Data Modeling with the Sequence Ontology

Chris Mungall

Berkeley Drosophila Genome Project

SO Instances

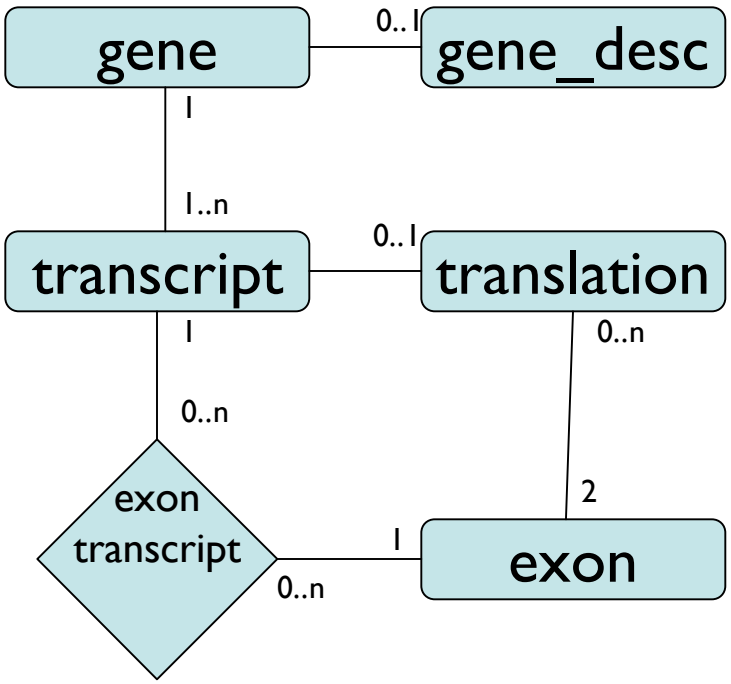
- What would an instance of a SO term look like?
- Minimum info:
  - ID, SO type, names/synonyms/labels
- Very useful info:
  - sequence location, relationships to other instances
- Optional info
  - relationships to other OBO terms, relationships to other values (eg heterozygosity for seq_variants)
- We need a *formalism* to represent SO instances

What do we mean by data model?

- A data model is a framework for capturing knowledge in a way that is computable
  - We need a data model for recording SO instances
- Data model formalisms
  - Relational (eg SQL Databases)
  - Hierarchical (eg XML; NCBI ASN.1)
  - Object Oriented (OO DBs; OO languages; UML)
  - Ontology formalisms (obo; protégé; DLs)
  - Ad hoc flat file formats (tab delimited; custom)
- Multiple formalisms are suitable for modeling SO instances

Relational model

- solid theoretical basis
- excellent for data management and querying
  - robust DBMSs
  - SQL standard
- BUT: no type system!
  - rigid models
- degenerate variations:
  - tab delimited files
    - eg GFF



ensembl relational schema

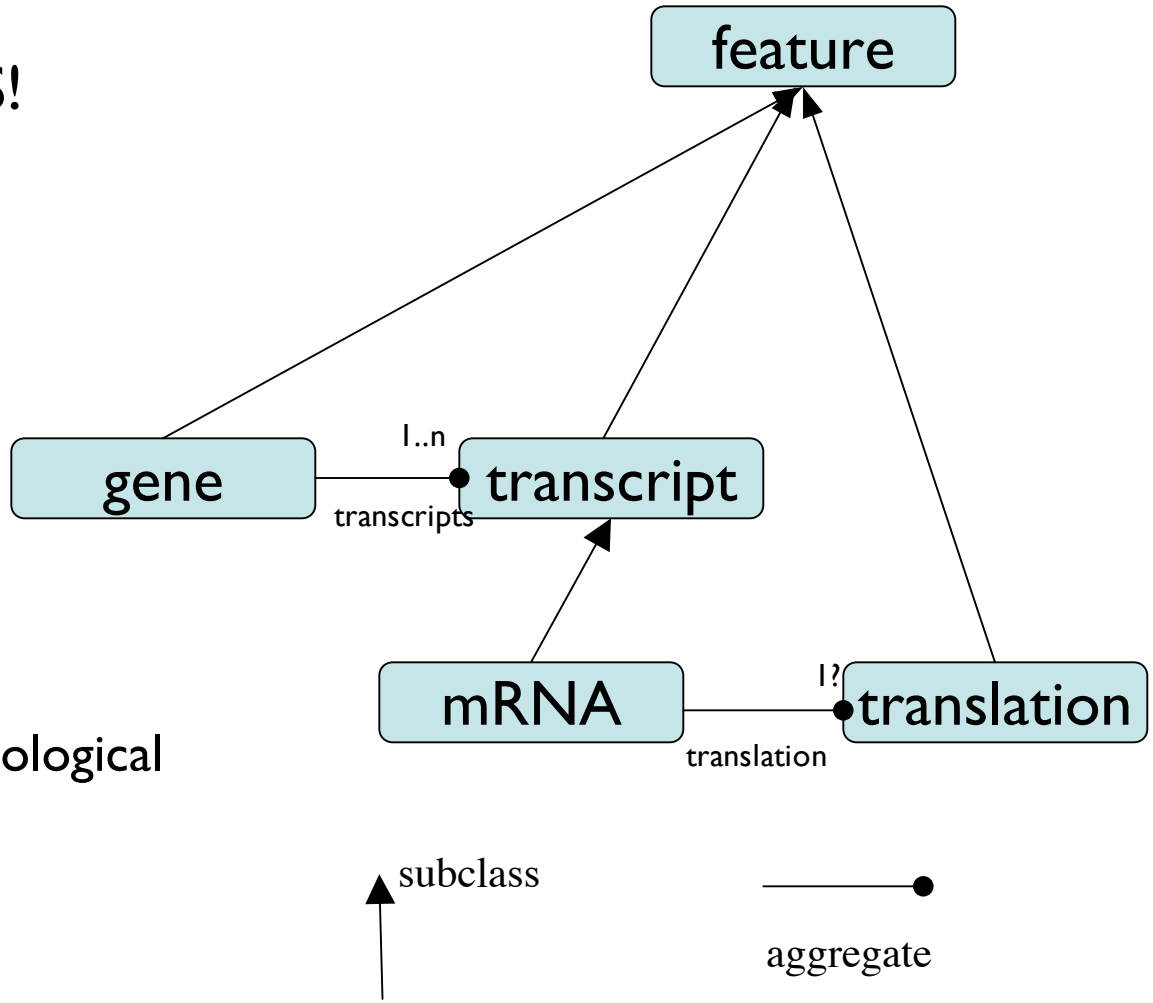
Hierarchical formalisms

- real data is often nested
- good for data exchange
- maps (reasonably) well to relational
- no proper type system!
  - types and properties as elements

```
<gene id="CG1234">
  <name>foo</name>
  <transcript id="CG1234-A">
    <name>foo-A</name>
    <seq>GCCA…</seq>
    <translation id="CG1234-P1">
       <name>foo-protein-1</name>
       <seq>MKVV….</seq>
       <pos start=132 end=561>
    </translation>
    <exon>
       <pos start=200 end=300>
    </exon>
    <exon>
       <pos start=500 end=800>
    </exon>
  </transcript>
</gene>
```

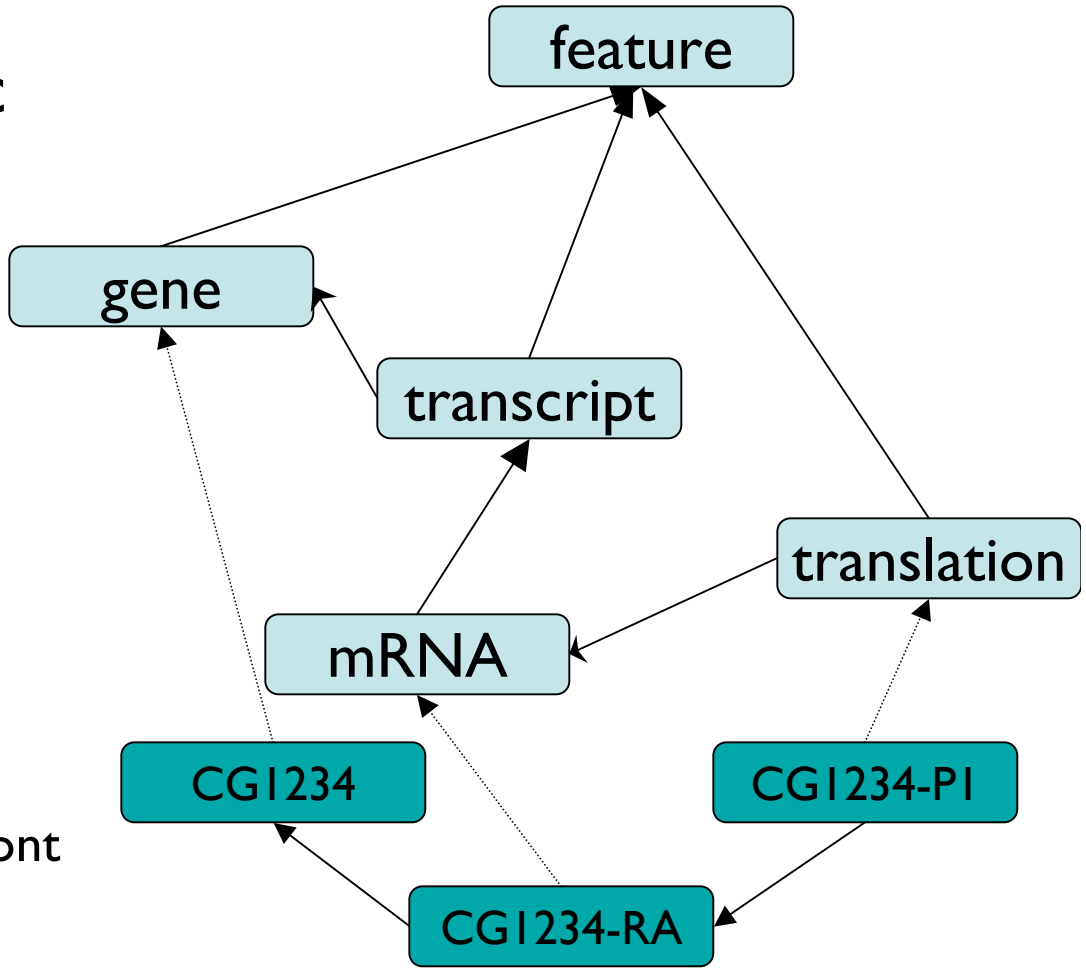
Object Oriented

- type system? YES!
- lacks theoretical foundations
- standards? tools?
  - OQL?
  - UML?
  - Perl/Java code?
- religious belief:
  - OO is bad for biological modeling



Ontology formalisms

- Type system centric
- Variations
  - obo
  - frame-based
    - similar to OO
  - logic-based
- Tools less mature
  - hybrid models are most pragmatic
    - relational or xml + ont

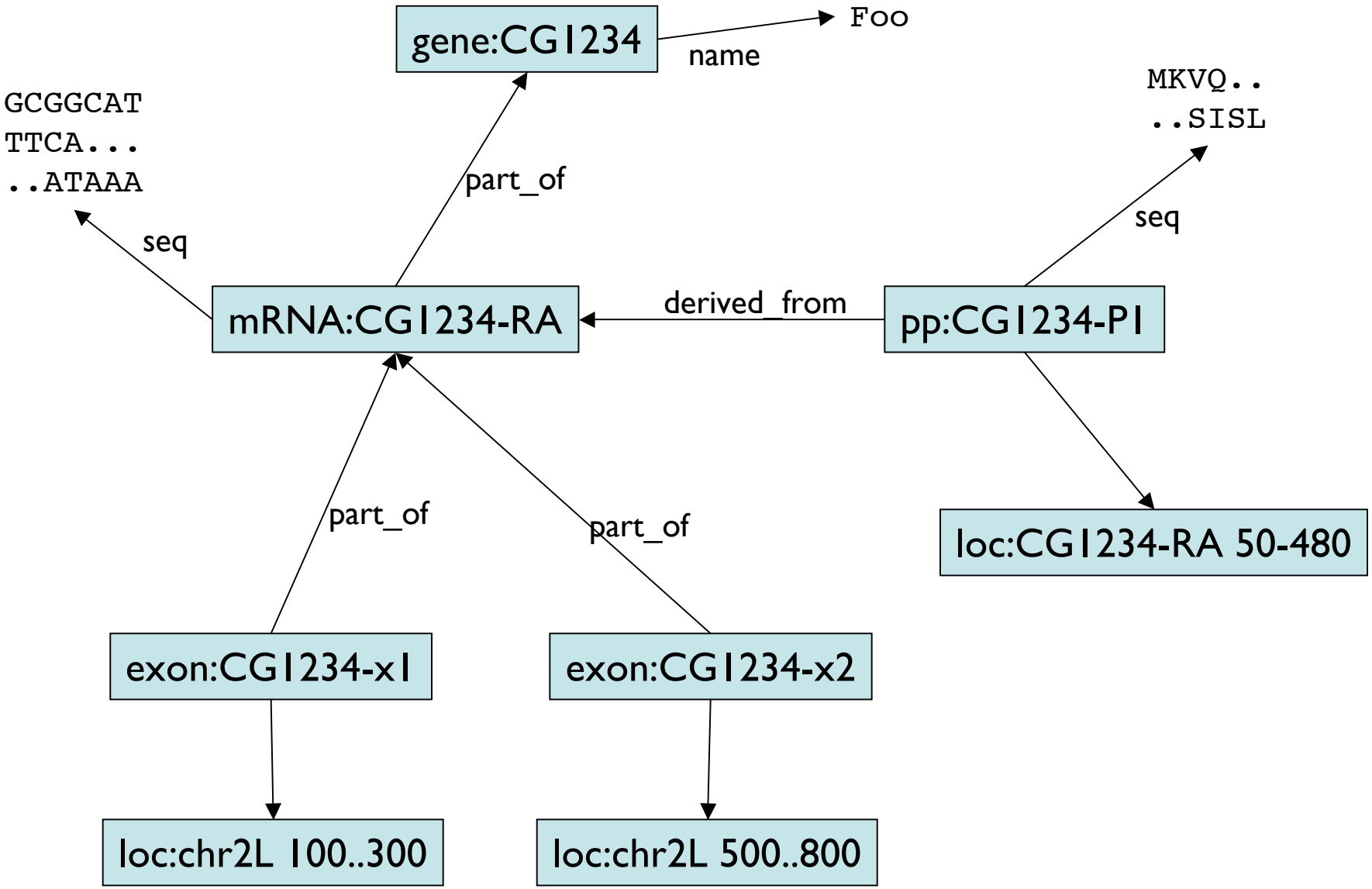


Hybrid Formalisms

- To represent SO instances we must choose a formalism
- Bio-Ontologies are not just for attaching metadata to existing data
- Ontologies can be used to enhance or replace traditional data modeling (relational, xml, object)
  - software and database flexibility and interoperability
- SO can be used for strongly-typing a weakly typed traditional datamodel

SO-based datamodels

- Datamodel has minimal typing
- Classes (SO terms) in ontology
  - C = gene, exon, regulatory_region, ..
- Instances
- Sequence locations
- Relationship and property types
- Relationships and property assignments
  - binary (typed) relationships between instances
    - **CG1234-RA** *part_of* **CG1234**
  - property assignment: between an instance and a datatype value
    - **SNP000000123** *heterozygosity* 0.45


gene:CG1234
Foo
name
GCGGCAT
TTCA...
..ATAAA
part_of
MKVQ..
..SISL
seq
seq
mRNA:CG1234-RA
derived_from
pp:CG1234-P1
part_of
part_of
loc:CG1234-RA 50-480
exon:CG1234-x1
exon:CG1234-x2
loc:chr2L 100..300
loc:chr2L 500..800

loc:seq		type	loc:start	loc:end	loc:str		relationships
2L		gene	1	800	+		ID=CG1234; Name=Foo
2L		mRNA	1	800	+		ID=CG1234-RA; Parent=CG1234; seq=GCGG..
2L		CDS	151	300	+		ID=CG1234-P1; Parent=CG1234-RA; aa=MVKQ…
2L		CDS	501	780	+		ID=CG1234-P1; Parent=CG1234-RA; aa=MVKQ..
2L		exon	101	300	+		ID=CG1234-x1; Parent=CG1234-RA
2L		exon	501	800	+		ID=CG1234-x2; Parent=CG1234-RA

Advantages of SO-based datamodels

- Flexibility
  - unlimited configurations for instances and datatype values in a graph
  - dicistronic genes; trans splicing; RNA editing
- Robustness
  - all types belong to SO
  - relationships restricted by SO
- Practicality
  - can be combined with a simple relational/xml/object model

Existing SO datamodels

- GFF3 - tab delimited text
- Chado - relational
  - XML mappings:
    - ChadoXML
    - ChaosXML
  - Object mappings:
    - CGL (perl)
- BioPerl?? (only containment hierarchies)
- RDF/OWL?
- Any datamodel can be *enhanced* by SO

  the above datamodels are *reliant* on SO for typing

Tools: go-dev

- java: DAG-Edit
- go-perl
  - event based parsers
  - objects for manipulating ontologies as graphs

Tools: BioPerl

- Parsers and writers for GFF3
- Writers for ChadoXML and ChaosXML
- Bio::SeqFeature::Tools::TypeMapper
  - maps feature types to SO
  - infers relationship type between features
- Bio::SeqFeature::Tools::Unflattener

  generates SO feature graph from genbank records

Tools: Chado & Chaos

- http://www.gmod.org
- Chado schema
  - cvs: schema/chado/
- ChaosXML tools
  - cvs: schema/chado/chaos-xml/

Chado SO layer

- Chado uses a generic relational model with weak typing
  - feature, featureloc, featureprop, feature_relationship, cvterm
- The Chado-SO layer creates virtual tables for all SO types and relationships

```
SELECT avg(seqlen) FROM exon;
SELECT count(distinct intron_id)/
       count(distinct gene_id)
FROM gene2intron
```

Current shortcomings of SO based datamodels

- Relationship types not yet fully specified in SO
  - domains, ranges
  - datatype properties
  - cardinality [eg dicistronic transcripts have >= 2 pp]
- Lack of easy to use validation tools
- Too flexibible???
- Underspecification: many ways of saying the same thing

New obo / DAG Edit extensions: cardinality

```
[Typedef]
name: derives_from
inverse_of: derives

[Term]
id: SO:xxxxx
name: dicistronic_mRNA
*is_a: SO:mRNA
*relationship: derives SO:polypeptide
                {card=2}
```

```
[Term]
id: SO:xxxxx
name: polycistronic_mRNA
*is_a: SO:mRNA
*relationship: derives SO:polypeptide
                {mincard=2}
```

* indicates completeness (necessary and sufficient conditions)

Relationships

[Typedef]
name: makes_aminoacid
domain: tRNA
range: CO:aminoacid

[Property]
name: encodes_anticodon
domain: tRNA
range: datatype:string

[Term]
id: SO:xxxxx
name: alanyl_tRNA
relationship: makes_aminoacid CO:alanine
relationship: encodes_anticodon one_of(**GCA GCC GCG GUA**)

Feature Graph Equivalencies

- There are different ways to represent the same data using different feature graphs
- SO does not proscribe or prescribe
- GFF3 and chado/chaos docs suggest (different) specific variations
  - chado: gene, transcript, exon
- GFF3 can "hide" some features like exons as transcript split locations
- SO could be used to provide mathematical definitions in order to do automatic conversions

GFF3 vs chado; gene models

GFF3 - canonical protein coding gene

I = (gene,mRNA+,5'UTR+,3'UTR+,CDS+)

R= (mRNAgene[m:1], CDS:mRNA[m:m],
5'UTR:mRNA[1:1], 3 5'UTR:mRNA[1:1])

GFF3 - alternate representation

I = (gene,mRNA+,exon+,CDS+,5'UTR*,3'UTR*)

R= (mRNA:gene,exon:mRNA,CDS:mRNA,UTR:mRNA)

GFF3 - minimal model (eg when UTR is unknown)

I = (gene,CDS+)

R= (CDS:gene[m:m])

Chado/Chaos - canonical protein coding gene

I = (gene,mRNA+,exon+,polypeptide+,intron*,UTR*)

R= (mRNA:gene[m:m],exon:mRNA[m:m],
polypeptide:mRNA[m:m])

Mapping between equivalent feature graphs

- Flexibility can be a good thing
- But it also makes it harder to write programs
- Logical definitions of SO classes can help

Computable definitions

```
[Rule]
forall exon(x1) exon(x2)
   consecutive(t,x1,x2) <=>
   exists(intron(i)
            start(i,t)=end(x1,t)
            end(i,t)=start(x2,t)
[Rule]
forall intron(i) <=>
  exists(donor_ss(d)
           start(d,t)=start(i,t))
  exists(acceptor_ss(a)
           end(a,t)=end(a,t))
```

```
[Rule]
forall mRNA(t)
  derives_from(p,t) <=>
  exists(five_prime_utr(u)
           start(u,t)=0
           end(u,t)=start(p,t))
[Rule]
forall mRNA(t)
  derives_from(p,t) <=>
  exists(three_prime_utr(u)
          start(u,t)=end(p,t)+3
          end(u,t)=length(t))
```

Computable definitions

[Rule]
forall gene_defnX(g)
transcript(t)
part_of(t,g) <=>
connected_by_exons(t,t')
part_of(t',g)

[Rule]
forall gene_defY(g)
gene_product(p)
derives_from_part(p,g) <=>
overlaps_on_genome(p,p')
derives_from_part(p'g)

Future applications

- Validation
  - Check types and feature graph makes sense
  - Check properties and values are valid
- Automatic classification based on definitions
  - eg dicistronic_transcript
- Querying over implicit instances
  - introns, UTRs, splice sites

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