Knowledge models and inference frameworks for scientific discovery

With applications in systems biology

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Abstract

Scientific discovery is an active process of designing, testing, and improving theories about the natural world. To design an AI-robotic system that can automate this process is a grand challenge for 21st century science. This thesis examines the nature of scientific inquiry as it relates to machine learning, offering contributions to knowledge representations and reasoning frameworks, as well as demonstrations of their application in the field of systems biology.

Systems biology is an integrationist approach to biological science, meaning we treat organisms as complex systems whose behaviour is dictated by the interaction of their constituent parts. Because eukaryotic organisms are extremely complex systems, research progress in systems biology can be slow. Recent advances in robotics, and more importantly in artificial intelligence (AI), offer great opportunity for automating scientific discovery in this field.

Using the model organism *Saccharomyces cerevisiae*, baker's yeast, this thesis explores: the philosophical and practical motivations for the use of automation in biological research; the structure of knowledge models, experimental data, and hypotheses in systems biology; and computational models of metabolism, a core component of systems biology.

The first main contribution is a first-order logic framework for modelling cellular physiology, which enables abduction of hypotheses for improvement of knowledge models, coupling a set of predicates and clauses expressing biochemical reaction processes with an efficient automated theorem prover (ATP), iProver. The second main contribution of this thesis is an ontology for describing theory changes and hypotheses in a semantic and storage-efficient manner. The third main contribution is an application of graph neural networks (GNNs) to learn knowledge graph embeddings that are grounded both in empirical data and ontology structures. And the final main contribution is an end-to-end demonstration of autonomous hypothesis generation and experimentation, with particular treatment of the modelling of hypotheses using existing and new ontology terms, so that the knowledge graphs can be exploited and improved by LLM agents and human scientists.

The contributions of this thesis serve to demonstrate the power of knowledge graphs as a basis for autonomous scientific discovery. Their structure can inform algorithmic hypothesis generation, interface with robotic systems for laboratory experiments, enable fast deduction and theory repair, and relate to the metadata of science. We also claim that scientific discovery should be viewed as a supervised learning problem rather than reinforcement learning,

and in the case of AI scientists, one of active learning. By mapping concepts from machine learning algorithms to the domain, we obtain systems that align with scientific values which leads to improved theories.

Keywords

Machine learning, first-order logic, abduction, automated theorem provers, knowledge modelling, ontologies, systems biology, metabolic modelling

Summary

Automation of scientific discovery

- Scientific discovery should be viewed by machine learning researchers as supervised learning, specifically as an active learning problem.

- Reinforcement learning is an unsatisfactory paradigm for scientific discovery, for several reasons: definition of the agent, environment, and reward gives rise to philosophical challenges; action–feedback time is not short; and the evaluation of reward function is not cheap, even if one could be defined.

- For other aspects of robot scientists, such as laboratory automation, reinforcement learning algorithms may be useful.

- The process of designing a robot scientist involves mapping the activities of the scientific method to appropriate agents and coordinating them.

- Logical models and LLMs can be combined in an agentic system to form and refine hypotheses, and to design experiments for a robot scientist.

- Several automation workflows were developed, and integrated into both human-driven and fully automated studies.

- Such automated experimentation lead to discovery of novel interactions between compounds in *S. cerevisiae.*

Knowledge representations

- By representing hypotheses using description logics, under a novel framework, and doing the same for experiment design and empirical data, we can efficiently reuse data to assess hypotheses, and construct clear, reproducible scientific knowledge.

- Knowledge graphs in biology, including those community-curated, can be used as the basis for first-order logic (FOL) theories of metabolism.

- We design an ontology to capture and explain changes to computational biology models. This ontology can be used as a schema for a model

revision database (knowledge graph), with each revision an unambiguous and storage efficient patch.

Inference methods

- Deductive inference on FOL theories of metabolism using an automated theorem prover (ATP) can: (a) predict growth/no-growth of *S. cerevisiae* strains in a minimal growth medium; and (b) predict expression of metabolic pathways of such strains.

- By extending an ATP to include algorithms for induction inference through reverse consequence finding, novel hypotheses about the biological system can be abduced from the logical theory.

- We present options for the evaluation of these hypotheses using internal consistency, external consistency, and predictive accuracy.

- Simulation models can be used to instantiate abstract hypotheses about uncharacterised genes in *S. cerevisiae* for comparison with empirical data. This is demonstrated on the previously uncharacterised open reading frame YGR067C, which we propose regulates genes related to ethanol consumption and respiration during the glucose phase of the diauxic shift.

- Incorporating measures of internal consistency (semantic loss) into GNN-based box embeddings significantly improves predictive power, demonstrated on a mutant strain fitness prediction task for *S. cerevisiae*. Semantic loss also enables the learning of box embeddings in the absence of a prediction task.

- Applying measures of parsimony (regularisation loss) increases the stability of training GNN-based box embeddings on knowledge graphs.

- Box embeddings learned using a GNN, to convey information from knowledge graph neighbours, learn the class hierarchy of the ontologies more effectively than without the GNN.

- Knowledge graph box embedding distance (from one set of embeddings to another) contains information that could be useful for evaluating candidate revisions to the graph.

List of Publications

Appended publications

This thesis is based on the following publications:

[**Paper I**] **A. H. Gower**, D. Brunnsåker, F. Kronström, G. K. Reder, R. S. Reiserer, I. A. Tiukova, K. Korovin, J. P. Wikswo, R. D. King, *The Use Of AI-Robotic Systems For Scientific Discovery*
Under submission.

[**Paper II**] F. Kronström, **A. H. Gower**, I. A. Tiukova, R. D. King, *RIMBO - An Ontology for Model Revision Databases*
In International Conference on Discovery Science (pp. 523–534). Cham: Springer Nature Switzerland. (October 2023). `https://doi.org/10.1007/978-3-031-45275-8_35`

[**Paper III**] **A. H. Gower**, K. Korovin, D. Brunnsåker, E. Y. Bjurström, P. Lasin, I. A. Tiukova, R. D. King, *LGEM$^+$: Automated Improvement of Metabolic Network Models and Model-Driven Experimental Design through Abduction*
To be submitted to PLoS Computational Biology. Extension of **Paper [a]**

[**Paper IV**] F. Kronström, **A. H. Gower**, D. Brunnsåker, I. A. Tiukova, R. D. King, *Graph Neural Network based hierarchy-aware Box Embeddings of Knowledge Graphs*
Under review at Neurosymbolic Artificial Intelligence. `https://neurosymbolic-ai-journal.com/system/files/nai-paper-881.pdf`

[**Paper V**] E. Y. Bjurström, **A. H. Gower**, P. Lasin, O. I. Savolainen, *Investigating uncharacterised genes in Saccharomyces cerevisiae using Robot Scientists*
Under submission to Scientific Reports.

[**Paper VI**] D. Brunnsåker, **A. H. Gower**, P. Naval, E. Y. Bjurström, F. Kronström, I. A. Tiukova, R. D. King, *Agentic AI Integrated with Scientific Knowledge: Laboratory Validation in Systems Biology*
Under review at Cell Patterns.

Other publications

The following publications were published during my PhD studies, or are currently in submission/under revision. However, they are not appended to this thesis, due to contents overlapping that of appended publications or contents not related to the thesis.

[a]   **A. H. Gower**, K. Korovin, D. Brunnsåker, I. A. Tiukova, R. D. King, *LGEM$^+$: A First-Order Logic Framework for Automated Improvement of Metabolic Network Models Through Abduction*
      In International Conference on Discovery Science (pp. 628–643). Cham: Springer Nature Switzerland. (October 2023). `https://doi.org/10.1007/978-3-031-45275-8_42`

[b]   D. Brunnsåker, G. K. Reder, N. K. Soni, O. I. Savolainen, **A. H. Gower**, I. A. Tiukova, R. D. King, *High-throughput metabolomics for the design and validation of a diauxic shift model*
      npj Systems Biology and Applications, Volume 9, Issue 1, Article number 11 (April 2023). `https://doi.org/10.1038/s41540-023-00274-9`

[c]   G. K. Reder, **A. H. Gower**, F. Kronström, R. Halle, V. Mahamuni, A. Patel, H. Hayatnagarkar, L. N. Soldatova, R. D. King, *Genesis-DB: a database for autonomous laboratory systems*
      Bioinformatics Advances, Volume 3, Issue 1 (August 2023). `https://doi.org/10.1093/bioadv/vbad102`

Statement of Contributions

Paper I Conceived the idea and main points. Conducted the literature research. Wrote the manuscript.

    Notes for committee I was invited to write this book chapter after delivering a talk at the 2023 AAAI Spring Symposium in San Francisco, which touched on some of the themes presented. The ideas in this chapter originated after reading my supervisor's paper, "Automating Science: Philosophical and Social Dimensions", and subsequent discussions with him and our group. The audience of the book is primarily machine learning researchers, and it seemed to me that there was missing from the literature a treatment of these philosophical questions about robot scientists in the context of machine learning paradigms. The goal with this work was to firstly identify which paradigms in machine learning are most applicable to robot scientists, and secondly to make the case for this in the context of the philosophy of science, in particular the natural sciences, a field that machine learning researchers are well-versed in. Consequently, the research I conducted for this chapter was primarily literature review and discussions with colleagues. Several of the key people who participated in these discussions are listed as co-authors, as well as the original list of collaborators from the talk I gave at AAAI[1], though I wrote the text of the chapter and formed its arguments.

Paper II Co-conceptualised the study. Conducted experiments to test and demonstrate revisions on Yeast8 GEM. Contributed to curation and preparation the data.

    Notes for committee The idea for this ontology came from discussions between Filip and I about the nature of a hypothesis in systems biology. We agreed that at the heart of any hypothesis was a change, and that these changes were not recorded in sufficient semantic detail in the extant research flows, particularly not when it came to automation, hence the focus of this work on theory revisions. Filip did the bulk of the design work for the ontologies, to which I provided feedback, and my contributions were in testing and demonstration, as well as curating domain data for the tests.

Paper III Co-conceptualised the study. Designed the logical predicate and clause structure. Developed and tested the code to generate logical

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[1] http://cogsys.org/symposium/discovery-2023/schedule.html

theory structures from GEMs. Prepared and curated the data. Designed and executed the experiments. Co-conducted the microarray expression data analysis. Designed and prepared the figures, wrote the manuscript.

Notes for committee This manuscript is an extension of a peer-reviewed conference paper, Paper [a], presented at Discovery Science in 2023. My main collaborator on this work was Konstantin Korovin, who is an expert in automated theorem provers, and is the author of iProver. We worked to identify improvements that we could make to iProver that would enable us to run the abduction algorithm; Konstantin implemented these improvements in iProver. I designed the experiments, and wrote the non-iProver code to implement them. The idea for FBA constraint as an internal consistency check came from discussion with Konstantin, which we implemented together as it involved changes both to iProver code and the Python scripts.

Paper IV Co-conceptualised the study. Co-designed and co-implemented the semantic and regularisation losses. Co-designed method for training of a model in the absence of a prediction task; wrote and tested code for the demonstration of this method. Designed the algorithm for link evaluation; wrote and tested code for this method. Designed and prepared Figures 7 and 8. Co-wrote the manuscript.

Notes for committee This work was an extension of a paper presented by Filip at the 19th International Conference on Neurosymbolic Learning and Reasoning. Having discussed with Filip the description logic formalism, we conceived the idea to try an extension to the work to learn using semantic losses. I helped to implement these, as well as to design and test regularisation losses. A motivation for this was eventually to use this technique to learn embeddings of an expanded ontology, including the description logic formalism used in Paper VI to describe hypotheses. Also with this application in mind, we came up with the idea of using box embedding distance to assess candidate revisions to the graph; I then designed and implemented this algorithm. I contributed to a significant rework of the manuscript from the conference paper, including many of the mathematical descriptions.

Paper V Co-conceptualised the study. Designed and wrote the code for the simulation methods. Wrote the automation scripts for the cultivation robot. Contributed to the data analysis.

Notes for committee Figure 1 captures the idea behind my contributions to this paper, that there are parallel choices made in experimental design and simulation design in order to arrive at data that are comparable. From this, I designed and implemented the simulations, and helped with the experimental design and implementation, as listed above.

Paper VI Co-conceptualised the study. Significant contributions to the design of the framework, including designing the generation and analysis agents and coordination. Co-designed the ontologies and databases. Contributed to the automation scripts for the cultivation robot. Designed and prepared Figure 5. Co-wrote the manuscript.

Notes for committee Drawing on my research for the book chapter (Paper I) on the scientific method, I identified the different tasks in the research cycle, which should be done with LLM agents, and how they might be coordinated. I worked closely with Daniel to design these agents and how they should prompt and re-prompt each other in different cases. I encoded the hypotheses in logic and helped in connecting these with the LLM outputs. Designed the description logic formalism, tested it with hypotheses, and made several rounds of revisions after testing. Also followed a query-based design process for the graph database, which required some revisions to the ontologies. Designed the automation scripts for the cultivation robot, Eve.