IBENS, Paris, the 12th January 2018

Norwegian University of Technology and Sciences

DrugLogics project: causality, modelling, drug predictions

PhD project and research stay at ENS

vasundra.toure@ntnu.no

@Vasundra_T
@DrugLogics

The DrugLogics Initiative

Towards the development of precision and personalised medicine

The DrugLogics Initiative

Towards the development of precision and personalised medicine

Crossover Research

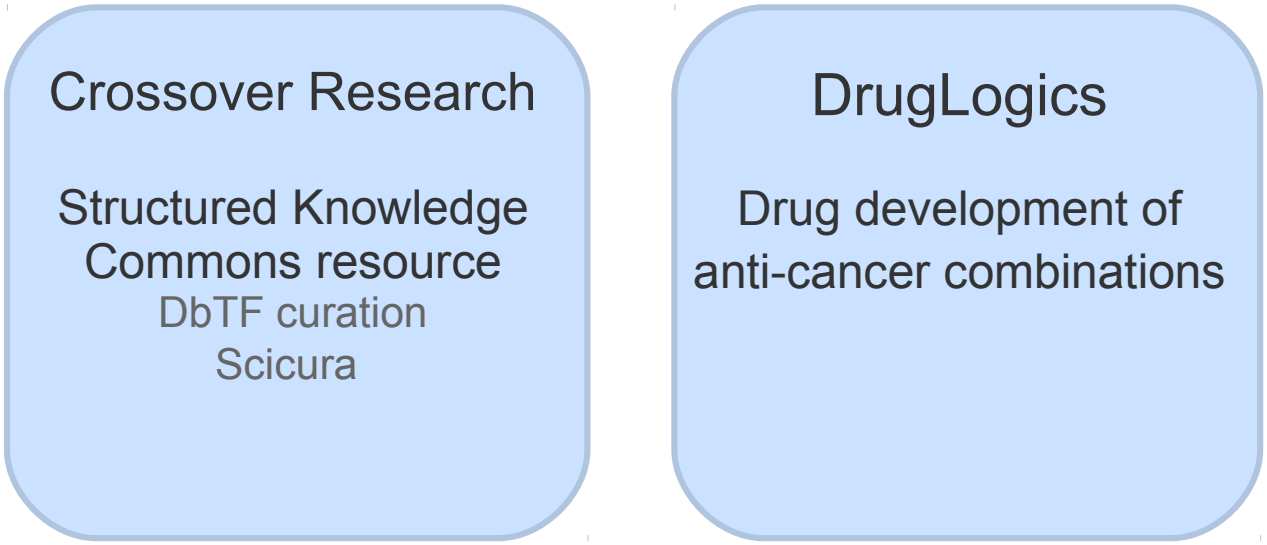
Structured Knowledge Commons resource

DbTF curation

Scicura

The DrugLogics Initiative

Towards the development of precision and personalised medicine



The DrugLogics Initiative

Towards the development of precision and personalised medicine

Crossover Research

Structured Knowledge Commons resource

DbTF curation

Scicura

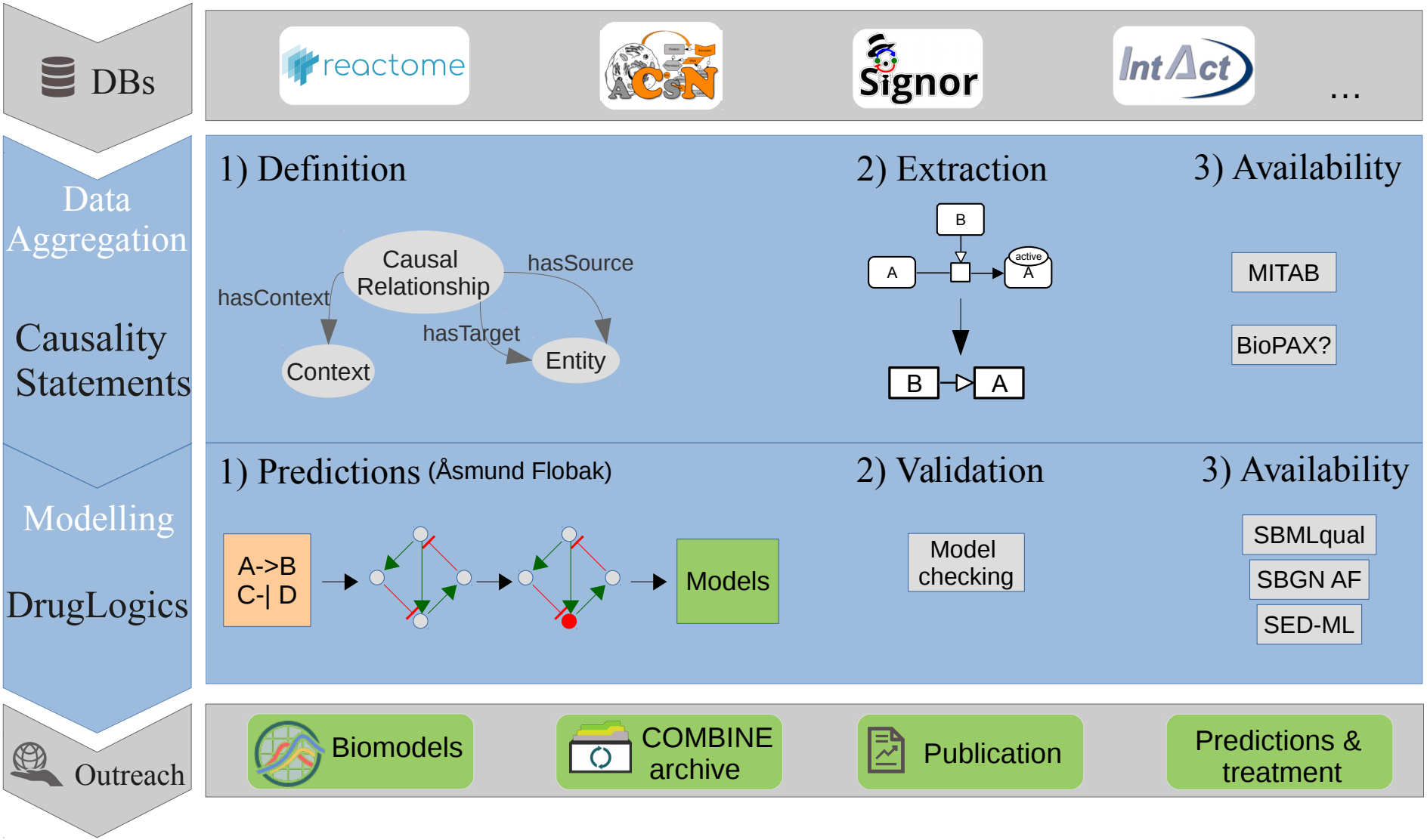
DrugLogics

Drug development of anti-cancer combinations

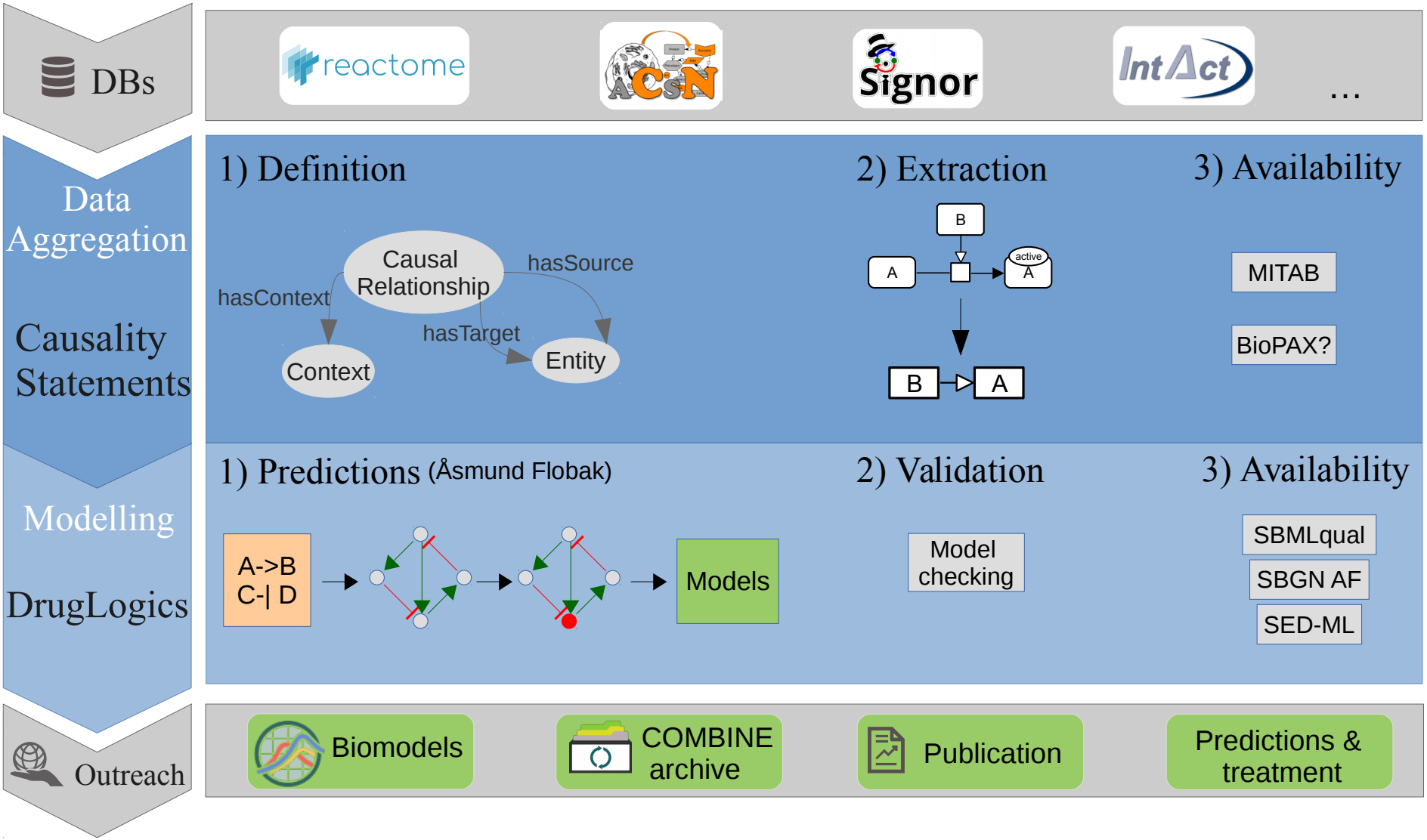
COLOSYS

Drug resistance prediction in colon cancer via computer models

Overview of the PhD project



Overview of the PhD project



What is a causal statement?

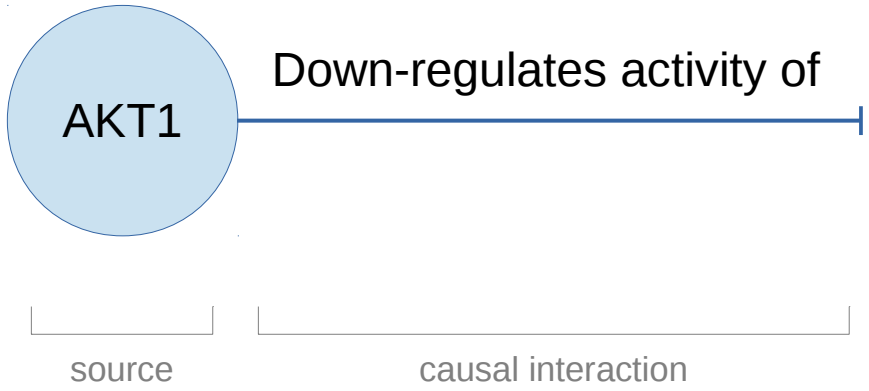
Causal interaction between biological entities (gene, RNA, protein, etc…)

What is a causal statement?

Causal interaction between biological entities (gene, RNA, protein, etc…)

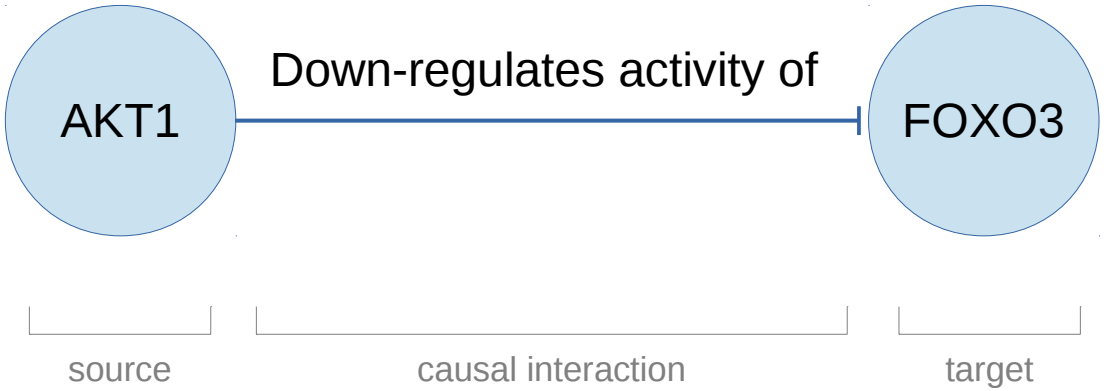
What is a causal statement?

Causal interaction between biological entities (gene, RNA, protein, etc…)



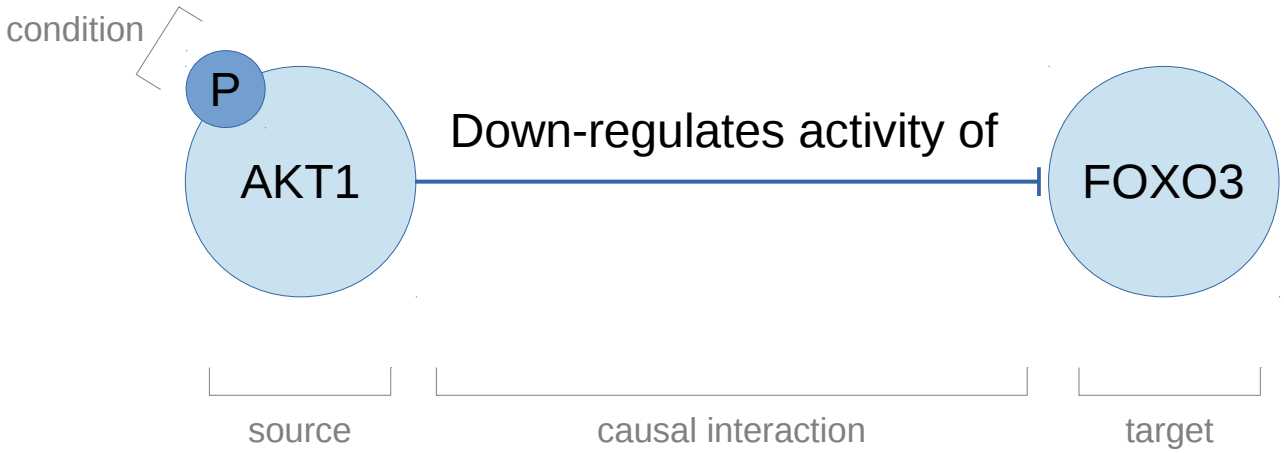
What is a causal statement?

Causal interaction between biological entities (gene, RNA, protein, etc…)



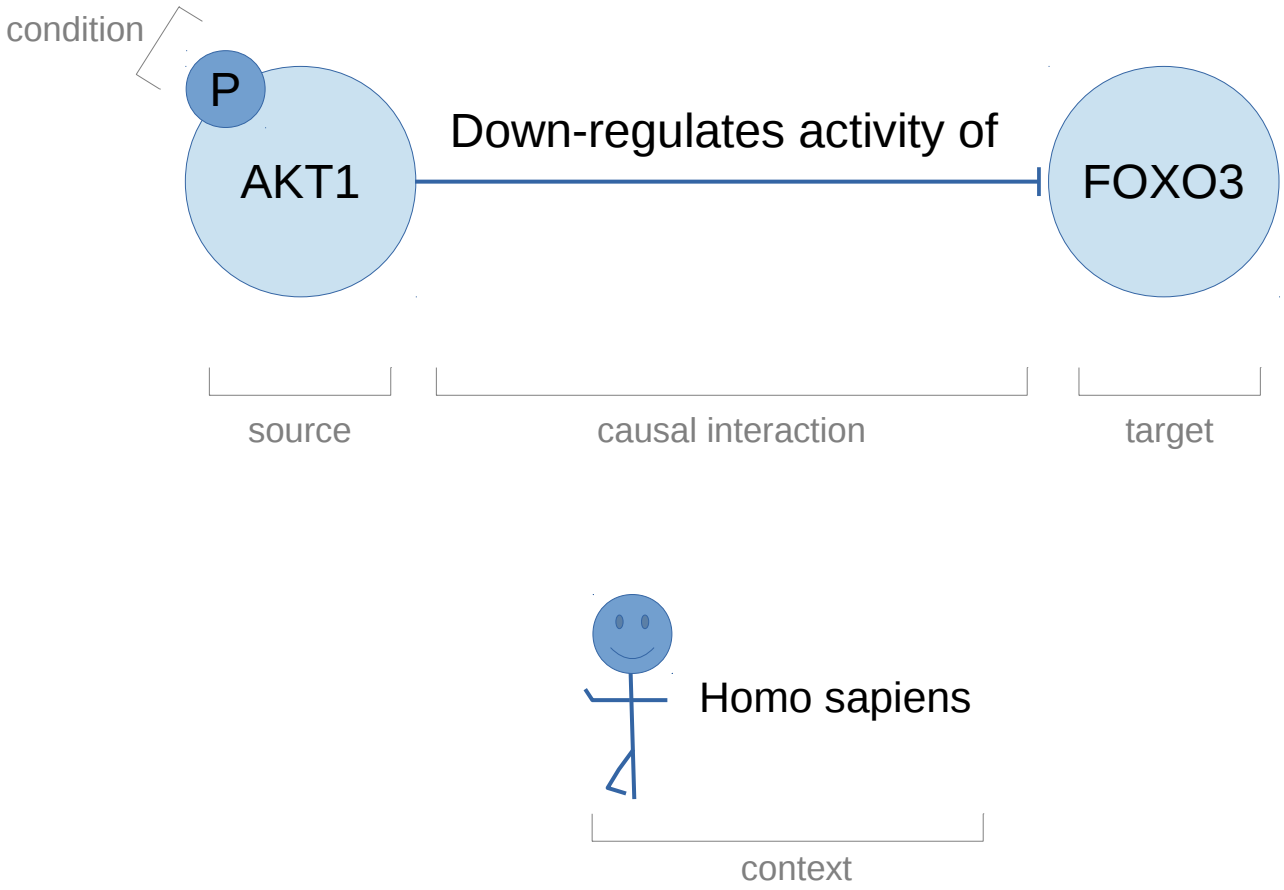
What is a causal statement?

Causal interaction between biological entities (gene, RNA, protein, etc…)



What is a causal statement?

Causal interaction between biological entities (gene, RNA, protein, etc…)

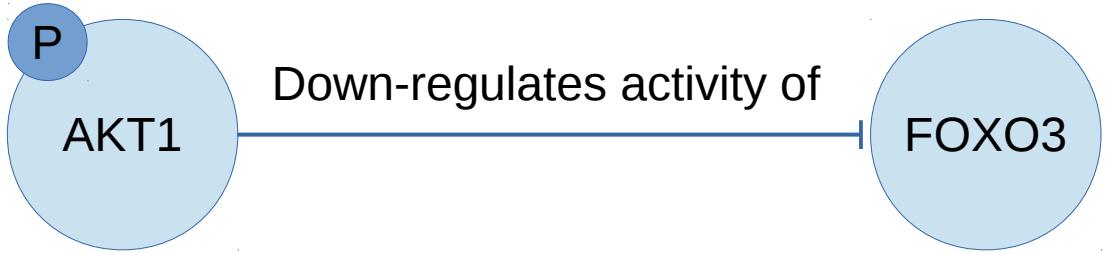


How to encode meaningful causal statements?

What is FOXO3's state?

When and where does this interaction occurs?

Which molecular function is down-regulated?



What is the regulation type?

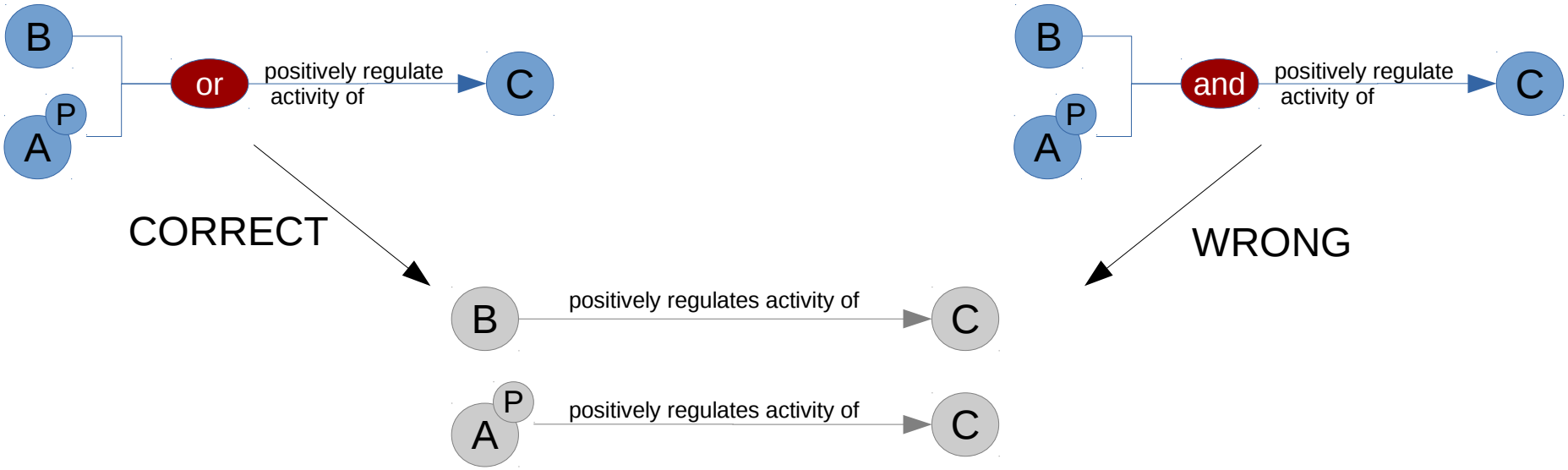
Is it a direct or indirect Interaction?

Representation of causality: current state

	Entities Identifiers	Directed	Causality annotation	Evidence	Format
MITAB2.7	Entrez gene/Ensembl embl/ddbj/genbank UniProtKB/RefSeq ChEBI	no	Free text: “causality statement:...”	PUBMED	tabular
Causaltab	Embl/ddbj/genbank UniprotKB/RefSeq ChEBI/PubChem ComplexPortal Signor_ID	yes	MI – causal interaction	PUBMED	tabular
GO-CAM	Gene symbols UniprotKB ChEBI	yes	Relation Ontology	PUBMED ECO	OWL
BEL	Mainly HGNC but flexible	yes	Own representation	Text with ontologies	BEL script, JSON

Representation of causality: what is missing?

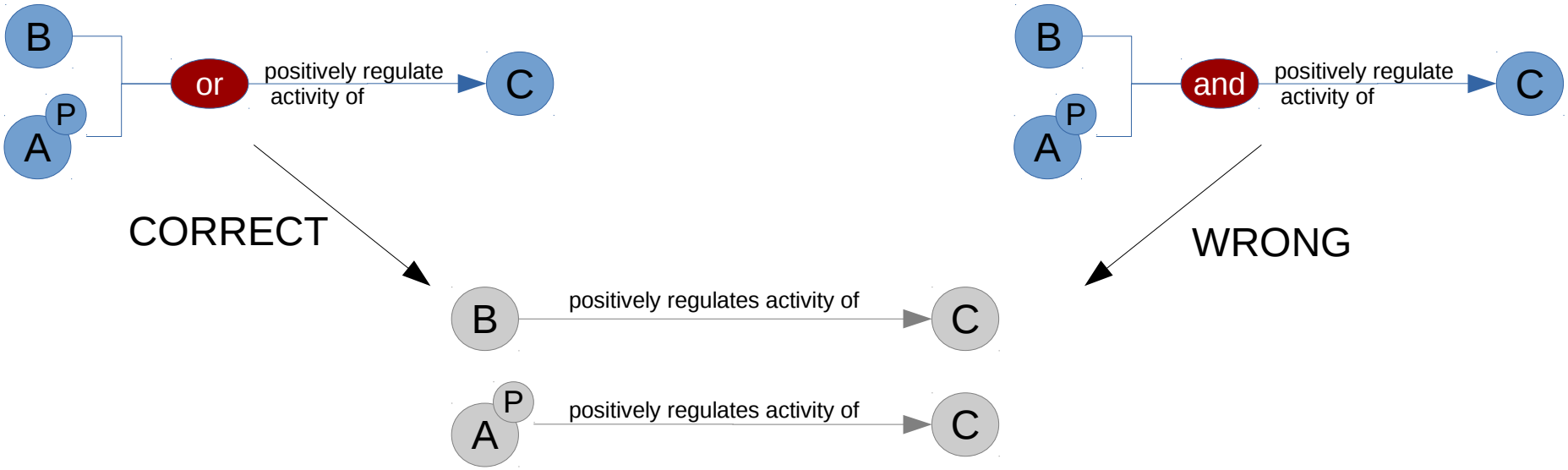
1) Multi-regulated causal interaction



→ introduce logics in formats

Representation of causality: what is missing?

1) Multi-regulated causal interaction



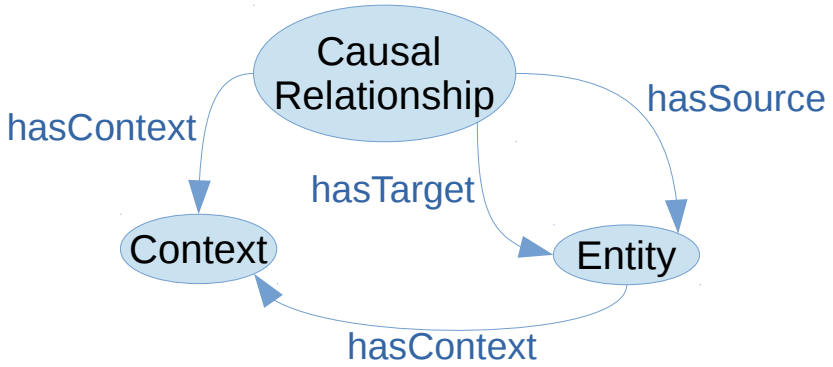
→ introduce logics in formats

2) Common structure for representing causality

→ Guideline for representing causality (MICAST)

Frame for defining context

Ontologies recommendation



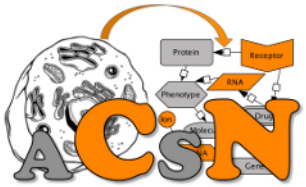
Extraction from prior knowledge

Aggregation of causal data from several existing resources

reactome

Pathways, reactions

~ 6 000 interactions



Pathways of cancer related signaling networks

~ 2 500 interactions

Signor

DB of causal interactions

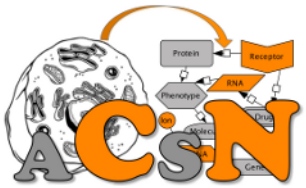
~ 20 000 interactions

IntAct

DB of molecular interactions

~ 800 interactions

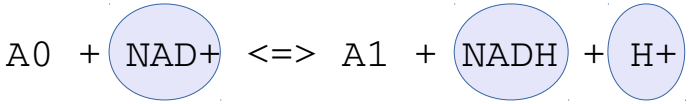
Questions / challenges raised



reactome

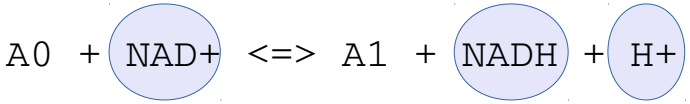
Questions / challenges raised

- Exclude trivial molecules



Questions / challenges raised

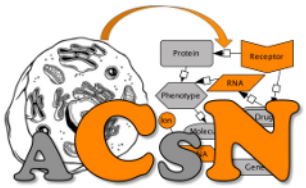
- Exclude trivial molecules



- Missing information

  ex: IDs for the modified mechanism type

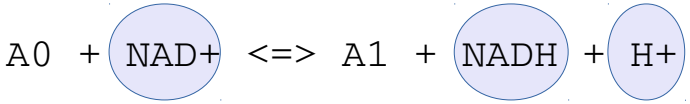
  Transfers
  Translocates from … to
  Transports
  Exchanges … for …
  Cotransports
  Regulates



reactome

Questions / challenges raised

- Exclude trivial molecules

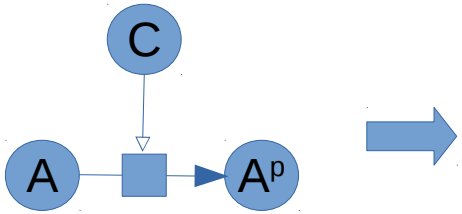


- Missing information

  ex: IDs for the modified mechanism type

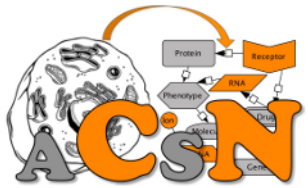
  Transfers
  Translocates from … to
  Transports
  Exchanges … for …
  Cotransports
  Regulates

- Inference of causal interactions from reaction networks



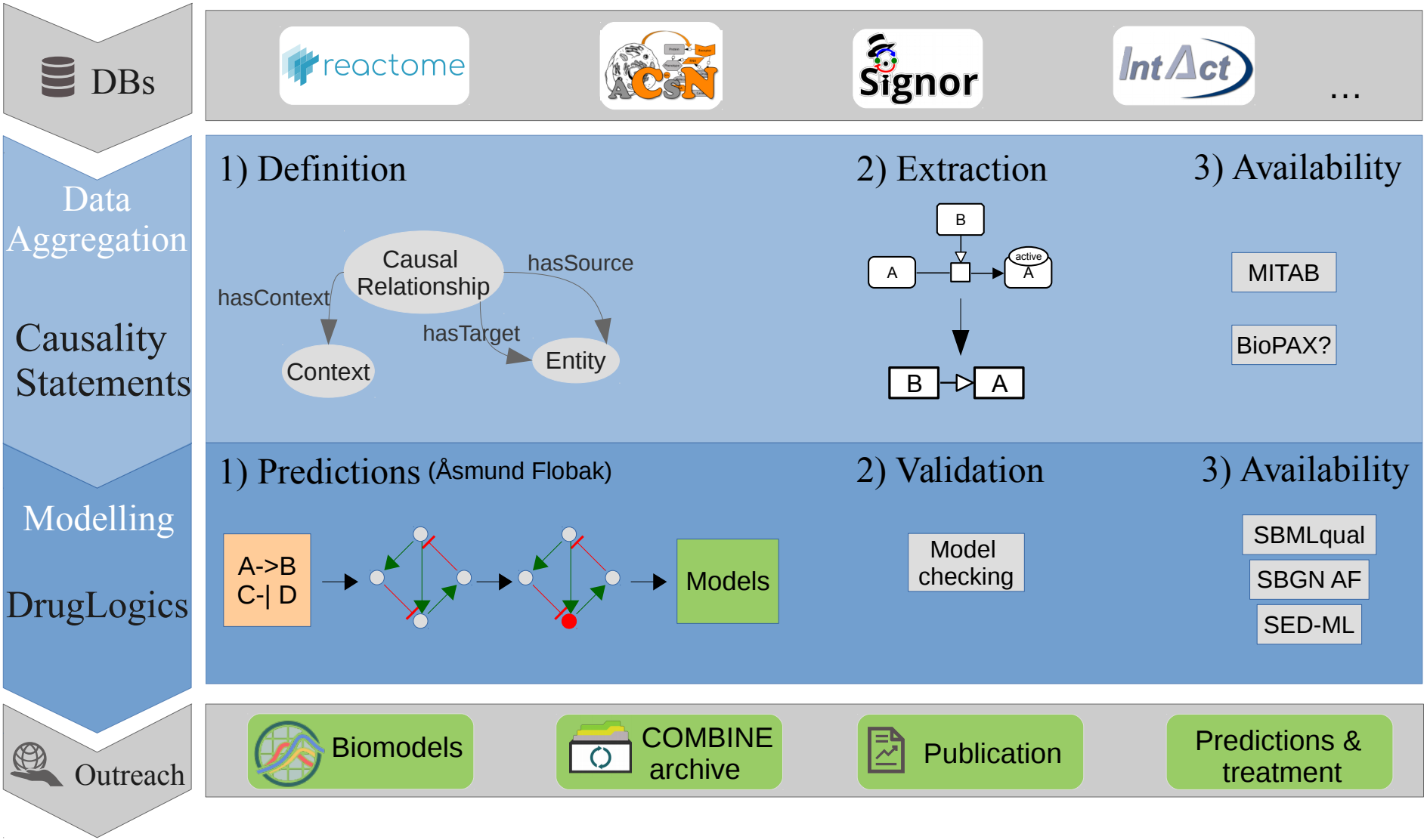
C -| A
C -> A^p
A -| A^p
A^p -| A

?

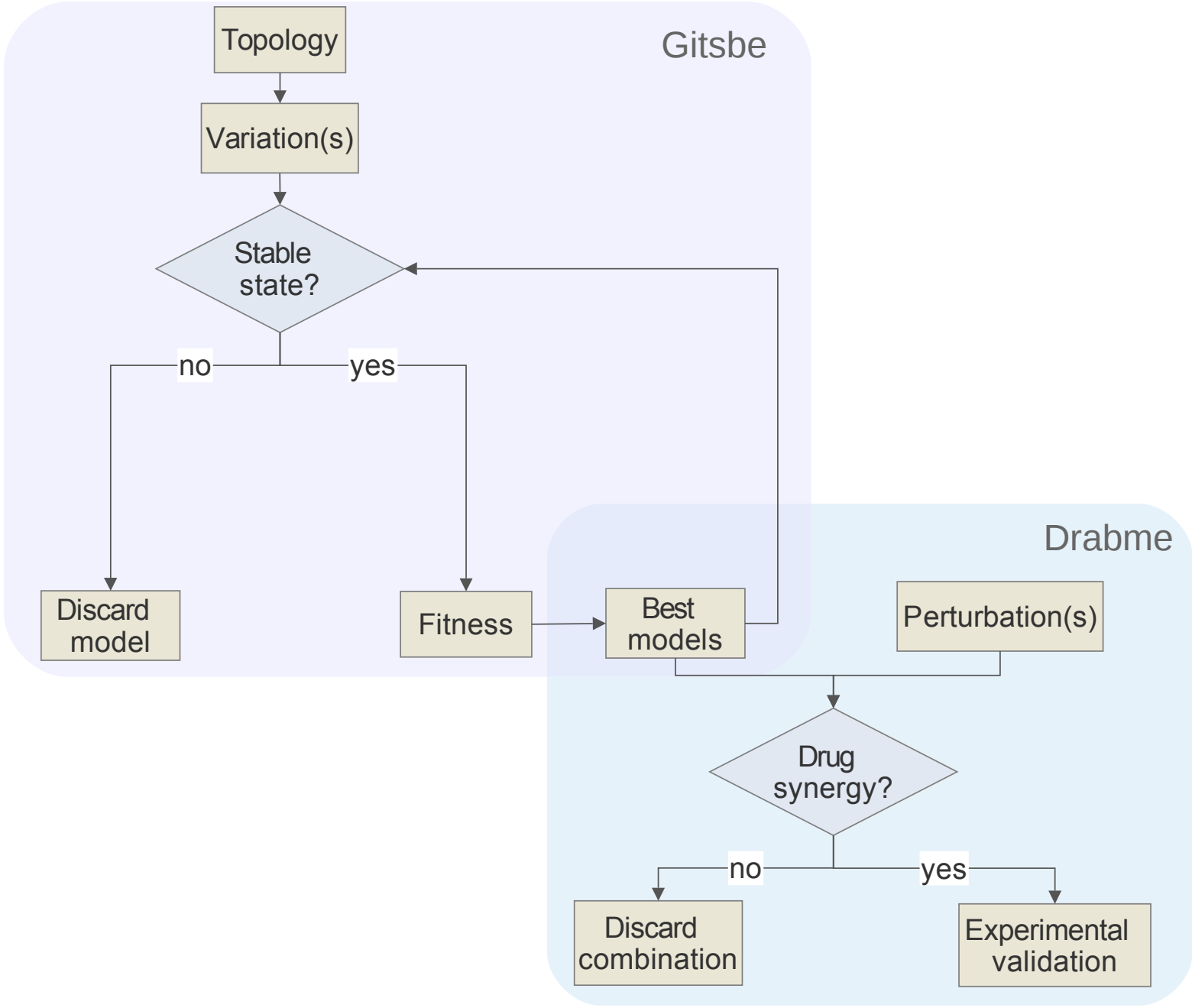


reactome

Overview of the PhD project

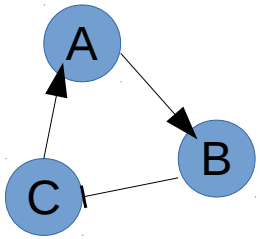


The DrugLogics' modelling pipeline



Stable states identification

- BNReduction algorithm (Veliz-cuba)
- Combination of network reduction and computational algebra
- Works fine up to 1000 nodes

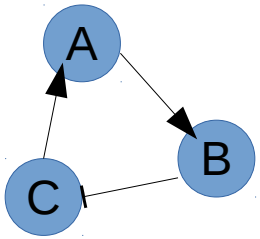


A B C
1 1 0

Trap space identification

- “Symbolic steady states”
- Highlight potential existence of complex attractors

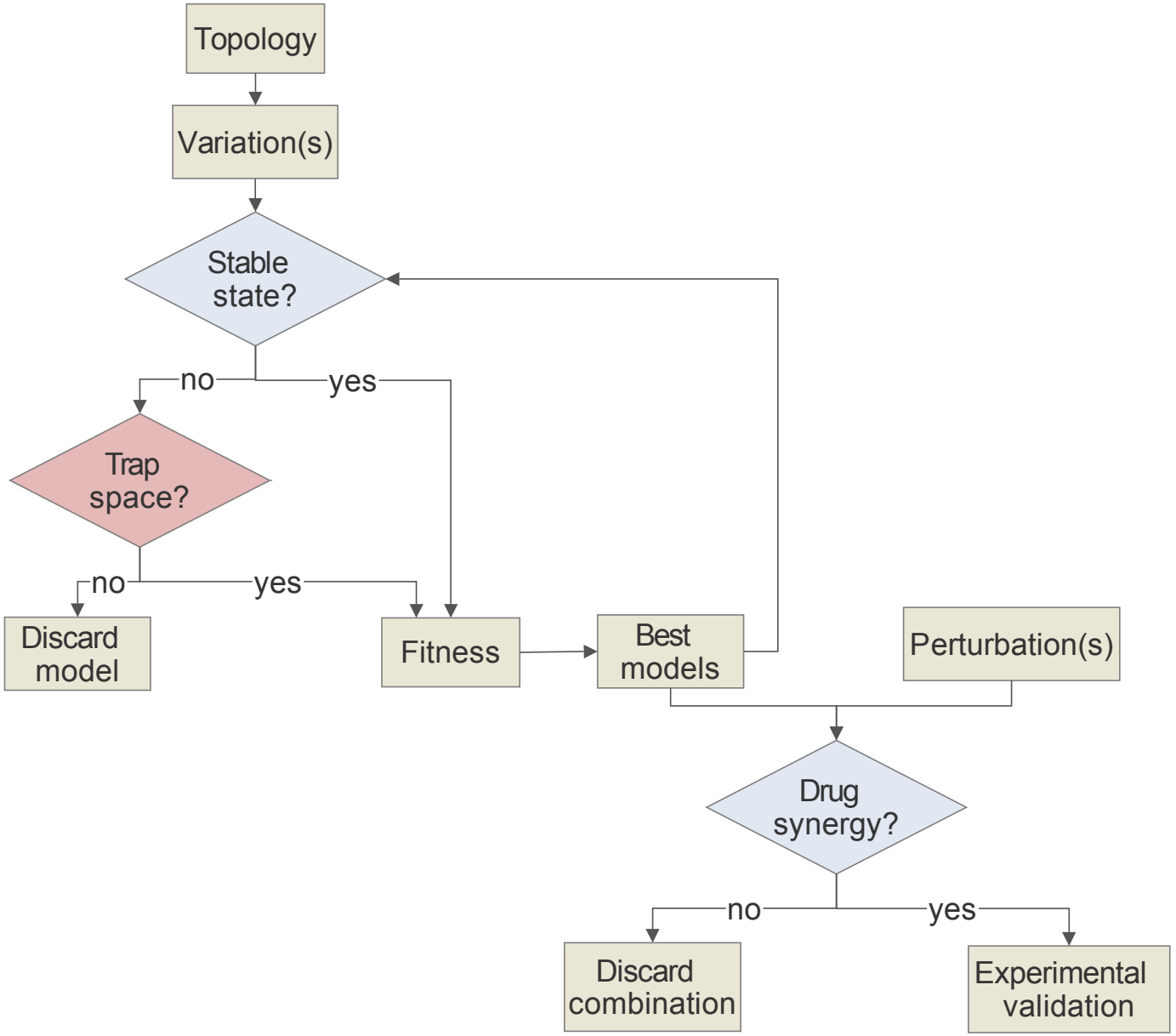
→ Use of bioLQM library



A B C
1 - 0

Scripting with GINsim and bioLQM

- Compute trap spaces



Scripting with GINsim and bioLQM

- Compute stable states for multiple combinations of perturbation

  → automation

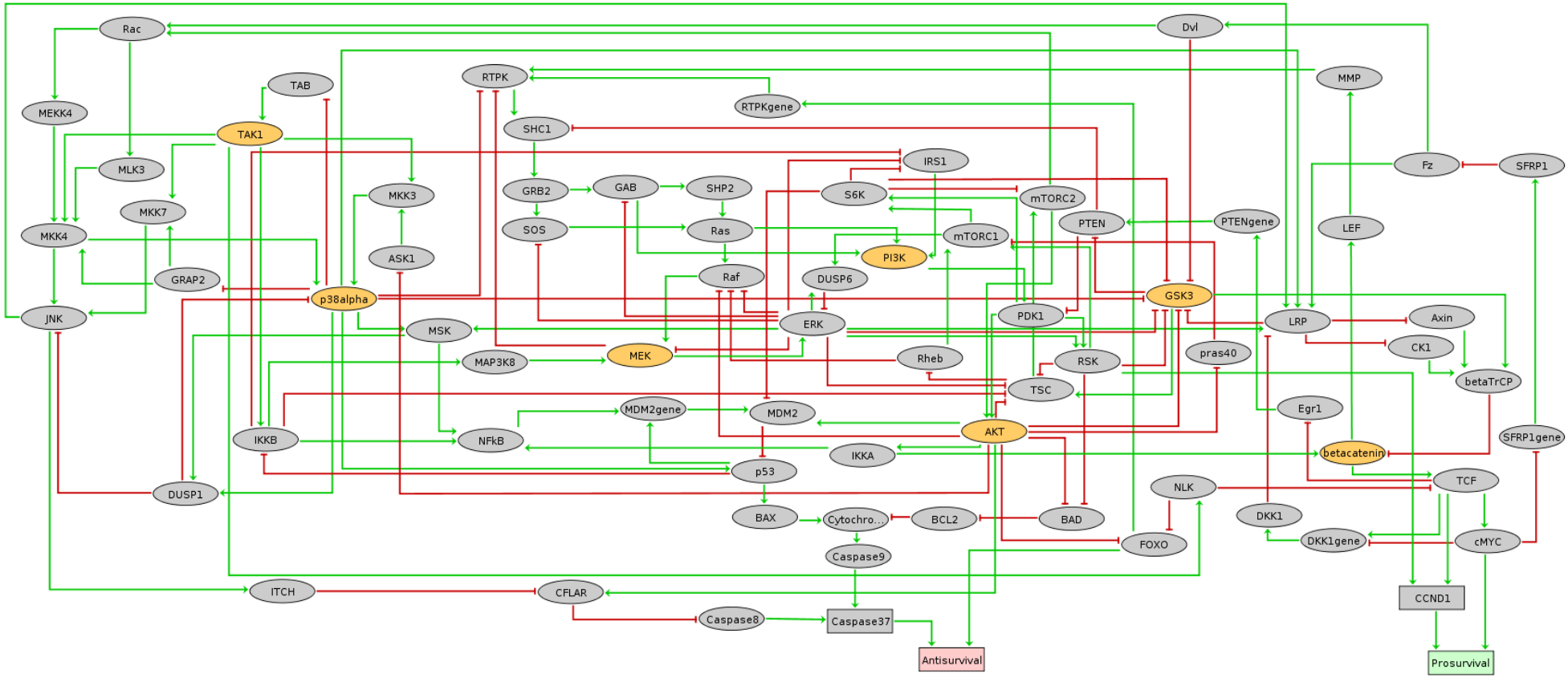
- Export into SBMLqual, ginml, bnet

  → standardardisation

Model Checking: validating our models

- NuSMV + temporal logic formulas
- Trap space reachability
- Findings on drug synergies?

Case study: gastric adenocarcinoma cells



- 77 nodes & 149 interactions
- 7 drugs
- 2 outputs: Prosurvival & Antisurvival

Thank you for your attention!

The DrugLogics team

Dept of Biology

Martin Kuiper
Steven Vercruysse
Wim De Mulder
Vladimir Mironov
Vasundra Touré
Stian Holmås
Rafel Riudavets

Dept of Clinical and Molecular Medicine

Astrid Lægreid
Liv Thommesen
Åsmund Flobak
Miguel Vazquez
Marcio Acencio
Barbara Niederdorfer
Evelina Folkesson
Kathleen Heck

Dept of Philosophy and Religious Studies

Rune Nydal
Ane Møller Gabrielsen
Anamika Chatterjee

NTNU
Norwegian University of Science and Technology

Acknowledgments

Andrei Zinovyev
Inna Kuperstein
Emmanuel Barillot

Antonio Fabregat
Steve Jupe
Noemi Del Toro
Sandra Orchard
Henning Hermjakob

Aurélien Naldi
Denis Thieffry

institutCurie

EMBL-EBI

1794 ENS ÉCOLE NORMALE SUPÉRIEURE

Funding:

NTNU Helse

ERACOSYSMED