Managing Genomic Data

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Programming for Biology
CSHL
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One problem people in bioinformatics may face:

Some nice people (possibly you) sequenced one or more organisms or strains, and then built them into assemblies (or if you're really lucky, full chromosomes). What now?

In addition, again if you're really lucky, you may have all sorts of data associated with these sequences, like expression, strains, genotypes, phenotypes, breeding info, physical maps. Seriously, now what?

GMOD is …

- A set of interoperable open-source **software** components for visualizing, annotating, and managing biological data.

- An active **community** of developers and users asking diverse questions, and facing common challenges, with their biological data.

Who uses GMOD?

Plus hundreds of others

GMOD Project

- Open Source
- Used to have two full time project staff:
  - Project Coordinator: Scott Cain
  - Help Desk: Amelia Ireland
- Components
  - Some have dedicated funding
  - Others are contributed
  - New components must have:
    - An open source license
    - Interoperability with other GMOD components
    - A good faith commitment of at lest 2 years of support
    - …

http://gmod.org/wiki/GMOD_Membership

GMOD is Software

Algorithms?

```
IndexExactSearch(W, z)
  CalculateD(W)
  return IndexRecur(W, |W| − 1, z, 1, |X| − 1)

CalculateD(W)
  k ← 1
  l ← |X| − 1
  z ← 0
  for i = 0 to |W| − 1 do
    k ← C(W[i]) + O′(W[i], k − 1) + 1
    l ← C(W[i]) + O′(W[i], l)
    if k > l then
      [illegible]
      k ← |X| − 1
      z ← z + 1
    D(i) ← z

IndexRecur(W, i, z, k, l)
  if z < D(i) then
    return ∅
  if i < 0 then
    return {[k, l]}
  I ← ∅
  I ← I ∪ IndexRecur(W, i − 1, z − 1, k, l)
  for each b ∈ {A, C, G, T} do
    k ← C(b) + O(b, k − 1) + 1
    l ← C(b) + O(b, l)
    if k < l then
      I ← I ∪ IndexRecur(W, i, z − 1, k, l)
      if b = W[i] then
        I ← I ∪ IndexRecur(W, i − 1, z, k, l)
      else
        I ← I ∪ IndexRecur(W, i − 1, z − 1, k, l)
  return I
```

Not really.

Plumbing!

GMOD Software

- Configurability and extensibility are central goals of GMOD.
  - GMOD tools are built to be reused
- Emphasize local installs
- Not a hosted solution (with a few exceptions)
- Not monolithic.
  - Most components can stand alone
  - Allows organizations to start slowly

GMOD Software

- Interoperability and data integration are also central goals of GMOD.
- You'll see several mechanisms in this talk
  - GFF3
  - Chado
  - Ontologies

Software

GMOD components can be categorized as

- **V** Visualization
- **D** Data Management
- **A** Annotation and Analysis

Software

You have

- Sequence
- Gene models
- Mapping data
- Alternative transcripts
- Expression
- SNP / variation
- Methylation
- GO terms
- Stocks / lines
- Publications / Attribution
- Orthology

GMOD Has

- A MAKER
- A Galaxy
- A Ergatis
- A ISGA
- A SOBA
- A Textpresso
- A Apollo
- V A Table Edit

- V GBrowse
- V WebGBrowse
- V JBrowse
- V CMap
- V GBrowse_syn
- V Sybil
- V SynView

- D Chado
- D Bio::Chado::Schema
- D ModWare
- A V Tripal

- D BioMart
- D InterMine

A Annotation & Analysis D Data Management V Visualization

GMOD Requirements

- Server
  - Most use Linux
- GMOD Systems Administrator
  - Understands Linux package management, a scripting language, command line interfaces, relational databases, …
  - Grad/Undergrad, half time when starting up.

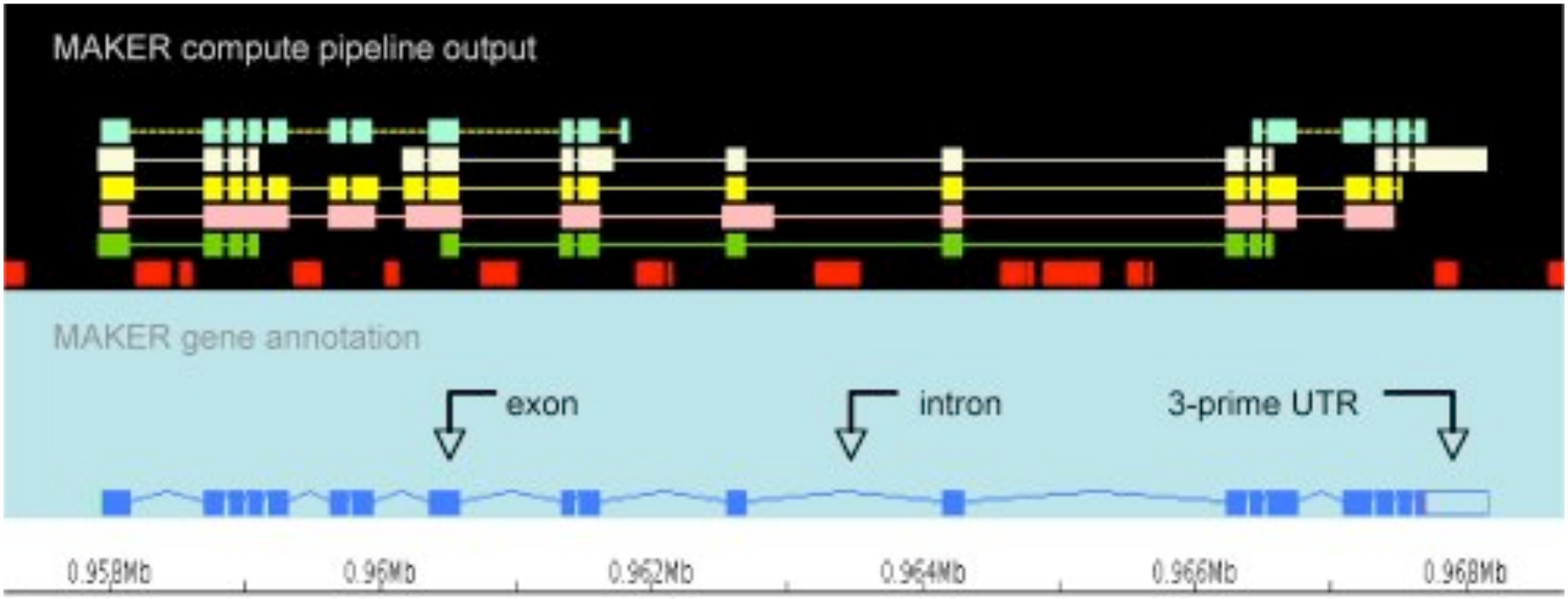
http://gmod.org/wiki/Computing_Requirements

MAKER

- Genome annotation pipeline for creating gene predictions
- Incorporates
  - SNAP, RepeatMasker, exonerate, BLAST
  - Augustus, FGENESH, GeneMark, MPI
- Other capabilities
  - Map existing annotation onto new assemblies
  - Merge multiple legacy annotation sets into a consensus set
  - Update existing annotations with new evidence
  - Integrate raw InterProScan results
- Maker Web Annotation Service

MAKER: An easy-to-use annotation pipeline designed for emerging model organism genomes, Brandi L. Cantarel, *et al.*, *Genome Res*. 2008. 18: 188-196

Minimizing “Edit distance”



SNAP *ab-initio* Gene Prediction
EST Alignment - EXONERATE
Protein Alignment - EXONERATE
Protein Alignment - BLASTX
EST Alignment - BLASTN
Repeats
MAKER gene annotation

MAKER Development

- MAKER

  2008. Based on early annotation pipelines developed by Mark Yandell at Celera.

- MAKER 2

  2011. Introduction of MPI parallelization, support for multiple gene predictors, GFF3 pass-through, and quality metrics like AED (Annotation Edit Distance) from the Sequence Ontology consortium.

- MAKER-P

  2015. Support for tRNA and snoRNA annotation. Improved parallelization on large plant genomes.

- MAKER 3

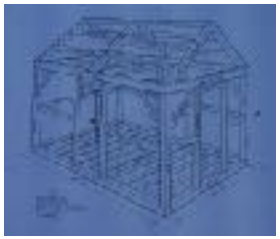
  2016. EVM (Evidence Modeler) support for improved annotation and user defined evidence probability weighting.

MAKER Resources

Home Page	http://www.yandell-lab.org/software/maker.html
Tutorial	http://gmod.org/wiki/MAKER_Tutorial
Mailing List	http://yandell-lab.org/mailman/listinfo/maker-devel_yandell-lab.org

Chado: A database schema for biological data

- A *schema* is a database design
  - Blueprint for a database, a way of organizing data
- Independent of specific data
  - Chado provides structure
  - You provide the hard work and data



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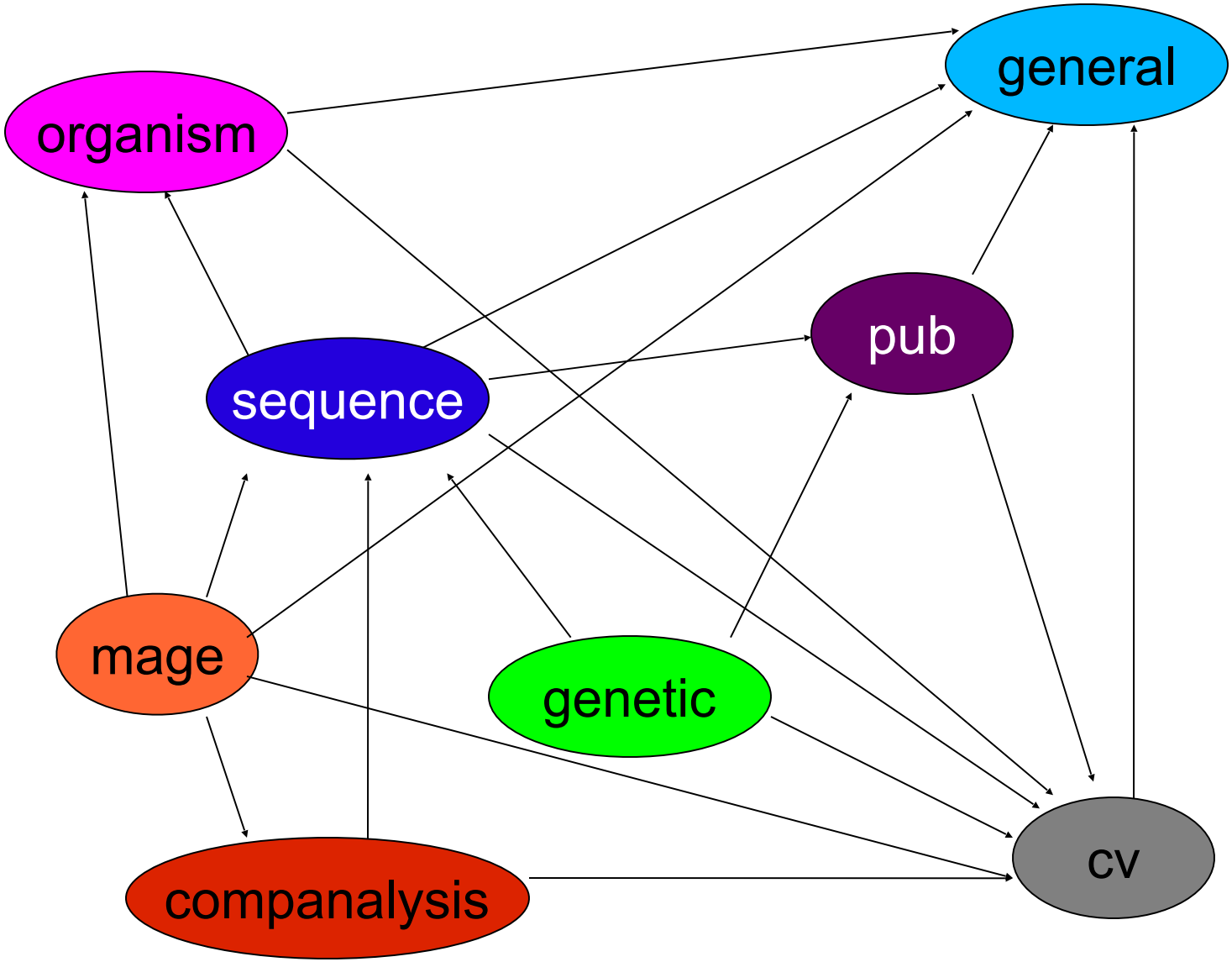
Why use Chado?

- Very good at genomic data
- Widely used
  - AphidBase, BeetleBase, dictyBase, FlyBase, SGN, SpBase, VectorBase, wFleaBase, …
- Integrates with other GMOD tools
- Community of support
- Modular, flexible and extensible
- Normalized (boring but important for data integrity)

Chado Modules

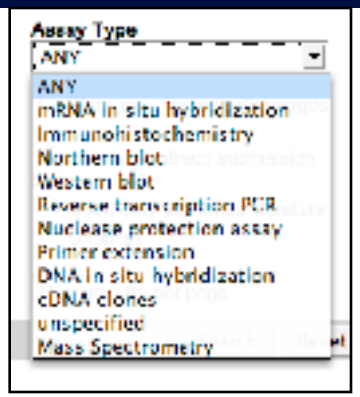


Controlled Vocabularies and Ontologies

Controlled Vocabulary (CV)

List of terms from which a value *must* come

Pull down menus are examples of CVs



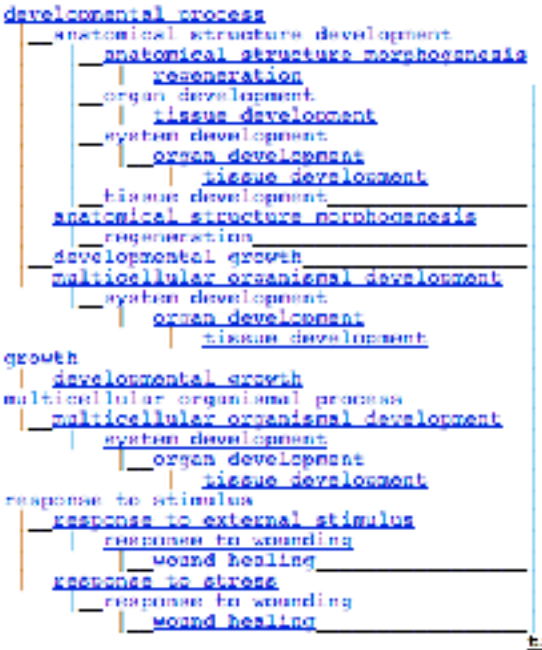
ZFIN assay type CV

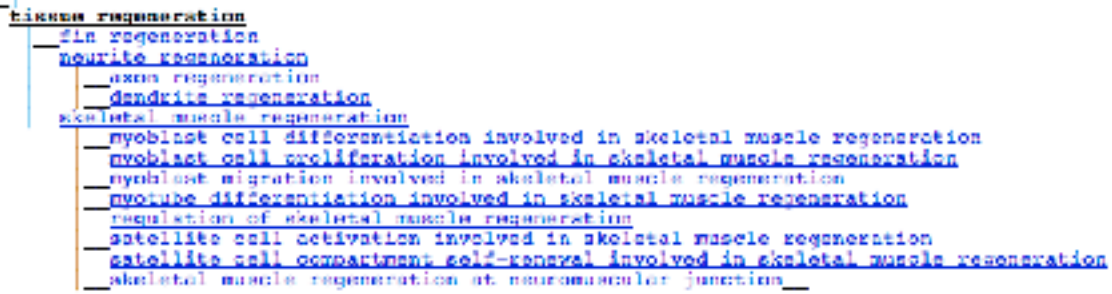
Ontology

Ontology = CV + rules + relationships between terms

Gene Ontology, Sequence Ontology

Many standard ontologies available from OBO

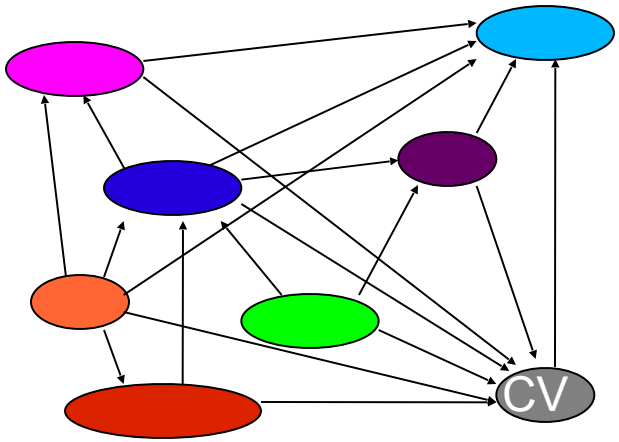




FlyBase CV Term Viewer:
GO term “tissue regeneration”

CVs and Ontologies in Chado

- Controlled vocabularies and ontologies are key in Chado
- Maximally used for
  - Integrity
  - Interoperability
- Can create your own, *but* …
  - Please use standard ontologies when they exist
  - See OBO: http://www.obofoundry.org/



Chado Resources

Home Page	http://gmod.org/wiki/Chado
Tutorial	http://gmod.org/wiki/Chado_Tutorial
Introduction	http://gmod.org/wiki/Introduction_to_Chado
Manual	http://gmod.org/wiki/Chado_Manual
Modules	http://gmod.org/wiki/GBrowse_Modules
Mailing List	https://lists.sourceforge.net/lists/listinfo/gmod-schema

Chado Web Front Ends

- Chado is a schema, a server side technology
- It is not a web front end or a desktop client

- Options for Chado web front ends:
  - Do it yourself
  - Tripal

Do it yourself

- GMOD provides some support in form of libraries
- Perl
  - Chado::AutoDBI (phasing out)
  - Modware → Bio::Chado::Schema
- Java
  - At least two projects under development
    - GOBL (the Berkeley/WebApollo people)
    - INRA (France) Hibernate-based
- Drupal / PHP
  - Three projects underway

Tripal

- Set of Drupal modules
  - Feature, Organism, Library, Analysis
  - Modules roughly correspond to Chado modules
  - Easy to create new modules
- Includes user authentication, job management, and data entry support

MarineGenomics.org

Stephen Ficklin, Meg Staton, Chun-Huai Cheng, …
Washington State University, Clemson University Genomics Institute

Tripal Resources

Home Page	http://gmod.org/wiki/Tripal
Tutorial	http://gmod.org/wiki/Tripal_Tutorial
User Guide	http://tripal.info/tutorials/v3.x
Example	https://www.rosaceae.org
Mailing List	https://lists.sourceforge.net/lists/listinfo/gmod-tripal

Chado Web: DIY or Tripal?

Do It Yourself
More work
Get exactly what you want

Tripal
User authentication
Data entry
Actively developed
Well documented
Easy to extend
Drupal

> What really made us decide to switch over to Drupal was that we needed authentication mechanisms, customized data entry mechanisms, and the ability to add social networking features and other non-biological components to our sites. Drupal supported all of this and was widely used, well documented, and well supported.
>
> Stephen Ficklin, Lead Tripal Developer

This is not necessarily an either/or choice

JBrowse

- GMOD's 2nd generation genome browser
- It's fast
- Completely new
  - Client side rendering
  - Heavily AJAX
  - JSON, Nested Containment Lists

JBrowse: A next-generation genome browser, Mitchell E. Skinner, Andrew V. Uzilov, Lincoln D. Stein, Christopher J. Mungall and Ian H. Holmes, Genome Res. 2009. 19: 1630-1638

JBrowse Future Plans

- An ecosystem comparable to GBrowse
  - Glyph library, user defined glyphs, callbacks, track sharing, …
- Comparative genomics (more on that later)
- Community Annotation
  - User authentication
  - User uploadable and sharable tracks and annotation
- Server side tools for integrated analysis

JBrowse Resources

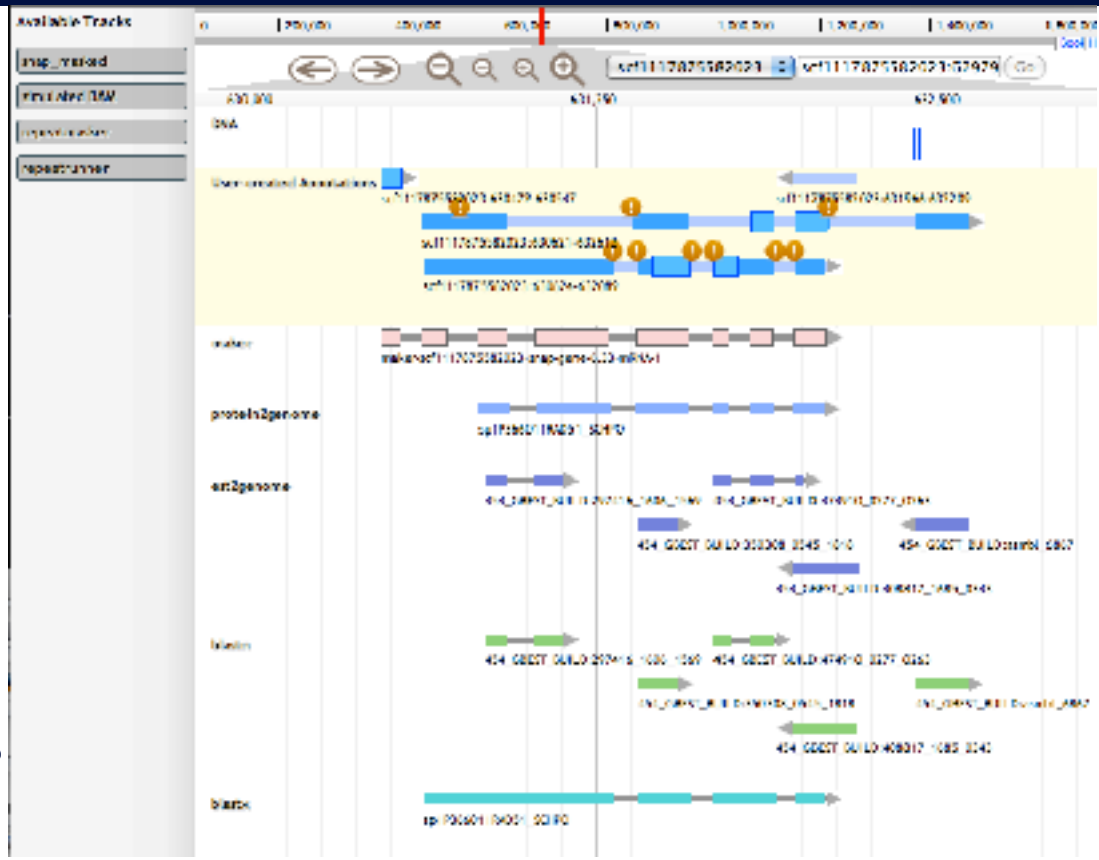
Home Page	http://jbrowse.org
Admin Tutorial	http://gmod.org/wiki/JBrowse_Tutorial_PAG_2017
Configuration	http://jbrowse.org/code/jbrowse-master/docs/config.html
Example site	http://staging.wormbase.org/tools/genome/jbrowse/
Mailing List	https://lists.sourceforge.net/lists/listinfo/gmod-ajax

GBrowse or JBrowse

GBrowse
Robust ecosystem
Feature rich
Large user base
Track sharing

JBrowse
Very fast
Rapidly growing user base
Lots of future development
Easy to configure

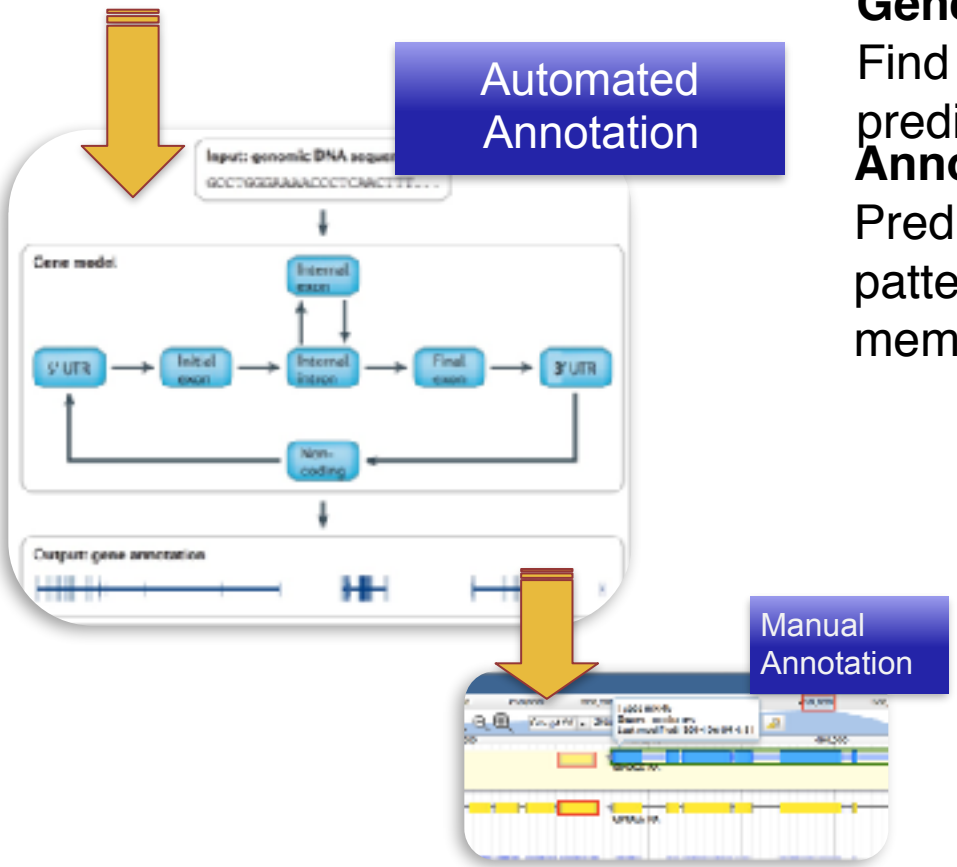
Apollo (used to be called WebApollo)



- GMOD's genome annotation editor
- Add and refine annotations.
- Based on JBrowse
- Multiple simultaneous users
- Keep track of evidence, curator
- Used in several community annotation efforts

Apollo

Automated Identification is not Perfect



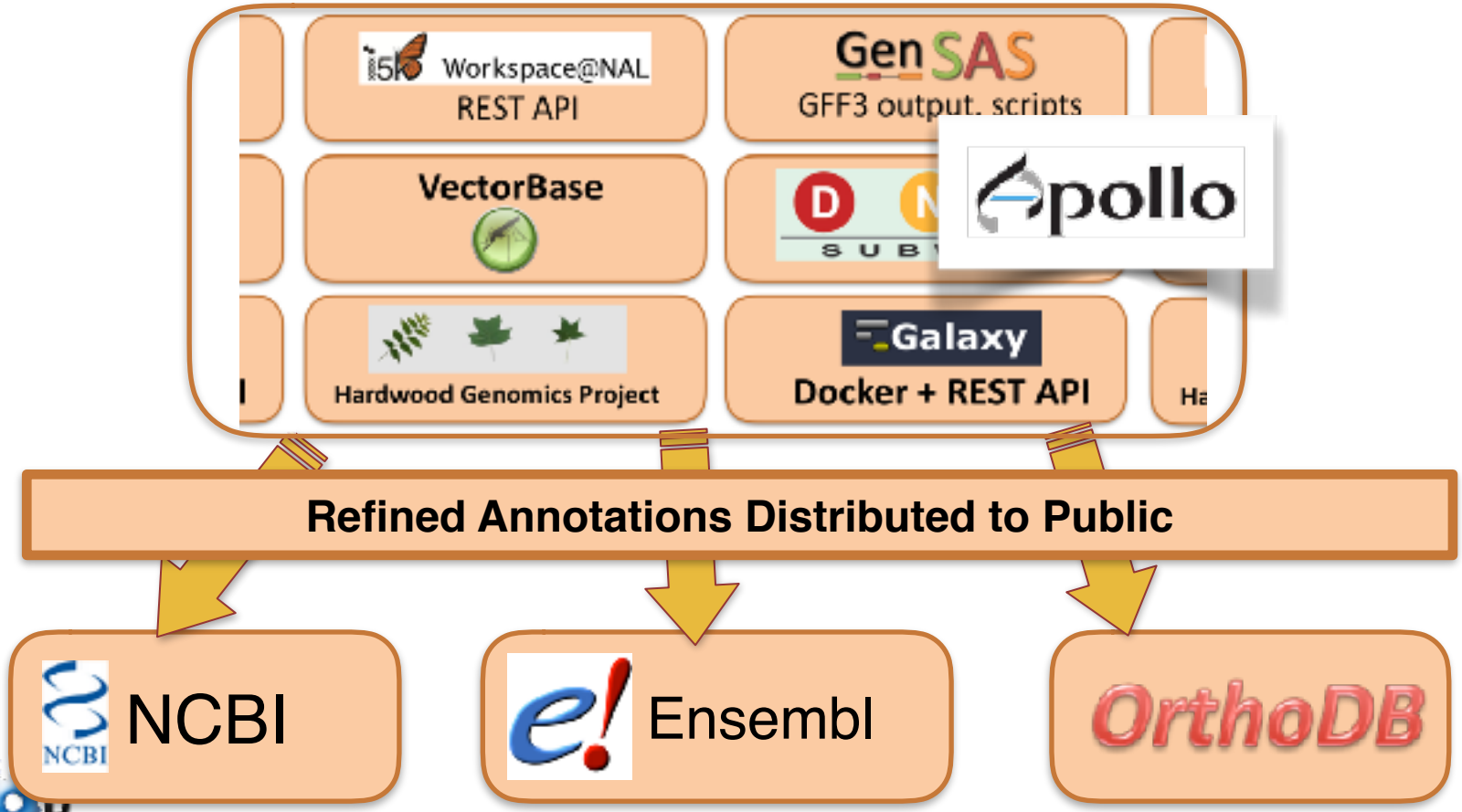
Generation of Gene Models
Find ORFs, multiple rounds of gene prediction

Annotation of Gene Models
Predicting function, expression patterns, metabolic network memberships

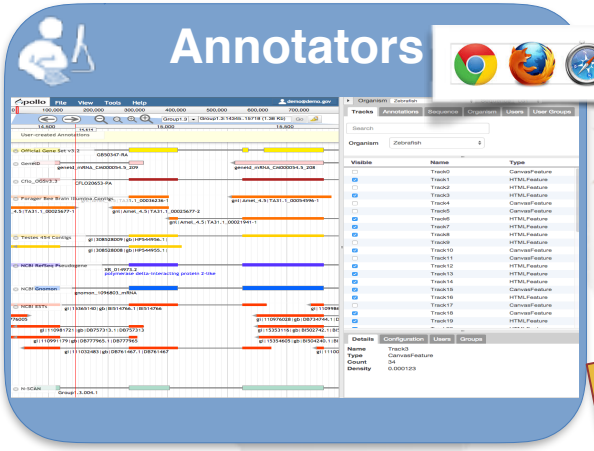
- Assembly errors can cause fragmented annotations
- Limited coverage makes precise identification difficult

Apollo: Used to Produce High Quality Annotations

- Over 100 organizations use Apollo
- Multiple genomes and labs per server



Apollo is a Tool for Collaborative Annotation



- Web-based Editor
- Visual feedback
- Real-time collaborative
- JBrowse genomic browser

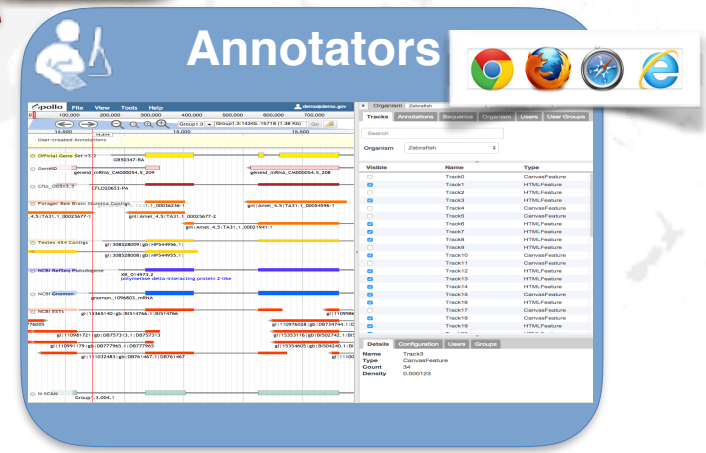


Photo Credits: i5K; Alex Wild at http://www.alexanderwild.com/: leaf cutter ant, ensign wasp; Leo Bukeboom: *Nasonia vitripennis* jewel wasp; Wikimedia Commons: *Apis mellifera* honey bee; Mike MacNeil USDA/ARS Fort Keogh LARRL: *Bos taurus* cow.

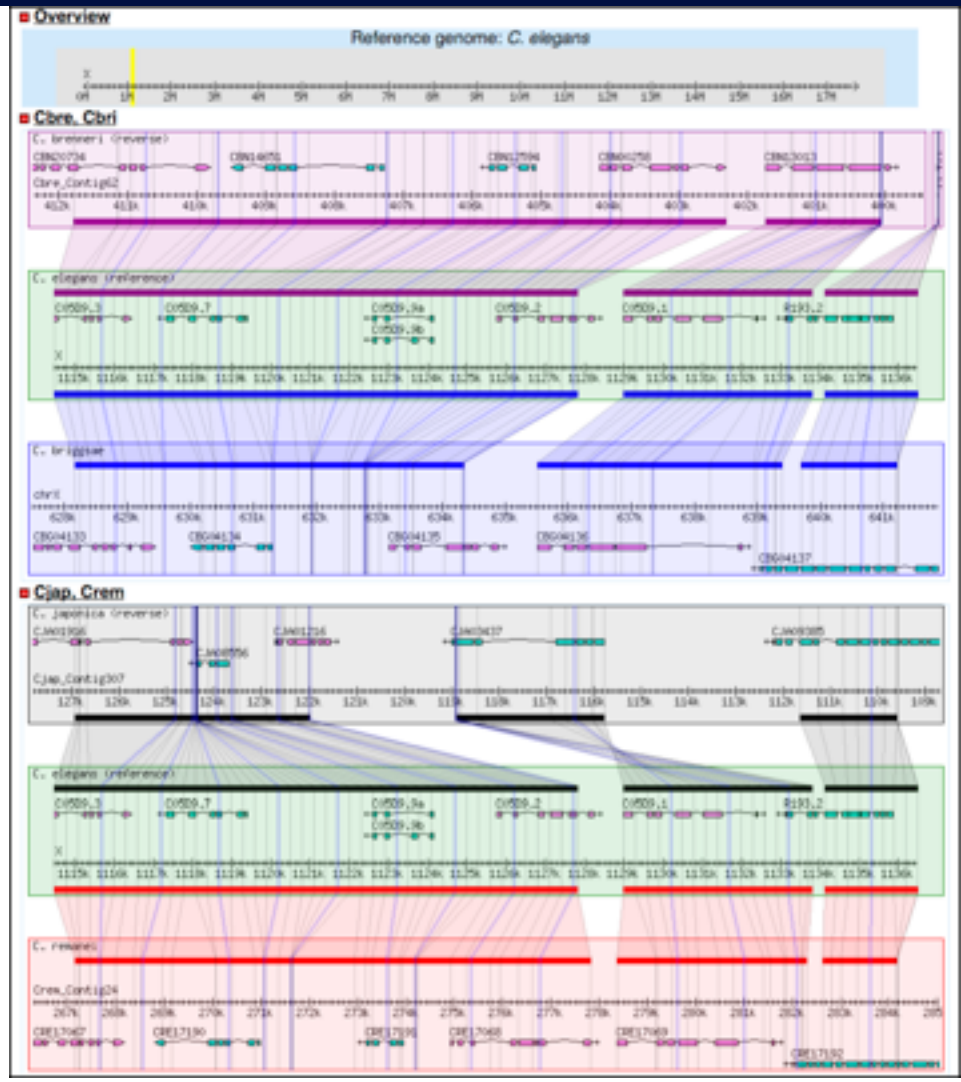
Apollo Resources

Home Page	http://apollo.berkeleybop.org/
Documentation	http://genomearchitect.github.io/documentation/
Demo	http://genomearchitect.github.io/demo/
Mailing List	apollo@lists.lbl.gov

Apollo

GBrowse_syn

- GBrowse based comparative genomics viewer
- Shows a reference sequence compared to 2 or more others
- Can also show any GBrowse-based annotations

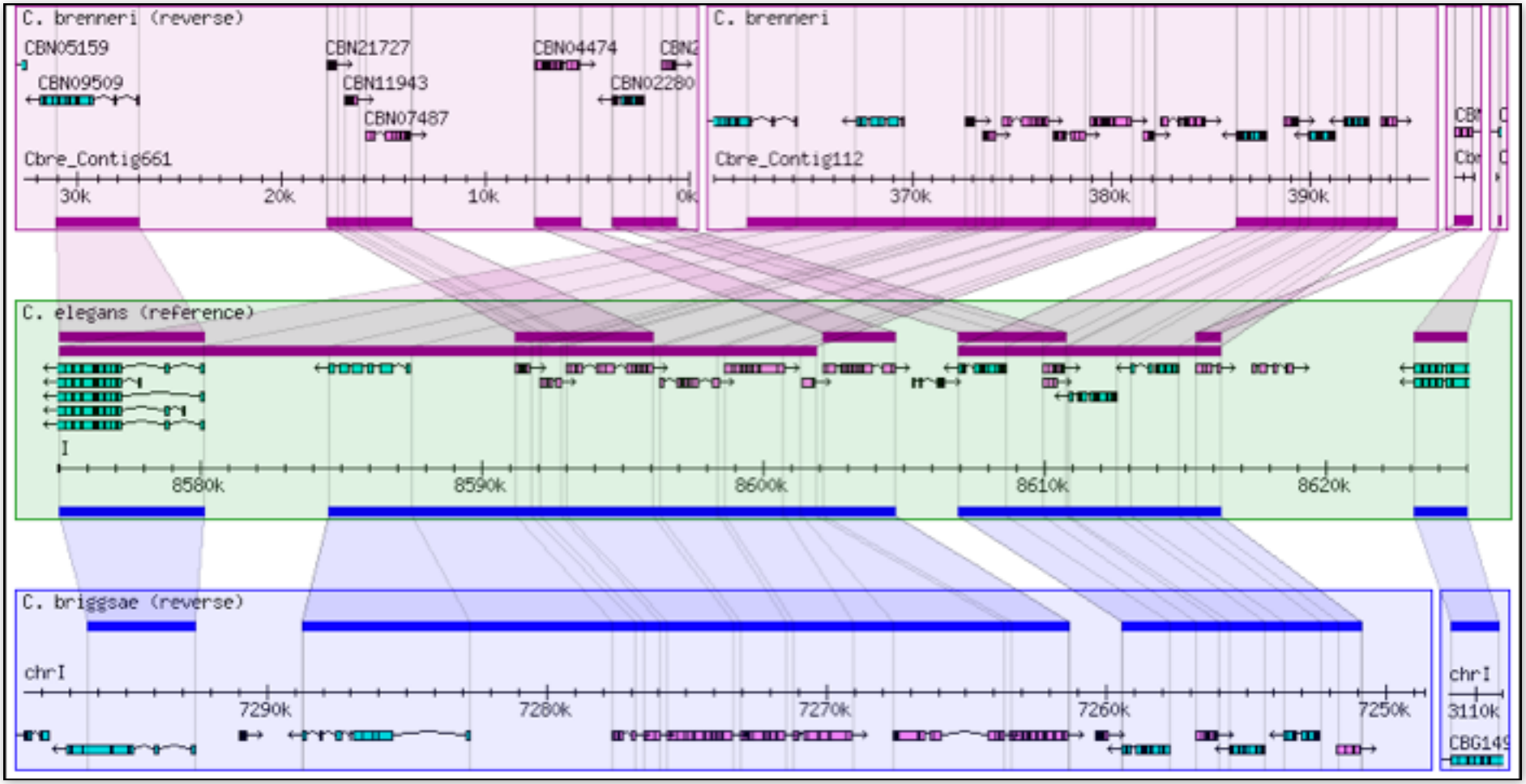


Example comparing *C. elegans* to 4 other species at WormBase

GBrowse syn

Sheldon McKay, University of Arizona

GBrowse_syn



Syntenic blocks do not have to be colinear
Can also show duplications

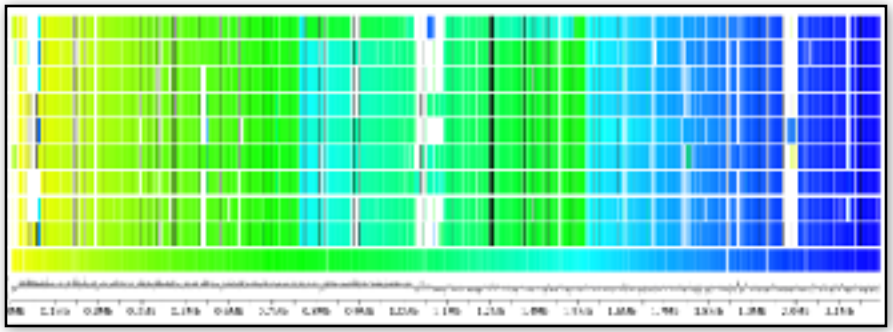
Sheldon McKay, OICR

GBrowse_syn Resources

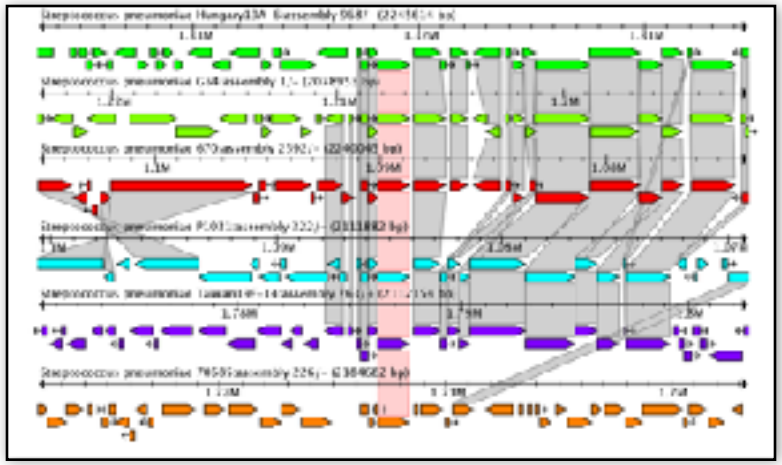
Home Page	http://gmod.org/wiki/GBrowse_syn
Tutorial	http://gmod.org/wiki/GBrowse_syn_Tutorial
User Help	http://gmod.org/wiki/GBrowse_syn_Help
Configuration	http://gmod.org/wiki/GBrowse_syn_Configuration
Example	http://www.wormbase.org/cgi-bin/gbrowse_syn/
Mailing List	https://lists.sourceforge.net/lists/listinfo/gmod-gbrowse

SynView and Sybil

Sybil

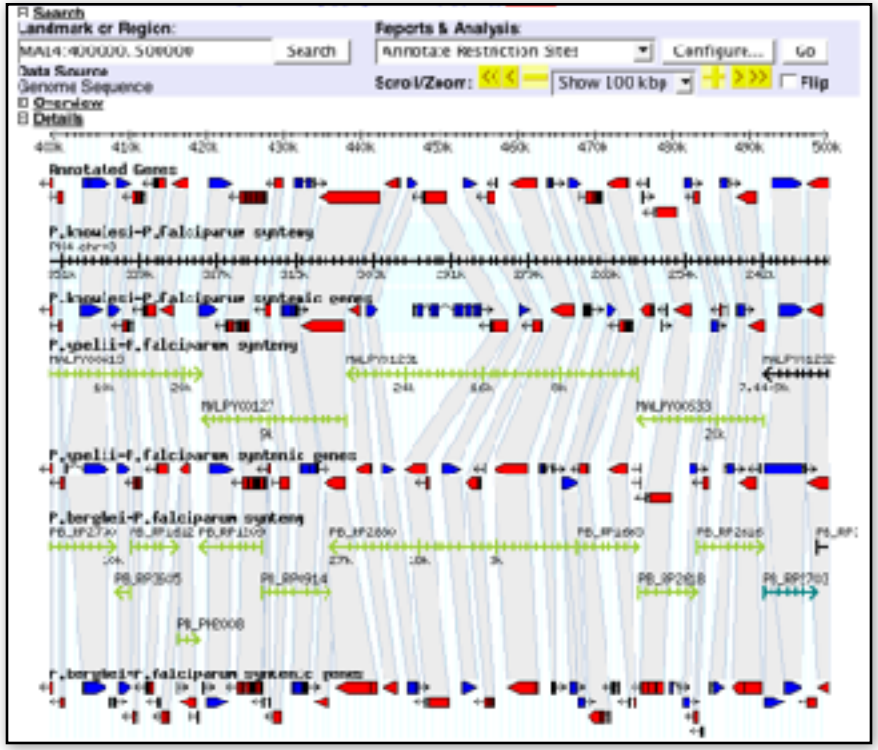


Whole Genome Gradient Display



Cluster Report

SynView



Sybil: Methods and Software for Multiple Genome Comparison and Visualization. Crabtree, *et al.*; in Gene Function Analysis, ed. by Michael F. Ochs (2007)

SynView: a GBrowse-compatible approach to visualizing comparative genome data. Haiming Wang, *et al.*; in Bioinformatics 22 (18)

GBrowse_syn or Sybil or SynView?

GBrowse_syn
Scalable (sort of)
Familiar interface
Extensive documentation
Growing user community

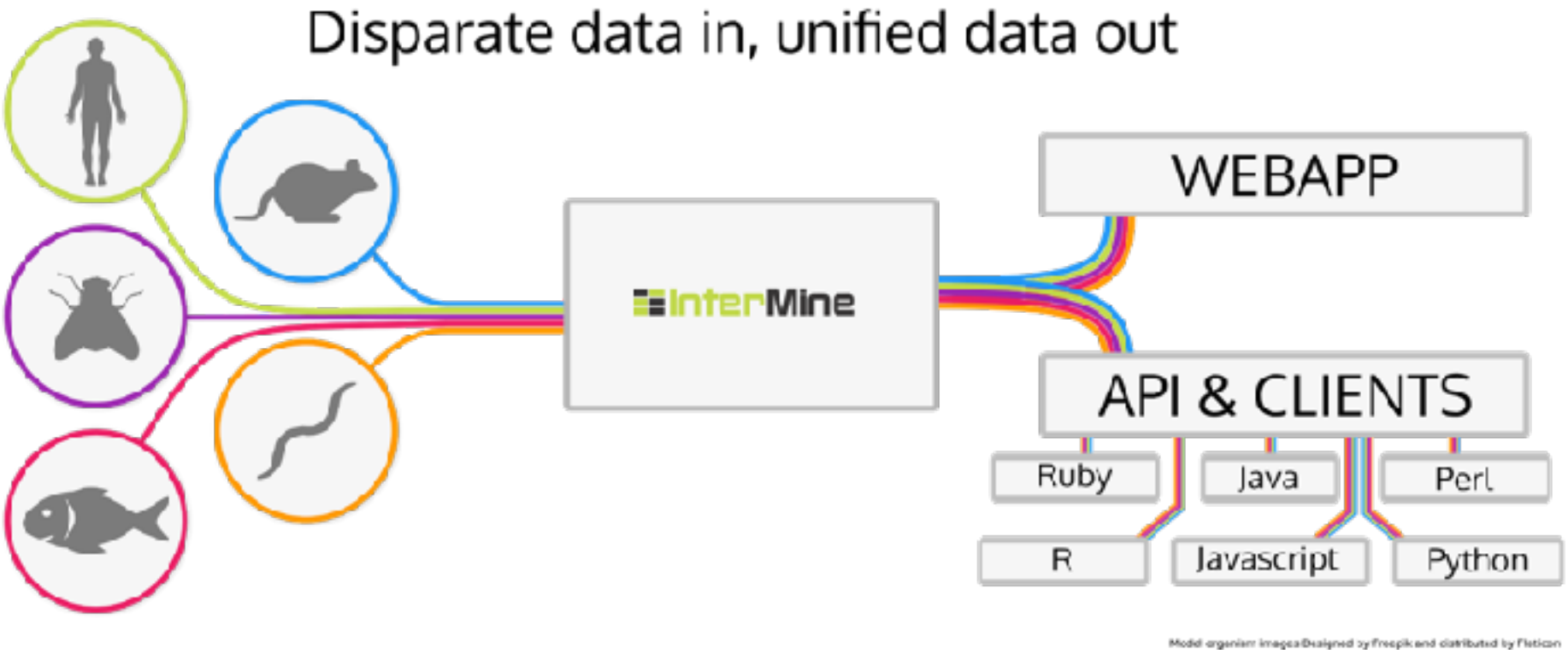
SynView
Scalable
Runs inside GBrowse 1

Sybil
Scalable
Whole genome and
other unique visualizations
Built on Chado

BioMart and InterMine

- Chado well-suited for setting up organism databases that have
  - Easy to use query interface to support common types of questions
  - Unified, coherent presentation of information
- BioMart and InterMine
  - Allow users to ask complex queries on all data
  - At the expense of having to do more work

InterMine: What is it?



Who uses InterMine

Over 30 installations, mostly at MODs, like FlyMine, YeastMine, WormMine, Wheat3BMine.

Others as well though, like TargetMine (drug discovery) and Shaare (gene candidate prioritization).

What do they use it for:

1. Genomic
2. Pathways
3. Interactions (complex and binary)
4. Protein structures
5. GO and other ontologies (Mammalian phenotype, etc)
6. Protein domains
7. Variation
8. Expression and regulation
9. Lots more ...

What can you do with InterMine

1. Keyword search
2. Query results
    1. Column summaries
3. List Analysis
    1. Visualizations - heat maps, expression.
    2. Enrichment
4. Template queries - quick forms to make for searches that your users do often
5. My account

6. All data is integrated, fast performance

GFF3

- The common file format of GMOD for genomic annotation
- Tab delimited, 9 column format
- Supported by Chado, GBrowse, JBrowse, CMap, Apollo, InterMine, BioMart, Galaxy, ….

http://gmod.org/wiki/GFF3

GMOD.org

A wiki, of course. GMOD.org is the hub for all things related to the project:

- Documentation
- News
- Links
- Calendar
- Tutorials
- HOWTOs
- Glossary
- Overview
- Talks/Posters
- Mailing Lists
- …

Mailing Lists

- Several project and topic based lists
- Many component-specific lists
- Mailing lists are very active
- Nabble archive of all lists

http://gmod.org/wiki/GMOD_Mailing_Lists

Acknowledgements

Literally, too many to count (OK, that was figurative, but it's really a lot!)

Each of these projects has a group of people that contribute code or testing or feedback. Actually counting them up would be too hard.

Thanks, and now lets look at some of the websites I referred to earlier…