Inferring Causality in Microbial Communities

Goals and Challenges

Niklas Pfister

May 9, 2023

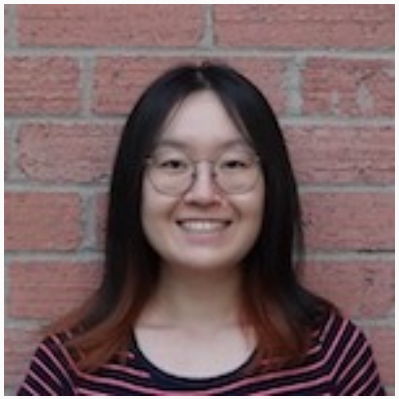
Two-day meeting - DSTS

novo nordisk fonden
Benefiting people and society

UNIVERSITY OF COPENHAGEN

Collaborators

At the University of Copenhagen



Shimeng Huang

Anton Rask Lundborg

At Helmholtz AI in Munich

Elisabeth Ailer

Niki Kilbertus

Microbiome

What is the microbiome and why is it important?

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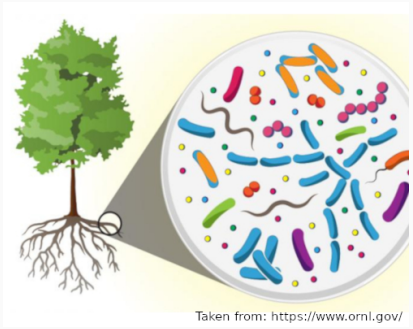

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Taken from: https://drannwellness.com/

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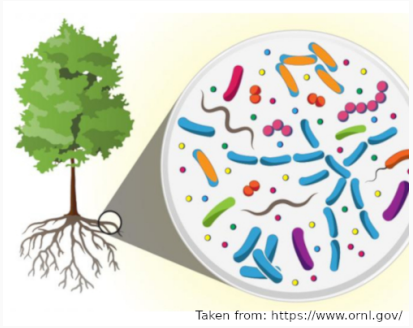
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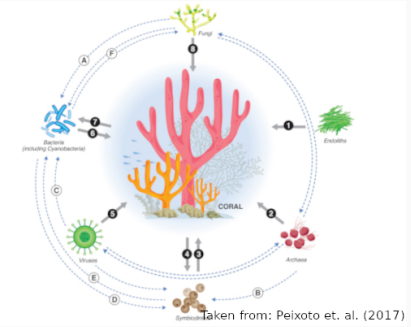
Taken from: Peixoto et. al. (2017)

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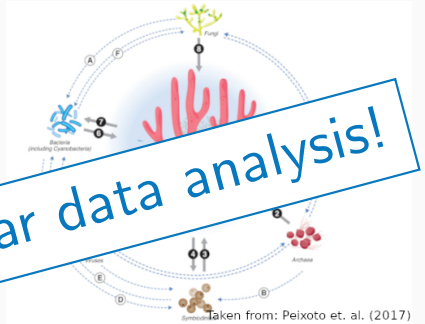

Wide range of applications, but very similar data analysis!

H

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Measuring the microbiome

(1) Extract sample and preprocess

(2) Perform sequencing:

- marker gene sequencing (amplify specific DNA target)
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(substantially more complex in reality)

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Problems:

- compositional (more recently, absolute measures are also possible)
- multiple sources of bias (host DNA, amplification bias, ...)
- zero-inflated and high-dimensional
- varies substantially over time

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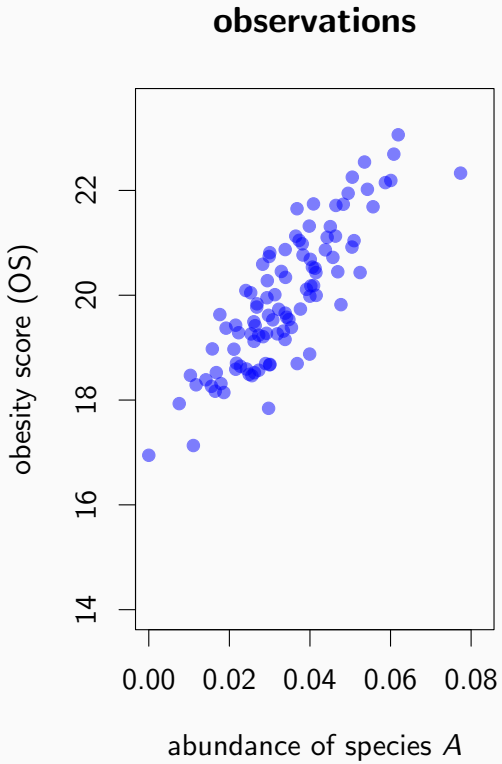
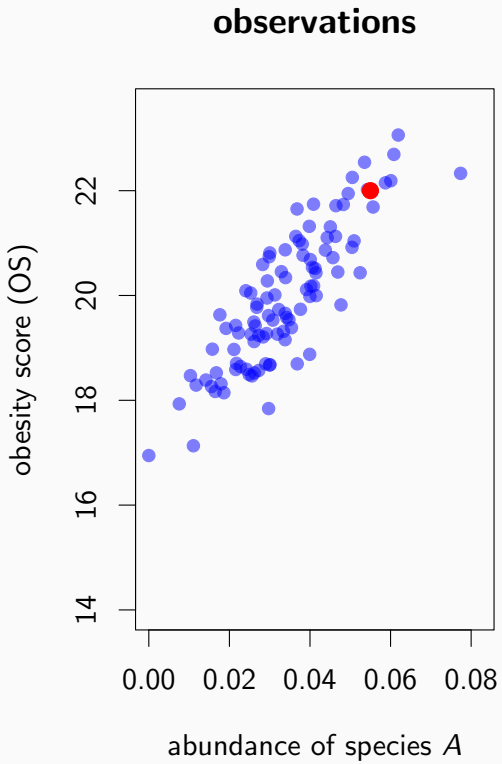
Shared goal: Infer underlying causal mechanism!

Causality

What is a causal model and how is it different from an observational statistical model?


observations
obesity score (OS)
14
16
18
20
22
0.00
0.02
0.04
0.06
0.08
abundance of species A

Question: What if species A is removed for a specific mouse?



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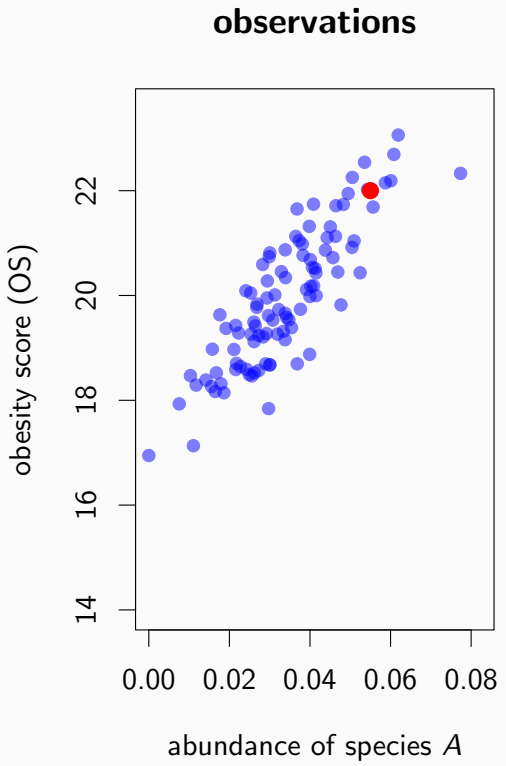

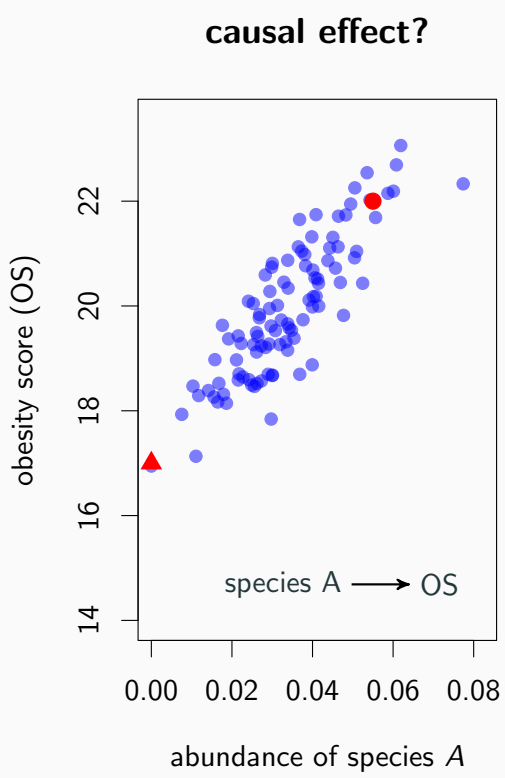

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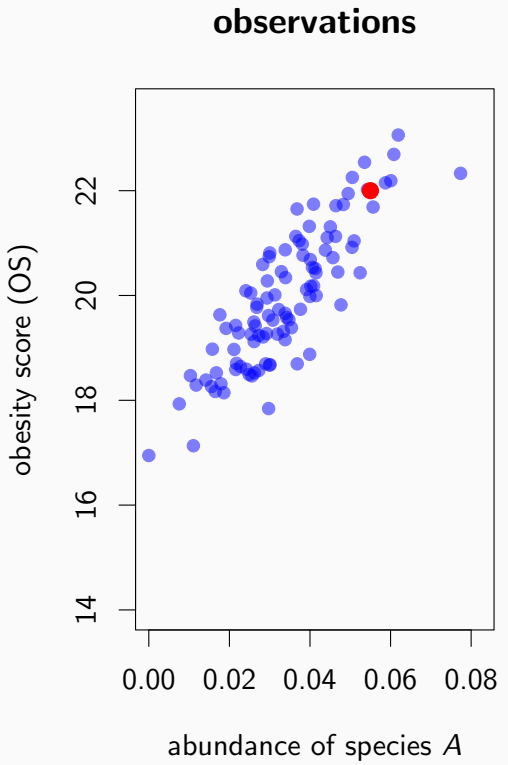

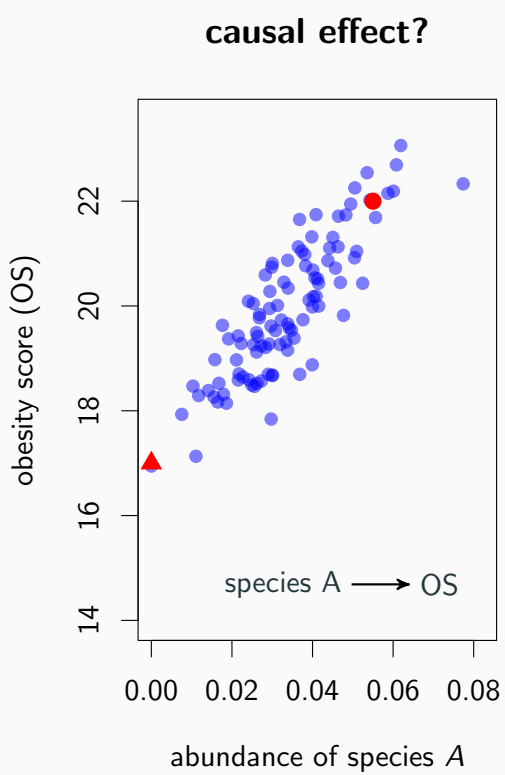

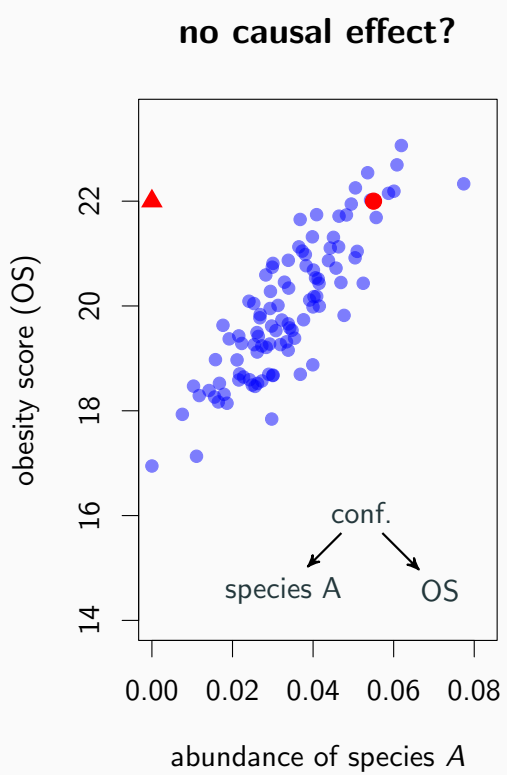

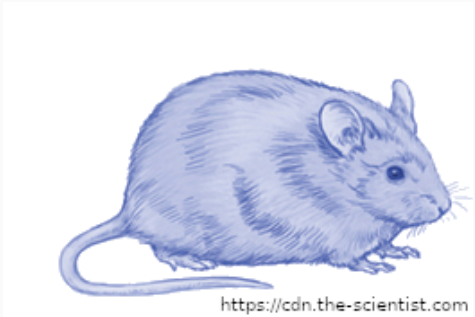

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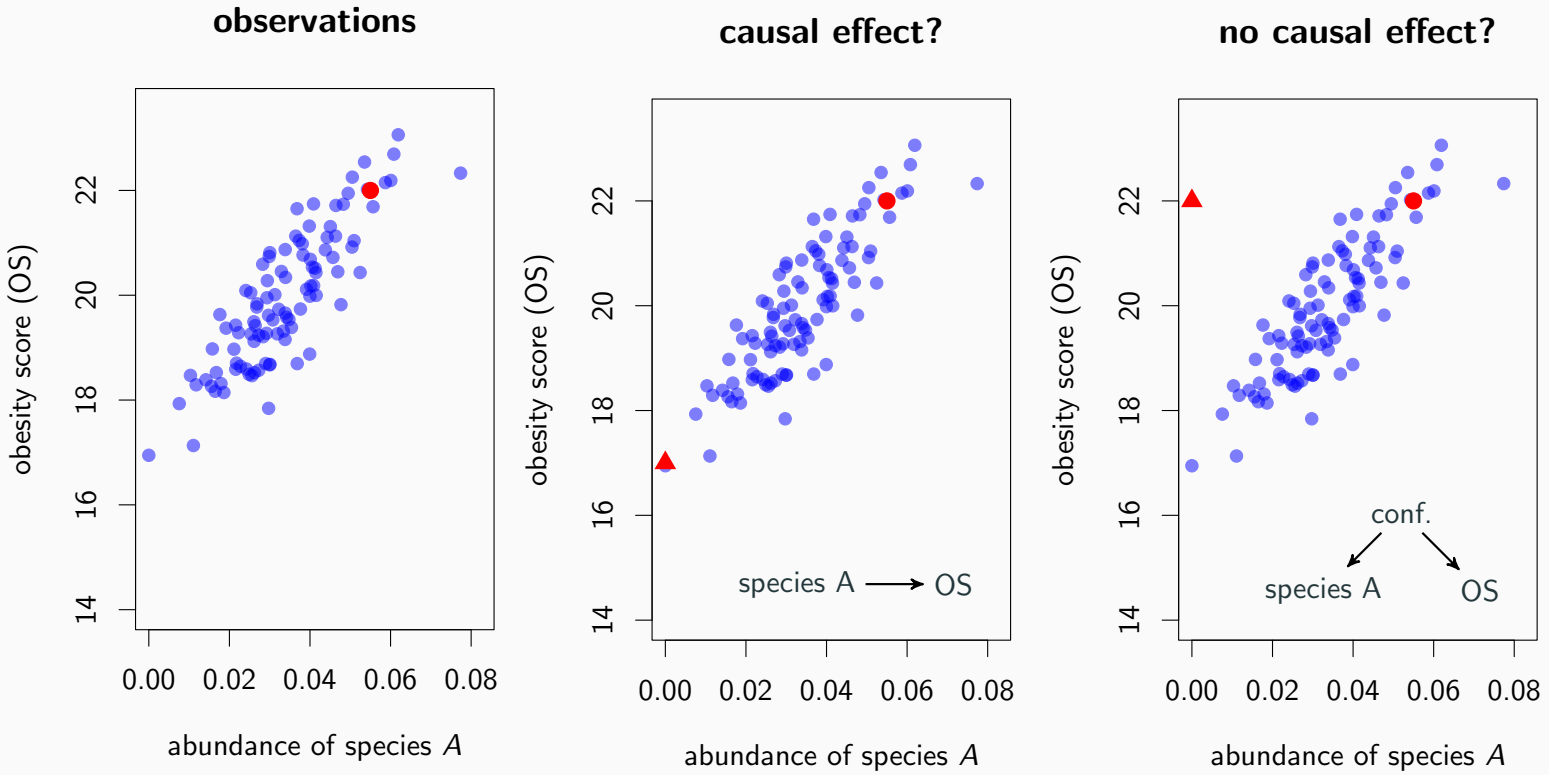

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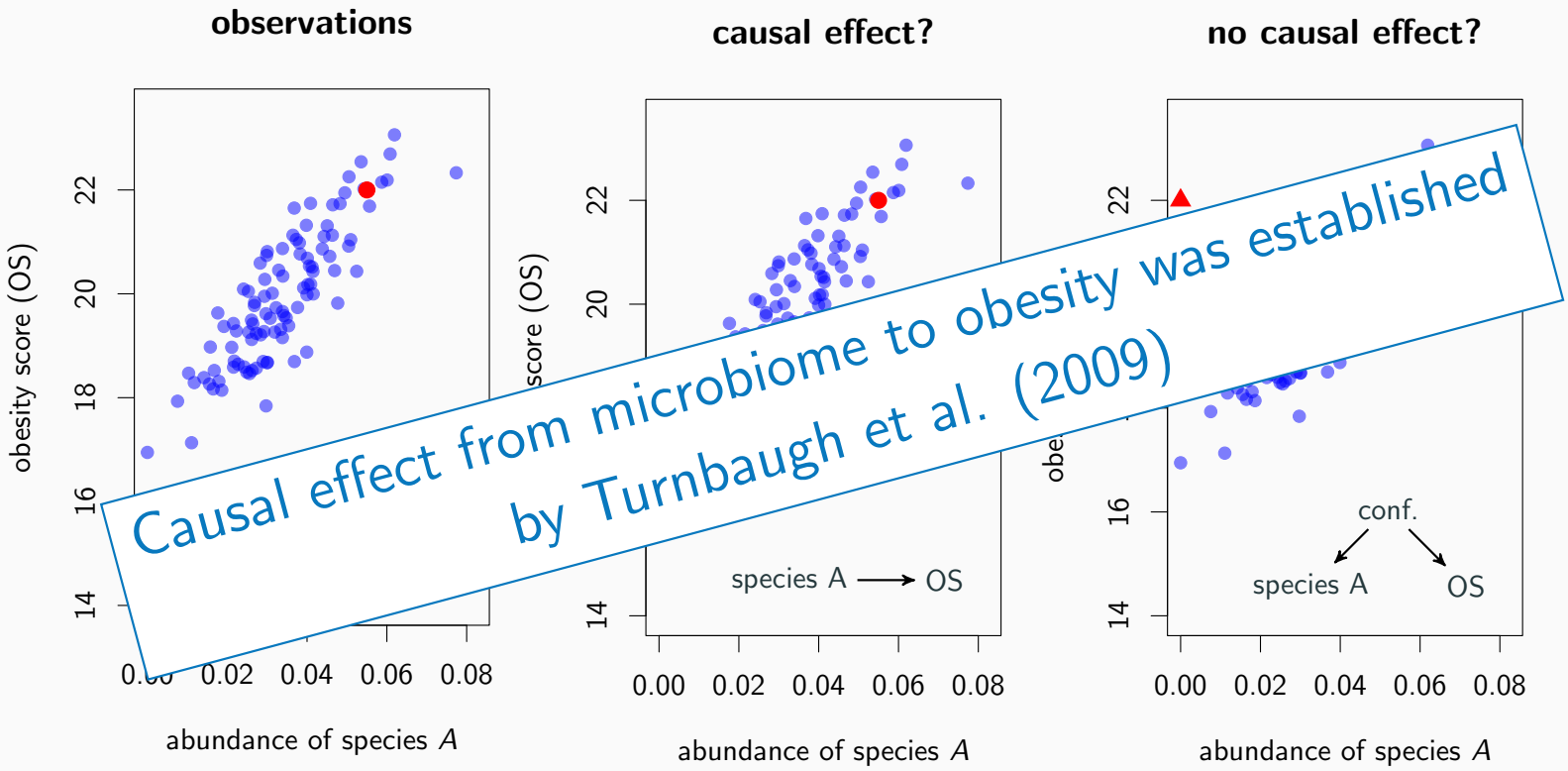

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Two main types of models exist:

- Potential outcome models (Imbens and Rubin (2015))
  - starts from a set of interventions
- Structural causal models (Pearl (2009))
  - starts from the causal mechanism

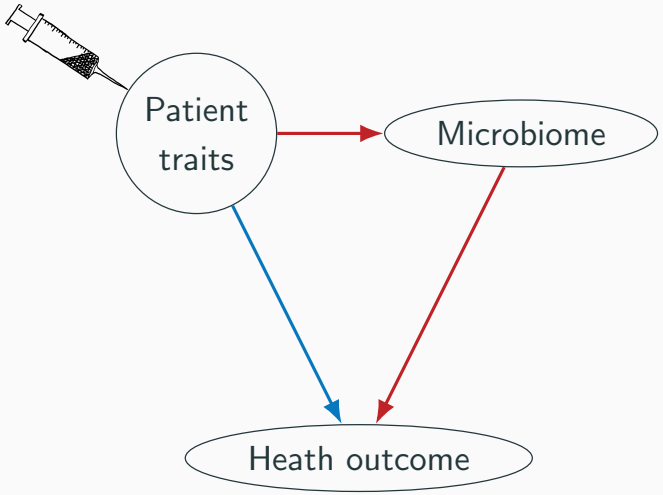
$\rightarrow$ Equivalent, but provide different perspective/focus.

Two challenges with microbiome data

Model specification and confounding

Challenge 1: Model specification

Example: Microbiome-mediated effect of drugs. How can we decompose the causal effects of a drug?



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Micobe level Composition level Proxy level

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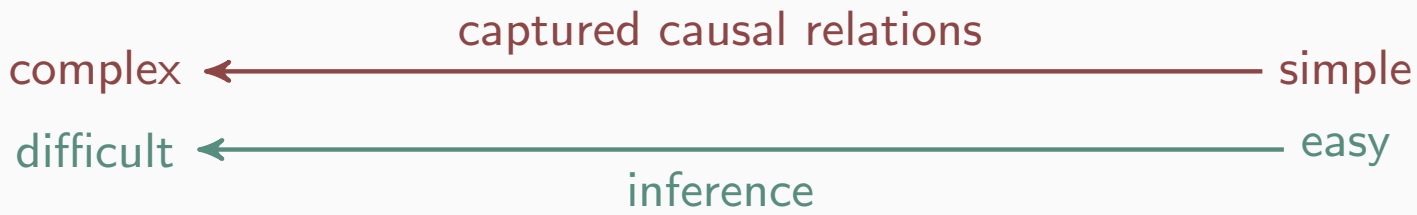

Compositional level

Simple mechanistic model

- $Y \in \mathbb{R}$ response of interest
- $X = (X^1, \ldots, X^n) \in \mathbb{R}^d$ predictor variables
- Structural causal model encodes the relation of X on Y,

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Goal: Learn causal effects corresponding to interventions that modularly increase individual coordinates, i.e.,

$$I^j(x_0) := \mathbb{E}[\tfrac{\partial}{\partial x^j} f(x_0, \epsilon)]$$

$\rightarrow$ Similarly, averaged effect $I^j := \mathbb{E}[\tfrac{\partial}{\partial x^j} f(X, \epsilon)]$.

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Problem: Individually changing a single coordinate in compositional vector is meaningless.

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Compositional level

Simple compositional mechanistic model

- $Y \in \mathbb{R}$ response of interest
- $Z = (Z^1, \ldots, Z^n) \in \Delta^d$ predictor variables, where $\Delta^d = \{z \in [0,1]^d \mid \sum_{j=1}^d z^j = 1\}$ is the simplex.
- Structural causal model encodes the relation of Z on Y,

$$Y = f(Z, \epsilon) \quad \text{with} \quad Z \perp\!\!\!\perp \epsilon$$

Goal: Learn causal effects corresponding to interventions that modularly increase individual coordinates relative to the others, i.e.,

$$I^j(z_0) := \mathbb{E}[\tfrac{\partial}{\partial c} f(\phi^j(z_0, c), \epsilon)\big|_{c=1}] \quad \text{(CFI)}$$

with $\phi^j(z, c) = (s_c z^1, \ldots, s_c z^{j-1}, c^j, s_c z^{j+1}, \ldots, s_c z^d)$.

Further considerations for model specification

- Complex data structure

  high-dimensional, sparse (many zeros), compositional

  - What types of statistical procedures apply?

- Integration of multiple data types

  prior knowledge (e.g., phylogenetic structure), host traits

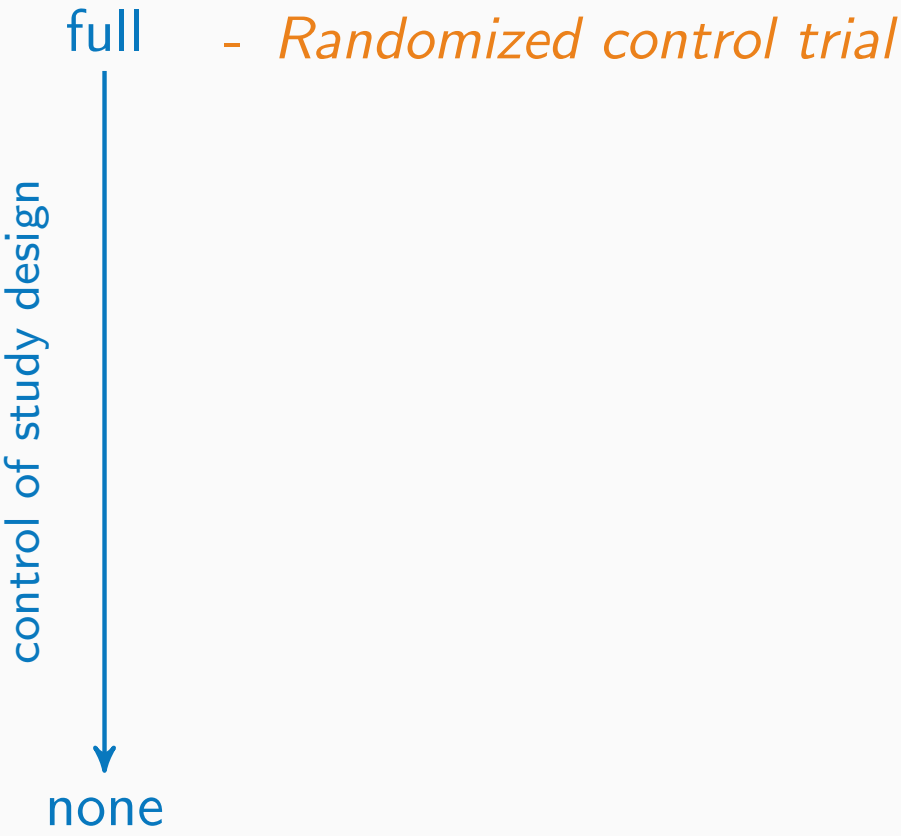
  - How should this be included in causal analysis?

- Volatile over time

  microbiome may oscillate over time

  - When do we need to account for time and when not?

Challenge 2: Confounding



Challenges: requires targeted interventions, expensive, difficult outside of the lab

Challenge 2: Confounding

- *Randomized control trial*

- *Procedures with no prior causal knowledge*

  (e.g., score- or constraint-based)

Challenges: model entire system, often under-identified, difficult to achieve uncertainty quantification

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- *Adjustment/inverse probability weighting*
  (e.g., many semiparametric approaches)

- *Procedures with no prior causal knowledge*
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Challenges: lots of prior knowledge about causal structure, no unobserved confounding (ignorability)

Challenge 2: Confounding

- *Randomized control trial*
- *Invariance based methods*
  (e.g., instrumental variables/Mendelian randomization)
- *Adjustment/inverse probability weighting*
  (e.g., many semiparametric approaches)
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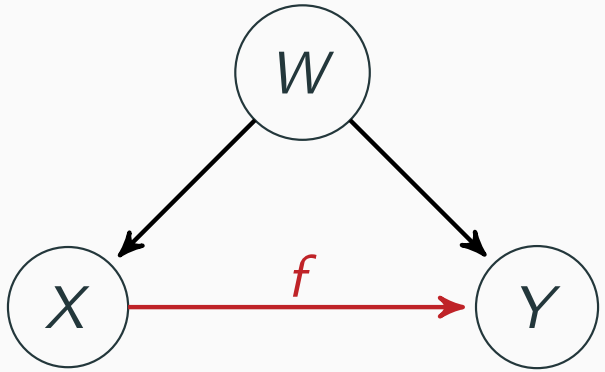
Challenges: some causal structure is assumed, requires heterogeneous study design

Causal inference with observed confounding

- response Y, e.g. health outcome
- treatment variable X, e.g., microbiome or individual microbe
- covariates W, e.g., age, diet



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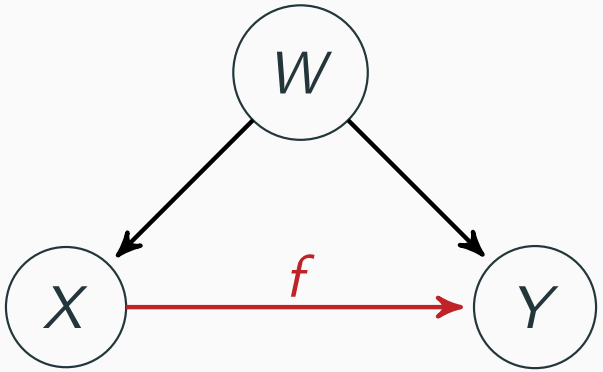

assumed causal structure

Goal: Learn the function f.

- Adjustment: Learn f by regressing Y on X and W jointly and marginalizing out W (outcome model)
- Inverse probability weighting: Learn $X|W$ and use it to reweight data so that edge $W \to X$ is removed (propensity model)

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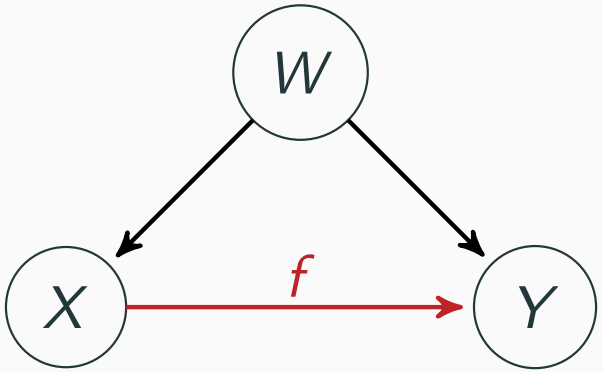

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Next talk: Combines both to achieve parametric rates!

Conclusions

- Microbial communities are important parts of biological systems.
- Research questions in microbiome sciences are causal in nature.
- Two challenges when learning causal effects:
  (1) Model specification: compositional (+ other structure)
  (2) Confounding: Requires causal methods

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- **Solutions?** Coming in next talk...

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- **Solutions?** Coming in next talk...

Thank you!

- Pearl, J. (2009). *Causality.* Cambridge university press.
- Imbens, G. W. and Rubin, D. B. (2015). *Causal inference in statistics, social, and biomedical sciences.* Cambridge University Press.
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