Biological Database Design Week 3

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Question and Answer

- Discuss homework
- Q & A on last two weeks’ material

Sequence Data

- Bioinformatics has traditionally focused on handling sequence data
- Many sequence databases are not relational
  - Particularly old ones: implemented prior to good DBMS support for CLOBs
  - GenBank and Swiss-Prot: originally flat file DBs, now have some relational storage
  - SRS (Sequence Retrieval System)
    - Popular way to handle sequences
    - Flat file based
    - Originally developed at EMBL/EBI, commercialized by Lion, sold to BioWisdom, online SRS servers available at EBI and elsewhere

Sources of Sequence Data

- Public
    - NCBI
        - GenBank = all sequences
        - RefSeq = curated sequences
    - ExPASY
        - SWISS-PROT = highly curated protein sequences
        - TrEMBL = uncurated protein sequences (translated EMBL)
- Private
    - Incyte (out of the genomics business)
    - Celera (out of the sequencing business)
- Proprietary
    - In house sequencing efforts

Sequence Data

- A typical sequence “entry” contains:
    - Sequence text
    - Metadata
- Metadata is not uniform across sources
    - Will almost always have the species
    - Curated data sources will usually have:
        - Meaningful name (‘Mitogen-Activated Protein Kinase’)
        - Some indication of function
    - Uncurated data sources are often annotated by computer
        - Names often “similar to protein X” or “hypothetical protein”

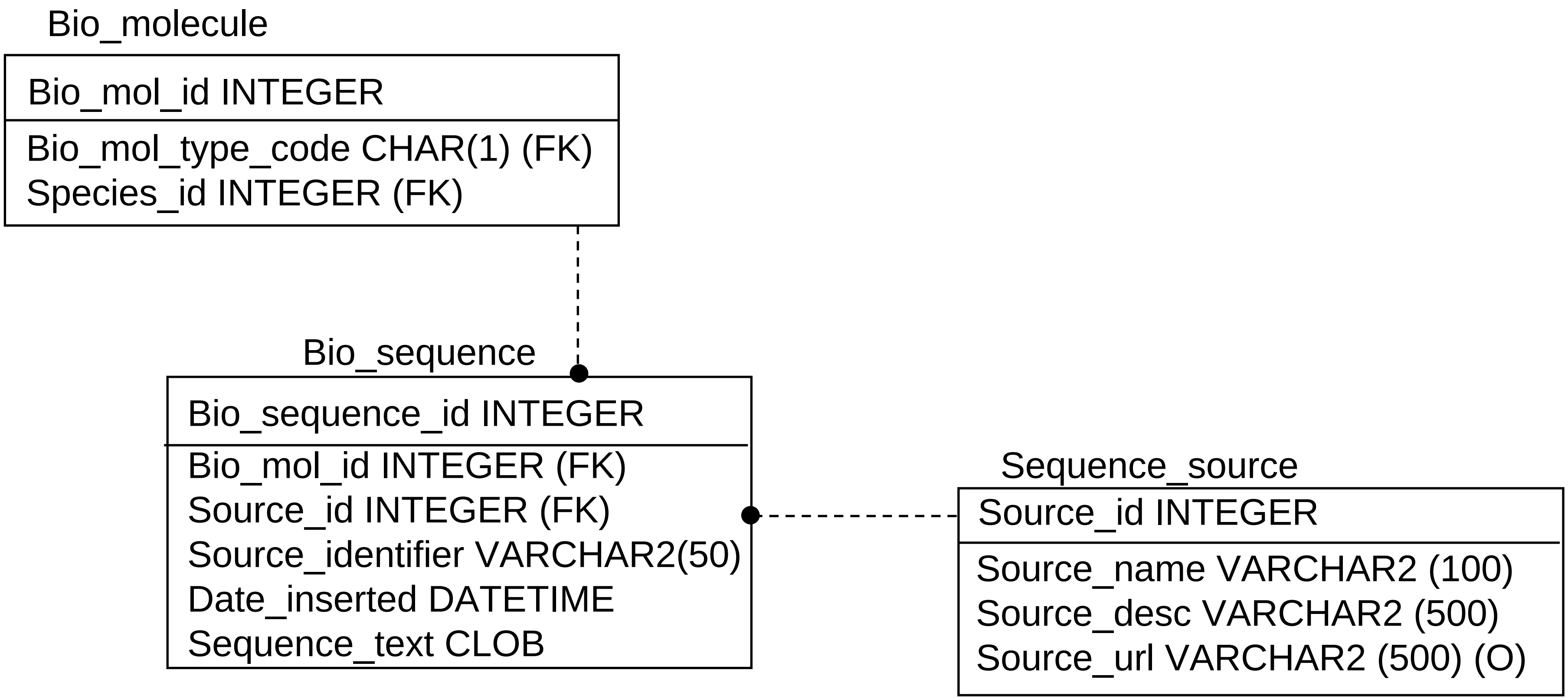
Molecule to Sequence Relationship

- The same “protein” or “gene” can be represented by multiple sequence entries
- Different databases often have slightly different sequences
    - Start codon selection
    - Initiator methionine included or not
    - SNPs (single nucleotide polymorphisms)
    - Sequencing errors
    - Splice variants (a headache in their own right)

Molecule to Sequence Relationship

- Difficult to ascertain when two sequences are the “same” molecule
- Requires scientists to set appropriate rules for your database
  - I’ve used 90 – 95% identity over at least 50 residues
  - Exact cutoffs depend on need for accuracy vs. need for inclusiveness
- Some databases bypass the issue and treat each sequence individually
  - Potential for lots of data duplication
  - Decision is ultimately made based on database scope

Relational Implementation



Bio_molecule

Bio_mol_id INTEGER

Bio_mol_type_code CHAR(1) (FK)
Species_id INTEGER (FK)

Bio_sequence

Bio_sequence_id INTEGER

Bio_mol_id INTEGER (FK)
Source_id INTEGER (FK)
Source_identifier VARCHAR2(50)
Date_inserted DATETIME
Sequence_text CLOB

Sequence_source

Source_id INTEGER

Source_name VARCHAR2 (100)
Source_desc VARCHAR2 (500)
Source_url VARCHAR2 (500) (O)

Sequence Text

- Protein and nucleotide
  - Nucleotides translate to proteins at 3 base pairs per amino acid
  - DNA sequences contain introns: unexpressed DNA “inserted” into gene
- Large range in size of sequence text
  - Common to study ESTs (~300 – 500 base pairs)
  - Smallest proteins are ~50-200 amino acids
  - Largest protein is titin, which has ~27,000 amino acids
  - Genomic DNA can be millions of base pairs long

Searches on Sequence Text

- Exact match
  - Not very useful, because small variations can occur in sequences that are scientifically "the same"
  - Used to remove (or flag) obvious redundancies
  - Some uses in intellectual property
- Global match (e.g., ClustalW)
  - Finds optimal alignment over entire length of two sequences
  - Allows insertions and substitutions
  - Not good at identifying matching regions within sequences that also have unmatched regions

Searches on Sequence Text

- Local match (e.g., BLAST)
  - Most common method of searching sequence DBs
  - Looks for regions of alignment within two sequences
  - Allows insertions and substitutions
- Motif or domain searches
  - Look for regions of sequence that match known patterns
  - Used to infer function
  - Search for characteristic motifs (BLOCKS, PRINTS, PROSITE)
  - Search for domains (Pfam, SMART)
  - Allow insertions and substitutions

Sequence Searching in RDBs

- Can’t perform searches on CLOBs in standard SQL
  - RDBMS-specific availabilty of search features
- No easy way to implement the most useful types of searches in standard SQL
- Not all substitutions are equal
  - Some substitutions are more “conservative” than others
  - Preserve basic chemical properties of amino acid
  - Use a “substitution matrix such as BLOSSUM to specify “cost” of substitutions
  - Choice of substitution matrix may depend on personal preference, goals of project

Sequence Searching in RDBs

- Usually search on sequence text outside of relational database
- BLAST runs on a “database” of sequences in FASTA format
- Two options
  - Store sequences in database, but dump to FASTA for BLAST
  - Store sequences in FASTA flat files, reference these in database
  - Either way, DB and flat files can get out of sync
  - Storing sequences in database makes DB “gold standard”
- Oracle 10g implements BLAST searches in the database

Sequences as Non-Atomic Data

- In some databases, sequences are split into a table in which each amino acid or base pair is a row
- This is done when there is a need to store data about individual positions in the sequence
- Intermediate solutions: “break out” certain regions to store as individual residues
  - Functional motifs
  - Duplicates data

Sequence Metadata

- Metadata = data about data
  - Sequence is primary data
- Some metadata is a property of a particular sequence
  - Biophysical measurements: isoelectric point, extinction coefficents
- Some metadata is a property of the gene or protein that the sequence represents
  - Biological data: function, subcellular localization
- Species metadata can go either way
  - Depends on how you choose to handle orthologs in your database
  - Messiness of functional variation among orthologs means that a protein/gene is usually best associated with a single species

Sequence Species

- Species data is really a hierarchy
- For most applications, storing the full hierarchy is out of scope
  - Exceptions
    - Evolutionary biology
    - If need ability to perform deep searches on species (for "all mammals", etc.)
- Usually need at least scientific name and one common name
  - Some people will also provide basic classifications: specifics depend on scope of DB
- Can link to/incorporate NCBI's taxonomy DB
  - www.ncbi.nlm.nih.gov/Taxonomy

Sequence Function

- Two types of function (at least!)
  - Biochemical
    - The chemical process for which the protein/gene is responsible
    - Examples: kinase, calcium-binding
    - Enzymes: cross-reference EC (Enzyme commission) numbers (ENZYME: http://www.expasy.org/enzyme/)
    - Non-enzymes and enzymes: cross-reference molecular function Gene Ontology (http://www.geneontology.org)
  - Cellular/Process
    - The cellular pathway or process in which the protein/gene participates
    - Examples: DNA repair, long term potentiation
    - Cross-reference biological process Gene Ontology

Sequence Function

- Link to disease states may be considered a type of function, too
    - ICD codes (http://www.who.int/classifications/icd/en/)
- One gene or protein may be involved in multiple biochemical and cellular functions
    - Many enzymes have multiple binding sites
    - Many signal transduction proteins participate in multiple pathways
- There are always exceptions to standard ontologies
- If a scientist's favorite gene doesn't fit the standard ontology, and he can't explain why, he won't store the data!
    - Always provide a comment field

Additional Metadata

- Too numerous to list
  - Chromosome
  - Ligand binding sites
  - Intron locations
  - Active site residues
- Highly dependent on interests of group using database
- Often difficult to classify
- Constantly expanding list
- Some text, some numeric

Metadata Issues

- Due to incomplete nature of biological research, the features that are available vary widely by molecule
  - If you try to make a table with a column for each feature, you will have a lot of NULLs
  - Alternatively, making each feature its own table leads to an explosion of tables in your schema

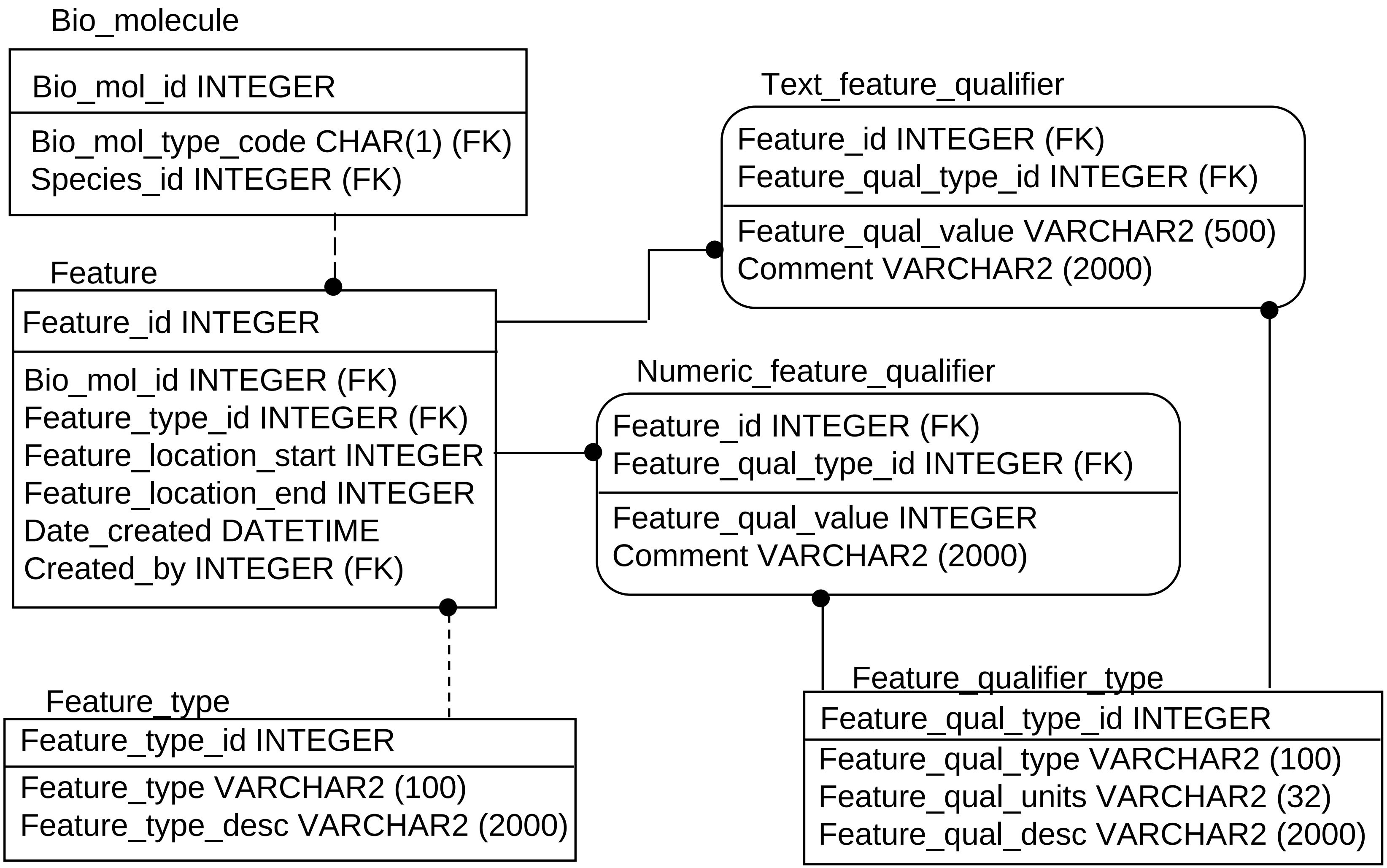
Additional Metadata

- Most public databases handle additional metadata as “feature table”
  - GenBank/EMBL feature table
    - Each feature has a location (optional: without location, feature is assumed to apply to entire sequence)
    - Features have “keys” (identifying names)
    - Features can have qualifiers (in GenBank spec, some are mandatory)
    - Example: primer-binding site feature
      - Key = primer_bind
      - Optional qualifiers: allele, citation, db_xref, evidence, gene, label, locus_tag, map, note, standard_name, PCR_conditions
  - Swiss-Prot has similar feature design
    - Comments apply to entire sequence
      - Examples: function, tissue specificity
    - Features are assigned a location
      - Examples: domain, binding site, post-translationally modified residue

Entity-Attribute-Value Design

- Standard design pattern used in many fields
- Values in table specifiy the feature, feature qualifier, and feature value
- If database needs to store features that apply only to regions of the sequence, add a “location” column
  - Requires separate tables for feature and qualifier, to avoid duplicating location
- Consider making feature type and feature qualifier lookup tables
  - Prevents duplicate names for same feature
- Store text and numeric features separately
  - Preserve ability to use numeric aggregate functions
  - Store units of numeric features

Relational Implementation



Bio_molecule

Bio_mol_id INTEGER

Bio_mol_type_code CHAR(1) (FK)
Species_id INTEGER (FK)

Feature

Feature_id INTEGER

Bio_mol_id INTEGER (FK)
Feature_type_id INTEGER (FK)
Feature_location_start INTEGER
Feature_location_end INTEGER
Date_created DATETIME
Created_by INTEGER (FK)

Text_feature_qualifier

Feature_id INTEGER (FK)
Feature_qual_type_id INTEGER (FK)

Feature_qual_value VARCHAR2 (500)
Comment VARCHAR2 (2000)

Numeric_feature_qualifier

Feature_id INTEGER (FK)
Feature_qual_type_id INTEGER (FK)

Feature_qual_value INTEGER
Comment VARCHAR2 (2000)

Feature_type

Feature_type_id INTEGER

Feature_type VARCHAR2 (100)
Feature_type_desc VARCHAR2 (2000)

Feature_qualifier_type

Feature_qual_type_id INTEGER

Feature_qual_type VARCHAR2 (100)
Feature_qual_units VARCHAR2 (32)
Feature_qual_desc VARCHAR2 (2000)

Difficulty Classifying Biological Data

- Biology is often a very “fuzzy” science
- Data is incomplete: scientists are constantly forming and discarding hypotheses
- Nature has a seemingly infinite way of combining features
- Dilemma
  - “Fuzziness” is real and important
  - Need “hard” classifications to support truly deep queries
  - Compromise
    - Make classification system user-extensible
    - Provide comment fields into which all of the real ambiguity can be entered

Tracking the Source of Data

- It is often desirable to track the source of features
  - Particularly if features may be entered by users (rather than downloaded from source databases only)
  - Also desirable because different source databases may provide contradictory metadata
- Lack of “feature source” tracking has created a problem with function annotations in public databases
  - Sequence A is annotated as a kinase because of sequence similarity with Sequence B
    - Sequence B turns out not to be a kinase
    - More likely: Sequence A has same basic structure as Sequence B, but lacks kinase function
  - Sequence C is annotated as a kinase because of similarity to Sequence A
  - If none of the “function transfers” are traceable, the function annotations cannot be trusted

Tracking the Source of Data

- In science, it is important to be able to lookup and evaluate source reference
- Science is incomplete
  - Your research contradicts the data in the database
  - Which is in error? Are both right, and we don’t see the full picture yet?
  - Scientist needs to return to original source and evaluate the experiment

Tracking the Source of Data

- Gold standard is publication in peer reviewed journal
- Usually, but not always, indexed in PubMed (www.ncbi.nlm.nih.gov/PubMed)
- Other sources
  - Chemistry journals
  - Dissertations (rarely read, let alone cited…)
  - Webpages
  - Internal company reports

Tracking the Source of Data

- Reference data is actually quite complex
- In many applications, it is enough to link to PubMed
  - I usually provide ability to create internal, non-structured reference object for things not indexed in PubMed
- If need to allow queries into references, must store the reference itself
  - Find all features supported by papers on which Joe Q. Scientist is an author
- NCBI allows downloading of an XML version of reference, which is easy to parse into your database
- Object Management Group Bibliographic Query Service (OMG-BQS) model
  - http://www.ebi.ac.uk/~senger/openbqs
  - The class diagram is in the specification section
  - Moves frequently. Google "OpenBQS" to find it.

Sequence Versioning

- Some public databases now version their sequences
  - Example: RefSeq
  - Sequence is identified by an accession number and a version
    - NM_005842.2
  - In general, only latest version of sequence is available
- Must decide how to handle versioning in your database
  - Keep all versions or latest version only?
  - If you keep all versions, do you associate different versions of the same sequence with each other?
  - What happens to any metadata added to the sequence when a new version comes out?

Questions to Ask

- Is your primary interest the sequences or the proteins/genes they represent? (Or both?)
  - Tells you whether you can simplify one or the other
- Do you need to search over “aggregate” species designations?
  - Tells you how much of the species hierarchy you need to store
- Do you need to search on details of supporting data, or just link to it?
  - Tells you whether you need to store all reference data, or just a link to it
- Do you need to associate data with a particular version of a sequence?
  - Tells you whether you need to track versions

Additional Data Models

- ENSEMBL data model
  - Relational database for ENSEMBL
  - Used to be available: can no longer find it on the Ensembl website.
- bioSQL
  - http://obda.open-bio.org
  - From the Open Bioinformatics Foundation (open-bio.org)
- aMAZE
  - Interesting data model for representing function
  - http://www.amaze.ulb.ac.be
  - Representing and analysing molecular and cellular function using the computer. J. van Helden, et. al. (2000) Biol. Chem. 381:921-935.

Homework

- Reading for this week's class
  - GenBank portion of the NCBI handbook, UniProt user manual (on website)
- Homework: Project plans are due next week

- Reading for next week's class
  - Paper discussing GeneLogic's approach to managing gene expression data
  - Implementing LIMS: A "How To" Guide
- Optional reading for next week's class
  - Nature Genetics paper on MIAME (strongly recommended, but will require a trip to the library)
  - A computer scientist's explanation of microarrays (strongly recommended for those not familiar with the technique)
  - MAGE-ML paper