UNIVERSITÀ DELLA CALABRIA

DIPARTIMENTO DI MATEMATICA E INFORMATICA

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87036 Rende (CS) – ITALIA

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UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

DISCo DIPARTIMENTO DI INFORMATICA SISTEMISTICA E COMUNICAZIONE

Bayesian (Causal) networks for Healthcare, Medicine and Biology

Fabio Stella
University of Milan-Bicocca
Department of Informatics, Systems and Communication

Summary

- **Machine Learning**
- **The Story Behind the Data**
- **The Ladder of Causation**
- **Bayesian (causal) networks**
- **Healthcare, Medicine and Biology**

Bayesian (Causal) networks for Healthcare, Medicine and Biology

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Machine Learning

— an ongoing revolution —

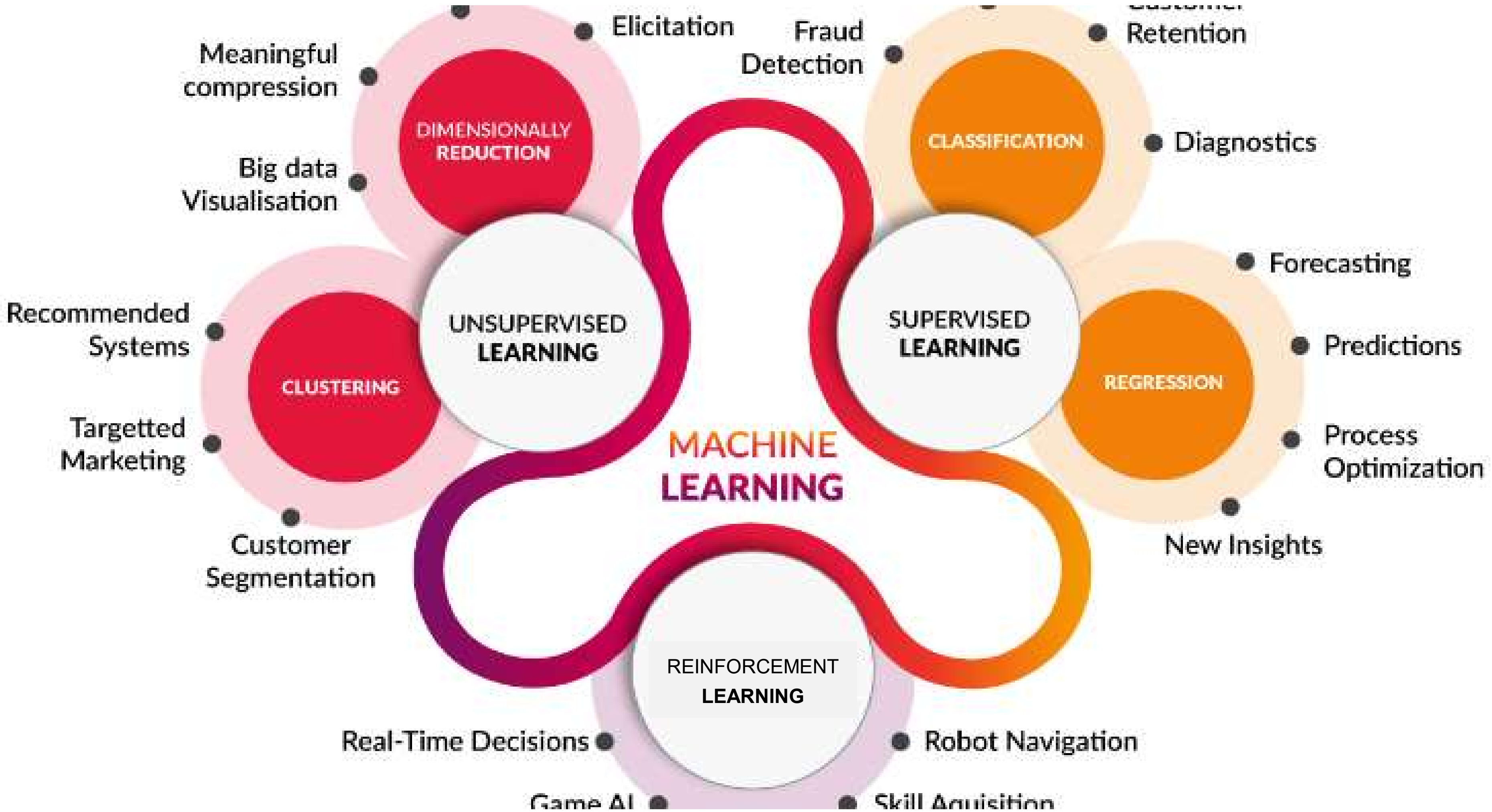
Reinforcement Learning

- Learn by interacting with the environment
- The environment reacts to our decisions/actions
- Sequential learning, only at the end of the game we know our performance (reward/punishment)

2016: World Go Champion Beaten by Deep Learning

Machine Learning

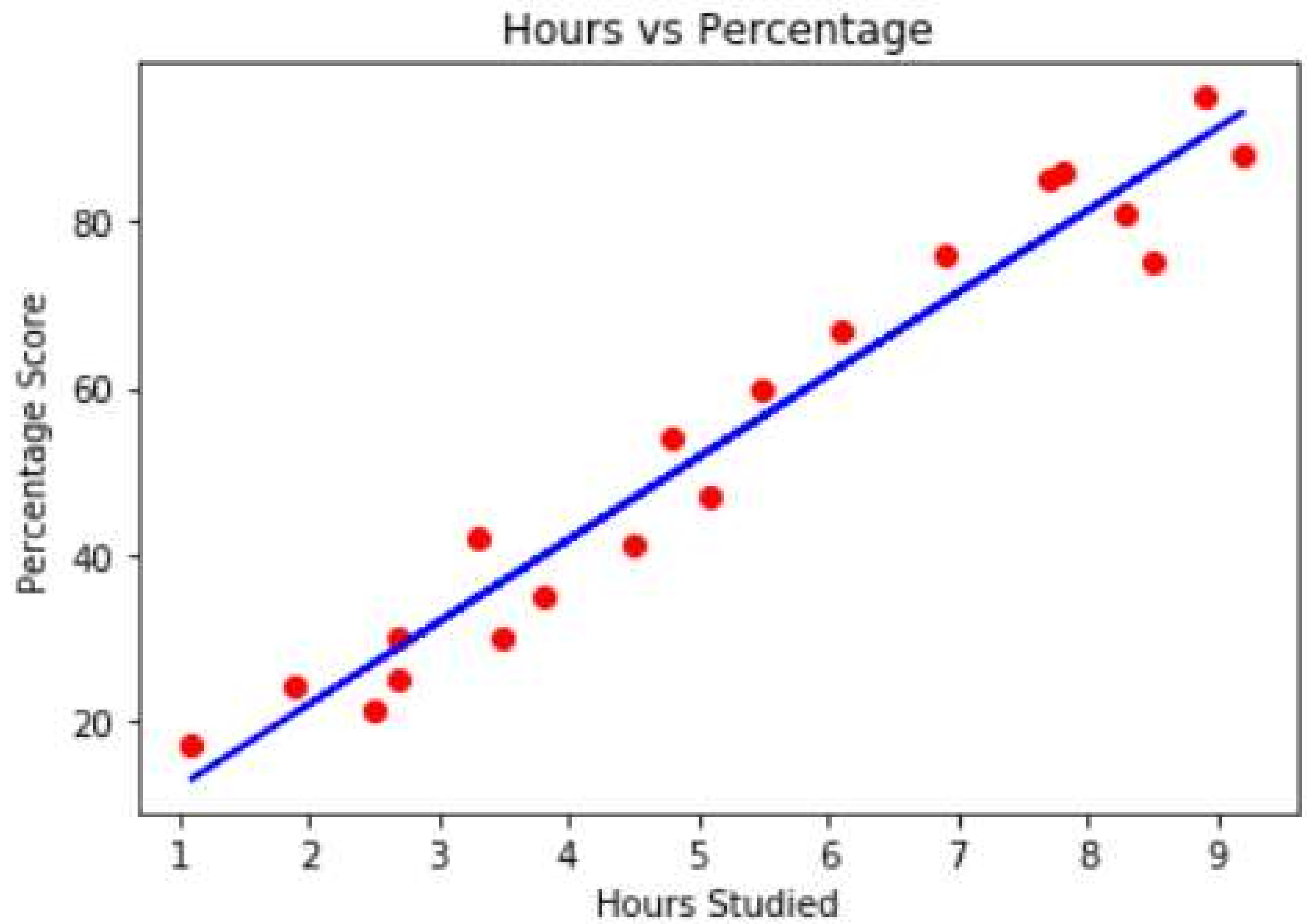
- Many different names for learning



But most of machine learning nowadays
is just **curve fitting**

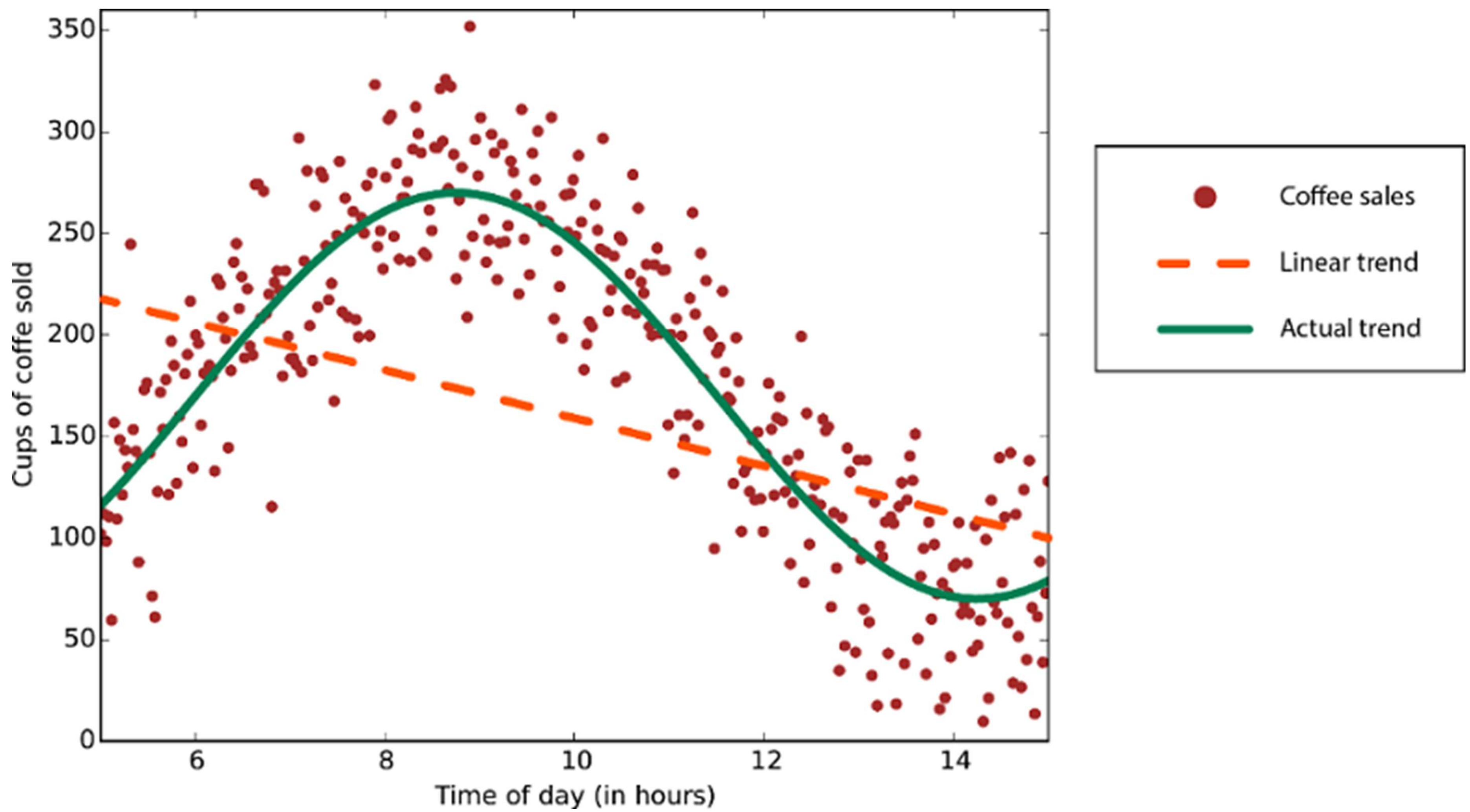
Machine Learning

- Curve fitting (correlations) - linear



Machine Learning

- Curve fitting - nonlinear

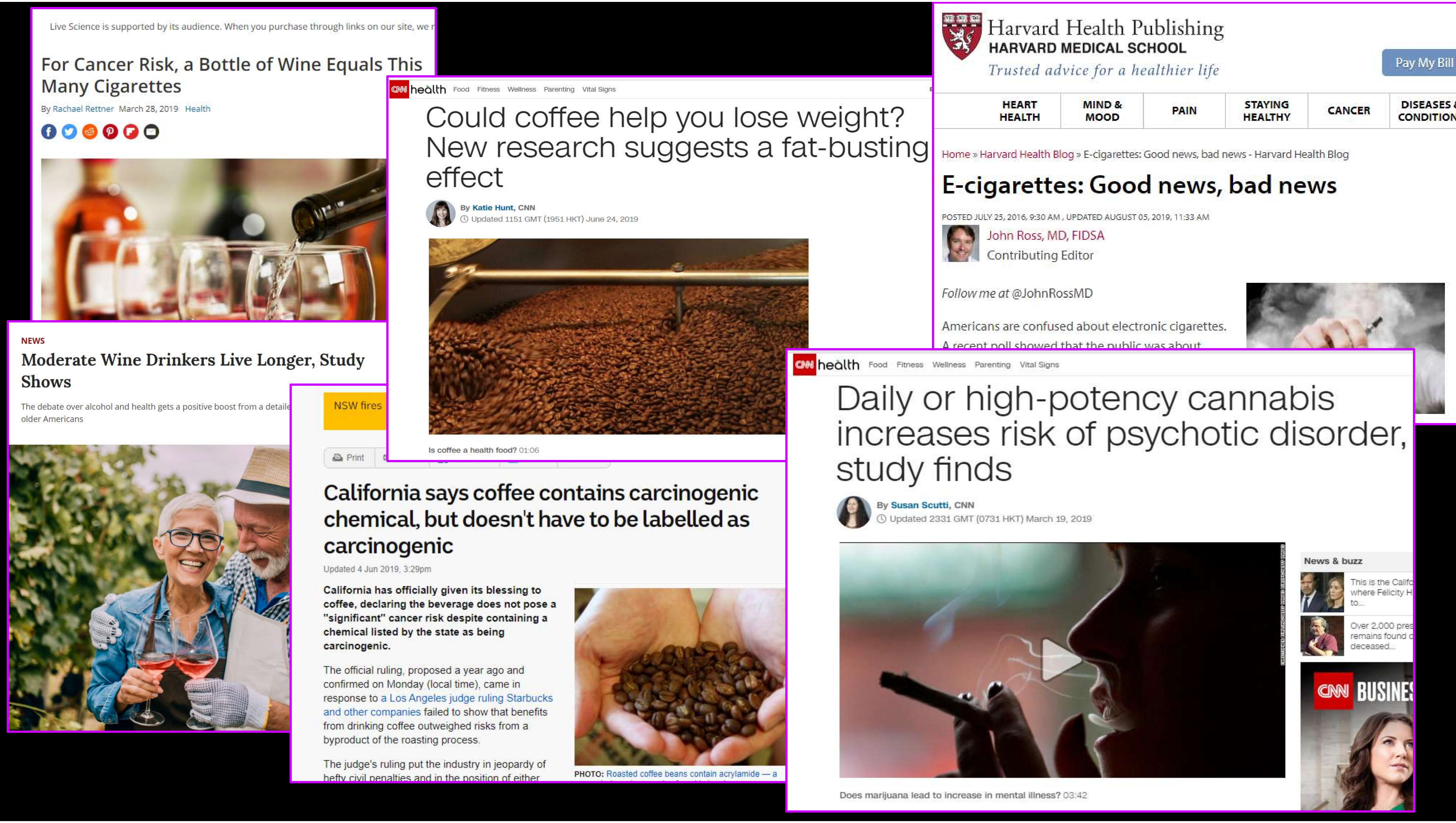


Machine Learning

- Deep Neural Networks

Highly dimensional, highly nonlinear

curve fitting



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California says coffee contains carcinogenic chemical, but doesn't have to be labelled as carcinogenic
Updated 4 Jun 2019, 3:29pm
California has officially given its blessing to coffee, declaring the beverage does not pose a "significant" cancer risk despite containing a chemical listed by the state as being carcinogenic.
The official ruling, proposed a year ago and confirmed on Monday (local time), came in response to a Los Angeles judge ruling Starbucks and other companies failed to show that benefits from drinking coffee outweighed risks from a byproduct of the roasting process.
The judge's ruling put the industry in jeopardy of
PHOTO: Roasted coffee beans contain acrylamide — a
CNN health Food Fitness Wellness Parenting Vital Signs
Could coffee help you lose weight? New research suggests a fat-busting effect
By Katie Hunt, CNN
Updated 1151 GMT (1951 HKT) June 24, 2019
Is coffee a health food? 01:06
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POSTED JULY 25, 2016, 9:30 AM , UPDATED AUGUST 05, 2019, 11:33 AM
John Ross, MD, FIDSA
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Americans are confused about electronic cigarettes.
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Daily or high-potency cannabis increases risk of psychotic disorder, study finds
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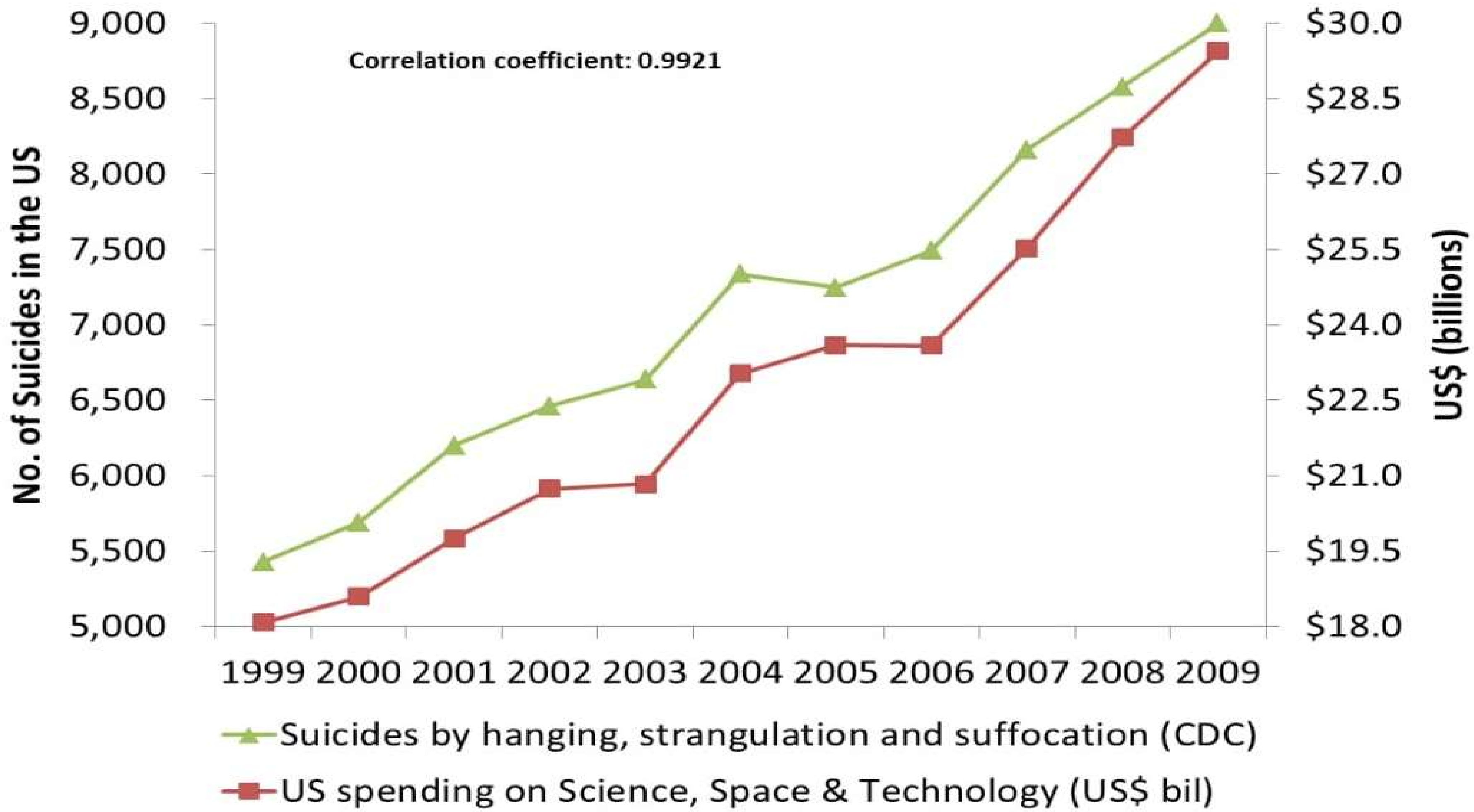
Machine Learning

- Spurious Correlations

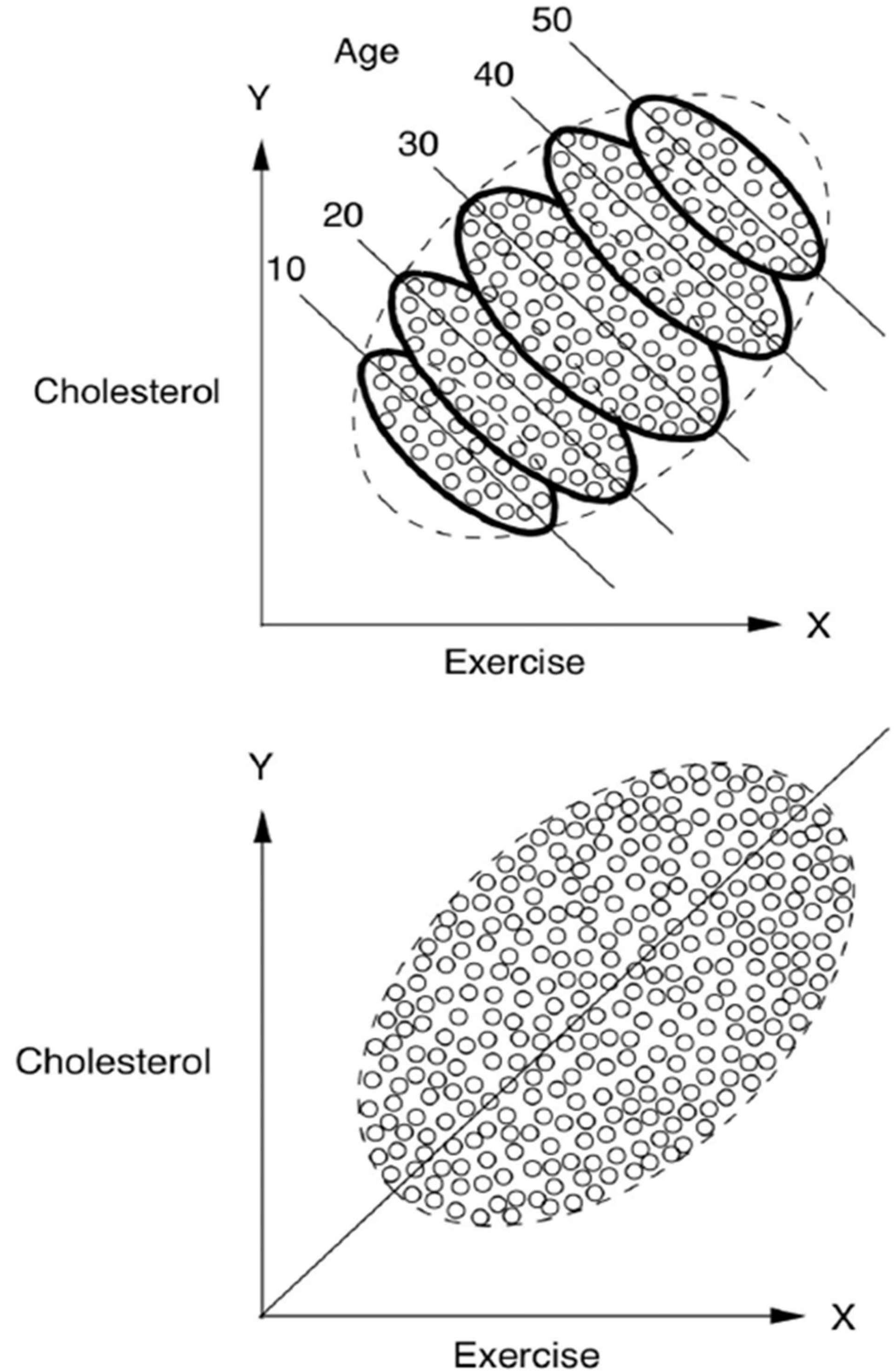
Fitting can be highly misleading



[Spurious Correlations]

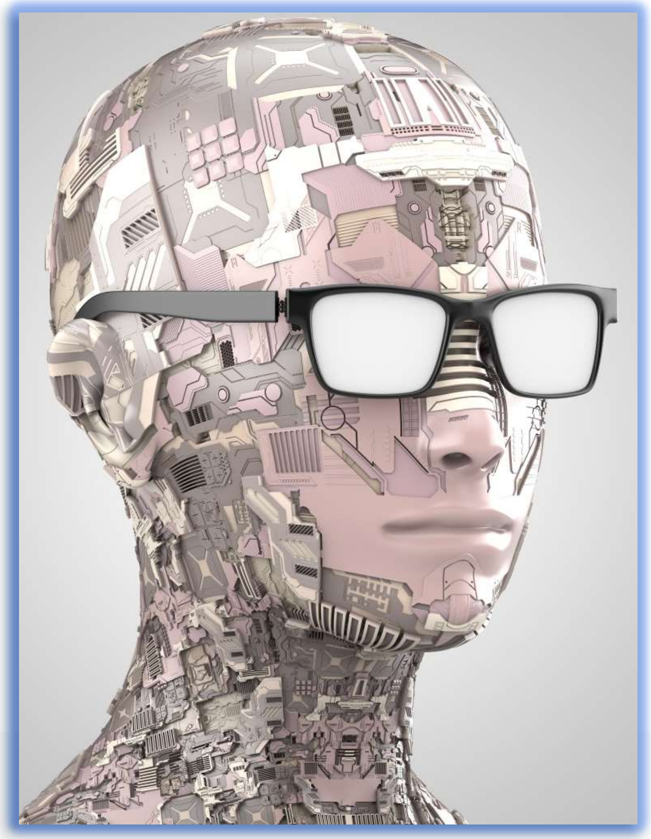
An elementary problem (or not?)

- The way we collect and aggregate data matters a lot but being acknowledged is not enough to learn from data alone
- No matter how many (observational) data are available, we will never know which is the true story



Causation is the key

- What we (computers so far) miss is **causal knowledge** for predicting the consequences of **actions**
- Causation for us is a synonym of **understanding**
- Actual intelligence needs **causal knowledge**
- But **causal knowledge is not in the data**!



The Story Behind the Data

— why causality matters? —

Simpson's Paradox

- Named after **Edward Simpson** (born 1922)
- A group of sick patients are given the option to try a new drug
- Among those who took the drug, a lower percentage recovered than among those who did not
- However, when we **partition by gender**, we see that:
  - *more* men taking the drug recover than do men are not taking the drug, and
  - *more* women taking the drug recover than do women are not taking the drug!

The drug appears to help men and women, but hurts the general population

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Example 1.2.1 We record the recovery rates of 700 patients who were given access to the drug. A total of 350 patients chose to take the drug and 350 patients did not. The results of the study are shown in **Table 1.1**.

Table 1.1 Results of a study into a new drug, with gender being taken into account

	Drug			No Drug		
	patients	recovered	% recovered	patients	recovered	% recovered
Men	87	81	93%	270	234	87%
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Drug vs non-drug takers recovery rates:

- 93% vs 87% male (the drug helps)

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Drug vs non-drug takers recovery rates:

- 73% vs 69% female (the drug helps)

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Drug vs non-drug takers recovery rates:

- 78% vs 83% general population! (the drug hurts) ???

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Drug vs non-drug takers recovery rates:

- 93% vs 87% male
- 73% vs 69% female
- 78% vs 83% general population!

Should a doctor prescribe the drug; to whom?

Should a policy maker approve the drug for use?

Understand the causal story behind the data

- What mechanism generated the data?
- Suppose: estrogen has a negative effect on recovery
  - Women less likely to recover than men, regardless of the drug

From the data:

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Conclusion: the drug appears to be harmful but it is not

- If we select a drug taker at random, that person is more likely to be a woman
- Hence less likely to recover than a random person who doesn't take the drug

Causal Story

- Being a woman is a common cause of both drug taking and failure to recover.
- To assess the effectiveness we need to compare subjects of the same gender.

(Ensures that any difference in recovery rates is not ascribable to estrogen)

Data Segregation

- We have solved the problem using gender-segregated data
- Then let's just segregate the data whenever possible, right?

WRONG!!!

- Consider a drug affecting recovery by lowering blood pressure (BP)
- Unfortunately, it has also a toxic effect

Table 1.2 Results of a study into a new drug, with posttreatment blood pressure taken into account

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- Only by BP-segregating the data we can see the toxic effect
- It makes no sense to segregate the data; we should use the combined data

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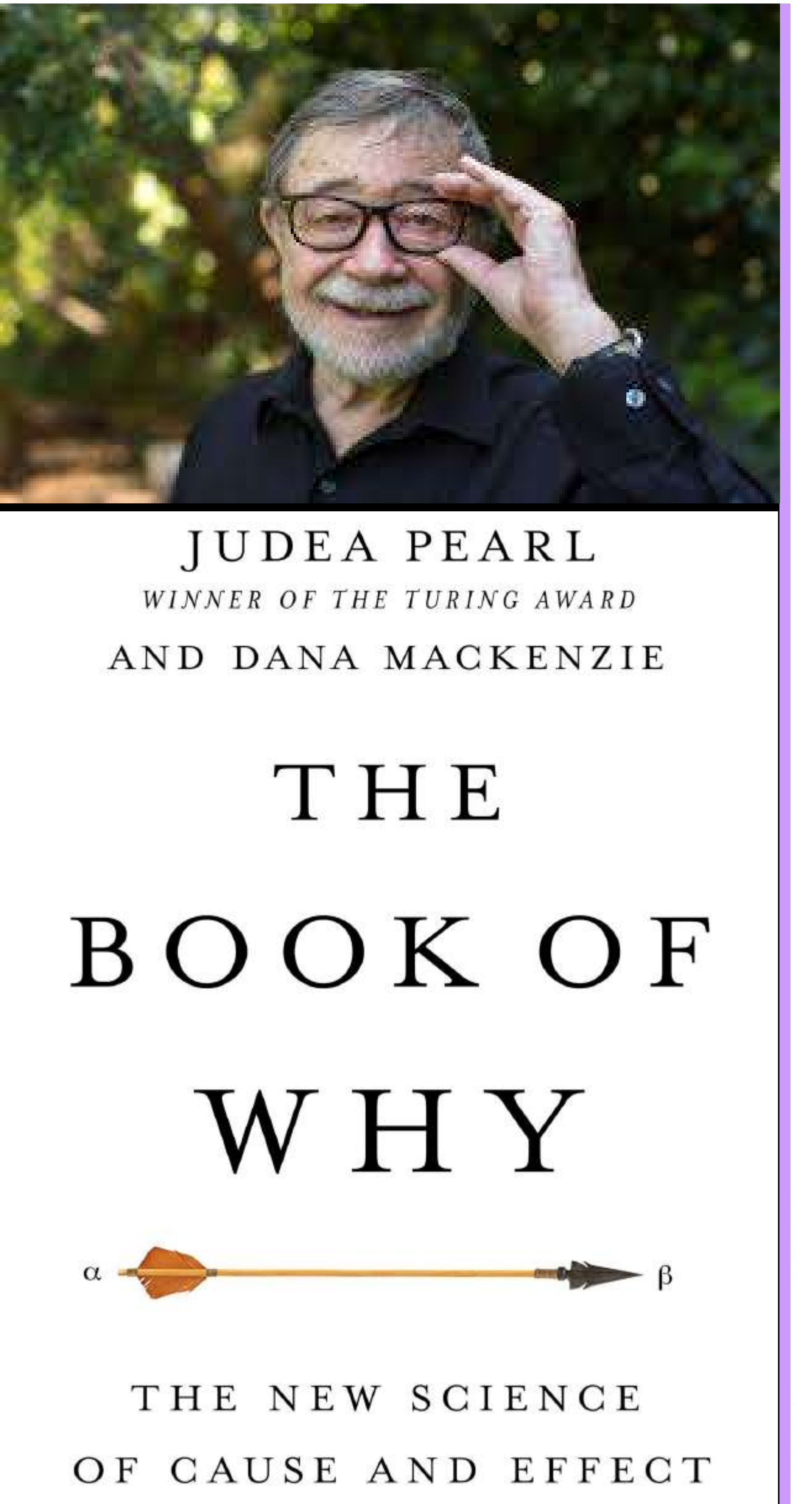
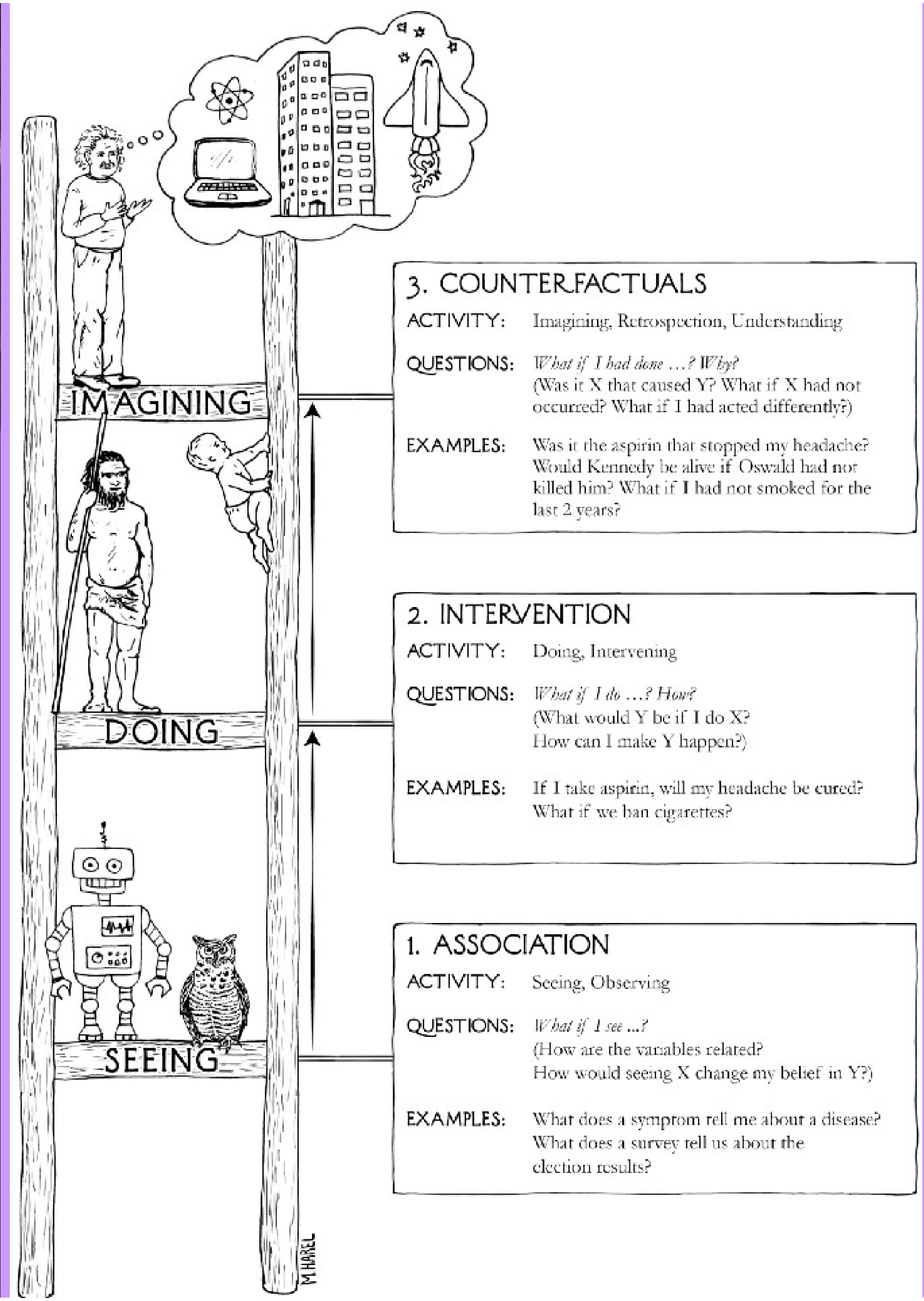
Note that the data are the same of Simpson's Paradox.

The Ladder of Causation

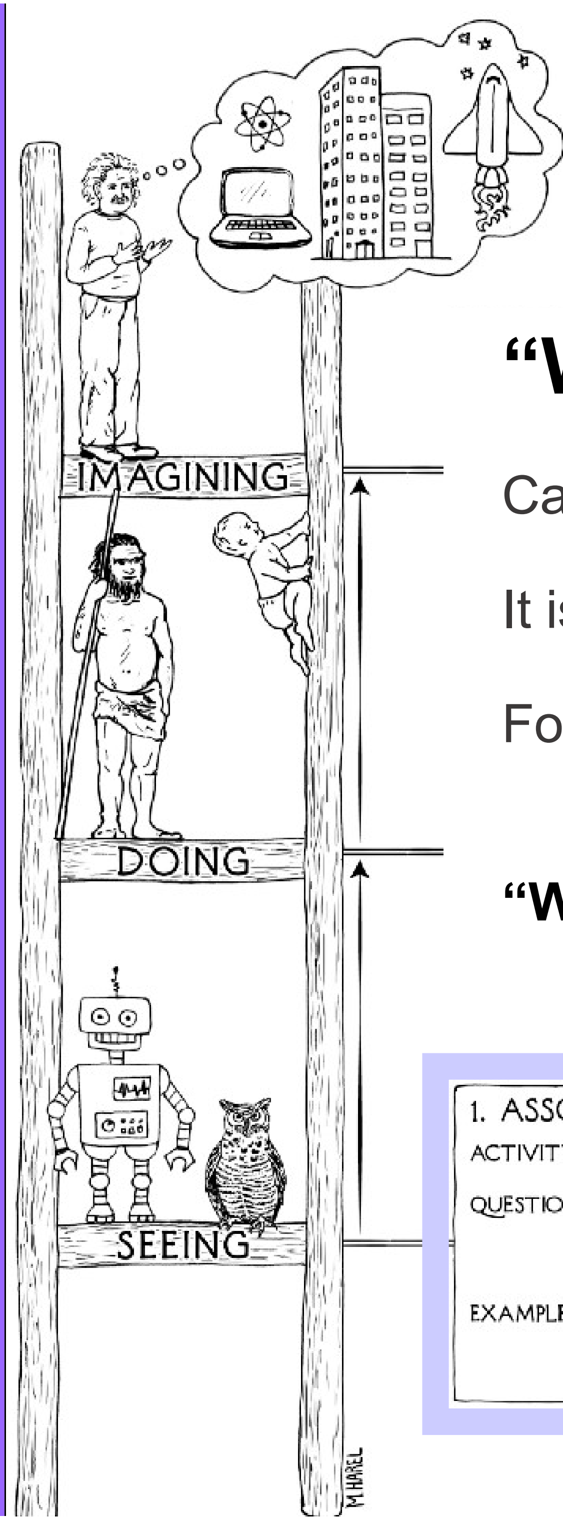
— How to climb it —





The Ladder of Causation

Seeing; we are looking for regularities in observations.



“What if I see …?”

Calls for predictions based on passive observations.

It is characterized by the question **“What if I see …?”**

For instance, imagine a medical doctor asking,

“What does a symptom tell me about a disease?”

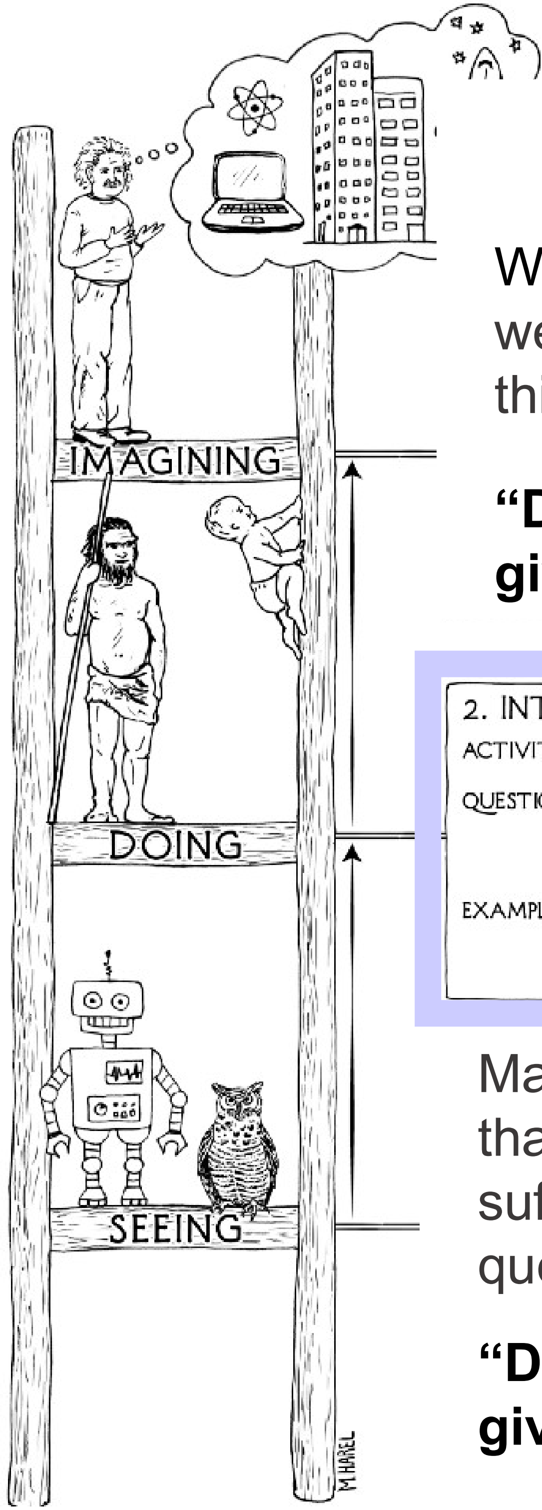
1. ASSOCIATION

ACTIVITY: Seeing, Observing

QUESTIONS: *What if I see ...?*
(How are the variables related?
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?

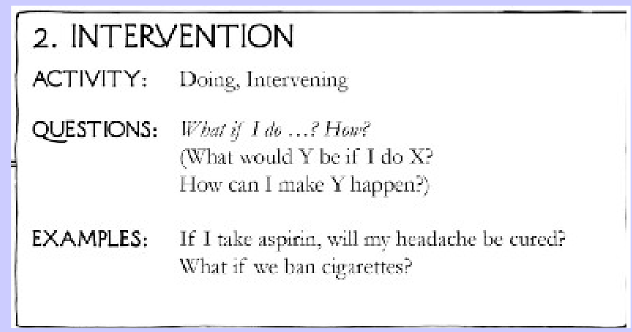
Intervention; ranks higher than association because it involves not just seeing but changing what is.



"What if do …?" & "How?"

We step up to the next level of causal queries when we begin to change the world. A typical question for this level is

"Does the patient recover whether I prescribe a given drug?"



2. INTERVENTION

ACTIVITY: Doing, Intervening

QUESTIONS: *What if I do …? How?*
(What would Y be if I do X?
How can I make Y happen?)

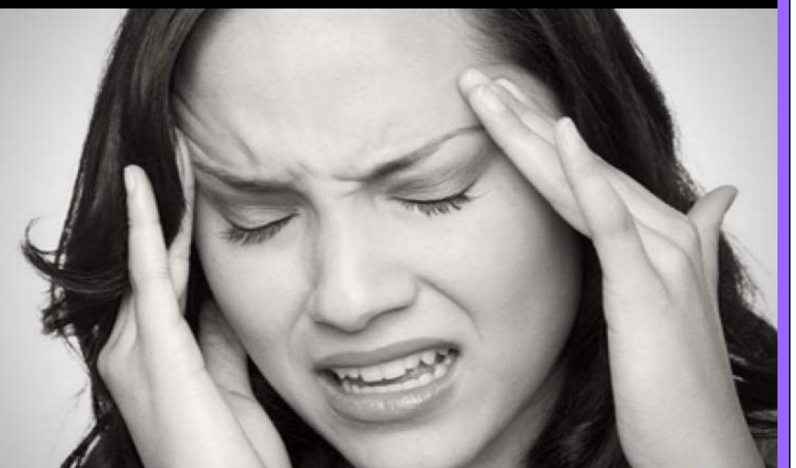
EXAMPLES: If I take aspirin, will my headache be cured?
What if we ban cigarettes?

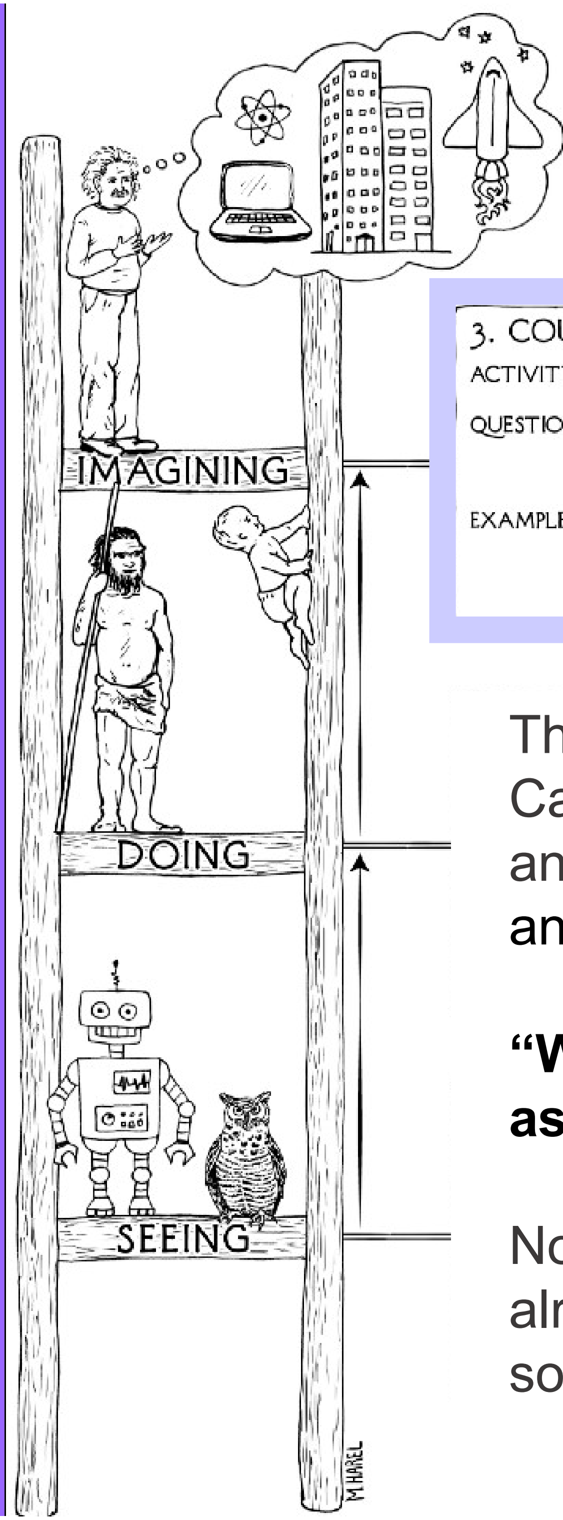
This already calls for a new kind of knowledge, absent from the data, which we find at rung two of the Ladder of Causation, **Intervention**.

Many scientists have been quite traumatized to learn that none of the methods they learned in statistics is sufficient even to articulate, let alone answer, a simple question like

"Does the patient recover whether I prescribe a given drug?"

Counterfactuals; ranks higher than intervention because it involves **imagining**, **retrospection** and **understanding**.





"What if I had done …?" & "Why?"

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 for the last 2 years?

We might wonder, My headache is gone now, but

- **Why?**
- **Was it the aspirin I took?**
- **The food I ate?**
- **The good news I heard?**

These queries take us to the top rung of the Ladder of Causation, the level of **Counterfactuals**, because to answer them we must go back in time, change history, and ask,

"What would have happened if I had not taken the aspirin?"

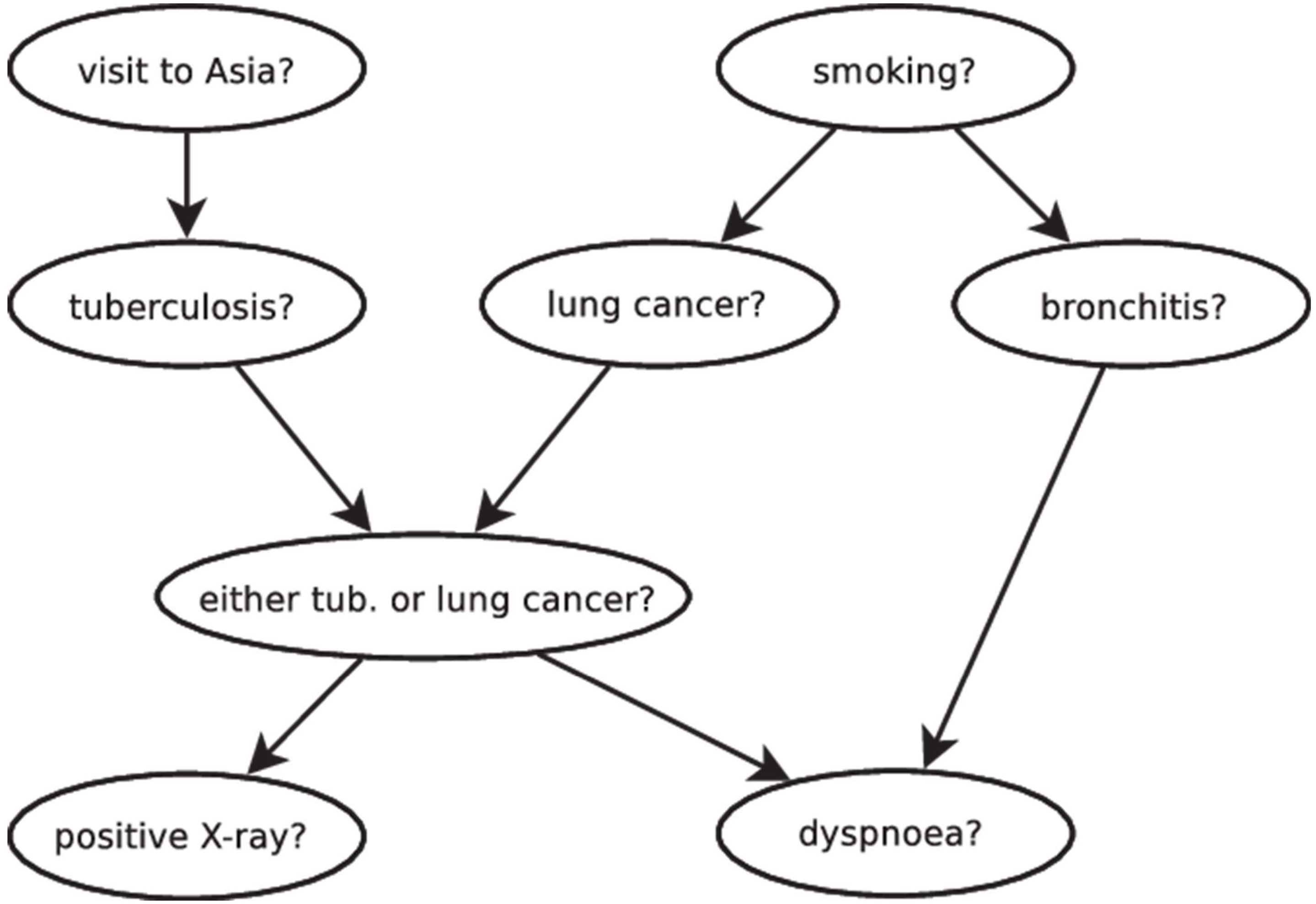
No experiment in the world can deny treatment to an already treated person and compare the two outcomes, so we must import a whole new kind of knowledge.

Bayesian (causal) Networks

— basic definitions —

Bayesian Networks

- We want a representation and reasoning system that is based on conditional (and marginal) independence
  - Compact yet expressive representation
  - Efficient reasoning procedures
- Bayesian Networks are such representation
  - Named after Thomas Bayes
  - Term coined in 1985 by Judea Pearl
  - Their invention changed the primary focus of AI from logic to probability



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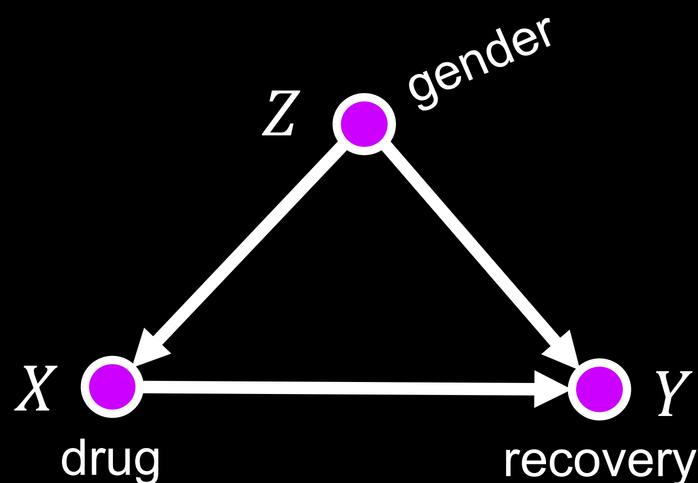

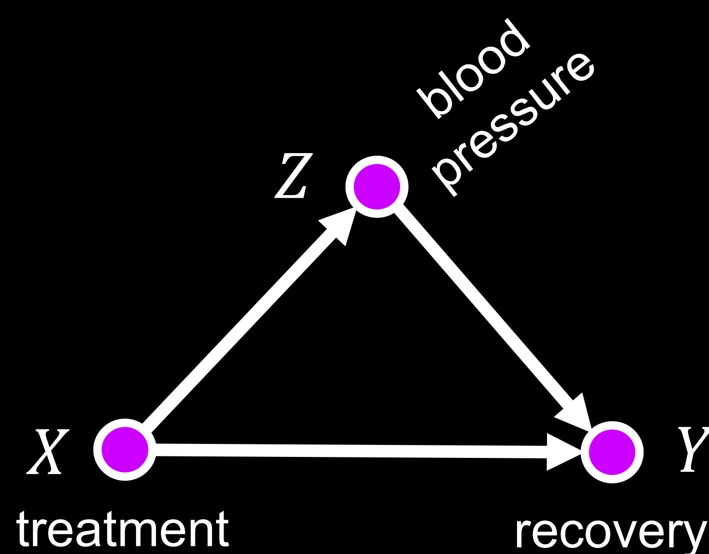

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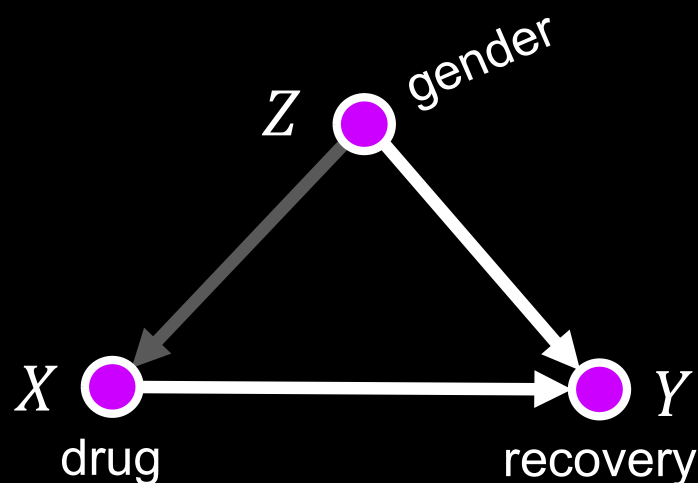
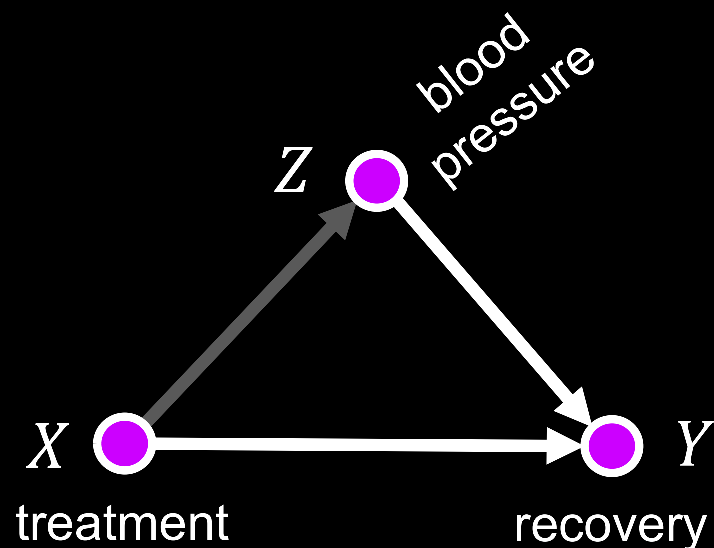




Simpson's Paradox

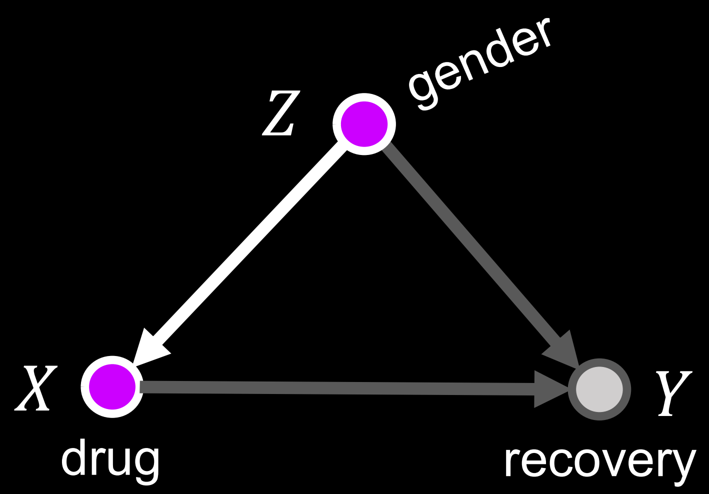
- Named after Edward Simpson (born 1922)
- A group of sick patients are given the option to try a new drug
- Among those who took the drug, a lower percentage recovered than among those who did not
- However, when we partition by gender, we see that:
  - *more* men taking the drug recover than do men are not taking the drug, and
  - *more* women taking the drug recover than do women are not taking the drug!

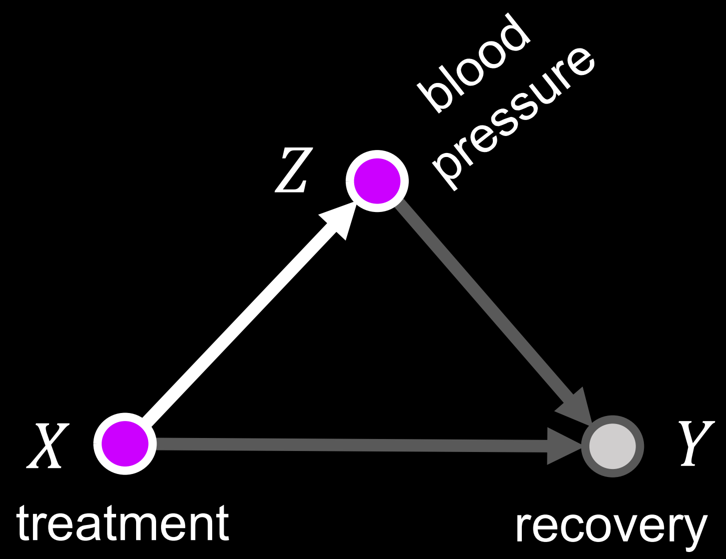
Table 1.1 Results of a study into a new drug, with gender being taken into account

	Drug			No Drug		
	patients	recovered	% recovered	patients	recovered	% recovered
Men	87	81	93%	270	234	87%
Women	263	192	73%	80	55	69%
Combined data	350	273	78%	350	289	83%

Table 1.2 Results of a study into a new drug, with posttreatment blood pressure taken into account

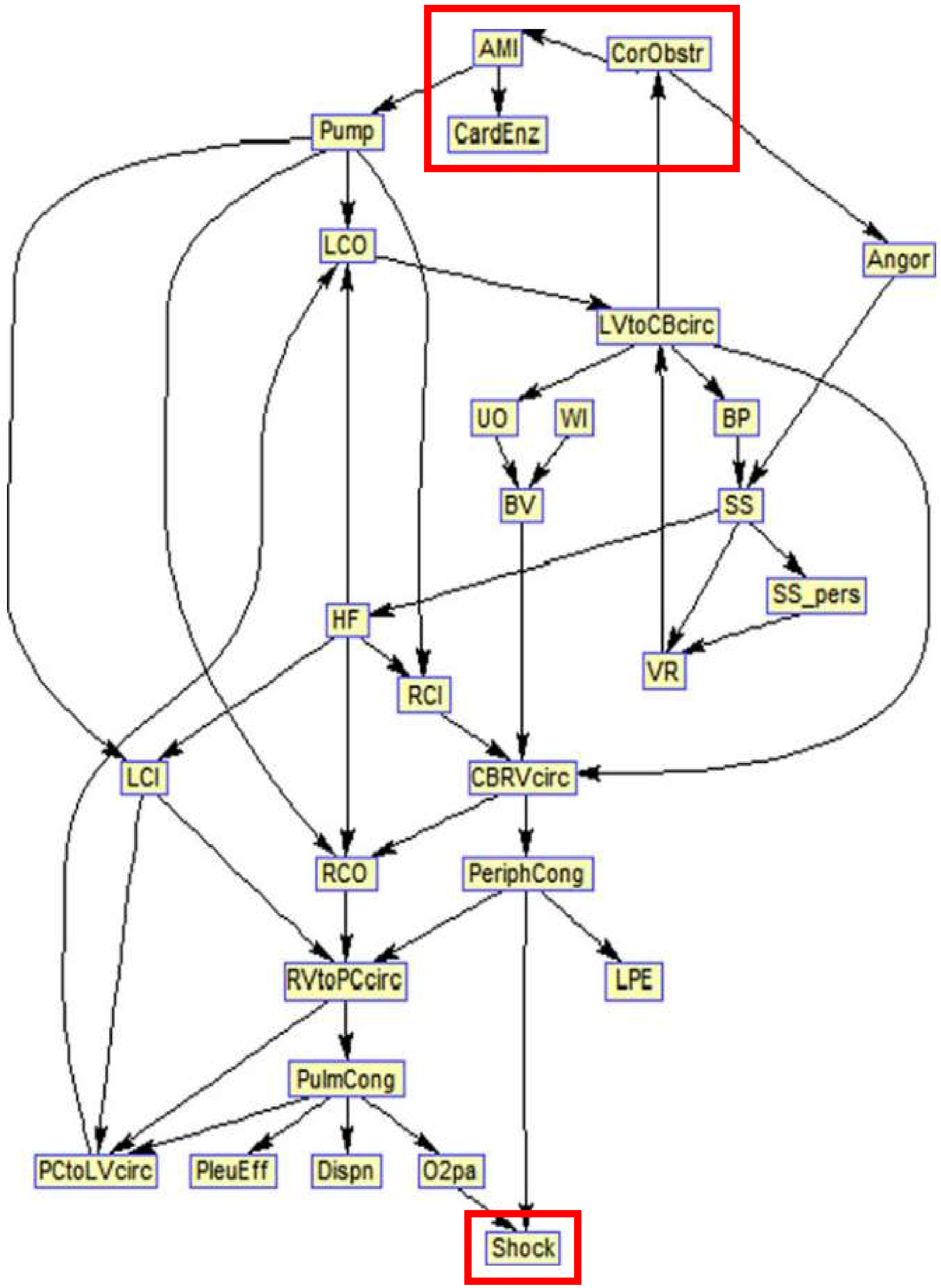
	No Drug			Drug		
	patients	recovered	% recovered	patients	recovered	% recovered
Low BP	87	81	93%	270	234	87%
High BP	263	192	73%	80	55	69%
Combined data	350	273	78%	350	289	83%

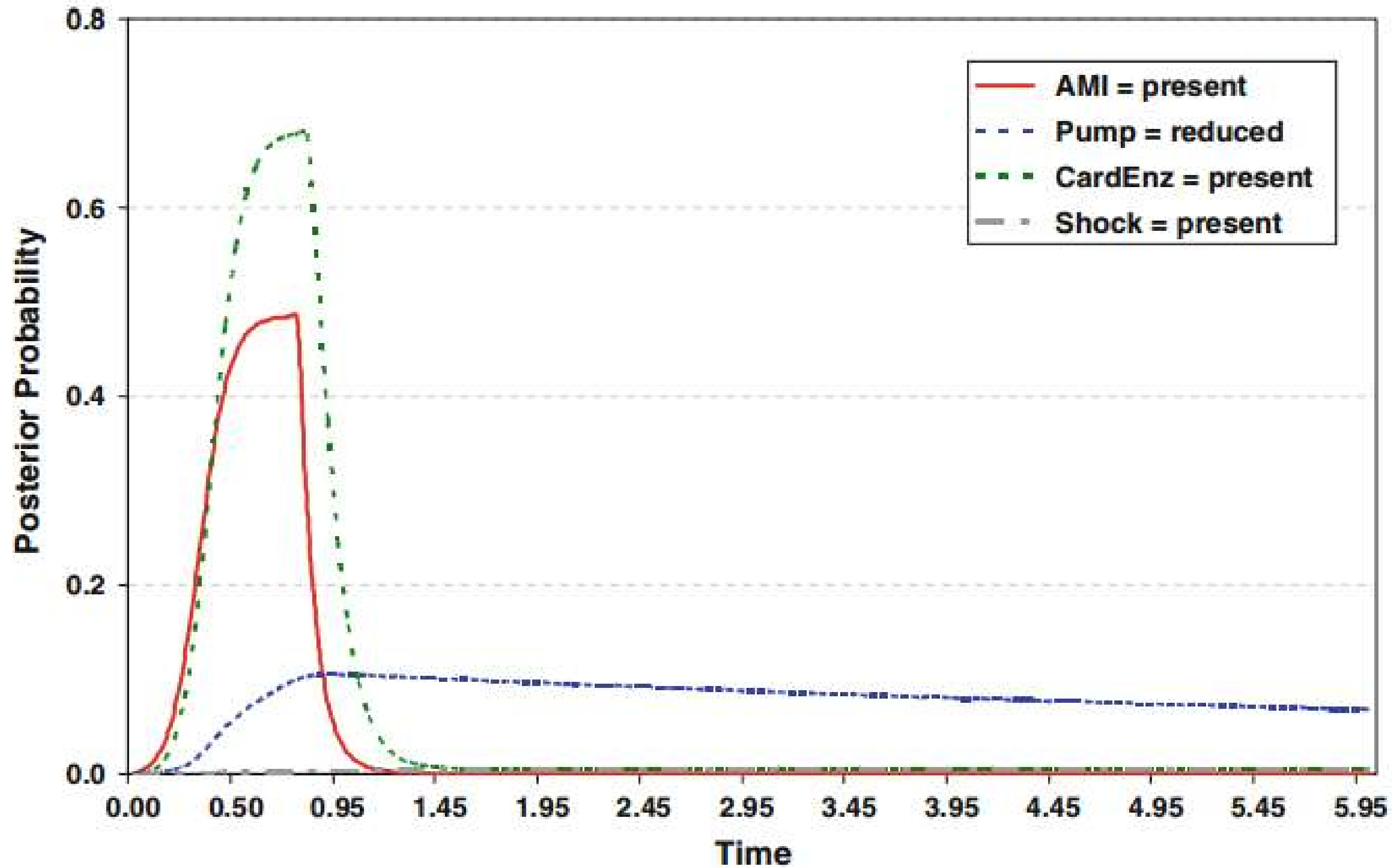




Healthcare, Medicine and Biology

— past and running research projects @MADLab —





Gatti, E., Luciani, D., & Stella, F. (2011). *A continuous time Bayesian network model for cardiogenic heart failure*. Flexible Services and Manufacturing Journal, 24 (2), 496-515.

Stella, F. and Amer, Y. (2012), Continuous time Bayesian network classifiers. *Journal of Biomedical Informatics*, 45, 1108–1119.

120 trajectories × 7 movements

Movement id	Description
1	Abduction-adduction of the upper limb on a frontal plane
2	Abduction-adduction of the upper limb on a sagittal plane
3	External rotation of the forearm
4	Flexion-extension of the elbow
5	Pronation-supination of the forearm
6	Functional activity: eating
7	Functional activity: combing

6 classes

Class index	Correctness	Speed	Description
1	Correct	Slow	Reference
2	Correct	Average	Reference
3	Correct	Fast	Reference
4	Incorrect	Average	Movement too small
5	Incorrect	Average	Typical compensatory action (first)
6	Incorrect	Average	Typical compensatory action (second)

2 classes

Microbial Communities in the Tropical Air Ecosystem

- **Case of Study** - A mixture of microorganisms is constantly present in the environment surrounding us. The atmosphere is no exception to this observation [1].
- **Methodology** - Structural Causal Models (SCM) learned from partial temporal order and observational data.

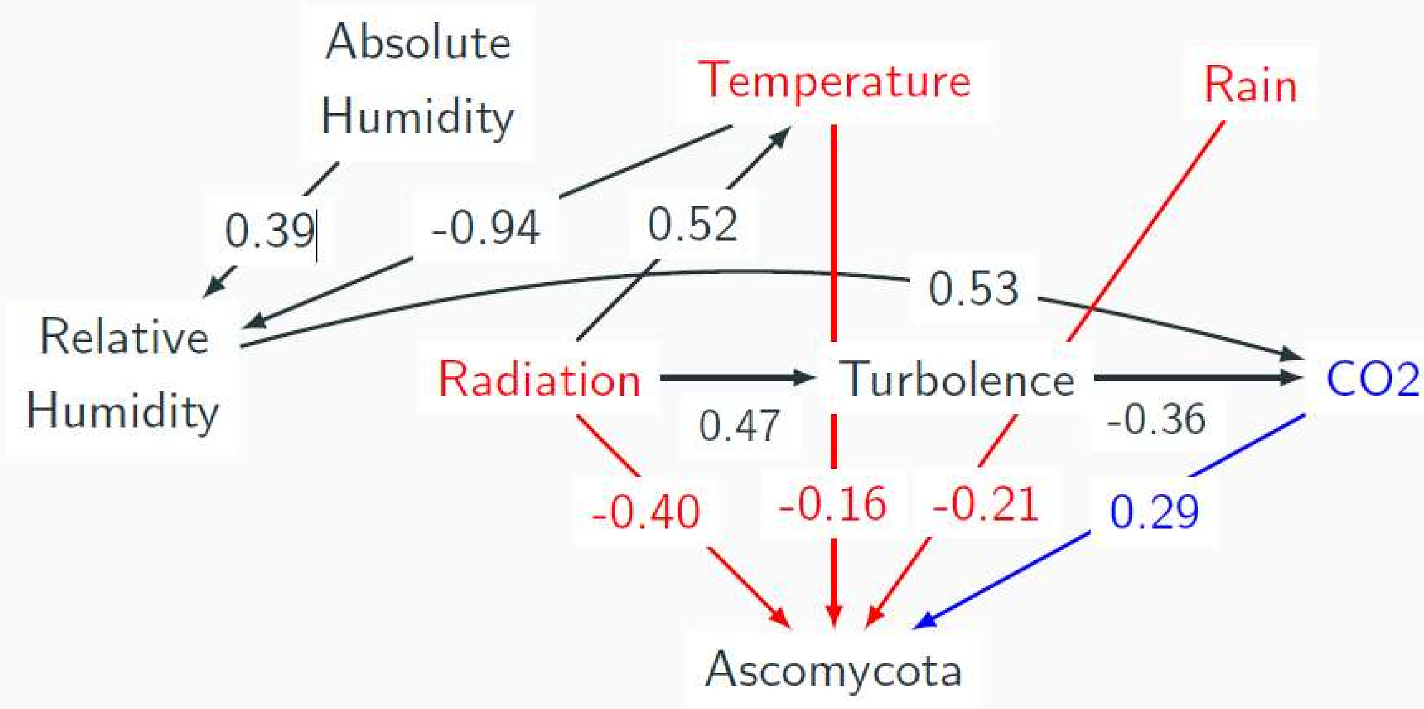


Figure 1: Estimated SCM for Ascomycota.

[1] E. S. Gusareva, E. Acerbi, K. J. Lau, *et al.*, "Microbial communities in the tropical air ecosystem follow a precise diel cycle," *Proceedings of the National Academy of Sciences*, vol. 116, no. 46, pp. 23 299–23 308, 2019.

Table 1 Performance comparison of CTBNs, DBNs and GC on simulated data for different network dimensions. Organism *E.coli* (top) and *S. cerevisiae* (bottom). The data shown here corresponds to Figure 3

Method	NETs size	Mean precision	Mean recall	Mean F_1
GC	10	0.46	0.68	0.54
	20	0.40	0.70	0.49
	50	0.24	0.82	0.37
	100	0.16	0.82	0.27
DBNs	10	0.90	0.29	0.41
	20	0.55	0.42	0.47
CTBNs	10	0.66	0.58	0.61
	20	0.72	0.48	0.57
	50	0.53	0.57	0.54
	100	0.45	0.51	0.48
Random	10	0.16	0.55	0.24
	20	0.11	0.51	0.18
	50	0.03	0.49	0.06
	100	0.02	0.50	0.04

Method	NETs size	Mean precision	Mean recall	Mean F_1
GC	10	0.42	0.75	0.52
	20	0.28	0.81	0.41
	50	0.22	0.78	0.34
	100	0.14	0.80	0.23
DBNs	10	0.62	0.53	0.56
	20	0.60	0.57	0.58
CTBNs	10	0.95	0.58	0.69
	20	0.72	0.70	0.70
	50	0.64	0.56	0.59
	100	0.56	0.51	0.53
Random	10	0.18	0.59	0.27
	20	0.07	0.49	0.12
	50	0.05	0.50	0.08
	100	0.02	0.50	0.05

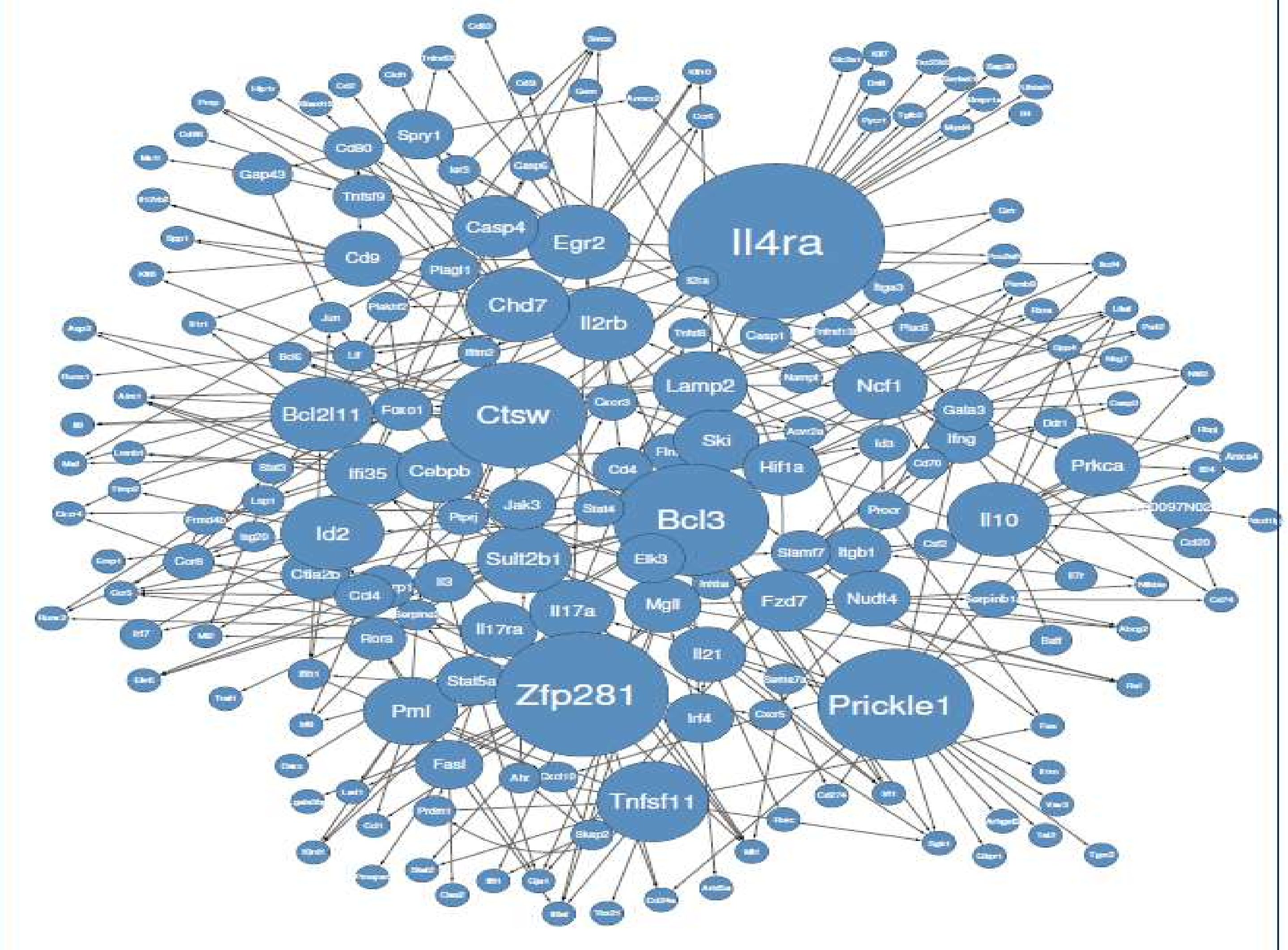
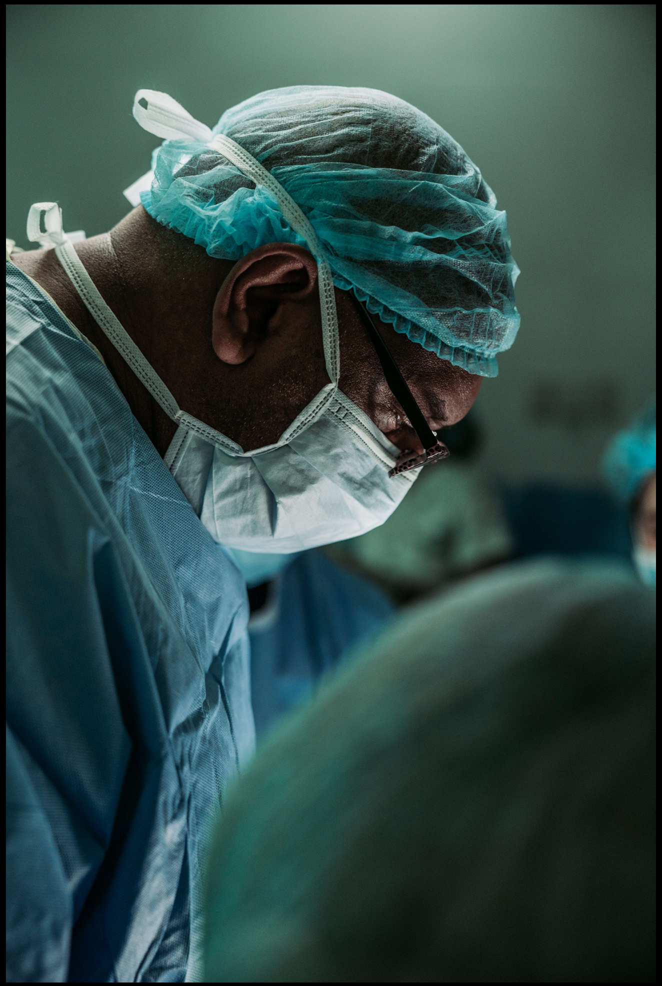
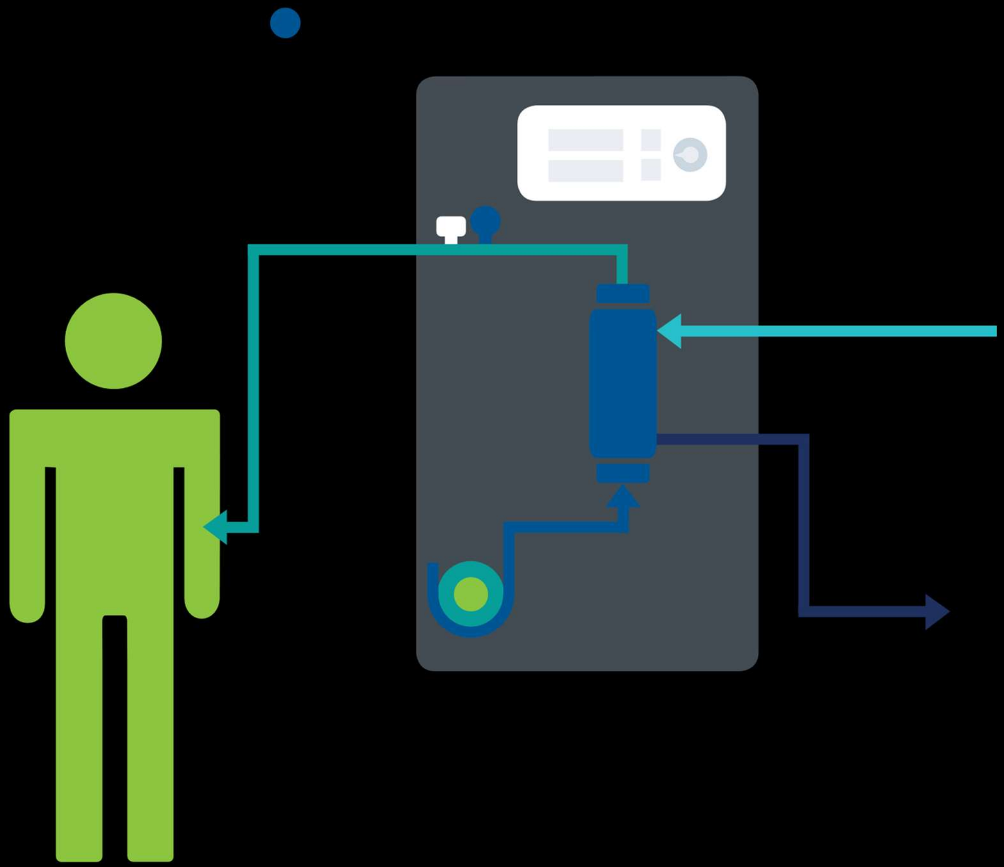


Figure 7 IL6+TGFβ1 inferred network. Node sizes are proportional to the number of outgoing arcs.

Acerbi, E., Vigano, E., Poidinger, M., Mortellaro, A., Zelante, T., & Stella, F. (2016).
Continuous time Bayesian networks identify prdm1 as a negative regulator of th17 cell differentiation in humans.
Scientific Reports, 6, 23128.

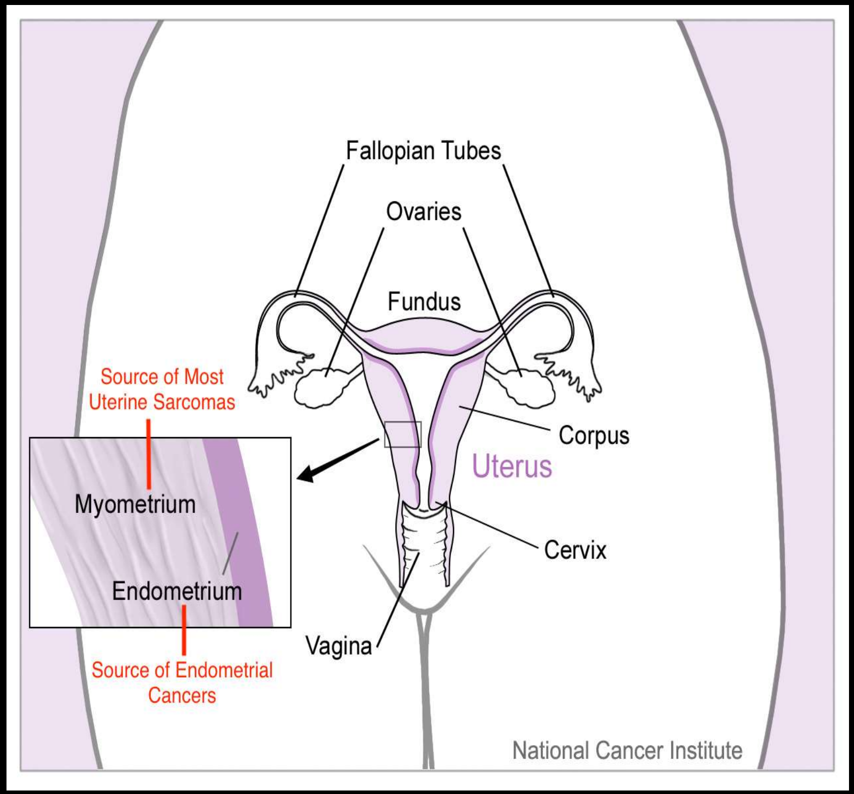
Personalized Arterovenous Fistula Management through utility maximization with Influence Diagrams

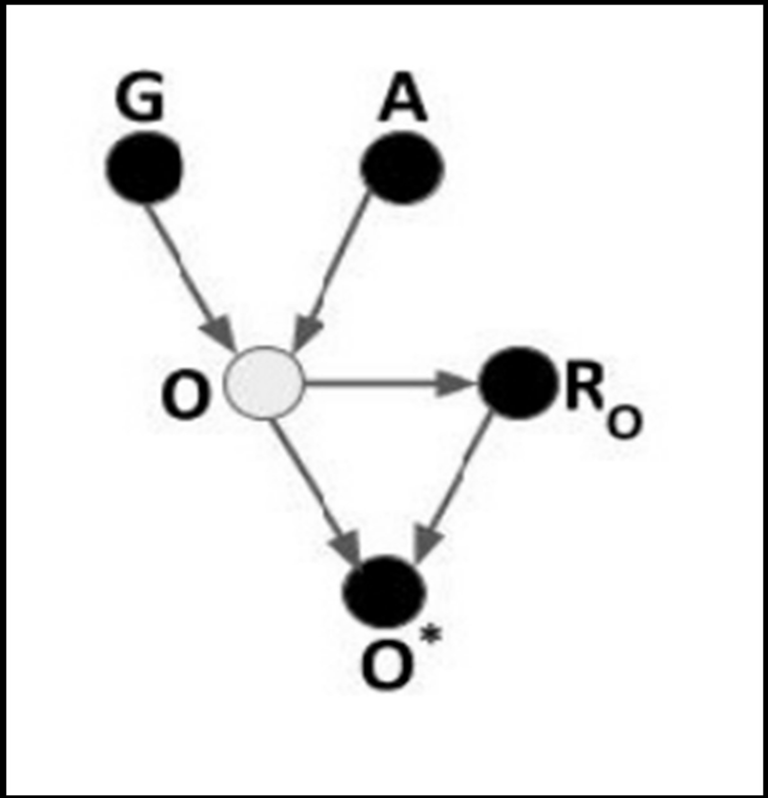


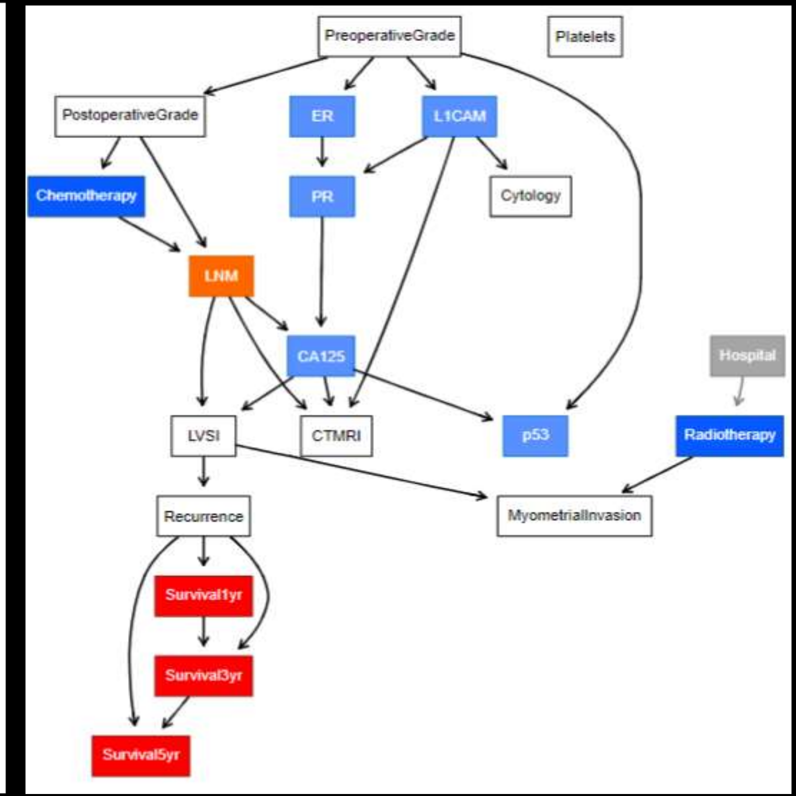


Bregoli, A., Neri, L., Botler, M., Schumacher, E., Peralta, R., Ponce, P., & Bellocchio, F. (2021).
Personalized Arterovenous Fistula Management through Utility Maximization with Influence Diagram.
In Proceedings of SMARTERCARE@ AI*IA (pp. 61-66).

Causal Discovery for Multicentric Study on Endometrial Cancer



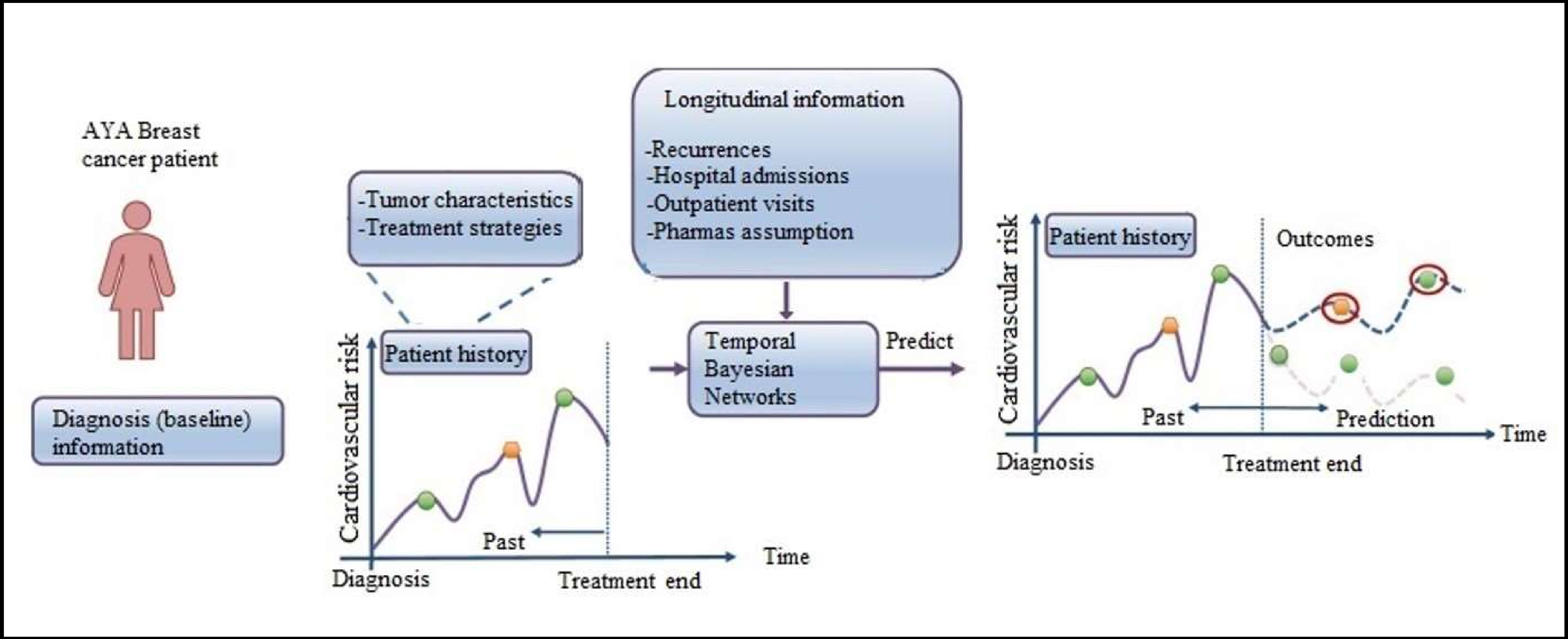




Zanga, Alessio, Alice Bernasconi, Peter J.F. Lucas, Hanny Pijnenborg, Casper Reijnen, Marco Scutari and Fabio Stella.
Risk Assessment of Lymph Node Metastases in Endometrial Cancer Patients: A Causal Approach.
Proceedings of HC@AIxIA 2022: 1st AIxIA Workshop on Artificial Intelligence For Healthcare (2022).

Zanga, Alessio, Alice Bernasconi, Peter J.F. Lucas, Hanny Pijnenborg, Casper Reijnen, Marco Scutari and Fabio Stella.
Causal Discovery with Missing Data in a Multicentric Clinical Study.
(In-Press) AIME 2023: 21st International Conference of Artificial Intelligence in Medicine (2023).

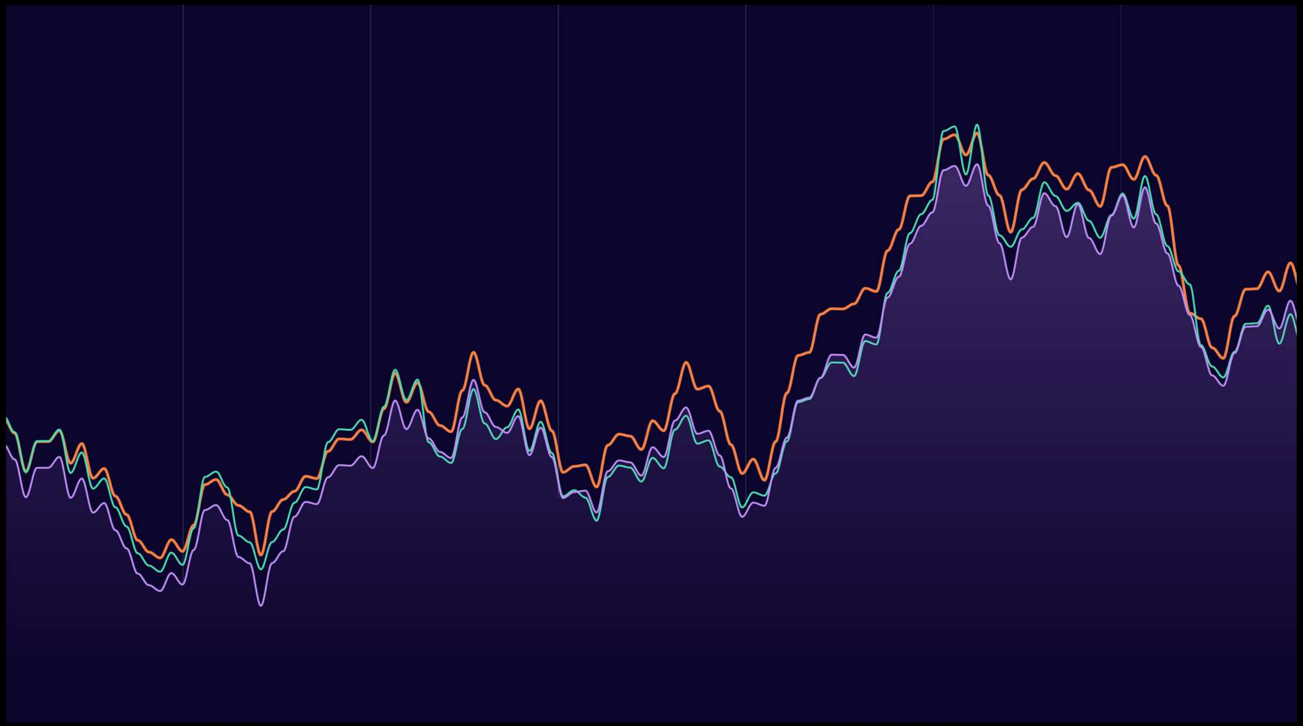
Prediction of Cardiovascular Diseases in Adolescent and Young Breast Cancer Patients

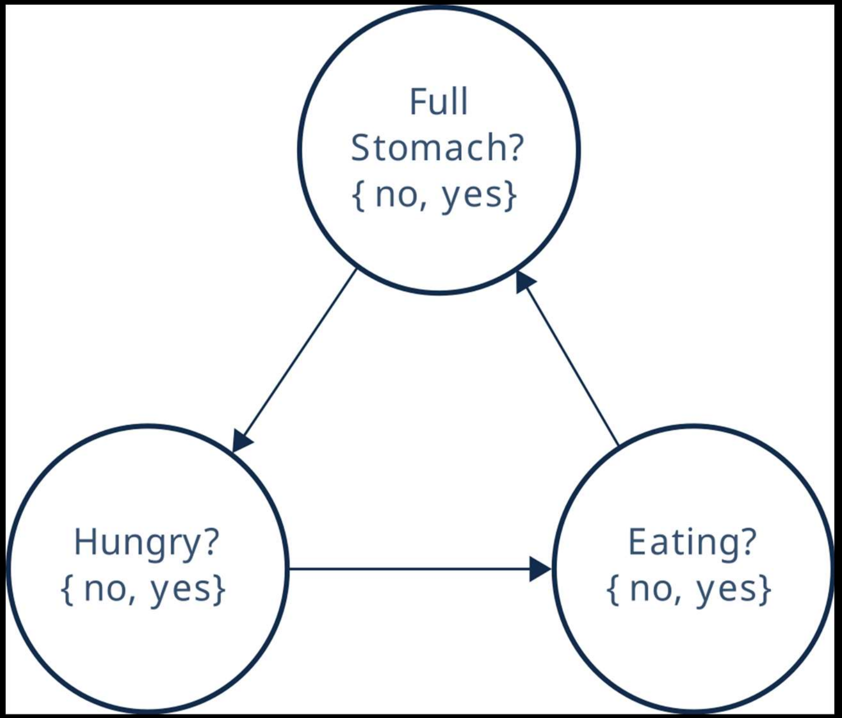


To what extent, with a better understanding of causal mechanisms, it may be possible to identify, predict and explain individual susceptibility to cardiotoxicity prior to starting cancer-related treatments in AYA with BC?

pRedicting cardiOvascular diSeAses iN adolescent and young breast caNcer pAtients (ROSANNA)

Constraint Based Structure Learning for Continuous Time Bayesian Network





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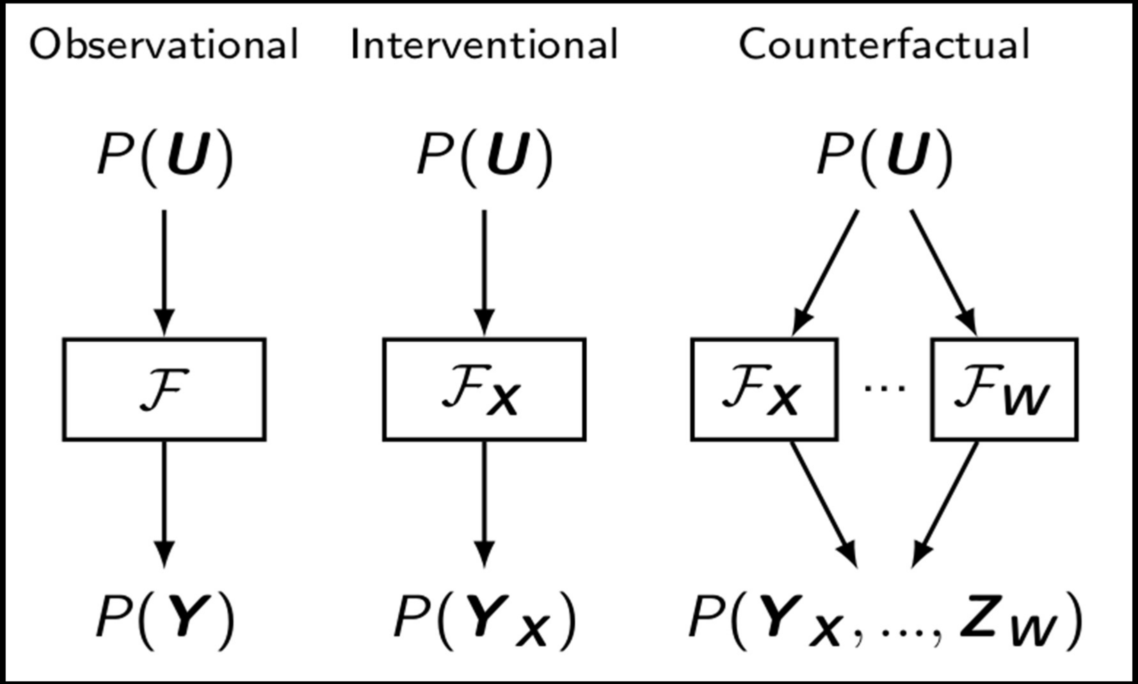
Villa-Blanco, C., Bregoli, A., Bielza, C., Larranaga, P., & Stella, F. (2022, September).
Structure learning algorithms for multidimensional continuous-time Bayesian network classifiers.
In International Conference on Probabilistic Graphical Models (pp. 313-324). PMLR.

Causal Discovery from Interventional Data



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International Journal of Approximate Reasoning 151 (2022): 101-129.

MG-PerMed - Personalising myasthenia gravis medicine: from “one-fits-all” to patient-specific immunosuppression - ERA-PerMed, 01/03/2023-28/02/2026.

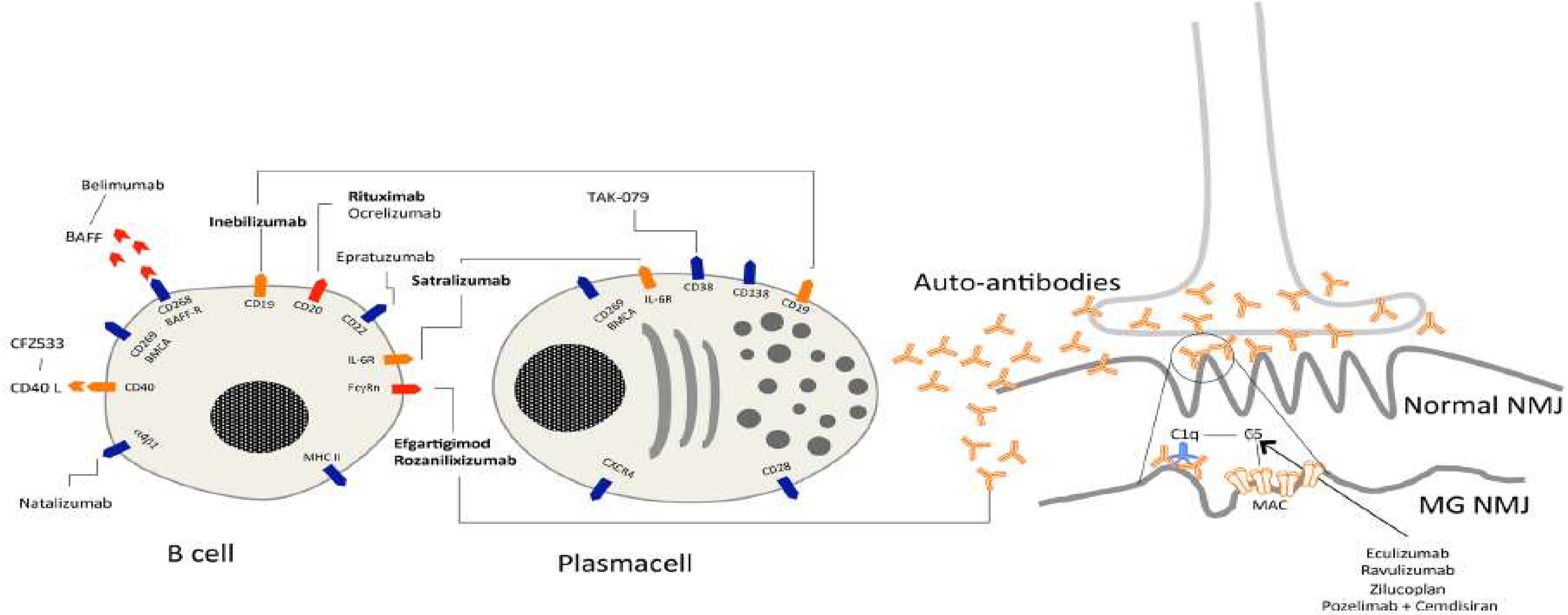
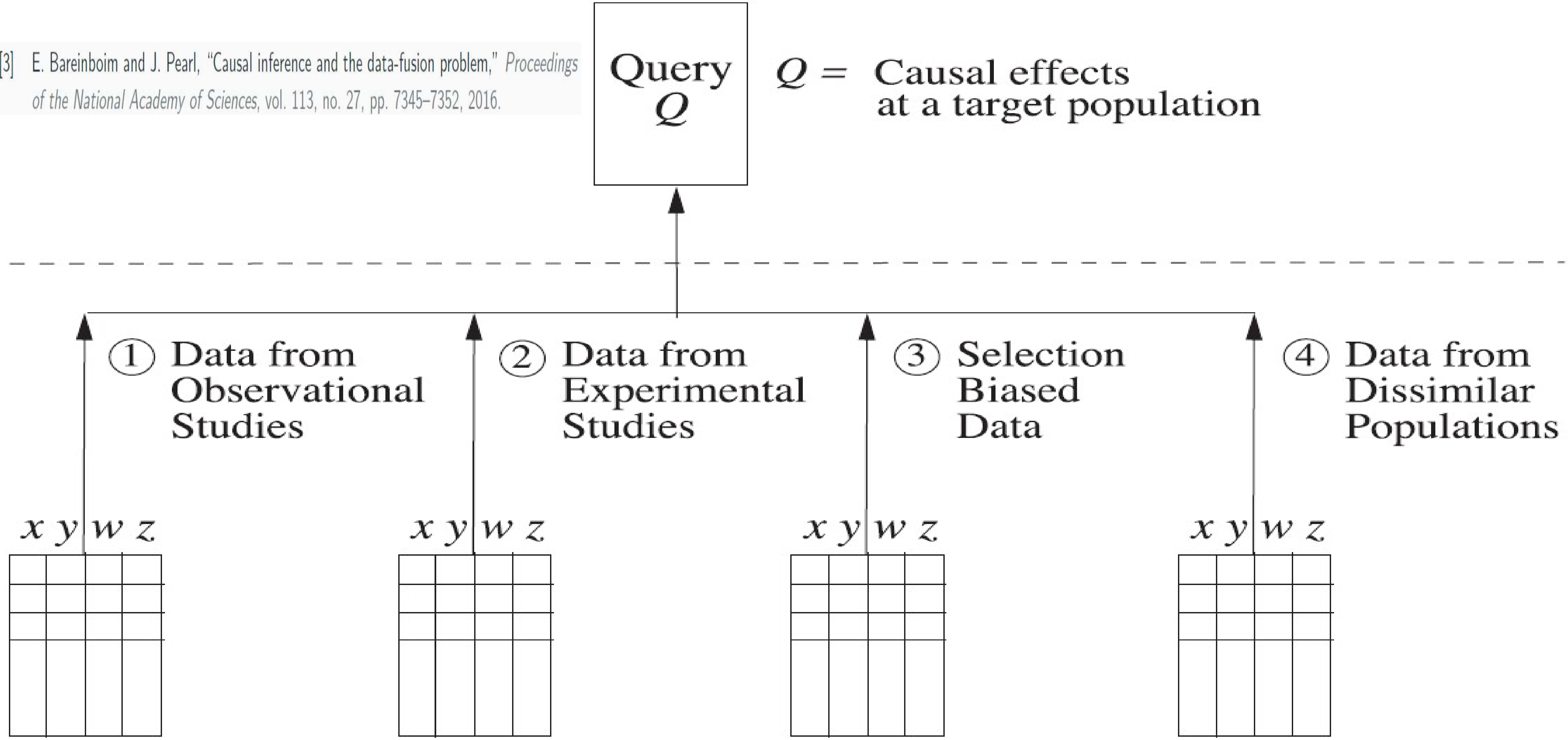


Fig. 1 Schematic representation of the terminal B cells lineage and antibodies involved in the autoimmune attack to the neuromuscular junction. B lymphocytes, plasma cells, and some of the key molecules involved in the immune activation are represented together with available monoclonal antibodies and biologicals targeting CD molecules or receptors. In bold, drugs are effective on different cells. MG, myasthenia gravis; NMJ, neuromuscular junction; MAC, membrane attack complex

Data Fusion and Federated Causal Discovery - "Intelligent Ecosystem to improve the governance, the sharing, and the re-use of health Data for Rare Cancers-IDEA4RC" - 2022-2026

[3] E. Bareinboim and J. Pearl, "Causal inference and the data-fusion problem," *Proceedings of the National Academy of Sciences*, vol. 113, no. 27, pp. 7345–7352, 2016.



Warning!!! Advertisement!!!

— why do I recommend Bayesian (causal) networks? —

Seven reasons for choosing Bayesian (causal) networks

- Exploit domain experts' knowledge — *useful bias*
- Missing data management — *harmful bias*
- Effectively combine experimental and observational data
- Data efficient — *limited amount of data*
- Model uncertainty
- Interpretable
- Effective decision making — *address transportability issues*

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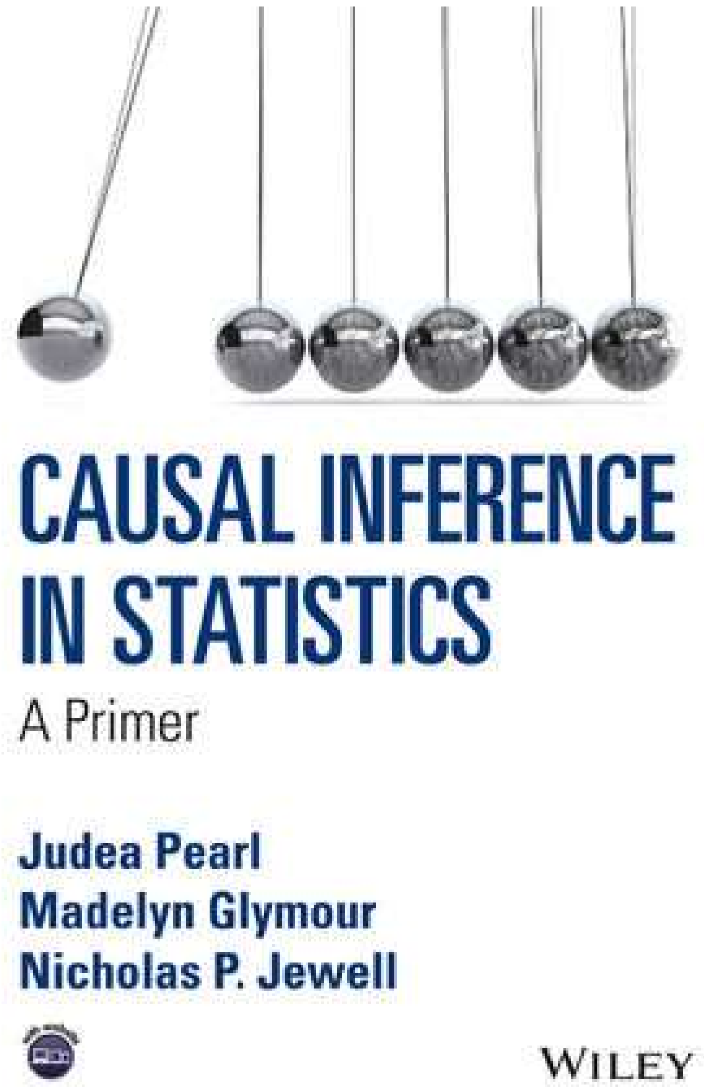
References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DOI:10.1145/3271625
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or Animal-Like
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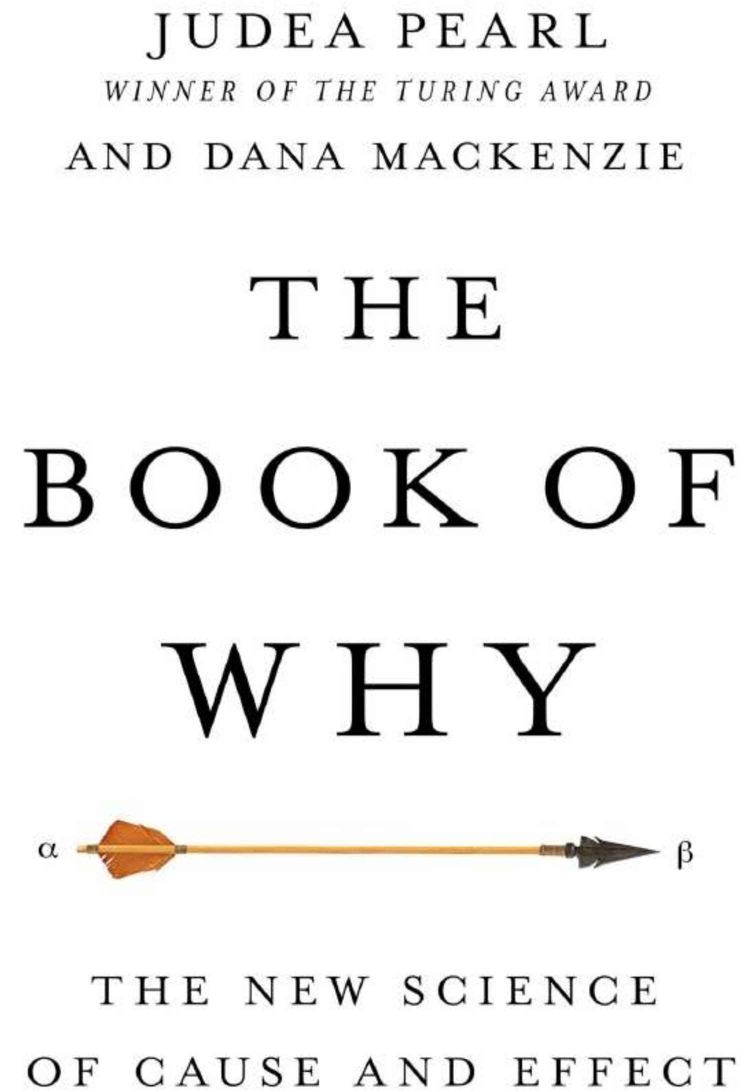
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