Short course – Summer 2010
Clinical Ontology in Practice

June 15-17, 2010

Clinical Ontology in Practice

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Objectives

- Learn about clinical ontologies
  - History
  - Design principles, formalisms and tools
  - What are they?
  - What are they used for?
- Work with clinical ontologies
  - Search, browse, navigate, query with application programming interfaces
  - Analyze, compare
  - Specific clinical uses (e.g., decisions support, natural language processing, medication reconciliation, e-prescription)
  - Specific issues (e.g., mapping across ontologies, ontologies and information models)

Agenda

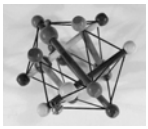
Tuesday, June 15 *(lecture)*	Introduction to Biomedical Ontologies	Design Principles, Formalisms and Tools for Biomedical Ontologies	Biomedical Ontologies - Content and structure - Function
Wednesday, June 16 *(hands-on)*	UMLS	SNOMED CT LOINC	RxNorm NDF-RT
Thursday, June 17 *(discussion)*	Decision support Medication reconciliation	E-prescribing Natural language processing	Mapping across ontologies Value sets

References Review articles

- Bodenreider O, Stevens R.
  Bio-ontologies: current trends and future directions.
  Brief Bioinform. 2006 Sep;7(3):256-74.
- Cimino JJ, Zhu X.
  The practical impact of ontologies on biomedical informatics.
  Yearb Med Inform. 2006:124-35.
- Bodenreider O.
  Biomedical ontologies in action: role in knowledge management, data integration and decision support.
  Yearb Med Inform. 2008:67-79.

References Bio-ontology courses

- Barry Smith, U. Buffalo / NCBO
  - http://ontology.buffalo.edu/smith/Ontology_Course.html
- Stefan Schulz, U. Freiburg, Germany / KR-MED 2008 tutorial
  - http://www.kr-med.org/2008/index.html



Medical
Ontology
Research

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Short course – Summer 2010
Clinical Ontology in Practice

June 15, 2010 – Session #1

Introduction to Biomedical Ontologies

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Outline

- Historical perspective
- Introduction to biomedical terminologies through an example
- Biomedical terms as names for biomedical classes
- Terminological relations as a surrogate for ontological relations

Historical perspective

Why biomedical terminologies?

- To support a theory of diseases
- To classify diseases
- To support epidemiology
- To index and retrieve information
- To serve as a reference

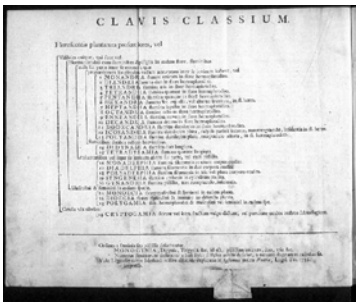
To support a theory of diseases

- Hippocrates
  - Dismisses superstition
  - Four humors
    - Blood
    - Phlegm
    - Yellow bile
    - Black bile
- Thomas Sydenham (1624-1689)
  - *Medical observations on the history and cure of acute diseases* (1676)

To classify diseases (and plants)

- Carolus Linnaeus (1707-1778)
  - *Genera Plantarum* (1737)
  - *Genera Morborum* (1763)
- François Boissier de La Croix a.k.a. F. B. de Sauvages (1706-1767)
  - *Methodus Foliorum* (1751)
  - *Nosologia Methodica* (1763/68)
- William Cullen (1710-1790)
  - *Synopsis Nosologiae Methodicae* (1785)

From plants…



… to diseases

- Four categories (W. Cullen)
  - Fevers
  - Nervous disorders
  - Cachexias
  - Local diseases

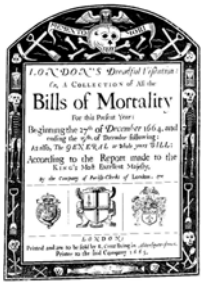
"The distinction of the genera of diseases, the distinction of the species of each, and often even that of the varieties, I hold to be a necessary foundation of every plan of physic, whether dogmatical or empirical."
– William Cullen, Edinburgh, 1785
Synopsis Nosologia Methodicae

(Cited by Chris Chute)

To support epidemiology

- John Graunt (1620-1674)
  - Analyzes the vital statistics of the citizens of London
- William Farr (1807-1883)
  - Medical statistician
  - Improves Cullen's classification
  - Contributes to creating ICD
- Jacques Berthillon (1851-1922)
  - Chief of the statistical services (Paris)
  - Classification of causes of death (161 rubrics)

London Bills of Mortality



Limitations of existing classifications

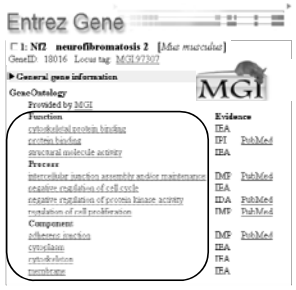
"The advantages of a uniform statistical nomenclature, however imperfect, are so obvious, that it is surprising no attention has been paid to its enforcement in Bills of Mortality. Each disease has, in many instances, been denoted by three or four terms, and each term has been applied to as many different diseases: vague, inconvenient names have been employed, or complications have been registered instead of primary diseases. The nomenclature is of as much importance in this department of inquiry as weights and measures in the physical sciences, and should be settled without delay."
– William Farr
First annual report.
London, Registrar General of England and Wales, 1839, p. 99.

To index and retrieve information

- Biomedical literature
  - MEDLINE (15M citations from 4600 journals)
  - Manually indexed
  - Medical Subject Headings (MeSH)
- Genome
  - Model organism databases (Fly, Mouse, Yeast, …)
  - Manually / semi-automatically curated
  - Gene Ontology

MEDLINE and MeSH

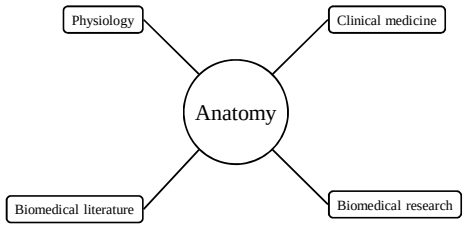
Mouse Genome Database and GO



To serve as a reference

- Reference terminology/ontology
  - Universally needed
  - Developed independently of any purposes
  - Reusable by many applications
- Examples
  - VA National Drug File (NDF)
  - Foundational Model of Anatomy (FMA)
  - SNOMED CT

Anatomy in Biomedicine

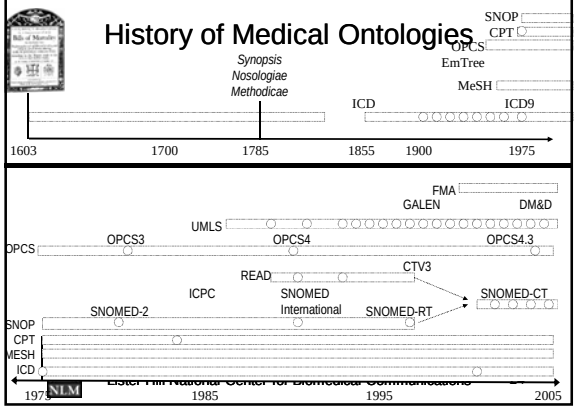


Administrative terminologies

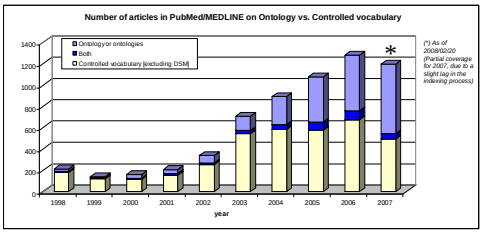
- Coding patient records
  - International Classification of Primary Care (ICPC)
  - SNOMED
  - Read Codes
- Reporting claims to health insurance companies
  - Current Procedural Terminology (CPT)
  - International Classification of Diseases (ICD-9 CM)
  - Healthcare Common Procedure Coding System (HCPCS)

[Bodenreider, BIB 2006] *(courtesy of J. Rogers)*

History of Medical Ontologies

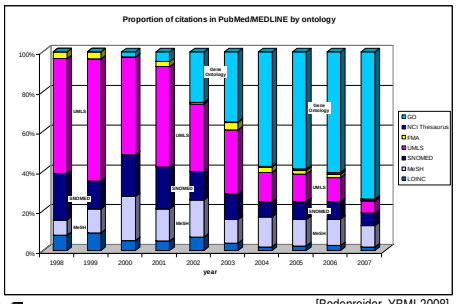


Biomedical ontology in PubMed



[Bodenreider, YBMI 2008]

Biomedical ontologies in PubMed



[Bodenreider, YBMI 2008]

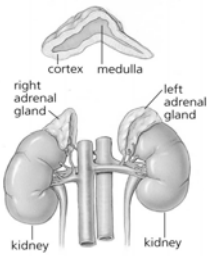
Introduction to biomedical terminologies through an example

Guy's Hospital, London

Thomas Addison (1795-1860)

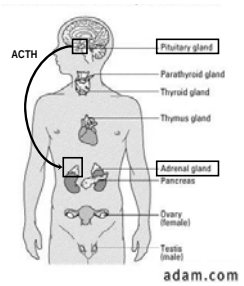
Addison's disease

- Addison's disease is a rare endocrine disorder
- Addison's disease occurs when the adrenal glands do not produce enough of the hormone cortisol
- For this reason, the disease is sometimes called chronic adrenal insufficiency, or hypocortisolism



Adrenal insufficiency Clinical variants

- Primary / Secondary
  - Primary: lesion of the adrenal glands themselves
  - Secondary: inadequate secretion of ACTH by the pituitary gland
- Acute / Chronic
- Isolated / Polyendocrine deficiency syndrome



Addison's disease: Symptoms

- Fatigue
- Weakness
- Low blood pressure
- Pigmentation of the skin (exposed and non-exposed parts of the body)
- …

AD in medical vocabularies

- Synonyms: different terms
  - Addisonian syndrome — eponym
  - Bronzed disease
  - Addison melanoderma
  - Asthenia pigmentosa — symptoms
  - Primary adrenal deficiency
  - Primary adrenal insufficiency
  - Primary adrenocortical insufficiency
  - Chronic adrenocortical insufficiency — clinical variants
- Contexts: different hierarchies

Internal Classification of Diseases

CHAPTER 4

Endocrine, nutritional and metabolic diseases (E00-E90)

Disorders of other endocrine glands (E20-E35)

E27 Other disorders of adrenal gland

E27.0 Other adrenocortical overactivity
Overproduction of ACTH, not associated with Cushing's disease
Premature adrenarche
Excludes1: Cushing's syndrome (E24 -)

E27.1 Primary adrenocortical insufficiency
Addison's disease
Adrenocortical insufficiency NOS
Autoimmune adrenalitis
Excludes1: Addison only phenotype adrenoleukodystrophy (E71.428)
arrylbiodosis (E85)
tuberculous Addison's disease (A18.7)
Waterhouse-Friderichsen syndrome (A39.1)

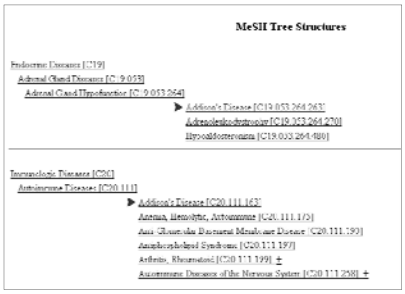
E27.2 Addisonian crisis
Adrenal crisis
Adrenocortical crisis

E27.3 Drug-induced adrenocortical insufficiency
Code first (T36-T50) to identify drug

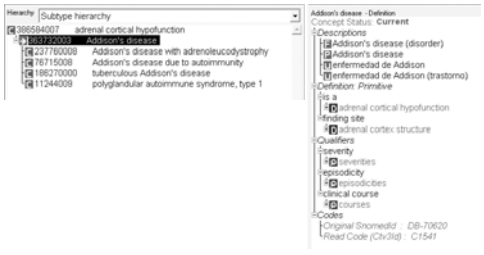
E27.4 Other and unspecified adrenocortical insufficiency

Draft ICD-10 CM Tabular Page 180 June 2003

Medical Subject Headings



SNOMED CT



Biomedical terms as names for biomedical classes

Terms reflecting valid classes

- Pulmonary anthrax
- BRCA1 protein
- Coronary artery
- Coronary artery bypass
- ...
  - Non-insulin dependent diabetes mellitus
  - Non-Hodgkin lymphoma
  - Non-steroidal anti-inflammatory drugs
  - Non-opioid analgesics
  - Non-invasive medical procedure

Issues

- Multiple terms for a class
- Multiple classes for a term
- Presence of non-ontological features in terms
- Composite terms

Multiple terms for a class

- Synonymy
  - Left coronary artery
  - LCA
  - Arteria coronaria sinistra
  - Addison's disease
  - Primary adrenocortical insufficiency
- "Clinical synonymy" (vs. identity)
  - Abdominal swelling
  - Swollen abdomen
  - Addison's disease
  - Primary adrenocortical insufficiency
  - Posttransfusion hepatitis
  - Posttransfusion viral hepatitis

vs. Waterhouse-Friderichsen Syndrome

Multiple classes for a term

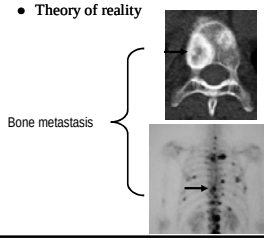
- Polysemy
  - Cold
    - Cold
    - Common cold
    - Cold
    - Cold temperature
    - COLD
    - Chronic Obstructive Airway Disease
- Truncated terms
  - Calcium
    - Calcium
    - Ca^{++}
    - Coagulation factor IV
    - Calcium
    - Calcium measurement

Non-ontological features in terms

- Epistemological features
  - Gallbladder calculus without mention of cholecystitis
  - Diarrhea of presumed infectious origin
  - Replacement of unspecified heart valve
  - ...

Ontology vs. Epistemology

- Ontology
  - Invariants in reality
    - Classes (universals)
    - Relations between them
  - Theory of reality
- Epistemology
  - Knowledge about such entities
  - Perception of reality



Bone metastasis

Bone metastasis
diagnosed by CT scan

Bone metastasis
diagnosed by Tc99m bone scintiscan

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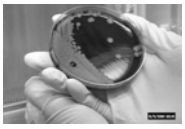
Composite terms

- Sentence-like terms
  - Several classes and their relations
  - May contain epistemological features
- Tuberculosis of adrenal glands, tubercle bacilli not found (in sputum) by microscopy, but found by bacterial culture



More composite terms

- Nontraffic accident involving being accidentally pushed from motor vehicle, except off-road motor vehicle, while in motion, not on public highway, driver of motor vehicle injured
- Determine whether the elder patient and caretaker have a functional social support network to assist the patient in performing activities of daily living and in obtaining health care, transportation, therapy, medications, community resource information, financial advice, and assistance with personal problems
- Telephone call by a physician to patient or for consultation or medical management or for coordinating medical management with other health care professionals (eg, nurses, therapists, social workers, nutritionists, physicians, pharmacists); complex or lengthy (eg, lengthy counseling session with anxious or distraught patient, detailed or prolonged discussion with family members regarding seriously ill patient, lengthy communication necessary to coordinate complex services of several different health professionals working on different

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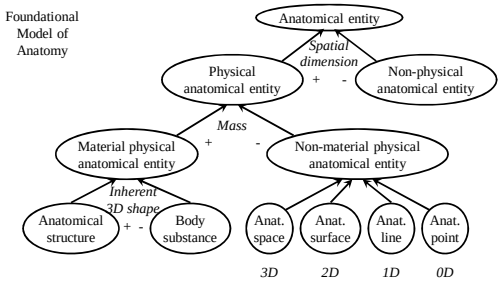
Terminological relations as a surrogate for ontological relations

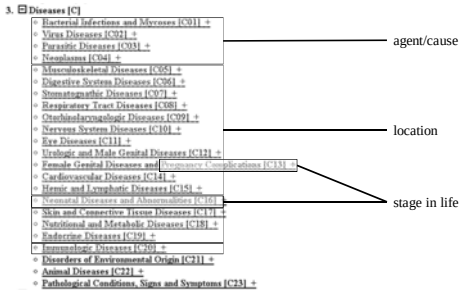
Issues

- Lack of explicit classificatory principle
- Underspecification of the relations
- Thesaurus relations
- Limited depth in hierarchies “by design”

Explicit classificatory principle



No explicit classificatory principle

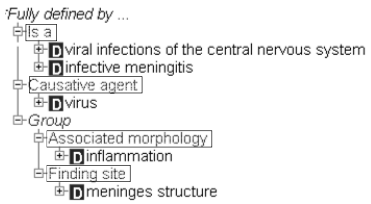


1. Certain infectious and parasitic diseases
2. Neoplasms
3. Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
4. Endocrine, nutritional, and metabolic diseases
5. Mental and behavioral disorders
6. Diseases of nervous system
7. Diseases of the eye and adnexa
8. Diseases of the ear and mastoid process
9. Diseases of circulatory system
10. Diseases of respiratory system
11. Diseases of digestive system
12. Diseases of the skin and subcutaneous tissue
13. Diseases of the musculoskeletal system and connective tissue
14. Diseases of the genitourinary system
15. Pregnancy, childbirth, and the puerperium
16. Certain conditions originating in the newborn (perinatal) period
17. Congenital malformations, deformations and chromosomal abnormalities
18. Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
19. Injury, poisoning and certain other consequences of external causes
20. External causes of morbidity
21. Factors influencing health status and contact with health service

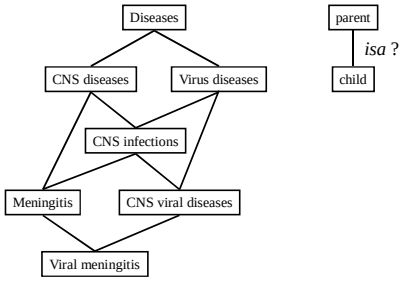
- Attribute
- Body structure
- Clinical finding
- Context-dependent categories
- Environments and geographical locations
- Events
- Observable entity
- Organism
- Pharmaceutical / biologic product
- Physical force
- Physical object
- Procedure
- Qualifier value
- Social context
- Special concept
- Specimen
- Staging and scales
- Substance

Fully specified relations

Viral meningitis in SNOMED CT

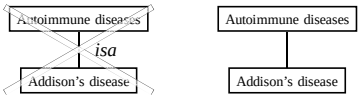


Underspecification of the relations

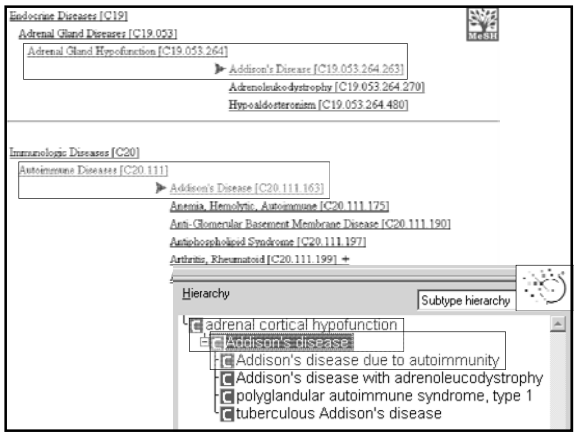


Thesaurus relations

- Addison's disease
  - Due to auto-immunity in 80% of the cases
  - Other causes include tuberculosis



Relations used to create hierarchical structures
vs. hierarchical relations



Accidents in MeSH

Environment and Public Health [G03]
Public Health [G03.850]
Accidents [G03.850.110]
Accident Prevention [G03.850.110.060] +
Accidental Falls [G03.850.110.085]
Accidents, Aviation [G03.850.110.185]
Accidents, Home [G03.850.110.205]
Accidents, Occupational [G03.850.110.250] +
Accidents, Radiation [G03.850.110.285]
Accidents, Traffic [G03.850.110.320]
Drowning [G03.850.110.500] +

Limited depth in hierarchies "by design"

- Term identifier (code) used to record the position in the hierarchy
  - Limited number of digits available
  - May hide part of the structure
- Terminologies: ICD, SNOMED, …

E84 Cystic fibrosis
Includes: mucoviscidosis
E84.0 Cystic fibrosis with pulmonary manifestations
Use additional code to identify any infectious organism present, such as:
Pseudomonas (B96.5)
E84.1 Meconium ileus in cystic fibrosis
Excludes1: meconium ileus not due to Cystic fibrosis (P75)
E84.2 Cystic fibrosis with gastrointestinal manifestations
Excludes2: meconium ileus in cystic fibrosis (E84.1)
E84.8 Cystic fibrosis with other manifestations

Cystic fibrosis in ICD

E84 Cystic fibrosis
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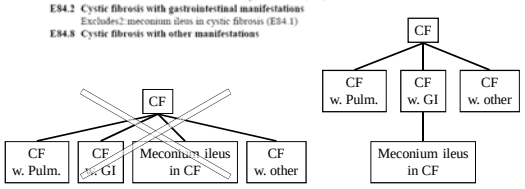

Conclusions

Conclusions ☹

- Biomedical terms
  - reflect some aspects of biomedical reality
    - Although the primary concern of terminology is naming, not reflecting reality
  - often convey additional features (e.g., epistemology)
- Biomedical terminology tends to offset part of the complexity
  - but often reflects utility

Conclusions ☺

- Biomedical terminologies can help populate biomedical ontologies
- Resources needed
  - Linguistic analysis of terms
  - Statistical analysis of terms in a corpus / annotation database (dependence relations)
  - Manual curation

Short course – Summer 2010
Clinical Ontology in Practice

June 15, 2010 – Session #2

Design Principles, Formalisms and Tools for Biomedical Ontologies

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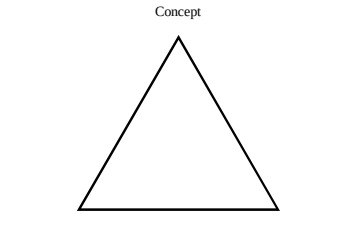
Overview

- Definitions
  - Ontologies vs. other artifacts
  - Kinds of ontologies
- Some principles of formal ontology
  - Top-level categories
  - Categories of relationships
- Formalisms and tools

Definitions

Introduction



Ogden-Richards

Definitions

- The *What* question
  - Objects in the world
    - With their properties
    - With their relations to other objects
  - Also: events, processes, and states
- Explicit specification of a conceptualization
  - Support software applications
- Domain ontology reflects
  - Underlying reality
  - Theory of the domain

Examples of use

- Natural language processing
- Access to heterogeneous sources of information (e.g., Semantic Web)
- Systems engineering
- Interoperability

Ontology vs. other artifacts

- Ontology
  - Defining types of things and their relations
- Terminology
  - Naming things in a domain
- Thesaurus
  - Organizing things for a given purpose
- Classification
  - Placing things into (arbitrary) classes
- Knowledge bases
  - Assertional knowledge

[Smith, KR-MED 2006]
[Chute, JAMIA 2000]

(Controlled) Terminology

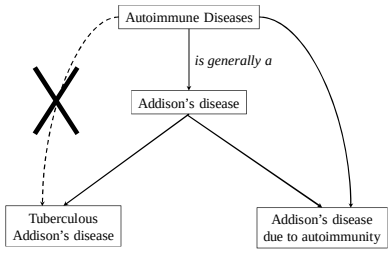
- Objective: naming things
- Example: Current Procedural Terminology (CPT)
- Shared understanding
  - Agreement on what terms to use
  - Utility-driven (arbitrary)

Telephone call by a physician to patient or for consultation or medical management or for coordinating medical management with other health care professionals (eg, nurses, therapists, social workers, nutritionists, physicians, pharmacists); complex or lengthy (eg, lengthy counseling session with anxious or distraught patient, detailed or prolonged discussion with family members regarding seriously ill patient, lengthy communication necessary to coordinate complex services of several different health professionals working on different

Thesaurus

- Objective: organize things for a purpose
  - e.g., information retrieval
    - Organization by relatedness
- Example: Medical Subject Headings (MeSH)
  - Indexing/retrieval of biomedical articles
- Relations used in hierarchies vs. hierarchical relations

Thesaurus vs. ontology



Classification

- Objective: placing things into classes
- Characteristics
  - Single inheritance (tree)
  - Idiosyncratic inclusion/exclusion criteria

E10 **Insulin-dependent diabetes mellitus**
[See before E10 for subdivisions]
Includes: diabetes (mellitus):
- brittle
- juvenile-onset
- ketosis-prone
- type I

Excludes: diabetes mellitus (in):
- malnutrition-related (E12.-)
- neonatal (P70.2)
- pregnancy, childbirth and the puerperium (O24.-)

glycosuria:
- NOS (R81)
- renal (E74.8)

impaired glucose tolerance (R73.0)
postsurgical hypoinsulinaemia (E89.1)

Classification

- Characteristics (continued)
  - Everything must be classified, including
    - When there is no specific slot (NEC)
    - When there is insufficient information (NOS)

E84 **Cystic fibrosis**
Includes: mucoviscidosis
E84.0 **Cystic fibrosis with pulmonary manifestations**
E84.1 **Cystic fibrosis with intestinal manifestations**
Meconium ileus+ (P75*)
Excludes: meconium obstruction in cases where cystic fibrosis is known not to be present (P76.0)
E84.8 **Cystic fibrosis with other manifestations**
Cystic fibrosis with combined manifestations
E84.9 **Cystic fibrosis, unspecified**

Knowledge Bases

- Objective: represent knowledge needed for a given application
- Example: drug knowledge bases
- Assertional knowledge
  - Vs. definitional knowledge in ontologies
  - Often probabilistic
- Examples of assertions
  - Indications of a drug
  - Signs and symptoms of a disease

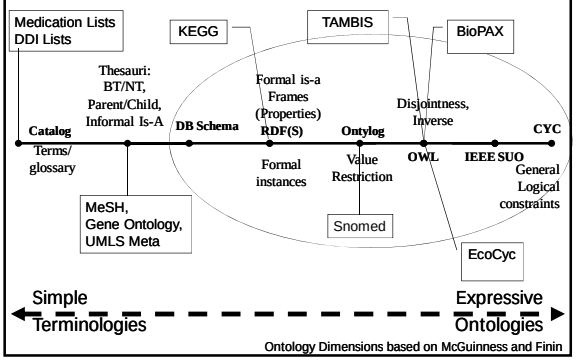
Fuzzy borders

- Some ontologies also collect names
  - FMA
- Some terminologies also provide formal definitions
  - SNOMED CT
- Some terminologies/ontologies include both definitional and assertional knowledge
  - SNOMED CT

Types of resources

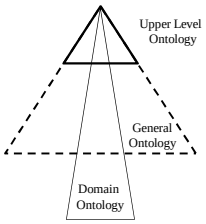
- Lexical resources
  - Collections of lexical items
  - Additional information
    - Part of speech
    - Spelling variants
  - Useful for entity recognition
  - UMLS SPECIALIST Lexicon, WordNet
- Ontological resources
  - Collections of
    - kinds of entities (substances, qualities, processes)
    - relations among them
  - Useful for relation extraction
  - UMLS Semantic Network, BioTop
- Terminological resources
  - Collections lexical items + identifiers
    - Useful for entity resolution
      - UMLS Metathesaurus

The Knowledge Semantics Continuum



Ontology Dimensions based on McGuinness and Finin

Kinds of ontologies



Application ontologies

Ontology-related issues

- Creation
- Merging
- Alignment
- Validation

Formal Ontological Principles

Formal ontological distinctions

- Universal vs. individual
- Continuant vs. occurent
- Independent vs. dependent

Universal vs. Individual

- Universal = *category*
- Synonyms
  - Kind, Type, (Class)
- Examples
  - eyeball
  - blood pressure
  - conference

instantiation

- Individual = *instance*
- Synonyms
  - Particular, Token
- Examples
  - my right eyeball
  - my blood pressure (132/79)
  - AMIA Annual Symposium 2003

Continuant vs. Occurrent

- Continuant = *Continues to exist through time*
- Synonyms
  - Substance
- Examples
  - tennis racquet
  - mitochondrion
  - insulin production

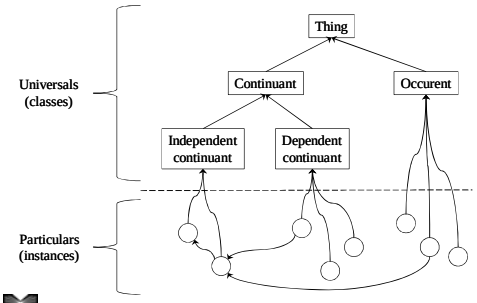
- Occurrent = *Unfolds through time*
- Synonyms
  - Process
- Examples
  - tennis tournament
  - metabolism
  - producing insulin

Independent vs. Dependent

- Independent = *Can exist without support from other entities*
- Examples
  - virus
  - molecule
  - plant

- Dependent = *Require support from other entities for its existence*
- Examples
  - viral infection
  - DNA binding
  - food

Formal ontology Upper level



Formal ontological distinctions

- Basic distinctions in many top-level ontologies
  - Generic: BFO, DOLCE
  - Biomedical: BioTop, UMLS Semantic Network
- Condition the relations between various types of entities
  - Relations
    - Between instances (e.g., *part_of* [at time])
    - Between classes (e.g., *isa*, *part_of* [atemporal])
    - Between one instance and one class (*instance_of*)

[Smith, Genome Biology 2005]

Formal ontology in practice

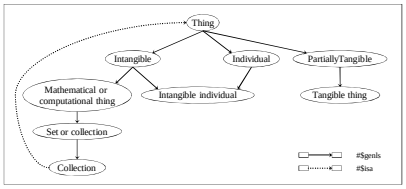
- Provides foundational classes and relations
  - Upper level ontologies
  - Relation ontology
- Provides a framework for analyzing entities and relations

Examples

General ontologies

- OpenCyc
  - General ontology
  - Cycorp, Inc (D. Lenat & al.)
  - Over 1M hand-coded assertions
  - http://www.opencyc.org
- WordNet
  - Electronic lexical database
  - Princeton University (G. Miller & al.)
  - Over 100,000 synsets
  - http://wordnet.princeton.edu/

Top level in OpenCyc



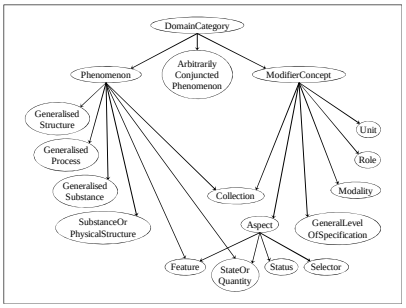
Top level in WordNet

- Abstraction
- Activity
- Entity
- Event
- Group
- Location
- Natural phenomenon
- Possession
- Psychological feature
- Shape
- State

GALEN

- Generalised Architecture for Languages, Encyclopaedias, and Nomenclatures in Medicine
- European Union project (A. Rector & al.)
- Over 25,000 concepts (primitives)
- http://www.opengalen.org

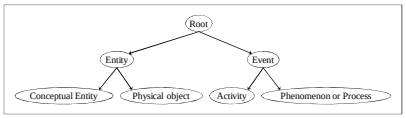
Top level in GALEN



UMLS Semantic Network

- Definitional knowledge in the biomedical domain
- NLM (A. McCray & al.)
- Content
  - 133 semantic types
  - 54 types of relationship
  - 6700 semantic relations
- http://semanticnetwork.nlm.nih.gov

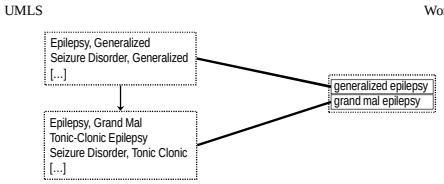
Top level in the Semantic Network



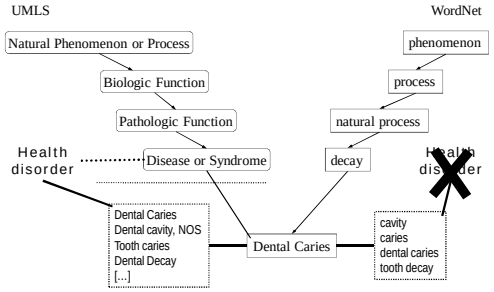
Differences between ontologies

Examples

Granularity, plesionymy



Differing categorization



Formalisms and Tools

Ontology and Formalism

- Frames
- Description logics
  - OWL DL
- First-order logic

- OBO Format
  - Conversion to OWL DL

Tools for ontology developers

- Protégé
  - Publicly available
  - Frames and DL
  - Classifier
  - Supports many file formats (import/export)
  - Large community of users
  - Well supported
  - http://protege.stanford.edu/

http://protege.stanford.edu/

- OBO-Edit
  - Specific to the biomedical/OBO community
  - Simpler than Protégé ("tool for biologists")
  - http://oboedit.org/

Short course – Summer 2010
Clinical Ontology in Practice

June 15, 2010 – Session #3

"High-Impact" Biomedical Ontologies

A Structural Perspective

Olivier Bodenreider

Lister Hill National Center
for Biomedical Communications
Bethesda, Maryland - USA

Overview

- Structural perspective [J. Cimino, YBMI 2006]
  - What are they (vs. what are they for)?
- "High-impact" biomedical ontologies
  - International Classification of Diseases (ICD)
  - Logical Observation Identifiers, Names and Codes (LOINC)
  - SNOMED Clinical Terms
  - Foundational Model of Anatomy
  - Gene Ontology
  - RxNorm
  - Medical Subject Headings (MeSH)
  - NCI Thesaurus
  - Unified Medical Language System (UMLS)

International Classification of Diseases

ICD Characteristics (1)

- Current version: ICD-10
- Type: Classification
- Domain: Disorders
- Developer: World Health Organization (WHO)
- Funding: WHO
- Availability
  - Publicly available: No
  - Repositories: UMLS [ICD9-CM in NCBO BioPortal]
- URL: http://www.who.int/classifications/icd/en/

ICD Characteristics (2)

- Number of
  - Concepts: 12,318
  - Terms: 1 per concept (tabular)
- Major organizing principles:
  - Tree (single inheritance hierarchy)
  - No explicit classification criteria
    - Idiosyncratic inclusion/exclusion mechanism
  - .8 slots for Not elsewhere classified (NEC)
  - .9 slots for Not otherwise specified (NOS)
- Formalism: Proprietary format

ICD Top level

Chapter	Blocks	Title
I	A00-B99	Certain infectious and parasitic diseases
II	C00-D48	Neoplasms
III	D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
IV	E00-E90	Endocrine, nutritional and metabolic diseases
V	F00-F99	Mental and behavioural disorders
VI	G00-G99	Diseases of the nervous system
VII	H00-H59	Diseases of the eye and adnexa
VIII	H60-H95	Diseases of the ear and mastoid process
IX	I00-I99	Diseases of the circulatory system
X	J00-J99	Diseases of the respiratory system
XI	K00-K93	Diseases of the digestive system
XII	L00-L99	Diseases of the skin and subcutaneous tissue
XIII	M00-M99	Diseases of the musculoskeletal system and connective tissue
XIV	N00-N99	Diseases of the genitourinary system
XV	O00-O99	Pregnancy, childbirth and the puerperium
XVI	P00-P96	Certain conditions originating in the perinatal period
XVII	Q00-Q99	Congenital malformations, deformations and chromosomal abnormalities
XVIII	R00-R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
XIX	S00-T98	Injury, poisoning and certain other consequences of external causes
XX	V01-Y98	External causes of morbidity and mortality
XXI	Z00-Z99	Factors influencing health status and contact with health services
XXII	U00-U99	Codes for special purposes

ICD Example

- Idiosyncratic inclusion/exclusion criteria

E10 **Insulin-dependent diabetes mellitus**
[See before E10 for subdivisions]
Includes: diabetes (mellitus):
- brittle
- juvenile-onset
- ketosis-prone
- type I

Excludes: diabetes mellitus (in):
- malnutrition-related (E12.-)
- neonatal (P70.2)
- pregnancy, childbirth and the puerperium (O24.-)

glycosuria:
- NOS (R81)
- renal (E74.8)

impaired glucose tolerance (R73.0)
postsurgical hypoinsulinaemia (E89.1)

ICD Example

- Not elsewhere classified (NEC)
- Not otherwise specified (NOS)

E84 **Cystic fibrosis**
Includes: mucoviscidosis
E84.0 **Cystic fibrosis with pulmonary manifestations**
E84.1 **Cystic fibrosis with intestinal manifestations**
Meconium ileus+ (P75*)
Excludes: meconium obstruction in cases where cystic fibrosis is known not to be present (P76.0)
E84.8 **Cystic fibrosis with other manifestations**
Cystic fibrosis with combined manifestations
E84.9 **Cystic fibrosis, unspecified**

Logical Observation Identifiers, Names and Codes (LOINC)

LOINC®

LOINC Characteristics (1)

- Current version: 2.30 (Feb. 2010)
- Type: Controlled terminology*
- Domain: Laboratory and clinical observations
- Developer: Regenstrief Institute
- Funding: NLM
- Availability
  - Publicly available: Yes
  - Repositories: UMLS
- URL: www.regenstrief.org/loinc/loinc.htm

LOINC Characteristics (2)

- Number of
  - Concepts: 50k active codes (2.18) (2 annual releases)
  - Terms: n/a*
- Major organizing principles:
  - No hierarchical structure among the main codes
  - 6 axes
    - Component (analyte [+ challenge] [+ adjustments])
    - Property
    - Timing
    - System
    - Scale
    - [Method]
- Formalism: "DL-like"

LOINC Example

- *Sodium:SCnc:-Pt:Ser/Plas:Qn*
  [the molar concentration of sodium is measured in the plasma (or serum), with quantitative result]

Axis	Value
Component	Sodium
Property	SCnc – Substance Concen-tration (per volume)
Timing	Pt – Point in time (Random)
System	Ser/Plas – Serum or Plasma
Scale	Qn – Quantitative
Method	--

SNOMED Clinical Terms

SNOMED CT Characteristics (1)

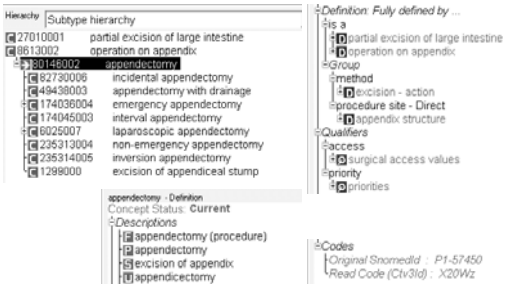
- Current version: January 31, 2010 (2 annual releases)
- Type: Reference terminology / ontology
- Domain: Clinical medicine
- Developer: IHTSDO
- Funding: IHTSDO
- Availability
  - Publicly available: Yes* (in member countries)
  - Repositories: UMLS
- URL: http://www.ihtsdo.org/

SNOMED CT Characteristics (2)

- Number of
  - Concepts: ~310,000 active concepts (Jan. 31, 2010)
  - Terms: ~800,000 active "descriptions"
- Major organizing principles:
  - Utility for clinical medicine (e.g., assertional + definitional knowledge)
  - Model of meaning (incomplete)
  - Rich set of associative relationships
  - Small proportion of defined concepts (many primitives)
- Formalism: Description logics (KRSS)

SNOMED CT Top level

SNOMED CT Example



Foundational Model of Anatomy

FMA Characteristics (1)

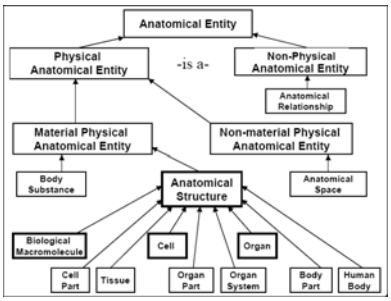
- Current version: ? (no fixed release schedule)
- Type: Ontology
- Domain: Anatomy (anatomical structures)
- Developer: U. Washington, Department of Biological Structure
- Funding: NLM (grants and contract) and others
- Availability
  - Publicly available: Yes
  - Repositories: [UMLS] / OBO / NCBO BioPortal
- URL: http://fma.biostr.washington.edu/

FMA Characteristics (2)

- Number of
  - Concepts: ~72k
  - Terms: ~1.5 / concept
- Major organizing principles:
  - Explicit classificatory criteria
  - Distinct *isa* and *part_of* hierarchies
  - Additional spatial relations (e.g., adjacency)
  - Multiple levels of granularity (organism to sub-cellular)
- Formalism: Frames (Protégé)
  - Conversion to OWL Full and OWL DL available

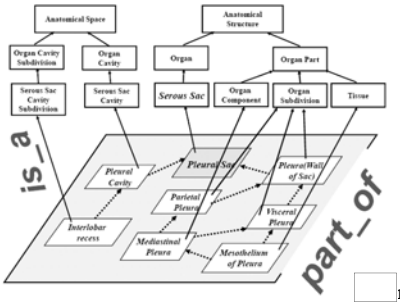
FMA Top level

(Courtesy of C. Rosse)



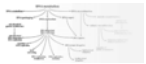
FMA Example

(Courtesy of C. Rosse)



123

Gene Ontology



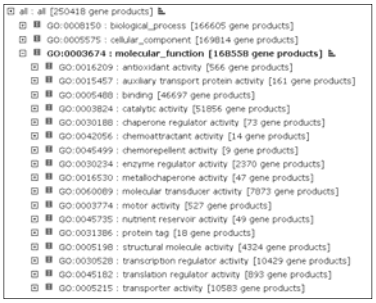
Gene Ontology Characteristics (1)

- Current version: n/a (daily/monthly releases)
- Type: Controlled vocabulary
- Domain: Molecular biology
- Developer: GO Consortium
- Funding: NIH (grants)
- Availability
  - Publicly available: Yes
  - Repositories: UMLS / OBO / NCBO BioPortal
- URL: http://www.geneontology.org/

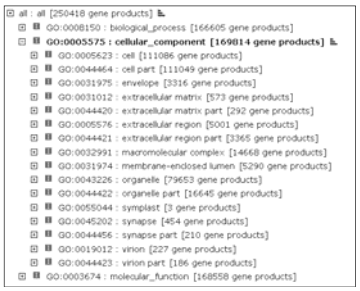
Gene Ontology Characteristics (2)

- Number of
  - Concepts: 27,800 (July 22, 2009)
  - Terms: 2.15 per concept
- Major organizing principles:
  - 3 major hierarchies
    - Molecular function
    - Cellular component
    - Biological process
  - Relations (within hierarchies): *isa*, *part_of*, *regulates*
  - No relations between concepts across hierarchies
- Formalism: OBO format

Gene Ontology Top level (MF)

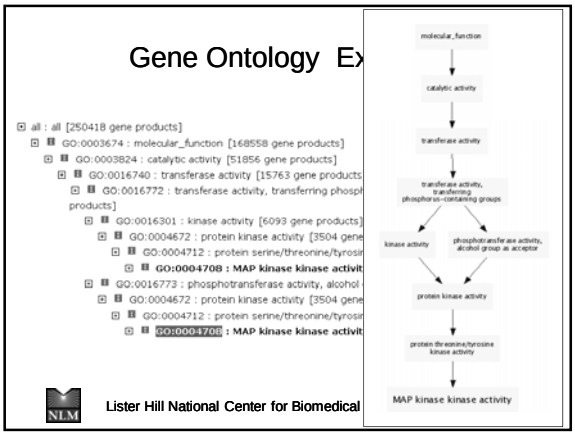


Gene Ontology Top level (CC)



Gene Ontology Top level (BP)

Gene Ontology Ex



RxNorm

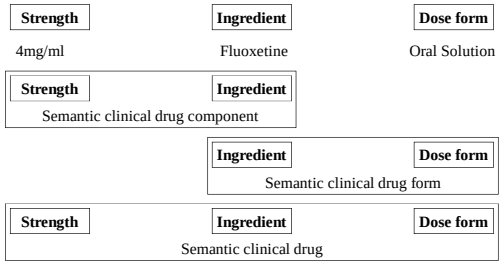
RxNorm Characteristics (1)

- Current version: June 7, 2010 (monthly releases)
- Type: Controlled terminology
- Domain: Drug names
- Developer: NLM
- Funding: NLM
- Availability
  - Publicly available: Yes*
  - Repositories: UMLS
- URL: http://www.nlm.nih.gov/research/umls/rxnorm/

RxNorm Characteristics (2)

- Number of
  - Concepts: 166k
  - Terms: ~1 term per concept
- Major organizing principles:
  - Generic vs. brand
  - Combinations of Ingredient / Form / Dose
  - No hierarchical structure
  - Links to all major US drug information sources
  - No clinical information
- Formalism: UMLS RRF format

RxNorm Normalized form

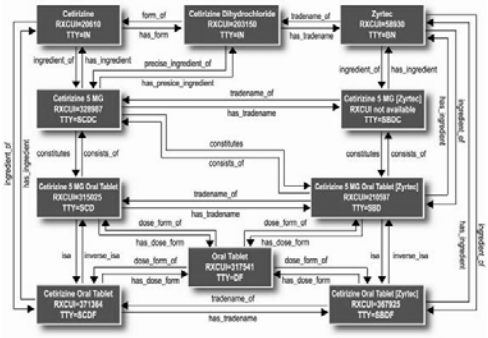


Rx Norm Generic *vs.* Brand

Generic		Brand
Ingredient (IN)	⟷	Brand name (BN)
Clinical drug form (SCDF)	⟷	Branded drug form (SBDF)
Clinical drug component (SCDC)	⟷	Branded drug component (SBDC)
Clinical drug (SCD)	⟷	Branded drug (SBD)

tradename_of

RxNorm Relations among drug entities



Medical Subject Headings (MeSH)

MeSH Characteristics (1)

- Current version: 2010 (yearly releases)
- Type: Thesaurus / Controlled vocabulary
- Domain: Biomedicine
- Developer: NLM
- Funding: NLM (Library Operations)
- Availability
  - Publicly available: Yes
  - Repositories: UMLS / NCBO BioPortal
- URL: http://www.nlm.nih.gov/mesh/

MeSH Characteristics (2)

- Number of
  - Concepts: 25,588 descriptors (2010)
  - Terms: 7.5 per descriptor
- Major organizing principles:
  - Descriptor + entry terms
    (also: Qualifiers, Supplementary concepts)
  - Thesaurus relations (RB/RN/RO)
- Formalism: Thesaurus / Proprietary XML DTD

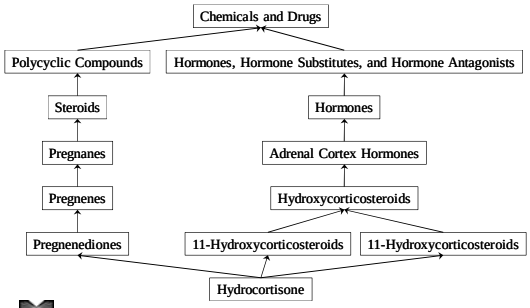
MeSH Top level

1. Anatomy [A]
2. Organisms [B]
3. Diseases [C]
4. Chemicals and Drugs [D]
5. Analytical, Diagnostic and Therapeutic Techniques and Equipment [E]
6. Psychiatry and Psychology [F]
7. Biological Sciences [G]
8. Natural Sciences [H]
9. Anthropology, Education, Sociology and Social Phenomena [I]
10. Technology, Industry, Agriculture [J]
11. Humanities [K]
12. Information Science [L]
13. Named Groups [M]
14. Health Care [N]
15. Publication Characteristics [V]
16. Geographicals [Z]

MeSH Example (terms)

MeSH Heading	Hydrocortisone
Tree Number	D04.808.745.745.654.600
Tree Number	D06.472.040.585.353.476
Tree Number	D06.472.040.585.478.392
Scope Note	The main glucocorticoid secreted by the ADRENAL CORTEX. Its synthetic counterpart is used, either as an injection or topically, in the treatment of inflammation, allergy, collagen diseases, asthma, adrenocortical deficiency, shock, and some neoplastic conditions.
Entry Term	11-Epicortisol
Entry Term	Cortifar
Entry Term	Cortisol
Entry Term	Cortril
Entry Term	Epicortisol
Entry Term	Hydrocortisone, (11 alpha)-Isomer
Entry Term	Hydrocortisone, (9 beta,10 alpha,11 alpha)-Isomer

MeSH Example (hierarchies)



NCI Thesaurus

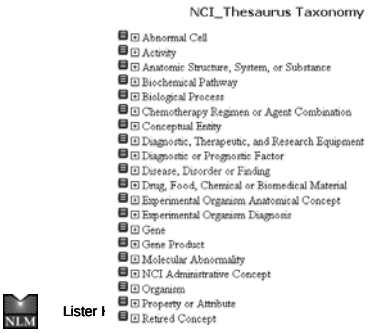
NCI thesaurus Characteristics (1)

- Current version: 10.05d (~monthly releases)
- Type: Controlled terminology / ontology
- Domain: Cancer
- Developer: NCI Center for Bioinformatics
- Funding: NCI
- Availability
  - Publicly available: Yes
  - Repositories: UMLS / OBO / NCBO BioPortal
- URL: http://nciterms.nci.nih.gov/

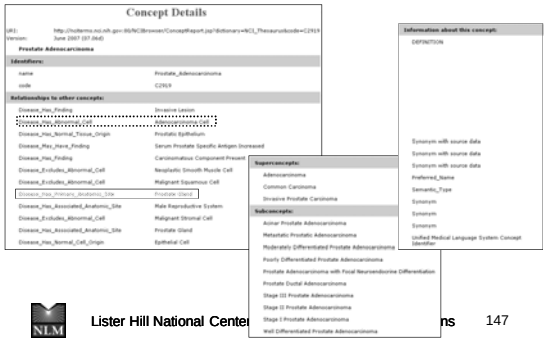
NCI thesaurus Characteristics (2)

- Number of
  - Concepts: ~60,000
  - Terms: 2.68 per concept
- Major organizing principles:
  - Subsumption hierarchy
  - Rich set of associative relationships
  - Small proportion of defined concepts (many primitives)
  - Links to many external resources
- Formalism: OWL Lite

NCI thesaurus Top level



NCI thesaurus Example



Unified Medical Language System (UMLS)

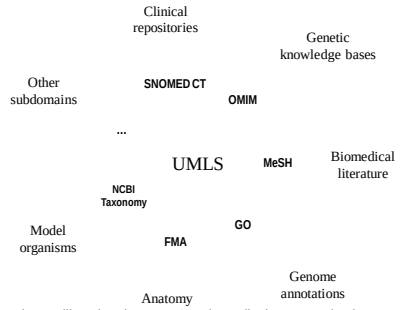
UMLS Characteristics (1)

- Current version: 2010AA (2 annual releases)
- Type: Terminology integration system
- Domain: Biomedicine
- Developer: NLM
- Funding: NLM (intramural)
- Availability
  - Publicly available: Yes* (cost-free license required)
  - Repositories: UMLS
- URL: http://umlsks.nlm.nih.gov/

UMLS Characteristics (2)

- Number of
  - Concepts: 2.2M (2010AA)
  - Terms: ~10M
- Major organizing principles (Metathesaurus):
  - Concept orientation
  - Source transparency
  - Multi-lingual through translation
- Formalism: Proprietary format (RRF)

UMLS Integrating subdomains



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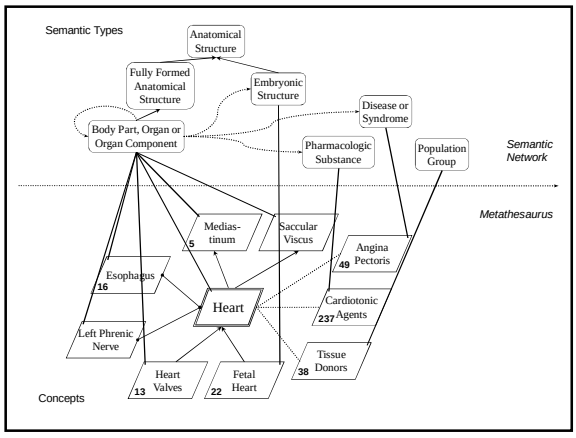
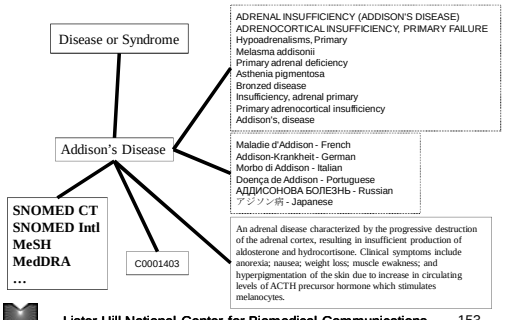


Addison's Disease: Concept



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Metathesaurus Concepts (2010AA)

- Concept (~ 2.2M) CUI
  - Set of synonymous concept names
- Term (~ 7.5M) LUI
  - Set of normalized names
- String (~ 8.2M) SUI
  - Distinct concept name
- Atom (~ 10M) AUI
  - Concept name in a given source

A0066000 Headache (MeSH)
A0065992 Headache (ICD-10)
S0046854

A0066007 Headaches (MedDRA)
A12003304 Headaches (OMIM)
S0046855

L0018681

A0540936 Cephalodynia (MeSH)
S0475647

L0380797

C0018681

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Recap

Name	Scope	# concepts	Median	Subs. Hier	Version
SNOMED CT	Clinical medicine (patient records)	310,314	2	yes	July 31, 2007
LOINC	Clinical observations and laboratory tests	46,406	3	no	Version 2.21 (no "natural language" names)
FMA	Human anatomical structures	~72,000	?	yes	(not yet in the UMLS)
Gene Ontology	Functional annotation of gene products	22,546	1	yes	Jan. 2, 2007
RxNorm	Standard names for prescription drugs	93,426	1	no	Aug. 31, 2007
NCI Thesaurus	Cancer research, clinical care, public information	58,868	2	yes	2007_05E
ICD-10	Diseases and conditions (health statistics)	12,318	1	no	1998 (tabular)
MeSH	Biomedicine (descriptors for indexing the literature)	24,767	5	no	Aug. 27, 2007
UMLS .	Terminology integration in the life sciences	1,4 M	2	n/a	2007AC (English only)

[Bodenreider, YBMI 2008]

Short course – Summer 2010
Clinical Ontology in Practice

June 15, 2010 – Session #4

Biomedical Ontologies in Action

A Functional Perspective on Biomedical Ontologies

Olivier Bodenreider

Lister Hill National Center
for Biomedical Communications
Bethesda, Maryland - USA

Overview

- Functional perspective [Bodenreider, YBMI 2008]
  - What are they for (vs. what are they)?
- "High-impact" biomedical ontologies
- 3 major categories of use
  - Knowledge management (indexing and retrieval of data and information, access to information, mapping among ontologies)
  - Data integration, exchange and semantic interoperability
  - Decision support and reasoning (data selection and aggregation, decision support, natural language processing applications, knowledge discovery).

Knowledge management

Knowledge management

Annotating data and resources

Terminology in ontology

- Ontology as a source of vocabulary
  - List of names for the entities in the ontology (ontology vs. terminology)
- Most ontologies have some sort of terminological component
  - Exceptions: GALEN, LOINC
- Not all surface forms represented
  - Often insufficient for NLP applications
  - Large variation in number of terms per concept across ontologies

Annotating data

- Gene Ontology
  - Functional annotation of gene products in several dozen model organisms

- Various communities use the same controlled vocabularies
- Enabling comparisons across model organisms
- Annotations
  - Assigned manually by curators
  - Inferred automatically (e.g., from sequence similarity)

GO Annotations for Aldh2 (mouse)

GO Annotations in Tabular Form (Text View) (GO Grap

Category	Classification Term	Evidence
Molecular Function	aldehyde dehydrogenase (NAD) activity	IEA
Molecular Function	oxidoreductase activity	IEA
Molecular Function	oxidoreductase activity	IEA
Cellular Component	mitochondrion	IDA
Biological Process	metabolic process	IEA
Biological Process	oxidation reduction	IEA

http:// www.informatics.jax.org/

GO ALD4 in Yeast

GO Annotations — *All **ALD4** GO evidence and references*

*View Computational GO annotations for **ALD4***

Molecular Function

Manually curated
- aldehyde dehydrogenase (NAD) activity (IDA, IMP, ISS)
- aldehyde dehydrogenase [NAD(P)+] activity (IDA)

Biological Process

Manually curated
- ethanol metabolic process (IMP)

Cellular Component

Manually curated
- mitochondrial nucleoid (IDA)
- mitochondrion (IMP, ISS)

High-throughput
- mitochondrion (IDA)

http://db.yeastgenome.org/

GO Annotations for ALDH2 (Human)

Function						
GO:0016491	oxidoreductase activity	interpro	IEA	IPR015590	UniProt	9606
GO:0016491	oxidoreductase activity	interpro	IEA	IPR016160	UniProt	9606
GO:0016491	oxidoreductase activity	interpro	IEA	IPR016162	UniProt	9606
GO:0016491	oxidoreductase activity	interpro	IEA	IPR016161	UniProt	9606
GO:0016491	oxidoreductase activity	sp_kw	IEA	KW-0560	UniProt	9606
GO:0004029	aldehyde dehydrogenase (NAD) activity	1206115	TAS		FINC	9606
GO:0004030	aldehyde dehydrogenase [NAD(P)+] activity	8603321	TAS		FINC	9606
GO:0009055	electron carrier activity	8603321	TAS		UniProt	9606
GO:0004029	aldehyde dehydrogenase (NAD) activity	enzyme	IEA	1.2.1.3	UniProt	9606

http://www.ebi.ac.uk/GOA/

Indexing the biomedical literature

- MeSH
  - Used for indexing and retrieval of the biomedical literature (MEDLINE)
- Indexing
  - Performed manually by human indexers
    - With help of semi-automatic systems (suggestions) e.g., Indexing Initiative at NLM
  - Automatic indexing systems

MeSH MEDLINE indexing

1: Anesth Analg. 2008 Jun;106(6):1813-9.

Related Articles, Links

Full Text Anesth Analg

Free cortisol in sepsis and septic shock.

Bendel S, Karlsson S, Perttilä V, Laisa P, Varpula M, Ruokonen E, Finnsepsis Study Group

Collaborators (26)

Department of Intensive Care, Kuopio University Hospital, PL 16222 Kuopio, Finland. Stepan.Bendel@kuh.fi

BACKGROUND: Severe sepsis activates the hypothalamopituitary axis, increasing cortisol production. In some studies, hydrocortisone substitution based on an adrenocorticotropic hormone-stimulation test or baseline cortisol measurement has improved outcome. Because only the free fraction of cortisol is active, measurement of free cortisol may be more important than total cortisol in critically ill patients. We measured total and free cortisol in patients with severe sepsis and related the concentrations to outcome. METHODS: In a prospective study, severe sepsis was defined according the American College of Chest Physicians/Society of Critical Care Medicine criteria. Blood samples were drawn within 24 h of study entry. Serum cortisol was analyzed by electrochemiluminescence immunoassay. The Coolens method was used for calculating serum free cortisol concentrations. RESULTS: Blood samples were collected from 125 patients, of whom 62 had severe sepsis and 63 septic shock. Hospital mortality was 21%. Calculated free serum cortisol correlated well with serum total cortisol ($r = 0.90$, $P < 0.001$). There was no difference in the total cortisol concentrations in patients with sepsis and septic shock (728 +/- 386 nmol/L vs 793 +/- 439 nmol/L, $P = 0.44$). Nonsurvivors had higher calculated serum free (209 +/- 151 nmol/L) and total (980 +/- 458 nmol/L) cortisol concentrations than survivors (119 +/- 111 nmol/L, $P = 0.002$, and 704 +/- 383 nmol/L, $P = 0.002$). Depending on the definition, the incidence of adrenal insufficiency varied from 8% to 54%. CONCLUSIONS: Clinically, calculation of free cortisol does not provide essential information for identification of patients who would benefit from corticoid treatment in severe sepsis and septic shock.

MeSH MEDLINE indexing

MeSH Terms:
- Adrenal Cortex Function Tests
- Adrenal Insufficiency/blood*
- Adrenal Insufficiency/drug therapy
- Adrenal Insufficiency/mortality
- Adult
- Biological Markers/blood
- Female
- Finland/epidemiology
- Hospital Mortality
- Humans
- Hydrocortisone/blood*
- Hydrocortisone/therapeutic use
- Kaplan-Meier Estimate
- Male
- Predictive Value of Tests
- Prospective Studies
- Sepsis/blood*
- Sepsis/drug therapy
- Sepsis/mortality
- Severity of Illness Index
- Shock, Septic/blood*
- Shock, Septic/drug therapy
- Shock, Septic/mortality
- Treatment Outcome

Substances:
- Biological Markers
- Hydrocortisone

MeSH MEDLINE indexing

1: Expert Opin Investig Drugs. 2008 Apr;17(4):497-509.

Related Articles, Links

Expert Opinion Full text article at www.expertopin.com

Replacement therapy for Addison's disease: recent developments.

Lovås K, Husebye ES

University of Bergen, Institute of Medicine, Section of Endocrinology, 5021 Bergen, Norway. Kristian.lovas@helse-bergen.no

BACKGROUND: The hormone deficiencies in Addison's disease (primary adrenal insufficiency) are conventionally treated with oral glucocorticoid and mineralocorticoid replacement but the available therapies do not restore the physiological hormone levels and biorhythm. Despite such treatment these patients self-report impaired health-related quality of life (HRQoL) and recent research has indicated increased mortality. OBJECTIVE/METHODS: We review the literature and recent developments in replacement therapy. RESULTS/CONCLUSION: Patients with Addison's disease require mineralocorticoid replacement, i.e., fludrocortisone 0.05 - 0.20 mg once daily. Starting doses of glucocorticoids should be 15 - 20 mg for hydrocortisone or 20 - 30 mg for cortisone acetate, divided into two or three doses, and preferentially weight-adjusted. There are indications that the synthetic glucocorticoids have undesirable metabolic long-term effects, which make them less suitable as first-line treatment. Timed-release hydrocortisone tablets and continuous subcutaneous hydrocortisone infusion are promising new treatment modalities. Studies of replacement with the adrenal androgen dehydroepiandrosterone (DHEA) in adrenal failure have shown inconsistent benefit on HRQoL. DHEA, or possibly testosterone replacement is likely to be beneficial for selected groups of patients with Addison's disease but this remains to be shown. We here give our opinion of the best treatment and future direction of research in this area.

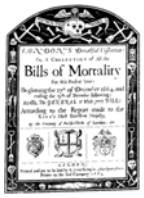
MeSH MEDLINE indexing

MeSH Terms:
- Addison Disease/blood
- Addison Disease/drug therapy*
- Androgens/administration & dosage*
- Androgens/therapeutic use
- Dosage Forms
- Drug Administration Routes
- Drug Administration Schedule
- Glucocorticoids/administration & dosage*
- Glucocorticoids/adverse effects
- Glucocorticoids/blood
- Glucocorticoids/deficiency
- Hormone Replacement Therapy*
- Humans
- Mineralocorticoids/administration & dosage*
- Mineralocorticoids/adverse effects
- Mineralocorticoids/blood
- Mineralocorticoids/deficiency
- Quality of Life
- Treatment Outcome

Substances:
- Androgens
- Dosage Forms
- Glucocorticoids
- Mineralocorticoids

ICD9-CM Coding clinical data

- ICD9-CM
  - Used for coding clinical data e.g., for billing purposes
- Other uses of ICD
  - Morbidity and mortality reporting worldwide



Knowledge management

Accessing biomedical information

Resources for biomedical search engines

- Synonyms
- Hierarchical relations
- High-level categorization
- Co-occurrence information
- Translation

MeSH "synonyms" MEDLINE retrieval

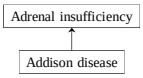
- MeSH entry terms
  - Used as equivalent terms for retrieval purposes
  - Not always synonymous
- Increase recall without hurting precision

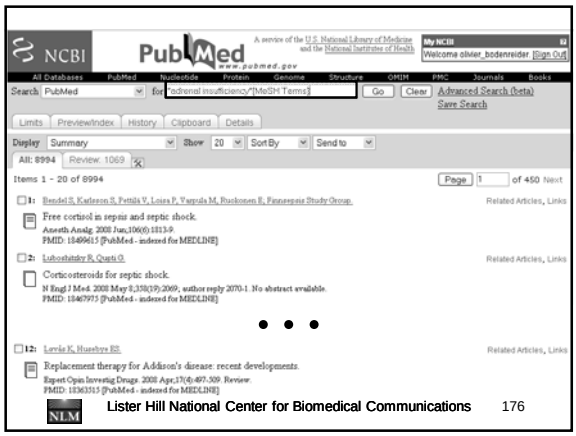
MeSH Heading	Addison Disease
Entry Term	Addison's Disease
Entry Term	Primary Adrenal Insufficiency
Entry Term	Primary Adrenocortical Insufficiency

MeSH "synonyms" MEDLINE retrieval

MeSH hierarchies MEDLINE retrieval

- MeSH "explosion"
  - Search for a given MeSH term and all its descendants
  - A search on Adrenal insufficiency also retrieves articles indexed with Addison disease

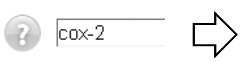


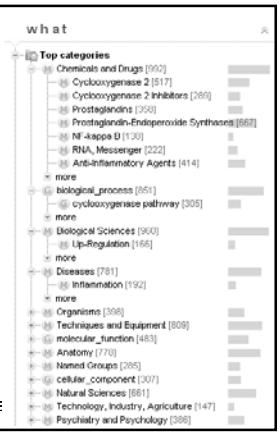


Co-indexing

gopubmed
Searching is now sorted!

http://www.gopubmed.com/





Knowledge management

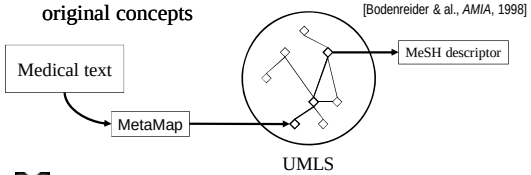
Mapping across biomedical ontologies

Reusing information

- Clinical information coded with SNOMED CT
  - Mapped to ICD9-CM and CPT for billing purposes
  - Mapped to ICD-O for epidemiology purposes
- Existing mapping tables created by terminology developers as an incentive to use SNOMED CT

Reusing tools

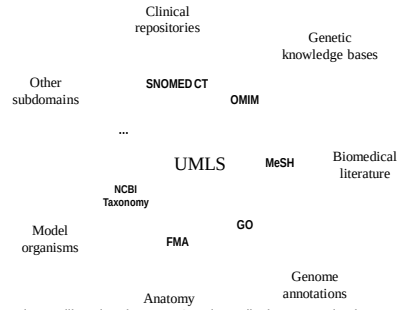
- For noun phrases extracted from medical texts, map to UMLS concepts (MetaMap) [Aronson & al., *JAMIA*, 2010]
- Then, select from the MeSH vocabulary the concepts that are the most closely related to the original concepts [Bodenreider & al., *AMIA*, 1998]



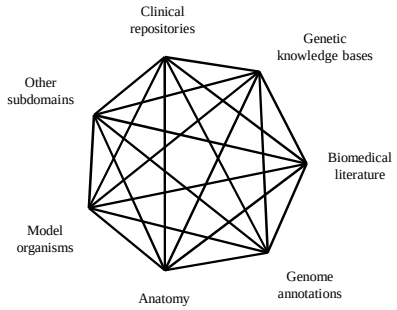
Terminology integration systems

- Terminology integration systems (UMLS, RxNorm) help bridge across vocabularies
- Uses
  - Information integration
  - Ontology alignment
  - Medication reconciliation

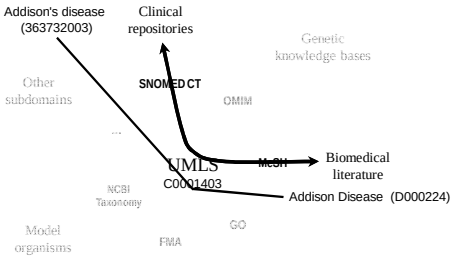
Integrating subdomains



Integrating subdomains



Trans-namespace integration



Data integration, exchange and semantic interoperability

Data integration, exchange and semantic interoperability

Information exchange and semantic operability

"Standards"

- Ontologies help standardize patients data
  - Facilitate the exchange of data across institutions
  - Help connect "islands of data" (silos)
- LOINC
  - Exchange of laboratory data
  - In conjunction with HL7 messaging

Semantic interoperability projects BRIDG

- Biomedical Research Integrated Domain Group
  - Information model for clinical research
  - Interoperability between clinical trials information systems
  - Ontologies provide value sets to the information model

Semantic interoperability projects CDA

- Clinical Document Architecture (CDA R2)
  - Formal representation of clinical statements
    - Clinical observations
    - Medication administration
    - Adverse events
  - Associate an information model (HL7 RIM) with terminologies (LOINC, SNOMED CT, RxNorm)

Semantic interoperability projects caCORE

- Cancer Common Ontologic Representation Environment
  - Infrastructure developed to support an interoperable biomedical information system for cancer research
  - Uses the NCI Thesaurus as a component

Data integration, exchange and semantic interoperability

Information and data integration

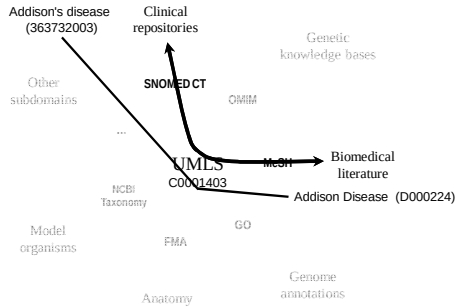
Approaches to data integration

- Warehousing
  - Sources to be integrated are transformed into a common format and converted to a common vocabulary
  - Normalization through ontologies (e.g., GO annotations)
- Mediation
  - Local schema (of the sources)
  - Global schema (in reference to which the queries are made)
  - Ontologies help define the global schema and map between local and global schemas (OntoFusion, ARIANE)

Ontologies and integration

- Terminology integration systems help bridge across terminolgies and the domains they represent
- Mappings across ontologies enable the integration of namespaces in the Semantic Web

Trans-namespace integration



Decision support and reasoning

Data selection

- The structure of biomedical ontologies helps define groups of values from a high-level value
  - Vs. enumerating all possible values
- Useful for data selection in clinical studies
- ICD is used pervasively for this purpose
  - E.g., Study on supraventricular tachycardia (SVT), based on 2 high-level ICD codes
- Similarity with the definition of value sets for use in the information model

Data aggregation

- Ontologies help partition/aggregate data in data analysis
  - Clinical studies: Study a variable in groups of patients corresponding to the top level categories in ICD
  - Biology studies: Functional characterization of gene expression signatures with high-level concepts from the Gene Ontology
    - Recent trend: co-clustering

Decision support

- Clinical decision support
  - Ontologies help normalize the vocabulary and increase the recall of rules
  - Ontologies provide some domain knowledge and make it possible to create high-level rules (e.g., for a class of drugs rather than for each drug in the class)
- Other forms of decision support
  - Based on automatic reasoning services for OWL ontologies (e.g., grading gliomas with NCIt)

Natural language processing applications

- Ontologies provide background domain knowledge for NLP applications
  - Question answering
  - Document summarization
  - Literature-based discovery
- The UMLS is often used, but other specific resources have been developed

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Knowledge discovery

- By standardizing the vocabulary in a given domain, ontologies are enabling resources for knowledge discovery through data mining
- Less frequently, the structure of the ontology is leveraged by data mining algorithms
- Example of available datasets
  - ICD-coded clinical data (in conjunction with non-clinical information, e.g., environmental data)
  - Annotation of gene products to the GO (function prediction)

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Barriers to usability of biomedical ontologies

Availability

- Many ontologies are freely available
- The UMLS is freely available for research purposes
  - Cost-free license required
- Licensing issues can be tricky
  - SNOMED CT is freely available in member countries of the IHTSDO
- Being freely available
  - Is a requirement for the Open Biomedical Ontologies (OBO)
  - Is a de facto prerequisite for Semantic Web applications

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Discoverability

- Ontology repositories
  - UMLS: 156 source vocabularies (biased towards healthcare applications)
  - NCBO BioPortal: ~200 ontologies (biased towards biological applications)
  - Some overlap between the two repositories
- Need for discovery services

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Formalism

- Several major formalism
  - Web Ontology Language (OWL) – NCI Thesaurus
  - OBO format – most OBO ontologies
  - UMLS Rich Release Format (RRF) – UMLS, RxNorm
- Conversion mechanisms
  - OBO to OWL
  - LexGrid (import/export to LexGrid internal format)

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Ontology integration

- *Post hoc* integration, form the bottom up
  - UMLS approach
  - Integrates ontologies "as is", including legacy ontologies
  - Facilitates the integration of the corresponding datasets
  - Current harmonization efforts (e.g., IHTSDO)
- Coordinated development of ontologies
  - OBO Foundry approach
  - Ensures consistency *ab initio*
  - Excludes legacy ontologies

Quality

- Quality assurance in ontologies is still imperfectly defined
  - Difficult to define outside a use case or application
- Several approaches to evaluating quality
  - Collaboratively, by users (Web 2.0 approach)
    - Marginal notes enabled by BioPortal
  - Centrally, by experts
    - OBO Foundry approach
- Important factors besides quality
  - Governance
  - Installed base / Community of practice

Short course – Summer 2010
Clinical Ontology in Practice

June 16, 2010 – "Hands-on" Sessions

Exploring Clinical Ontologies

Olivier Bodenreider

Lister Hill National Center
for Biomedical Communications
Bethesda, Maryland - USA

UMLS UMLSKS

- UMLSKS (Knowledge Source Server)
  http://umlsks.nlm.nih.gov/
- Search by term: appendectomy (C0003611)
  - (default) RRF view (atom-centric)
  - Lexical View (normalized strings / lexical units)
  - Relations
  - Co-occurrence Info
  - Contexts (paths to root)
- Search by code
  - R73.0 (Postprocedural hypoinsulinaemia)

UMLS UMLSKS

- Notes
  - Ambiguity: appendectomy, heart, calcium
  - Several kinds of lexical matches (exact, normalized, approximate)

UMLS Semantic Navigator

- Available under UMLSKS
  (bottom of left-hand side pane)
- Search by term:
  - appendectomy (C0003611)
  - Addison's disease (C0001403)
- Concept-centric vs. atom-centric
- Selection of hierarchical relations (and co-occurrences)
- Transitive reduction on/off

UMLSKS API

- UMLSKS Developer's Guide (http://umlsks.nlm.nih.gov/)
- Authentication vs. UMLSKS services
- SOAP-based (examples and documentation mostly for java, but usable with other environments, e.g., Perl, .NET)

SNOMED CT

- Multiple web-based browsers available
  - U. Sydney browser (specific to SNOMED CT) http://www.it.usyd.edu.au/~hitru/sct/A1.cgi
  - Virginia Tech browser (specific to SNOMED CT) http://terminology.vetmed.vt.edu/SCT/menu.cfm
  - The SNOMED CT Browser © (specific to SNOMED CT) http://www.medicalclassifications.com/SNOMEDbrowser/
  - BioPortal http://www.bioontology.org/BioPortal
  - NCI Term Browser http://nciterms.nci.nih.gov/

SNOMED CT

- Search concepts
  - Appendectomy (80146002)
  - Simvastatin (387584000)
  - Addison's disease (363732003)
- Notes
  - No post-coordination services in standard browsers
  - Some standalone browsers offer additional services (CliniClue, SNOB)
  - Search on Addison's disease in The SNOMED CT Browser © does not return ant results

LOINC

- Multiple web-based browsers available
  - RELMA (specific to LOINC) web version of a standalone application http://loinc.org/relma *NB: Citrix ICA Client required*
  - BioPortal (LOINC 2.26) http://www.bioontology.org/BioPortal
  - NCI Term Browser (LOINC 2.24) http://nciterms.nci.nih.gov/

LOINC BioPortal

- BioPortal
  - Graphical interface
    - Search for Lithium, then navigate down the tree
  - web services http://www.bioontology.org/wiki/index.php/NCBO_REST_services
    - Ontology Id: 1350
    - Get ID for latest version
      - http://rest.bioontology.org/bioportal/virtual/ontology/1350
      - Returns: 40400
    - Get the "first" 50 terms
      - http://rest.bioontology.org/bioportal/concepts/40400/all?pagesize=50&pagenum=1

LOINC NCI Term Browser

- NCI Term Browser
  - Search for Lithium, then navigate through the Relationships tab
  - Search by code
- Search concept
  - Substance concentration of lithium in urine (quantitative)
  - Lithium:Substance Concentration:Point in time:Urine:Quantitative
  - 25463-1

RxNorm RxNav

- RxNav
  http://umlsks.nlm.nih.gov/
  (launch the browser)
- Search by string (default): zyrtec, clopidogrel
  - Restrict the graph to one particular clinical drug: double-click on Cetirizine 10 MG Oral Tablet
  - RxCUI is displayed in the information bar in the bottom when clicking on a drug entity (e.g., RxCUI for Cetirizine 10 MG Oral Tablet = 309130)
  - Right-click on Cetirizine 10 MG Oral Tablet
  - View NDCs to open a window with the list of NDCs for this drug
  - View Drug Label → link out to DailyMed

RxNorm RxNav

- Search by ID (select ID in the drop-down "Search by" menu
  - NDC, with search string 00781168401 (one of the NDC from the list obtained from Cetirizine 10 MG Oral Tablet)
  - SNOMED ID, with search string 1039008
    - Returns: 103|C0000618||6-Mercaptopurine
- Packs: Search for z-pak
  - Packs displayed with double diamonds in the clinical drug / generic pack and branded drug / branded pack boxes

RxNorm SOAP API

- RxNorm SOAP API (demo client)
  http://mor.nlm.nih.gov/perl/rxnav_api_demo.pl
- Functions
  - getRxNormVersion( )
  - getIdTypes()
  - findRxcuiById(00904582941, *309130*) → 309130
  - getAllRelatedInfo(309130)
- Documentation
  http://rxnav.nlm.nih.gov/RxNormAPI.html

RxNorm REST API

- Test resources
  - http://rxnav.nlm.nih.gov/REST/spellingsuggestions?name=sulfametoxasol
  - http://rxnav.nlm.nih.gov/REST/rxcui/10180
  - http://rxnav.nlm.nih.gov/REST/rxcui/309130/properties
  - http://rxnav.nlm.nih.gov/REST/rxcui/309130/ndcs
  - http://rxnav.nlm.nih.gov/REST/rxcui/151399/related?rela=tradename_of
- Documentation
  http://rxnav.nlm.nih.gov/RxNorm_RESTful_UserGuide.pdf

NDF-RT

- RxNav (pilot version integrating NDF-RT)
  http://rxnav.nlm.nih.gov/rxnavdemo.jnlp
- Search for clopidogrel (RxNorm tab)
  other example: cetirizine
  - Double-click on clopidogrel 75 MG Oral Tablet
  - Click on the NDF-RT tab
  - Explore the relations to the different categories of entities (Drug, Disease, Dose form, …)

PARTNERS HEALTHCARE

Short course – Summer 2010
Clinical Ontology in Practice

June 16, 2010 – Discussion Sessions

Issues and Challenges Related to Clinical Ontologies

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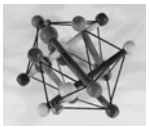
Topics

- NLP / indexing
- PHR / consumer health information
- Decision support (drugs)
- Decision support (other)
- Medication reconciliation
- E-prescribing
- CPOE
- Problem list
- Terminology services
- Value sets
- Terminology management (versioning)
- Mapping / integration
- Meaningful use
- Health information exchange
- Clinical documentation

Questions

- What are some of the issues and challenges related to this topic?
- Do ontologies contribute to the solution? Which ones? Which features?
- Have you learned anything that is applicable towards this issue?



Medical Ontology Research

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