Introduction to Chado

From GMOD

Contents

What's a chado?

- At first, a database for FlyBase: incredibly interesting dataset
- A database for **very** deep curation
- An integrated database
- A database that is generic enough to use for any organism

Chado - the way of tea

Why the reference to tea? According to ancient GMOD lore, legend has it that creators Chris Mungall and Dave Emmert were drinking tea in a tea house when they developed the first design that eventually became Chado.

What Documentation Exists for chado?

This Wiki is currently the best source of documentation for Chado. Here are more useful pages in the Wiki:

- Getting Started
- Chado Manual
- Best Practices

A Modular Schema

Chado Module List

- Audit - for database audit trails
- Companalysis - for data from computational analysis
- Contact - for people, groups, and organizations
- Controlled Vocabulary (cv) - for controlled vocabularies and ontologies
- Expression - for summaries of RNA and protein expresssion
- General - for identifiers
- Genetic - for genetic data and genotypes
- Library - for descriptions of molecular libraries
- Mage - for microarray data
- Map - for maps without sequence
- Natural Diversity (ND) - for multiple experiments, such as phenotyping and genotyping
- Organism - for taxonomic data
- Phenotype - for phenotypic data
- Phylogeny - for organisms and phylogenetic trees
- Publication (pub) - for publications and references
- Sequence - for sequences and sequence features
- Stock - for specimens and biological collections
- WWW -

There are *dependencies* between the modules.

This page is focused on the sequence module; we will also discuss parts of the cv module as ontologies are crucial to how chado represents all data.

The actual chado tables themselves are not discussed in attribute-by-attribute detail; this can be browsed by checking out the Chado Manual.

One of the main strengths of chado is that it brings the sequence and genetics views of the world together.

Let's look at the chado conceptualisation of the world before diving in to the schema design.

The Sequence Module and Features

Definition

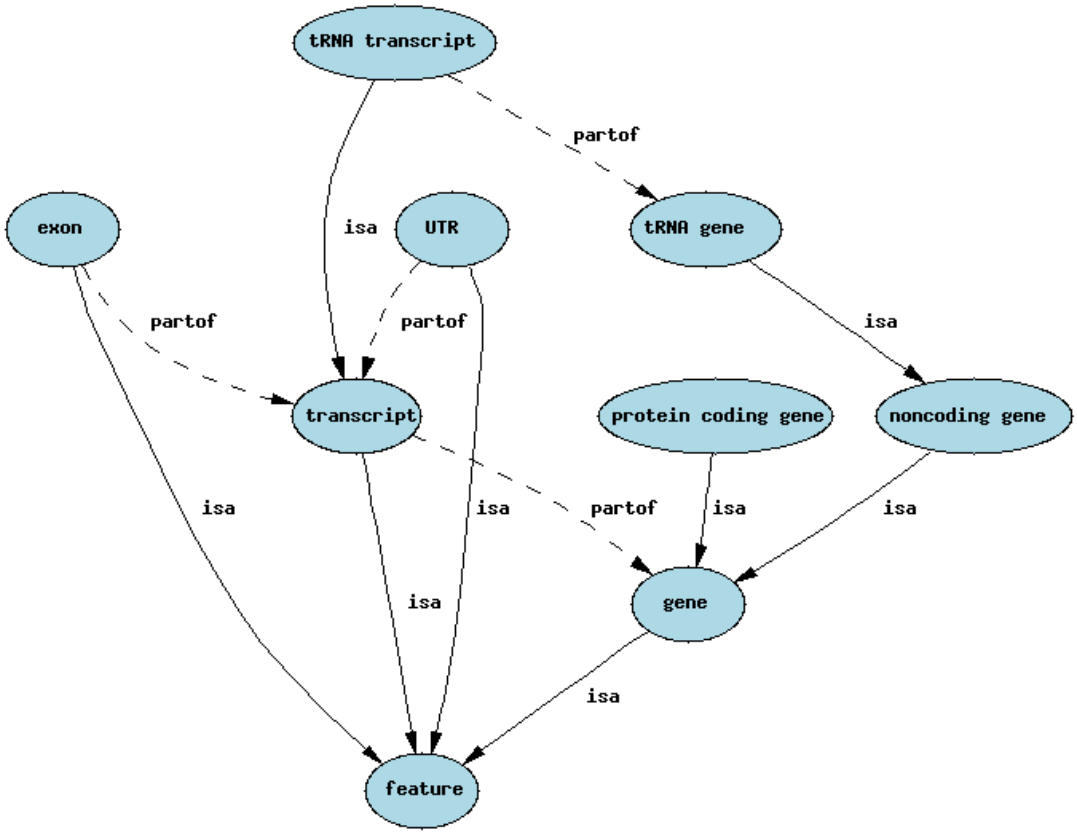
- A feature is a *thingy*
- A feature is a *potentially localisable*

- A feature is further defined by an ontology

Feature Types: an *Ontology*

One way of representing ontologies is through a graph model, with nodes representing concepts and edges representing *relationship types* between the concepts.

Simplified Sequence Ontology



is_a: subtypes, specialisation/generalization
part_of: compositional

Some other feature types

- HSP
- protein domain
- chromosome arm
- contig
- scaffold
- regulatory region
- variation features: insertions, deletions, SNPs

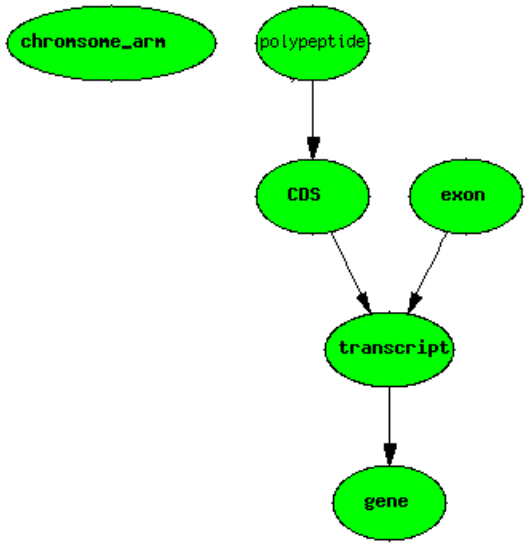
Feature Graphs

The nodes in the graph represent instances of features - the arcs in these cases represent compositional relationships (although other relationship types are possible). Feature graphs do **not** represent positional or spatial relationships - we will get to that later. For more on representing genes also see Chado Best Practices.

Problem/Question:

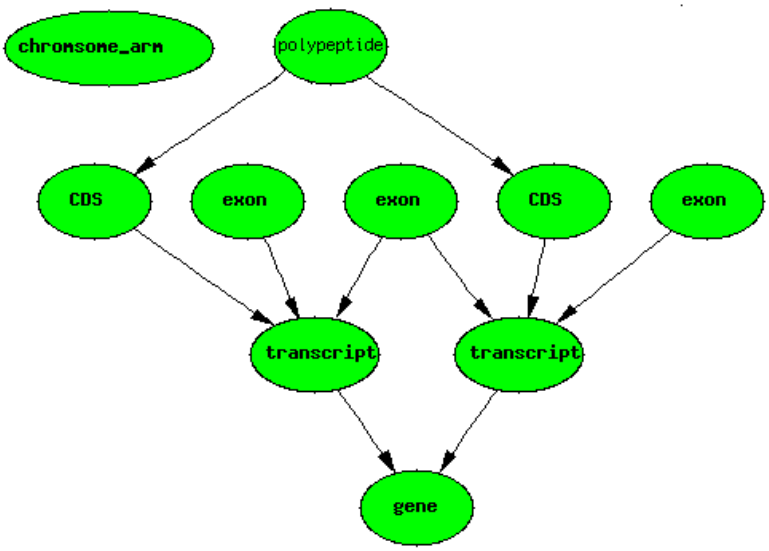
The compositional relationships are a subset of the relationships from gene to CDS in SO. How does one decide where to simplify the graph?

Basic Central Dogma Example



One gene, one transcript, one exon, one protein

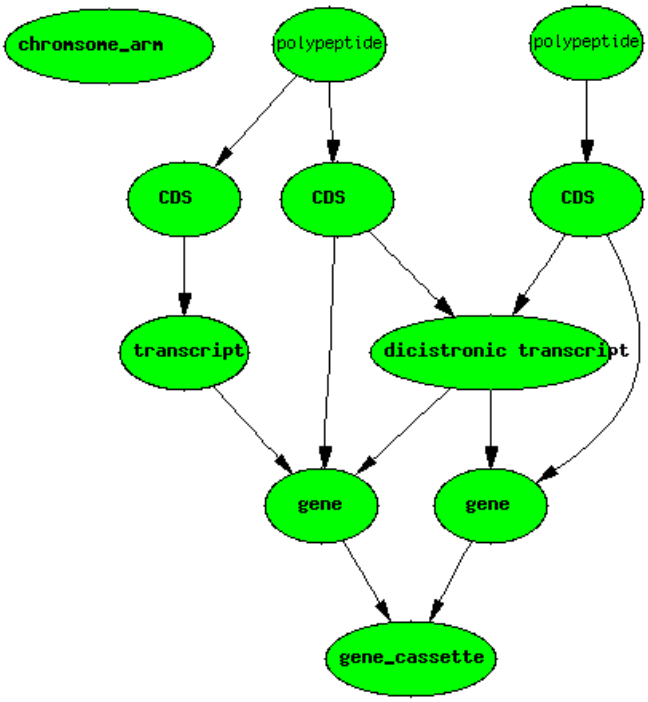
Alternate Splicing



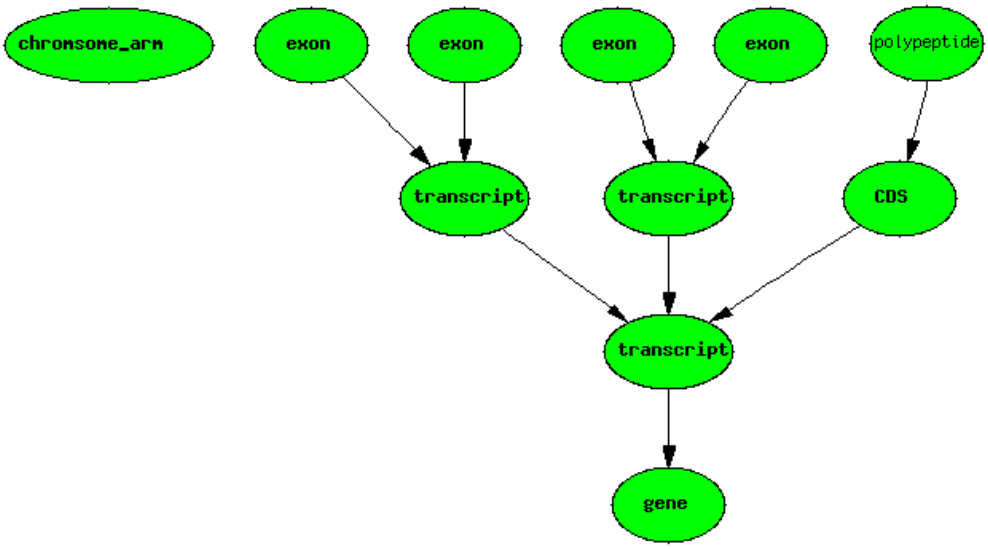
Dicistronic Gene

A dicistronic gene is a gene with a mRNA that codes for two distinct non-overlapping CDSs. Dicistronic genes (see for example, the [Drosophila Adh and Adhr genes http://www.flybase.org/reports/FBgn0000056.html]) have totally distinct gene products deriving from the same transcript. To confuse matters, the two polypeptides are commonly referred to as being derived from two distinct genes (e.g. Adh and Adhr). In a database such as [FlyBase http://flybase.org/], there are 3 gene IDs stored in the database - one for each of the two non-overlapping genes, and one for the gene cassette.

Dicistronic genes make it difficult to have a formal definition of gene that corresponds nicely with how biologists use the term.



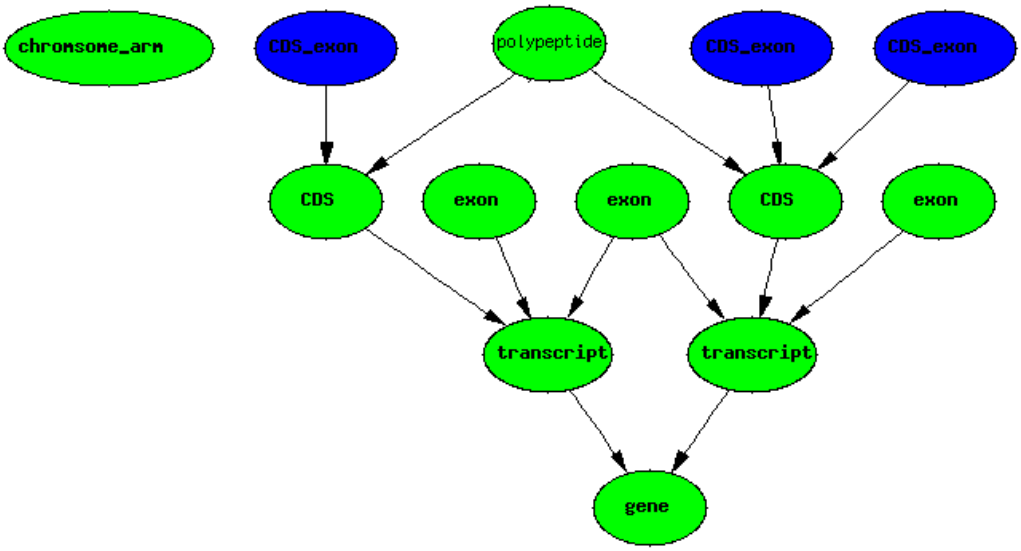
Trans-splicing



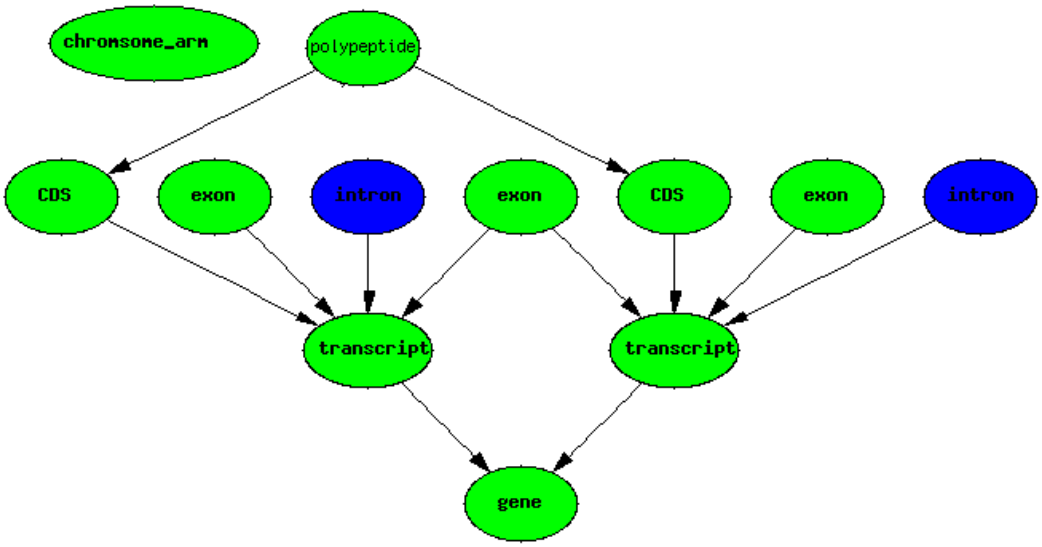
Other cases of trans-splicing may involve spatially distributed primary transcripts.

Feature Graph Transformations

CDS boundaries + exons IMPLIES CDS exons



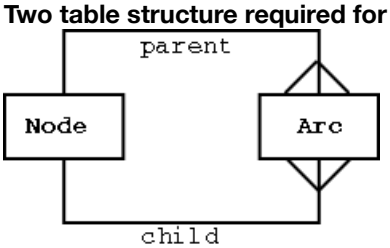
exons IMPLIES introns



Representing Graphs in a Relational Database

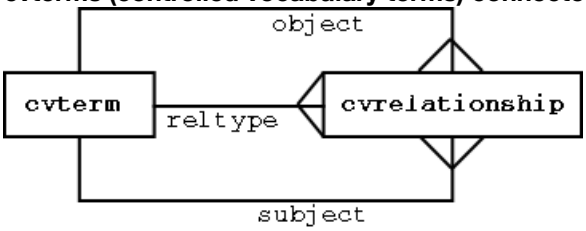
A graph can be defined as a collection of **Edges** (arcs) and **Vertices** (nodes).

Two table structure required for representing graphs



Representing Ontology Graphs in Chado

cvterms (controlled vocabulary terms) connected by cvrelationships

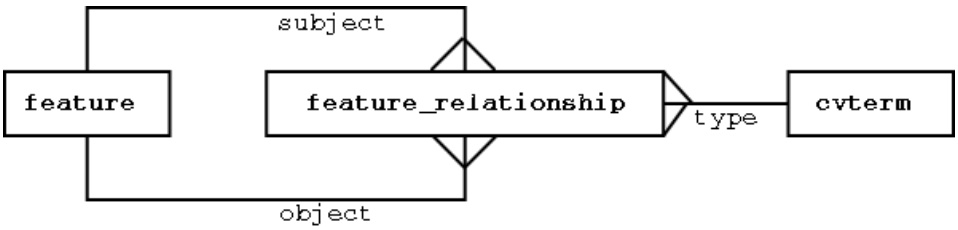


The relationship type is a controlled term in itself. Each cvrelationship can be thought of as a SUBJECT PREDICATE OBJECT statement (eg "GPCR *is-a* transmembrane_receptor).

The structure above is exactly the same as the RDF datamodel - many modern ontology languages (eg DAML, OWL) are layered on top of RDF, so the above structure ensures we will be able to represent all the most advanced ontological concepts.

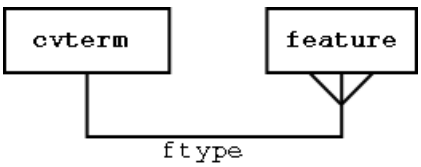
Representing Feature Graphs in Chado

features are the nodes - feature_relationships are the arcs



Note: the different classes of features could be modeled relationally; the principle is to keep the stable stuff modeled relationally, and the fluid/extensible stuff modeled in an ontology that sits in a generic database structure.

Features are typed

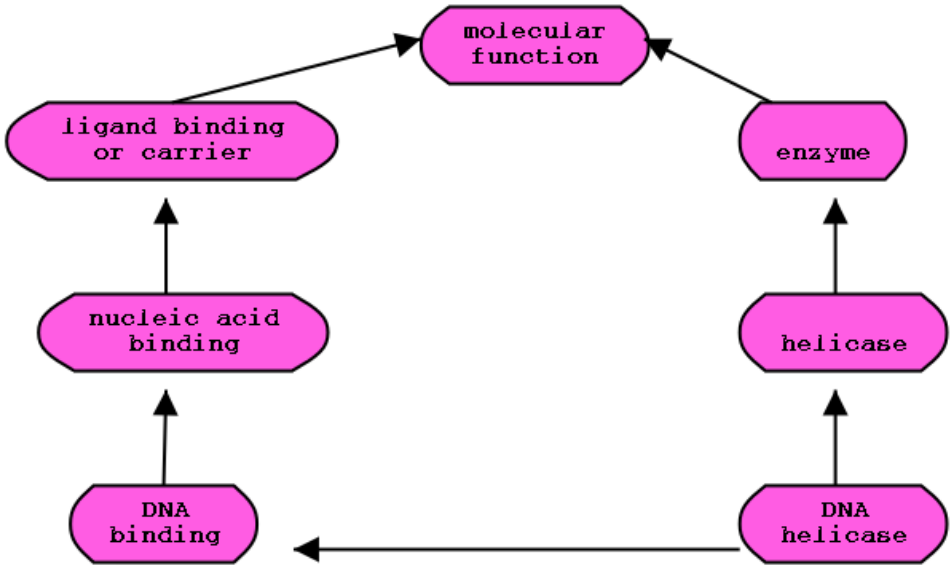


Querying Graphs

Most implementations of SQL are *non-recursive*.

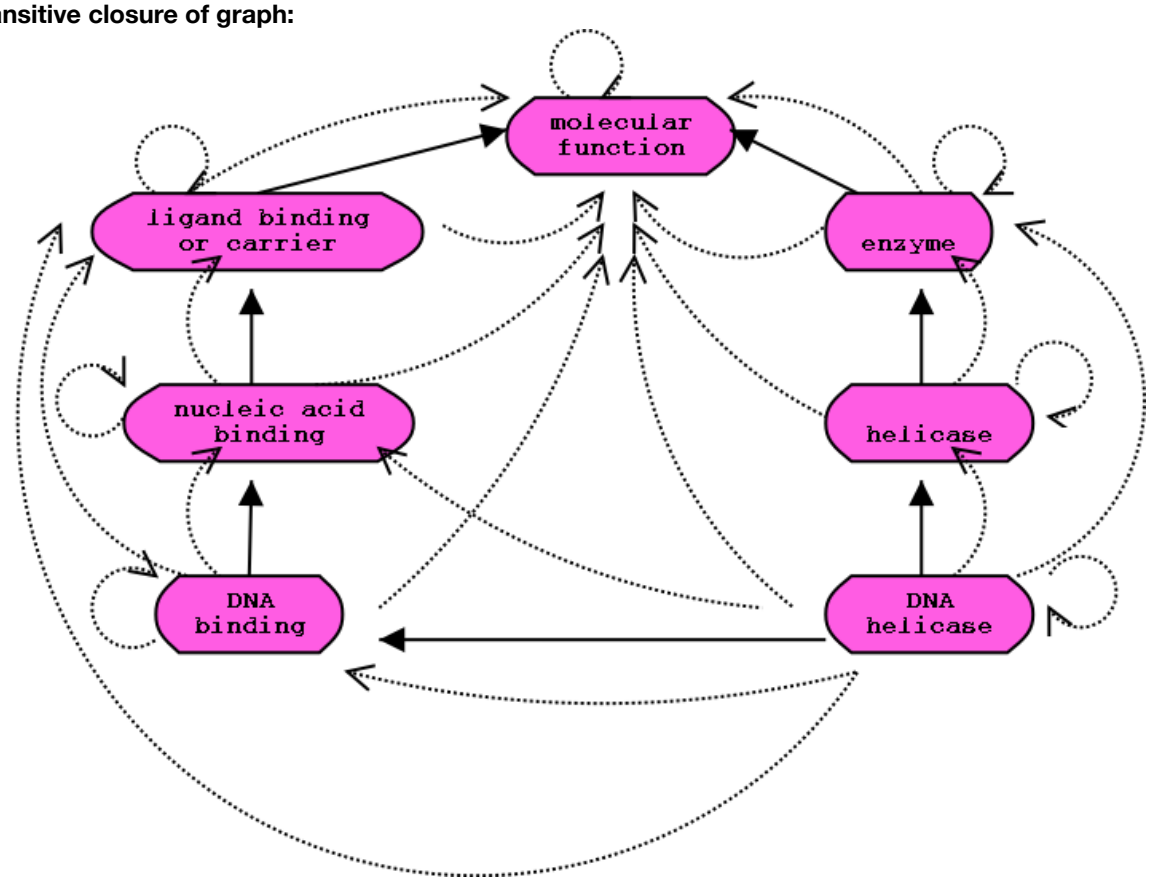
Problem: find all genes; find all genes (generic) find all noncoding genes find all protein coding genes find all tRNA genes find all snRNA genes find all snoRNA genes ...etc eek!

Solution: pre-compute *transitive closure* (http://en.wikipedia.org/wiki/Transitive_closure)



GO Ontology subgraph

Transitive closure of graph:



Solid lines represent the actual relationships. The collection of dotted lines is the closure of the relationships.

```
forall x      ALWAYS TRUE:     x R* x
```

```
x R y            IMPLIES:     x R* y
```

```
x R y,  y R* z    IMPLIES:     x R* z
```

Using views to simplify queries

The following view uses the cvpath table, which includes the closure of the *is_a* relationship.

```
CREATE VIEW fgene AS
  SELECT
    feature.*
  FROM
    feature INNER JOIN cvpath ON (feature.ftype_id = cvpath.subjterm_id)
    INNER JOIN cvterm ON (cvpath.objterm_id = cvterm.cvterm_id)
  WHERE cvterm.termname = 'gene';
```

At Flybase we will mostly be using chado in *data-mining* mode - i.e. we will be querying, not updating. This means we can *materialize* views for speed.

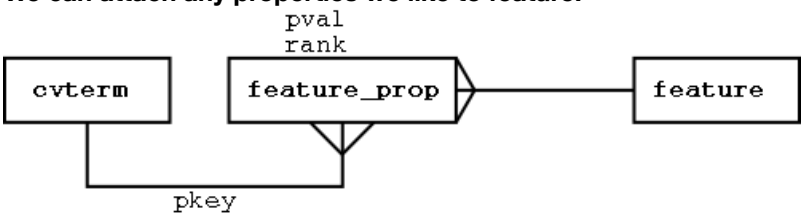
Extensible Attributes

The chado relational model defines a fixed set of attributes for a feature:

Field	Required	Description
dbxref_id	no	namespaced identifier (foreign key)
name	no	A not-guaranteed-unique identifier that is useful to a human
uniquename	yes	name or identifier that is unique in the database
residues	no	DNA, RNA or protein sequence
md5checksum	no	signature of sequence
seqlen	no	length of sequence (may be present even if residues is absent)
type_id	yes	Sequence Ontology (http://sequenceontology.org) feature type (foreign key)

What happens if we want to include other attributes specific to certain projects, or specific to certain feature types? We can use an extensible feature property paradigm:

We can attach any properties we like to feature:

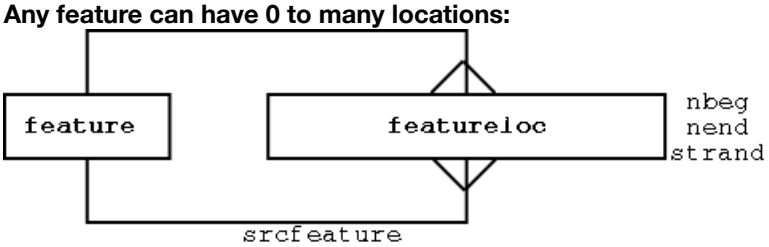


Localising Features in Sequence Coordinates

All sequence localisations are with respect to another feature.

A feature can have multiple locations - however, "split" locations are **not** used (for an example of a split location, look at how Genbank represents a transcript).

Any feature can have 0 to many locations:



Each location is relative to another feature (the **srcfeature**)

The **featureloc** table includes the following attributes:

- fmin - 5' boundary of features
- fmax - 3' boundary of features
- strand: the direction of the feature, relative to srcfeature

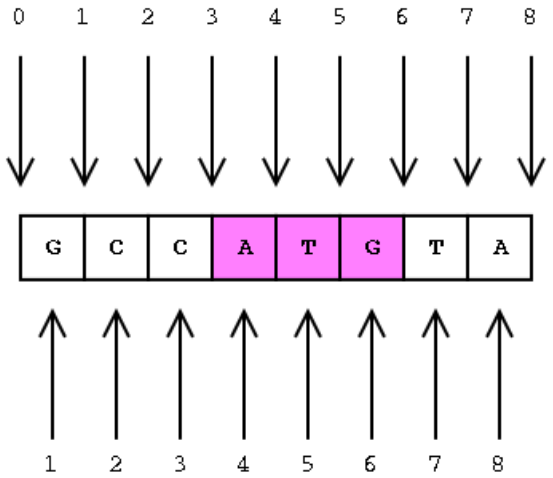
locations have *directional semantics* (like mathematical vectors). this is different from the min/max semantics used by e.g. Bioperl (http://bioperl.org), genbank

Interbase Coordinates

Chado uses *interbase* coordinates.

Interbase counts spaces, not bases. It is a 0-based coordinate system; counting starts at zero. This coordinate system is appealing for a variety of mathematical reasons. Standard (eg genbank, blast) coordinate systems do not allow for a natural representation of zero-length features. An example of a zero-length feature is a cleavage site that is between, but does not include, 2 amino acids. Using interbase coordinates the total number of base pairs in a feature is calculated by subtracting the starting coordinate from the ending coordinate, without the need for an off-by-1 addition required by other coordinate systems. (In general, much mathematical utility is enabled by the number zero.)

Interbase coordinates (top) and base-oriented (below)



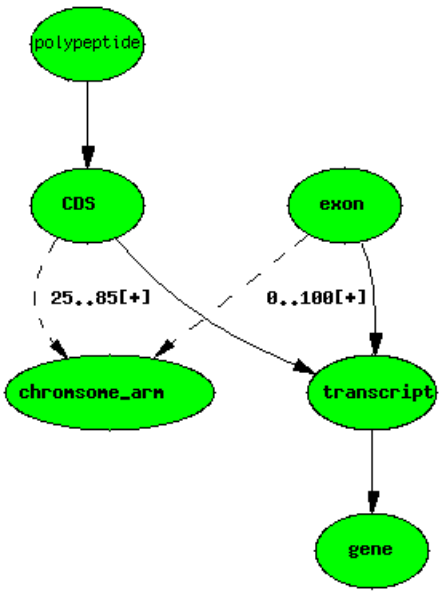
The position of the ATG in interbase is [3, 6] (between the 3rd and 6th gaps)
The position of the ATG in base coordinates is [4, 6] (between 4th and 6th bases inclusive)

Note the different arithmetic for calculating length in these two systems.

Unlike mathematical vectors, we must also explicitly store the directionality (strand). Even though this is surplus to requirements most of the time, it is required for zero-length features, and for circular chromosomes.

Basic example - with locations

Central dogma - with exons and CDSs localised

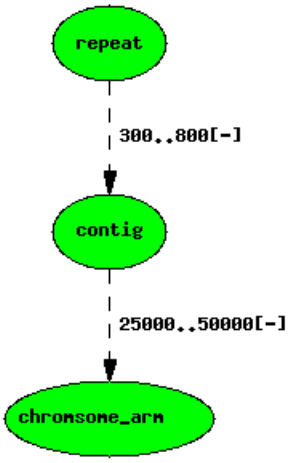


Using the principle of minimal storage (do not store anything that does not increase the *information content* of the database - i.e. nothing redundant), we store only exon and CDS boundary localisations. In the Berkeley Drosophila Genome Project (BDGP) (http://www.fruitfly.org/) data warehouse instantiation of Chado, we may choose to store locations for all features where known - this can vastly simplify some queries, but care must be taken to make sure we don't end up with inconsistent data.

For the most part, infering the boundaries of composite features requires fairly simple graph transformations, although care must be taken for the genes that break central dogma rules.

Locations can be nested

A repeat localised to a contig, itself on a chromosome arm

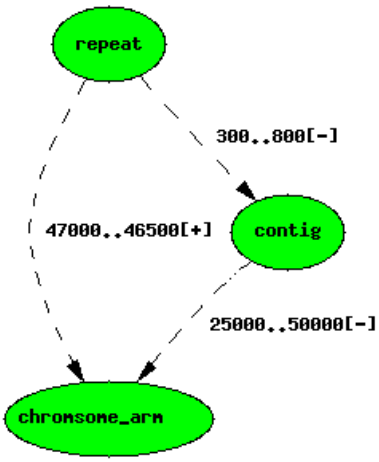


featurelocs are represented by dashed lines.

Note that the position of the repeat on the chromosome arm is implicit, and can be calculated with a simple graph transform, but following the principle of minimal storage, we do not store this in the management database.

If we wish to store the redundant position in a for-querying copy of the db, chado allows us this option - we can have as many locations as we like for a feature. We use an extra attribute called **locgroup** to distinguish locations. locgroup=0 is conventionally used for the non-redundant location.

The repeat feature now has two locations



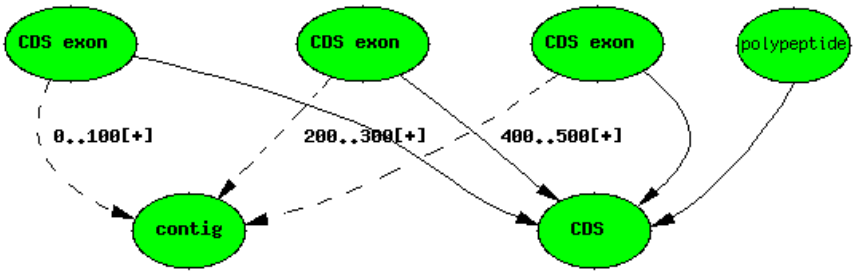
If you look at the underlying data, you will see that the featureloc that locates the repeat on the arm has a locgroup values of **1**.

Computational analysis: Predictions

All predictions are handled analagously to standard central dogma cases. Compute results have scores, and are attached to tuples in the analysis table - this is what distinguishes them from "annotations".

Genscan predicts CDSs and CDS exons (not genes in the Sequence Ontology sense). A typical Genscan prediction may look like this:

Genscan 3-exon 'gene' prediction

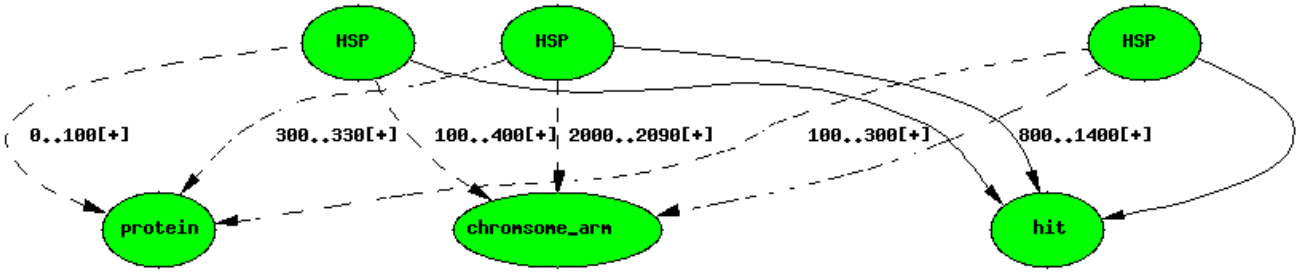


Computational analysis: Similarity results

Pairwise similarities (e.g. BLAST) and multiple alignments (e.g. CLUSTAL) are represented differently.

Pairwise alignments produce **HSP**s. HSPs are scored features with two locations - one on the query, one on the subject.

Blast hit with 3 HSPs



Each HSP has two featurelocs. featureloc has an attribute *rank* to order the locations; by convention 0 is the query rank and 1 is the subject rank.

Computational analysis: Multiple alignments

These are treated analagously to pairwise alignments - just add more locations.

Variation features

Variation features (e.g. SNPs, insertions, deletions) are treated in a similar fashion to pairwise alignments.

Bioperl and chado mapping

There are important differences between the Bioperl and chado models.

Bioperl allows a feature to have multiple non-contiguous locations. Even though the chado schema allows multiple locations, attaching multiple non-contiguous locations is a violation of the chado semantics. To cope with this, we create extra features for the sublocations. For instance, for a transcript, we would create an exon for each of the sublocations.

If you parse a genbank file including variations (e.g. SNPs) into Bioperl objects, you will get a feature with two properties of type "allele". This can be represented using chado; however, the chado semantics state that these variations should be represented using multiple locations.

Acknowledgements

Schema design

- Dave Emmert
- Colin Wiel
- Stan Letovsky
- ShengQuiang Shu
- Pinglei Zhou
- Suzanna Lewis

Chado beta testers and other feedback

- Mark Yandell
- Aubrey de Grey

About this Page

- This page is a Wikified version of a presentation by Chris Mungall (http://archive.is/ENOJk).

Categories: Chado Modules | Pages with problems or questions | Chado

---