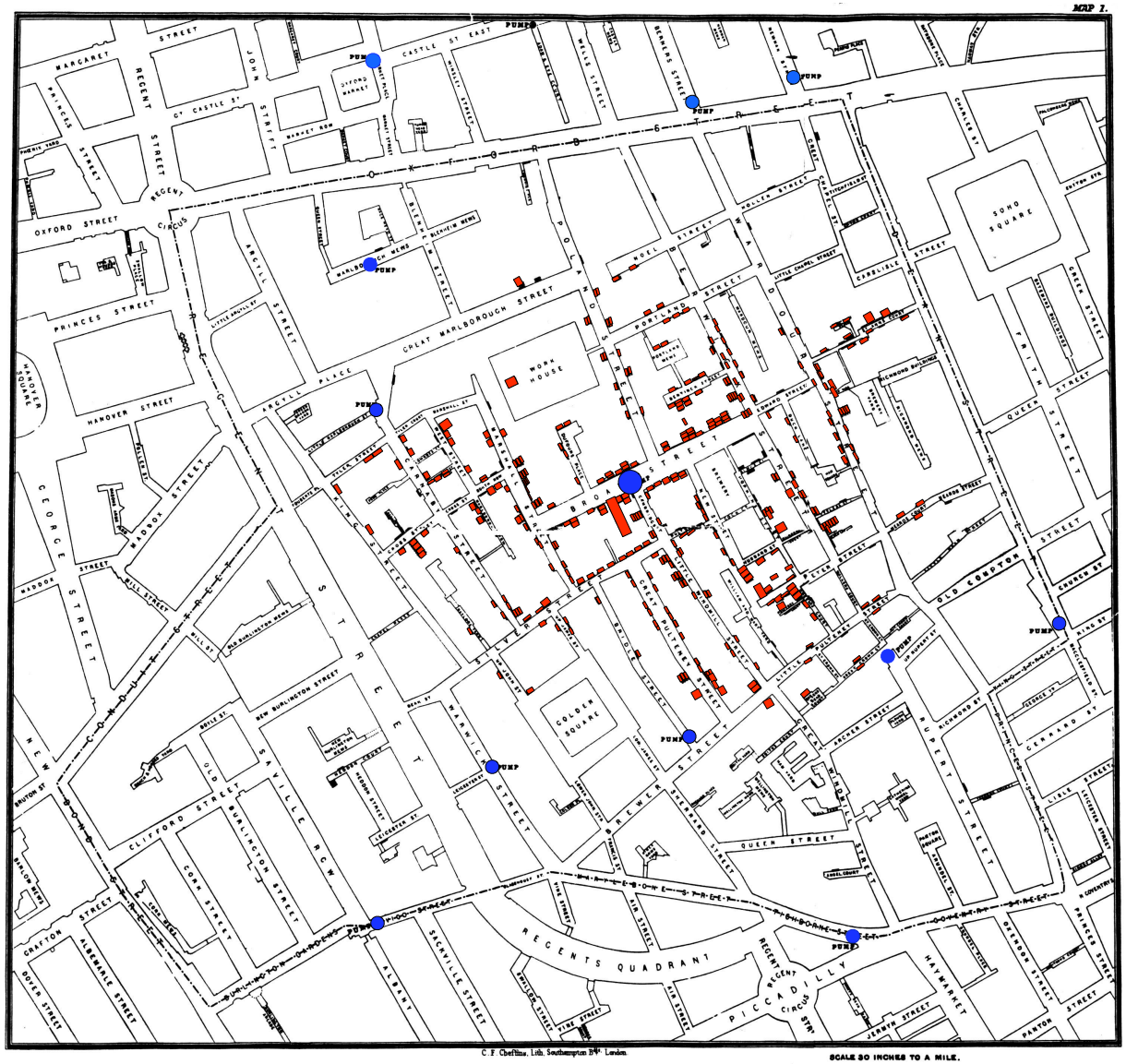
Big Mechanism

Paul Cohen

2014/01/31

Big Data, 1854



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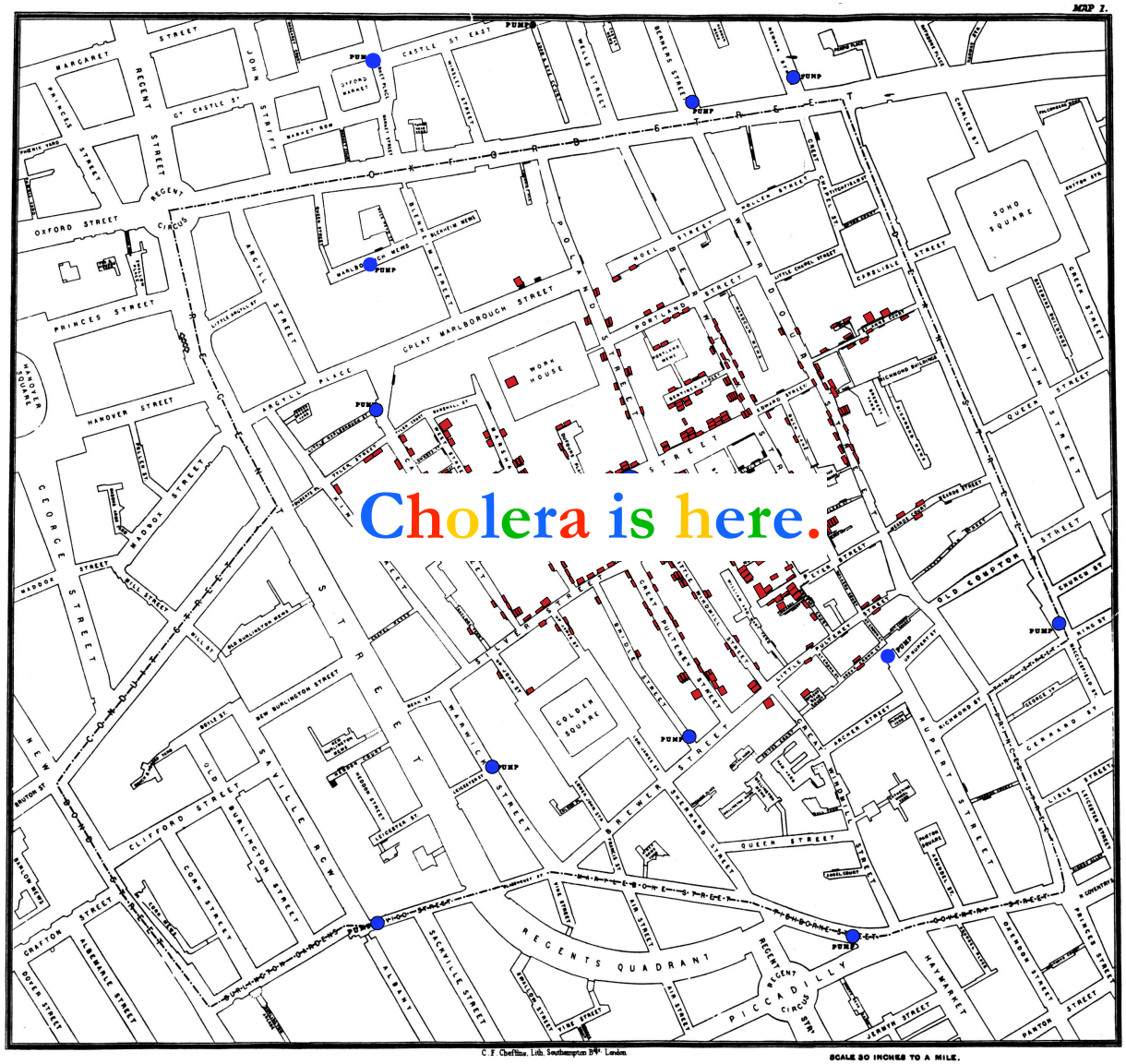
Big Data, 2013



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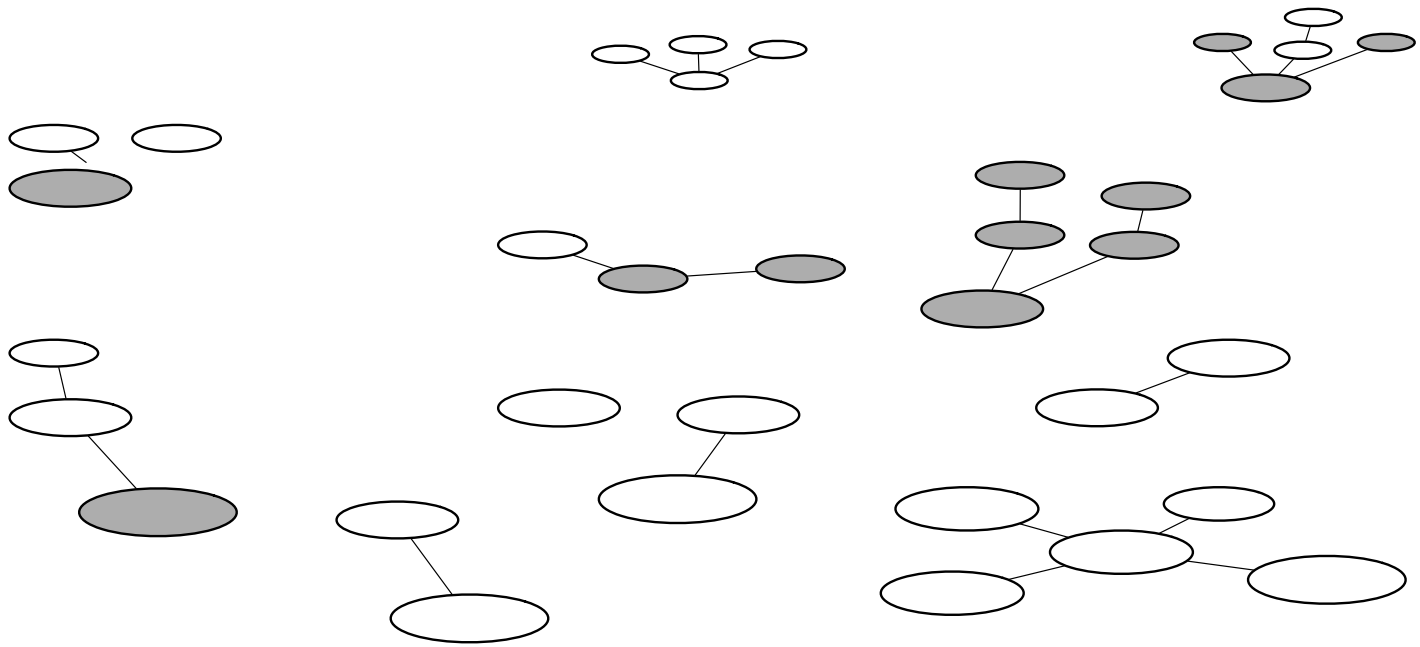
The Problem

We need to understand the mechanisms of big, complicated systems.

But our knowledge of these mechanisms is increasingly fragmented, voluminous and inconsistent.



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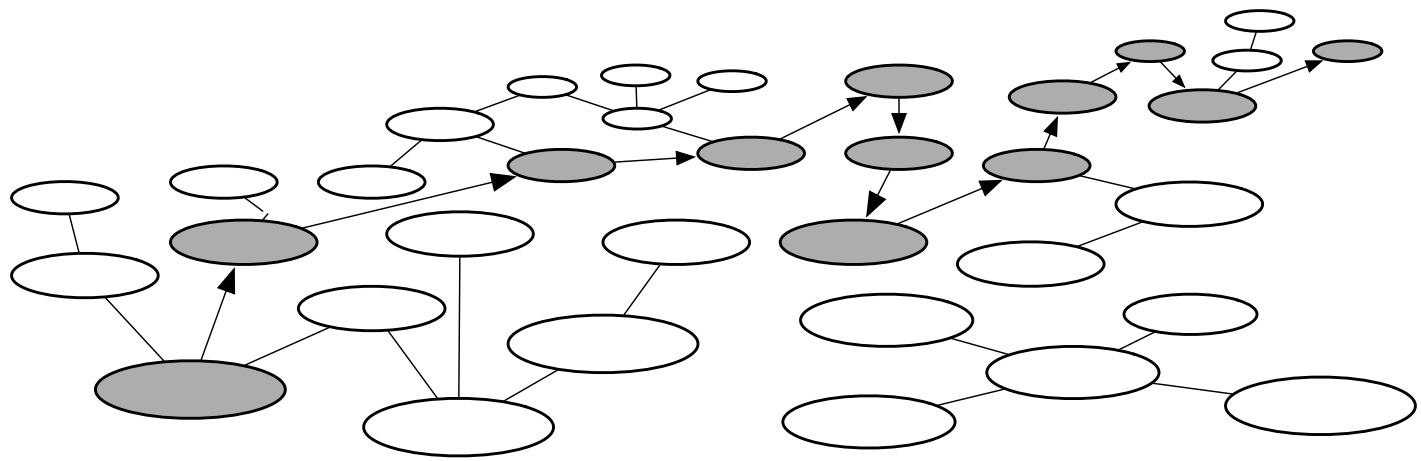
The Solution: Read, Assemble, Explain

We need to understand the mechanisms of big, complicated systems.

But our knowledge of these mechanisms is increasingly fragmented, voluminous and inconsistent.

The Solution: Make computers **read** documents and data, and **assemble** the fragments they contain into Big Mechanisms that **explain** causes and effects within systems.



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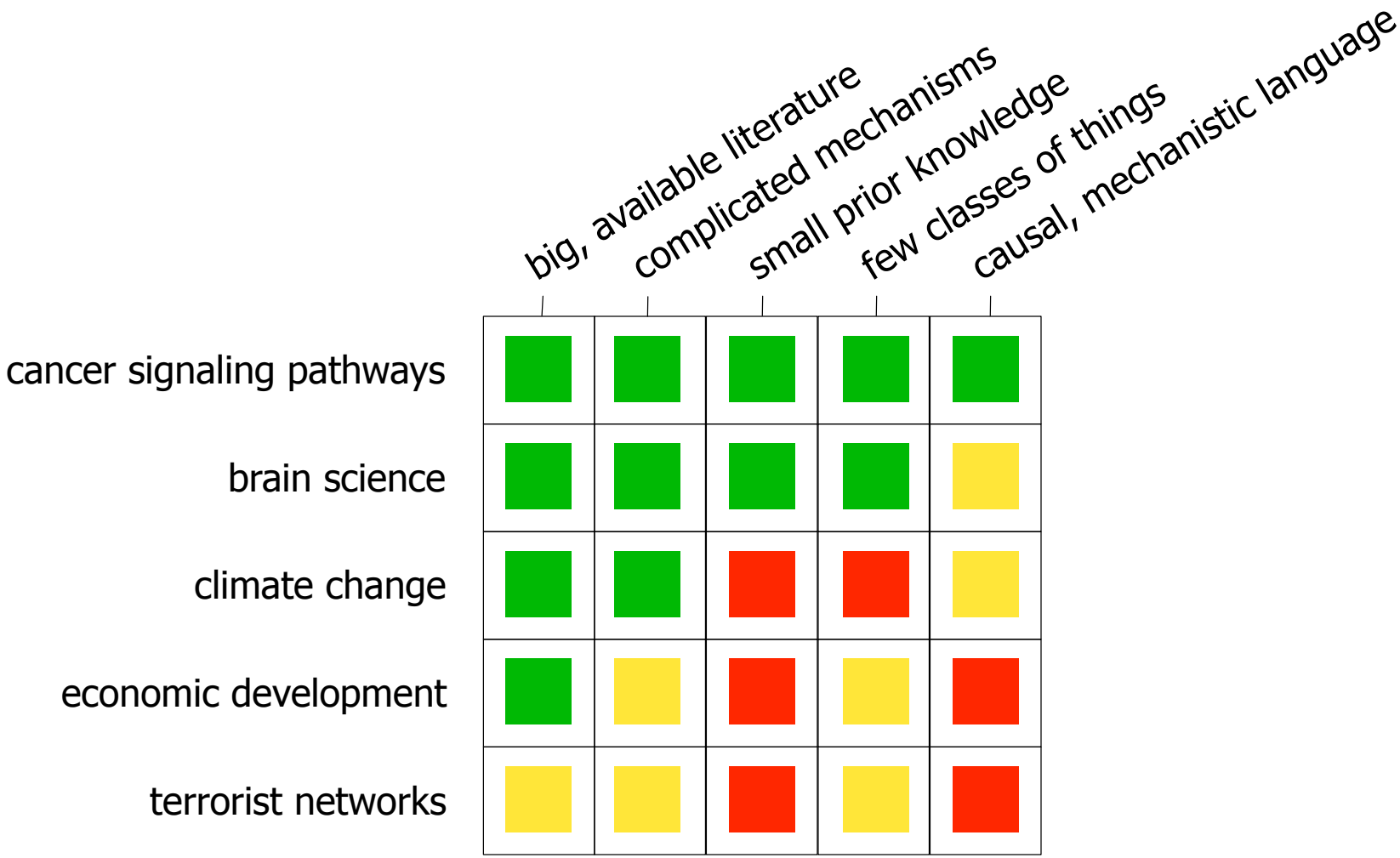
Read, Assemble, Explain for Which Systems?



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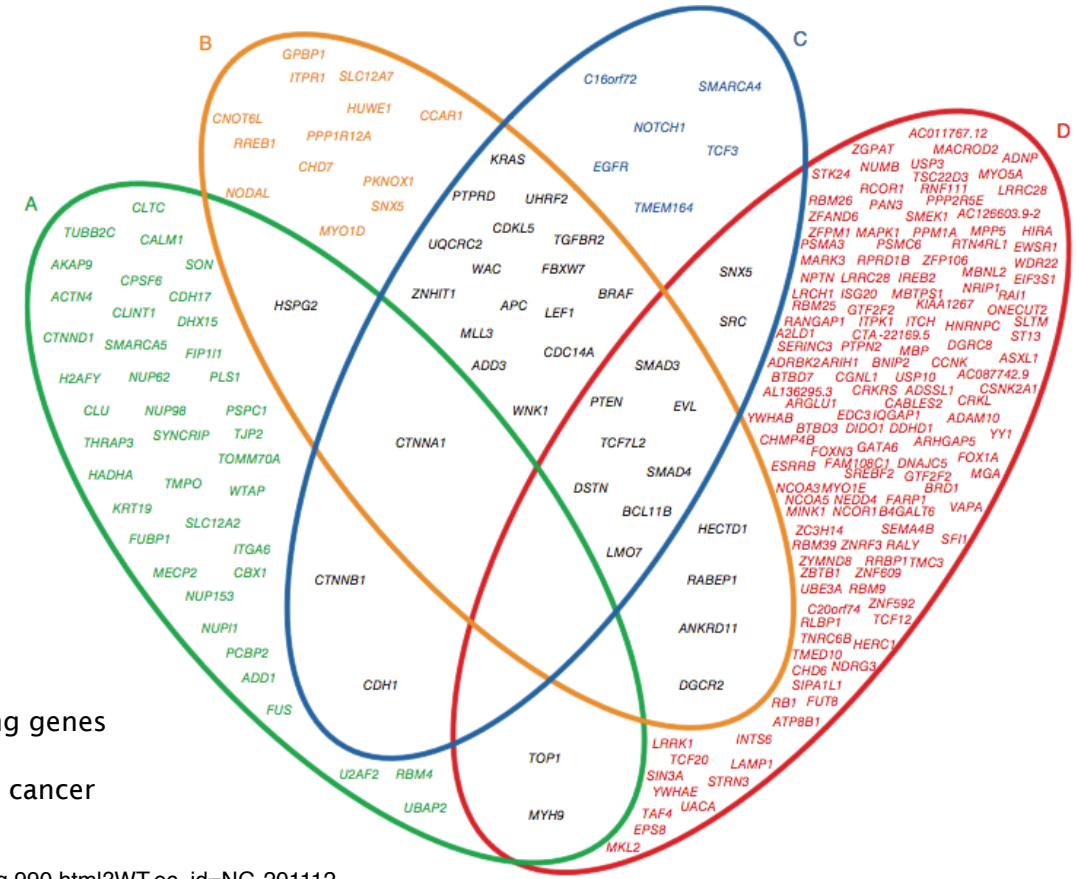
Complicated Systems

Cancer biology is a complicated system.

Different authors estimate that on average 7 – 15 somatic mutations are required for a normal human cell to undergo malignant transformation.

The proteins and genes in the figure are *all* implicated in colorectal cancer.



1. Force mutagenesis
2. Find common insertion sites (CIS)

A. Proteins coded by CISs
B. Human orthologs of CIS-containing genes
C and D. Previously reported human orthologs associated with colorectal cancer

Source: Nature Genetics 2011
http://www.nature.com/ng/journal/v43/n12/full/ng.990.html?WT.ec_id=NG-201112

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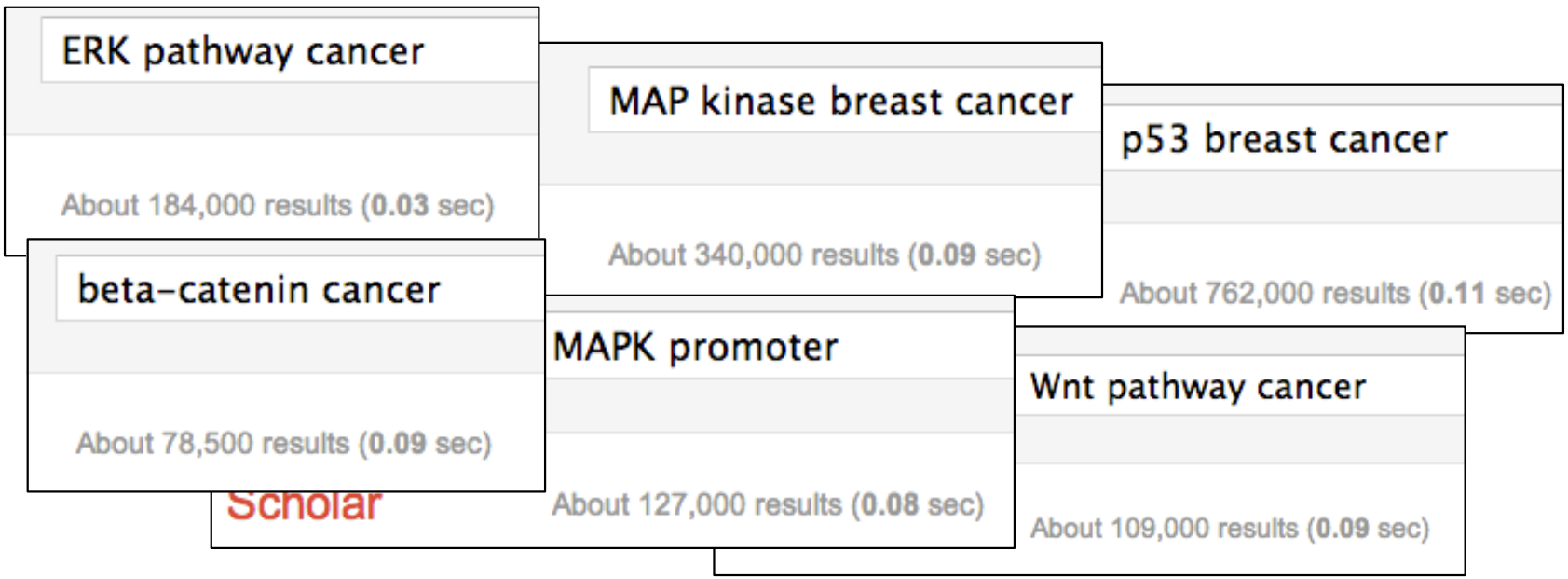
Knowledge is Fragmented and Voluminous

Cancer biology knowledge is fragmented and voluminous:



PubMed contains 23,000,000 abstracts and grows at roughly 500,000 abstracts per year (source: PubMed)

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Knowledge is Inconsistent

Cancer biology knowledge is inconsistent:

"We observed remarkably poor agreement (consistently less than 10%) among different databases regarding pathway components."

"What constitutes a 'canonical' pathway is database specific. This inconsistency ... may reflect underlying biology, in that signal transduction events are often context-dependent, or it may reflect the absence of a controlled vocabulary."

"This raises a significant problem for mechanistic modeling, since ... it is not clear which genes/proteins to include for modeling or experimental measurement."

– Kirouac et al. BMC Systems Biology 2012, 6:29
http://www.biomedcentral.com/1752-0509/6/29

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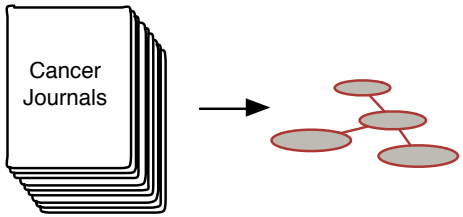
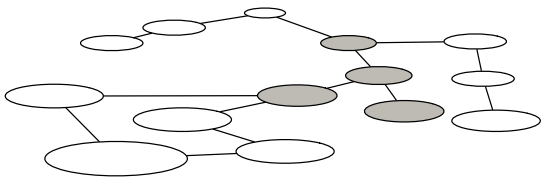
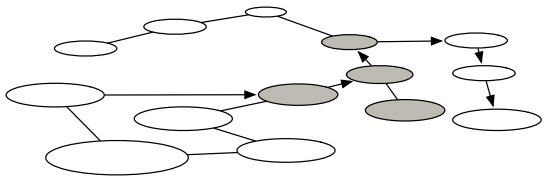
Technology Development Tasks



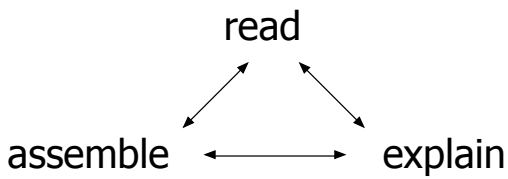
Read papers in cancer biology and extract causal fragments of signaling pathways, represented at all relevant semantic levels.



Assemble causal fragments into more complete pathways; discover and resolve inconsistencies.



Explain phenomena in signaling pathways. Answer questions, including "reaching down to data," when it is available.



Integrate reading, assembly and explanation in a non-pipeline architecture that provides flexible control.

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The Reading Task: Technology Challenges

Current reading technology extracts semantically shallow assertions; this program intends to "go deep" to extract causality, kinetics, abstraction.

Involvement	"β-catenin is a critical component of Wnt-mediated transcriptional activation"
Causal/Promotion	"ARF6 activation promotes the intracellular accumulation of β-catenin."
Kinetic	"L-cells treated with the GSK3β inhibitor LiCl (50 mM) or the proteasome/calpain inhibitor MG132 (25 μM) showed a marked increase in β-catenin fluorescence within 30 – 60 min"
Modular	"...via a mechanism that involves the endocytosis of growth factor receptors and robust activation of extracellular signal-regulated kinase."

Shallower

Deeper

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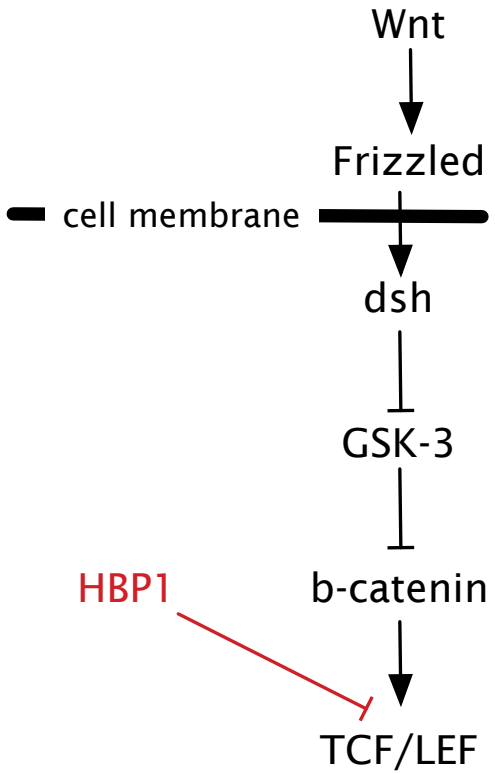
The Reading Task: The Language

HBP1 is a repressor of the cyclin D1 gene and inhibits the Wnt signaling pathway. The inhibition of Wnt signaling and growth requires a common domain of HBP1. The apparent mechanism is an inhibition of TCF/LEF DNA binding through physical interaction with HBP1.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC125566/#



Everything except HBP1 inhibition was known before this 2001 article was published.

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The Reading Task: Previous Results

Extracting Regulatory Gene Expression Networks from PubMed

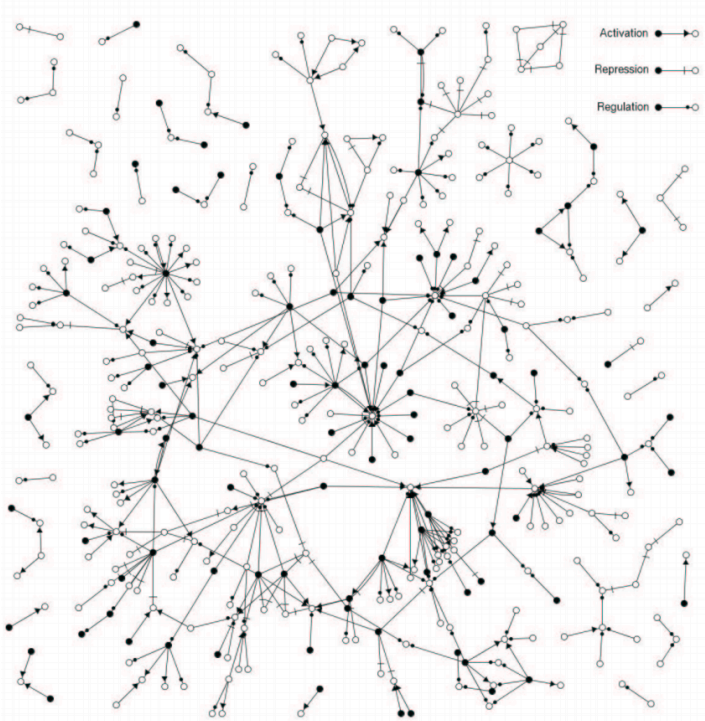
Saric, Jensen, Ouzounova, Rojas & Bork EMBL, Heidelberg, Germany

Extracted a regulatory network of 441 pairwise relations from 58,664 PubMed abstracts about Brewers' Yeast.

Semantic accuracy of 83 – 90% for different roles (e.g., nx_prom, contain)

Extremely small problem!

Semantically shallow (no kinetics, modules, etc.); "... we decided against trying to extract how the regulation take place."



[nx_prom the ATR1 promoter region]
[$contain$ contains]
[nx_uas_pt
  [$dt-a$ a] [bs binding site] [for for]
  [$nx\_activator$ the GCN4 activator protein]]

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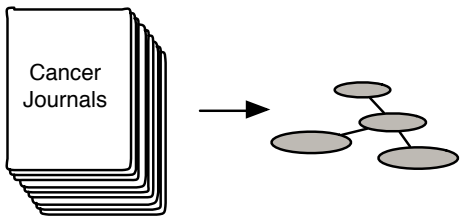
Technology Development Tasks



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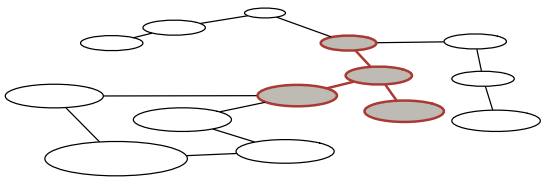

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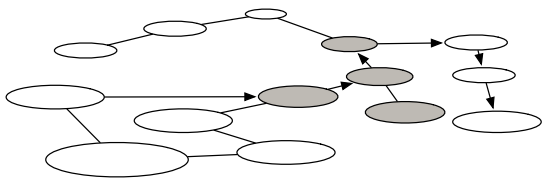

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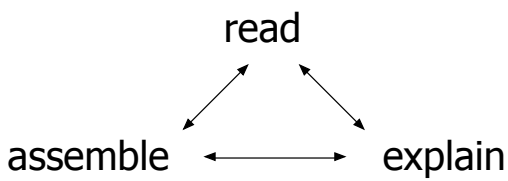

Integrate reading, assembly and explanation in a non-pipeline architecture that provides flexible control.

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The Assembly Task – Technology Challenges

Which entities "match up"? Are fragments semantically consistent? In which formal language is Big Mechanism to be represented?

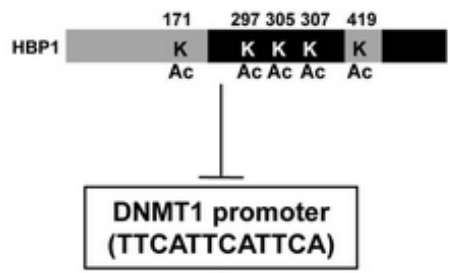
Fragment 1

HBP1 is a **repressor** of the **cyclin D1 gene** and inhibits the Wnt signaling pathway.

HBP1 ⊣ Cyclin D1

Fragment 2

HBP1 represses the **DNMT1 promoter** through sequence-specific binding (of the type TTCATTCATTCA) and the activity of **HBP1** itself is regulated through acetylation at any of 5 sites in **the protein.**



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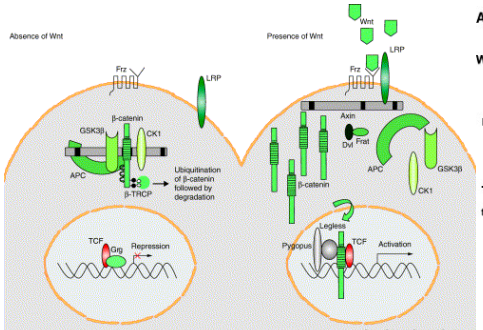
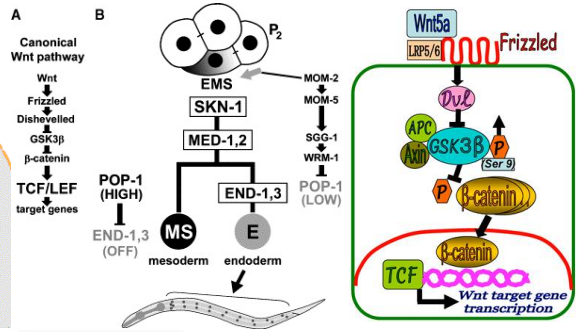
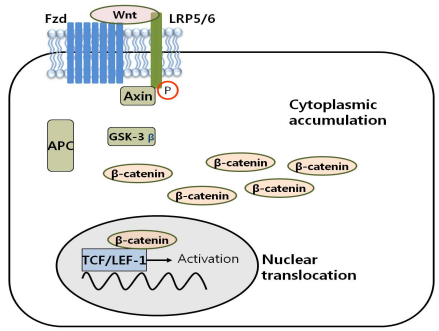
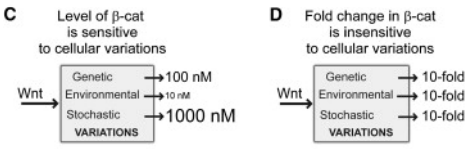
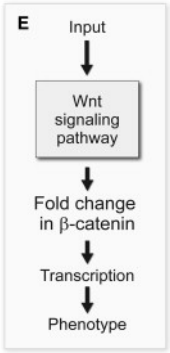
The Assembly Task – Ad Hoc Representation

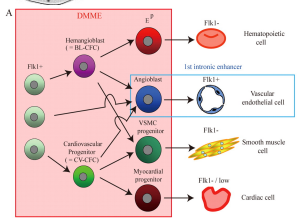


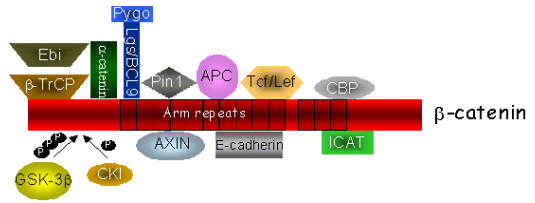


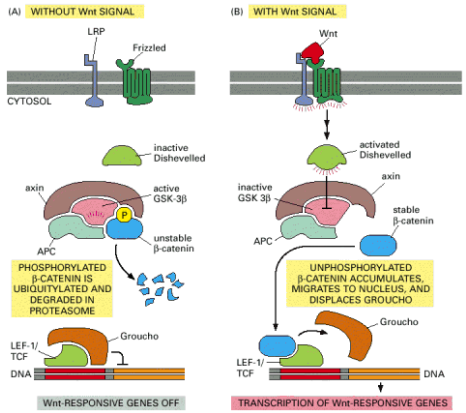


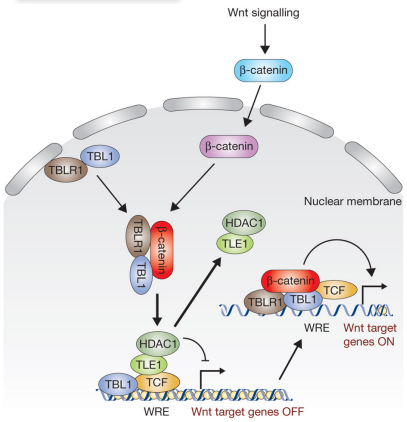


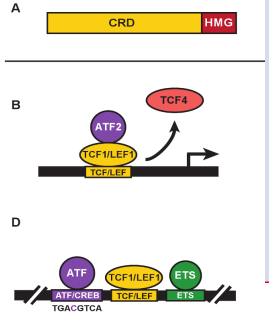


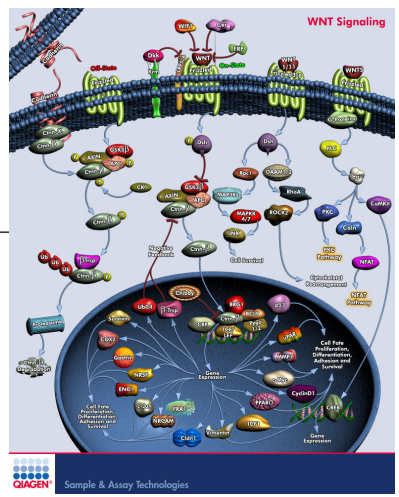












Source:
Paul Cohen

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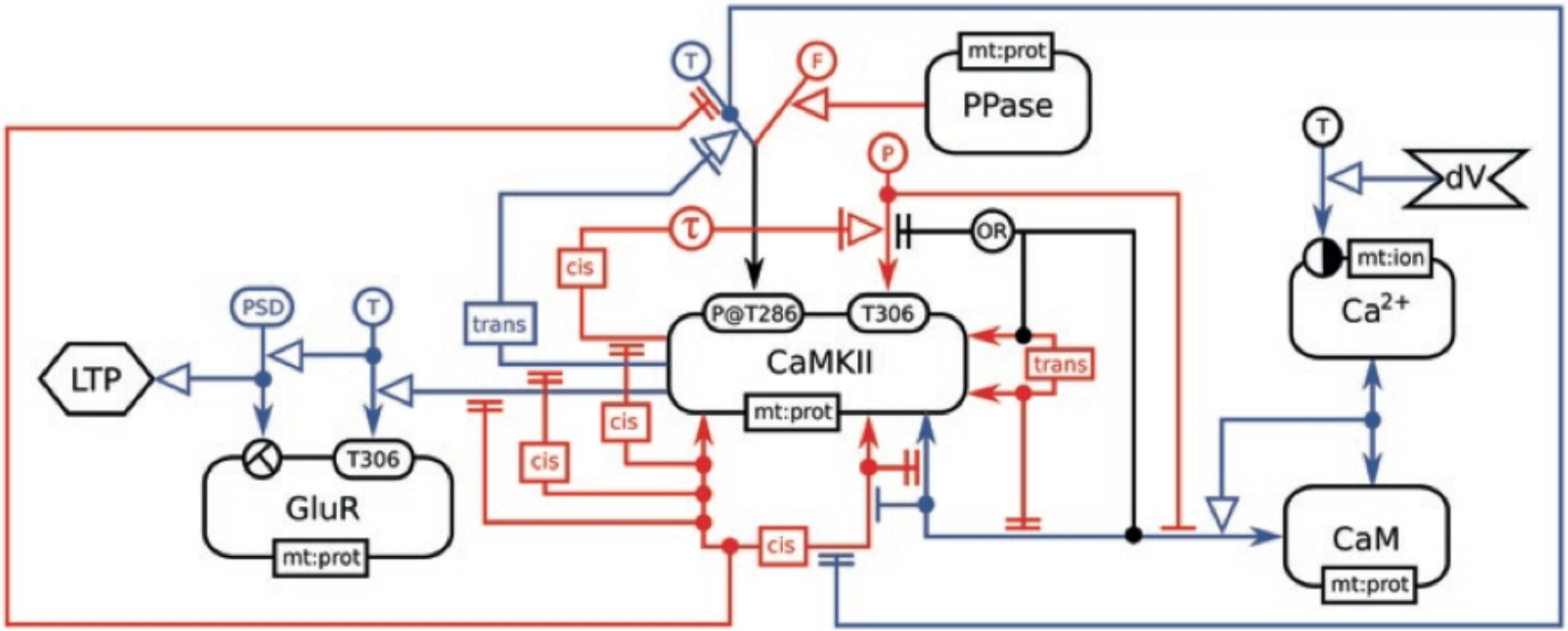
The Assembly Task – Previous Results

Toward a standard cell biology modeling language:



Manual encoding of process of long-term potentiation at synapses

Source: The Systems Biology Graphical Notation. Nature Biotechnology volume 27 number 8 2009
http://www.nature.com/nbt/journal/v27/n8/full/nbt.1558.html

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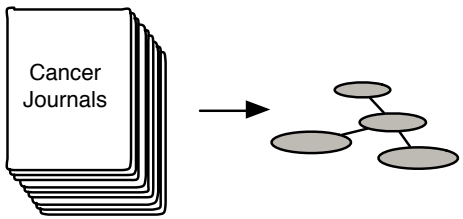
Technology Development Tasks



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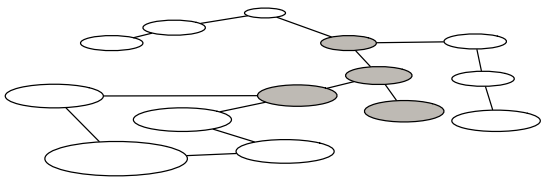

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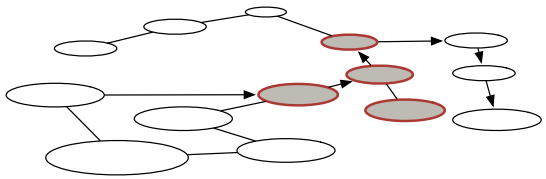

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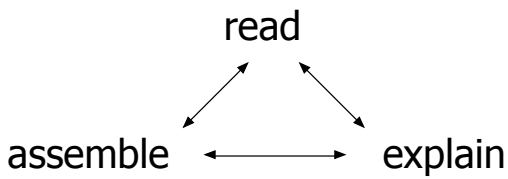

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The Explanation Task – Technology Challenges

Diverse reasoning methods – probabilistic, deductive, abductive, kinetic simulation, qualitative simulation – and data mining methods, all contribute to explanations; which are best, when, and what's missing?

Examples:

- Can a contradiction in a causal model be resolved by a kinetic model?
- What are likely consequences of enabling or inhibiting a protein?

- Use data to evaluate pathway models
- Use data to create or modify pathway models

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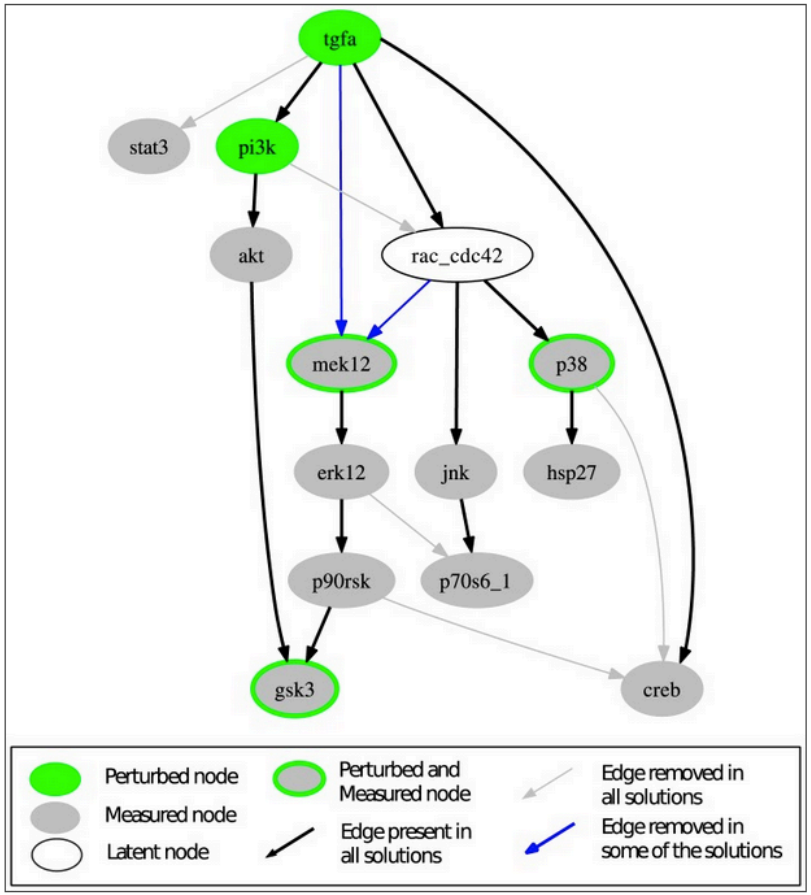
The Explanation Task – Previous Results



Source:
http://www.ncbi.nlm.nih.gov/pubmed/24039561

Detecting and Removing Inconsistencies between Experimental Data and Signaling Network Topologies Using Integer Linear Programming on Interaction Graphs.

Melas, Samaga, Alexopoulos, and Klamt.

[We] predict the possible qualitative changes (up, down, no effect) of the activation levels of the nodes for a given stimulus. We detect and remove inconsistencies between measurements and predicted behavior ... [We] detect interactions ... and provide suggestions for new interactions that, if included, would significantly improve the goodness of fit.

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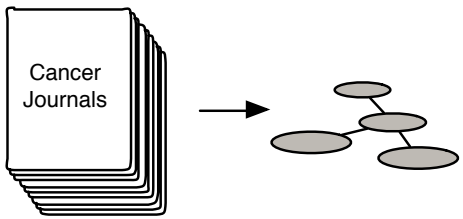
Technology Development Tasks



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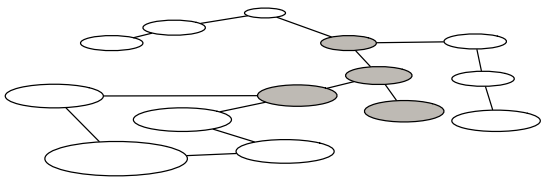

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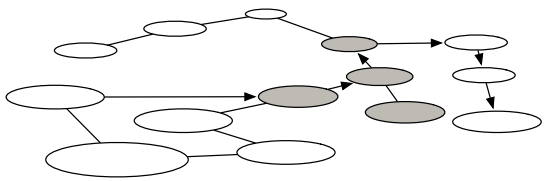

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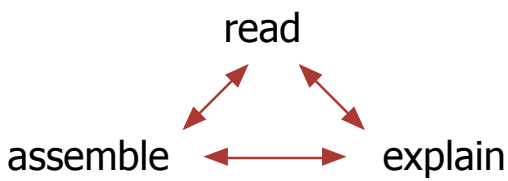

Integrate reading, assembly and explanation in a non-pipeline architecture that provides flexible control.

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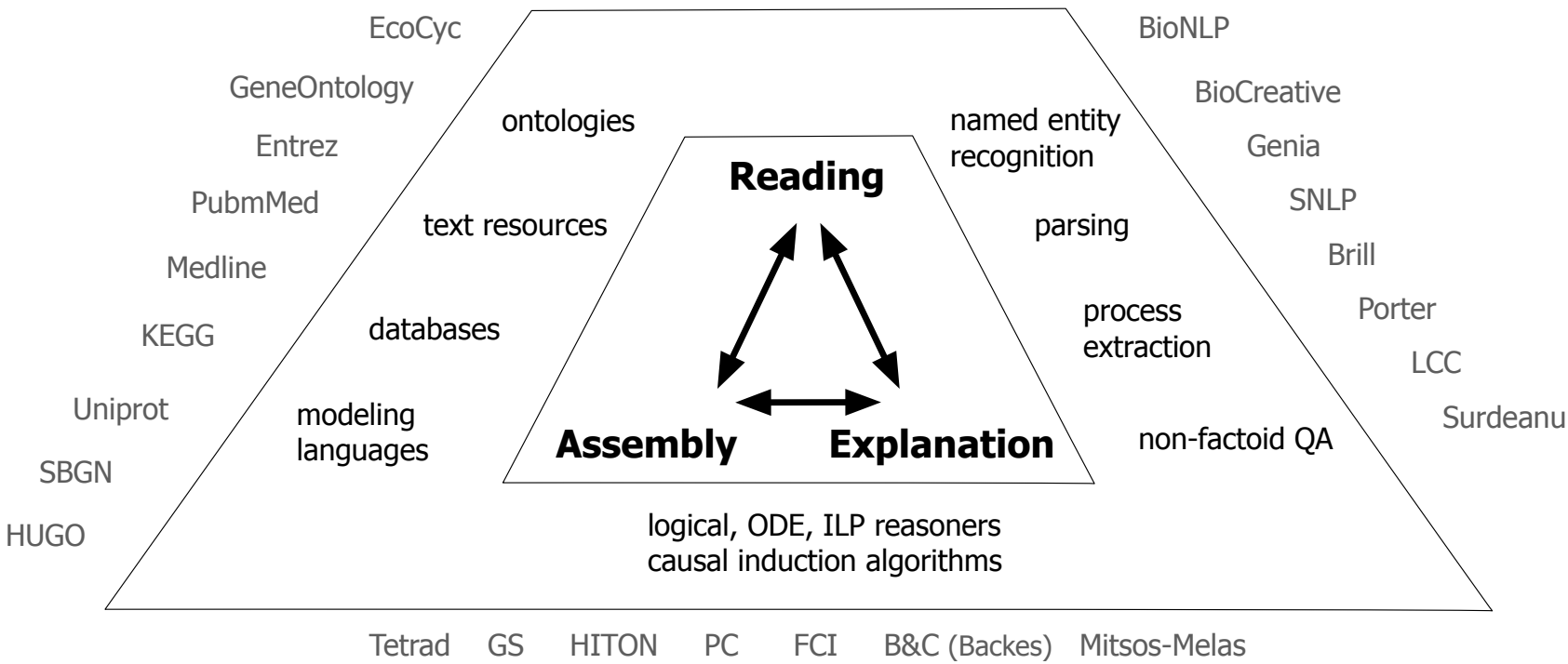
The Integration Task – Technology Challenges

Reading, Assembly and Explanation shouldn't be pipelined but should use each other opportunistically. Need flexible, non-pipelined control, plus significant software integration.



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Conclusion

It's a big problem

Distinct communities to coordinate

statistical NLP

systems biology

knowledge-based NLP

data mining

ontology, databases

representation and reasoning

mathematical biology

Many domains

Potentially a new way to do science

BIG MECHANISM

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