
TRANSLATING LITERATURE INTO CAUSAL GRAPHS

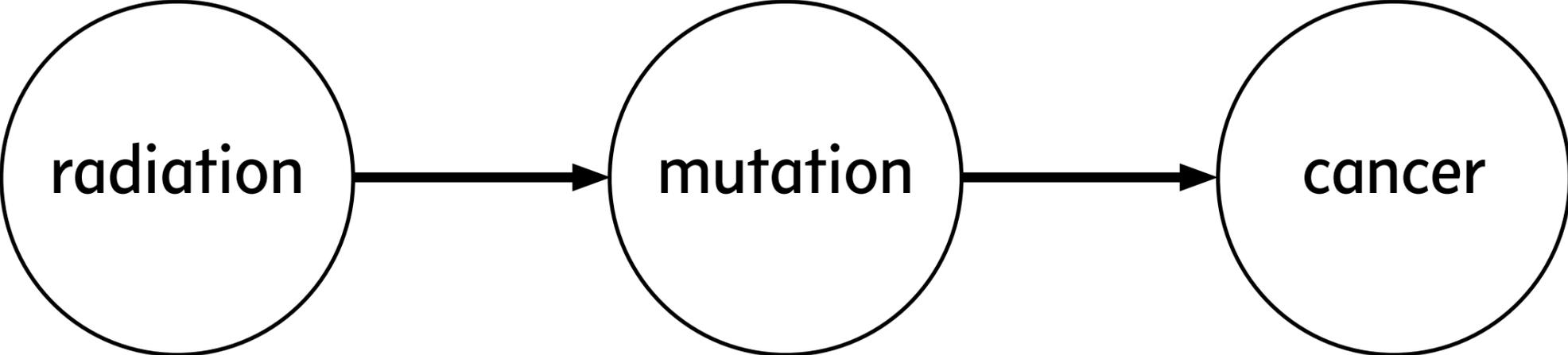
TOWARD AUTOMATED EXPERIMENT SELECTION

NICHOLAS J. MATIASZ

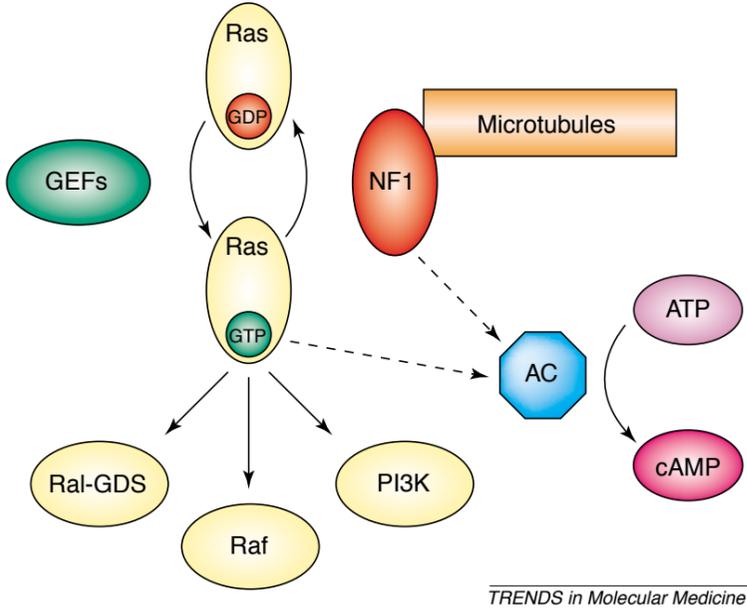
JUSTIN WOOD, WEI WANG, ALCINO J. SILVA, WILLIAM HSU

UCLA

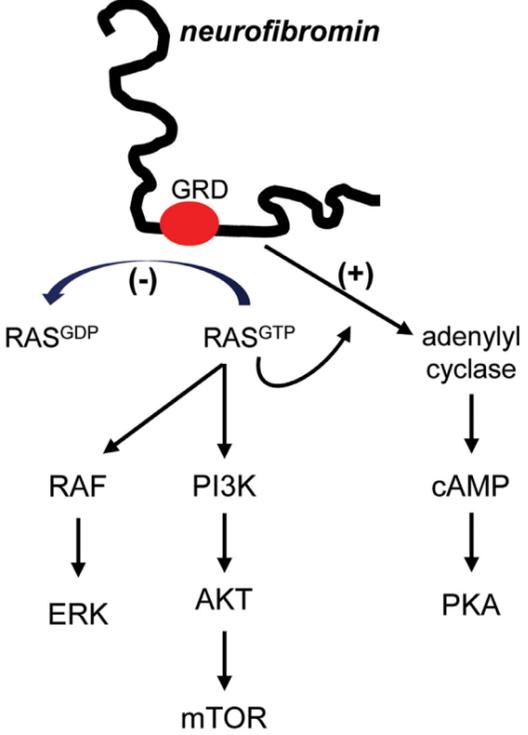
Causal graph



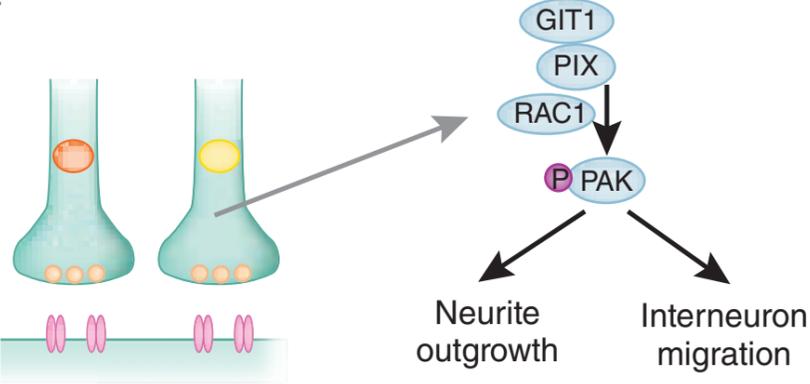
Biological pathway diagrams resemble causal graphs



[1]



[2]



[3]

Biological pathway diagrams can't be stitched together

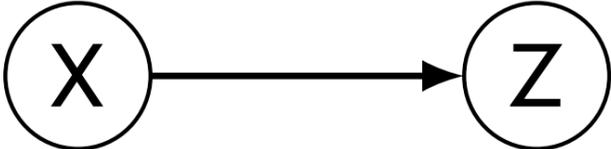
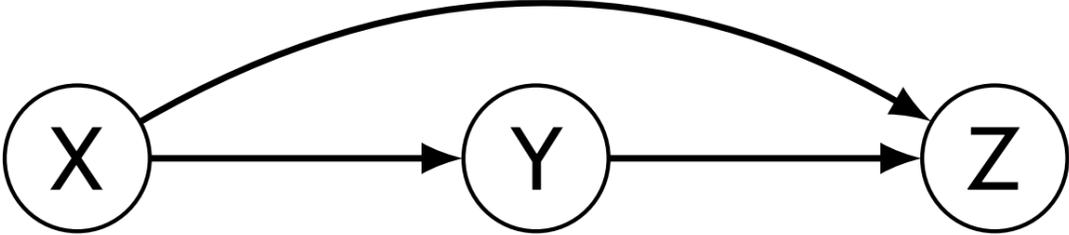


diagram 1



diagram 2

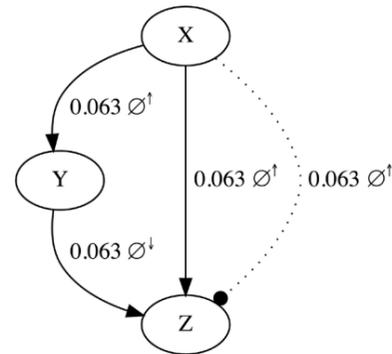


stitched diagram

A pipeline for stitching empirical results



studies in literature



research map



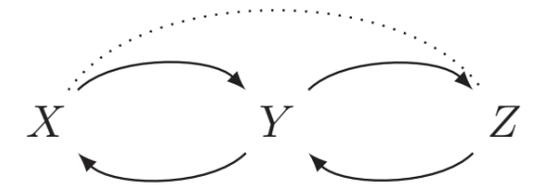
$$\begin{aligned}
 X &\not\perp\!\!\!\perp Y \mid \emptyset \parallel \emptyset \\
 Y &\not\perp\!\!\!\perp Z \mid \emptyset \parallel \emptyset \\
 X &\not\perp\!\!\!\perp Z \mid \emptyset \parallel \emptyset \\
 X &\perp\!\!\!\perp Z \mid Y \parallel \emptyset
 \end{aligned}$$

causal constraints



$$\begin{aligned}
 X &\longrightarrow Y \longrightarrow Z \\
 X &\longleftarrow Y \longrightarrow Z \\
 X &\longleftarrow Y \longleftarrow Z
 \end{aligned}$$

causal graphs

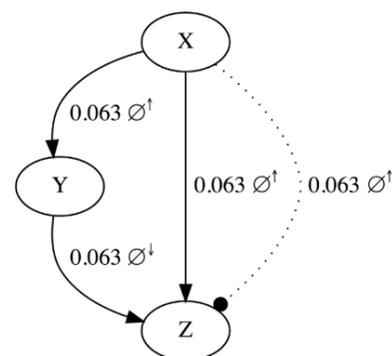


degrees of freedom

A pipeline for stitching empirical results



studies in literature

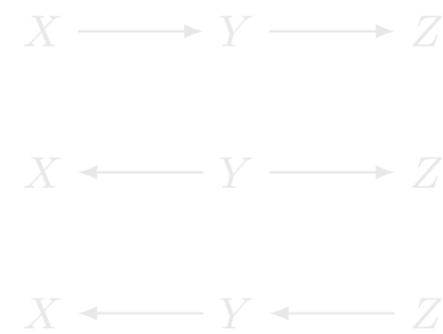


research map

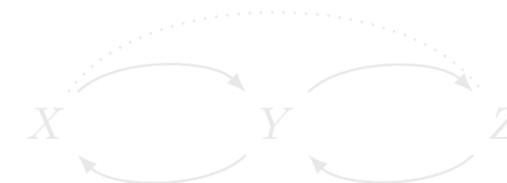


$$\begin{aligned}
 X &\not\perp Y \mid \varnothing \parallel \varnothing \\
 Y &\not\perp Z \mid \varnothing \parallel \varnothing \\
 X &\not\perp Z \mid \varnothing \parallel \varnothing \\
 X &\perp Z \mid Y \parallel \varnothing
 \end{aligned}$$

causal constraints



causal graphs



degrees of freedom

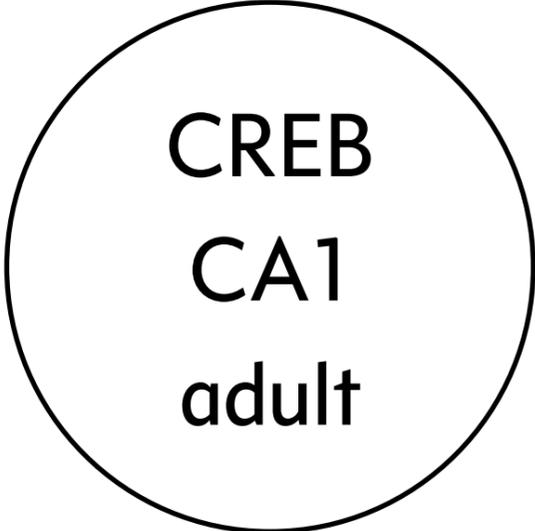
The research map representation

NODE

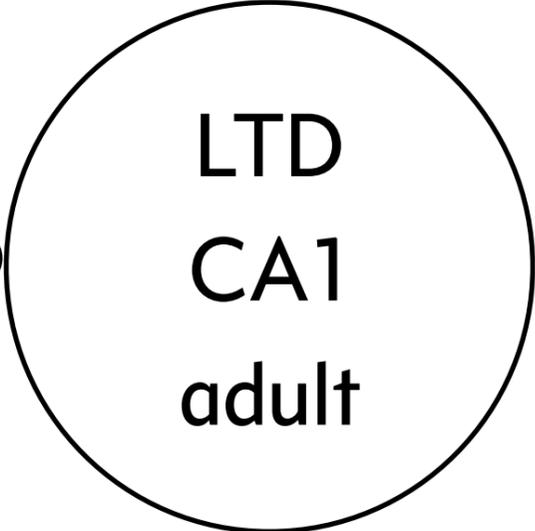
What

Where

When



↑ ∅ ↓



STUDY DESIGN

Intervention

Positive ↑

Negative ↓

Observation

Positive ∅[↑]

Negative ∅[↓]

RELATION

Excitatory →

Inhibitory —|

None●

RESULT

Increase +

No change 0

Decrease -

[4]

Cell, Vol. 87, 1327-1338, December 27, 1996, Copyright © 1996 by Cell Press

The Essential Role of Hippocampal CA1 NMDA Receptor-Dependent Synaptic Plasticity in Spatial Memory

Jin Z. Tain, Patricia T. Hearty, and Suzanne Tonegawa
Howard Hughes Medical Institute
Center for Learning and Memory
Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Summary
We have produced a mouse strain in which the deletion of the NMDAR1 gene is restricted to the CA1 pyramidal cells of the hippocampus by using a new and general method that allows CA1-restricted gene knockout. The mutant mice were subjected to a battery of behavioral tests. Adult mice lose NMDA receptor-mediated synaptic currents and long-term potentiation in the CA1 synapse and exhibit impaired spatial memory but unimpaired nonspatial learning. Our results strongly suggest that activity-dependent modifications of CA1 synapses, mediated by NMDA receptors, play an essential role in the acquisition of spatial memory.

Introduction
It has long been hypothesized that memory storage in the mammalian brain involves modifications of the synaptic connections between neurons. Hebb (1949) introduced an influential theory consisting of principles that neurons must exhibit for implementing associative memory. An important principle, known as the Hebb rule, is that "constituted activity" when the presynaptic and postsynaptic neurons are active simultaneously, their connections become strengthened. It is well established that NMDA-type glutamate receptors (NMDARs) can implement Hebb's rule at the synaptic level, and they are thus considered the crucial synaptic elements for the induction of activity-dependent synaptic plasticity. NMDARs act as coincidence detectors because they require both presynaptic activity (glutamate released by an active terminal) and postsynaptic activity (depolarization that relieves the Mg²⁺ block) as a condition for channel opening (Mayer et al., 1984; Moradpour and Mayer, 1996). Active NMDAR channels allow calcium influx into the postsynaptic cell, which triggers a cascade of biochemical events resulting in synaptic changes. Long-term potentiation (LTP) is a widely used paradigm for measuring synaptic efficacy, and its induction requires, in at least one of its forms, the activation of NMDARs (Bliss and Lomo, 1973; Bliss and Collingridge, 1993). Conventionally, NMDAR-dependent LTP is elicited by giving a strong pattern of electrical stimulation (25–100 Hz train for 1 s to 10 s), which triggers a rapid and lasting increase in synaptic strength.

The hippocampus is the most intensively studied region for the importance of NMDARs in synaptic plasticity and memory. It is well known that lesions of the hippocampus in humans and other mammals produce severe amnesia for certain memories (Bliss and Mizser, 1987; Morris et al., 1982; Zola-Morgan et al., 1985; reviewed by Squire, 1987). Importantly, it has been demonstrated that blockade of NMDARs in the hippocampus leads to blockade of synaptic plasticity and also to memory impairment (reviewed by Morris et al., 1991). Recently, and Nicol, 1990; Harris and Gustafsson, 1992; Morris et al., 1993) were the first to show that rats that received infusion of AP5 into the hippocampus were deficient in performing a spatial memory task in which the animals are required to form multiple spatial relations between a hidden platform in a circular pool located on a water maze) and visible objects in the surrounding environment and swim to the platform to escape from the water. Subsequently, this issue was reinvestigated by using "gene knockout" mice. These genetically engineered mice lack a gene encoding a component that is thought to be at the downstream of activated NMDARs in the biochemical cascade for LTP induction (reviewed by Chen and Tonegawa, 1997). For example, mice with a deletion in the gene encoding the a subunit of calcium-calmodulin-dependent protein kinase II (CaMKII) display impaired LTP in the CA1 region of the hippocampus and a deficit in spatial learning (Suzuki et al., 1992a, 1992b).

Even though the results of these genetic and pharmacological experiments are consistent with the notion that hippocampal LTP is the synaptic mechanism for spatial memory, other interpretations cannot be excluded. For instance, in the case of the gene knockout mice, even in the region lacking the gene of interest, consequently, all of the functions of the gene product, not only its role in LTP induction, are affected in the mutant. Hence, it is possible that spatial memory is independent of hippocampal LTP and that the memory deficit in mutants arises from lack of the gene product in other functions (such as developmental roles). Likewise, in pharmacological studies the target of the AP5 infusion is not restricted to the hippocampus (Buckley et al., 1991). Therefore, NMDARs expressed in neurons in the neighboring neocortex (and other brain areas) are also inhibited to a varying extent. Since NMDARs continue to act as coincidence detectors for the induction of excitatory synapses in the neocortex (reviewed by Christie, 1996), it is likely that the infused AP5 may impair not only LTP induction in the hippocampus but also the computational ability of neocortical regions that play an important role in spatial memory.

A more definitive method to test the hypothesis that the deletion is restricted to a certain region of a certain cell type within the brain. As described in the accompanying article (Tain et al., 1996 [this issue of Cell]), we have exploited the Cre/loxP recombination system derived

[5]

Autophosphorylation at Thr²⁸⁶ of the α Calcium-Calmodulin Kinase II in LTP and Learning

Karl Peter Giese, Nikolai B. Fedorov, Robert K. Filipkowski, Alcino J. Silva*

The calcium-calmodulin-dependent kinase II (CaMKII) is required for hippocampal long-term potentiation (LTP) and spatial learning. In addition to its calcium/calmodulin-dependent activity, CaMKII can undergo autophosphorylation, resulting in CaMKII-independent activity. A point mutation was introduced into the αCaMKII gene that blocked the autophosphorylation of threonine at position 286 (Thr²⁸⁶) of this kinase without affecting its CaMKII-dependent activity. The mutant mice had no memory impairment in the Morris water maze. Thus, the autophosphorylation of CaMKII at Thr²⁸⁶ appears to be required for LTP and learning.

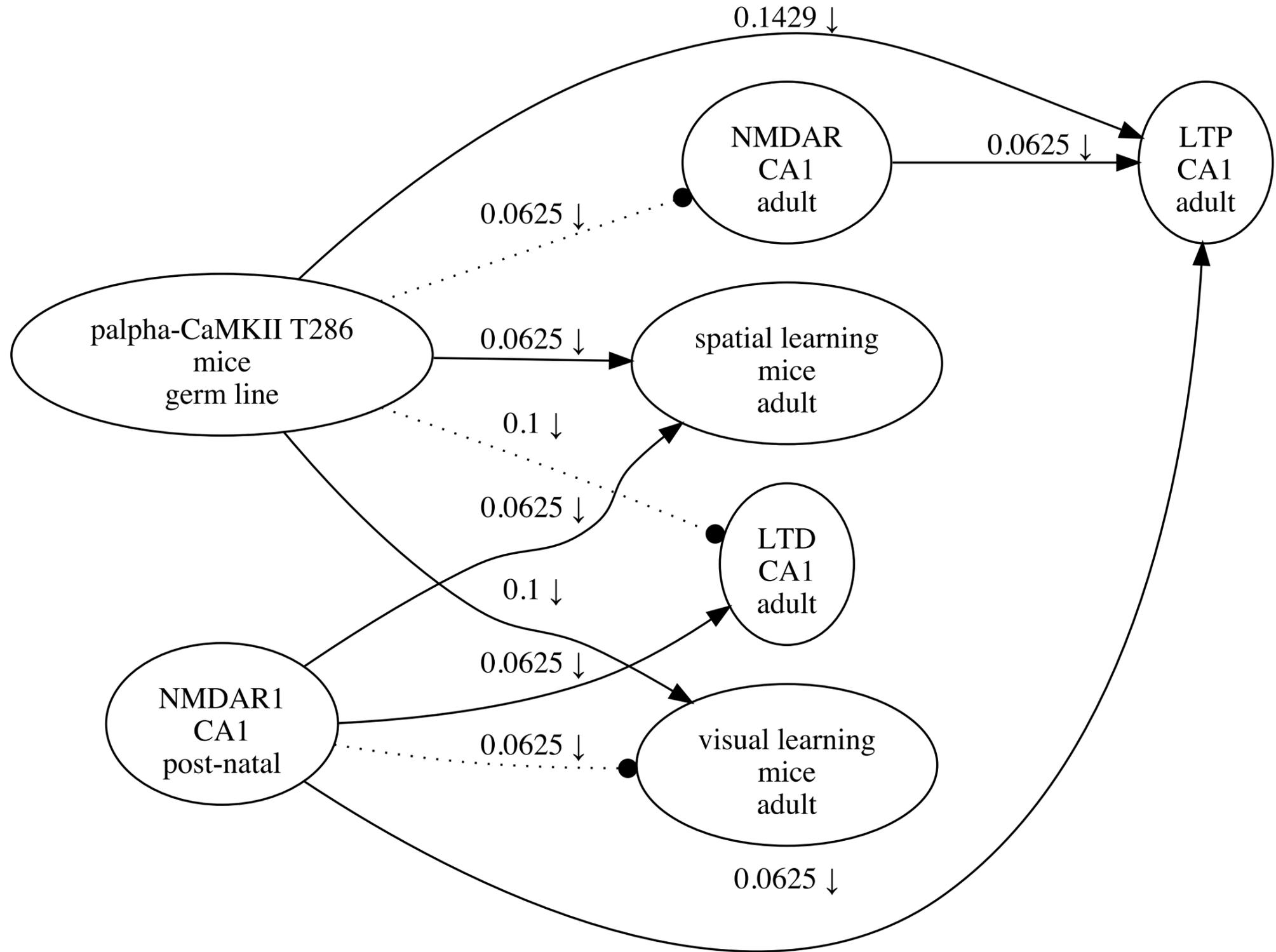
Long-term changes in synaptic strength (LTP) are thought to underlie learning and memory. It is well established that the calcium-calmodulin-dependent kinase II (CaMKII) is required for hippocampal long-term potentiation (LTP) and spatial learning. In addition to its calcium/calmodulin-dependent activity, CaMKII can undergo autophosphorylation, resulting in CaMKII-independent activity. A point mutation was introduced into the αCaMKII gene that blocked the autophosphorylation of threonine at position 286 (Thr²⁸⁶) of this kinase without affecting its CaMKII-dependent activity. The mutant mice had no memory impairment in the Morris water maze. Thus, the autophosphorylation of CaMKII at Thr²⁸⁶ appears to be required for LTP and learning.

CaMKII is a serine/threonine kinase that is activated by calcium and calmodulin. It is a major component of the postsynaptic density and is involved in a variety of cellular processes, including synaptic plasticity, cell cycle regulation, and cell differentiation. The α isoform of CaMKII is the most abundant and is the primary isoform involved in LTP and learning. The αCaMKII gene encodes a protein of 468 amino acids, with a conserved catalytic domain and a regulatory domain. The regulatory domain contains several phosphorylation sites, including Thr²⁸⁶, which is the site of autophosphorylation. Autophosphorylation at Thr²⁸⁶ is thought to be required for the sustained activity of CaMKII during LTP and learning.

Methods used in this study include: generation of αCaMKII^{Thr286} mutant mice using Cre/loxP recombination; behavioral testing in the Morris water maze; electrophysiological recordings from hippocampal slices; immunoblotting and immunoprecipitation; and in vitro kinase assays.

Results show that αCaMKII^{Thr286} mutant mice exhibit normal spatial learning and LTP induction in the hippocampus. However, there is a significant reduction in the amplitude of LTP in these mice compared to wild-type controls. This suggests that autophosphorylation at Thr²⁸⁶ is required for the full expression of LTP, but not for its induction. The mutant mice also show normal spatial learning, indicating that the autophosphorylation of CaMKII at Thr²⁸⁶ is not essential for learning per se, but rather for the synaptic plasticity changes that underlie learning.

Conclusions drawn from this study are that: (1) Autophosphorylation of CaMKII at Thr²⁸⁶ is required for the full expression of LTP in the hippocampus. (2) The autophosphorylation of CaMKII at Thr²⁸⁶ is not essential for learning in the Morris water maze. (3) The autophosphorylation of CaMKII at Thr²⁸⁶ is a key event in the signaling pathway that links LTP to learning.



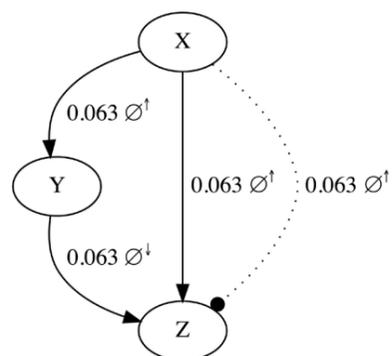
studies in literature

research map

A pipeline for stitching empirical results



studies in literature



research map



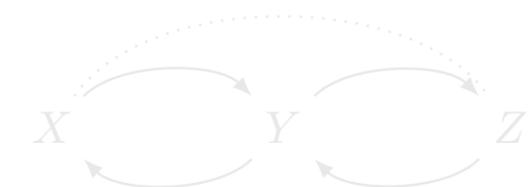
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causal constraints



$$\begin{aligned} X &\longrightarrow Y \longrightarrow Z \\ X &\longleftarrow Y \longrightarrow Z \\ X &\longleftarrow Y \longleftarrow Z \end{aligned}$$

causal graphs



degrees of freedom

Constraint on causal structure

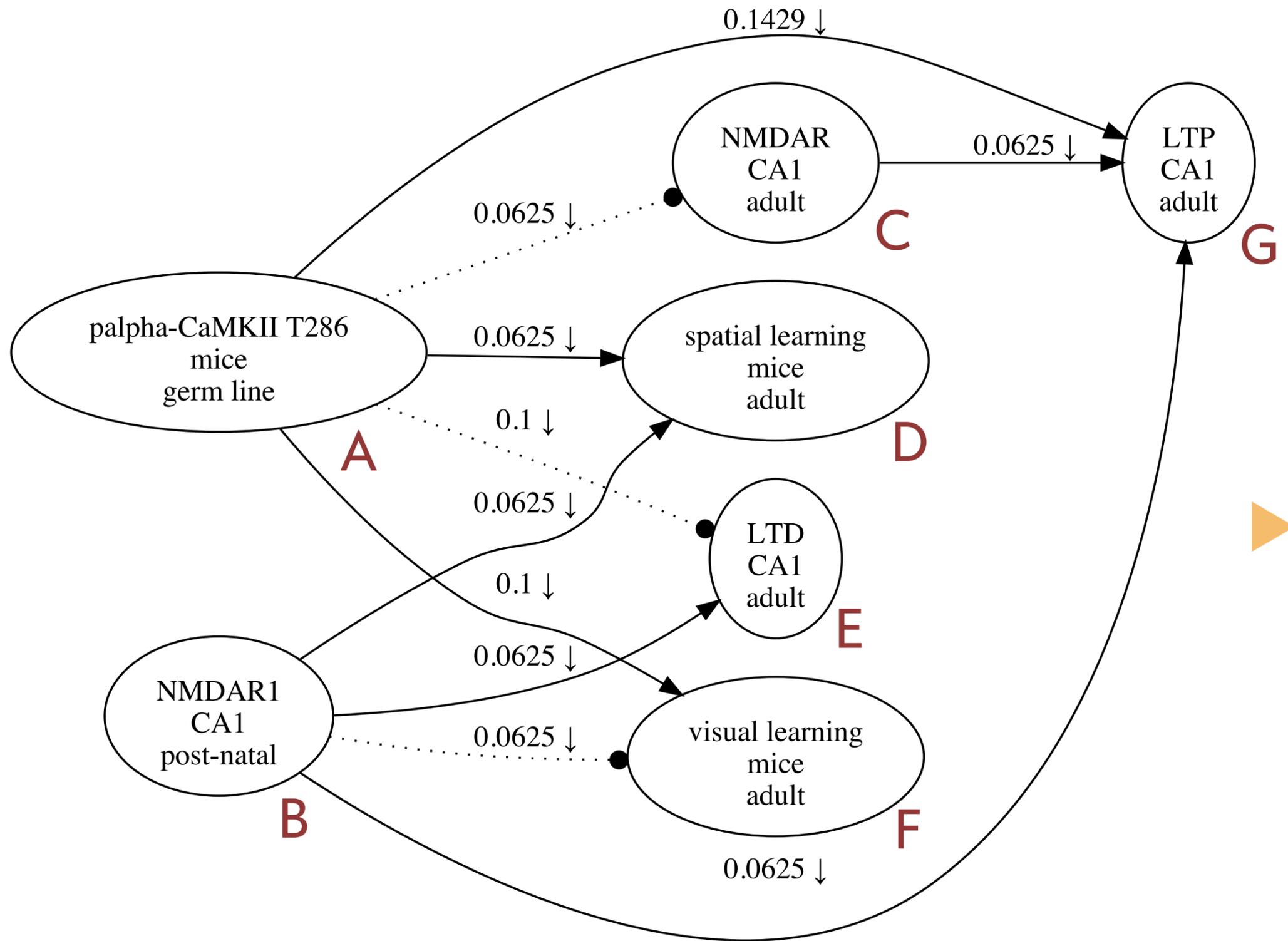
$$X \perp\!\!\!\perp Y \mid \mathbf{C} \parallel \mathbf{J}$$

X and Y are **independent**, conditioned on set **C**, intervening on set **J**

$$X \not\perp\!\!\!\perp Y \mid \mathbf{C} \parallel \mathbf{J}$$

X and Y are **dependent**, conditioned on set **C**, intervening on set **J**

C and **J** can be the empty set (\emptyset)



research map

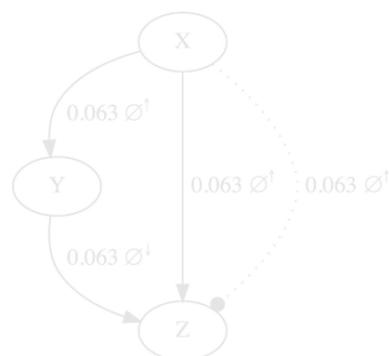
causal constraints

A	⊥	G		∅		A
A	⊥	C		∅		A
A	⊥	D		∅		A
A	⊥	E		∅		A
A	⊥	F		∅		A
B	⊥	D		∅		B
B	⊥	E		∅		B
B	⊥	F		∅		B
B	⊥	G		∅		B
C	⊥	G		∅		C

A pipeline for stitching empirical results



studies in literature



research map



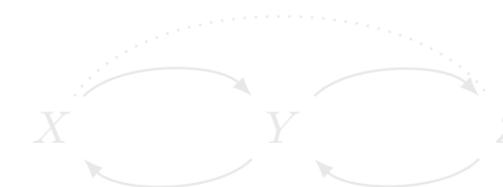
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causal constraints



$$\begin{aligned} X &\longrightarrow Y \longrightarrow Z \\ X &\longleftarrow Y \longrightarrow Z \\ X &\longleftarrow Y \longleftarrow Z \end{aligned}$$

causal graphs



degrees of freedom

Constraint-based Causal Discovery: Conflict Resolution with Answer Set Programming [6]

Antti Hyttinen and **Frederick Eberhardt**

California Institute of Technology
Pasadena, CA, USA

Matti Järvisalo

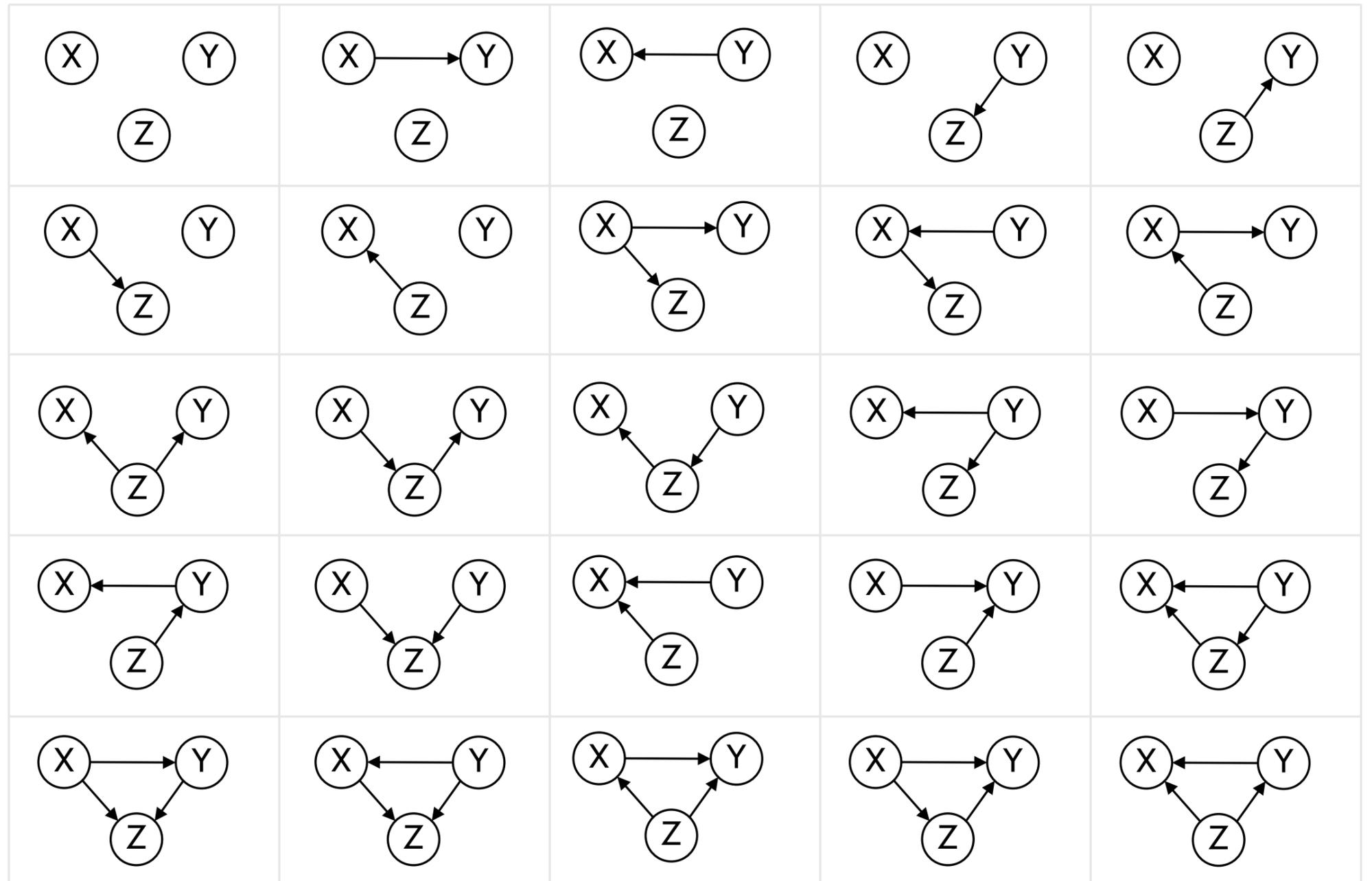
HIIT & Department of Computer Science
University of Helsinki, Finland

Abstract

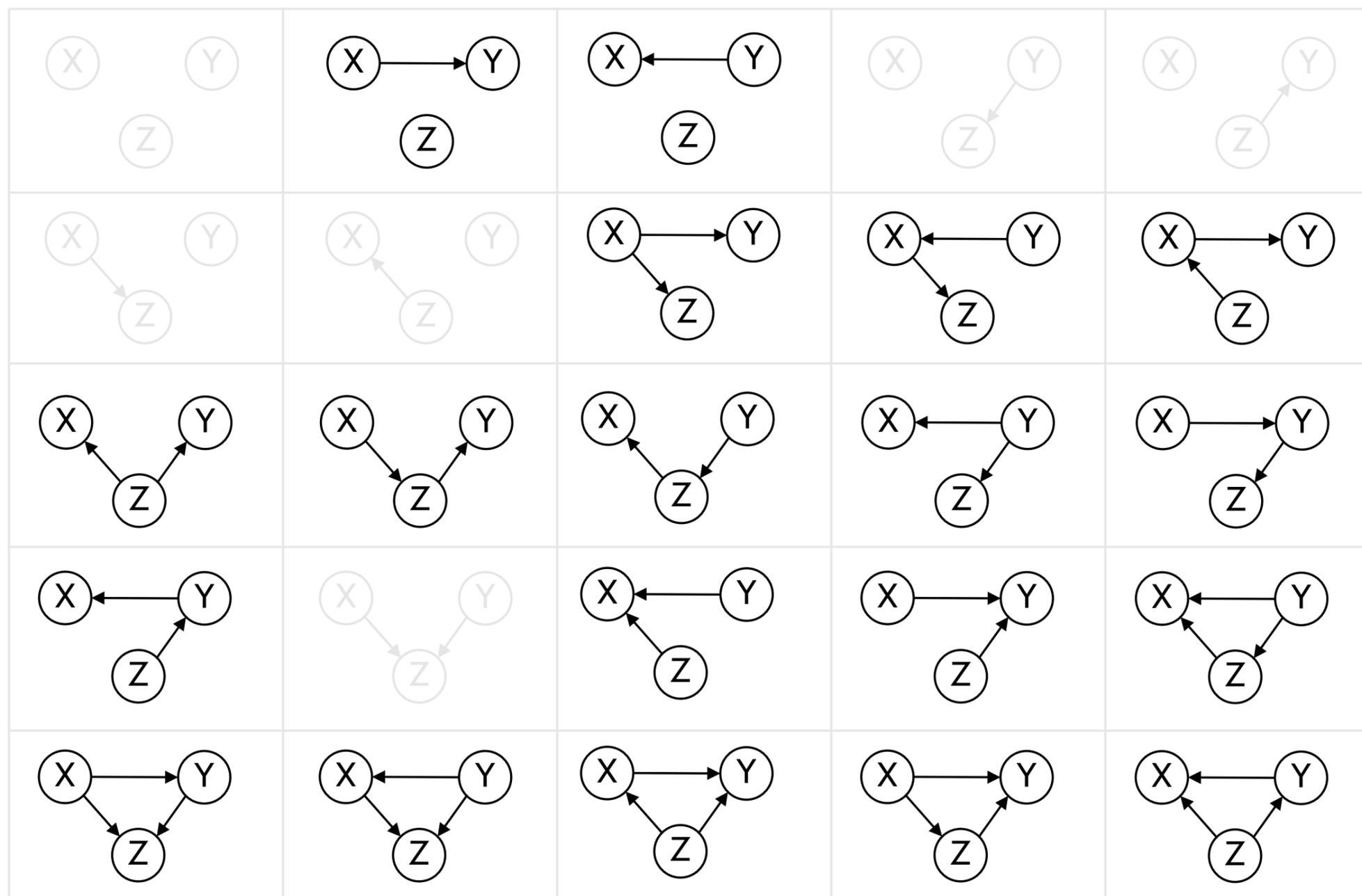
Recent approaches to causal discovery based on Boolean satisfiability solvers have opened new opportunities to consider search spaces for causal models with both feedback cycles and unmeasured confounders. However, the available methods have so far not been able to provide a principled account of how to handle conflicting constraints that arise from statistical variability. Here we present a new approach that preserves the versatility of Boolean constraint solving *and* attains a high accuracy despite the presence of statisti-

faithfulness (Spirtes et al., 1993). Unlike many other approaches, these constraint-based causal discovery methods can allow for the presence of latent confounders, feedback cycles and the utilisation of several (partially overlapping) observational or experimental data sets.

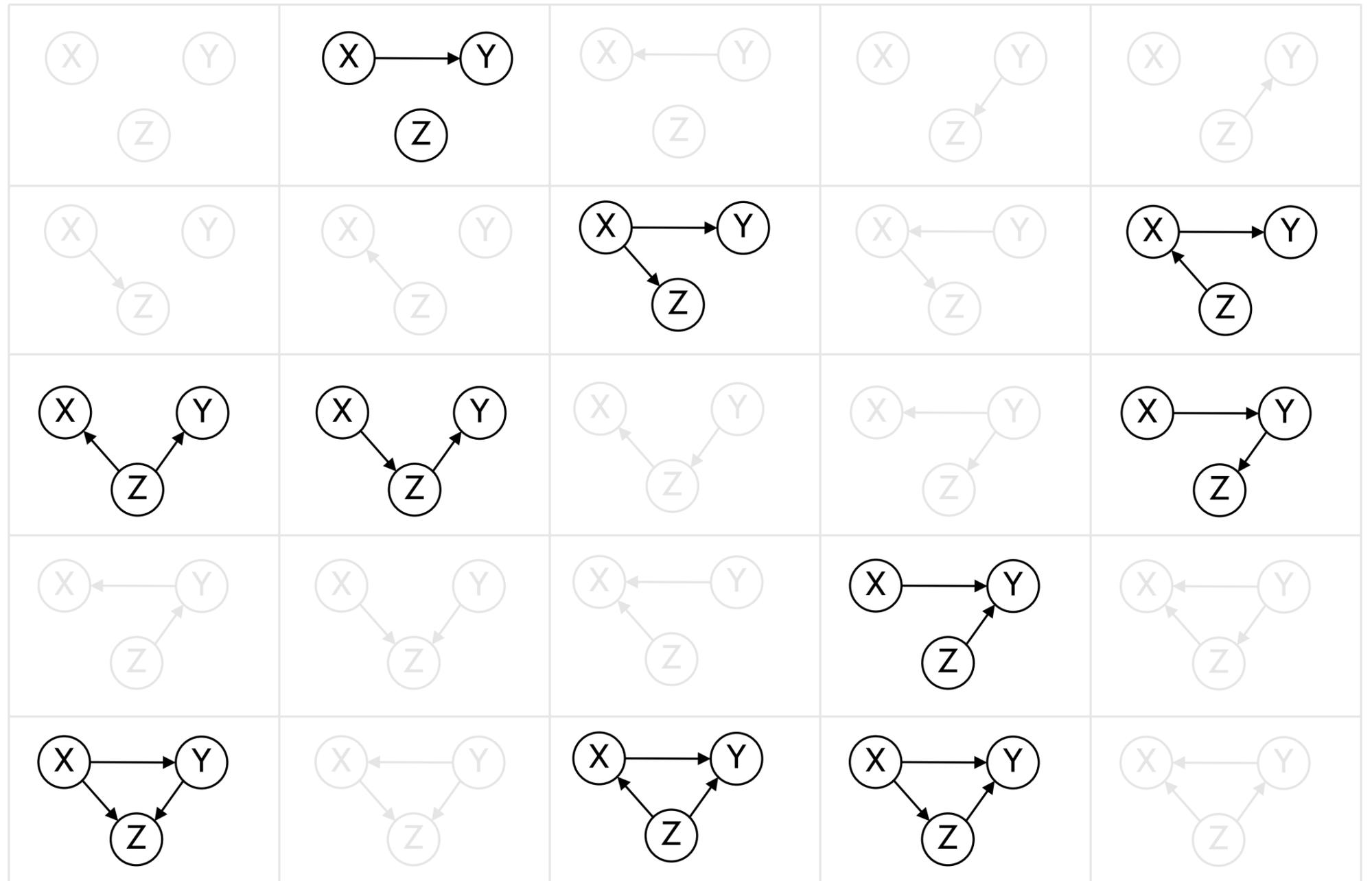
Even without experimentation (or additional assumptions, such as time order), and despite the generality of the model space, constraint-based methods can infer some causal orientations on the basis of *v-structures* (unshielded colliders). A v-structure in a graph is a triple of variables, such as $\langle x, z, y \rangle$ in Figure 1, where z is a common child of x and y , but x and y are non-adjacent in the graph. V-structures can be identified because of the specific (in)dependence rela-



$X \perp\!\!\!\perp Y \mid \emptyset \parallel \emptyset$



$X \perp\!\!\!\perp Y \mid \emptyset \parallel \emptyset$
 $X \perp\!\!\!\perp Y \mid \emptyset \parallel Y$



$X \perp\!\!\!\perp Y \mid \emptyset \parallel \emptyset$
 $X \perp\!\!\!\perp Y \mid \emptyset \parallel Y$

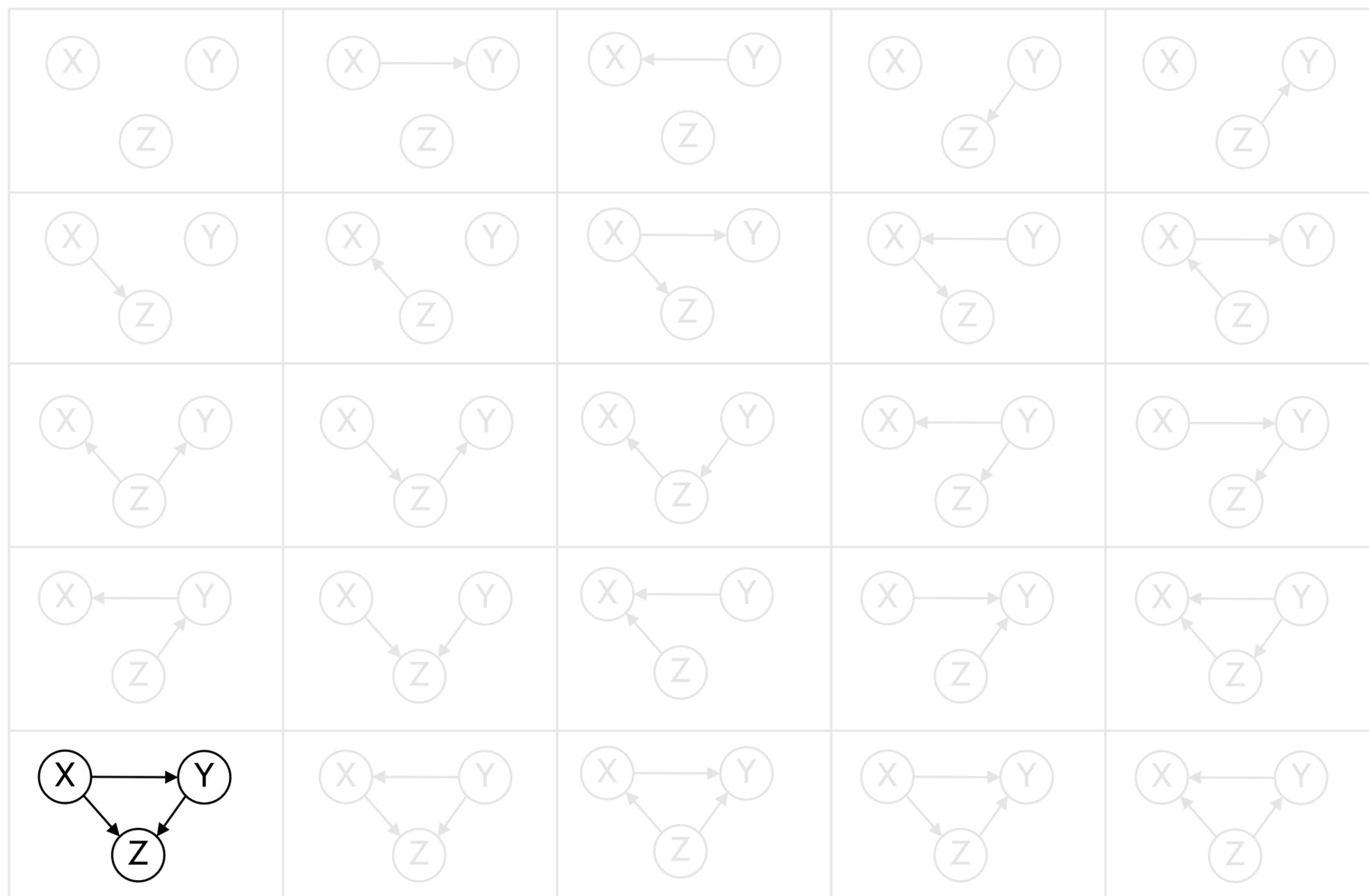
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$X \perp\!\!\!\perp Y \mid \emptyset \parallel \emptyset$
 $X \perp\!\!\!\perp Y \mid \emptyset \parallel Y$

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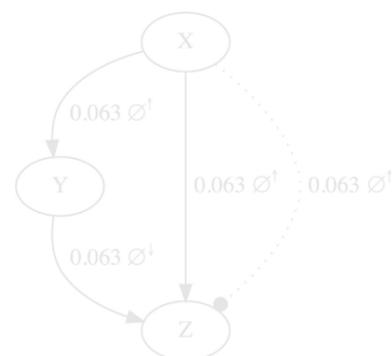
With conflicting constraints, we minimize
 the summed weight of unsatisfied constraints.

$$G^* \in \operatorname{argmin}_{G \in \mathcal{G}} \sum_{k \in \mathbf{K}: G \neq k} w(k) \quad [6]$$

A pipeline for stitching empirical results



studies in literature



research map



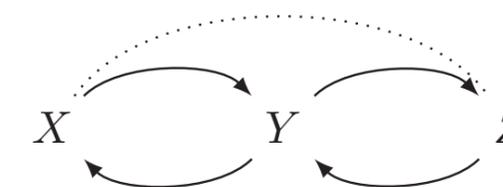
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causal constraints



$$\begin{aligned} X &\longrightarrow Y \longrightarrow Z \\ X &\longleftarrow Y \longrightarrow Z \\ X &\longleftarrow Y \longleftarrow Z \end{aligned}$$

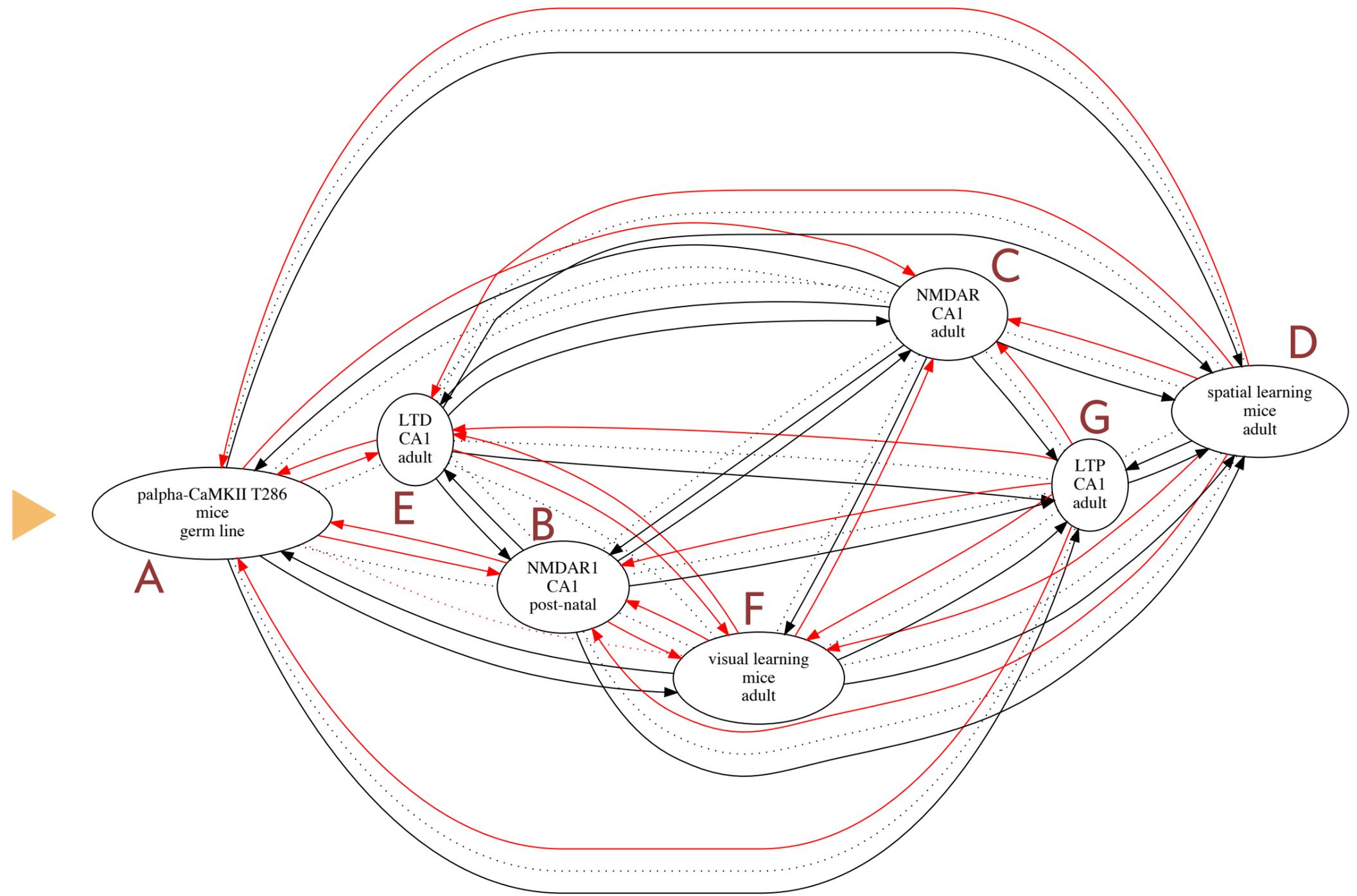
causal graphs

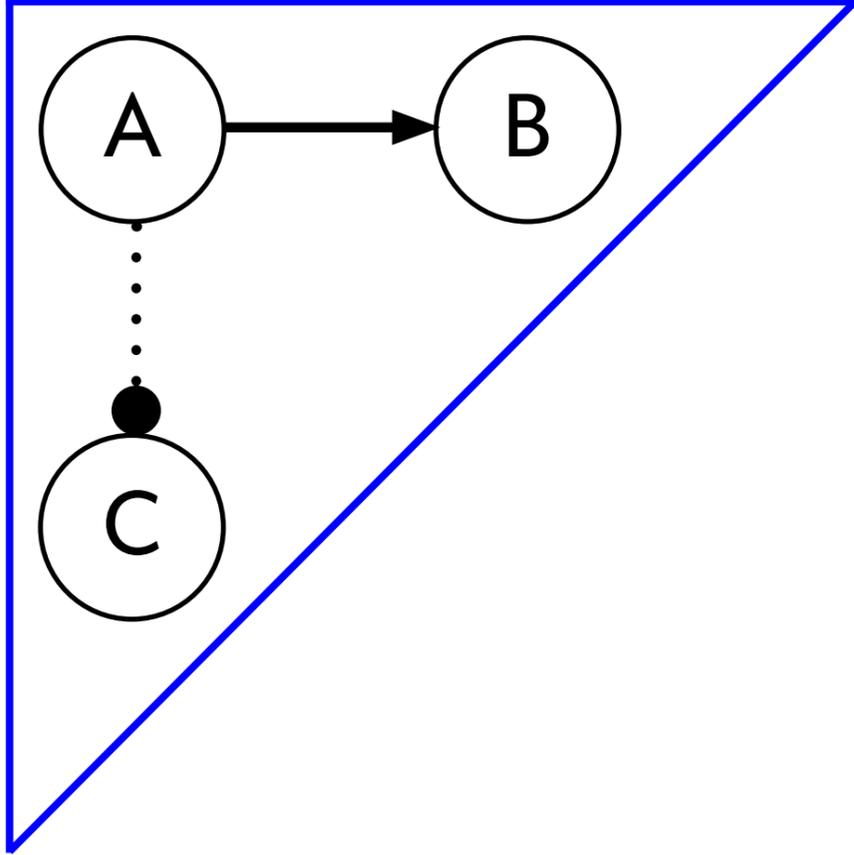


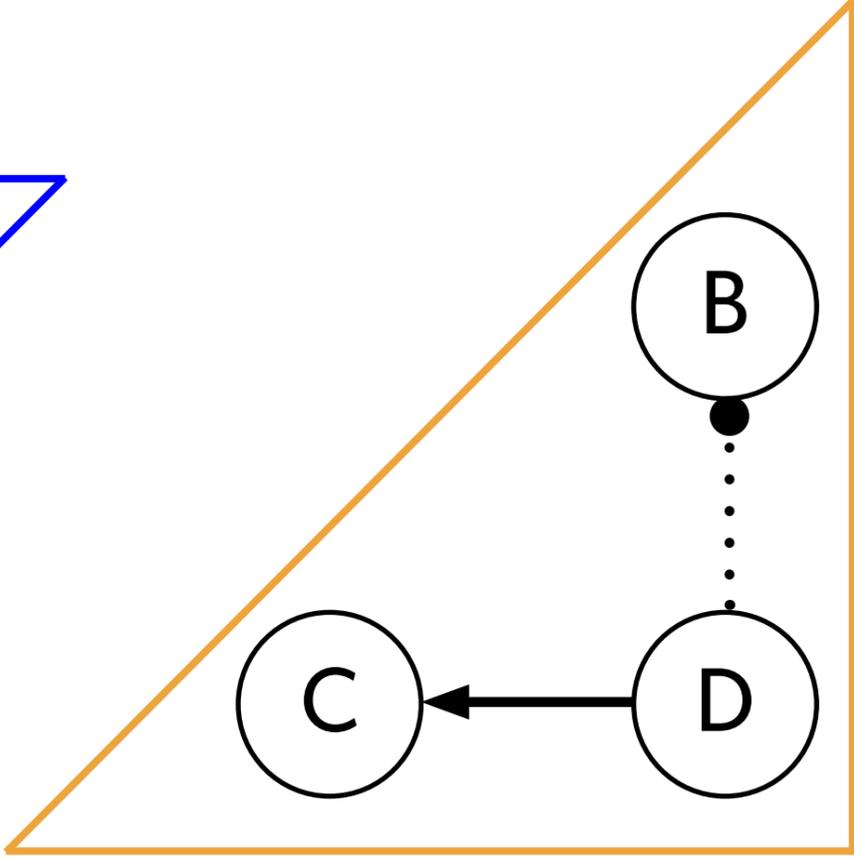
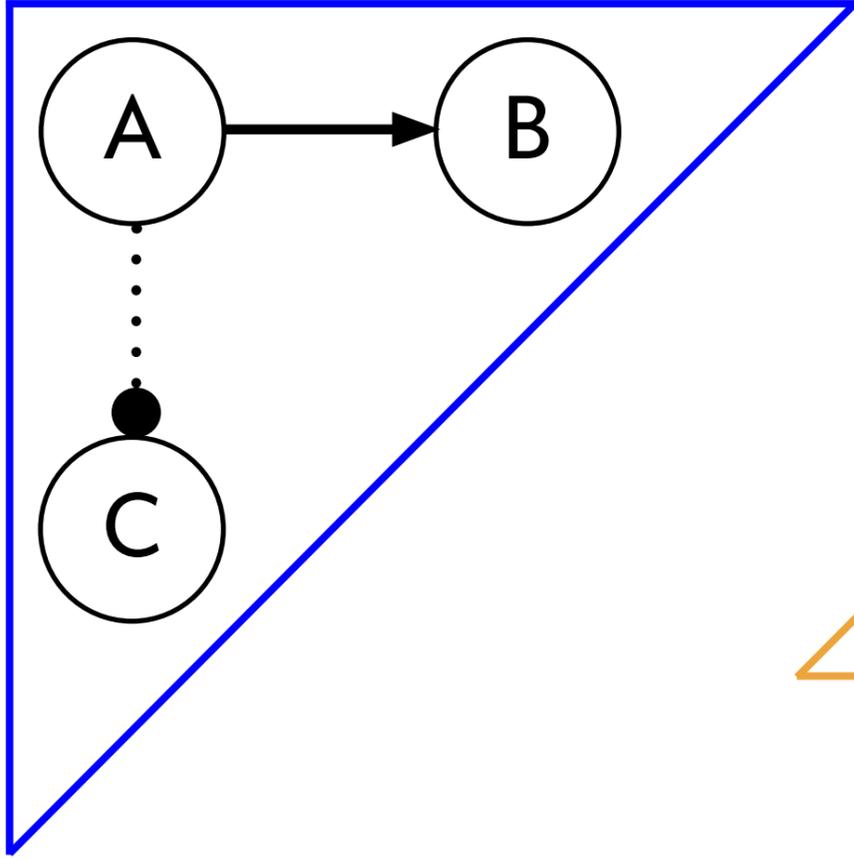
degrees of freedom

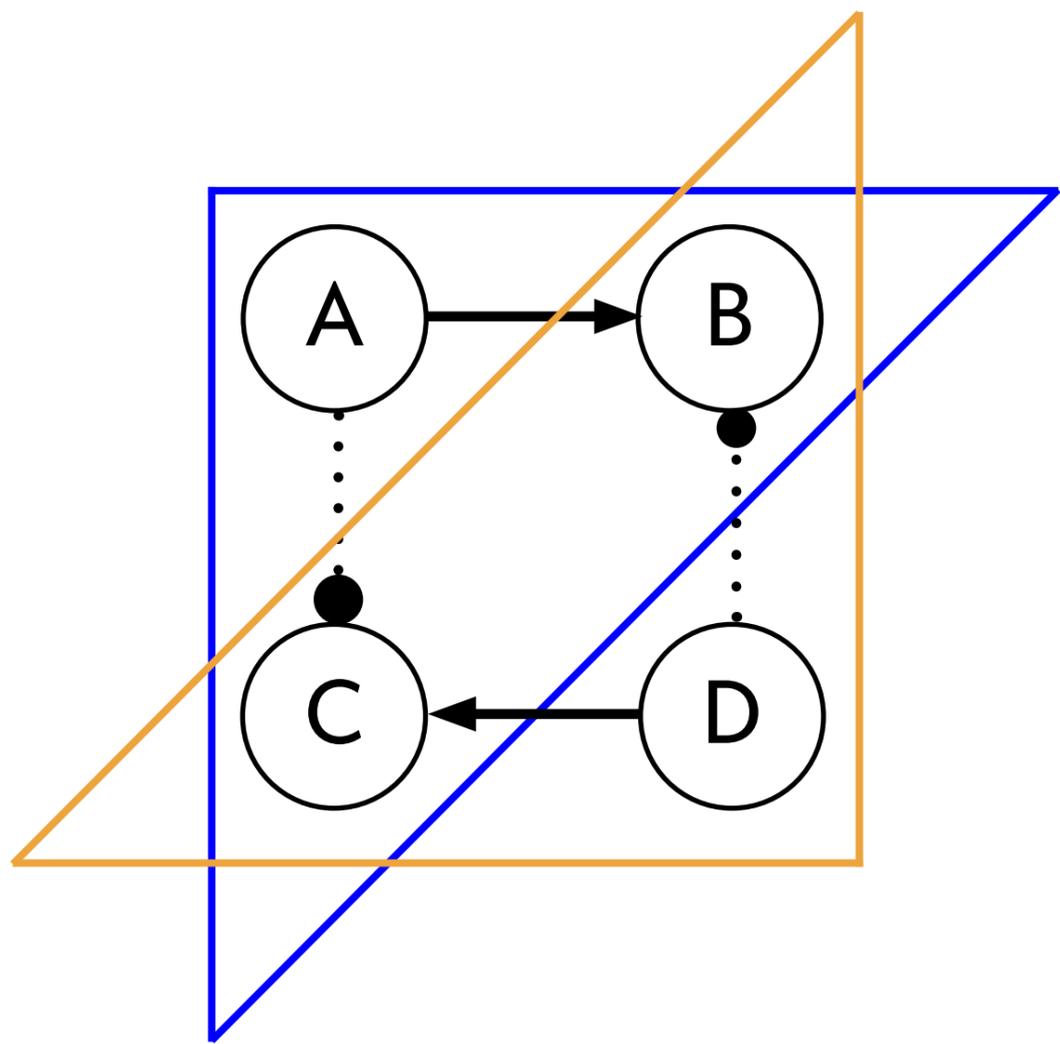
A	U	G		∅		A
A	⊥	C		∅		A
A	U	D		∅		A
A	⊥	E		∅		A
A	U	F		∅		A
B	U	D		∅		B
B	U	E		∅		B
B	⊥	F		∅		B
B	U	G		∅		B
C	U	G		∅		C

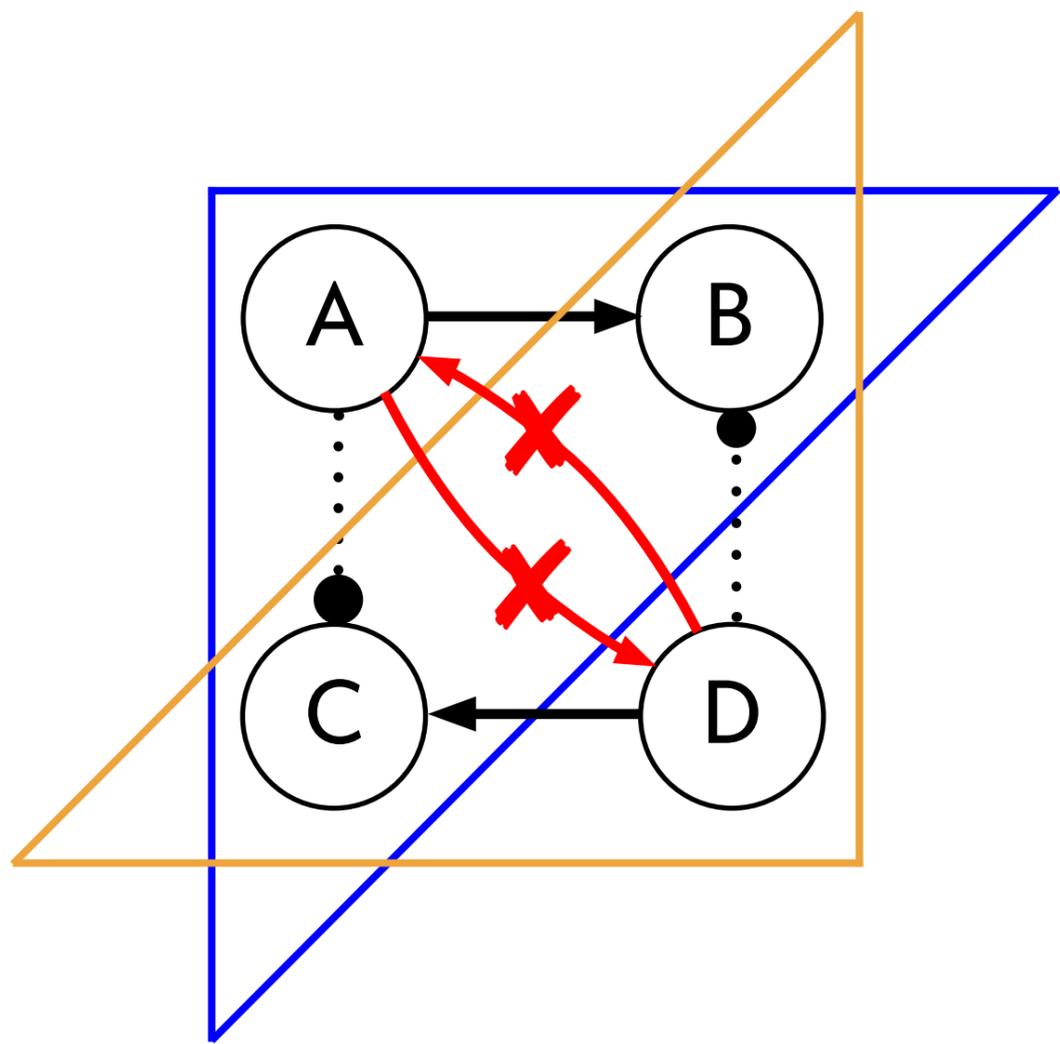
edge(A,B)?







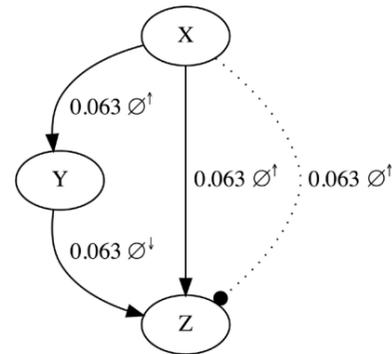




A pipeline for stitching empirical results



studies in literature

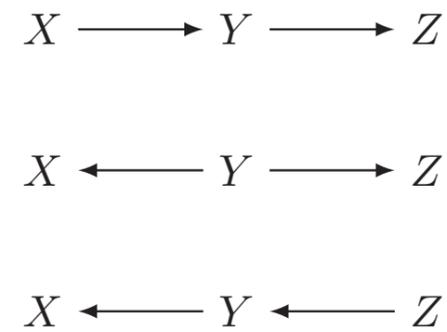


research map

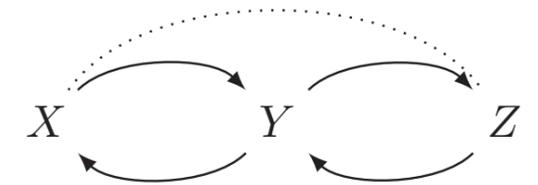


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 Y &\not\perp\!\!\!\perp Z \mid \emptyset \parallel \emptyset \\
 X &\not\perp\!\!\!\perp Z \mid \emptyset \parallel \emptyset \\
 X &\perp\!\!\!\perp Z \mid Y \parallel \emptyset
 \end{aligned}$$

causal constraints



causal graphs



degrees of freedom

- [1] R. M. Costa & A. J. Silva (2003). Mouse models of neurofibromatosis type I: bridging the GAP. In *TRENDS in Molecular Medicine* 9(1):19–23.
- [2] D. H. Gutmann, L. F. Parada, A. J. Silva, & N. Ratner (2012). Neurofibromatosis type 1: Modeling CNS dysfunction. In *Journal of Neuroscience* 32(41):14087–14093.
- [3] Y. S. Lee & A. J. Silva (2011). Modeling hyperactivity: of mice and men. In *Nature Medicine* 17(5):541–542.
- [4] J. Z. Tsien, P. T. Huerta, & S. Tonegawa (1996). The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. In *Cell* 87(7):1327–1338.
- [5] K. P. Giese, N. B. Fedorov, R. K. Filipkowski, & A. J. Silva (1998). Autophosphorylation at Thr²⁸⁶ of the calcium-calmodulin kinase II in LTP and learning. In *Science* 279(5352):870–873.
- [6] A. Hyttinen, F. Eberhardt, & M. Jarvisalo (2014). Constraint-based causal discovery: Conflict resolution with answer set programming. In *Proceedings of the 30th Conference on Uncertainty in Artificial Intelligence (UAI)*.

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TOWARD AUTOMATED EXPERIMENT SELECTION

NICHOLAS J. MATIASZ

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