Synthesizing Clinical Trials for Evidence-based Medicine: a Representation of Empirical and Hypothetical Causal Relations

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Introduction

In medicine, clinical trials are the de facto method for measuring causal relations. A longstanding challenge is synthesizing this causal information for evidence-based medicine. We have developed a free web application, ResearchMaps, which uses a machine-interpretable format to record both empirical and hypothetical causal statements reported in clinical trial literature. Translational researchers can use our software's graph-based interface to aggregate and interpret results from multiple clinical trials.

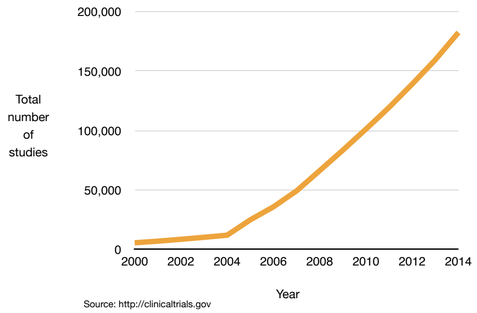
In the clinical trial literature, a lot of knowledge remains unused simply because it exists as unstructured free-text. ResearchMaps gives machine-readable structure to this causal information. Our software is a step toward the automation of experiment planning and hypothesis generation. Grounding these processes in formal logic and automating them with software has the potential to revolutionize the scientific method.

This poster presents:

- how researchers can record and visualize causal relations
- annotation guidelines for extracting causal information
- preliminary annotation results for lung cancer literature

The growth of the literature

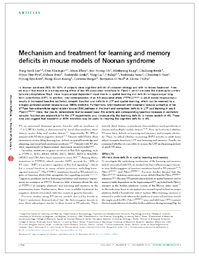
Total number of registered studies on ClinicalTrials.gov

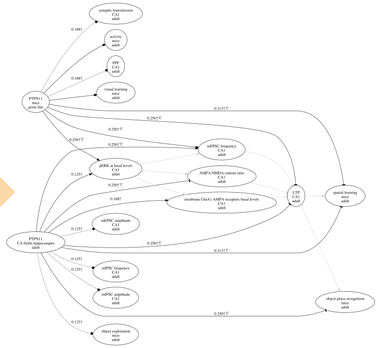


Source: http://clinicaltrials.gov

ResearchMaps — researchmaps.org

Originally developed for the neurosciences, ResearchMaps is a free web application that records experiments and visualizes the causal relations suggested by the results. After entering the experiments reported in an article, the user is presented with a graphical representation of causal relations.


Mechanism and treatment for learning and memory deficits in mouse models of Noonan syndrome

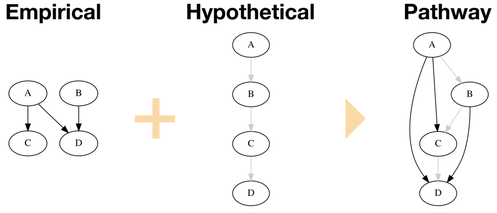


- excitatory →
- inhibitory ⊣
- no relation ●

- positive manipulation ↑
- negative manipulation ↓
- non-intervention ∅
- multi-connection ∇

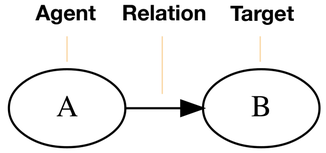
Empirical and hypothetical relations

Many biological phenomena are described as biochemical cascades, or signal pathways. When an article reports experiments dealing with only a subset of the entities in a pathway, the resulting graph does not make the pathway evident. To address this problem, ResearchMaps models both empirical and hypothetical relations. An empirical relation represents the results of an actual experiment, while a hypothetical relation represents a putative result.



Annotation guidelines

To translate ResearchMaps to the clinical domain, and to formalize the extraction of causal information from free-text, we created a set of annotation guidelines.



Agent

An entity that, with or without experimental manipulation, undergoes a change in state that is believed to cause a change in another entity (Target).

Target

An entity that either

- undergoes a change in state that is believed to result directly — either in whole or in part — from a preceding change in state of another entity (Agent), or
- does not change its state, regardless of a preceding change in state of another entity.

Relation

A directed relationship between an agent and a target that describes how the target is expected to change as a result of a specific change in the agent.

- increase (quantity or probability)
- decrease (quantity or probability)
- no change (quantity or probability)

Evidence

Statistical and other information that captures the precise experimental context in which a casual relation holds true. Examples include:

- statistical test
- p-value

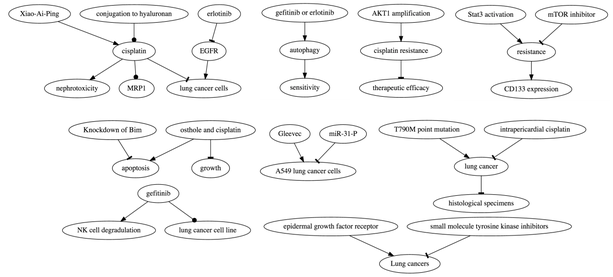
References

Landreth A, Silva AJ. The need for research maps to navigate published work and inform experiment planning. Neuron. 2013; 79(3):411–415.

ClinicalTrials.gov. Trends, Charts, and Maps [Internet]. Bethesda (MD): National Library of Medicine (US). 2000–2015. Available from: https://clinicaltrials.gov/ct2/resources/trends.

Annotation results

Per our guidelines, we annotated literature on non-small cell lung cancer — particularly studies of drugs and gene expression. We then used the ResearchMaps framework to create a graphical representation of this information, a portion of which is shown below.



Discussion

- We need to annotate causal statements with respect to a specific ontological representation of all the phenomena involved.
- We can use contextual evidence to assign weights to causal relations reported in different sources.
- Our guidelines seek to decouple the two tasks of (1) representing the phenomena and (2) describing each causal relation.

Summary of Conclusions

- We need a formal representation of causal information to fully leverage the knowledge in the clinical trial literature.
- A formal representation of causality should include representations of both qualitative and quantitative evidence.
- ResearchMaps is an excellent tool for recording and analyzing causal information.
- ResearchMaps's visualization of causal information facilitates experiment planning and hypothesis generation, processes that can be automated with an appropriate machine-interpretable representation of causality.