Information-based Causal Modeling (IBCM) and Applications

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April 10, 2019
Goals

• Provide Hill-like criteria for assessing consistency of data with the hypothesis of a *manipulative* causal exposure-response, using information rather than association
  – How much will changing exposure X *change* subsequent probability distribution of effect Y, given levels of other direct causes of Y (e.g., age, sex, smoking, income)?
    • *Not* association-based (Hill/IARC/regression), attributive (burden of disease), predictive (Granger), counterfactual/potential outcomes (propensity score, MSM), structural (Simon), mechanistic, or but-for (legal) causation
  – Needed for decisions and policy recommendations
  – Information in bits = reduction in conditional entropy of Y | X

• Minimize or eliminate untested assumptions
  – Use causal graphs to articulate and test causal hypotheses
    • Direct effects, total effects, CPTs, pathways of mechanisms
  – Test invariant causal predictions (ICP) vs. make counterfactual assumptions
Example of an information-based DAG: What exactly does it mean?

Direct vs. total effects of age and income on heart disease risk
Arrow = not conditionally independent of Ambiguity of counterfactual income levels

Many packages provide algorithms and principles to identify (causal) DAGs from data

- Conditional independence (constraint-based algorithms): Causes are informative about their effects
  - *dagitty, bnlearn packages; CompareCausalNetworks* package
- Likelihood principle (score-based algorithms): Valid causal models explain the data (i.e., make it not too unlikely).
  - Choose DAG model to maximize likelihood of data (*bnlearn* package)
- Composition principle: If $X \rightarrow Z \rightarrow Y$, then $\frac{dy}{dx} = (\frac{dz}{dx})*(\frac{dy}{dz})$
  - Path analysis, *lavaan* package
- Granger principle: Predictively useful information flows from causes to their effects over time (*granger.test, bnstruct*)
- Model error specification principle: Causes reveal simplicity
  - effect = f(cause) + error; *LiNGAM* packages
- Invariance of causal CPTs (*InvariantCausalPrediction* package): Completely described causal relationships are universal
Proposed criteria for consistency with manipulative causal exposure-response

1. Mutual information: Causes are informative about their direct effects.

2. Directed dependence: Information flows from causes to effects over time.

3. Internal consistency: Estimates of the same effect using different adjustment sets (e.g., common causes) are not significantly different.

Proposed criteria for manipulative causal exposure-response

5. **Coherence**: Path from exposure to response through causal biological network

6. **Causal mediation confirmation**: Changes in exposure explain quantitative changes in mediating variables and resulting response(s)
   – Chain of accountability (HEI): $X \rightarrow Z \rightarrow Y$

7. **Refutation**: Data reject alternative (non-causal) explanations
Directed acyclic graph (DAG) model

- What does it mean?
  - Arrows into *Smoking*?
  - Non-causal (BN): factors joint pdf
  - Causal: CPTs also represent invariant causal mechanisms
- When are arrows “causal”?
  - Directed information flow
  - Homogeneous CPTs (latent vars.)
- How to learn DAG from data?
  - Test conditional independence implications, CPT invariance and homogeneity, compositionality
- Use in risk assessment?
  - Partial dependence plots for direct and total causal effects of interest
- How trustworthy are the results?
  - Non-parametric model ensembles
  - Robustness to different algorithms and principles

Arrows represent dependence (mutual information) between variables

Not necessarily manipulative causation

Some causal links lack clear directions (*MaritalStatus ↔ Income*)
Estimating a response CPT

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• How to learn DAG from data?
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• Use in risk assessment?
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• How trustworthy are the results?
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Model = dependencies + causal CPTs
Partial dependence plot for natural direct causal effect in DAG model

Risk of heart disease

Partial Dependence on "Income"

"Income"
Updating Hill for manipulative causation: Mutual information

<table>
<thead>
<tr>
<th>Bradford-Hill considerations</th>
<th>Modern causal discovery and inference principles</th>
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| **Strength** of association: Stronger associations are more likely to be causal | • *Mutual information principle*: Causes are informative about their direct effects and help to predict their values.  
• *Conditional independence version*: Effects are not conditionally independent of their direct causes.  
• Direct causes contain at least as much information about their effects as do more remote indirect causes |

Hill’s strength and consistency considerations often fail (mislead) in practice (Ioannidis, 2016; Pearl and Mackenzie, 2018). Strong association usually indicates strong biases or confounding. Consistency of effects estimates (e.g., regression coefficients) in different populations may indicate common omitted confounders, p-hacking.

Mutual information (arrow in DAG) provides a useful non-parametric alternative

Mutual information may be positive even if correlation is zero \((y = x^2)\) or zero even if correlation is positive (spurious regression)
Direct causes are adjacent to their effects in valid causal graphs

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No evidence in DAG that PM2.5 is a direct cause of increased heart disease risk (adjacency)

Can bound maximum size of undetected effect (missing arrow)
## Updating Hill for manipulative causation: Consistency

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• *Conditional independence version*: Effects are not conditionally independent of their direct causes.  
• Direct causes contain at least as much information about their effects as do more remote indirect causes |
| **Consistency** of findings across populations, study designs, times, locations, investigators, etc. | • *Internal consistency*: Similar effects are estimated using different adjustment sets  
• *External consistency*: Causal laws, expressed as conditional probability tables (CPTs), are invariant, homogeneous, and transportable across study settings |

External consistency: *Invariant causal prediction* (ICP) property of CPTs across studies provides a testable foundation for making unambiguous counterfactual predictions.

*Homogeneity* of CPTs within and across studies provides a testable basis for managing latent variables. (If homogeneity fails, use finite mixture distributions, HMMs, etc.)
Invariant causal prediction (ICP)

• Testable property of response CPTs
  – Study ID does not help to predict response

• Uses of ICP:
  – Generalize from individual study results
    • Invariant causal CPTs can be “transported” across study settings, allowing predictions in novel settings
  – Synthesize studies with overlapping variables
  – Detect omitted/unobserved causes (latent variables) via homogeneity tests of response CPTs

• Provides sound basis for counterfactual causality
ICP addresses challenge of ambiguous (model-dependent) counterfactual predictions

Scientific Method

1. Ask a question
2. Do background research
3. Construct a hypothesis
4. Test your hypothesis by doing an experiment
5. Analyze your data and draw a conclusion
6. Report your results (Was your hypothesis correct?)

Results depend on modeling choices
### Temporality: Causes precede their effects

- **Directed dependence principle:** Information flows from causes to their effects over time.
- **Predictive causation principle:** Changes in causes help to predict changes in their effects.
- Techniques: Granger causality tests, transfer entropy, directed information graphs, dynamic Bayesian networks.
- LiNGAM principle for linear non-Gaussian models: Prediction error distributions vary simply and predictably with predicted values.

There are many ways to orient arrows from data (Granger, DBN, DIG, homoscedasticity, exogeneity, compositionality ...)

But directions of some arrows may not be uniquely determined by data, or may not be clearly defined/interpretable conceptually → Data constrain possible causal graphs.
Coherent causal explanation/biological plausibility: Identify paths (explanations) from exposure to response through causal biological network, consistent with data

QRA: exposure → [PBPK] → internal dose → [PD] → response

Causal mediation confirmation:

Compositionality: If $X \rightarrow Z \rightarrow Y$ is valid, then $\frac{dY}{dX} = (\frac{dY}{dZ})(\frac{dZ}{dX})$

Chapman-Kolmogorov: $P(y \mid x) = \sum_z P(z \mid x)P(y \mid z)$
Special cases in Hill considerations (No new criteria needed)

| Experiment: Reducing exposure reduces effect | • Exogenous changes in causes produce predictable changes in the probability distributions of their effects that can be calculated via CPTs. |
| Specificity of effects: A specific cause produces a specific effect | • Connectivity: One or more directed paths in a causal graph lead from causes to their effects.  
• Direct effects of a cause are its children in a causal graph |
| Biological gradient: Larger responses at higher exposures | • Variations in direct causes help to predict and explain variations in their (possibly joint) effects via a CPT |
## Final step: Refute alternative (non-causal) explanations

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<tr>
<th>Non-causal explanation</th>
<th>Methods for addressing non-causal associations</th>
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<tbody>
<tr>
<td><strong>Unobserved (latent) confounders</strong> (Pearl and Mackenzie, 2018)</td>
<td>These can be tested for and their effects modeled and controlled for using the <em>Tetrad, Invariant Causal Prediction</em>, and <em>BACKSHIFT</em> algorithms, among others.</td>
</tr>
<tr>
<td><strong>Spurious regression</strong> in time series or spatial observations with trends** (Yule, 1926)</td>
<td>Spurious regression arising from coincident trends can be detected and avoided by using conditional independence tests and predictive causation (e.g., Granger causality) instead of regression models.</td>
</tr>
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<td><strong>Collider bias; stratification or selection bias</strong> (Cole et al., 2010; Pearl and Mackenzie, 2018)</td>
<td>A study that stratifies or matches individuals on certain variables, such as membership in an occupation, or an analysis that conditions on certain variables by including them on the right-hand side of a regression model, can induce exposure-response associations if the variables conditioned, matched, or stratified on are common descendents of the exposure and response variables. The association does not indicate causality between exposure and response, but that they provide alternative explanations of an observed value. Such biases can be avoided by using <em>dagitty</em> to compute adjustment sets and conditioning only on variables in an adjustment set.</td>
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**Refute non-causal explanations for exposure-response association**

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<th>Other threats to internal validity (Campbell and Stanley, 1963)</th>
<th>Threats to internal validity (e.g., regression to the mean, coincident historical trends, sample selection or attrition biases, reporting biases, etc.) were enumerated by Campbell and Stanley (1963), who also discuss ways to refute them as plausible explanations, when possible, using observational data.</th>
</tr>
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<td><strong>Model specification errors</strong> (Lenis et al., 2018; Linden et al., 2017; Pirracchio et al., 2015)</td>
<td>Model specification errors arise when an analysis assumes a particular parametric modeling form that does not accurately describe the data-generating process. Assuming a linear regression model when there are nonlinear effects present is one example; omitting high-order interactions terms is another. Model specification errors can be avoided by using non-parametric model ensemble methods such as PDPs.</td>
</tr>
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<td><strong>P-hacking</strong>, i.e., adjusting modeling assumptions to produce an association (e.g., a statistically significantly positive regression coefficient). (Fraser et al., 2018)</td>
<td>Automated modeling using CAT or packages such as <em>randomForest</em> and <em>bnlearn</em> to automate modeling choices such as which predictors to select, how to code them (i.e., aggregate their values into ranges), and which high-order interactions to include can help to avoid p-hacking biases.</td>
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Refute non-causal explanations for exposure-response association

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<th><strong>Omitted errors in explanatory variables.</strong> (Rhomberg et al., 2011)</th>
<th>Using job exposure matrices, remote-sensing and satellite imagery for pollutant concentration estimation, or other error-prone techniques for estimating exposures, creates exposure estimates for individuals that can differ substantially from their true exposures. In simple regression models, omitting errors from the estimated values of explanatory variables tends to bias regression coefficients toward the null (i.e., 0), but the bias can be in either direction in multivariate models, and failing to carefully model errors in explanatory variables can create false-positive associations. These errors and biases can be avoided by modeling errors in explanatory variables.</th>
</tr>
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<td><strong>Omitted interdependencies among explanatory variables.</strong> (Pearl and Mackenzie, 2018; Textor et al., 2016)</td>
<td>Regression models that ignore dependencies among right-hand side variables can create non-causal exposure-response associations. This can be avoided by using <em>dagitty</em> to compute adjustment sets for the causal effect of exposure on response and then conditioning on variables in an adjustment set to estimate that effect.</td>
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</table>
Proposed criteria can be made operational via statistical tests

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<th>Criterion</th>
<th>Test</th>
<th>Methods</th>
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<tr>
<td>Mutual information</td>
<td>Reject null hypothesis that $Y$ is conditionally independent of $X$</td>
<td>Reject null hypothesis if $X$ and $Y$ are linked in DAG models learned from data by causal discovery algorithms (e.g., those in the bnlearn package). Other tests for independence (e.g., chi-squared tests) can also be used.</td>
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<td>Directed dependence</td>
<td>For longitudinal data: Reject null hypothesis that future values of $Y$ are conditionally independent of past values of $X$, even after conditioning on past values of $Y$ and other variables.</td>
<td>Reject null hypothesis if $X$ and $Y$ are linked in DBNs or DIGs learned from data (e.g., via the bnstruct package). Granger tests can also be used for time series data.</td>
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<tr>
<td></td>
<td>For cross sectional data: Reject null hypothesis that direction of dependence is undetermined by data.</td>
<td>Reject null hypothesis if constraints determining the direction of an arrow can be identified from data (e.g., using LiNGAM, BACKSHIFT, or Simon-Iwasaki causal ordering)</td>
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## Operational criteria

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<th>Operational criteria</th>
<th>Internal consistency</th>
<th>External consistency</th>
<th>Causal mediation confirmation</th>
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<td>Do not reject null hypothesis that</td>
<td>Do not reject null hypothesis that effects estimated from different adjustment sets are the same</td>
<td>Do not reject null hypothesis that response CPTs estimated from different studies or data sets are the same</td>
<td>Do not reject the null hypothesis that variations in $Y$ caused by variations in $X$ are explained by resulting variations in mediating variables (e.g., as described by the Chapman-Kolmogorov identities implied by an explanation in the form of a probabilistic causal graph model)</td>
</tr>
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<td>effects estimated from different</td>
<td>Reject null hypothesis if confidence bands for effects estimated from different adjustment sets do not overlap.</td>
<td>Reject null hypothesis if study ID is a parent of response in DAG models learned from data.</td>
<td>Reject null hypothesis if variations in mediating variables do not explain variations in $Y$ for different values of $X$ (e.g., if a chi-squared test rejects the conditional independence and Chapman-Kolmogorov implications of the explanation).</td>
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<td>adjustment sets are the same</td>
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<th>Causal coherence &amp; biological plausibility</th>
<th>Reject the null hypothesis that identified biologically plausible pathway(s) directed from $X$ to $Y$ cannot explain the observed dependence of $Y$ on $X$.</th>
<th>Reject the null hypothesis if one or more biologically plausible coherent causal explanations (pathways in a causal biological network) are identified that can explain the dependence of $Y$ on $X$.</th>
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<td>Refutation of non-causal explanations</td>
<td>Reject the null hypothesis that the observed statistical dependence of $Y$ on $X$ has a non-causal explanation</td>
<td>Reject the null hypothesis if threats to validity are refuted (Campbell and Stanley, 1963).</td>
</tr>
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Summary: Information-based causal perspectives

• Focus specifically on manipulative causation
• Quantify causal exposure-response dependence
  – Multiple paths/explanations for association
    • Qualitative determination of causality is not well-defined
  – Partial dependence plots for effects of interest
• Connect exposure to response probability via paths in causal graphs and causal biological networks
• Test implications of hypothesized manipulative causal exposure-response explanations using data
  – Mutual information, directed information flow, internal and external consistency (ICP), coherent explanation, CMC
• Refute non-causal explanations using data
• Result: Assess consistency of evidence with manipulative causal interpretation of exposure-response dependence using information in data sets
Thanks!