Modelling and Analysis in Bioinformatics: Inferring gene regulation

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Last week: Simulation of gene expression

$X$ is system state, i.e. numbers of each molecule species

Reactions:

$$\alpha_{j1}X_{i1} + \cdots + \alpha_{jn}X_{in} \rightarrow \beta_{1j}X_{o1} + \cdots + \beta_{nj}X_{on}, \quad j = 1, \ldots, M$$

$c$ are the known reaction rates
Last week: Simulation of gene expression

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- Stochastic simulation algorithm (SSA; Gillespie, 1977)
  1. Sample time until next reaction ($\tau$)
  2. Sample which reaction (depends on rates), simulate it
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$$\alpha_{j1}X_{ij1} + \cdots + \alpha_{jn}X_{ijn} \rightarrow \beta_{j1}X_{oj1} + \cdots + \beta_{jn}X_{ojn}, \quad j = 1, \ldots, M$$

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- Deterministic differential equation model
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c are the known reaction rates

- Stochastic simulation algorithm (SSA; Gillespie, 1977)
  1. Sample time until next reaction (\( \tau \))
  2. Sample which reaction (depends on rates), simulate it

- Deterministic differential equation model

- Stochastic differential equation model
Warmup for this week

- Given a set of observed variables, how to select ones that are related?
Warmup for this week

- Given a set of observed variables, how to select ones that are related?
- ... that are *causally* related?
Warmup for this week

- Given a set of observed variables, how to select ones that are related?
- ... that are causally related?
- How to infer gene regulatory relationships?
Learning goals for this week

- To understand reasons for difference of correlation and causality
- To recognise basic regulatory network inference methods
- To design regulatory network inference projects
- To apply simple methods for regulatory network inference
What is a gene regulatory network?

- How should the arcs be interpreted?
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- How should the arcs be interpreted?
  - Interaction active somewhere?
What is a gene regulatory network?

- How should the arcs be interpreted?
  - Interaction active somewhere?
  - Interaction active at a given condition?
What is a gene regulatory network?

- How should the arcs be interpreted?
  - Interaction active somewhere?
  - Interaction active at a given condition?
  - Rate-limiting interaction at a given condition?
Outline

Motivation

Causal inference

Experimental methods for regulatory network inference

Computational methods for regulatory network inference

Conclusion and next steps
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Conclusion and next steps
I USED TO THINK CORRELATION IMPLIED CAUSATION.

THEN I TOOK A STATISTICS CLASS. NOW I DON'T.

SOUNDS LIKE THE CLASS HELPED. WELL, MAYBE.
Correlation and causation

Figure 1. Correlation between Countries’ Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

Image from Messerli (2012), doi:10.1056/NEJMon1211064
Correlation and causation examples

- Drownings and ice cream sales in the summer
- Number of pirates and global average temperature
- Diet, health and lifestyle
- ...
Linear dependence

- As we saw, *correlation does not imply causation*.
- Assume two random variables $X$ and $Y$ related by
  \[ X = a \cdot Y + \epsilon \]
- We can equivalently solve
  \[ Y = (X - \epsilon)/a \]
- Similar reasoning also applies with non-linear dependencies
- In general not possible to tell which of two variables causes which
Direct and indirect links

- In general, we would like to distinguish between direct and indirect links
- Assume three random variables $X$, $Y$ and $Z$ related by
  \[ Y = b \cdot Z + \epsilon_Y \]
  \[ X = a \cdot Y + \epsilon_X \]
- $X$ will also depend on $Z$:
  \[ X = a \cdot b \cdot Z + a \cdot \epsilon_Y + \epsilon_X \]
- Similar reasoning also applies with non-linear dependencies
- Additional assumptions needed to separate direct and indirect links
How to infer causality

- Interventions
- Randomisation
  - Double blinding
- Clever experimental design
Drinking and mortality: long-term follow-up of drinking-discordant twin pairs.

Sipila P1, Rose RJ2, Kaprio J1,3,4.

Abstract
AIMS: To determine if associations of alcohol consumption with all-cause mortality replicate in discordant monozygotic twin comparisons that control for familial and genetic confounds.

DESIGN: A 30-year prospective follow-up.


PARTICIPANTS: Same-sex twins, aged 24-60 years at the end of 1981, without overt co-morbidities, completed questionnaires in 1975 and 1981 with response rates of 89% and 84%. 15,607 twins were available for mortality follow-up from the date of returned 1981 questionnaires to December 31, 2011. 14,787 twins with complete information were analysed.

MEASUREMENTS: Self-reported monthly alcohol consumption, heavy drinking occasions (HDO), and alcohol-induced blackouts. Adjustments for age, gender, marital and smoking status, physical activity, obesity, education and social class.

FINDINGS: Among twins as individuals, high levels of monthly alcohol consumption (≥259 grams/month) associated with earlier mortality (HR = 1.63, 95% confidence interval (CI) = 1.47-1.81). That association replicated in comparisons of all informatively drinking-discordant twin pairs (HR = 1.91, 95% CI = 1.49-2.45) and within discordant monozygotic (MZ) twin pairs (HR = 2.24, 95% CI = 1.31-3.85), with comparable effect size. Smaller samples of MZ twins discordant for HDO and blackouts limited power; a significant association with mortality was found for multiple blackouts (HR = 2.82, 95% CI = 1.30-6.08), but not for HDO.

CONCLUSIONS: The associations of high levels of monthly alcohol consumption and alcohol-induced blackouts with increased all-cause mortality among Finnish twins cannot be explained by familial or genetic confounds; the explanation appears to be causal.

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KEYWORDS: Alcohol drinking; alcoholic intoxication; binge drinking; causality; confounding factors; follow-up studies; mortality; twins

PMID: 26359785 [PubMed - as supplied by publisher]
Another huge study found no evidence that cell phones cause cancer. What was the W.H.O. thinking? I think they just got it backward.

Huh?

Well, take a look.

You're not... there are so many problems with that.

Just to be safe, until I see more data I'm going to assume cancer causes cell phones.

https://xkcd.com/925/, CC-BY-NC
Two networks producing identical output

Image from Angulo et al. (2015), arXiv:1508.03559
What can help

- Combining data sets from different modalities
- Diverse data, perturbations
- Prior information, e.g. sparsity
- ...?
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Typical data types

1. TF knockouts
2. Expression data
3. TF binding data
4. (Chromatin accessibility data)
5. (Chromatin 3D structure data)
TF knockout data

- Experimental intervention to disable a gene
- Measure gene expression afterwards
- Challenge: dramatic perturbation
  - Example fruit fly genes: *eyeless*, *tinman*
  - Are we still studying the same network?
Expression data

- Data under diverse conditions
- Time series are very helpful
  - Otherwise difficult to identify dynamical parameters that may confound the network
- Experimental design—measurements are expensive!
TF binding data

- Useful for establishing a mechanism
- But:
  - Not all regulators bind directly to DNA (could bind via other TFs)
  - How to map enhancers to genes?
Computational alternatives

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Figure from Pique-Regi et al. (2011), doi:10.1101/gr.112623.110
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Computational methods for regulatory network inference
  Modelling dynamical systems
  Modelling static interactions

Conclusion and next steps
Regulatory network inference methods

- Modelling various data sets
  - Modelling knockouts
  - Dynamical models of time series
  - Prior knowledge from TF binding
- Regression methods
- Correlation and mutual information based approaches
Modelling knockouts

- Typical workflow: compare the expression of a gene before and after knockout or other perturbation
- Can also check the sign of change
- Combine data from multiple experiments to work out the network
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Linear dynamical systems

\[ \frac{dX(t)}{dt} = AX(t) \]

- Here \( A \) is a matrix of regulatory links
- Why:
  - Simple representation
  - Efficient inference algorithms
- Why not:
  - Unrealistic
Two regulators

\[
\begin{align*}
0 + 0 &= 0 \\
1 + 0 &= 1 \\
0 + 1 &= 1 \\
1 + 1 &= 2
\end{align*}
\]
Limit behaviour

- Consider a 1D linear differential equation:

\[ \frac{dx(t)}{dt} = ax(t) \]

- This has a solution (check!):

\[ x(t) = Ce^{at} \]

- Assume \( x(0) > 0 \). As \( t \to \infty \), either

  - If \( a > 0 \) \( x(t) \to \infty \)
  - If \( a < 0 \) \( x(t) \to 0 \)
Limit behaviour

- Consider a 1D linear differential equation:

\[
\frac{dx(t)}{dt} = ax(t)
\]

- This has a solution (check!):

\[
x(t) = Ce^{at}
\]

- Assume \( x(0) > 0 \). As \( t \to \infty \), either

\[
\begin{cases} 
  x(t) \to \infty & \text{if } a > 0 \\
  x(t) \to 0 & \text{if } a < 0
\end{cases}
\]
Limit behaviour

\[ \frac{d\mathbf{X}(t)}{dt} = A\mathbf{X}(t) \]

- In higher dimensions possibilities are only slightly more complex:
  - \(|\mathbf{X}(t)| \to \infty\)
  - \(|\mathbf{X}(t)| \to 0\)
  - \(\mathbf{X}(t)\) approaches a harmonic oscillator (sine curve)
- The behaviour depends on the eigenvalues of \(A\)
Non-linear dynamical systems

- More complex models
- Why:
  - Realistic model
- Why not:
  - More difficult to learn: more choices, more parameters
  - Less efficient algorithms
Granger causality

- Assume a linear discrete-time dynamical model between two variables \(x_1(t)\) and \(x_2(t)\):

\[
x_1(t) = \sum_{j=1}^{p} a_{11,j} x_1(t - j) + \sum_{j=1}^{p} a_{12,j} x_2(t - j)
\]

\[
x_2(t) = \sum_{j=1}^{p} a_{22,j} x_2(t - j) + \sum_{j=1}^{p} a_{21,j} x_1(t - j)
\]

- If a model with \(a_{12} \neq 0\) explains \(x_1\) better, it is said that \(x_2\) Granger-causes \(x_1\).

- This provides evidence that \(x_2\) may cause \(x_1\).

- But: Granger causality \(\neq\) causality
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Partial correlation

- Regular correlation coefficient

\[ \rho_{XY} = \text{Corr}(X, Y) = \frac{\text{Cov}(X, Y)}{\sigma_X \sigma_Y} \]

can be confounded by indirect links

- Possible solution: partial correlation given additional variables \( Z \)
  - Informally: compute the correlation of \textit{residuals of linear regression models given} \( Z \)
Gaussian Markov random field

- Undirected graphical model, edges denote dependence
- Gaussian marginals $\Rightarrow$ multivariate Gaussian joint distribution $\mathcal{N}(\mu, \Sigma)$
- Theorem: $\{i, j\} \notin E \Rightarrow (\Sigma^{-1})_{i,j} = 0$
- In words: the precision matrix $\Sigma^{-1}$ is sparse with non-zero elements corresponding exactly to edges in the dependency graph
Graphical lasso

- Previous sparsity property suggests model structure learning algorithms that promote such sparsity
- Given observations $X$, we aim to estimate the precision matrix $\Theta = \Sigma^{-1}$ by minimising

$$- \log p(X|\Theta) + \alpha \cdot \text{pen}(\Theta),$$

where the first term is negative log-likelihood and the second term is penalty that encourages sparsity
- Ideally $\text{pen}(\Theta) = \#\{(i, j)|\theta_{ij} \neq 0\}$ but computationally difficult
- **Graphical Lasso:** $\text{pen}(\Theta) = \sum_{i,j} |\theta_{ij}|$
  - Efficient convex optimisation + sparsity
Limitations of static interaction models

- Self-interactions?
- Loops resolved through time?
- Directionality difficult or impossible to resolve
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Tasks for the study circle on Thursday

Paper:

- D. Marbach et al.,
  doi:10.1038/nmeth.2016

Task for all:

- Read the paper to form an overview of the topic.
- You will not need to understand the details.
Next week: guest lectures

See the course website for details!