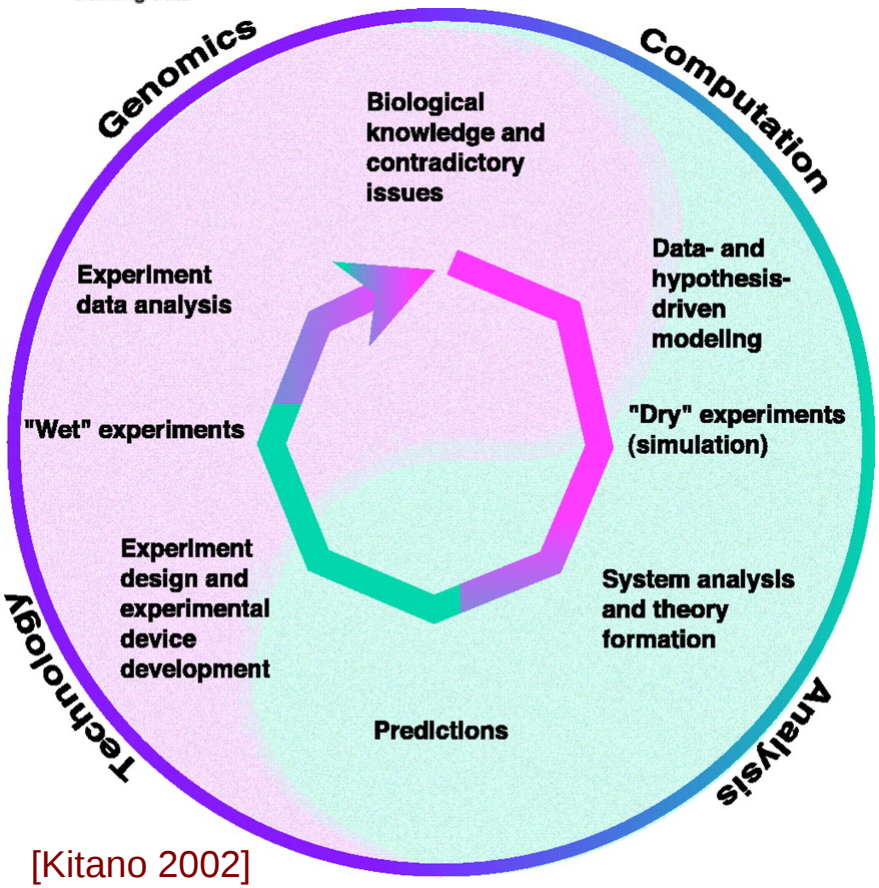



# Predictive Systems Biology




(Bonneau *et al*. 2007)

An important reality check for any model is: can it make accurate predictions of how the system will behave in novel circumstances? This can be regarded as a major goal of “systems biology”, and network-based models have a key role




[Kitano 2002]

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