1. Introduction to the Gene Ontology*
2. SNPdb

*Many of the GO slides courtesy of Pascale Gaudet, dictyBase curator, Northwestern University, Chicago, IL
Too Much Published Literature
...to read in order to find out what your gene does....

- **PubMed**: db of over 15 million citations
  - Basic search: rad51 → 3929 articles
  - Organism Limited search: rad51 AND Human (organism) → 2488
  - Disease Limited search: rad51 AND cancer → 1909

Why a gene ontology
Ontology

• Ontologies relate **facts** to **knowledge**

  • **facts**
    – may be known/unknown/little known
    – not attached to knowers
    – unchanging

  • **knowledge**
    – attached to knower
    – may disappear
Gene Ontology

- Gene *annotation* system
- Controlled *vocabulary* that can be applied to all organisms
- Used to describe *gene products*
How do you answer: What is it?

Example:

What is a cell?
Cell
Cell
Cell
Cell
Cell

Image from http://microscopy.fsu.edu
The same name can be used to describe different concepts
What is this?

- Glucose synthesis
- Glucose biosynthesis
- Glucose formation
- Glucose anabolism
- Gluconeogenesis

All refer to the process of making glucose from simpler components.
The same concept can be described with different names.
How do we solve this?

• The same name can be used to describe different concepts

• The same concept can be described using different names

→ Comparison is difficult – in particular across species or across databases

→ Solving this problem will enable natural language processing (and more)
What is the Gene Ontology?

A part of the solution!

- A controlled vocabulary that can be applied to all organisms

- Used to describe gene products - proteins and RNA - in any organism

• An **ontology** provides structure to concepts.
Ontology

• In philosophy, the most fundamental branch of metaphysics. It studies being or existence as well as the basic categories thereof—trying to find out what entities and what types of entities exist.
  – Wikipedia

• Ontologies provide controlled, consistent vocabularies to describe concepts and relationships, thereby enabling knowledge sharing
  – Gruber 1993
Ontology

Includes:
1. Terms
2. Definitions (spectrum of explicitness)
3. Logical relationships

"Definition" spectrum

Vague

Explicit
Ontology graph structure

- Nodes = **concepts** in the ontology
- Edges = **relationships** between the concepts
Ontology edges

- Terms are linked by two relationships
  - is-a
  - part-of
The value of any kind of data is greatly enhanced when it exists in a form that allows it to be integrated with other data. One approach to integration is through the annotation of multiple bodies of data using common controlled vocabularies or 'ontologies'. Unfortunately, the very success of this approach has led to a proliferation of ontologies, which itself creates obstacles to integration. The Open Biomedical Ontologies (OBO) consortium is pursuing a strategy to overcome this problem. Existing OBO ontologies, including the Gene Ontology, are undergoing coordinated reform, and new ontologies are being created on the basis of an evolving set of shared principles governing ontology development. The result is an expanding family of ontologies designed to be interoperable and logically well formed and to incorporate accurate representations of biological reality. We describe this OBO Foundry initiative and provide guidelines for those who might wish to become involved.
## core relationships

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Name</th>
<th>Relation properties</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBO_REL:is_a</td>
<td>is_a</td>
<td>[transitive] [reflexive] [anti-symmetric]</td>
<td>For continuants: C is_a C' if and only if: given any c that instantiates C at a time t, c instantiates C' at t. For processes: P is_a P' if and only if: that given any p that instantiates P, then p instantiates P'.</td>
</tr>
<tr>
<td>OBO_REL:part_of</td>
<td>part_of</td>
<td>[transitive] [reflexive] [anti-symmetric]</td>
<td>For continuants: C part_of C' if and only if: given any c that instantiates C at a time t, there is some c' such that c' instantiates C' at time t, and c <em>part_of</em> c' at t. For processes: P part_of P' if and only if: given any p that instantiates P at a time t, there is some p' such that p' instantiates P' at time t, and p <em>part_of</em> p' at t. (Here <em>part_of</em> is the instance-level part-relation.)</td>
</tr>
</tbody>
</table>
Simple hierarchies (Trees)

Single parent

Directed Acyclic Graphs

One or more parents

Relationships in OBO are directional. Cycles are not allowed.
An ontology is a Directed Acyclic Graph (DAG).

- protein complex
- organelle
- mitochondrion
- fatty acid beta-oxidation multienzyme complex

Relations:
- protein complex is-a part-of other protein complexes
- organelle is-a part-of other organelles
- mitochondrion is-a part-of fatty acid beta-oxidation multienzyme complex
True Path Rule

• The path from a child term all the way up to its top-level parent(s) must always be true

cell

® cytoplasm

® chromosome

® nuclear chromosome

® nucleus

® nuclear chromosome
GO: the Gene Ontology

Composed of Three sub-ontologies

What does it do?
Molecular Function

What processes is it involved in?
Biological Process

Where does it act?
Cellular Component

gene product
GO: Cellular Component

- where a gene product acts
Mitochondrial membrane paths
GO: Biological Process

![Diagram of metabolic pathways involving glucose, pyruvate, lactate, and amino acid intermediates.](Image)
GO: Molecular Function

- A single reaction or activity, not a gene product
- A gene product may have several functions
- Sets of functions make up a biological process
Molecular Function

Diagram showing the metabolic pathways related to glucose metabolism, including the Krebs cycle and the conversion of glucose to glyceral and into fatty acid metabolism.
Carbonate dehydratase activity
Anatomy of a GO term

term: gluconeogenesis

identifier: GO:0006094

definition: The formation of glucose from noncarbohydrate precursors, such as pyruvate, amino acids and glycerol.
No GO Areas

• GO covers ‘normal’ functions and processes
  – No pathological processes
  – No experimental conditions

• NO evolutionary relationships

• NO gene products

• NOT a system of nomenclature
GO is a tree.
Annotation of gene products with GO terms

Mitochondrial P450
Cellular component: mitochondrial inner membrane
GO:0005743

Biological process: Electron transport
GO:0006118

Molecular function: monooxygenase activity
GO:0004497

substrate + O_2 = CO_2 + H_2O product
Two types of GO Annotations:

- Electronic Annotation
- Manual Annotation

All annotations **must**:

- be attributed to a source
- indicate what evidence was found to support the GO term-gene/protein association
Manual Annotations

• High–quality, specific gene/gene product associations made, using:
  
  • Peer-reviewed papers
  
  • Evidence codes to grade evidence

**BUT** – is very time consuming and requires trained biologists
Electronic Annotations

• Provides large-coverage

• High-quality

**BUT** – annotations tend to use high-level GO terms and provide little detail.
Electronic Annotations: Methods

1. Database entries
   - Manual mapping of GO terms to concepts external to GO (‘translation tables’)
   - Proteins then electronically annotated with the relevant GO term(s)

2. Automatic sequence similarity analyses to transfer annotations between highly similar gene products
Manual Annotations: Methods

1. Extract information from published literature

2. Curators performs manual sequence similarity analyses to transfer annotations between highly similar gene products (BLAST, protein domain analysis)
In this study, we report the isolation and molecular characterization of the *B. napus* PERK1 cDNA, that is predicted to encode a novel receptor-like kinase. We have shown that like other plant RLKs, the kinase domain of PERK1 has serine/threonine kinase activity. In addition, the location of a PERK1-GFP fusion protein to the plasma membrane supports the prediction that PERK1 is an integral membrane protein…these kinases have been implicated in early stages of wound response…

PubMed ID: 12374299

Function: protein serine/threonine kinase activity GO:0004674

Component: integral to plasma membrane GO:0005887

Process: response to wounding GO:0009611

Thought: Can we do this by natural language processing?
Annotate to finest granularity

Annotating to GO:0030047 automatically annotates to all of its parents; thus a product is annotated to both protein modification AND cytoskeleton organization.
Unknown vs. Unannotated

• “Unknown” is used when the curator has determined that there is no existing literature to support an annotation.
  – Biological process unknown GO:0000004
  – Molecular function unknown GO:0005554
  – Cellular component unknown GO:0008372

• Annotation “unknown” is NOT the same as having no annotation.
  – No annotation means that no one has looked yet. Unknown means they looked and did not find.
# GO Evidence Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IEA</td>
<td>Inferred from <strong>Electronic Annotation</strong></td>
</tr>
<tr>
<td>NAS</td>
<td><strong>Non-traceable Author Statement</strong></td>
</tr>
<tr>
<td>TAS</td>
<td><strong>Traceable Author Statement</strong></td>
</tr>
<tr>
<td>ND</td>
<td><strong>No Data</strong></td>
</tr>
<tr>
<td>IDA</td>
<td>Inferred from <strong>Direct Assay</strong></td>
</tr>
<tr>
<td>*IPI</td>
<td>Inferred from <strong>Physical Interaction</strong></td>
</tr>
<tr>
<td>*IGI</td>
<td>Inferred from <strong>Genetic Interaction</strong></td>
</tr>
<tr>
<td>IMP</td>
<td>Inferred from <strong>Mutant Phenotype</strong></td>
</tr>
<tr>
<td>IEP</td>
<td>Inferred from <strong>Expression Pattern</strong></td>
</tr>
<tr>
<td>*IC</td>
<td>Inferred from <strong>Curator</strong></td>
</tr>
<tr>
<td>*ISS</td>
<td>Inferred from <strong>Sequence Similarity</strong></td>
</tr>
</tbody>
</table>

- *Manually annotated*  
- Use with annotation to unknown
## GO Evidence Codes

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<tr>
<td>*IC</td>
<td>Inferred from Curator</td>
</tr>
<tr>
<td>RCA</td>
<td>Inferred from Reviewed Computational Analysis</td>
</tr>
<tr>
<td>ND</td>
<td>No Data</td>
</tr>
</tbody>
</table>

**IDA:**
- Enzyme assays
- *In vitro* reconstitution (transcription)
- Immunofluorescence
- Cell fractionation

**TAS:**
- In the literature source the original experiments referred to are traceable (referenced).
## GO Evidence Codes: with/from

Additional information required for certain evidence codes

<table>
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</tr>
<tr>
<td>ND</td>
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</tr>
</tbody>
</table>

**IGI:**
- a gene identifier for the "other" gene involved in the interaction

**IPI:**
- a gene or protein identifier for the "other" protein involved in the interaction

**IC:**
- GO term from another annotation used as the basis of a curator inference
Evidence code, confidence

TAS/IDA
IMP/IGI/IPI
ISS/IEP
NAS
IEA

believe it
question it
Modifying the interpretation of an annotation: the Qualifier column

1. **NOT**
   - a gene product is NOT associated with the GO term
   - to document conflicting claims in the literature.

2. **Contributes to**
   - distinguishes between individual subunit functions and whole complex functions
   - used with GO Function Ontology

3. **Colocalizes with**
   - transiently or peripherally associated with an organelle or complex
   - used with GO Component Ontology
How to access the Gene ontology and its annotations

1. Downloads
   - Ontologies
   - Annotations: Gene association files
   - Ontologies and Annotations

2. Web-based access
   - AmiGO (http://www.godatabase.org)
   - QuickGO (http://www.ebi.ac.uk/ego)
   - GOrilla (http://cbl-gorilla.cs.technion.ac.il/)
   - Blast2GO (www.blast2go.com)
   - among others…
Proteomic Enrichment

Two sets of Genes

GO_RILLA

Enriched GO Terms Describing Function, Component, or Process

Gene Ontology enrichment analysis and visualization tool
• **Proteome** -- the protein content of the cell. Depends on species, cell type, conditions.

• **Transcriptome** -- the mRNA content of the cell. Depends on species, cell type, conditions.
RESEARCH ARTICLE

A novel hypothesis-unbiased method for Gene Ontology enrichment based on transcriptome data

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* mario.fruzangohar@adelaide.edu.au (MF); david.adelson@adelaide.edu.au (DLA)

Abstract

Gene Ontology (GO) classification of statistically significantly differentially expressed genes is commonly used to interpret transcriptomics data as a part of functional genomic analysis. In this approach, all significantly expressed genes contribute equally to the final GO classification. The method presented here introduces an alternative approach to GO enrichment analysis, which is designed to account for the contribution of each individual gene. By weighting each gene with a value that reflects its statistical significance, the method aims to provide a more accurate representation of the biological processes and molecular functions that are significantly enriched in the data.

Check for updates

OPEN ACCESS

Materials and methods

Incorporation of mRNA expression levels into GO enrichment

Given \( N \) genes \((g_1, \ldots, g_N)\) in \( K \) samples, we estimate the enrichment score (ES) of a GO term \( t \) in sample \( s \) \( ES_{t,s} \), when expression levels are given as RPKM (Reads per Kilo base per Million Reads)/FPKM (Fragments per Kilo base per Million Reads):

\[
ES_{t,s} = \sum_{i=1}^{n} \log_2 [e(i, s) + 1] \times I(i, t) \tag{1.1}
\]

or as microarray log fold change:

\[
ES_{t,s} = \sum_{i=1}^{n} \log_2 (2^{e(i,s)} + 1) \tag{1.2}
\]

Where \( e(i,s) \) is the expression level of gene \( g_i \) in sample \( s \) and \( I(i,t) \) is:

\[
I(i, t) = \begin{cases} 
1, & \text{if } g_i \text{ annotated by GO term } (t) \\
0, & \text{otherwise}
\end{cases}
\]

We then define an intermediate value for fold change \( (F) \) of GO term \( t \) from sample \( s \) to sample \( s+1 \) \( (F_{t,s}) \):

\[
ES_{t,s+1} / ES_{t,s} \tag{2}
\]

Finally, the average fold change of GO term \( t \) across all samples is defined as:

\[
F_t = \sqrt[k-1]{\prod_{s=1}^{k-1} F_{t,s}} \tag{3.1}
\]

or log transformed as:

\[
F_t = \frac{1}{k-1} \sum_{s=1}^{k-1} \log_2 F_{t,s} \tag{3.2}
\]
Case studies

Case study 1: Comparison of whole transcriptome based GO enrichment between minimally and highly pathogenic *Salmonella enteritidis*. We used RNA-Seq data for six *Salmonella enteritidis* [12] strains. For each gene in both groups of strains the RPKM counts were averaged.

Case study 2: Comparison of whole transcriptome based GO enrichment between AD and normal human brain. The results of whole transcriptome GO classification followed by outlier testing in AD and normal brains in Biological Process, Molecular Function and Cellular Component are presented in Fig 2. The most significant functions in AD were inflammation and fatty acid related functions including granulocyte colony-stimulating factor receptor binding, interleukin-1, alcohol dehydrogenase, neuromedin U receptor activity, and norepinephrine transmembrane transporter activity.
Research report

Brief isoflurane anaesthesia affects differential gene expression, gene ontology and gene networks in rat brain

Damon A. Lowes a, Helen F. Galley a✉, Alessandro P.S. Moura b, Nigel R. Webster a

Show more

https://doi.org/10.1016/j.bbr.2016.09.045

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Abstract

Much is still unknown about the mechanisms of effects of even brief anaesthesia on the brain and previous studies have simply compared differential expression profiles with and without anaesthesia. We hypothesised that network analysis, in addition to the traditional differential gene expression and ontology analysis, would enable identification of the effects of anaesthesia on interactions between genes. Rats (n = 10 per group) were randomised to anaesthesia with isoflurane in oxygen or oxygen only for 15 min, and 6 h later brains were removed. Differential gene expression and gene ontology analysis of microarray data was performed. Standard clustering techniques and principal component analysis with Bayesian rules were used along with social network analysis methods, to quantitatively model and describe the gene networks. Anaesthesia had marked effects on genes in the brain
GO analysis of transcriptomics of human cells treated with natural product

Figure modified from http://en.wikipedia.org/wiki/Image:Microarray-schema.jpg
courtesy of Shabana Shabeer, Albert Einstein School of Medicine
1. What is an ontology?
2. Why do we need ontologies?
3. What are the three gene ontologies?
4. Give an example of a is-a relationship in the Cellular Component ontology
5. Give an example of the part-of relationship in the Cellular Component ontology.
6. ...in the Molecular Function ontology.
7. ...in the Biological process ontology
8. What two things must every annotation have?
9. What are evidence codes?
10. What is the least confident evidence code?
SNPs
What are polymorphisms?

- Genetic differences between individuals in a population.
- Changes related to alleles
  - **Single nucleotide polymorphisms** (one base substitution)
    - Noncoding
    - Coding
      - synonymous -- same amino acid, different codon
      - non-synonymous
        - missense -- change in amino acid
        - nonsense -- stop codon
  - Frame-shifts
    - One or more base Insertion/deletion
How To View all SNPs associated with a gene
Starting with...

**a gene name**

1. Search the Gene database with the gene name. If you know the gene symbol and species, enter them as follows: tpo[gene] AND human[orgn]
2. Click on the Gene ID of the desired gene.
3. In the list of Links on the right, click "SNP:GeneView". If the link is not present, no SNPs are currently linked to this gene.

**a nucleotide or protein accession number** (e.g. NM_001126)

1. Search the Nucleotide or Protein database with the accession number.
2. In the Links menu in the upper right, click on "GeneView in dbSNP". If the link is not present, click on the "Gene" link in the same menu and continue at step 3 above under "a gene name".

**a nucleotide sequence**

1. Go to the BLAST home page and click "nucleotide blast" (blastn) under Basic BLAST.
2. Paste the sequence in the query box.
3. Enter the name of the organism of interest in the "Organism" box. Click the BLAST button.
4. Click on the desired sequence from the results.
5. Continue at step 2 under "a nucleotide or protein accession number" above.

**a protein sequence**

1. Go to the BLAST home page and click "protein blast" (blastp) under Basic BLAST.
2. Paste the sequence in the query box.
3. Enter the name of the organism of interest in the "Organism" box. Click the BLAST button.
4. Click on the desired sequence from the results.
5. Continue at step 2 under "a nucleotide or protein accession number" above.
### Search Gene database

#### Search results

**Items:** 2  
 Showing Current items.

<table>
<thead>
<tr>
<th>Gene ID</th>
<th>Name/Gene ID</th>
<th>Description</th>
<th>Location</th>
<th>Aliases</th>
<th>MIM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TPO</strong></td>
<td>Thyroid peroxidase [Homo sapiens (human)]</td>
<td>Chromosome 2, NC_000002.12 (1413461...1542727)</td>
<td>MSA, TDH2A, TPX</td>
<td>606765</td>
<td></td>
</tr>
<tr>
<td>THPO</td>
<td>Thrombopoietin [Homo sapiens (human)]</td>
<td>Chromosome 3, NC_000003.12 (184371935..184379688, complement)</td>
<td>MGDF, MKCSF, ML, MPLLG, THCYT1, TPO</td>
<td>600044</td>
<td></td>
</tr>
</tbody>
</table>

**Gene ID**

Contains basic description, gene location in chromosome coordinates.
Genomic regions, transcript, exons, and sequences are displayed in a gene viewer tool. The tool provides options such as:

- **Range ToolTip**
  - Range: 1492355 .. 1498015
  - Zoom On Range
  - Zoom To Sequence
  - Modify Range
  - Set New Marker For Selection
  - BLAST Search (Selection)
  - Primer BLAST (Selection)
  - Download FASTA (Selection)

Genomic Sequence: NC_000002.12: 1.4M..1.6M

The viewer supports actions like clicking on Genes, NCBI Homo sapiens, and other identifiers.
SNPs

gain, swipe and zoom...

gain...
This one is “missense” Asp → Glu mutation.
<table>
<thead>
<tr>
<th>ID</th>
<th>rsID</th>
<th>Gene</th>
<th>chr</th>
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<th>Minor</th>
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Go back to GenBank entry. On the right, find GeneView in the menu.
## Same SNP, in GeneView

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**Back to SNP summary page**

**Back to the chromosome browser**
Population descriptors: YRI: Yoruba in Ibadan, Nigeria, JPT: Japanese in Tokyo, Japan, CHB: Han Chinese in Beijing, China, CEU: CEPH (Utah residents with ancestry from northern and western Europe)
Linkage Disequilibrium

Triangle plot shows LD values using $r^2$ or D'/LOD scores in one or more HapMap populations.

Phased haplotype track shows all 120 chromosomes with alleles colored yellow and blue.
Tagging SNPs, tSNPs

• SNPs that are highly correlated are redundant information

• tSNPs are selected as the minimal non-redundant set of SNPs in a population, such that the genotypes can be reconstructed from the tSNPs.

• tSNPs allow genotyping with fewer steps
  – PCR amplification experiments determine which base is present.

• Block based tagging

Block based tagging requires that haplotype "blocks" first be inferred. In the majority of cases when you are investigating association within a candidate gene you are likely to start off with a large number of potential SNPs to choose from, and using various measures of linkage disequilibrium and inferred haplotypes it is possible to define 'haplotype blocks' of markers that are in strong LD with each other, but not with those in other blocks. The exact definition of a haplotype block is open to interpretation, and there are a number of different methods for choosing your haplotype blocks (Gabriel et al 2002, )
tSNPs (tag SNPs, Tagging SNPs) are SNPs that correlate strongly with other SNP, therefore they give information on the haplotype without having to sequence the whole genome.

Highly correlated SNP have high LD. SVD finds repeating, nearly identical rows in the haplotype matrix.
Uses of SNPs

• Personalized medicine
  – SNP-associated Sensitivity to
    – diseases
    – drugs
    – chemicals
    – pathogens
    – vaccines

• Livestock breeding
• Human migrations
Human migration out of Africa

Each individual has a set of SNPs and a family history, marking geographic location. Tree is built ignoring the geographic location, to model migration paths.

Two Uniparental lineages

mtDNA: mitochondrial DNA
NRY: nonrecombining region of the Y chromosome