Reproducible Science

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The AI grand challenge of accelerating science

The AI grand sub-challenge: reproducible science

• The reproducibility crisis: probably the most important problem the scientific community is facing.

• If remains unresolved, the credibility of science could be irrevocably damaged.

• “More that 70% of researchers have tried and failed to reproduce another scientist’s experiments, and more than half have failed to reproduce their own experiments” (1).

• Macleod et al state that in US “85% of research investment is wasted” (2).

Reasons for the non-reproducibility

- the complexity of scientific methods,
- poor experimental design,
- the non-availability of raw data, code, etc.
- the use of natural language i.e. English

“The argument is simply that by the word 'experiment' we refer to a situation where we can tell others what we have done and what we have learned and that, therefore, the account of the experimental arrangement and the results of the observations must be expressed in unambiguous language ...” (2)

Formal knowledge representation

- ~500 Ontologies in BioPortal, ~40 MI (Minimum Information for...), other standards, knowledge bases, ...
- The main focus is on declarative knowledge – not enough for the reproducibility!

“Recent calls to ... the research community, and funding agencies to improve rigor and reproducibility in science clearly point to the need to take a new approach to communicating not just the ‘what’ but the ‘how’ of science”

Formal representation of procedural knowledge

- OBI (the Ontology for Biomedical Investigations): e.g. OBI: data transformation, OBI: injection
- EFO (Experimental Factors Ontology): a systematic description of experimental variables for capturing experimental designs
- SMART (SeMAntic RepresenTation for Experimental Protocols): provenance, objectives,…
- EXACT (Experimental ACTions) ontology: definitions of typical actions and their properties

Not Enough!
Example: a Robot Scientist EVE

- Fully autonomous robotic system for drug (lead) discovery
- All aspects of scientific studies are formally recorded
- There are dedicated ontologies for Eve: equipment ontology, Eve (typical experiments), HELO (hypotheses), EXACT (protocols), UNO (uncertainties)
- Eve moved from Aberystwyth to Manchester
- Eve could not reproduce previous drug screening experiments
- The reason: a mode of shaking – it took two months to find out
- The level of granularity of the representation is
  - OR too low (for equipment)
  - OR too high (for humans)
European AdaLab project (2015-2018)

- We are developing a framework for semi-automated and automated knowledge discovery by teams of human and robot scientists.
- This framework integrates and advances: knowledge representation, ontology engineering, semantic technologies, machine learning, bioinformatics, and automated experimentation.
- We are evaluating the AdaLab framework on an important real-world application: cancer and ageing.
Overview of AdaLab
Generation of reproducible experimental protocols

research hypothesis

- gene YER152C encodes an enzyme E.C. 2.6.1.39

- addition of the metabolite lysine to a standard growth medium will differentially affect the growth of the yeast strain delta_YER152C compared to the wild type BBY4741

- experimental factor 1: growth of yeast train delta_YER152C
- experimental factor 2: concentrations of lysine
- control: growth of wild type BBY4741 with and without lysine
- randomisation: latin square

- action1: inoculate entity: yeast in growth medium
- volume: 35mL
- equipment: dispenser1
- equipment: 96-wells-plate
...

EXAMPLE

- KEGG: E.C.2.6.1.39
- SGD: S0000954
- GO: 0047536
- 2-oxoglutarate + L-2-aminoadipate

- rule: a strain with a gene removed is a proxy for the gene
- rule: addition of lysine can restore the growth of delta_YER152c
- rule: a control for a strain with a gene removed is a WT strain

- wild type (Mat A, BBY4741)
- lysine (C00449)
- ODs measurements
- EXACT: inoculate
- EVE: 96-well-plate
- EVE: dispenser1

knowledge layer

- domain ontologies
- lab specific ontologies
- experimental knowledge base
Generation of reproducible experimental protocols

**Constraints:**
- time, money
- 8h break
Generation of reproducible experimental protocols

Constraints:
- time
- money
- 8h break

Modifications:
- What can be changed?
- What cannot be changed?
- What is best to change?
• Construct a computational model, e.g., a network of genes that orchestrate a specific biological process of interest, that make experimentally testable predictions.

• Design and prioritize, orchestrate, and execute experiments.

• The task of designing an optimal experiment that provides the most valuable information at the lowest cost to help answer a chosen scientific question requires a careful exploration of the space of possible experiments, their relative cost, risk, and feasibility, in the context of all that is known.
UNO: uncertainties ontology

OWL ontology covering: event-related concepts, metadata concepts and probability types.
**PANDA:** probabilistic knowledge assembly framework

### Event Representation

- **event(ev):**
  - **supported(X):** 0.7:: supported(X) :- event(X), statement(Y), represents(Y, X), hasTruthValue(Y, true), combinedProb(Y).

### Combined Probability

- **combinedProb(Y):**
  - extractionProb(Y), provenanceProb(Y).

### Support for an Event

- **support for an event**
  - = disjoint sum of (combined) probabilities of different supporting statements, with each statement weighted by 0.7

### Combined Probability

- **combined probability**
  - = product of all probability scores

### Statements

- **statement(s1):**
  - represents(s1, ev).
  - hasTruthValue(s1, true).
  - 0.8::extractionProb(s1).
  - 0.7::provenanceProb(s1).

- **statement(s2):**
  - represents(s2, ev).
  - hasTruthValue(s2, true).
  - 0.7::extractionProb(s2).
  - 0.6::provenanceProb(s2).

### Probability Calculation

- **supported(ev) -> 0.392**
- **supported(ev) -> 0.570752**

Note the increase in the probability of corroborated(ev) on adding the second supporting statement.
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Questions?