Inferring Causal Networks in Plants

Inferring casual networks in planets can be done using many techniques oijoijoijwords  
  
General idea of causality from the book

The goal of causal inference is to discover whether the behavior of some node X causes the behavior of some node Y to change. If an increase in X’s value causes Y’s value to increase, then removing X from the network will prevent Y’s value from increasing. The value of X can also be manipulated in order to control the value of Y. Further, there may be several causal factors X1, 2, … Xk influencing Y some positively and some negatively. In our context nodes the Xs and Y are genes and their behaviors are expression values, but these ideas are also applicable in many other contexts such as ecological networks and so on..

Causal links may be detected experimentally by

1. Mutation: manipulating the behavior of a node (a particular gene in our case) and observing its effects on the network by performing:

* Experiments that excite the behavior of X.
* Experiments that depress the behavior of X.

2. Time Series: Causal links may also be inferred by

* Experiments that change the condition of an organism and then measure the behaviors of X and Y with closely spaced time points.

3. Steady State: General correlations can be found from experiments that change the condition of an organism and wait for the steady state. Effectively this is a degenerate case of the time series.

Overview of data types available (steady state, knockout, overexpression,  
and time series).  
-- Do we want to have a blurb about what the data looks like here or will this audience be familiar enough with that where it is fine? [Just a short description would help]

There are four basic types of experimental data available for use in gene network inference: Steady state, knockout, overexpression, and time series. Steady state data is a measurement taken after a perturbation is introduced to the network, and the network is allowed to settle into a “steady state” where the expression values of the genes have stopped changing. [Do we want an example here?] Knockout data is where a gene is removed from the organism. [Sometimes the knockout is the only perturbation.] Then a perturbation is introduced to this new gene network, and the results are compared to data that did not have the gene knocked out. Overexpression is similar to knockout data, except that instead of removing a gene, it is locked into a state of constantly being excited. A time-series experiment is when a perturbation is introduced to a network, such as in a steady-state experiment, but instead of waiting for the network to settle data is recorded at multiple time points until the network reaches a steady state. [Could add a sentence about how we can infer causality from each of these if we want] [Not needed but thanks]

Different tools (list with one sentence summary including the data  
types it works well with)  
There are many different tools available for gene network inference, encompassing a wide variety of theoretical approaches. Each of these tools uses a different approach to extract information from different data types. The basic idea behind all of these algorithms is to examine each possible edge between each pair of genes and give it a score, then rank those edges and select some number of the highest scored edges.

[Maybe these should go in a table?] No I like the prose, but they should be associated with ready they are for mutation, time series, or steady state.

Median-Corrected Z-Scores (MCZ) - Requires a dataset where each gene in the dataset is knocked out in turn. The idea is that if gene X influences gene Y, then knocking out gene X should change the value of gene Y. The amount of change in the knockout condition is compared to the median value of that gene across all experiments.

Network Identification by Multiple Regression (NIR) – Uses steady state data. Multiple-regression is used to causal edges in a network.

Gene Network Inference with Ensemble of Trees (GENIE3) – Uses steady-state data. GENIE3 works by creating a large number of regression trees, ranking the potential regulators for each gene from each tree, and then combining those ranked lists so that the most likely regulators are selected for each gene.

Context Likelihood of Relatedness (CLR) – Uses over-expression or knockout data. CLR computes the mutual information between each pair of genes and from that calculates the probability that each gene X is a regulator of gene Y.

Convex Optimization – Uses steady-state data. Convex optimization is a technique used to find weights that minimize some cost function.

Time-Delay ARACNE – Uses time-series data. Calculates the mutual information between gene X at time t and gene Y at time t+1 to build a network, and then prunes the weak edges.

Time-Lagged Context Likelihood of Relatedness (tlCLR) – Uses steady-state and time-series data. An extension of the CLR algorithm that takes into account differences in time in order to establish directionality between the edges.

Inferelator – Uses steady-state and time-series data. Inferelator uses differential equations to learn a sparse dynamical model for each gene.

Dynamic Factor Graphs (DFG) – Uses time-series data. DFG models the experimental noise in the data, subtracts that noise model out of the data, and then creates a network by learning sparse dynamical models for each gene.

Bayesian Network Inference with Java Objects (BANJO) – Uses time-series data. BANJO models each gene’s expression value at a time t by some combination of the expression of genes at time t-1.

Prose summary of results on simulated data  
(e.g. why combining different approaches  
can work etc.)  
the variety can help extract different bits of info

Etc [Yes, with nice pictures of workflows]

Simulation experiments showing which data types help the most.  
sims

Case study of Dynamic Factor Graphs on our time series data  
dfg case study

Enhanced case study with some overexpression data

Dfg overexpression results

[Perfect. The last four points are the key things that I want from you before you get busy on Jan 22.]