A Logical Deduction Tool for Assembling Rule-Based Models

Jean Yang

Harvard Medical School/

Carnegie Mellon University

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About Me

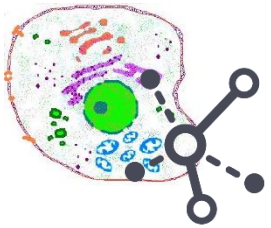
Mission: Trick people into writing code with (nice) guarantees by demonstrating that we can build useful systems in (surprisingly) clean ways.

Toolbox

- Logics for reasoning about programs and specifications
- Solvers for program verification and synthesis

Application Domains

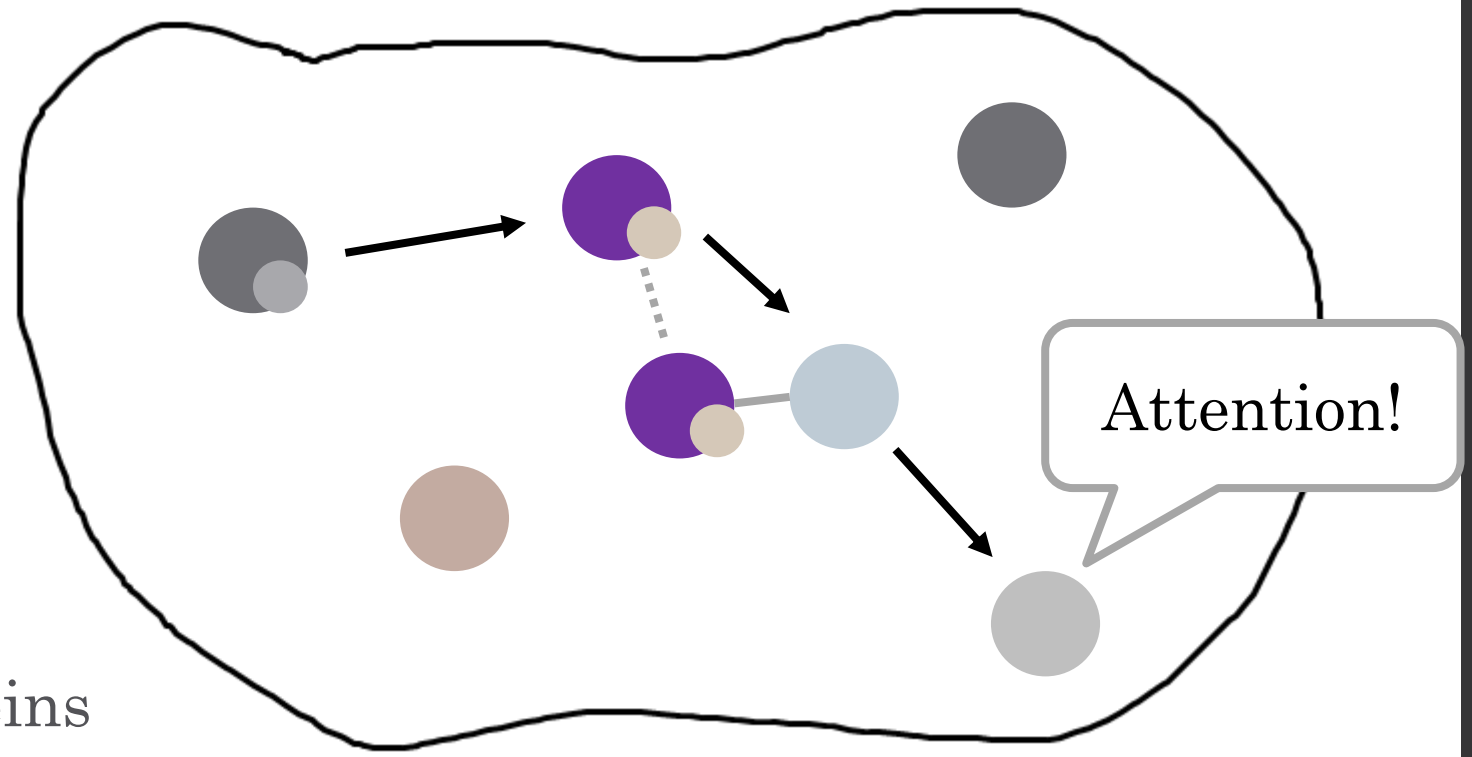
Security and privacy



Biological modeling

This talk

My Understanding of Cellular Signaling



Cell

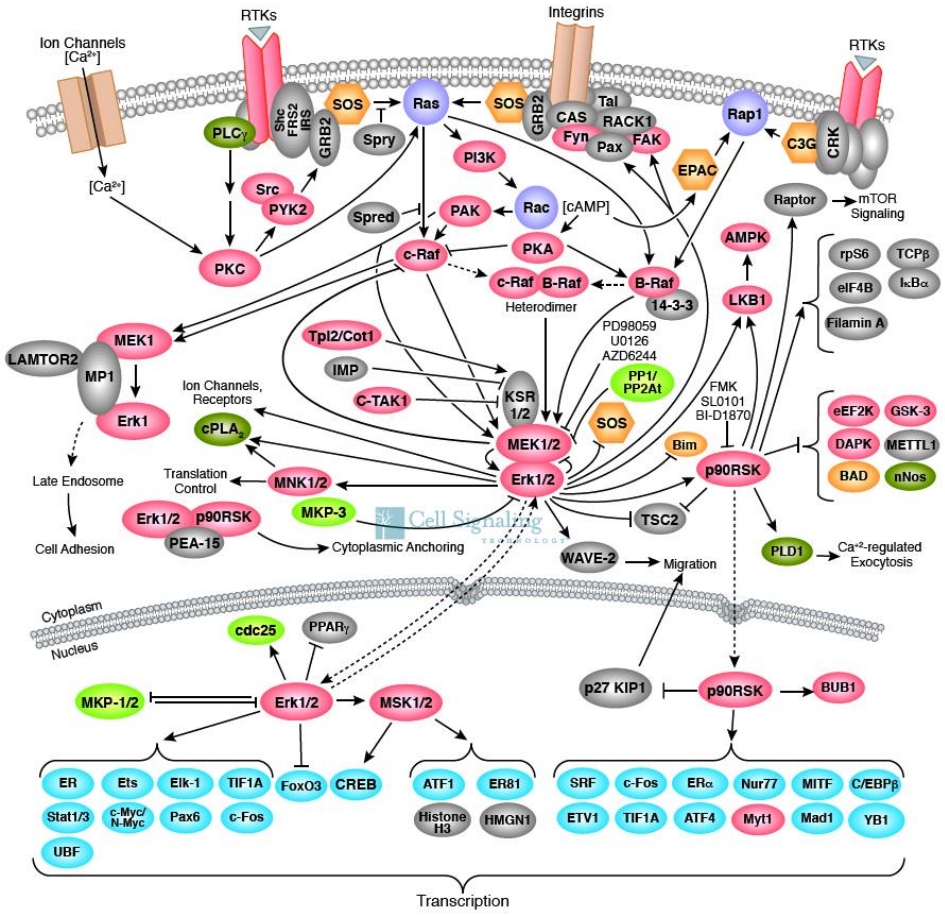
Proteins

Post-translational modification

→ Pathway

Goal: understand mechanism of cellular signaling pathways.

Problem: Cell Signaling Involves Many Interactions



- Understanding cell signaling would help with curing disease.
- Without more structure, hard to scale existing models.
- Left with heuristic approaches.

Programming Languages vs. Chemistry

$$\frac{\Gamma \vdash e \Downarrow \texttt{true} \qquad \Gamma \vdash e_1 \Downarrow v}{\Gamma \vdash \texttt{if}\ e\ \texttt{then}\ e_1\ \texttt{else}\ e_2 \Downarrow v}$$

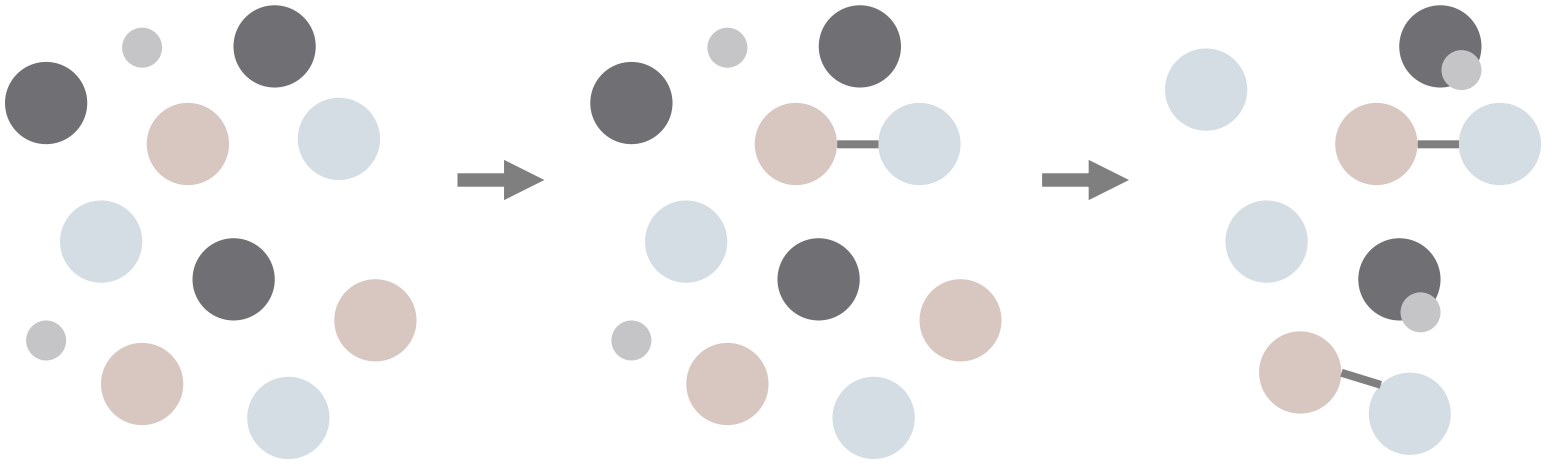
$$\frac{\Gamma \vdash e \Downarrow \texttt{false} \qquad \Gamma \vdash e_2 \Downarrow v}{\Gamma \vdash \texttt{if}\ e\ \texttt{then}\ e_1\ \texttt{else}\ e_2 \Downarrow v}$$

Programming language semantics

Chemical reaction semantics

Approach: Use Rewrite Rules Over Graphs

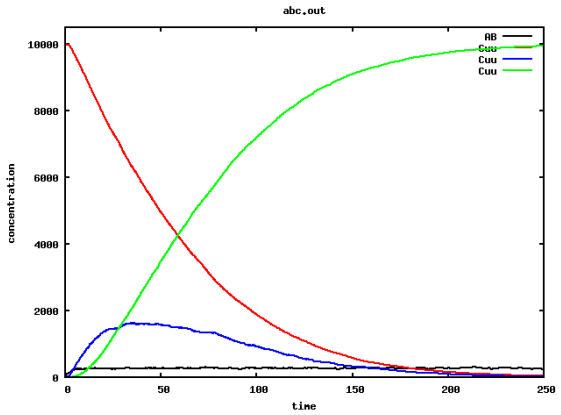
Initial mixture → One step → Final state



Mechanistic (Kappa) rules

Two Ways to "Run" Kappa Programs

Simulation to approximate differential semantics



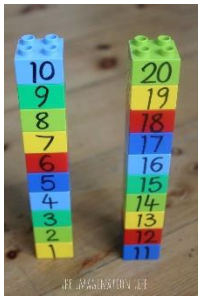
Continuous-time stochastic Monte Carlo simulation allows investigation of runtime behavior.

Analyzing rule structure via program analysis

Determine properties such as reachability, rule symmetries, and model coarse-graining.

Kappa Benefits

Compact rules facilitate model creation



Precise semantics allows sound analysis

Rules allow reasoning about causality

As Opposed To…

2.3.4 $\frac{\partial u}{\partial t} = k\frac{\partial^2 u}{\partial x^2}$, $u(0,t) = u(L,t) = 0$; $u(x,0) = f(x)$.

solution: $u(x,t) = \sum_{n=1}^{\infty} B_n e^{-k(n\pi/L)^2 t} \sin\frac{n\pi x}{L}$; set $\lambda_n = \left(\frac{n\pi}{L}\right)^2$

with $B_n = \frac{2}{L}\int_0^L f(x)\sin\frac{n\pi x}{L}dx$

(a) total energy:

$E(t) = csA\int_0^L u(x,t)dx = csA\sum_{n=1}^{\infty} B_n e^{-k\lambda_n t}\int_0^L \sin\frac{n\pi x}{L}dx$

now: $\int_0^L \sin\frac{n\pi x}{L}dx = -\frac{L}{n\pi}\cos\frac{n\pi x}{L}\Big|_0^L = \frac{L}{n\pi}(1-\cos n\pi) = \begin{cases}\frac{2L}{n\pi}, & n \text{ odd}\\ 0, & n \text{ even}\end{cases}$

hence: $E(t) = 2csA\sum_{n\,\text{odd}} \frac{L}{n\pi} B_n e^{-k\lambda_n t}$

(b) total inflow at $x=0$ ($F_L(t)$) and $x=L$ ($F_R(t)$):

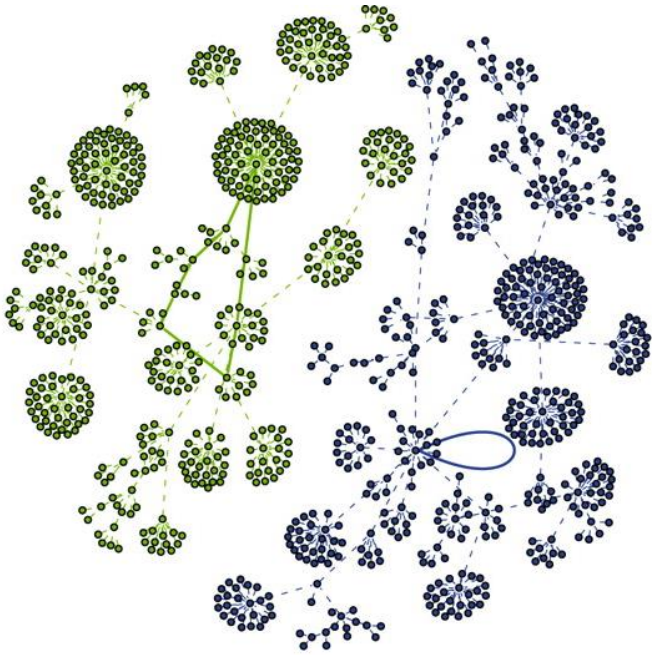
$F_L(t) = \phi(0)A = -K_0 A\frac{\partial u(0,t)}{\partial x} = -K_0 A\sum_{n=1}^{\infty} B_n e^{-\lambda_n k t}\frac{n\pi}{L}$

$F_R(t) = -\phi(L)A = K_0 A\frac{\partial u(L,t)}{\partial x} = K_0 A\sum_{n=1}^{\infty} B_n e^{-\lambda_n k t}\frac{n\pi}{L}(-1)^n$

net inflow: $F(t) = F_L(t) + F_R(t) = -2K_0 A\sum_{n\,\text{odd}} B_n\frac{n\pi}{L}e^{-k\lambda_n t}$.

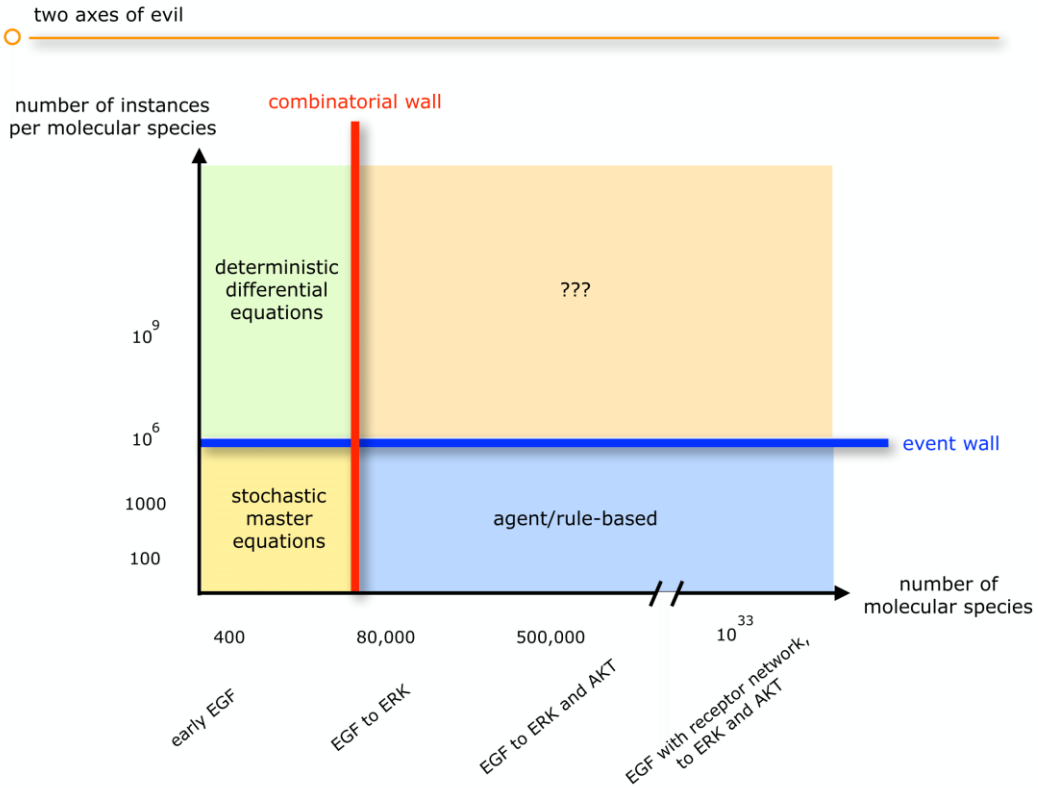
(net outflow $= -F(t)$)

Systems of differential equations



Boolean networks, Petri nets, etc.

Kappa in Context



Courtesy of Walter Fontana

This Talk

1. The difficulty of generating mechanistic models.
2. Syndra, a logical deduction framework for exploring models.
3. Ongoing and future work.

Problems: Kappa Models Difficult to Generate

'EGF.EGFR' EGF(r), EGFR(L,CR) -> EGF(r!1), EGFR(L!1,CR) @ 'k_on'

'EGF/EGFR' EGF(r!1), EGFR(L!1,CR) -> EGF(r), EGFR(L,CR) @ 'k_off'

'Shc.Grb2' Shc(Y~p), Grb2(SH2) -> Shc(Y~p!1), Grb2(SH2!1) @ 5*'k_on'

'Shc/Grb2' Shc(Y~p!1), Grb2(SH2!1) -> Shc(Y~p), Grb2(SH2) @ 'k_off'

'EGFR.Grb2' EGFR(Y1092~p), Grb2(SH2) -> EGFR(Y1092~p!1), Grb2(SH2!1) @ 'k_on'

'EGFR/Grb2' EGFR(Y1092~p!1), Grb2(SH2!1) -> EGFR(Y1092~p), Grb2(SH2) @ 'k_off'

'EGFR.Shc' EGFR(Y1172~p), Shc(PTB) -> EGFR(Y1172~p!1), Shc(PTB!1) @ 'k_on'

'EGFR/Shc' EGFR(Y1172~p!1), Shc(PTB!1) -> EGFR(Y1172~p), Shc(PTB) @ 'k_off'

'Grb2.SoS' Grb2(SH3n), SoS(PR,S~u) -> Grb2(SH3n!1), SoS(PR!1,S~u) @ 'k_on'

'Grb2/SoS' Grb2(SH3n!1), SoS(PR!1) -> Grb2(SH3n), SoS(PR) @ 'k_off'

'EGFR.int' EGFR(CR!1,N,C), EGFR(CR!1,N,C) -> EGFR(CR!1,N!2,C), EGFR(CR!1,N,C!2) @ 'k_on'

'EGFR/int' EGFR(CR!1,N!2,C), EGFR(CR!1,N,C!2) -> EGFR(CR!1,N,C), EGFR(CR!1,N,C) @ 'k_off'

'pY1092@EGFR' EGFR(N!1), EGFR(C!1,Y1092~u) -> EGFR(N!1), EGFR(C!1,Y1092~p) @ 'k_cat'

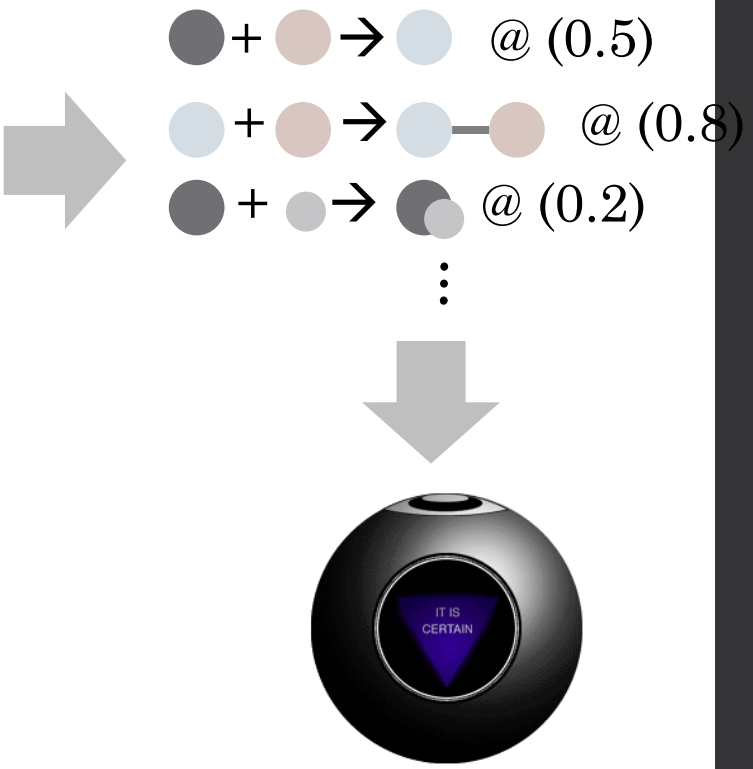
'pY1172@EGFR' EGFR(N!1), EGFR(C!1,Y1172~u) -> EGFR(N!1), EGFR(C!1,Y1172~p) @ 'k_cat'

'uY1092@EGFR' EGFR(Y1092~p) -> EGFR(Y1092~u) @ 'k_cat'

'uY1172@EGFR' EGFR(Y1172~p) -> EGFR(Y1172~u) @ 'k_cat'

From the SOS model

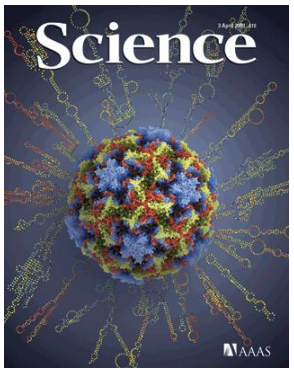
The Dream of Big Mechanism



Requires precise mechanistic reasoning!

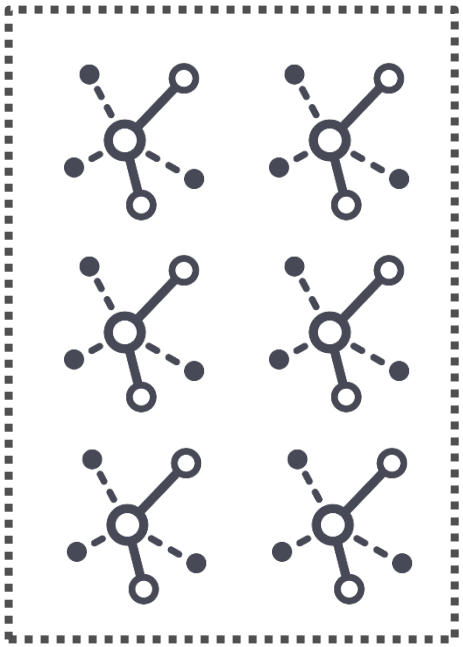
Obstacle: Natural Language is Ambiguous

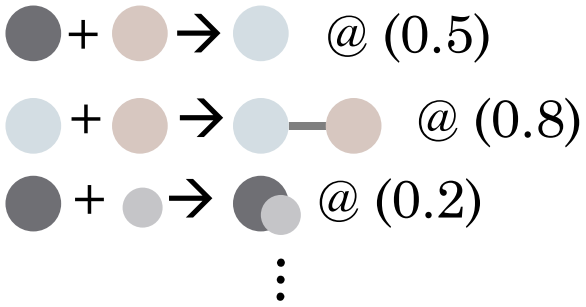
Imprecision of natural language



Scientific literature and databases

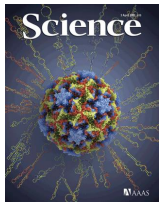
NLP





Can use **logical deduction** to navigate this space.

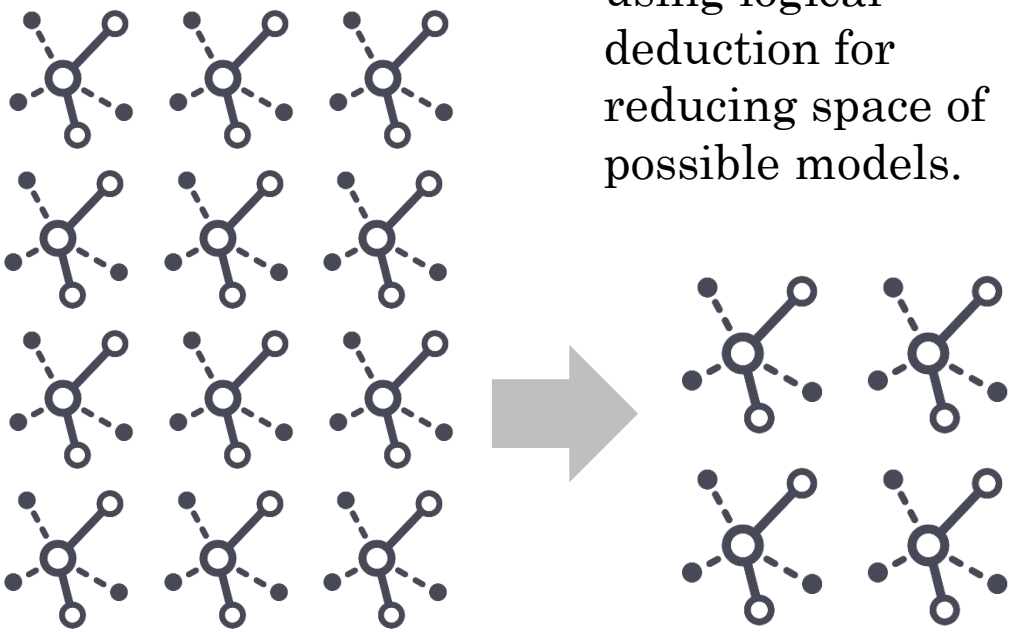
Our Solution: A Logical Tool for Inference



TRIPS parser

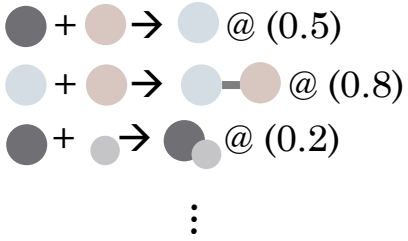
INDRA

1 Technique for using logical deduction for reducing space of possible models.



Rule-based mechanistic model

2 Tool implemented in Python using the Z3 SMT solver in the backend.

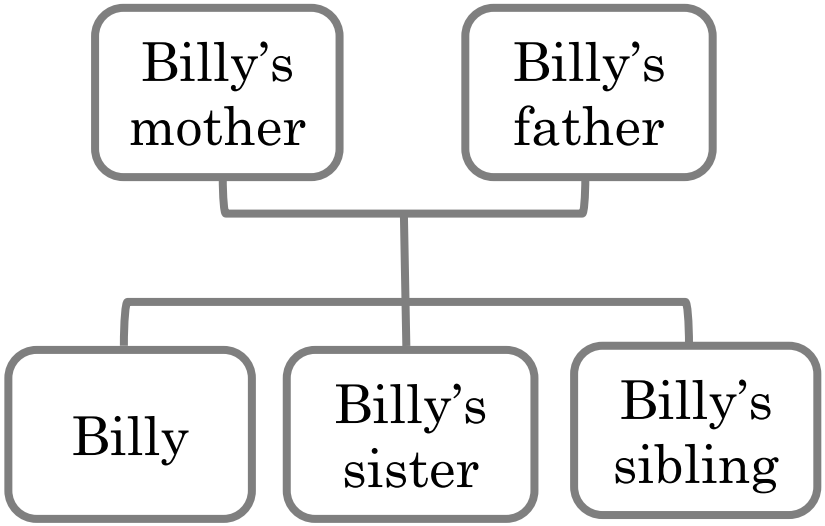


Running Non-Biology Example

Billy has a sibling.

Billy has a sister.

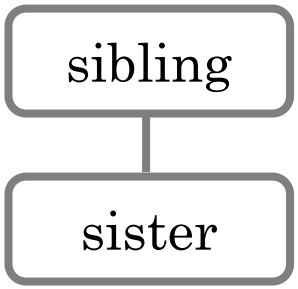
Billy's Family Tree



Using Domain Facts to Clean up Model

Domain fact: A sister is a kind of sibling.

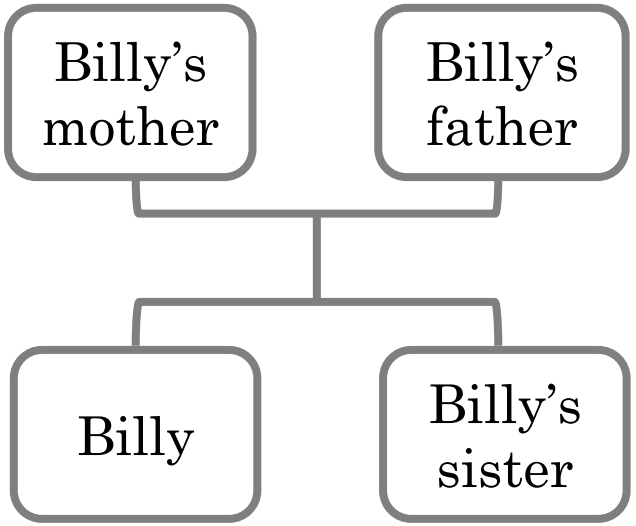
Specificity Hierarchy



Family member type

Gendered family member type

Billy's Family Tree

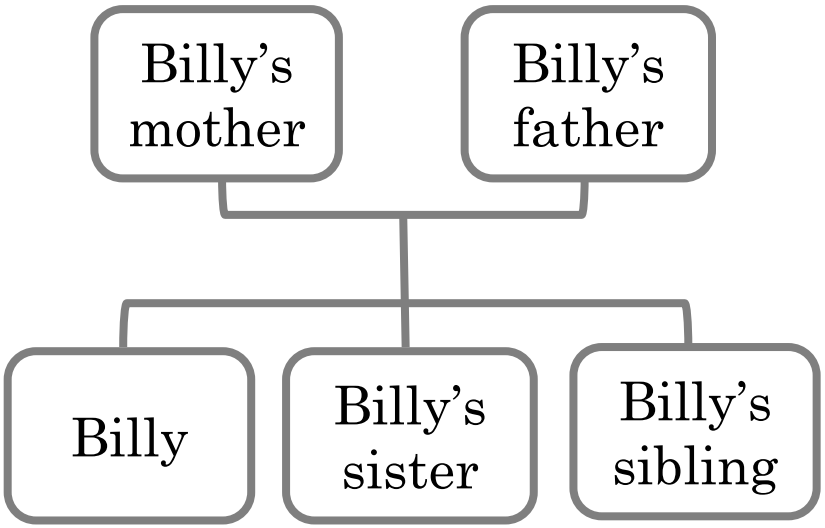


Things Get Harder with Implication

If we trust the neighbor, Billy has a sibling.

If we trust the neighbor, Billy has a sister.

Billy's Family Tree, if we trust the neighbor



Deducible Facts

$trust(neighbor) \Rightarrow has(Billy, sibling)$

Facts from literature

$\forall a. has(a, sister) \Rightarrow has(a, sibling)$

Domain fact

$trust(neighbor) \Rightarrow has(Billy, sibling)$

Deducible fact

Fact f is **deducible** (and thus redundant) if $\neg f$ is inconsistent with previous facts.

What About Specificity and Implication?

If we trust the neighbor, Billy has a sibling.

If we trust anybody, Billy has a sibling.

Relative Fact Specificity as Subtyping

Subtyping Atomic Statements

$$\forall a_1, a_2.\, genderedFamilyMember(a_1) <: familyMember(a_2)$$

Subtyping symbol

Subtyping Implications

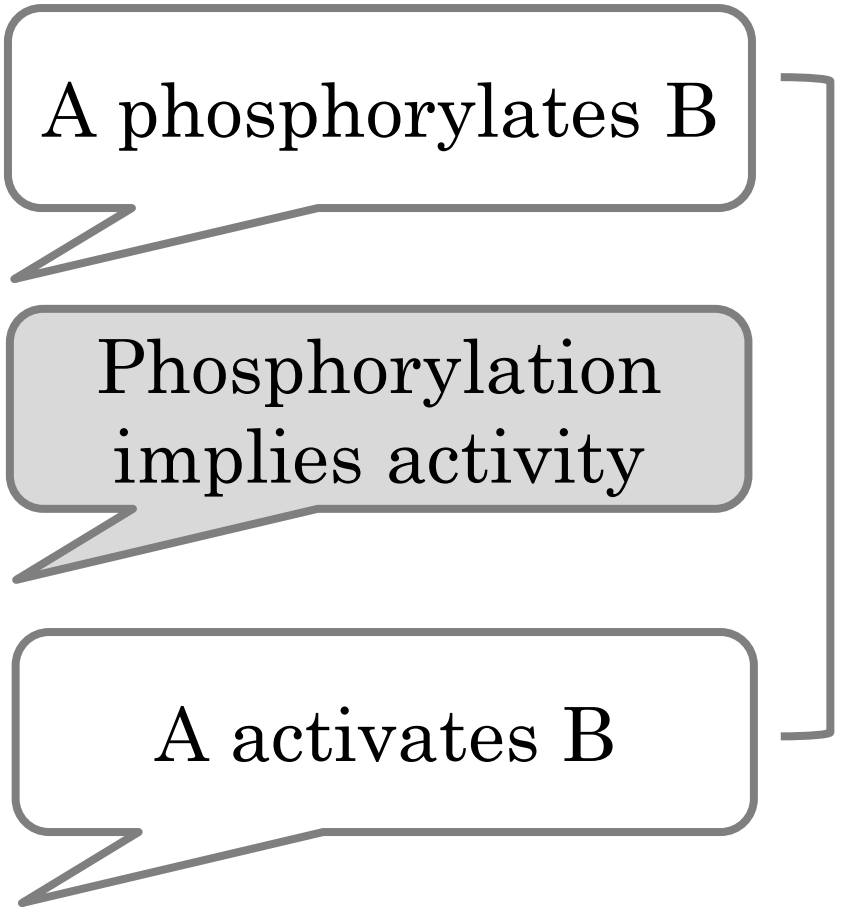
$$\frac{p_t <: p_s \qquad p_t \vdash q_s <: q_t}{p_s \Rightarrow q_s <: p_t \Rightarrow q_t}$$

Want $p_s \Rightarrow q_s$ to be consistent with any set of formulas $p_t \Rightarrow q_t$ is consistent with.

$$trust(neighbor) \Rightarrow has(Billy, sister) <: trust(neighbor) \Rightarrow has(Billy, sibling)$$

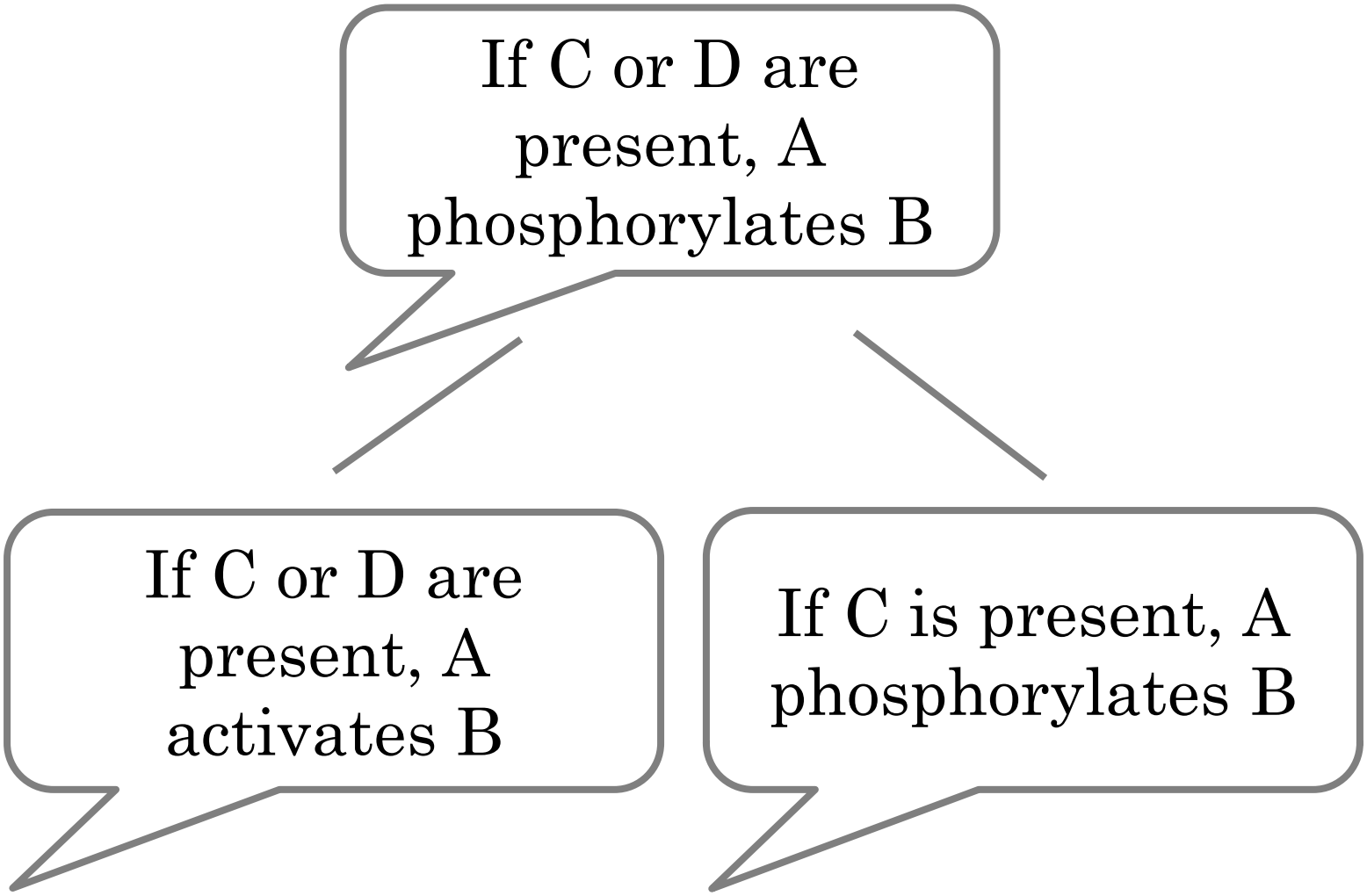
$$trust(anybody) \Rightarrow has(Billy, sibling) <: trust(neighbor) \Rightarrow has(Billy, sibling)$$

Domain Facts in Biology

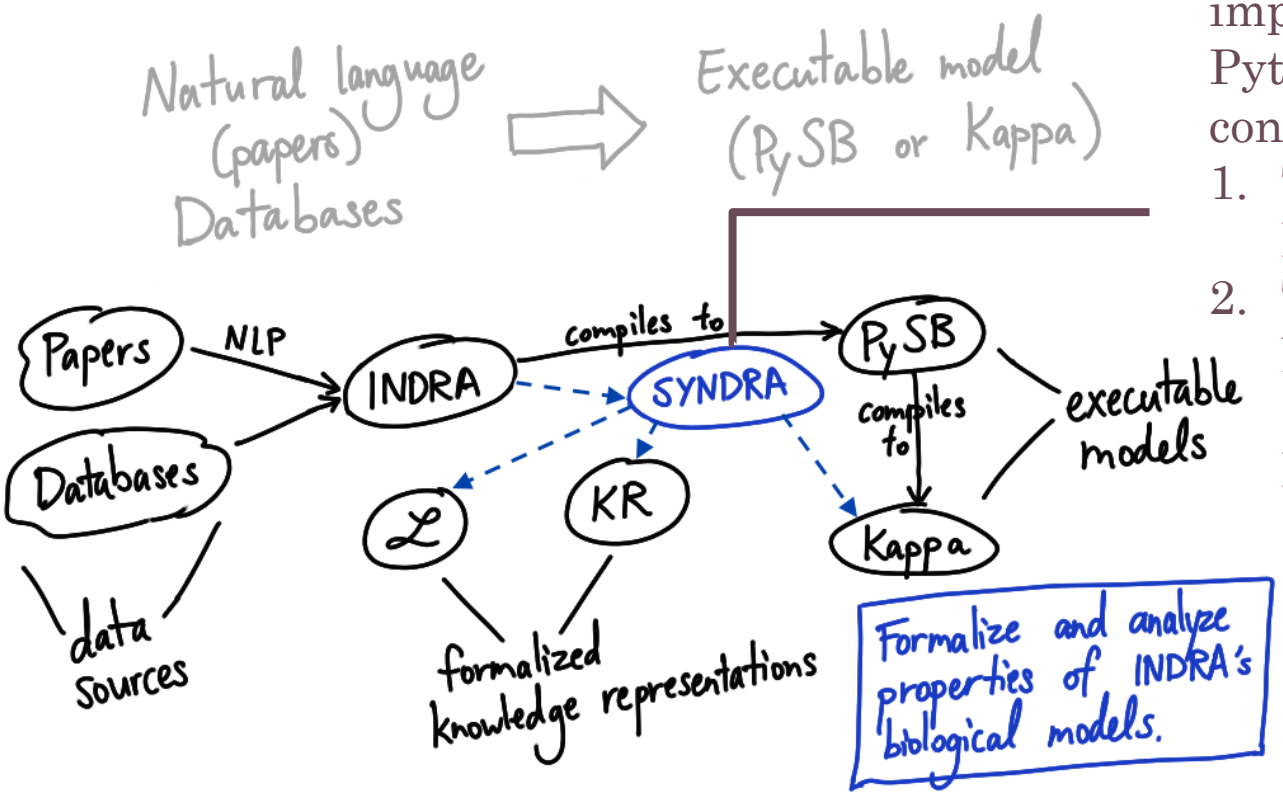


Can determine these are redundant, where "A phosphorylates B" is the more specific statement.

Hierarchy of Specificity



Design and Implementation of Syndra



Syndra is implemented in Python and contains:

1. Translation of L/Iota to Z3.
2. Translation of higher-level statements to L/Iota.

Image by Chelsea Voss.

Translating Statements to Graph Logic

A phosphorylates B

Phosphorylation implies activity

A activates B

Iota rules [Husson & Krivine]

preconditions $\langle G, \alpha \rangle$ postconditions

Set of allowable graphs

Actions over graphs

Phosphorylation in Terms of Iota Graph Predicates

"A phosphorylates B"

Precondition: A is active.

Precondition: B is not phosphorylated.

$$\langle G, \alpha \rangle$$

Postcondition: A is active.

Postcondition: B is phosphorylated.

Every model in the set of allowable graphs G must have one rule prescribing that A may phosphorylate B.

Phosphorylation as First-Order Logic

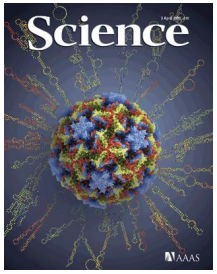
$$\forall A, B.\, PreLabeled(A, active)$$
$$\wedge\, PreUnlabeled(B, phosphorylated)$$
$$\wedge\, PostLabeled(A, active)$$
$$\wedge\, PostLabeled(B, Phosphorylated)$$

```
(declare-fun preLabeled (Int Int)
Bool)
(declare-fun preUnlabeled (Int Int)
Bool)
⋮
```

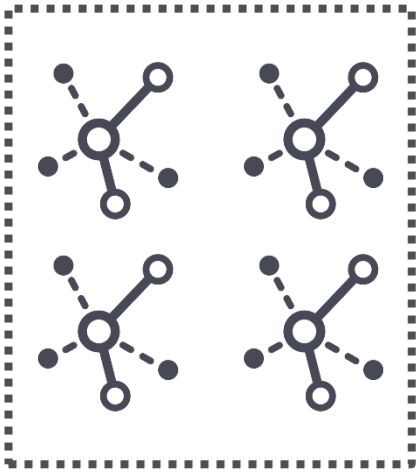
Ongoing Work

- Encoding more high-level properties.
- Finding more examples that integrate semantic/ontological reasoning with reasoning about graphs.
- Expanding engine capabilities to support queries of interest.

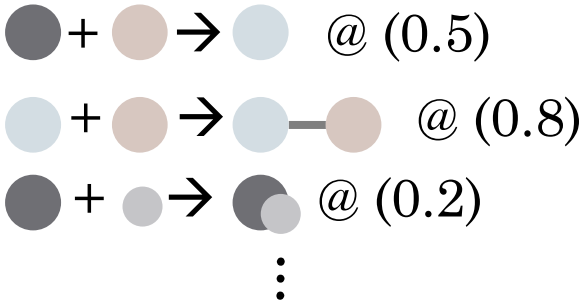
The Multiple Uses of a Knowledge Representation



Mechanistic knowledge from biologist's minds



Space of possible models



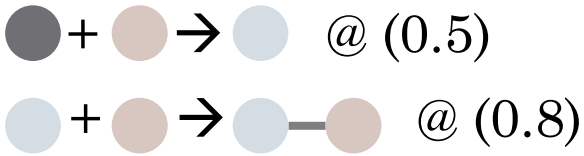
Rule-based models

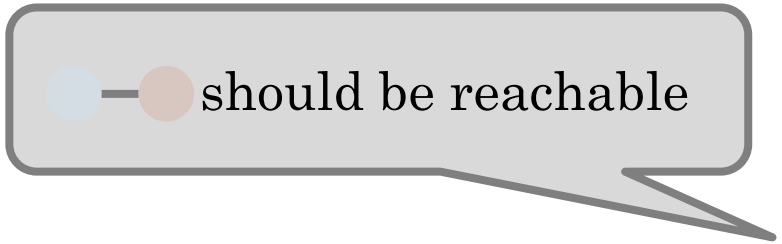
It looks like you're implementing a signaling pathway.

(But with better UI design, obviously.)

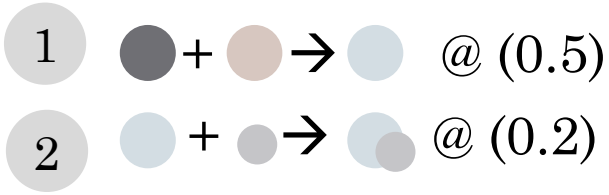
Oh, The Places You'll Go!

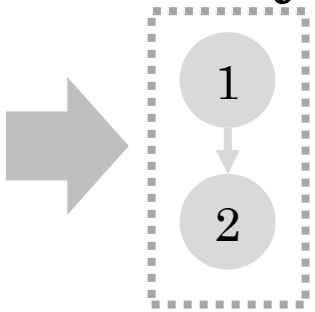
Reasoning about Structural Properties





Reasoning about Causality





This causal graph is called a **story.**

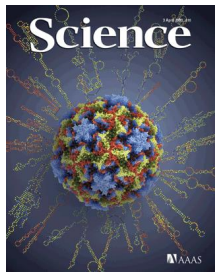
Ongoing work: relative frequency analysis for stories.

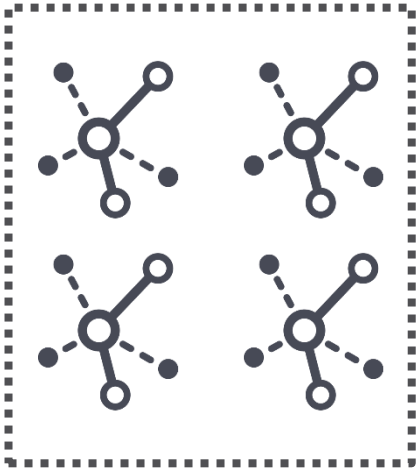
Big Question: Should We Go to the Dark Side?

If LRP5/6 is next to Axin, then it is likely to have been phosphorylated by CK1-alpha and GSK3-beta.

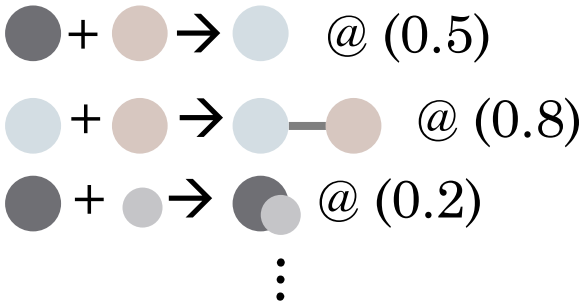
Note! It is still possible to get strong mathematical guarantees.

The Grand Plan

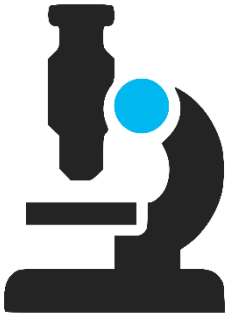




Space of
possible models



Rule-based models



Experiments,
diagnoses,
and
discoveries

Analyses
involving rule
structures and
rates

Some Open Questions

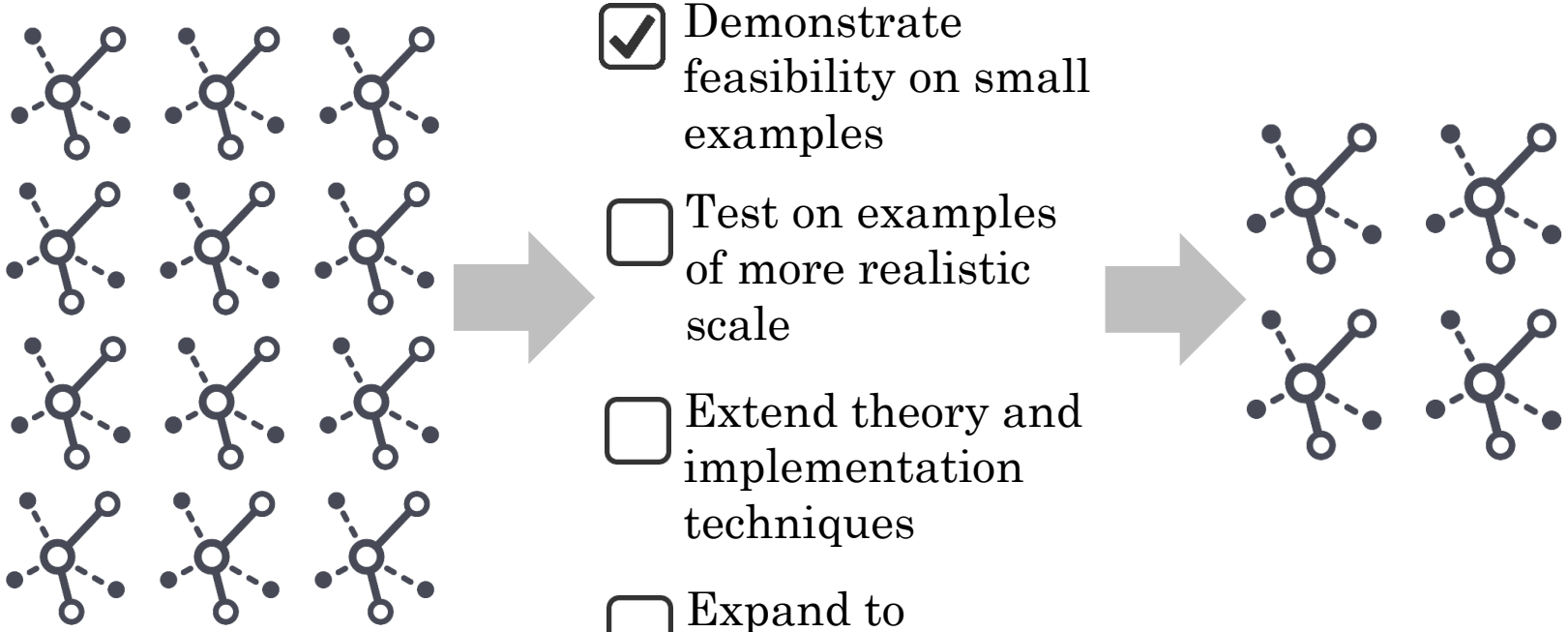
- What does the space of models from the literature actually look like?
- What are some examples where deep mechanistic reasoning is useful?
- What kinds of algorithms do we need to explore this space efficiently?

Talk to Us!

- Tell us about the kinds of domain knowledge you use when reading papers.
- Tell us your about the tricky mechanistic reasoning you do in your head.
- Try out Syndra for your own purposes and give us feedback!

Conclusions… So far

Logical deduction with mechanism is a promising missing piece in producing precise models. But logic alone won't answer all the questions!



- [x] Demonstrate feasibility on small examples
- [ ] Test on examples of more realistic scale
- [ ] Extend theory and implementation techniques
- [ ] Expand to probabilistic reasoning?

http://github.com/csvoss/syndra