Star-AI for the Analysis of Gene Data

Ralf Möller

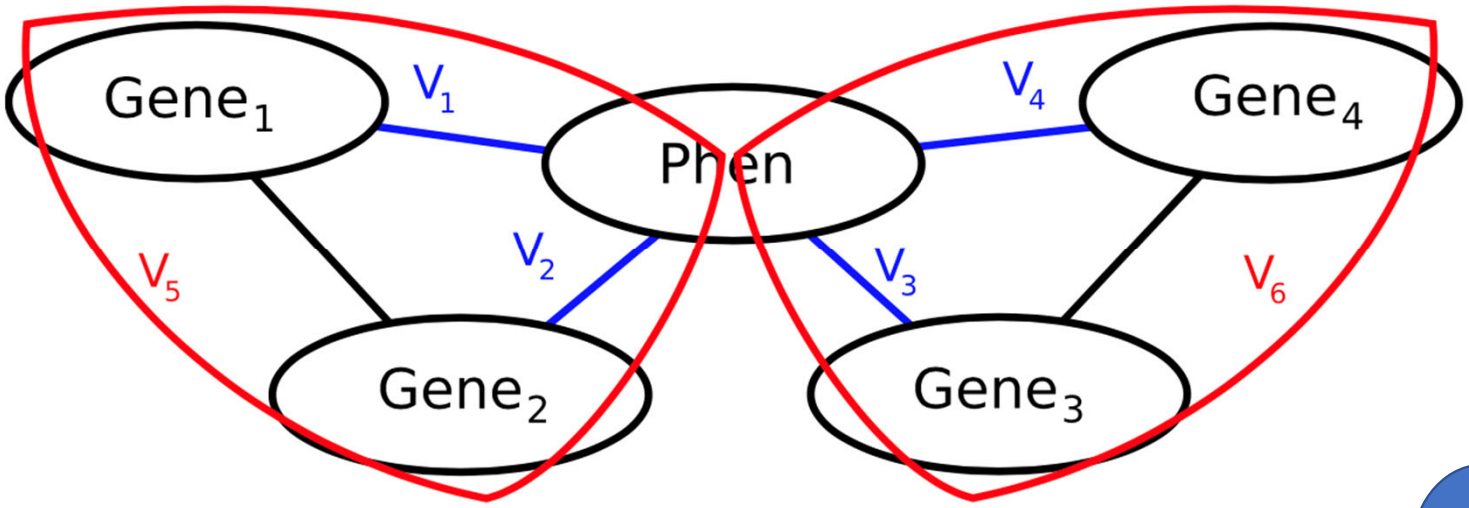
Presentation is based on:

Nikita, Sakhanenko, David Galas.
Markov Logic Networks in the Analysis of Genetic Data
Journal of Computational Biology, Volume 17, Number 11, pp. 1491–1508, **2010**.

Knowledge-based Genotype-Phenotype Associations

- Genome-wide association studies (GWAS) and similar statistical studies of g-p-linkage data assume simple additive models of gene interactions
  - Viewing compound effects of multiple genes on a phenotype as a sum of influences of each gene often misses a substantial part
  - Methods do not use any biological knowledge about underlying mechanisms
  - Unconstrained association searches require too many population samples, and can succeed only in detecting a limited range of effects
- Goal: Incorporate biological knowledge into statistical analysis
  - Need probability theory to capture uncertainty
  - Need FO Logic to avoid "model explosion"
- Claim: Can use Stochastic Relational AI (Star-AI) as an enabler
  - Complex, non-additive genetic interactions modeled
  - Learning with datasets of "reasonable" size

Model Joint Distribution w/ Markov Random Field



MRFs are too simple:
Model "explodes" with more complex interaction on many genes?

Propositional Logic

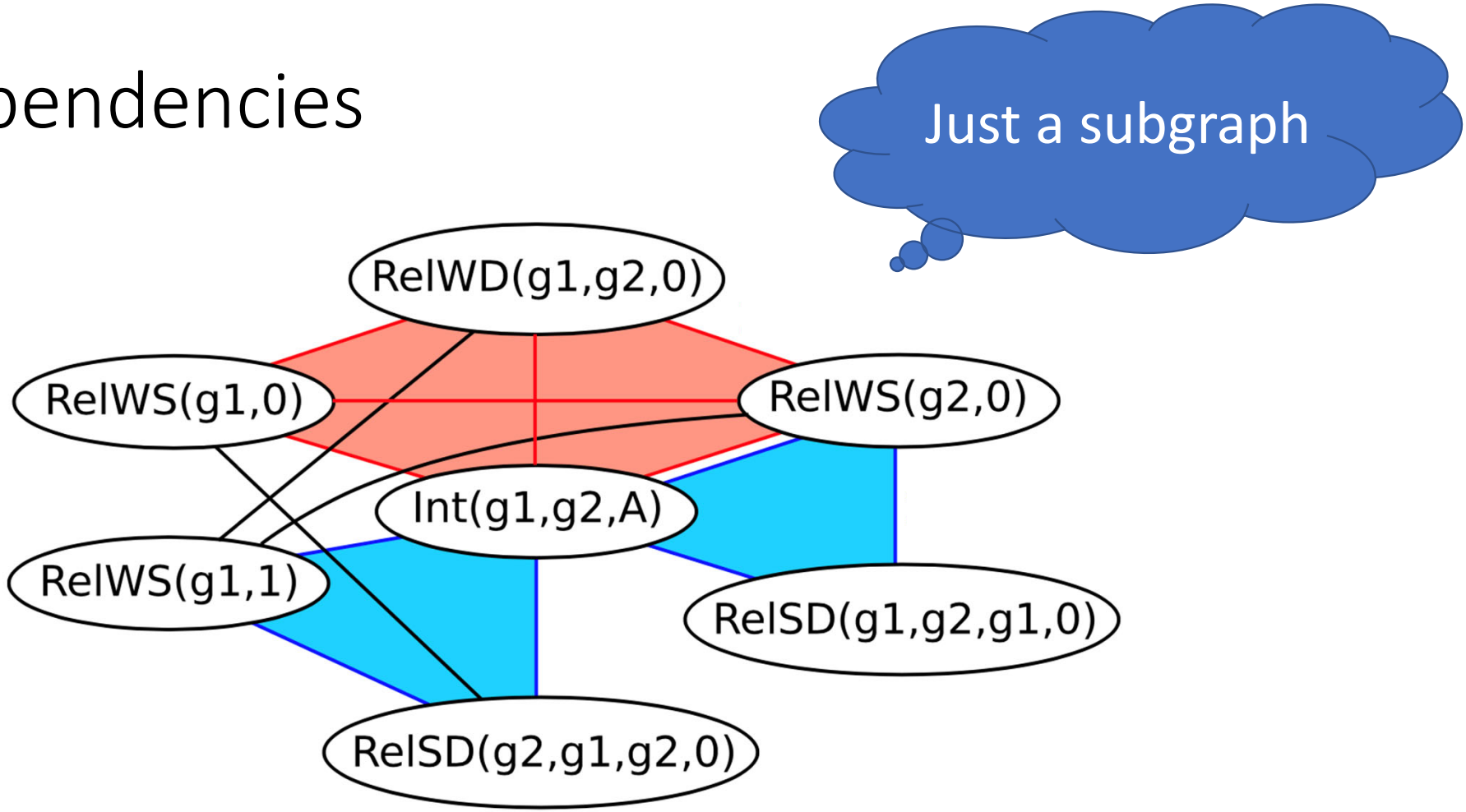
Why don't we use First-Order Logic?

FO-Signature for Biological Knowledge Base

- RelWS(x, v)
  - 2-argument predicate which captures a relation between a wild type and a single mutant
- RelWD(x, y, v)
  - Relation between a wild type and a double mutant
- RelSS(x, y, v)
  - Relation between two single mutants
- RelSD(x, y, x, v)
  - Relation between a single mutant and a double mutant
- Int(x, y, c)
  - Interaction between two genes wtih interaction type c

x, y: Genes: Domains {g1, g2}
v: Phenotype values: Domain {0, 1, 2}
c: Interaction types: Domain {A, B}

Dependencies

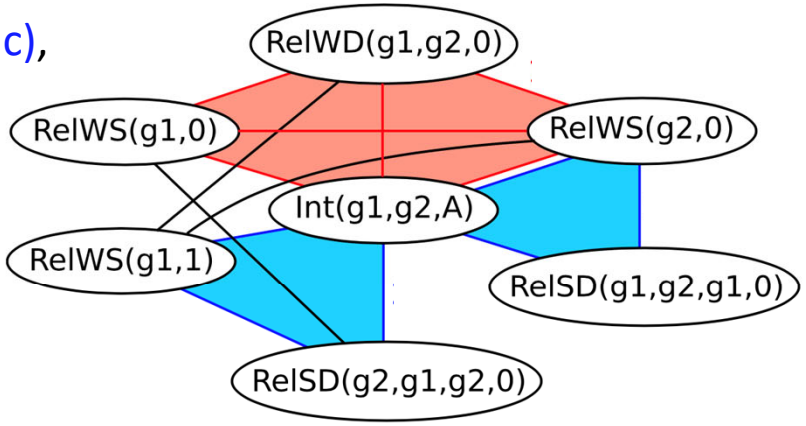


Objects, Relations, Uncertainty about Formulas

Markov Logic Network (MLN)

- Depending on the type of interaction between two genes Int(x, y, c), there is a dependency between RelWS(x, v) and RelSD(y, x, y, v)

- Three statements RelWS(x,v), RelWS(y,u), and RelWD(x,y,w), together determine the type of gene interaction Int(x, y, c)



1.5 $\forall x, y \in \{g1, g2\}, \forall c \in \{A, B\}, \forall v, u \in \{0, 1, 2\},$

$$\mathtt{Int}(x, y, c) \Rightarrow (\mathtt{RelWS}(x, v) \Leftrightarrow \mathtt{RelSD}(y, x, y, u))$$

2.1 $\forall x, y \in \{g1, g2\}, \forall c \in \{A, B\}, \forall v, u, w \in \{0, 1, 2\},$

$$\mathtt{RelWS}(x, v) \wedge \mathtt{RelWS}(y, u) \wedge \mathtt{RelWD}(x, y, w) \Rightarrow \mathtt{Int}(x, y, c).$$

Mathematics behind this representation language:

- Joint probability distribution over ground atoms (in this case Boolean randvars)
- Definition of jpd based on weights associated with formulas (details omitted for brevity)

Query Language

- What is the probability that a ground atom Q is true (event) given that every ground atom from a set $\{E_1, \ldots, E_m\}$ is true (conjunction of evidences)?

$$\Pr(Q \mid E_1 \wedge \ldots \wedge E_m, MLN)$$

- Query semantics based on MLN groundings

$$\Pr(Q \mid E_1 \wedge \ldots \wedge E_m, MLN) = \frac{\Pr(Q \wedge E_1 \wedge \ldots \wedge E_m \mid MLN)}{\Pr(E_1 \wedge \ldots \wedge E_m \mid MLN)}$$

$$= \frac{\sum_{\gamma \in \Gamma_Q \cap \Gamma_E} \Pr(\gamma \mid MLN)}{\sum_{\gamma \in \Gamma_E} \Pr(\gamma \mid MLN)},$$

where Γ_P is the set of *all possible configurations* where a ground predicate P is true, and $\Gamma_E = \Gamma_{E_1} \cap \ldots \cap \Gamma_{E_m}$.

Application: Yeast Sporulation

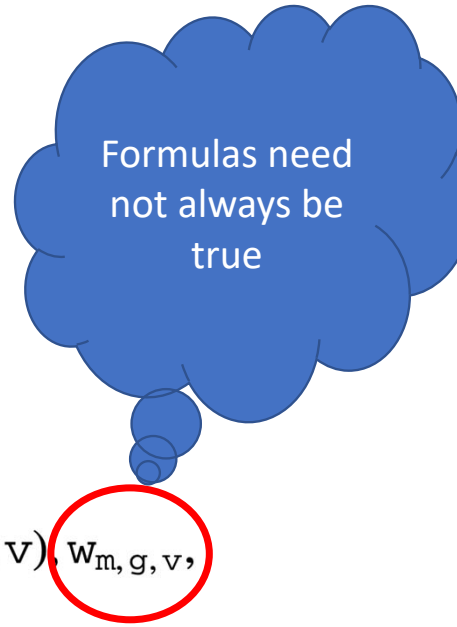
- Set of 374 progeny of a cross between two yeast strains (a wine and an oak strain) differing widely in their efficiency of sporulation
- For each of the progeny, the sporulation efficiency (phenotype) was measured and assigned a value from {very_low, low, medium, high, very_high}
- Each yeast progeny strain was genotyped at 225 markers uniformly distributed along the genome
  - Each marker takes on one of two possible values indicating whether it derived from the oak or wine parent genotype

Nikita, Sakhanenko, David Galas. **Markov Logic Networks in the Analysis of Genetic Data** Journal of Computational Biology, Volume 17, Number 11, pp. 1491–1508, **2010**.

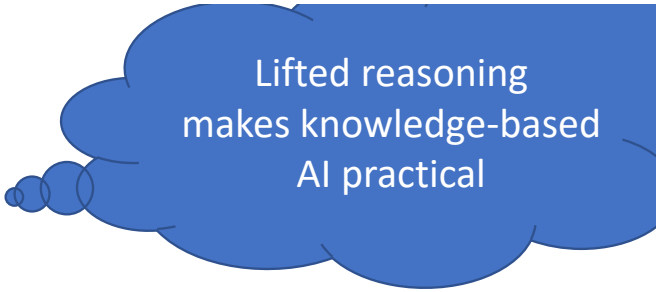
Example Knowledge Base and its Use

Model the effect of a single marker on the phenotype, i.e., sporulation efficiency:

- Signature of the model
  - G(s, m, g): Markers' genotype values across yeast crosses (evidence, predictor)
  - E(s, v): Phenotype (sporulation efficiency) across yeast crosses (target)
  - s: Strain
  - m: Marker
  - g: Genotype value (wine or oak parent)
  - v: Phenotype value (very_low, …, very_high)
  - w: Weight of the formula
- Information need: Find optimal strains
- KB: MLN patterns: $\forall \mathtt{strain} \in \{1, \ldots, 374\}, \mathtt{G}(\mathtt{strain}, \mathtt{m}, \mathtt{g}) \Rightarrow \mathtt{E}(\mathtt{strain}, \mathtt{v}), w_{\mathtt{m},\mathtt{g},\mathtt{v}},$
- Semantics: Formulas and their weights define probability distribution
- Queries: P(E(*Strain*, very_high)=true | G(42, m_1, g_1)=true, …, G(42, m_{17}, g_{23})=true)
- Answer to satisfy information need: Return strains with k-highest probability values



MLN Query Answering Algorithms



- Naïve grounding (combinatorial), then ground MRF QA
- Clever grounding (consider only relevant groundings, still combinatorial)
- Sampling (maybe quite inexact, approximation quality hard to control)
- Lifted query answering (exact, FPT: exponential in “tree width”, which is fixed for a model and small, linear in size of variable domains for liftable query classes)
  - Our preparatory works:

Tanya Braun.
Rescued from a Sea of Queries: Exact Inference in Probabilistic Relational Models
Dissertation 2020

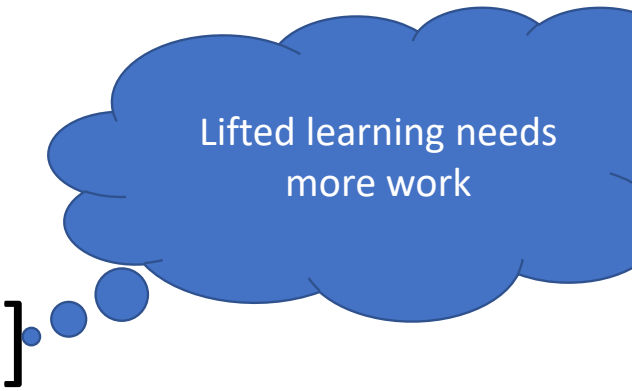
Tanya Braun, Ralf Möller, Marcel Gehrke.
https://www.ifis.uni-luebeck.de/index.php?id=672
Tutorial at ECAI 2020

MLN Learning from Application Data

Estimate ground joint probability distribution from data

Learning goal: Encode jpd in sparse form using MLNs

- Full MLN learning:
  - Take model signature from database schema
  - Determine suitable formulas from predicates in signature
  - Determine weights using maximum likelihood estimator
- Weight learning only (formulas given):
  - Determine weights using maximum likelihood estimator



Lise Getoor, Ben Taskar.
Introduction to Statistical Relational Learning.
MIT Press, 2007.

Challenges for Research

I do not merely “apply AI methods”
I do AI research:
Generalize intelligence across applications

- Develop Intelligent Agents for
  - Finding optimal targets for given predictors: Apply approach to gene analysis problems
  - Allow for cooperating agents to organize learning autonomously
    - Generalize results from precision medicine
- Deal with interaction of gene sequences in a genome rather than single genes?
  - Exploit results on temporal reasoning (dynamic Star-AI)?
  - Our preparatory work:

    Marcel Gehrke, Ralf Möller, Tanya Braun.
    Taming Reasoning in Temporal Probabilistic Relational Models
    in: Proceedings of the 24th European Conference on Artificial Intelligence (ECAI 2020), 2020.

    Marcel Gehrke.
    Taming Reasoning in Temporal Probabilistic Relational Models
    Dissertation 2021

- Compile MLNs into Lifted Tensor Networks for faster execution on a quantum computer?
  - Exploit entanglement of qubits in a lifted way to compute with “reasonable” number of qubits

    Nathan A. McMahon, Sukhbinder Singh & Gavin K. Brennen.
    A holographic duality from lifted tensor networks.
    npj Quantum Information volume 6, Article number: 36. 2020.

Bibliography

Application scenario:

- Nikita, Sakhanenko, David Galas. **Markov Logic Networks in the Analysis of Genetic Data**. Journal of Computational Biology, Volume 17, Number 11, pp. 1491–1508, 2010.

See also:

- Yi, N., Yandell, B.S., Churchill, G.A., et al. 2005. **Bayesian model selection for genome-wide epistatic quantitative trait loci analysis**. Genetics 170, pp. 1333–1344, 2005.
- Luc De Raedt, Kristian Kersting, Sriraam Natarajan and David Poole, **Statistical Relational Artificial Intelligence: Logic, Probability, and Computation**, Synthesis Lectures on Artificial Intelligence and Machine Learning. 2016

For QA as well as learning algorithms for Star-AI, see:

- https://www.ifis.uni-luebeck.de/index.php?id=672
- https://www.ifis.uni-luebeck.de/index.php?id=703&L=2