THE UNIVERSITY of TENNESSEE KNOXVILLE

Lecture 27: Causality

Sergei V. Kalinin

This and that

- The final is on the GitHub
- Feel free to choose equivalent problem, or use the methods we have learned for your own research problems

Materials Science cannot change overnight….

… but what is happening now comes very close

The inflection point (for theory): 2006

Predicting crystal structure by merging data mining with quantum mechanics

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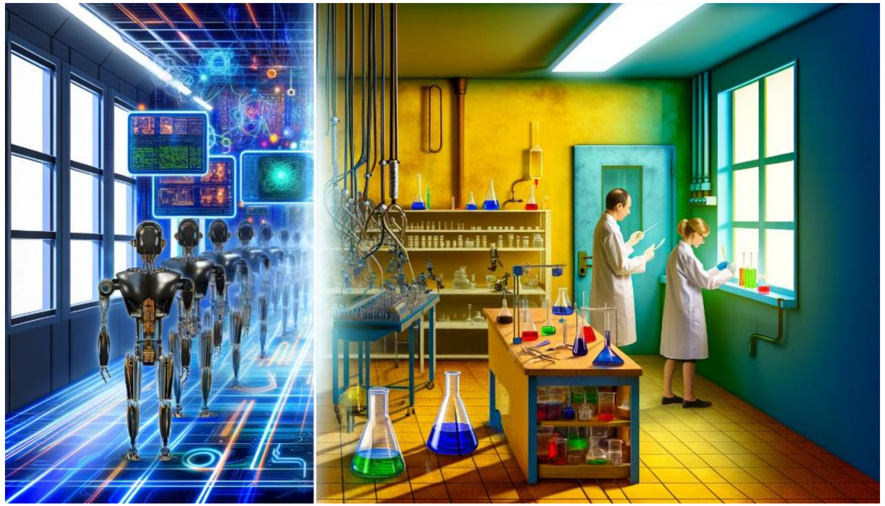
Publication by Gerd Ceder paper that is broadly seen as the inflection point launching Materials Genome Initiative in US and equivalent programs worldwide

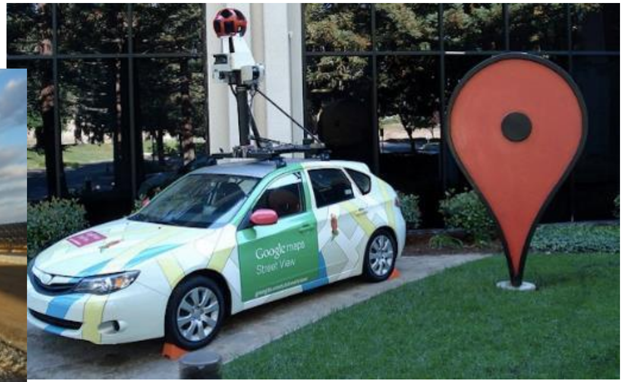
Launch of AWS (Amazon Web Services) made cloud computing a reality – allowing businesses and scientists alike have access to computational resources without the need to build and maintain clusters

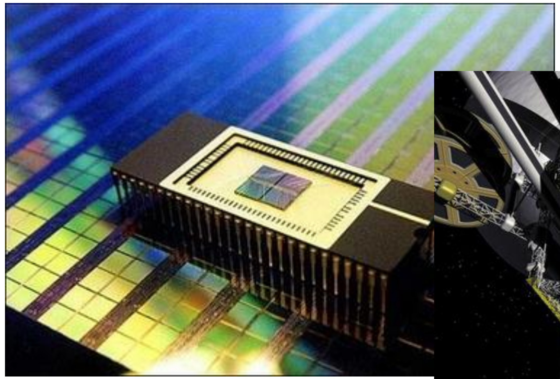
aws

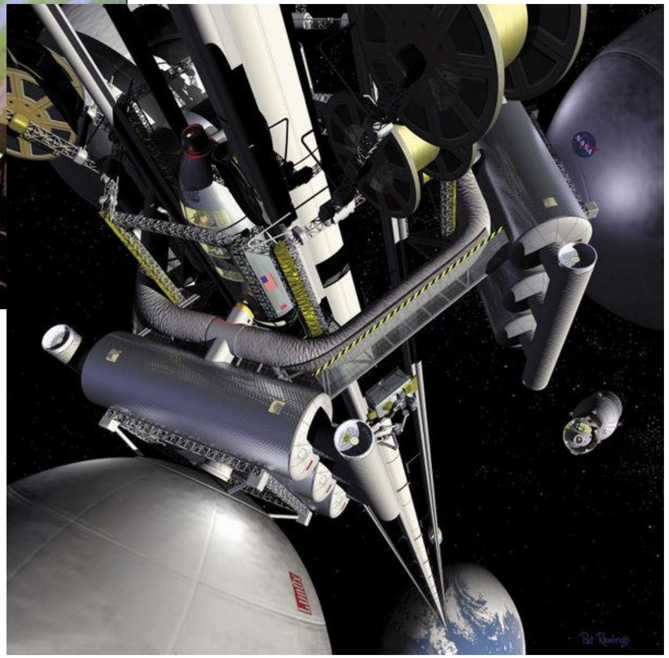


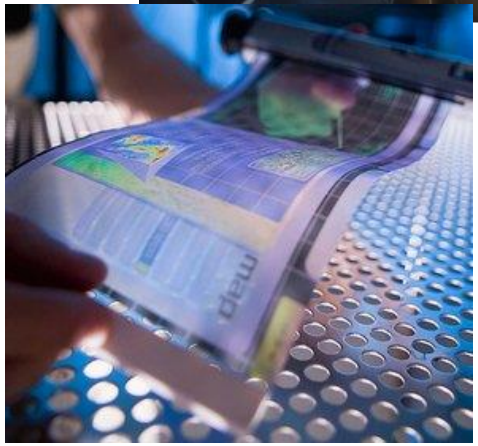
Machine learning in theory:
- Relative homogeneous workflows
- Known causal structure/lack of exogeneous factors
- Requires know-how, but relatively low entry barrier
- Easy to scale (given the funding)

The World is a Material Opportunity









Predicting crystal structure by merging data mining with quantum mechanics

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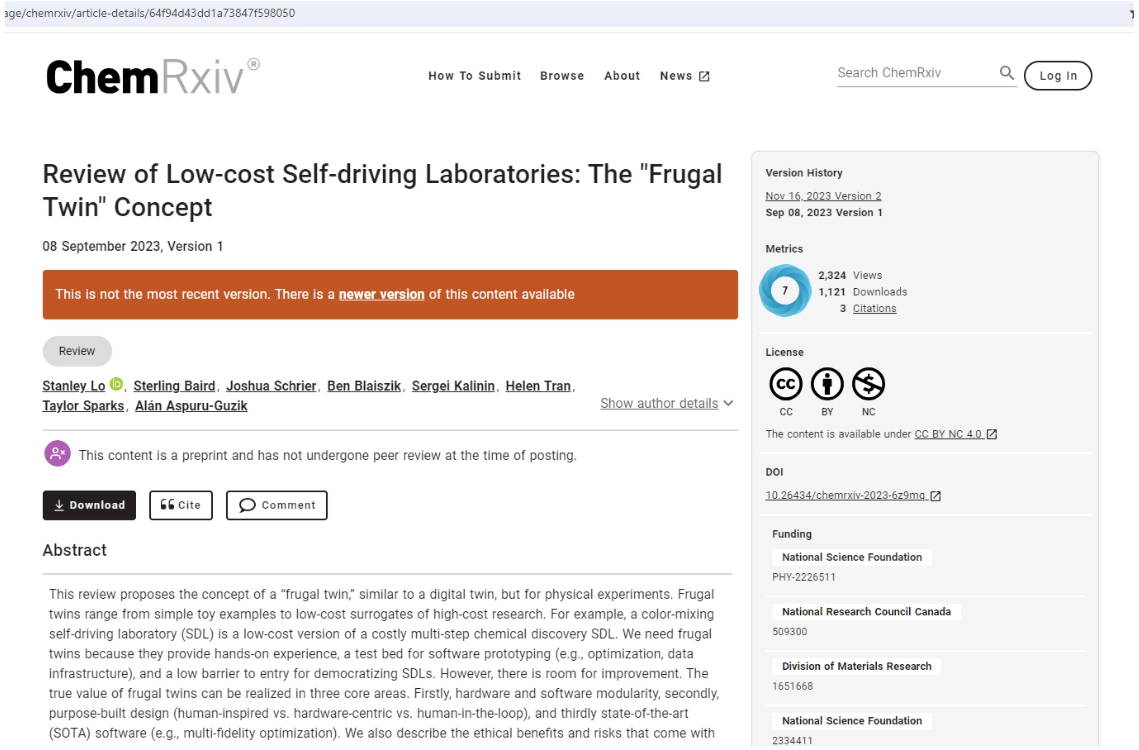
- **"Improve":** Renewable energy, structural materials
- **"Discover":** RT superconductivity, high mechanical stress materials
- **"Engineer":** Quantum computing, single-atom catalysts, biomolecules

Functionality, manufacturability, cost

The theory can only get you so far!

The inflection point (for experiment): ~2020

- **Before 2010:** A number of (usually) confidential efforts in industry
- **2010 - 2015:** Early adopters and visionaries (Cronin, Maryama, etc)
- **2015 – 2020:** The time of engineers
- **2020 – now:** Automated experimentation becomes broadly available with very low cost entry barries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Review of Low-cost Self-driving Laboratories: The "Frugal Twin" Concept

08 September 2023, Version 1

This is not the most recent version. There is a newer version of this content available

Review

Stanley Lo, Sterling Baird, Joshua Schrier, Ben Blaiszik, Sergei Kalinin, Helen Tran, Taylor Sparks, Alán Aspuru-Guzik Show author details

This content is a preprint and has not undergone peer review at the time of posting.

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Abstract

This review proposes the concept of a "frugal twin," similar to a digital twin, but for physical experiments. Frugal twins range from simple toy examples to low-cost surrogates of high-cost research. For example, a color-mixing self-driving laboratory (SDL) is a low-cost version of a costly multi-step chemical discovery SDL. We need frugal twins because they provide hands-on experience, a test bed for software prototyping (e.g., optimization, data infrastructure), and a low barrier to entry for democratizing SDLs. However, there is room for improvement. The true value of frugal twins can be realized in three core areas. Firstly, hardware and software modularity, secondly, purpose-built design (human-inspired vs. hardware-centric vs. human-in-the-loop), and thirdly state-of-the-art (SOTA) software (e.g., multi-fidelity optimization). We also describe the ethical benefits and risks that come with

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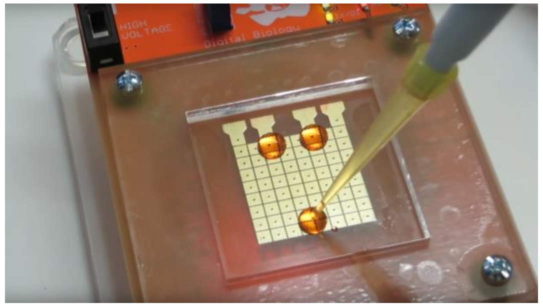
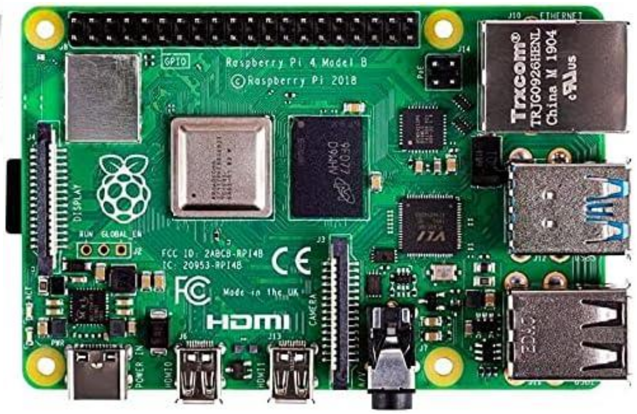




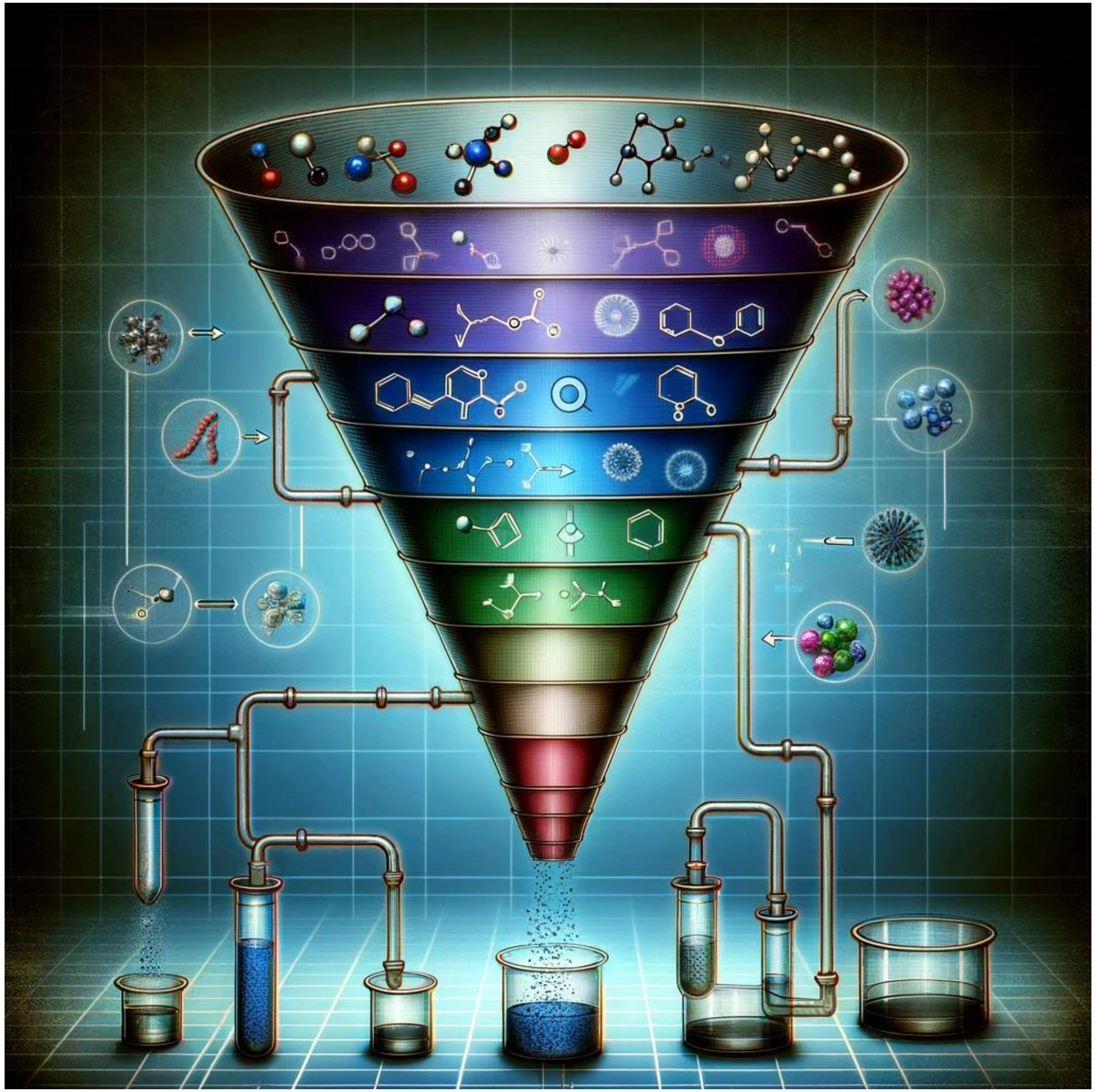
In 2012-2014, large number of theory-trained workforce (DFT, MD, FEA) has moved into AI/ML fields

Many are returning to their original domain areas, building start-ups and corporate research centers. Many of these gain valuation very rapidly (In Silico, Schroedinger, etc)

The value created by AI/ML is orders of magnitude below investment (autonomous driving, radiology, cashier less stores)

Real-world industries and manufacturing are looking for work force with the combination of **domain** and **ML/AI** expertise

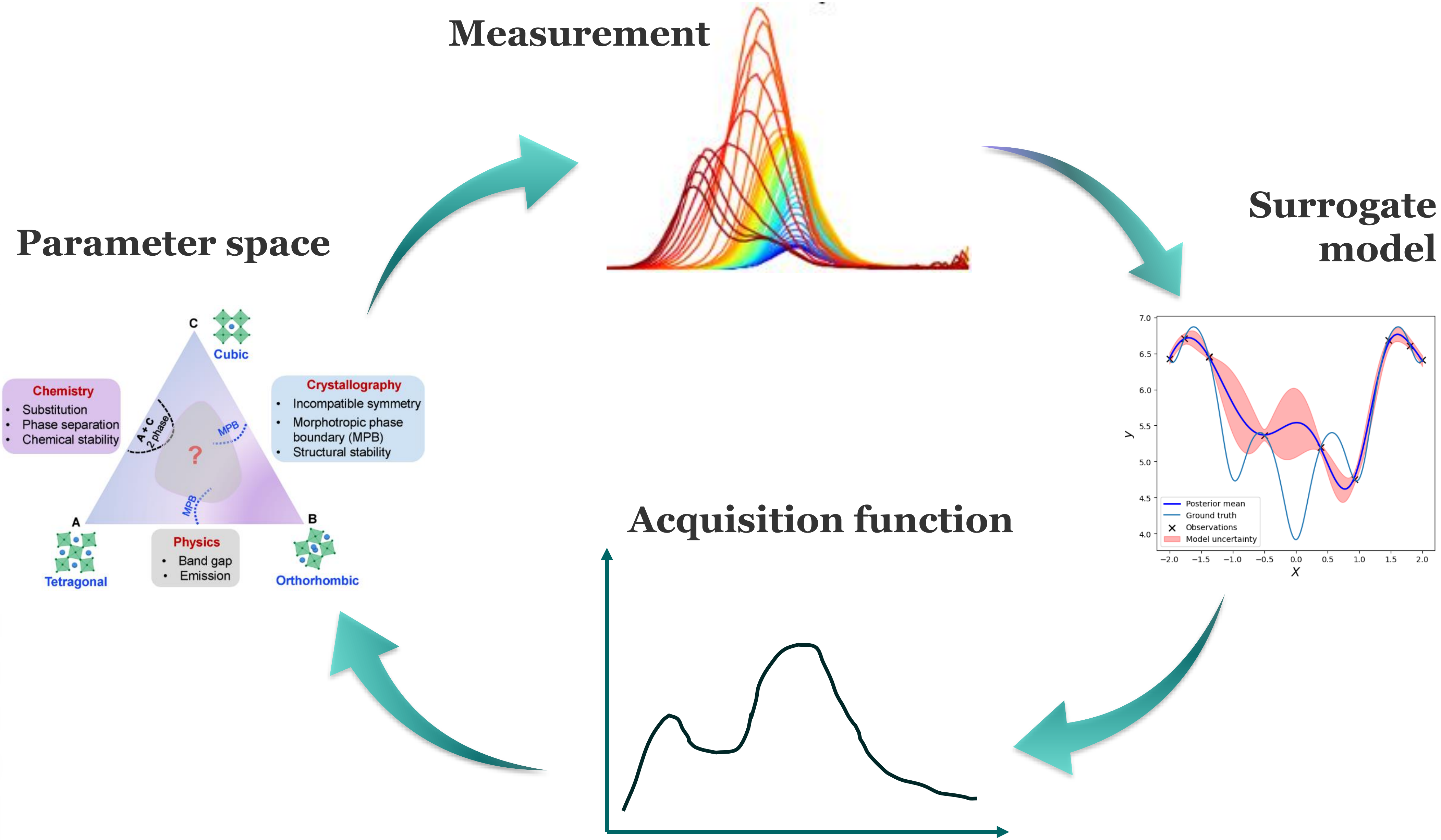
From ideal to real world



Big data approach

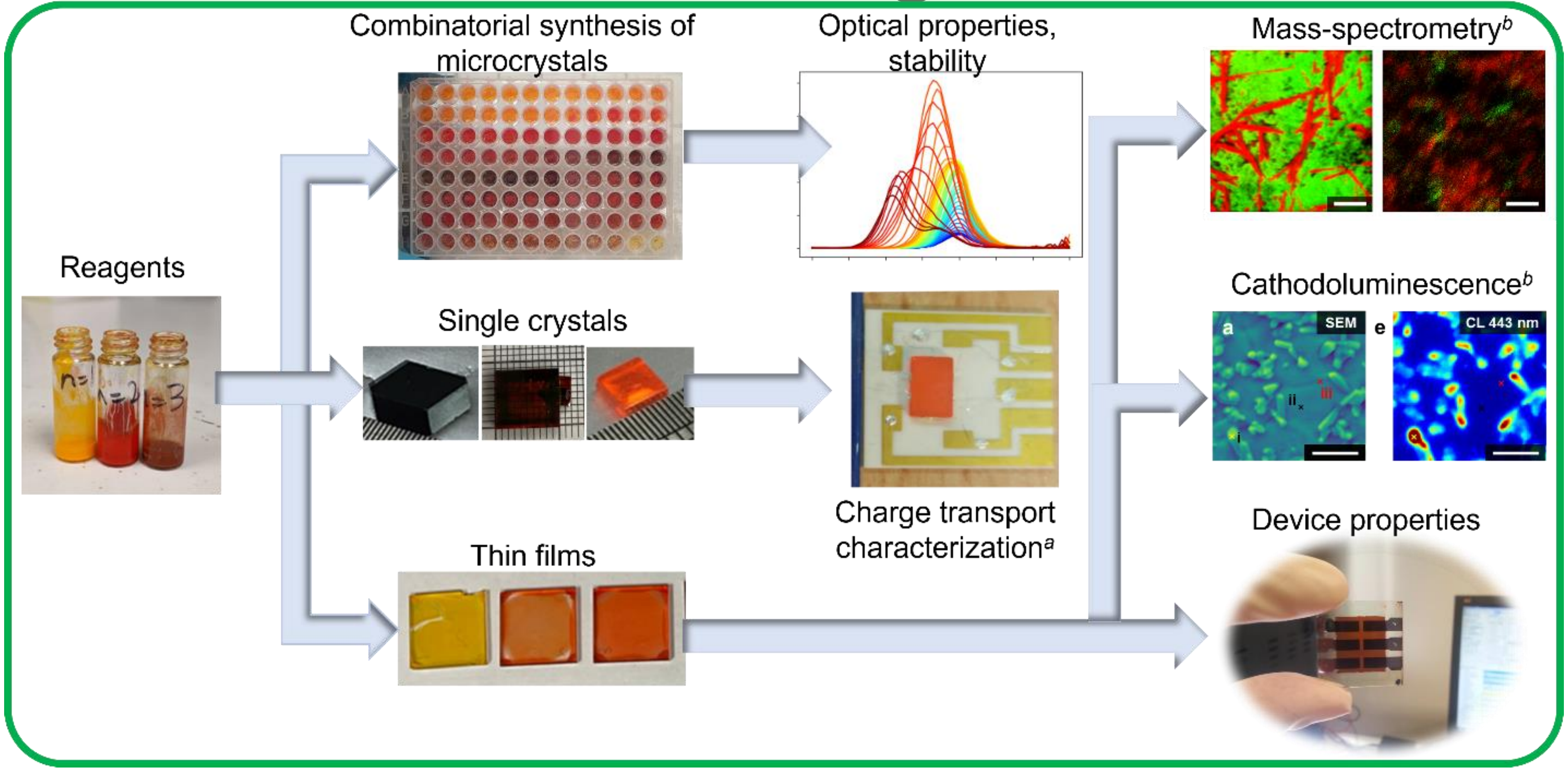
- Define (very) large search spaces
- Multiple down selection via more high-fidelity and expensive filter
- From *in silico* to *in materio*
- Feedback?

Classical Bayesian Optimization



Implicitly, we postulate that cost and gain are constant along the iterative cycle

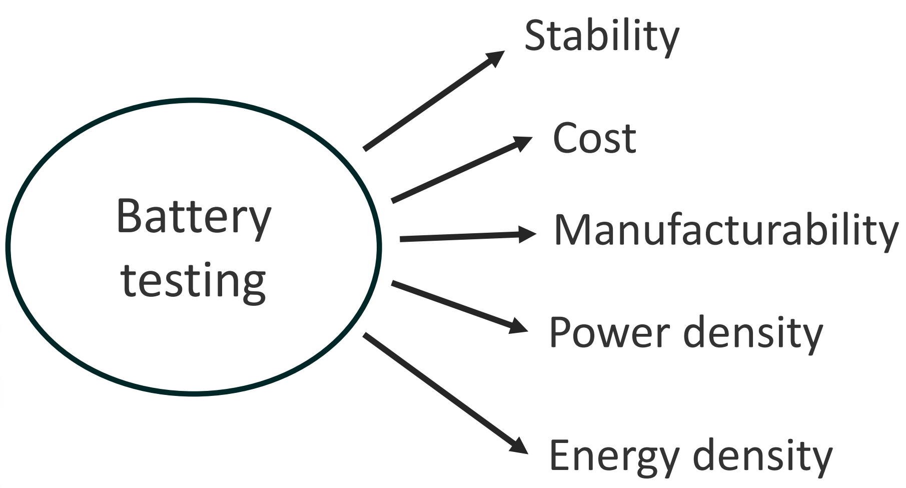
Real world decision making

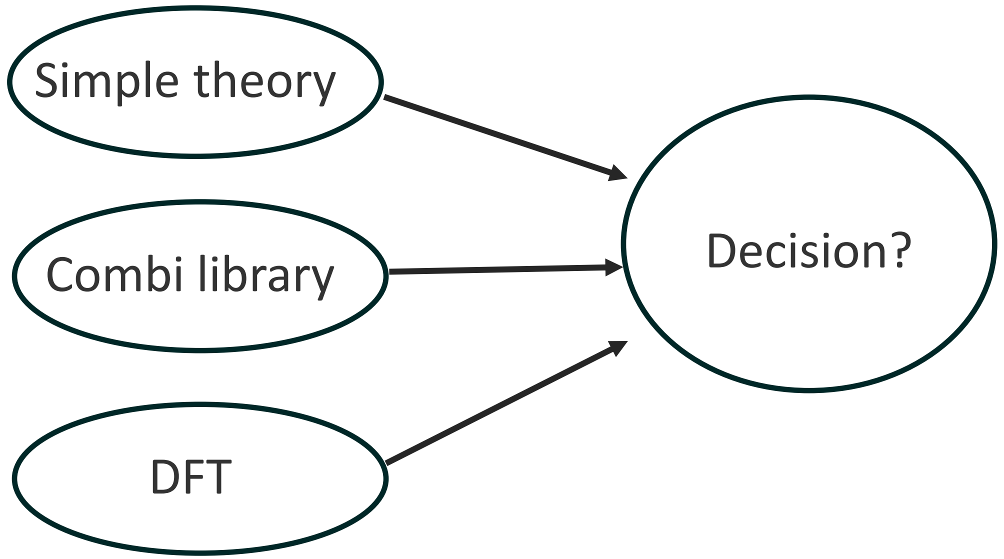


Workflow: ideation, orchestration, implementation

- Cost
- Value, reward, objective
- Policies

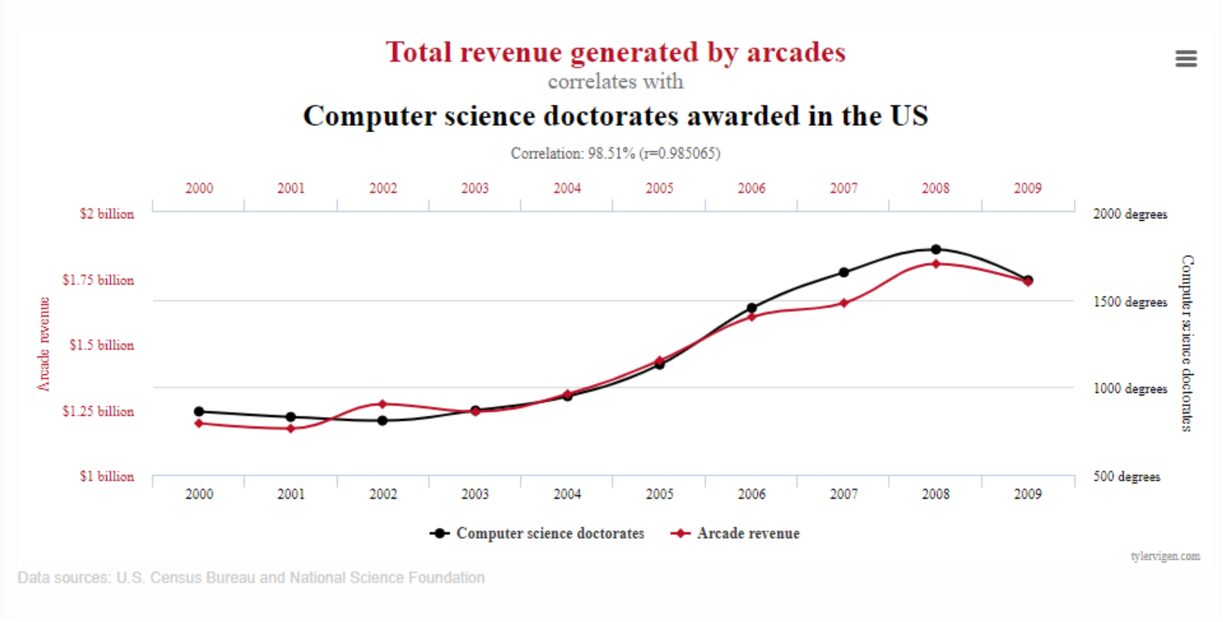
Decision making in complex environments

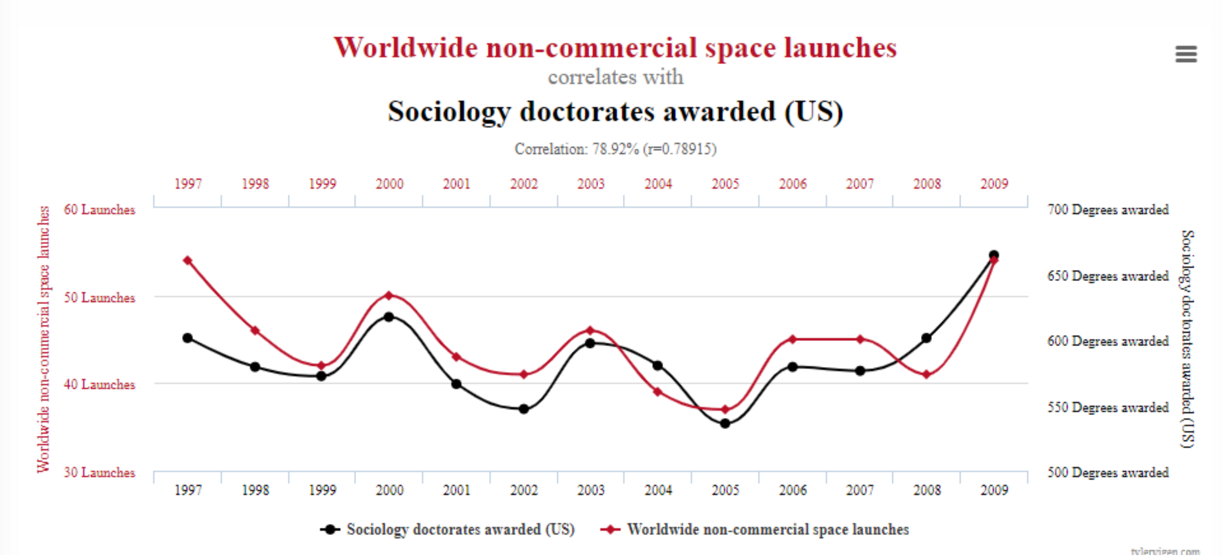




1. We need to balance multiple functionalities
2. Integrate multiple sources of data and make decisions considering costs, latencies, and beliefs

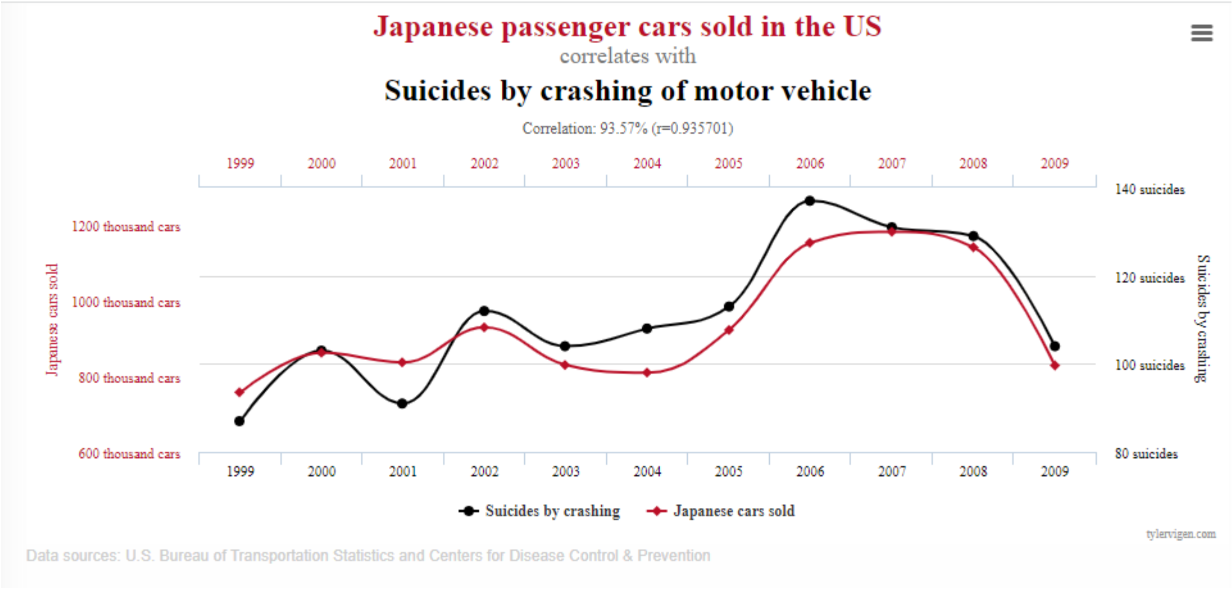
Correlation and causation

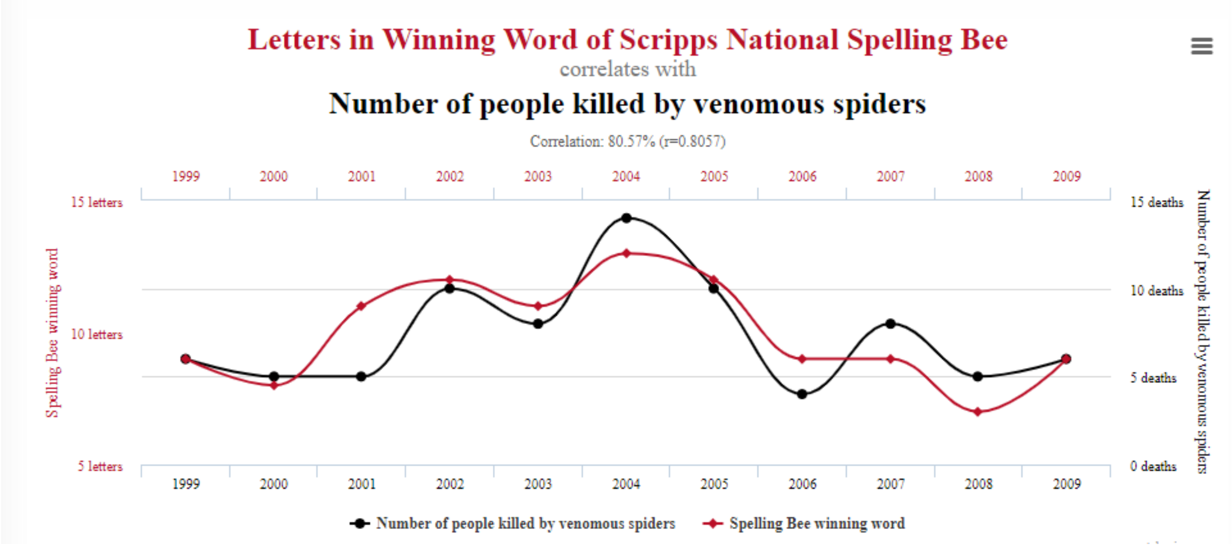




https://www.tylervigen.com/spurious-correlations

Correlation and causation





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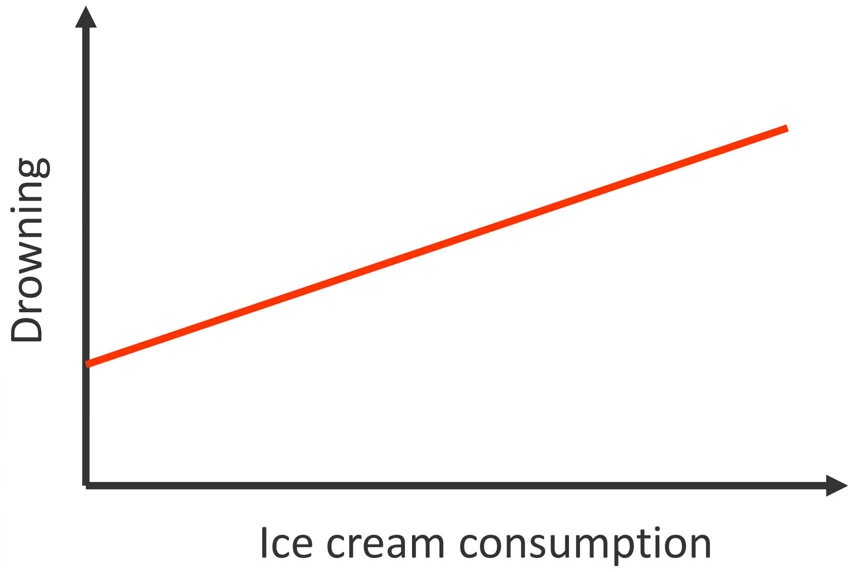
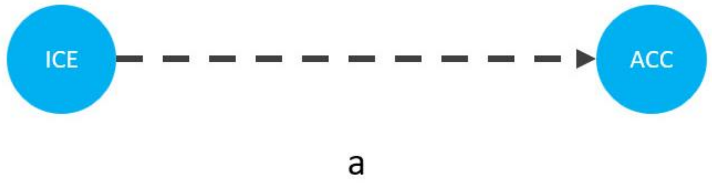
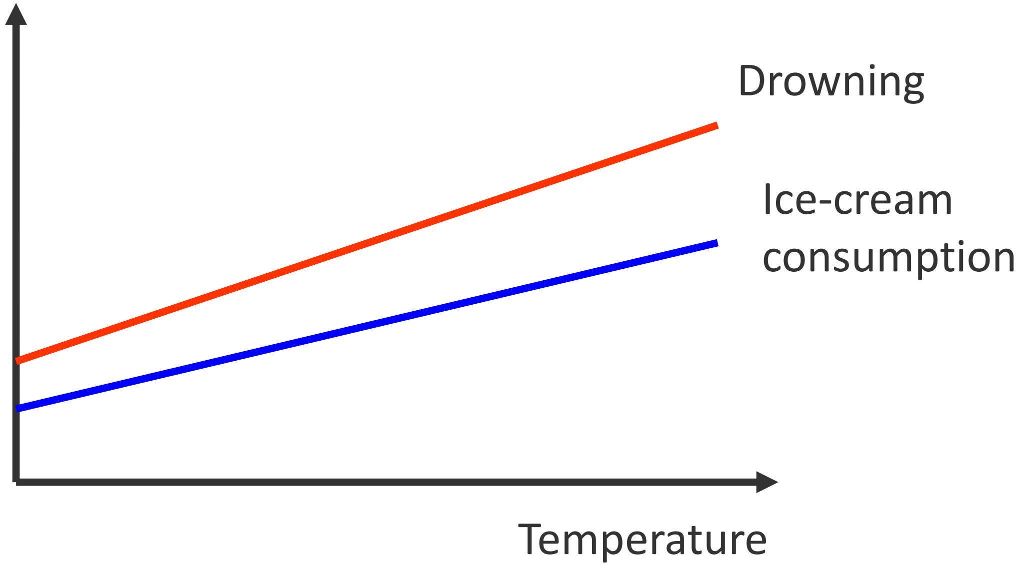
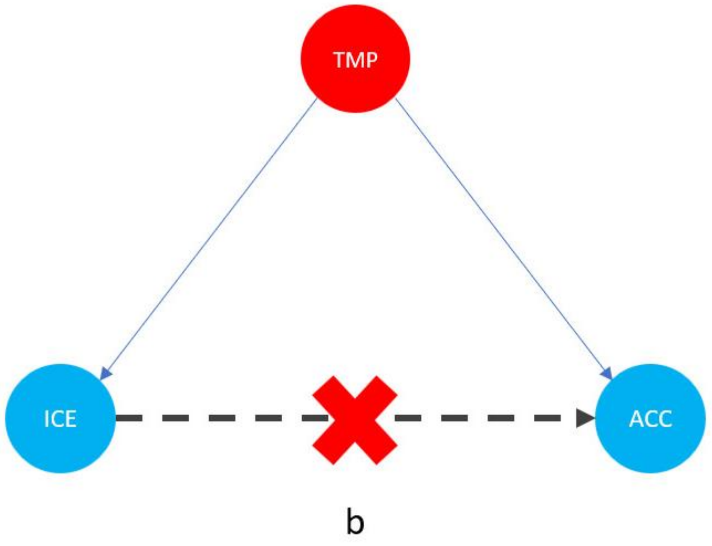
Ice-cream and drowning









From A. Molak, Causal Inference and Discovery in Python

Treatment effects

$$\tau_i = Y_i(1) - Y_i(0)$$

- τ_i is the treatment effect for person i
- $Y_i(1)$ is the outcome for person *i* when they received the treatment T
- $Y_i(0)$ is the outcome for the same person *i* given they did not receive the treatment

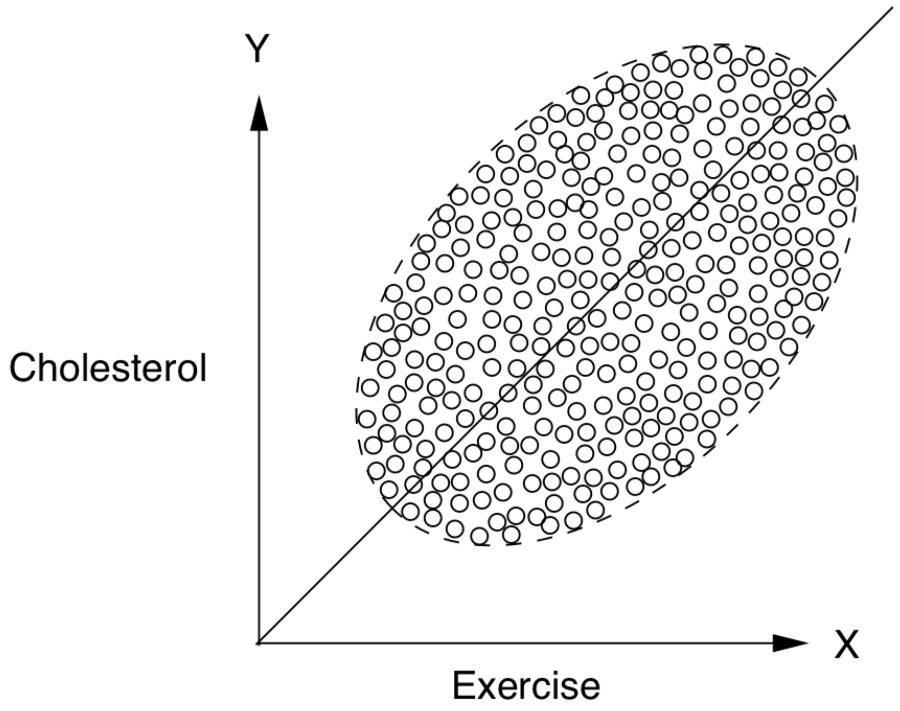
Very fundamental approach in:

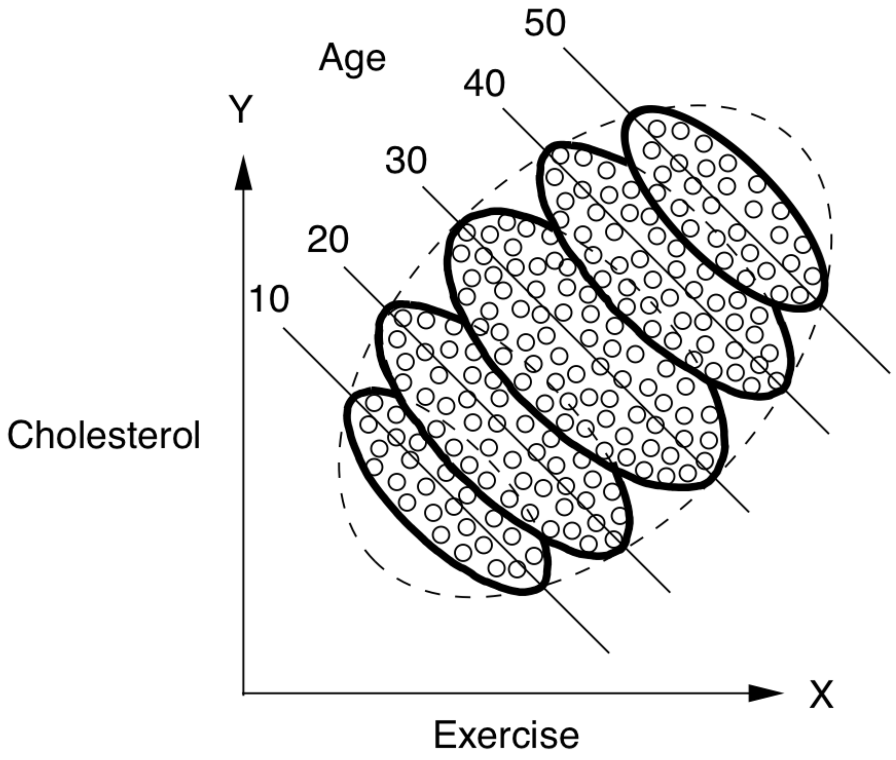
- Marketing
- Medicine
- And so on

But… How can the same person be treated and not treated?

From A. Molak, Causal Inference and Discovery in Python

Simpson paradox





Exercise is helpful in every age group but harmful for a typical person.

Is exercise helpful or not?

From J. Pearl presentation, Why - 19

Simpson paradox

Drug	A		B	
Blood clot	Yes	No	Yes	No
Total	27	95	23	99
Percentage	22%	78%	19%	81%

Drug	A		B	
Blood clot	Yes	No	Yes	No
Female	24	56	17	25
Male	3	39	6	74
Total	27	95	23	99
Percentage	22%	78%	18%	82%
Percentage (F)	30%	70%	40%	60%
Percentage (M)	7%	93%	7.5%	92.5%

- Simpson's paradox appears when data partitioning (which we can achieve by controlling for the additional variable(s) in the regression setting) significantly changes the outcome of the analysis.
- In the real world, there are usually many ways to partition your data.
- You might ask: okay, so how do I know which partitioning is the *correct* one?

From A. Molak, Causal Inference and Discovery in Python

Berkeley discrimination lawsuit

In the early 1970s, the University of California, Berkeley was sued for gender discrimination over admission to graduate school. Of the 8,442 male applicants for the fall of 1973, 44 percent were admitted, but only 35 percent of the 4,351 female applicants were accepted

Table 1: Data From Six Largest Departments of 1973 Berkeley Discrimination Case

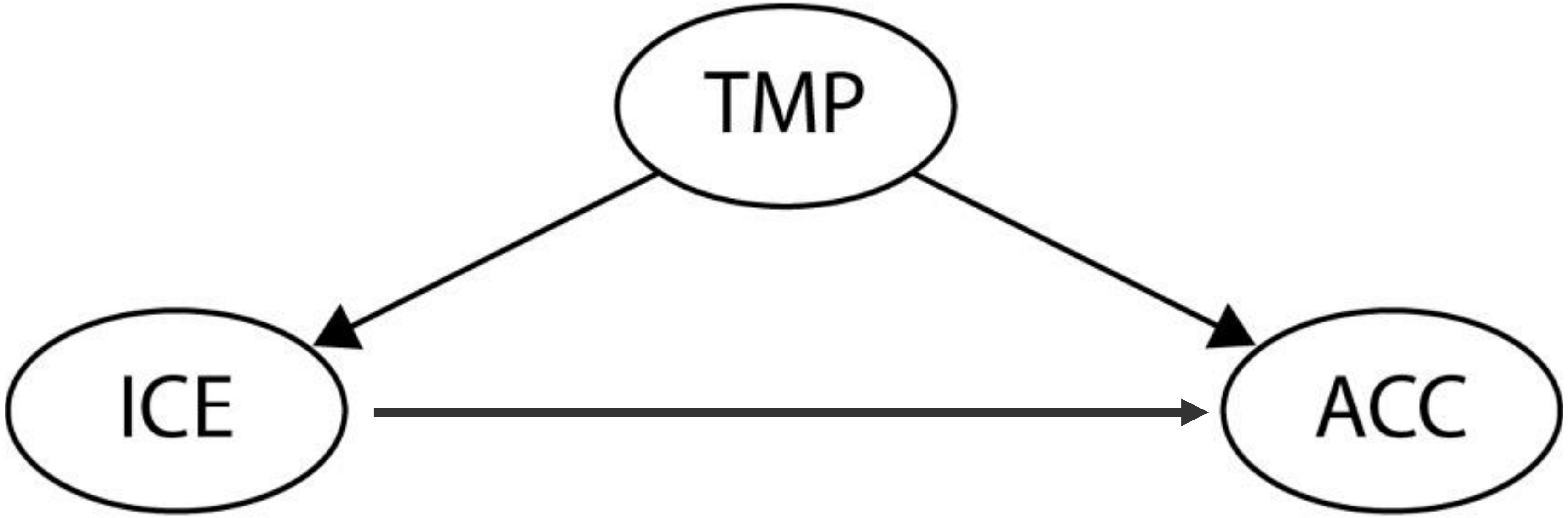
Department	Men		Women	
	Applicants	Admitted	Applicants	Admitted
A	825	62%	108	82%
B	560	63%	25	68%
C	325	37%	593	34%
D	417	33%	375	35%
E	191	28%	393	24%
F	272	6%	341	7%

Source: Bickel, Hammel, and O'Connell (1975); table accessed via Wikipedia at https://en.wikipedia.org/wiki/Simpson%27s_paradox

In the Berkeley case, the "paradox" occurred because women disproportionately applied to departments with low acceptance rates, as shown in the table above, while men disproportionately applied to departments with high acceptance rates.

https://www.brookings.edu/articles/when-average-isnt-good-enough-simpsons-paradox-in-education-and-earnings/

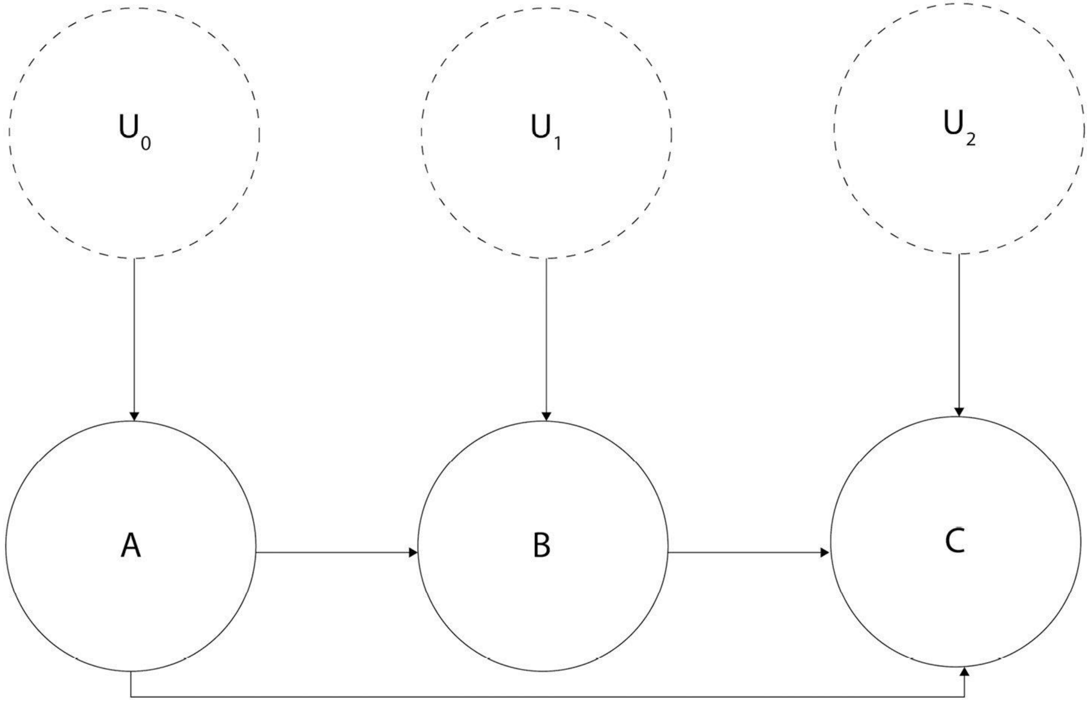
How can we even approach such problems?



- Observations give us correlations between temperature, ice cream consumption, and accident rate
- What we need to know is the causal links between these characteristics. Does change in ice cream consumption affect temperature or accident rate?
- But we cannot make an experiment!

From A. Molak, Causal Inference and Discovery in Python

Causal graphs



$$A := f_A(U_0)$$

$$B := f_B(A, U_1)$$

$$C := f_C(A, B, U_2)$$

- Here, := is an **assignment operator**, also known as a **walrus operator**. We use it to emphasize that the relationship that we're describing is *directional* (or asymmetric), as opposed to the regular equal sign that suggests a symmetric relation.

- And f_A, f_B, f_C represent arbitrary functions (they can be as simple as a summation or as complex as you want).

From A. Molak, Causal Inference and Discovery in Python

Do-operator

Conditioning: $P(X = x | Y = y)$

Intervention: $P(Y = 1 | do(X = 0))$

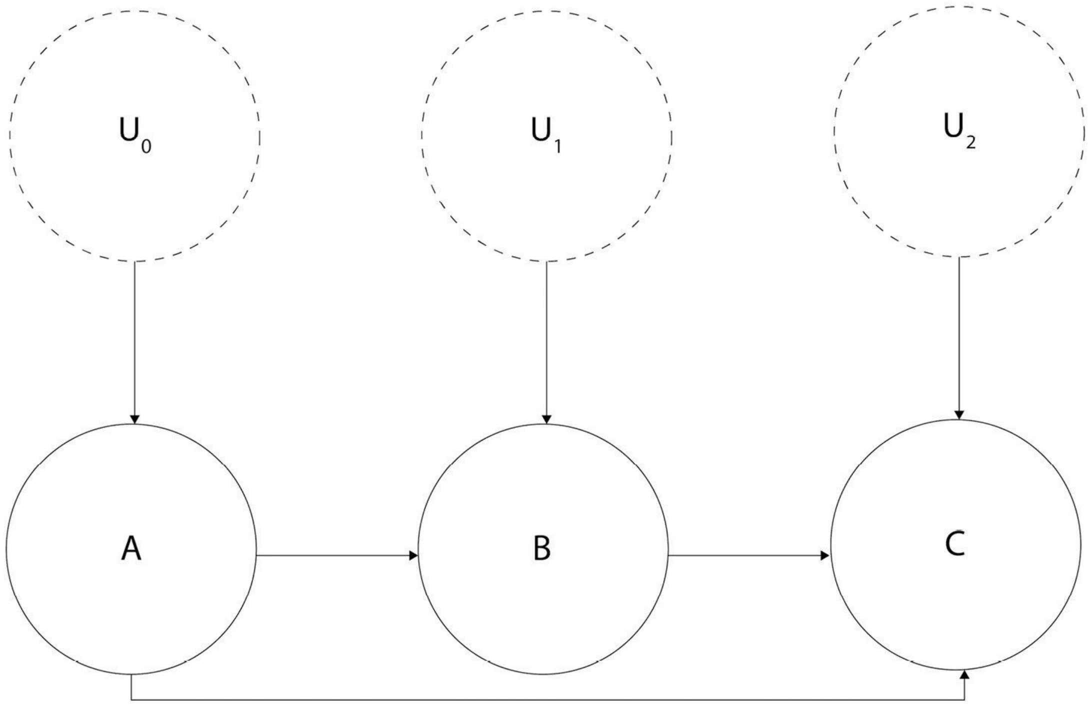
- Conditioning only modifies our *view* of the data, while intervening affects the distribution by *actively* setting one (or more) variable(s) to a *fixed value* (or a distribution).

- This is very important – intervention *changes* the system, but conditioning *does not*.

- You might ask, what does it mean that *intervention changes the system*? Great question!

From A. Molak, Causal Inference and Discovery in Python

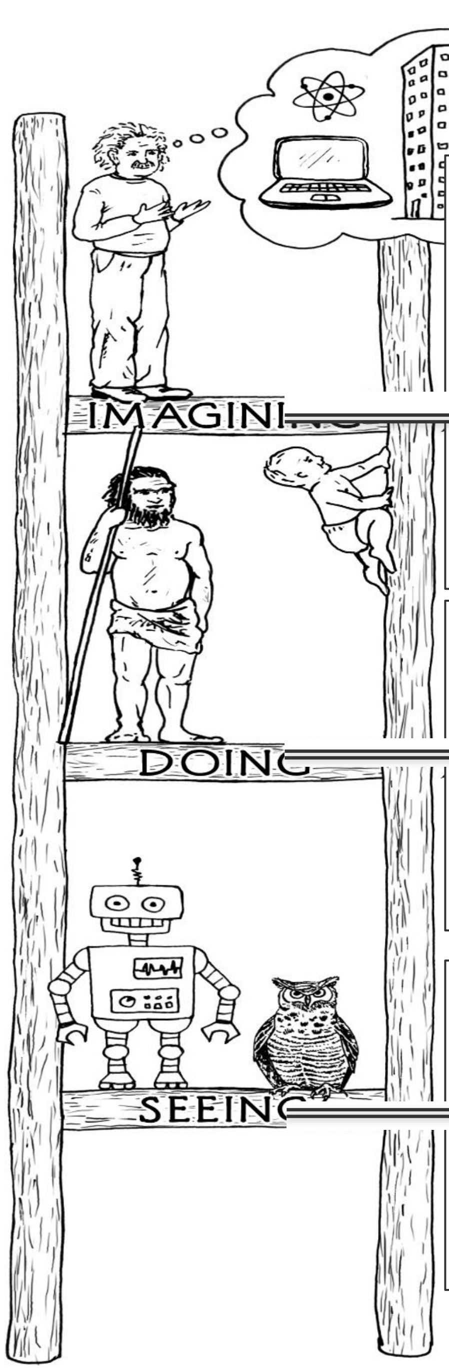
Properties of do - operator



- The change in B will influence the values of its descendants
- B will become independent of its ancestors

From A. Molak, Causal Inference and Discovery in Python

Ladder of causation



3. COUNTERFACTUALS

ACTIVITY: Imagining, Retrospection, Understanding

QUESTIONS: *What if I had done . . . ? Why?*
(Was it X that caused Y? What if X had not occurred? What if I had acted differently?)

EXAMPLES: Was it the aspirin that stopped my headache?
Would Kennedy be alive if Oswald had not killed him?
What if I had not smoked the last 2 years?

2. INTERVENTION

ACTIVITY: Doing, Intervening

QUESTIONS: *What if I do . . . ? How?*
(What would Y be if I do X?)

EXAMPLES: If I take aspirin, will my headache be cured?
What if we ban cigarettes?

1. ASSOCIATION

ACTIVITY: Seeing, Observing

QUESTIONS: *What if I see . . . ?*
(How would seeing X change my belief in Y?)

EXAMPLES: What does a symptom tell me about a disease?
What does a survey tell us about the election results?

How can we learn causality

- **Causal discovery** and **causal structure learning** are umbrella terms for various kinds of methods used to uncover causal structure from observational or interventional data.

- **Expert knowledge** is a term covering various types of knowledge that can help define or disambiguate causal relations between two or more variables. Depending on the context, expert knowledge might refer to knowledge from randomized controlled trials, laws of physics, a broad scope of experiences in a given area, and more.

- **Combining causal discovery and expert knowledge:** Some causal discovery algorithms allow us to easily incorporate expert knowledge as a priority. This means that we can either *freeze* certain edges in the graph or *suggest* the existence or direction of these edges.

From A. Molak, Causal Inference and Discovery in Python

Independence and conditional independence

- Notation for independence involves the symbol, $\perp\!\!\!\perp$ (usually called *double up tack*), whose form visually encodes the notion of orthogonality.

- We can express the fact that X and Y are independent in the following way:

$$P(X, Y) = P(X)P(Y) \qquad X \perp\!\!\!\perp Y$$

- The concept of independence plays a vital role in statistics and causality.

- Its generalization – **conditional independence** – is even more important. We say that X and Y are conditionally independent given Z, when X does not give us any new information about Y assuming that we observed Z.
-

$$P(X, Y|Z) = P(X|Z)P(Y|Z) \qquad X \perp\!\!\!\perp Y|Z$$

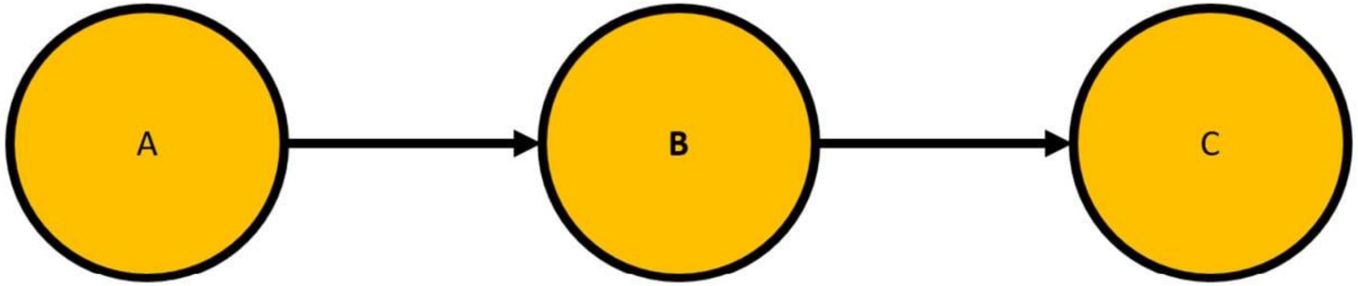
From A. Molak, Causal Inference and Discovery in Python

Conditional and unconditional independence

- We say that two nodes are *unconditionally* (or marginally) *independent* in the graph when there's *no open path* that connects them *directly* or *indirectly*.
- We say that two nodes, X and Y, are *conditionally independent* given (a set of) node(s) Z when Z blocks *all open paths* that connect X and Y.

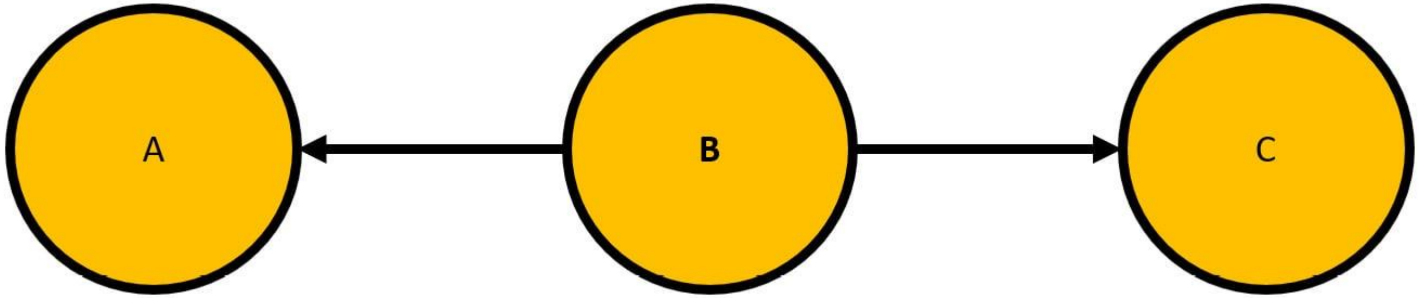
From A. Molak, Causal Inference and Discovery in Python

Chains and forks



$$A \perp\!\!\!\perp_G C \mid B$$

Chain 🔗

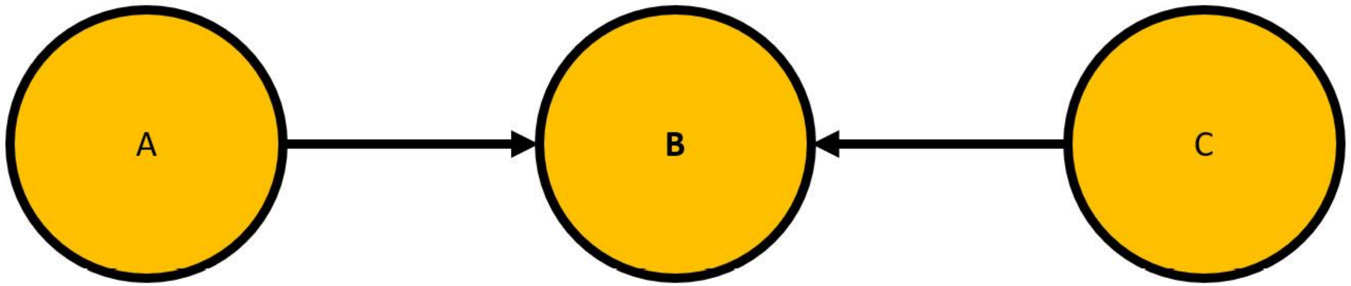


$$A \perp\!\!\!\perp_G C \mid B$$

Fork 🍴

From A. Molak, Causal Inference and Discovery in Python

Colliders



Collider 💥

$$A \perp\!\!\!\perp C$$

$$A \not\!\perp\!\!\!\perp C \mid B$$

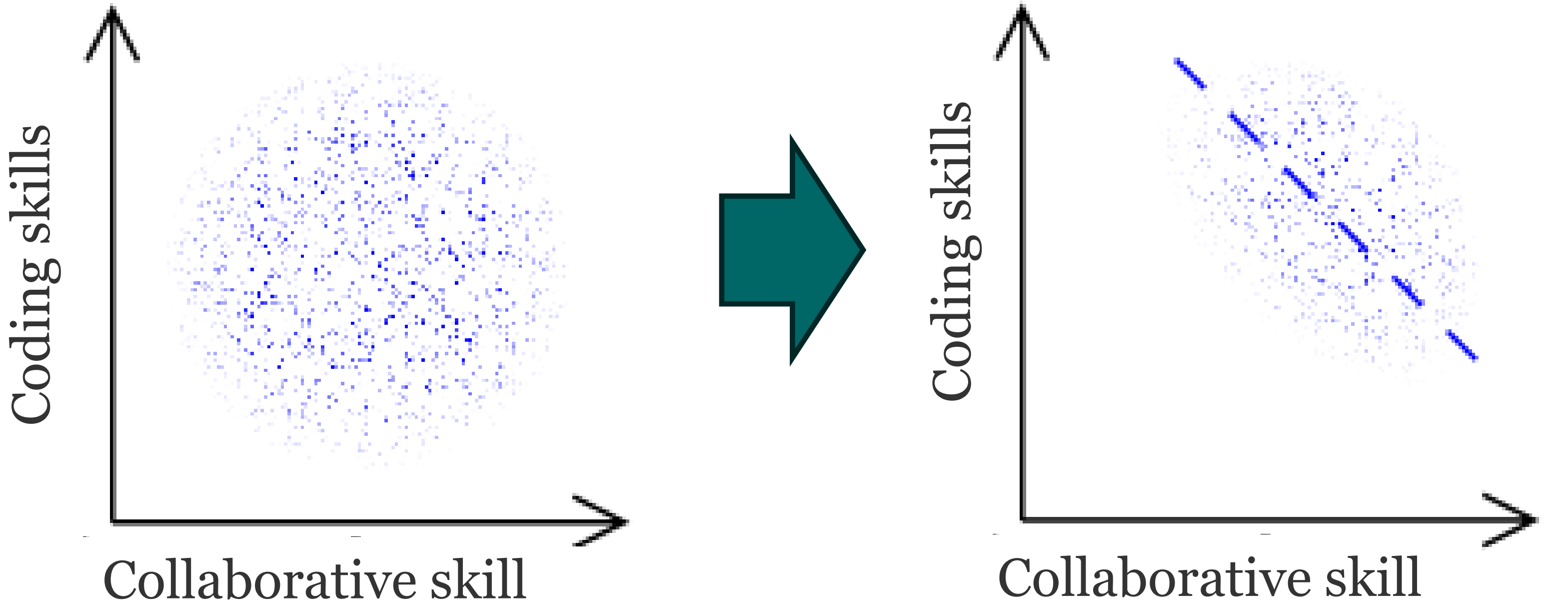
Imagine that both A and C randomly generate integers between *1* and *3*. Let's also say that B is a sum of A and C. Now, let's take a look at values of A and C when the value of B is 4. The following are the combinations of A and C that lead to B = 4:

- A = 1, C = 3
- A = 2, C = 2
- A = 3, C = 1

Although A and C are unconditionally independent (there's no correlation between them as they randomly and independently generate integers), they become correlated when we observe C !

From A. Molak, Causal Inference and Discovery in Python

Colliders and Berkson paradox



Many companies might hire people based on their skills and their personality traits. Imagine that company *X* quantifies a person's coding skills on a scale from one to five. They do the same for the candidate's ability to cooperate and hire everyone who gets a total score of at least seven. Assuming that coding skills and ability to cooperate are independent in the population (which doesn't have to be true in reality), you'll observe that in company *X*, people who are better coders are less likely to cooperate on average, and those who are more likely to cooperate have fewer coding skills. You could conclude that being non-cooperative is related to being a better coder, yet this conclusion would be incorrect in the general population.

https://en.wikipedia.org/wiki/Berkson%27s_paradox From A. Molak, Causal Inference and Discovery in Python

Estimator, estimate, and estimand

1. **Estimand**: The quantity or parameter that is intended to be estimated. It represents the true value of the parameter in the population. Suppose you're interested in the average height of adult men in a particular country. The actual average height of all adult men in that country is the estimand.

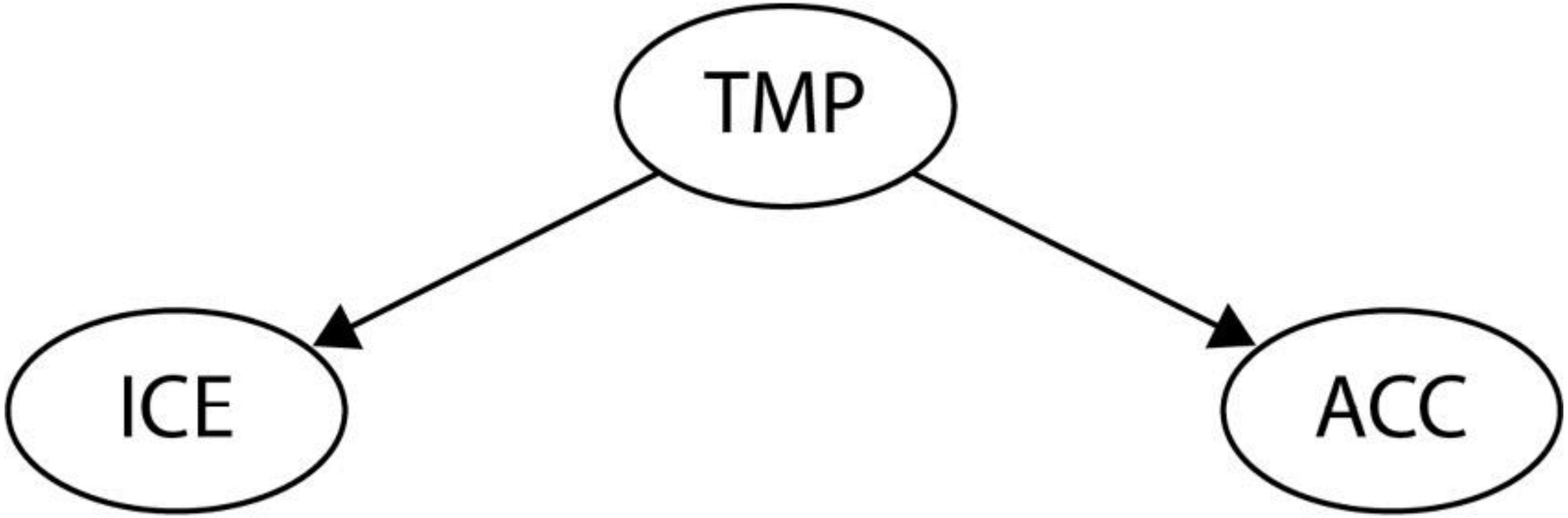
2. **Estimate**: The approximation or value obtained from the data to estimate the estimand. This is derived from a sample and used to infer information about the population. For example, from a sample of 1,000 adult men in the same country, you calculate an average height of 5 feet 9 inches. This value (5 feet 9 inches) is your estimate of the average height (the estimand).

3. **Estimator**: A rule, formula, or algorithm by which you derive the estimate from the data. It is a function of the sample data and is used to produce an estimate of the estimand. Here, the formula for calculating the mean (average) from a set of numbers is an estimator. When you apply this formula to your sample data, you obtain the estimate.

Estimator, estimate, and estimand

- **Estimand**: What you want to know (the actual, often unknown, value).
- **Estimate**: What you got from your sample data.
- **Estimator**: How you got it (the method or formula used).

Adjustment

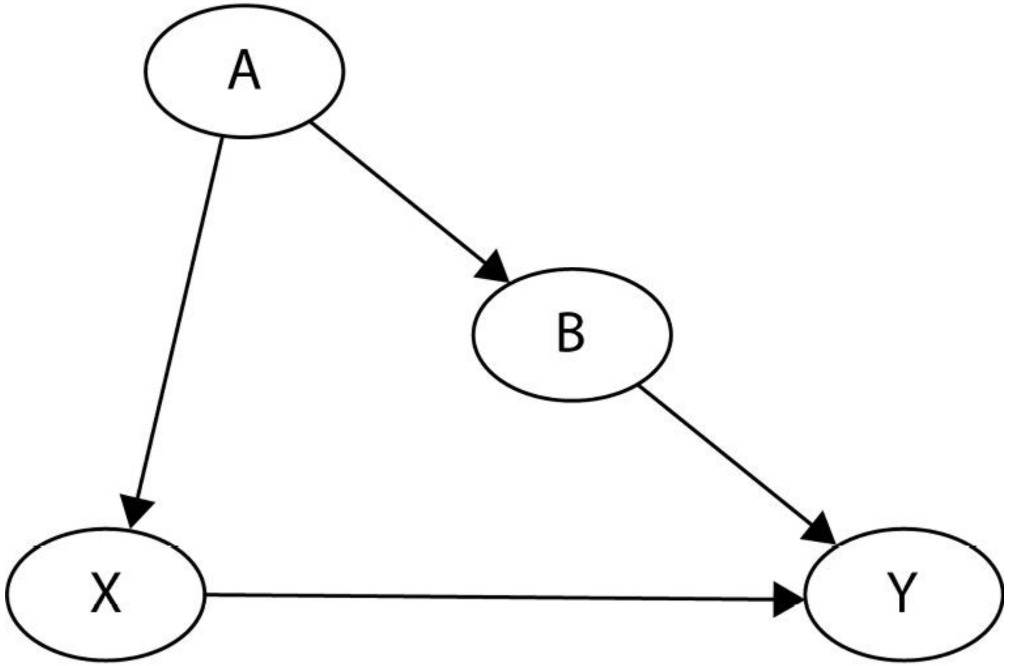


$$ACC \sim ICE + TMP$$

$$P(ACC|do(ICE)) = \sum_{tmp} P(ACC|ICE, TMP)P(TMP)$$

From A. Molak, Causal Inference and Discovery in Python

Back door criterion

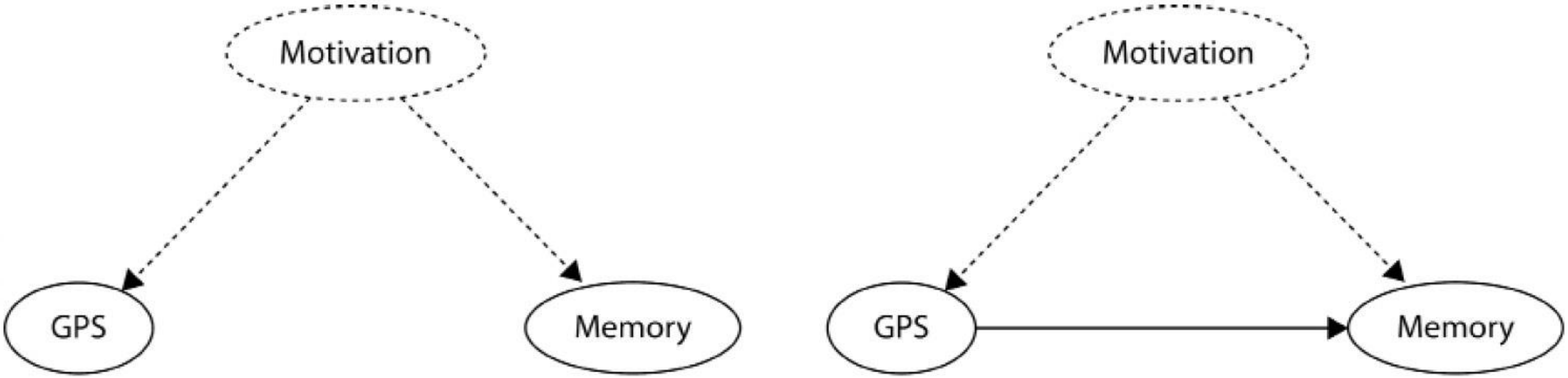


$$P(Y = y|do(X = x)) = \sum_a P(Y = y|X = x, A = a)P(A = a)$$
$$= \sum_b P(Y = y|X = x, B = b)P(B = b)$$

We can estimate effect even if one of A, B is unobserved!

From A. Molak, Causal Inference and Discovery in Python

Front door criterion and mediation



Observation: People that use GPS more have less good memory

Hypothesis 1: Usage of GPS precludes memory development

Hypothesis 2: There is a common (unobserved) factor that affects both GPS usage and memory

From A. Molak, Causal Inference and Discovery in Python

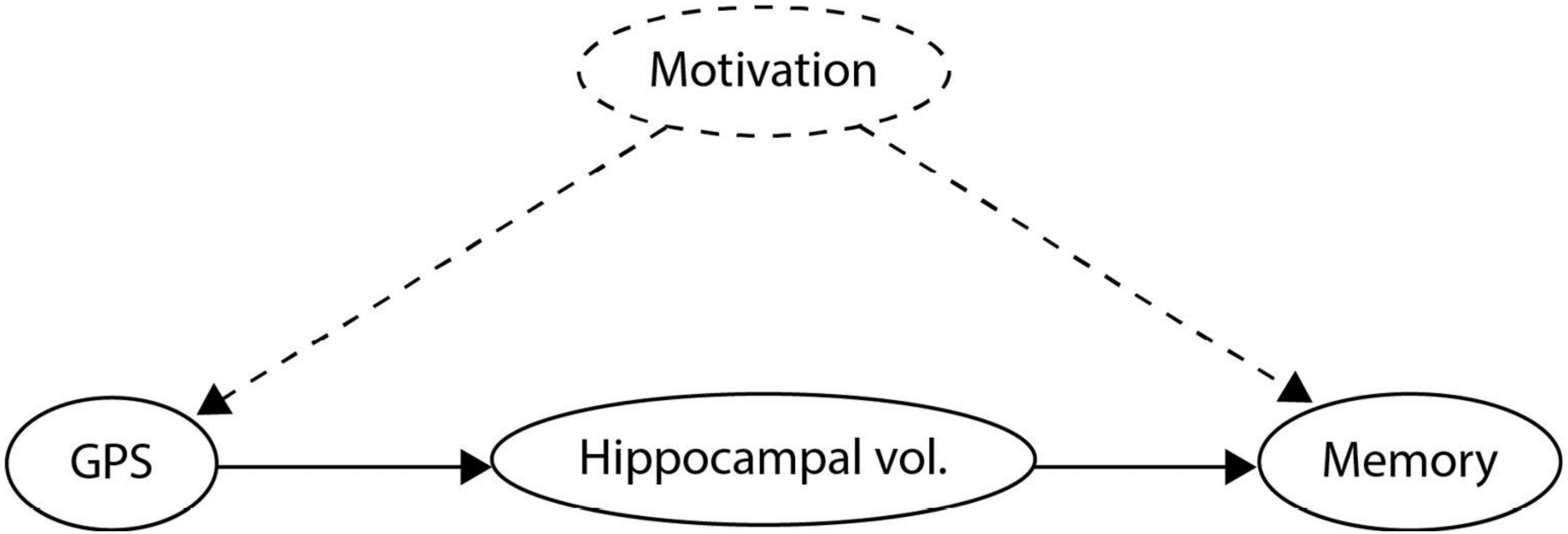
Mediation

- The influence of one variable X on another Y is *mediated* by a third variable, Z (or a set of variables, **Z**), when at least one path from X to Y goes through Z.

- Z *fully mediates* the relationship between X and Y when the only path from X to Y goes through Z.

- If there are paths from X to Y that do not pass through Z, the mediation is *partial*.

Front door criterion

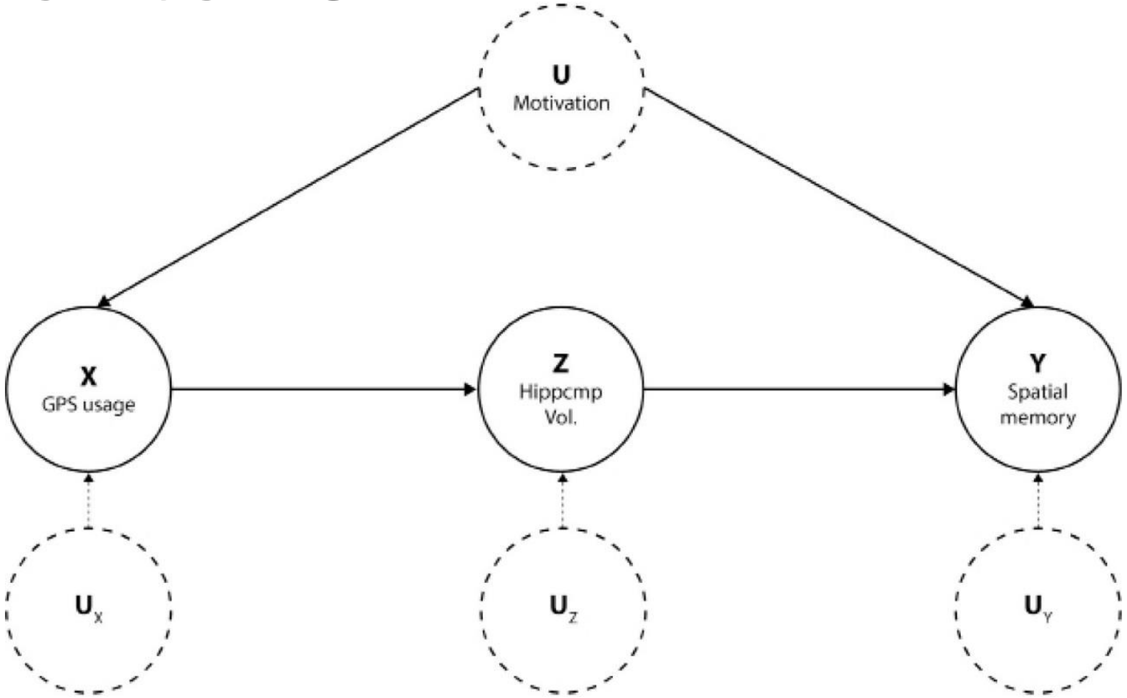


- We assume that hippocampal volume fully mediates the effects of GPS usage on a decline in spatial memory.
- The second important assumption we make is that motivation can only affect *hippocampal volume indirectly through GPS usage*.

If motivation would be able to influence hippocampal volume *directly*, front-door would be of no help. Luckily enough, the assumption that motivation cannot directly change the volume of the hippocampus seems reasonable (though perhaps you could argue against it!).

From A. Molak, Causal Inference and Discovery in Python

Front door criterion



$$P(Y = y|do(X = x)) = \sum_z P(Z = z|X = x) \sum_{x'} P(Y = y|X = x', Z = z)P(X = x')$$

- Fit a model, $Z \sim X$
- Fit a model, $Y \sim Z + X$
- Multiply the coefficients from model 1 and model 2

From A. Molak, Causal Inference and Discovery in Python

Do-calculus

- *Rule 1*: When an observation can be ignored:

$$P(Y = y|do(X = x), Z = z, W = w) = P(Y = y|do(X = x), W = w) \ \text{if} \left(Y \perp\!\!\!\perp Z|X, W\right)_{G_{\overline{X}}}$$

- *Rule 2*: When intervention can be treated as an observation:

$$P(Y = y|do(X = x), do(Z = z), W = w) = P(Y = y|do(X = x), Z = z, W = w) \ \text{if} \left(Y \perp\!\!\!\perp Z|X, W\right)_{G_{\overline{X}\underline{Z}}}$$

- *Rule 3*: When intervention can be ignored:

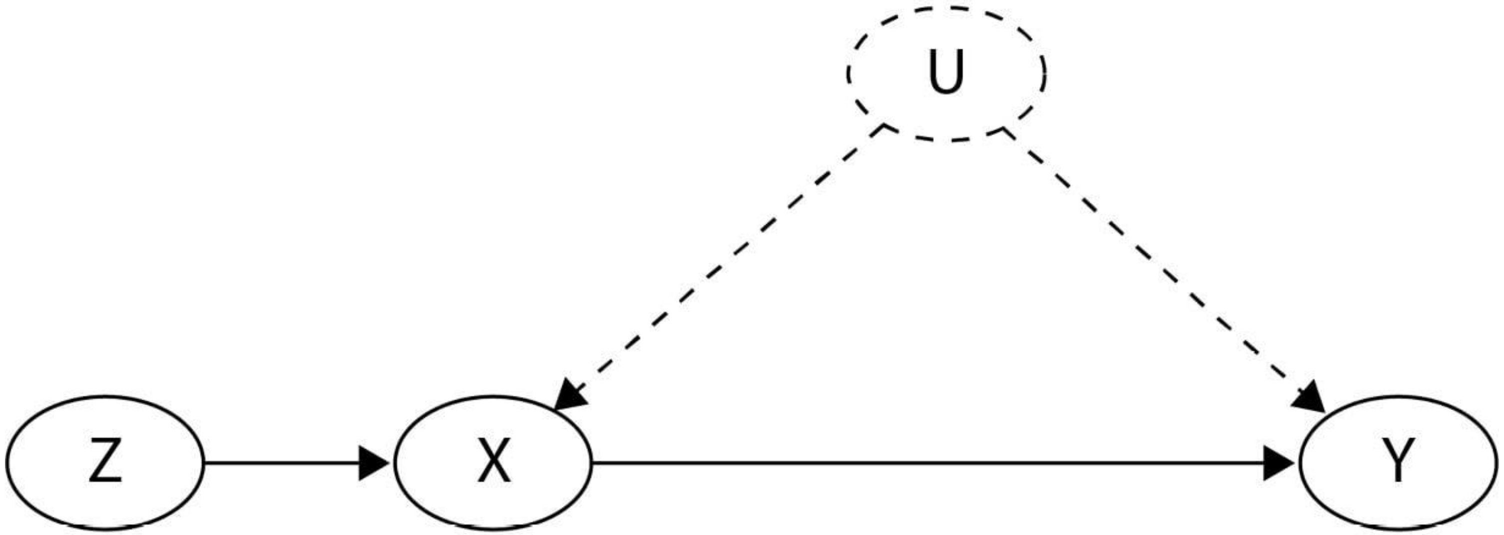
$$P(Y = y|do(X = x), do(Z = z), W = w) = P(Y = y|do(X = x), W = w) \ \text{if} \left(Y \perp\!\!\!\perp Z|X, W\right)_{G_{\overline{X,Z(W)}}}$$

Given a DAG G, we can say that $G_{\overline{X}}$ is a modification of G, where we removed all the *incoming* edges to the node X. We will call $G_{\underline{X}}$ a modification of G, where we removed all the *outgoing* edges from the node X. For example, will denote a DAG, $G_{\overline{X}\underline{Z}}$, where we removed all the incoming edges to the node X and all the outgoing edges from the node Z.

- **Good news:** do-calculus exists and is complete
- **Not so good news:** it can be quite incomprehensible and takes a while to learn
- **Super good news:** now there are codes (DoWhy) that allow us to apply it

From A. Molak, Causal Inference and Discovery in Python

Instrumental Variables



We’re interested in estimating the causal effect of X on Y .

- Cannot use the back-door criterion here because U is unobserved.
- Cannot use the front-door criterion because there’s no mediator between X and Y .

Instrumental Variables: require a special variable called an *instrument*, Z, to be present in a graph. An *instrument* needs to meet the following three conditions:

- The instrument, Z, is associated with X
- The instrument, Z, doesn’t affect Y in any way except through X
- There are no common causes of Z and Y

From A. Molak, Causal Inference and Discovery in Python

We want to study the effect of education (years of schooling) on earnings. However, the level of education might be influenced by many factors like family background, which also affect earnings. This correlation between the unobserved factors (like family background) and education can bias the results if you simply run a linear regression of earnings on education.

We need an instrument that is correlated with education but does not directly affect earnings except through education. Let's say we choose "proximity to college" as instrument.

Two-Stage Least Squares (2SLS) Regression:

1. Regress the potentially endogenous variable (education) on the instrument (proximity to college). This predicts the values of education that are not influenced by the unobserved confounders.

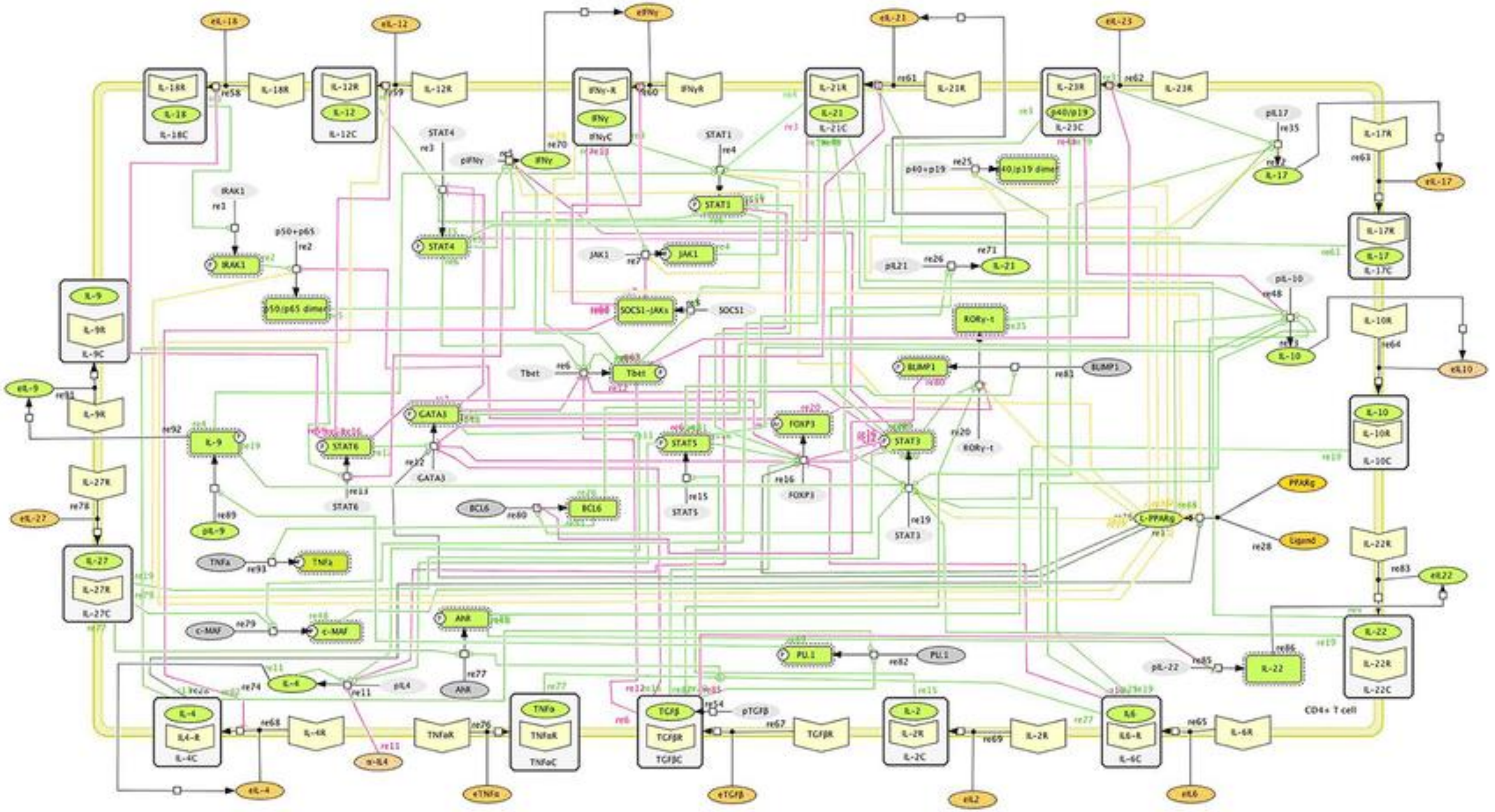
$$\text{Education} = \alpha + \beta * \text{ProximityToCollege} + \varepsilon$$

2. Regress the outcome (earnings) on the predicted values of education from the first stage

$$\text{Earnings} = \gamma + \delta * \text{PredictedEducation} + \zeta$$

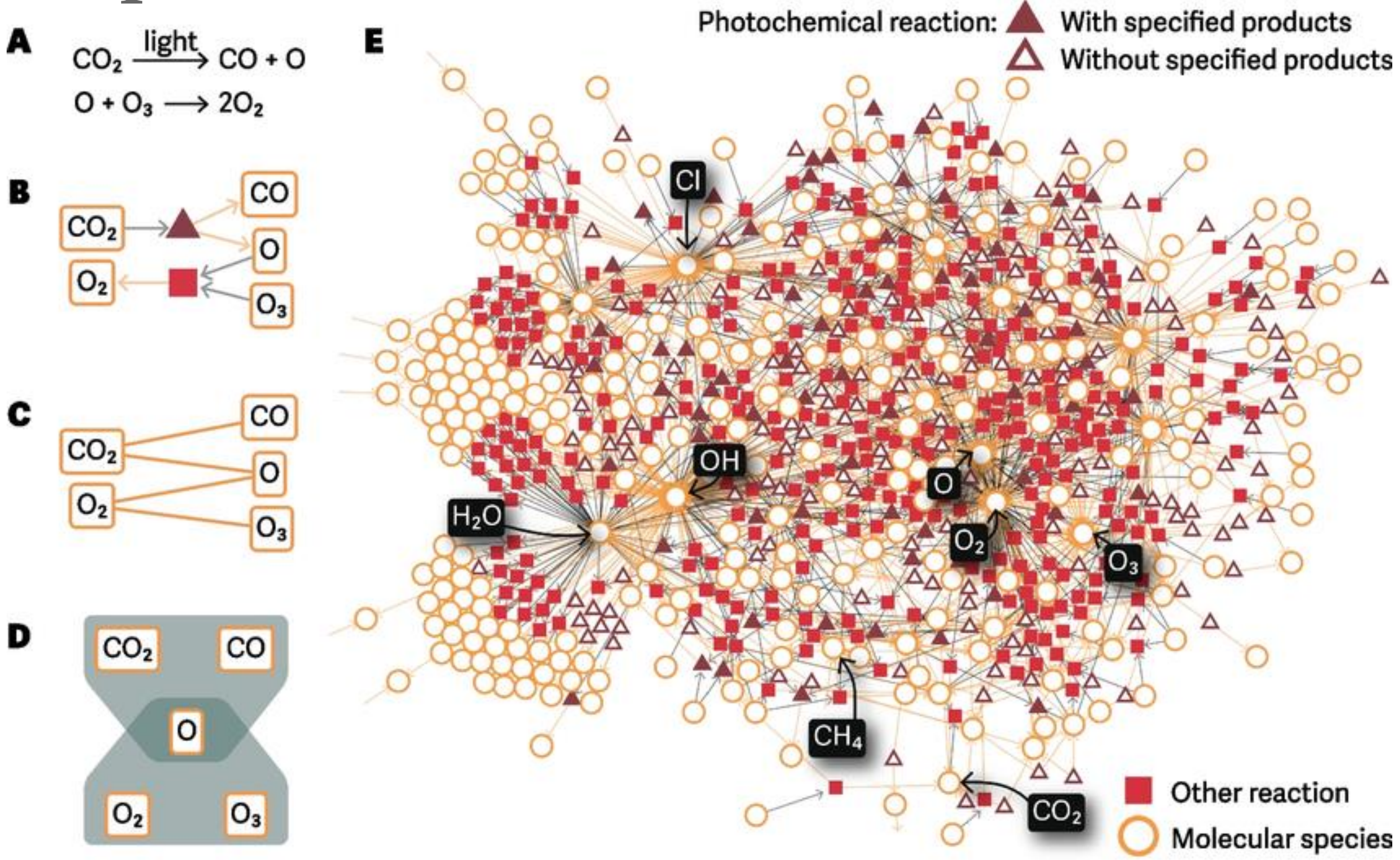
3. The coefficient δ on PredictedEducation in the second stage gives the estimated causal effect of education on earnings. This helps to isolate the variation in education that is independent of the unobserved confounders that also affect earnings.

Biochemical reaction networks



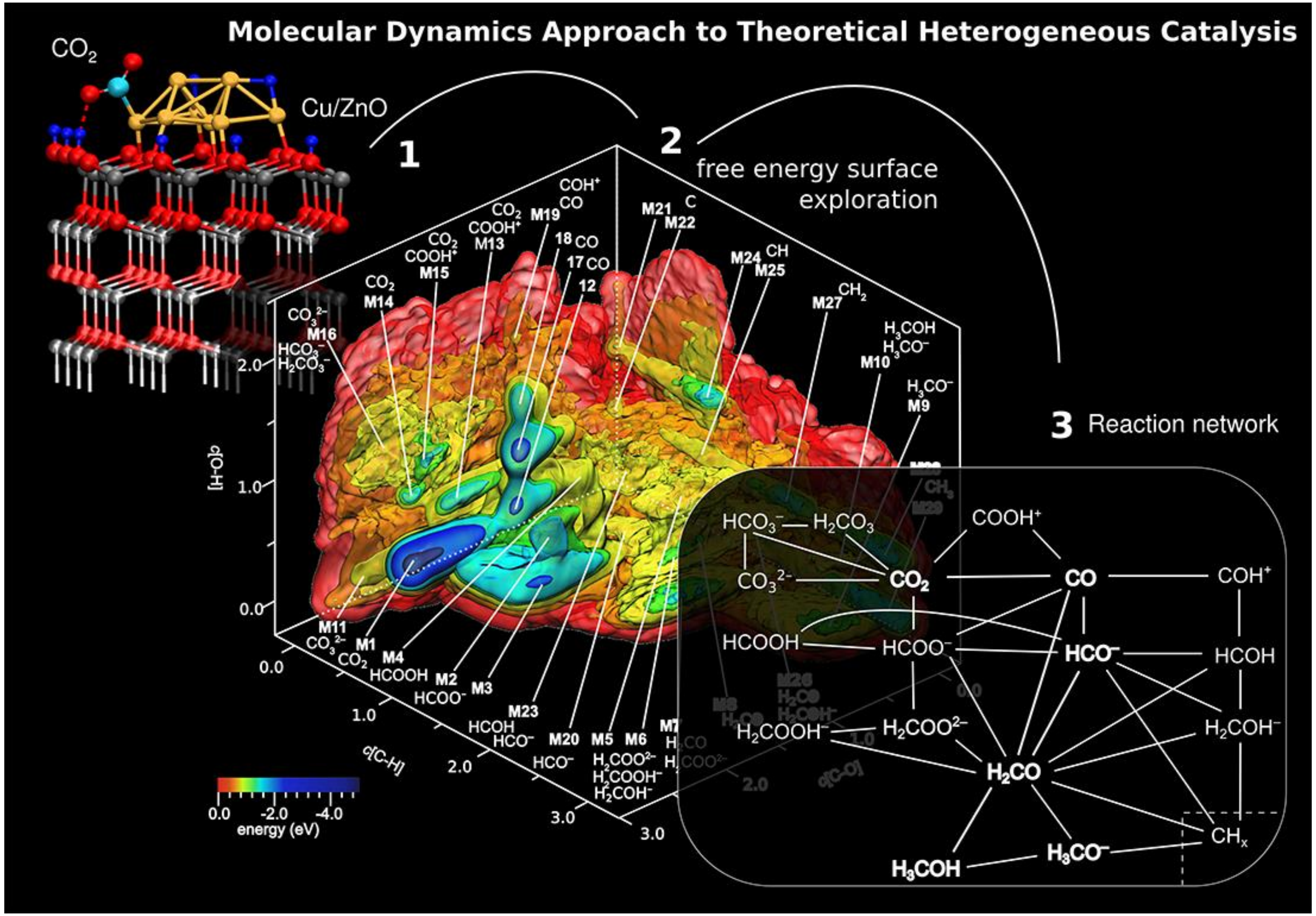
https://www.researchgate.net/figure/Main-intracellular-differentiation-pathways-of-a-single-CD4-T-cell-Systems-Biology_fig2_267753905

Atmospheric reaction networks



https://www.researchgate.net/figure/Network-structure-of-Earths-atmospheric-reaction-system-Panel-A-shows-a-minimal_fig4_368305699

Catalysis



https://www.gauss-centre.eu/results/materials-science-and-chemistry/theoretical-heterogeneous-catalysis-from-advanced-ab-initio-molecular-dynamics-simulations

Why causal inference is difficult?

- unmeasured confounders
- measurement error, or discretization of data
- mixtures of different causal structures in the sample
- feedback
- reversibility
- the existence of a number of models that fit the data equally well
- an enormous search space
- low power of tests of independence conditional on large sets of variables
- selection bias
- missing values
- sampling error
- complicated and dense causal relations among sets of variables,
- complicated probability distributions