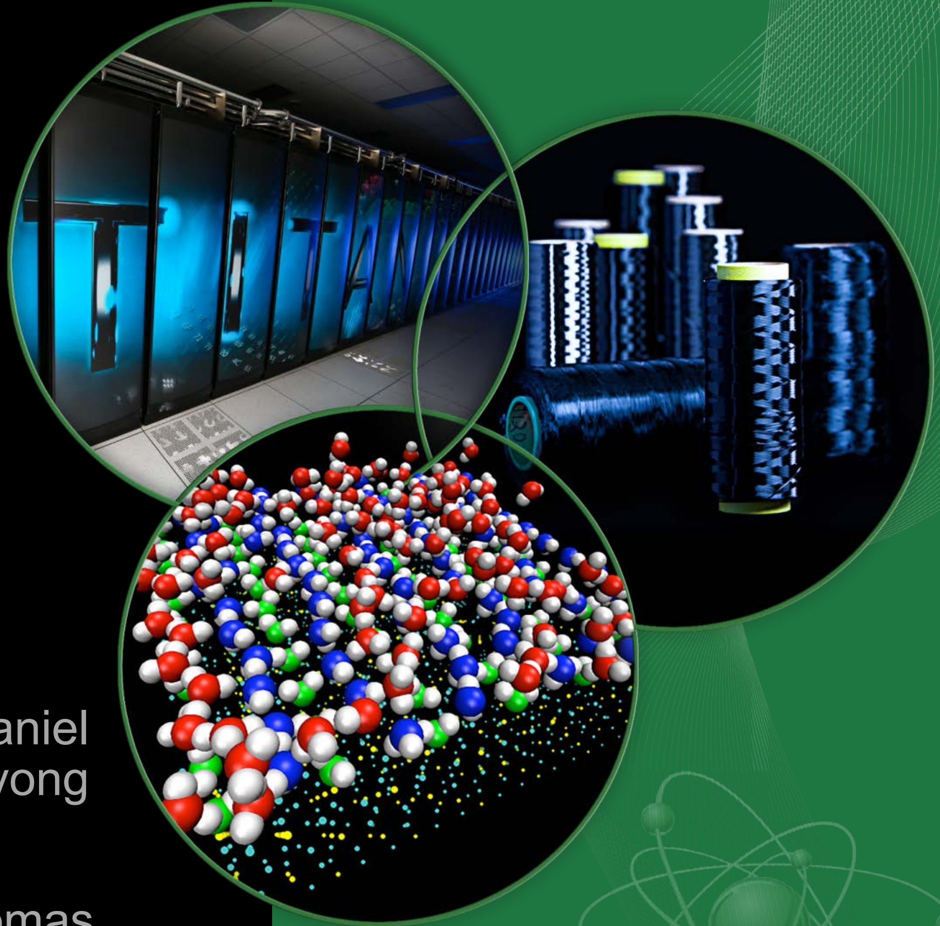
ORIGAMI: Oak Ridge Graph Analytics for Medical Innovation

An AI Workflow for Discovering Novel Associations in Massive Medical Knowledge Graphs



"Rangan" Sukumar , PhD

Data Scientist and Group Leader @ NCCS/OLCF

ORNL Team:

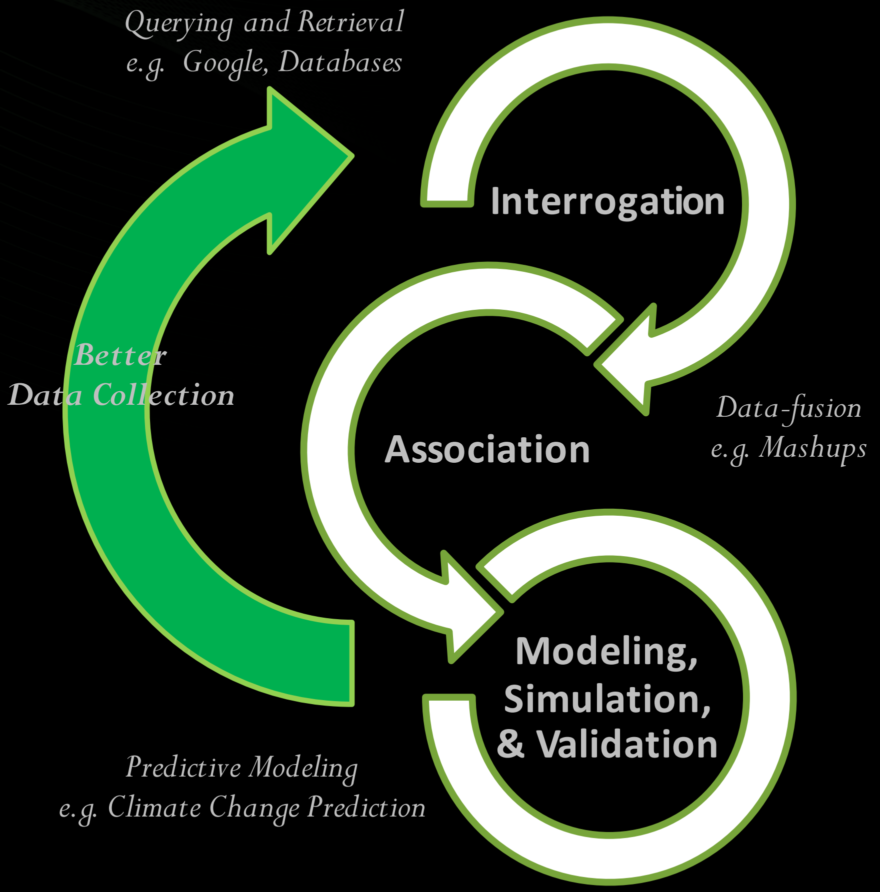
Larry Roberts, Matt Lee, Seung-Hwan Lim, Keela Ainsworth, Nathaniel Bond, Tyler Brown, Katie Senter, Alexandra Zakrzewska, Seokyong Hong, Yifu Zhao, Derek Kistler

Collaborators at the National Library of Medicine: Thomas Rindflesch, Marcelo Fiszman, Mike Cairelli

Academic Collaborators: Drs. Elliot Siegel (Maryland and Veterans Administration), Edward Chaum (UTHSC), Mark Wallace (Vanderbilt)

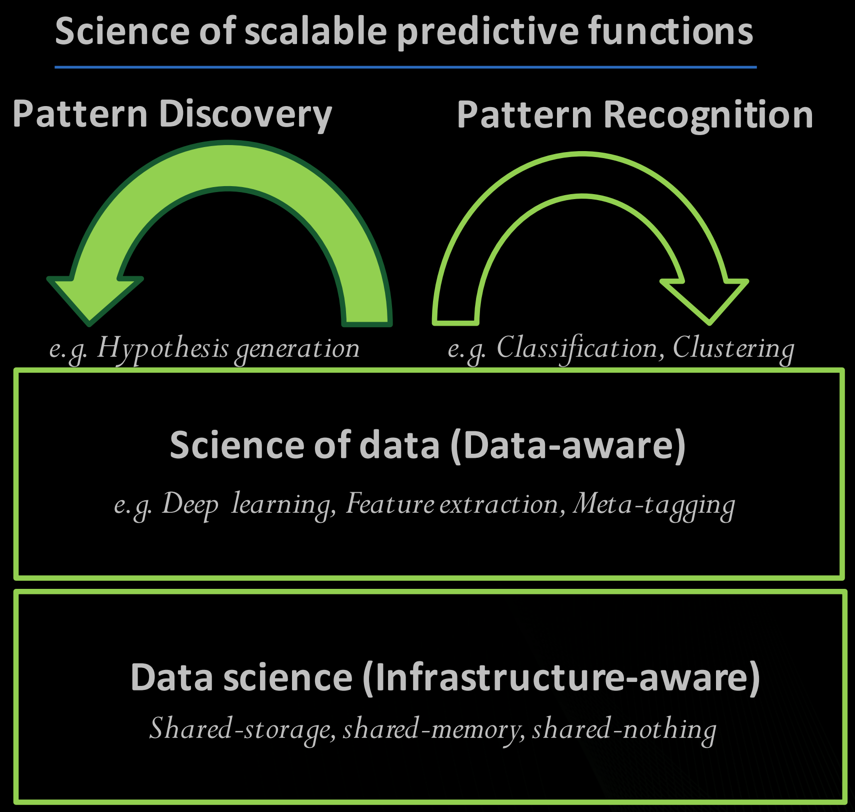
Group Vision: On-demand Data, Analytics and Workflows

The Lifecycle of Data-Driven Discovery



Domain Scientist's View

The Process of Data-Driven Discovery



Data Scientist's View

S.R. Sukumar, "Open Challenges in the Big Data Era – A Data Scientist's Perspective, IEEE Big Data , 2015.

What is ORiGAMI ?

An Artificial Intelligence Workflow for Discovering Novel Associations in Massive Medical Knowledge Graphs

The Genesis of ORiGAMI: On-demand Data

The National Library of Medicine

Number of papers processed	: ~23.5 million
Number of predications	: ~70 million
Number of distinct terms	: ~ 2 million
Number of “node-types”	: 133
Number of “relationships”	: 69

Dr. Thomas Rindflesch @ Health DataPalooza 2014

“We have a massive “heterogeneous” semantic graph that *researchers* need to query interactively…”

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Knowledge-Nurture Ecosystem for Data-Driven Discovery

A Grand Vision…

"We are missing out on an opportunity to accelerate discoveries….."

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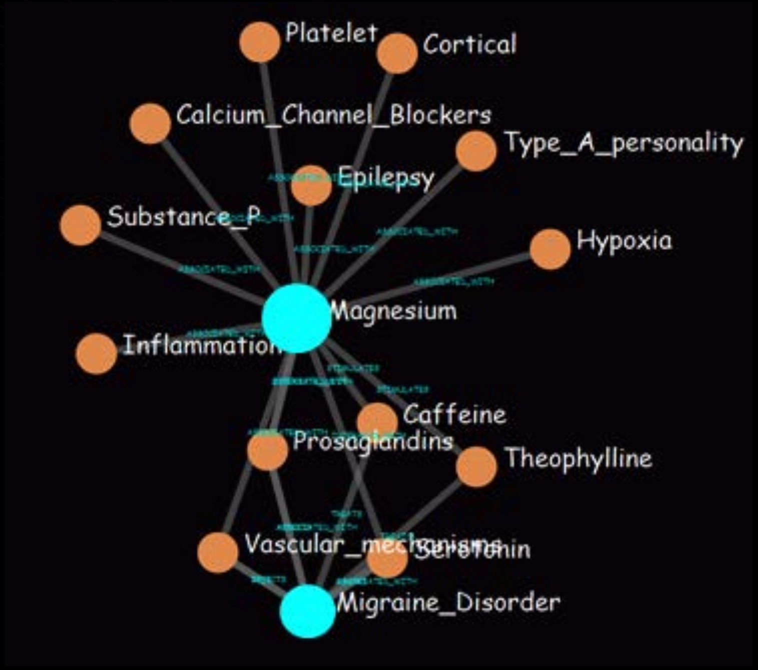
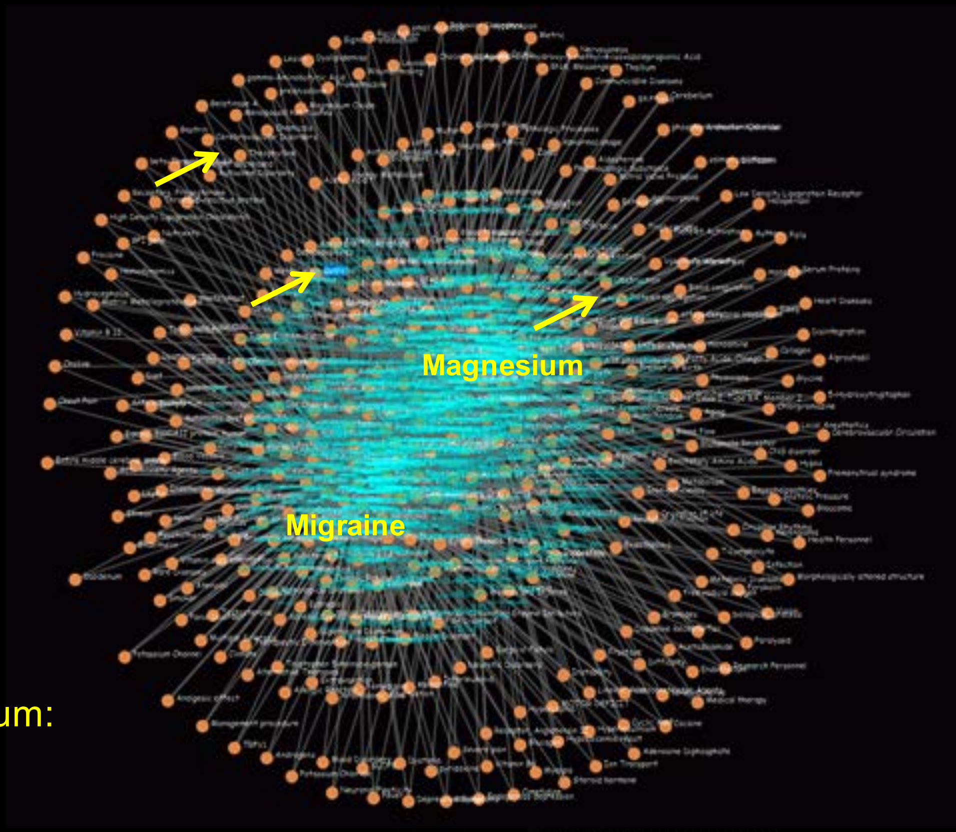
Where is the "Big Data" problem?

1987



Swanson, Don R. "Migraine and magnesium: eleven neglected connections." (1987).

2014



Today: There are 133,193 connections between migraine and magnesium.

We need a system to....

1. Big Data: Store, process, retrieve and reason with massive-scale datasets for newer discoveries.

2. Signal-to-Noise Ratio: Separate signal from noise when noise > signal

3. Hypothesis Generation: Given knowledgebase + new data, formulate ‘new interesting questions’.

4. Significance Ranking: Given different knowledge nuggets, find significant associations or predict future connections.

ORiGAMI Today: An Open Eco-System for Data-Driven Discovery

Open Data

National Library of Medicine's *Semantic Medline*

Subject	Predicate	Object
Influenza	ISA	RNA_Virus_Infections
Influenza	ISA	Viral_upper_respiratory_tract_infection
Influenza	INTERACTS_WITH	Influenza_A_Virus__H1N1_Subtype
Influenza	ISA	Acute_viral_disease
Influenza	ISA	Influenza_with_pneumonia_NOS
Influenza	AFFECTS	Maori_Population
Influenza	COEXISTS_WITH	Influenza_A_Virus__H3N2_Subtype
Influenza	COEXISTS_WITH	Mental_alertness
Influenza	INTERACTS_WITH	Dengue_Virus
Influenza	AFFECTS	Influenza_with_encephalopathy
Influenza	AFFECTS	Swine_influenza
.	.	.
.	.	.
.	.	.
Influenza	CAUSES	UPPER_RESPIRATORY_SYMPTOM
Influenza	CAUSES	Wheezing_symptom

70 million predications from 23.5 million PubMed articles

\+

Compute

ORNL's Compute and Data Environment for Science

64 Threadstorm processors, 2 TBs of shared memory connected to 125 TB of storage

504 compute cores, 5.4 TBs of distributed memory, and 576 TBs of local storage

\+

Open Algorithms

http://github.com/ssrangan

- Data-driven reasoning
  - Semantic
  - Graph-theoretic
  - Statistical
- Model-driven reasoning
  - Term-based
  - Path-based
  - Meta-pattern
  - Context-based
  - Analogy

Open API: http://hypothesis.ornl.gov

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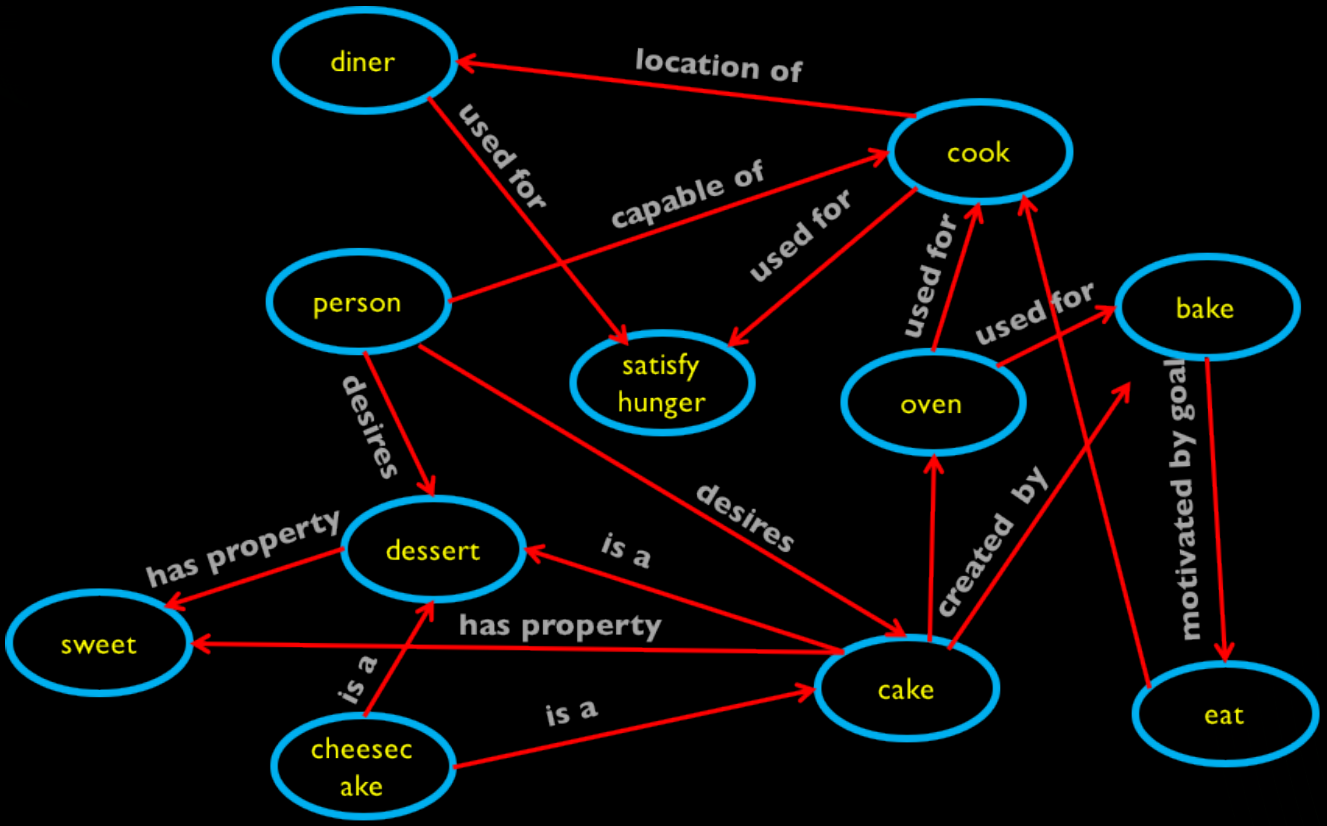
How does ORIGAMI work?

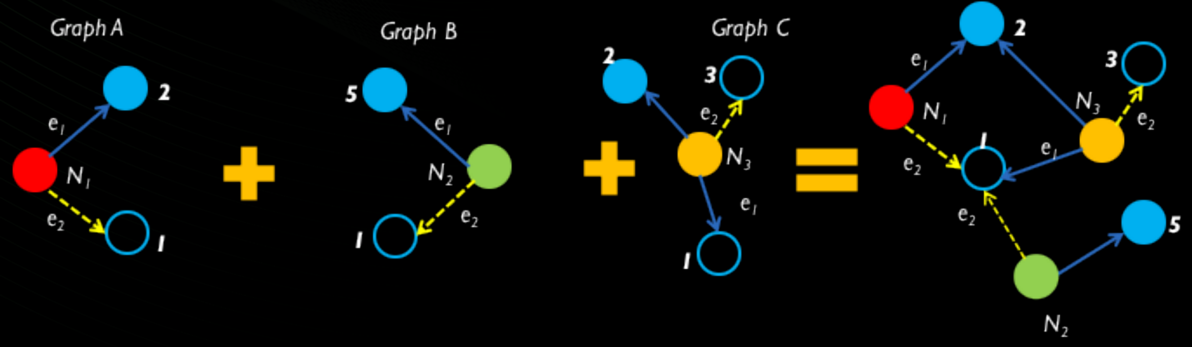
Takes Knowledge Graphs as input…



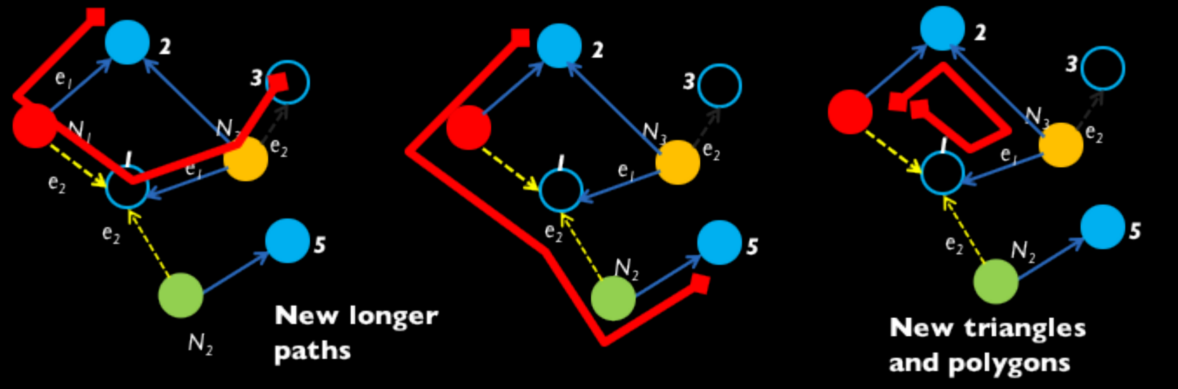
~3.4 M words, ~57 K types of relationships, ~10 million assertions

Graph-operations as "Apps" (Examples)

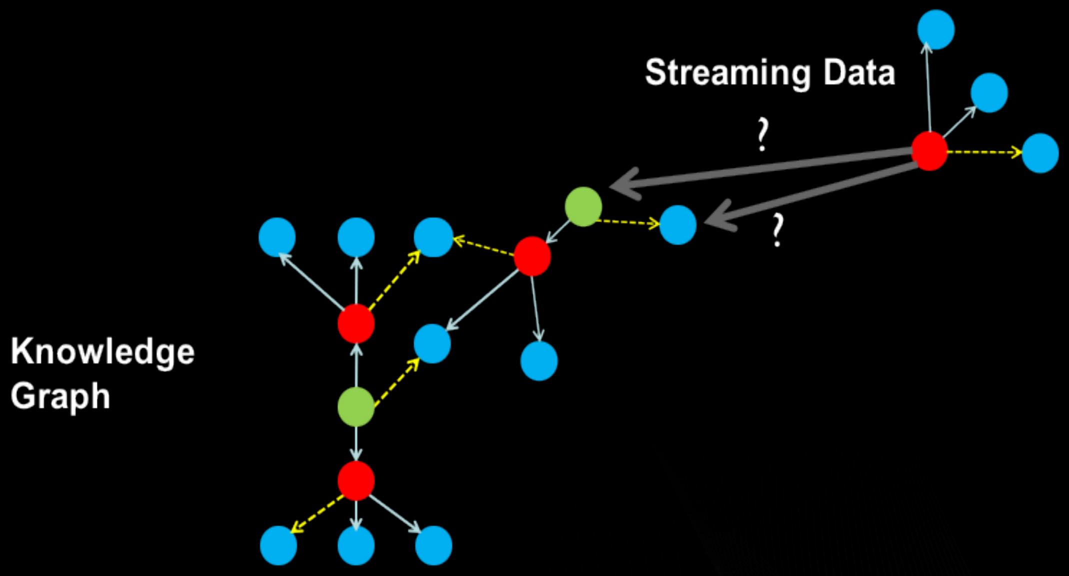
Extracting Novel and Useful Associations



Where are the new connections?
What are the "important" new connections?



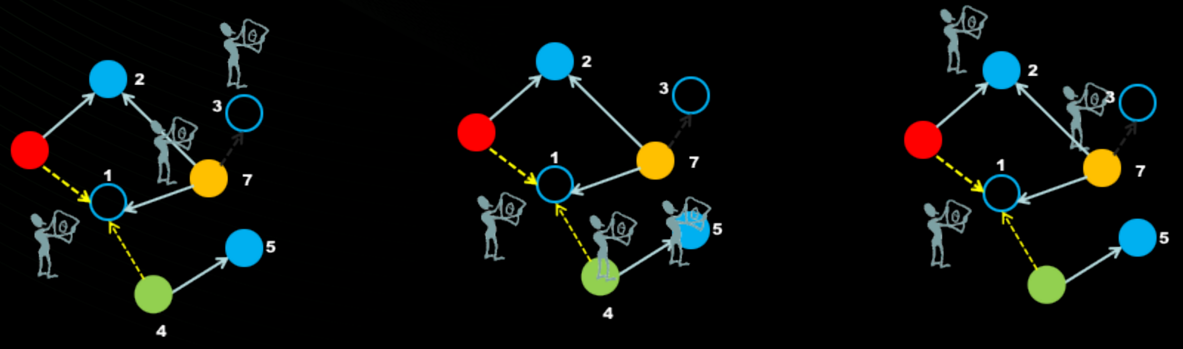
Predictive Inferencing using Recommender Algorithms



What is the probability of a particular edge to occur ?

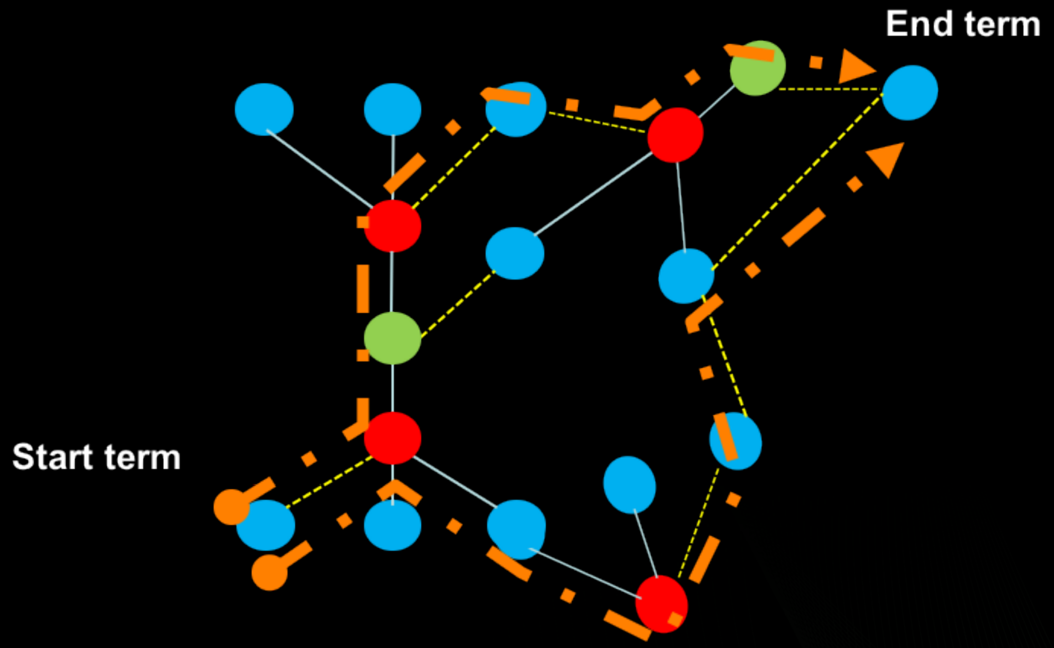
Graph-operations as “Apps” (Examples)

Information Foraging for Saliency Estimation



How to rank saliency of nodes and edges in the knowledge graph?

Path-based Reasoning



Out of the millions of possible paths, how do we find useful ones? How do we rank paths for significance and saliency?

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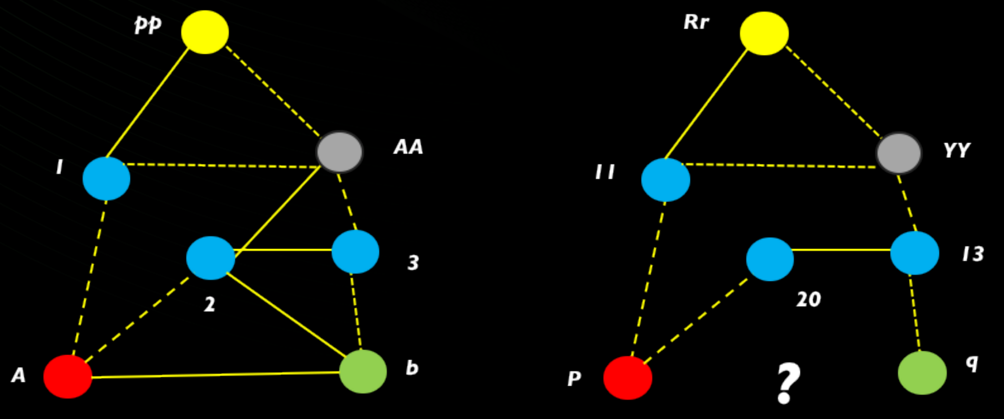
Graph-operations as "Apps" (Examples)

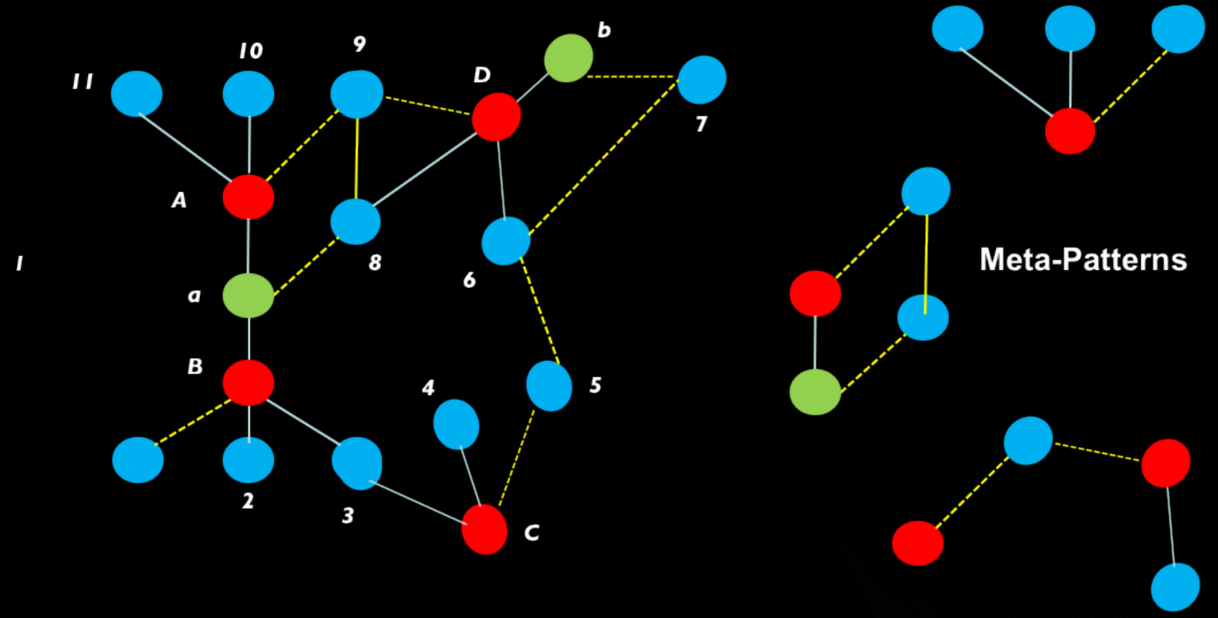
Analogy-based Reasoning

Example



When given an example, automatically learn meta-structure and "fill-in-the-blank" ?

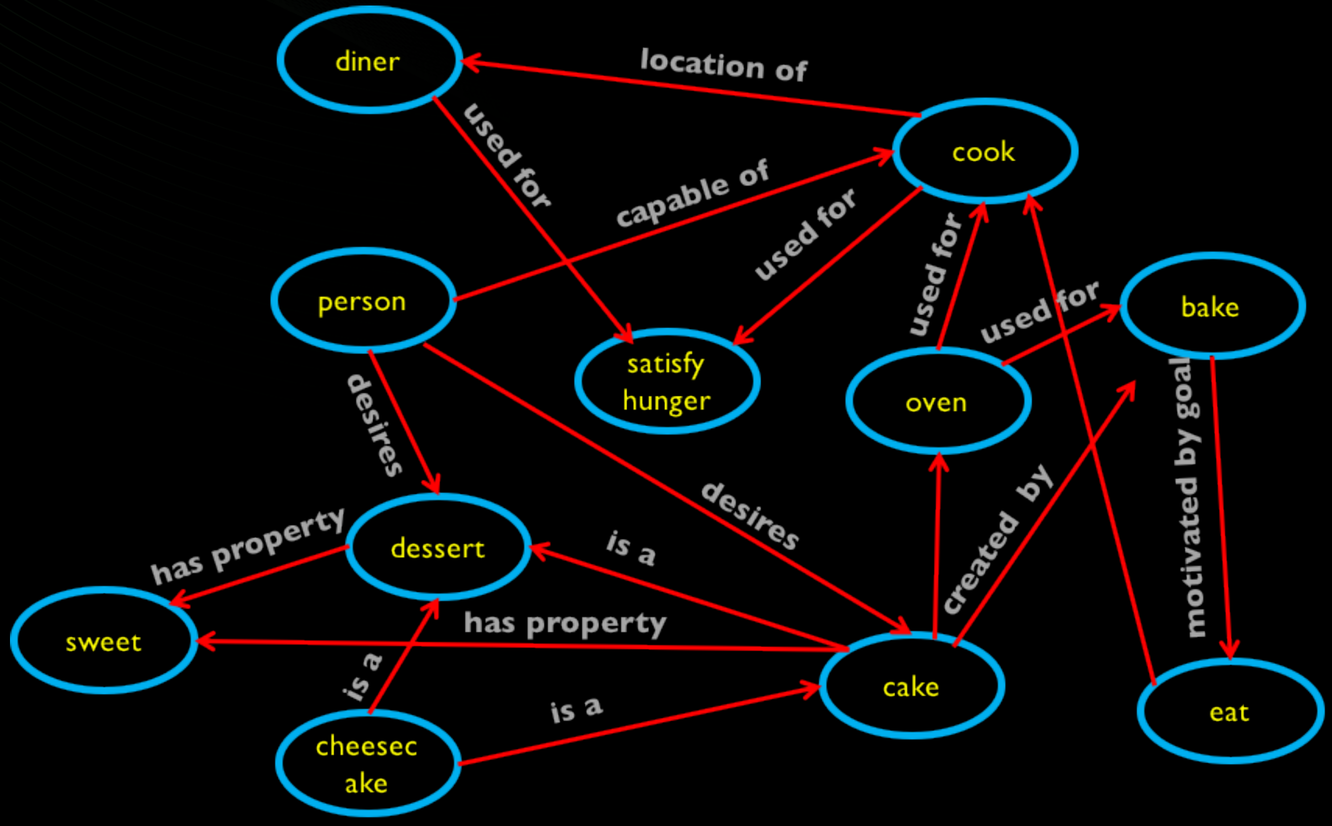
Meta-Pattern Reasoning



How to organize/search through knowledge graph based on meta-ontologies?

What do these "Graph-operations" enable ?

Semantic, Statistical and Logical Reasoning at Scale



~3.4 M words, ~57 K types of relationships, ~10 million assertions

Curious Question:

Are giraffes vegetarian ?

What do these "Graph-operations" enable ?

Semantic Reasoning : "Connect the dots"

Answer #1

Giraffes only eat leaves.
Leaves are parts of trees, which are plants.
Plants and parts of plants are disjoint from animals and parts of animals.
Vegetarians only eat things which are not animals or parts of animals.

Answer #2

Giraffes is a mammal.
Human is a mammal.
People are human.
People who eat only vegetables are vegetarians.

Answer #3

Giraffes are desired by people.
Horses are desired by people.
Horses do not eat meat.
Herbivores do not eat meat.
Herbivores are vegetarians.

What do these “Graph-Operations” enable ?

Statistical Reasoning : “Search for the evidence”

Answer #1

Deer is an animal.	Giraffe is an animal.
Deer is a mammal.	Giraffe is a mammal.
Deer has four legs.	Giraffe has four legs
Deer is a herbivore.	?
Herbivores are vegetarians.	?

Potential Answer #2

Horse is a large animal.	Giraffe is a large animal.
Horse sleeps standing.	Giraffe sleeps standing.
Horse has four legs.	Giraffe has four legs.
Horse is a mammal.	Giraffe is a mammal.
Horse is an animal.	Giraffe is an animal.
Horse only eat plants.	Giraffe eat leaves.
Horse is a herbivore.	?

What do these “Graph-Operations” enable ?

Logical Reasoning : “Filter noise from signal”

Extract Rules and Exceptions and Resolve:

A “is like” B. B “do not” C. D “only if” C. Therefore A “is not” D ?

A “is not like” B. B “do not” C. D “only if” C. Therefore A “may be” D ?

Giraffes are similar to deer, elephants, horses, cow, goat and sheep, toad, humans.

Elephants, horses, cow and goat are herbivores while humans, toads are not.

Result: Giraffes ‘may be’ vegetarian than not.

At scale: "How does Nexium treat Heartburn?"

This is an example of how our search works….

Nexium						Heartburn

Filling in the blanks….and then ranking it for significance…

Nexium	'Is a'	Esomeprazole	*'Reverse(Is a)'*	Proton Pump Inhibitors	*'Disrupts'*	Heartburn

Eksp Klin Gastroenterol. 2009;(4):86-92.

[Omeprazol and ezomeprazol pharmacokinetics, duration of antisecretory effect, and reasons for their probable changes in duodenal ulcer].

[Article in Russian]

Serebrova SIu, Starodubtsev AK, Pisarev VV, Kondratenko SN, Vasilenko GF, Dobrovol'skiĭ OV.

Abstract

There were authentic distinctions between the groups of healthy volunteers and patients with a peptic ulcer disease in Cmax, Tmax, AUC(0-t), AUC (0-infinity), Clt, Vd of omeprazole and Cmax of esomeprazole (Nexium, AstraZeneca). When the pharmacokinetics of omeprazole and ezomeprazole were compared in both groups, there were authentic distinctions in Cmax, AU(0-t), AUC(0-infinity), Clt, T1/2. The patients who had taken omeprazole the time of hypoacide condition was much shorter than in other groups. Disintegration test modeling pHmax for pH oscillation with large amplitude, that is typical for ulcer disease, demonstrated a possibility of early partial release of omeprazole, its acid-depended degradation and reduction of its bioavailability.

Aliment Pharmacol Ther. 2006 Sep 1;24(5):743-50.

Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis - a comparison of esomeprazole with other PPIs.

Edwards SJ[1], Lind T, Lundell L.

⊕ **Author information**

Abstract

BACKGROUND: No randomized controlled trial has compared all the licensed standard dose proton pump inhibitors in the healing of reflux oesophagitis.

AIM: To compare the effectiveness of esomeprazole with licensed standard dose proton pump inhibitors for healing of reflux oesophagitis (i.e. lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg).

METHODS: Systematic review of CENTRAL, BIOSIS, EMBASE and MEDLINE for randomized controlled trials in patients with reflux oesophagitis. Searching was completed in February 2005. Data on endoscopic healing rates at 4 and 8 weeks were extracted and re-analysed if not analysed by intention-to-treat. Meta-analysis was conducted using a fixed effects model.

RESULTS: Of 133 papers identified in the literature search, six were of sufficient quality to be included in the analysis. No studies were identified comparing rabeprazole with esomeprazole. A meta-analysis of healing rates of esomeprazole 40 mg compared with standard dose proton pump inhibitors gave the following results: at 4 weeks [relative risk (RR) 0.92; 95% CI: 0.90, 0.94; P < 0.00001], and 8 weeks (RR 0.95; 95% CI: 0.94, 0.97; P < 0.00001). Publication bias did not have a significant impact on the results. The results were robust to changes in the inclusion/exclusion criteria and using a random effects model.

CONCLUSION: Esomeprazole consistently demonstrates higher healing rates when compared with standard dose proton pump inhibitors.

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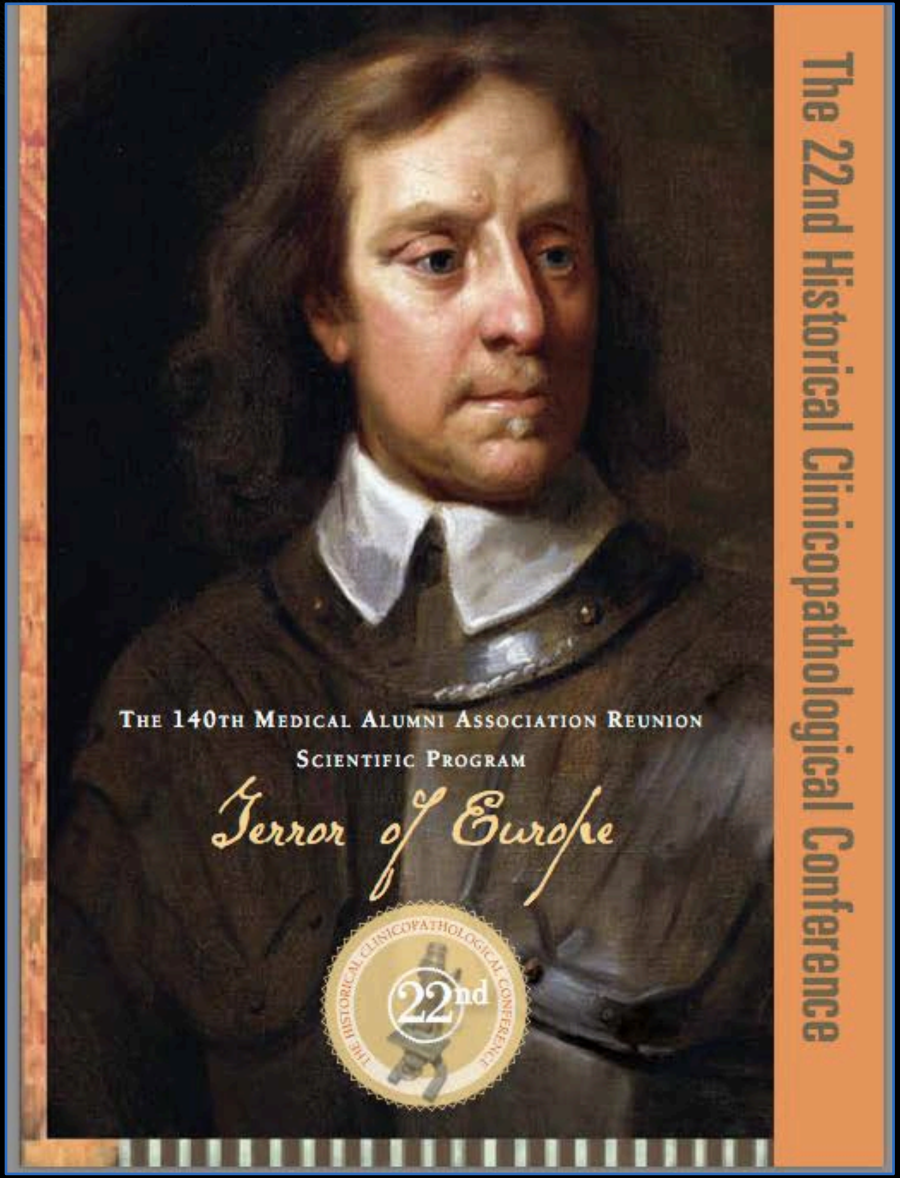
ORIGAMI @ Work…



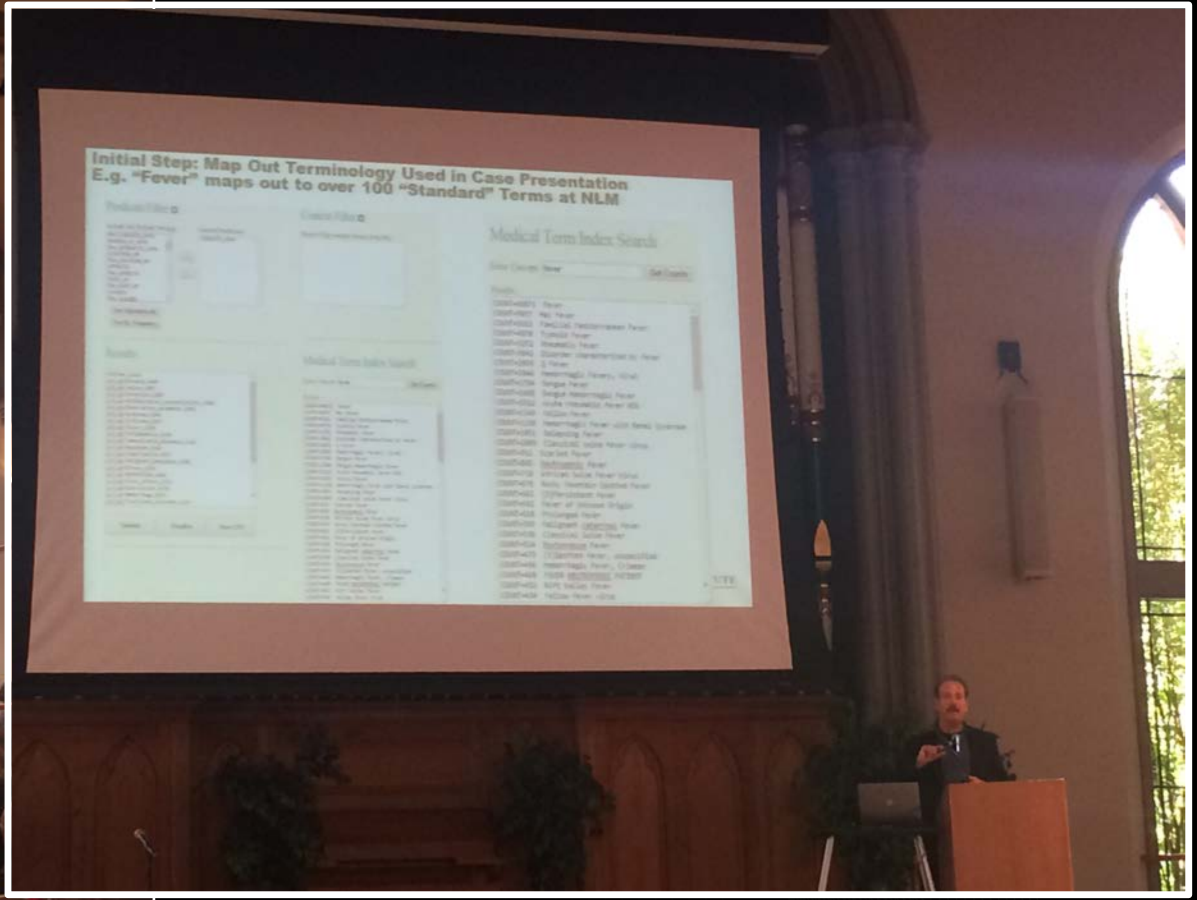
Success Stories : ORiGAMI @ Work

1. Historical Clinicopathological Conference, October 2015

2. Hamilton Eye Institute, UTHSC, Summer 2014

…..and many more in the pipeline.

ORiGAMI @ Work: Historical CPC 2015, Baltimore



The Historical CPC Question

Other ailments : Arthritis, Dysentery, Herpes Simplex Infections, Vesicular eruption, Nephrolithiasis, Primary Insomnia, Soldier

Welsh population
English Population
Longevity Hereditary

Peptic Ulcer
Irritable Bowel Syndrome
Pimples
Pustular acne

Neck Injuries

Multiple boils

Breast Cyst
Rash erythematous

Tertian fever
Cardiac arrhythmia
Intermittent fever
Intermittent pain
Sore Throat
Sweating

Age

Birth 29 45 48 57 59 Death

Our Method

Step 1: Associative Context Synthesis

Using Semantic and Logical Heuristics

Intermittent fever

Tertian fever

Arrhythmia

Intermittent pain

Sore Throat

Sweating

Multiple boils

Symptoms

Specific context heuristic

Still_s_Disease__Adult_Onset
Brachyspira_pilosicoli
Malaria
Reactive_Hemophagocytic_Syndrome
Brachyspira_aalborgi
Chronic_Childhood_Arthritis
Endemic_Diseases

Pattern-similarity heuristic

HIV_Infections
Tuberculosis
Rheumatoid_Arthritis
Anemia
Functional_disorder
Acquired_Immunodeficiency_Syndrome

Semantic-similarity heuristic

Malaria
Malaria__Cerebral
Malaria__Vivax
Plasmodium_falciparum_infection
Disseminated_Intravascular_Coagulation
Myocarditis
Quartan_malaria
Abdominal_mass
Airway_disease
Aspergillosis__invasive
Ataxia__cerebellar__acute
Auricular_chondritis

Soldier

Aggressive_reaction
Albers_Schonberg_disease
Hallucinogen_Persisting_Perception_Disorder
Stress_Disorders Post_Traumatic
Leishmaniasis Cutaneous
Oppenheim's_Disease
Achilles_bursitis

Welsh

iodothyronine_deiodinase_type_I
Iodide_Peroxidase
EMD_21388
thyronamine
type_II_5__deiodinase
2_mercaptoimidazole
Acrocephaly
Acute_appendicitis_NOS
Adrenocortical_carcinoma
Anxiety_neurosis__finding
Bronchiectasis
CDK8_gene_CDK8
Central_Nervous_System_Agents
Complement_component_C4_C4A
Congenital_anomaly_of_cartilage
DIO1_DIDO1
DIO2_gene_DIO2
DUOX1
DUOX2

Multiple boils

Empyema
Gangrenous_pneumonia
MRSA _infection
Meniere_s_Disease
Nosocomial_pneumonia
Pericarditis
Septicemia
Stenosis_unspecified

Our Method

Step 2: Conceptual Reasoning and Validation

Probabilistic filtering using context proximity

Intermittent fever

Tertian fever

Plasmodium_ovale
Malarial_hepatitis
Anopheles_darlingi
Mixed_infectious_disease
Plasmodium_species
Quartan_malaria
Plasmodium_falciparum_infection
Congenital_malaria

Sore Throat

Sweating

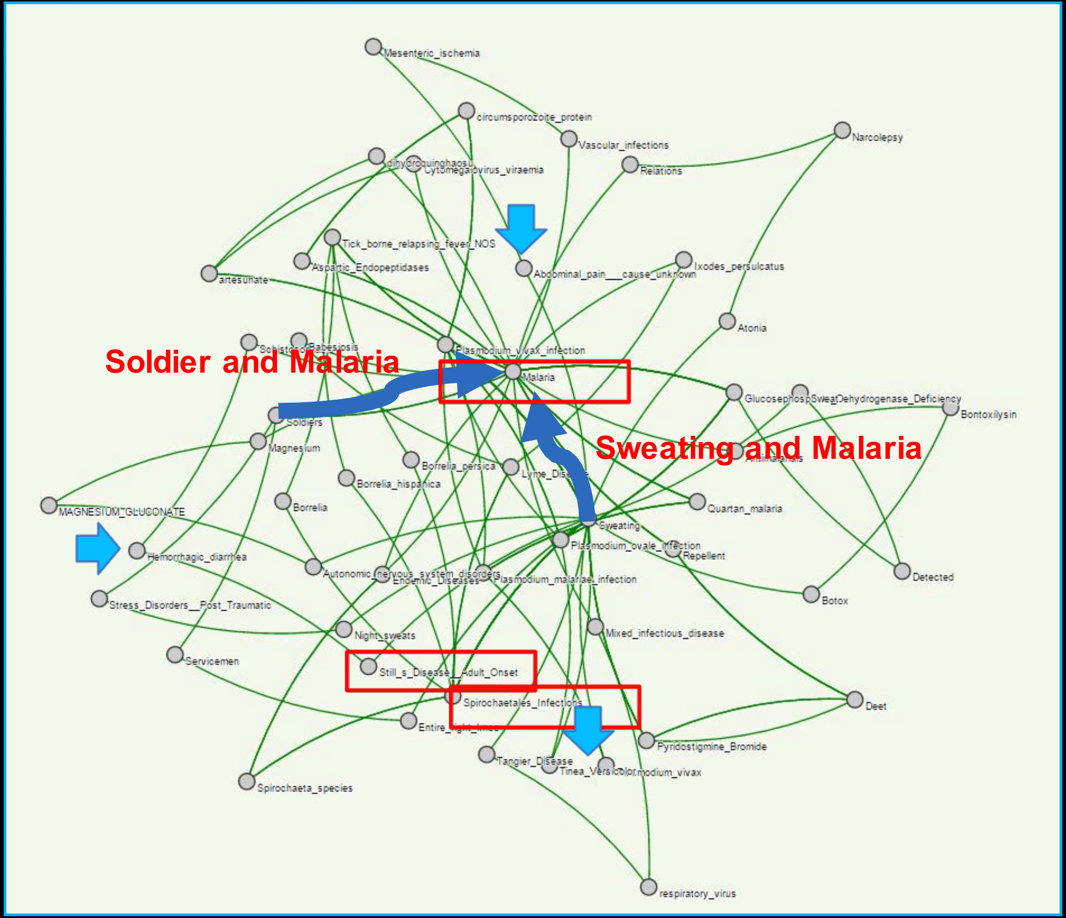
Multiple Boils

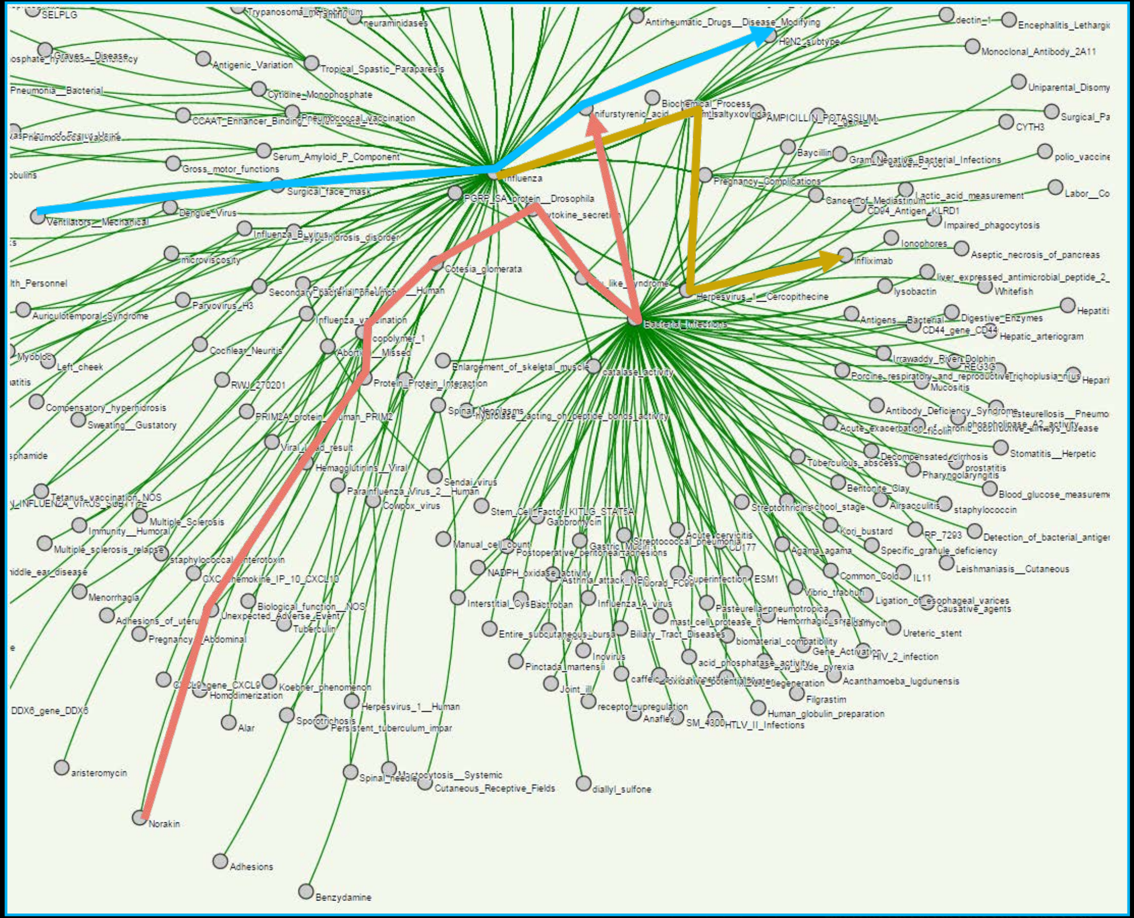
Gomphosis_structure
Adductor_spastic_dysphonia
Goblet_Cells
Cold_symptoms
Acute_radiation_proctitis
Common_Cold
Genu_varum
Amyloidosis__Familial
GLI3_gene_GLI3
Diver

Our Method

Step 3: Personalized Hypothesis Generation

Using Random walks with restarts





ORiGAMI 's Answers

Top 10 Hypothesis generated using ORiGAMI

Malaria
Lichen_disease
Urinary_tract_infection
Coccidiosis
Bacteremia
Encephalomyelitis_Western_Equine
Poisoning_syndrome
Adult_Still's Disease
MRSA (Staph Infection)
Septecemia

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ORiGAMI @ Work: Historical CPC 2015, Baltimore

Crowdsourcing the experts

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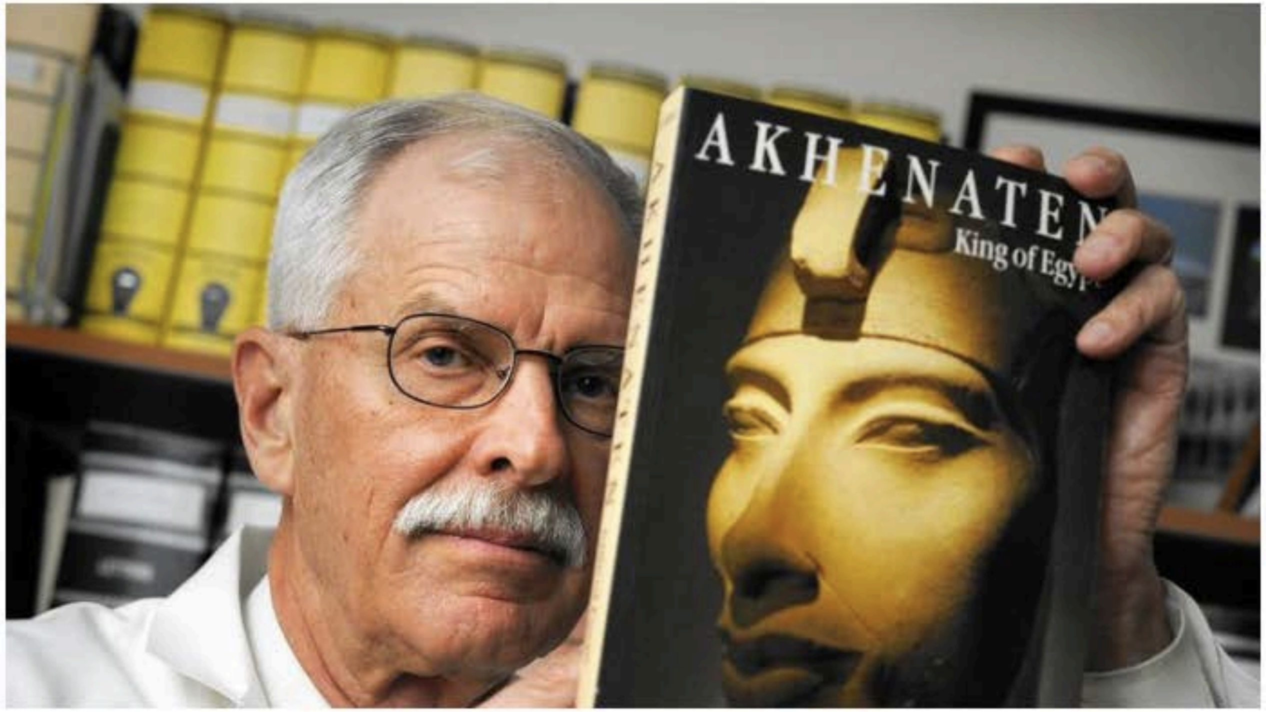
ORiGAMI @ LA Times and Washington Post

What killed Cromwell? Or Mozart? Sleuthing doctors take on the 'ultimate whodunit'



The Historical Clinicopathological Conference, launched by Dr. Philip A. Mackowiak, has examined the deaths of Herod the Great, Pericles and Akhenaten. (Lloyd Fox / Baltimore Sun)

In 4.5 seconds, ORIGAMI — short for Oak Ridge Graph Analytics for Medical Innovation — converged on virtually the same conclusion drawn after weeks of research and deliberation by Saint: Cromwell was done in by malaria.

"Who would I rather have making a diagnosis? It would be hands-down Dr. Saint," Siegel said. On the other hand, "if you told me there was a mystery disease and no one had any ideas about it and we needed some new insight ... I like the computer."

Questions ?

Time for a demo ?

Ecosystem offered using the App-Store Model

Framework of Knowledge Discovery for a future beyond the Big Data Era

PLUS

Programmatic-Python Login for Urika-like SPARQL End-points

Code Development

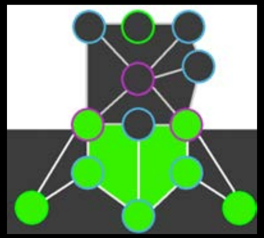
FELT

Flexible, Extract, Transform and Load Toolkit

Graph Creation

EAGLE-C

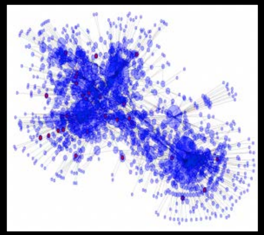
EAGLE 'Is a' algorithmic Graph Library for Exploratory-Analysis



Scalable Algorithms

GRAPH-IC

Graph- Interaction Console



Interactive Visualization

PAUSE

Predictive Analytics using SPARQL-Endpoints

Reasoning + Inference

KENODES

Knowledge Extraction using Network-Oriented Discovery Enabling System

Hypothesis Creation

Open Source @ https://github.com/ssrangan/gm-sparql

S.R. Sukumar et al., "EAGLE: An App-Store for the Urika-GD", Cray User Group Conference, 2015.

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UTHSC Use Case: Diabetic Retinopathy

Sample Measurements

Patient ID	Pregnant	Race	OD Condition	Age	HgbA1c	Cholest.
19	N	African	NPDR Severe + CSME	37	Null	185
43	N	Caucasian	No diabetic retinopathy	64	11.7	161
58	Y	Unknown	Null	33	10.2	220
104	N	Hispanic	Other	53	9.7	Null
135	N	African	NPDR Mild/Minimal - CSME	62	8.2	148

Images

Text

Comments
Poor quality images but adequate for diagnosis
Vascular tortuosity (congenital). No retinopathy
Mild ischemia (cotton woll spots) No hemorrhages or edema
possible mild drusen No DR evident
rare microaneurysms only f/u 12 months

Dataset: 7600 patients, 31 clinical lab measurements, at least 1 image and report per patient, about a 100 meta-data variables over 3 year period.

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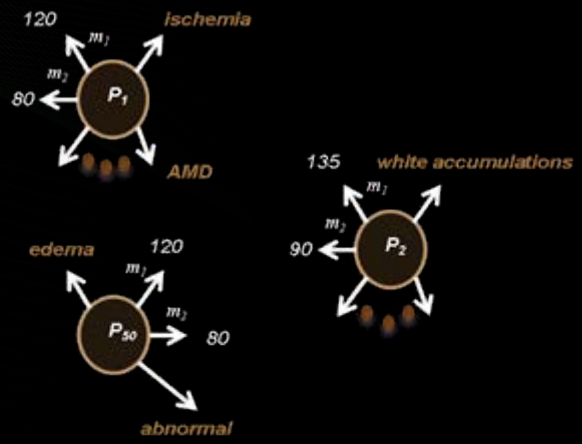
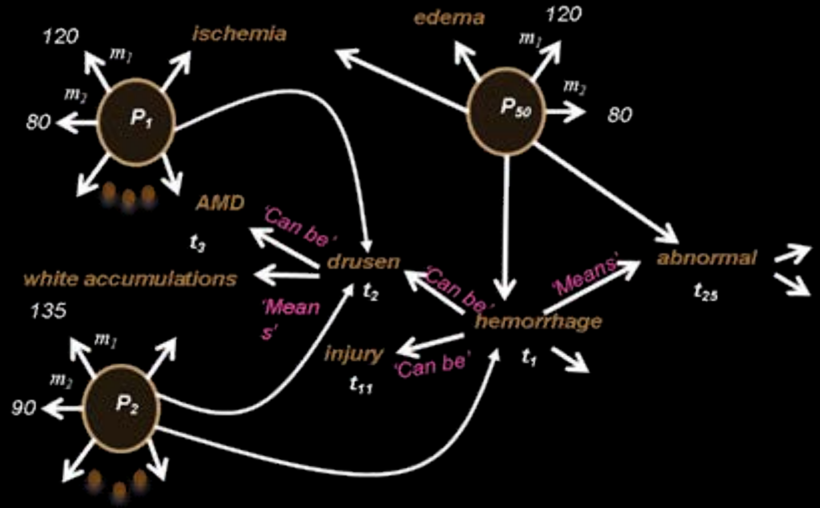
SME Knowledge + Data

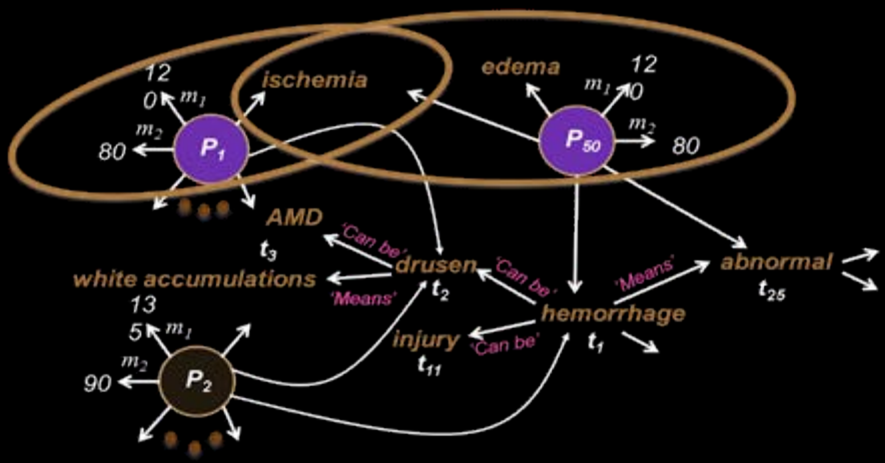
Convert data into RDF

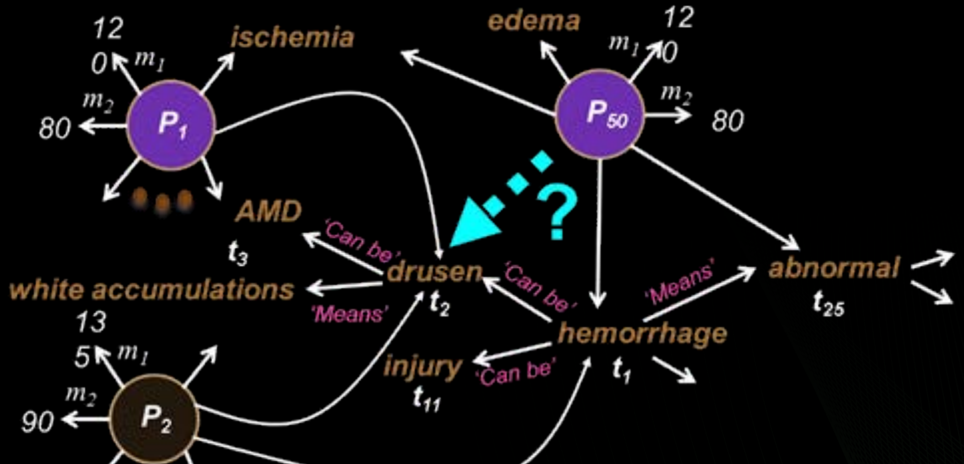




Integrate Knowledgebase

Find similar patients





Link Prediction

S. R. Sukumar, and K. C. Ainsworth. "Pattern search in multi-structure data: a framework for the next-generation evidence-based medicine." *In SPIE Medical Imaging*, pp. 90390O-90390O, February 2014.

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What did we find?

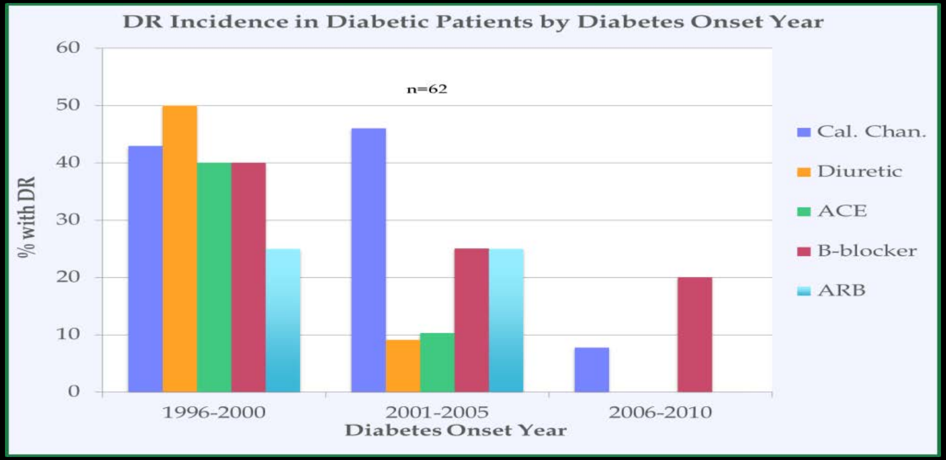
Simultaneous feature-subset and link prediction

Attributes common with top 100 similar patients without DR (> 80% support)

DM_Status: Normal routine history

DM_Problem: Hypertension

DM_Drug: Lisinopril



Attributes common with top 100 patients with DR (> 80% support)

DM_Medication : "INSULIN + PILL"

Condition_EE : "NPDR Mild/Minimal + CSME"

DM_Drug : ”Glyburide"

Diabetic Retinopathy (DR) and Beta Blockers (BB) in Cross-Sectional Data: Hypothesis Testing

Incidence of DR by Population Characteristic

Characteristic	Incidence of DR (%)	Total (n)	With DR (n)
BB	46.5	88	41
No BB	28.6	412	118
No BB + hypertension (HTN)	29.0	338	98
Diabetes mellitus (DM) onsett > 5 years	39.1	233	91
DM onsett ≤ 5 yr.	7.8	115	9
DM onsett > 5 yr. + BB	54.0	50	27
DM onsett ≤ 5 yr. + BB	14.3	14	2
DM onsett > 5 yr. no BB	35.7	207	74
DM onsett ≤ 5 yr. no BB	6.9	101	7

Incidence of DR: 2 × 2 Fisher's Exact Tests

BB vs. No BB

	DR	*No DR*
BB	41	47
No BB	118	294

p = 0.0010 (extremely statistically significant)

K. Senter, *S. R. Sukumar*, R.M. Patton and E. Chaum, “Using Clinical Data, Hypothesis Generation Tools and PubMed Trends to Discover the Association between Diabetic Retinopathy and Antihypertensive Drugs”, in the Proc. of the Workshop on Mining Big Data to Improve Clinical Effectiveness in conjunction with the IEEE Conference on Big Data, pp. 2366-2370, 2015.

What else did we find ?

start	p1	x1	p2	x2	p3	x3	p4	end	score
BETA_BLOCKER_TREATMENT	PREDISPOSES	Small_for_dates_unspecified	NEG_PREDISPOSES	Retinopathy_of_Prematurity	Rev_CAUSES	Impairment_level__total_impairment_of_both_eyes	Rev_NEG_CAUSES	Diabetic_Retinopathy	0.150231
BETA_BLOCKER_TREATMENT	PREDISPOSES	Small_for_dates_unspecified	Rev_CAUSES	Insulin_Like_Growth_Factor_I_Receptor	Rev_ASSOCIATED_WITH	Choroidal_Neovascularization	NEG_OCCURS_IN	Diabetic_Retinopathy	0.129785
BETA_BLOCKER_TREATMENT	PREDISPOSES	Small_for_dates_unspecified	NEG_PREDISPOSES	Retinopathy_of_Prematurity	CAUSES	RETINAL_VASCULAR	Rev_CAUSES	Diabetic_Retinopathy	0.090275
BETA_BLOCKER_TREATMENT	Rev_METHOD_OF	Consultation	AFFECTS	LANGUAGE_BARRIER	COEXISTS_WITH	Proliferative_diabetic_retinopathy	Rev_NEG_CAUSES	Diabetic_Retinopathy	0.066787
BETA_BLOCKER_TREATMENT	NEG_ADMINISTERED_TO	CARDIAC_PATIENT	NEG_LOCATION_OF	Cytotoxic_T_Lymphocyte_Associated_Protein_4	Rev_NEG_LOCATION_OF	Pichia_pastoris	Rev_AFFECTS	Diabetic_Retinopathy	0.056911
BETA_BLOCKER_TREATMENT	PREDISPOSES	Small_for_dates_unspecified	OCCURS_IN	Respiratory_Distress_Syndrome__Newborn	NEG_COEXISTS_WITH	Sepsis_of_the_newborn	Rev_MANIFESTATION_OF	Diabetic_Retinopathy	0.049392
BETA_BLOCKER_TREATMENT	PREDISPOSES	Small_for_dates_unspecified	Rev_COMPLICATES	Fetal_Membranes__Premature_Rupture	PRECEDES	Sepsis_of_the_newborn	Rev_MANIFESTATION_OF	Diabetic_Retinopathy	0.038918
BETA_BLOCKER_TREATMENT	Rev_STIMULATES	Exercise	STIMULATES	Primary_Prevention	AFFECTS	disabling_disease	Rev_PRECEDES	Diabetic_Retinopathy	0.028472
BETA_BLOCKER_TREATMENT	AFFECTS	Proarrhythmia	Rev_PREDISPOSES	KCNN4_IKZF1	Rev_INHIBITS	1_ethyl_2_benzimidazolinone	NEG_TREATS	Diabetic_Retinopathy	0.028253
BETA_BLOCKER_TREATMENT	Rev_STIMULATES	Exercise	STIMULATES	Decompressive_incision	AFFECTS	Anatomical_narrow_angle_glaucoma	COMPLICATES	Diabetic_Retinopathy	0.021810
BETA_BLOCKER_TREATMENT	AFFECTS	Generalized_ischemic_myocardial_dysfunction	Rev_OCCURS_IN	Mitral_Valve_Insufficiency	DISRUPTS	majority	Rev_DISRUPTS	Diabetic_Retinopathy	0.017509
BETA_BLOCKER_TREATMENT	PREDISPOSES	Small_for_dates_unspecified	OCCURS_IN	Respiratory_Distress_Syndrome__Newborn	DISRUPTS	majority	Rev_DISRUPTS	Diabetic_Retinopathy	0.016394
BETA_BLOCKER_TREATMENT	TREATS	Myocardial_degeneration	Rev_AFFECTS	Pathologic_Neovascularization	MANIFESTATION_OF	RETINAL_VASCULAR	Rev_CAUSES	Diabetic_Retinopathy	0.011820
BETA_BLOCKER_TREATMENT	PREDISPOSES	Small_for_dates_unspecified	Rev_PREVENTS	Analyzers__Physiologic__Middle_Ear__Acoustic_Reflectometry	DIAGNOSES	Human_Papillomavirus	INTERACTS_WITH	Diabetic_Retinopathy	0.008695
BETA_BLOCKER_TREATMENT	AFFECTS	Proarrhythmia	Rev_PREDISPOSES	Sodium_Channel_Blockers	AUGMENTS	peptide_binding	Rev_ASSOCIATED_WITH	Diabetic_Retinopathy	0.008520
BETA_BLOCKER_TREATMENT	PREDISPOSES	Small_for_dates_unspecified	Rev_PREDISPOSES	SPTB	AFFECTS	peptide_binding	Rev_ASSOCIATED_WITH	Diabetic_Retinopathy	0.007798
BETA_BLOCKER_TREATMENT	TREATS	Myocardial_degeneration	Rev_AFFECTS	Pathologic_Neovascularization	NEG_AFFECTS	RETINAL_VASCULAR	Rev_CAUSES	Diabetic_Retinopathy	0.007769
BETA_BLOCKER_TREATMENT	AFFECTS	Proarrhythmia	Rev_CAUSES	Sodium_Channel_Blockers	AUGMENTS	peptide_binding	Rev_ASSOCIATED_WITH	Diabetic_Retinopathy	0.003303