Genome Sequence Annotation

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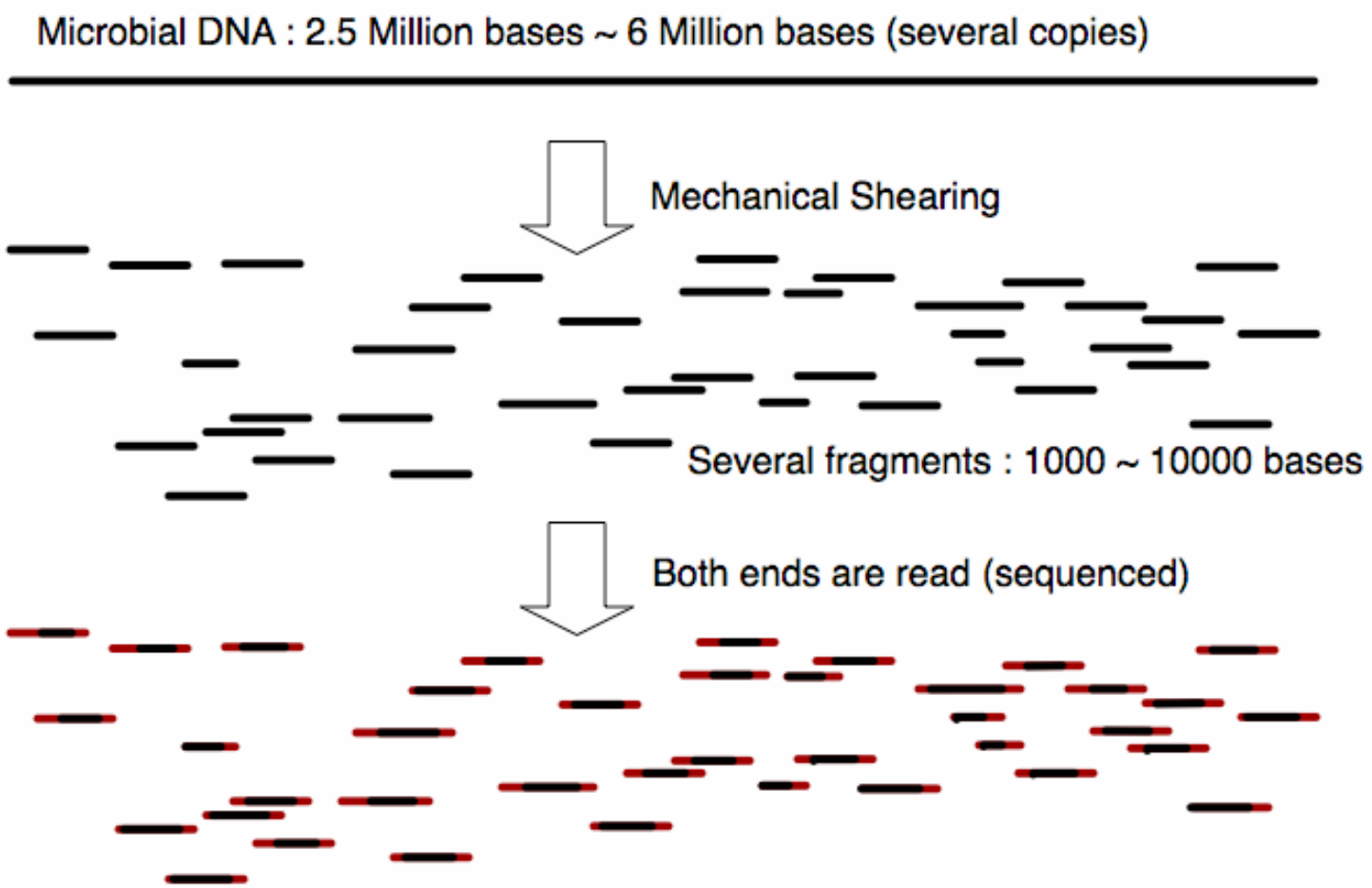
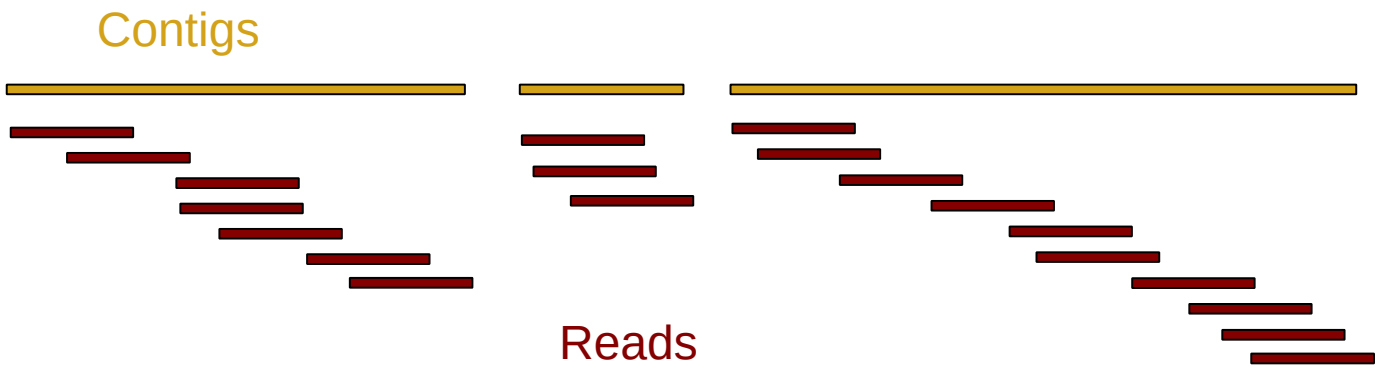
The input: genome assembly

- Sanger Method.
- Technology limitation on lengths.
- Walking primers.
- Shot-gun sequencing.

Shot-gun sequencing

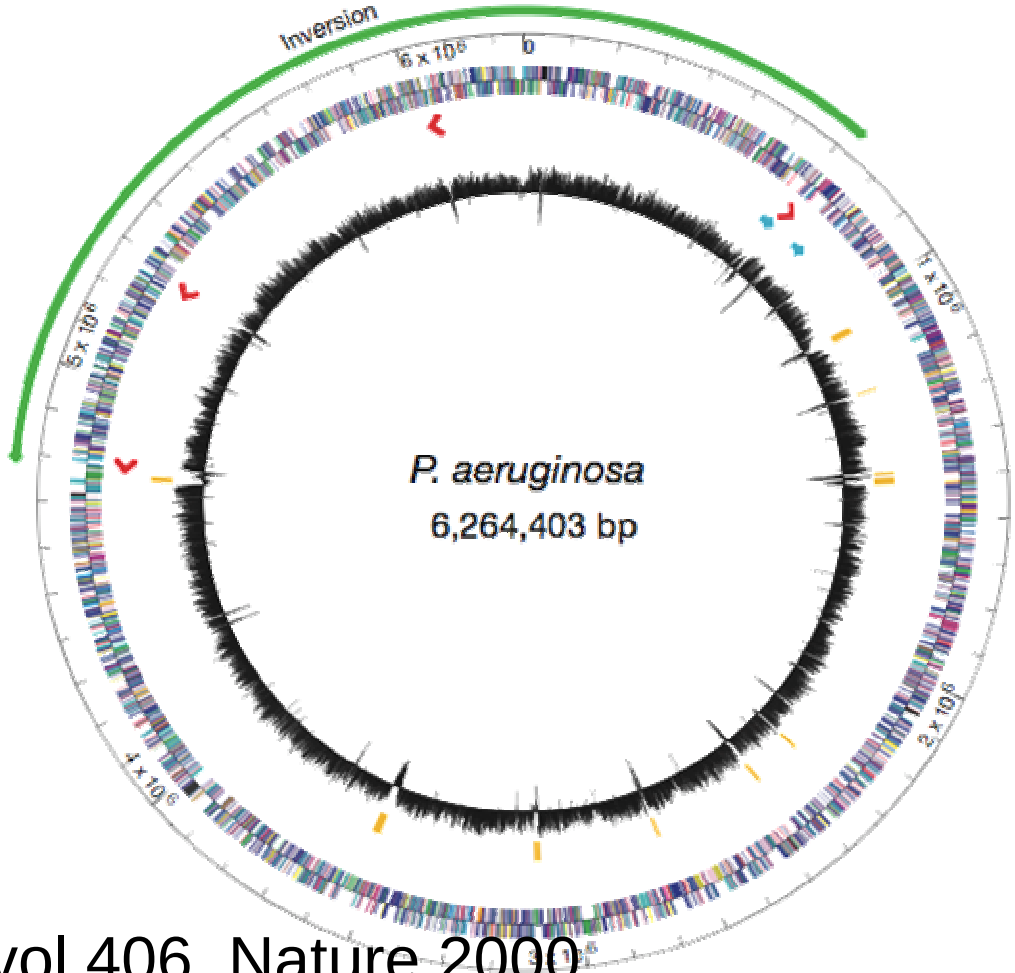


Assembly

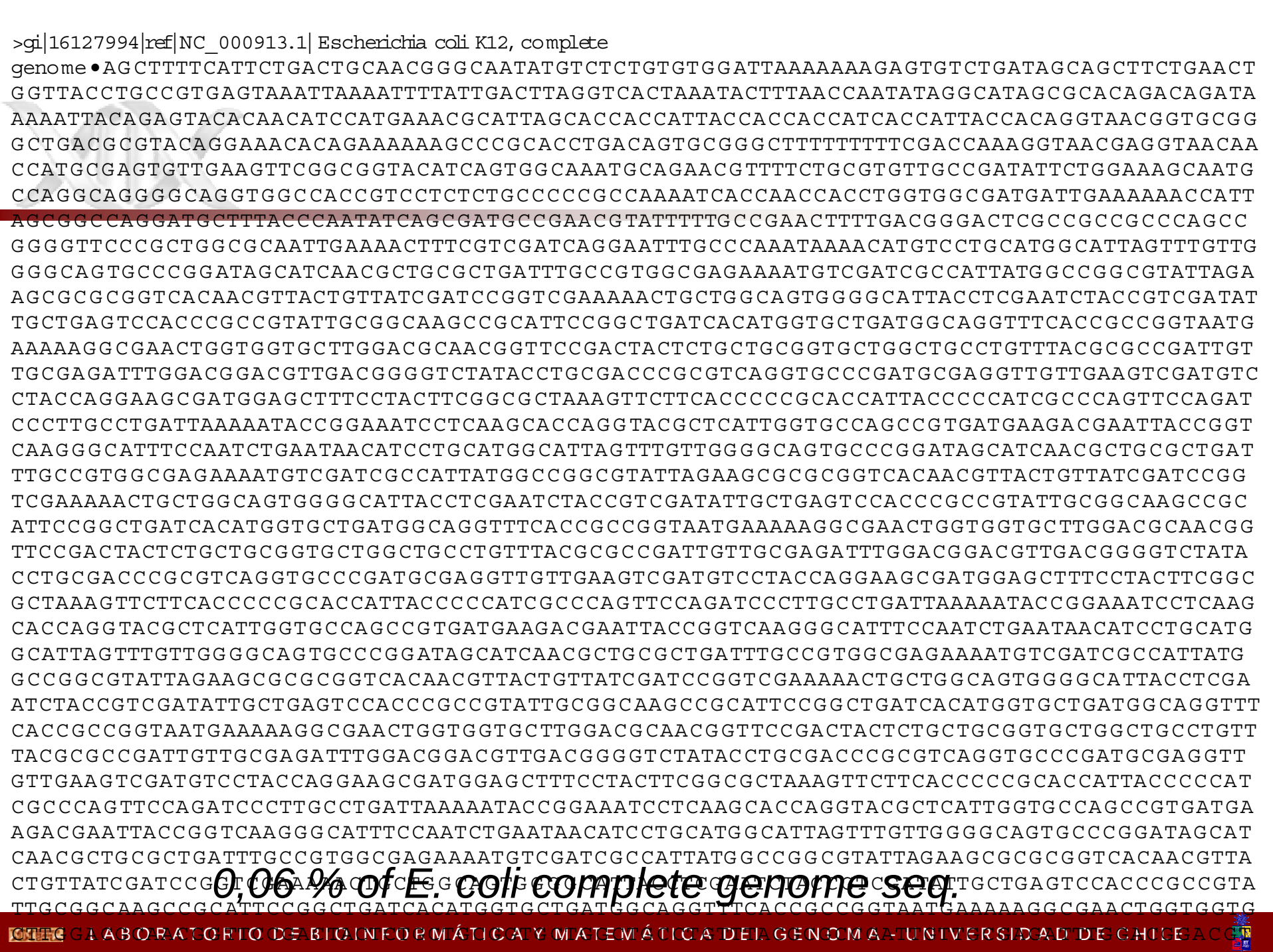


ACTTAGCGC...CTAGCTATCTATCTACTA...GTCA

Circular Genome



Stover et al, vol 406, Nature 2000

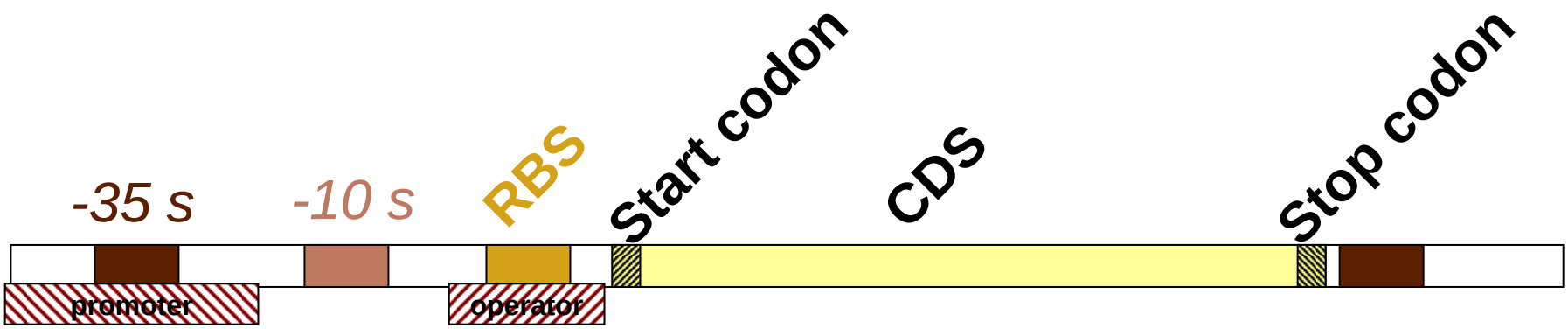


0,06 % of E. coli complete genome seq.

Sequence Features

- CDSs and accompanying signals.
- RNA Products
  - rRNA (16S, 23S).
  - tRNAs
  - ssRNAs
- Regulatory Binding Sites
- Insertion Sites
- Other Signals (especially in Eukaryonts)

Coding Sequences & Co.

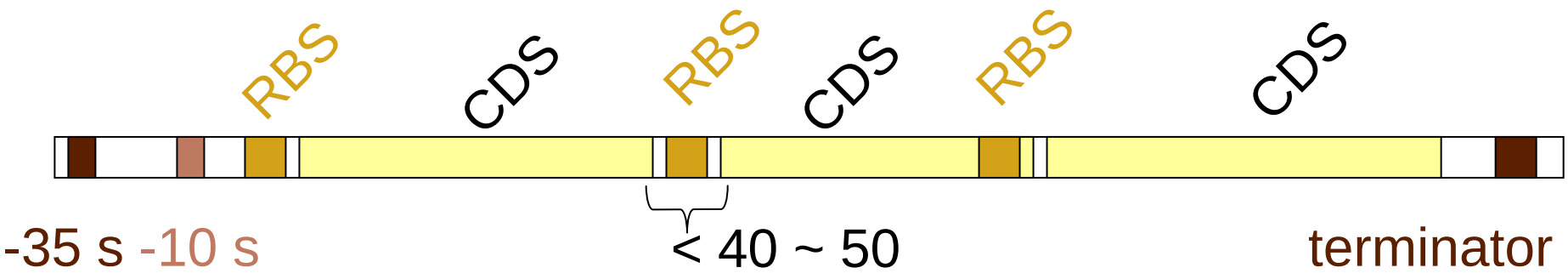


Transcription

Translation

"A CDS is a Coding ORF,
Not all ORFs are CDSs."

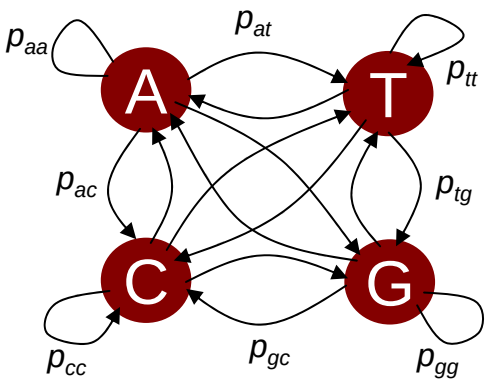
Related CDSs: Operons



Polycistronic transcripts; Operons.

Main approaches

- Automatic Marking:
  - Intrinsic: sequence statistics.
  - Extrinsic: alignment-based.
- Manual revision.



$P(\text{ATCGA}) = \pi_a p_{at} p_{tc} p_{cg} p_{ga}$

```
 Score =  907 bits (2344), Expect = 0.0
 Identities = 462/478 (96%), Positives = 462/478 (96%)

Query: 99  VPGLGPKRVKALWHELDVETVDQLTRAAREGRIRSIPGFGEKTEARILEALQAQIAAVPR 158
       VPGLGPKRVKALWHELDVETVDQLTRAAREGRIRSIPGFGEKTEARILEALQAQIAAVPR
Sbjct: 1   VPGLGPKRVKALWHELDVETVDQLTRAAREGRIRSIPGFGEKTEARILEALQAQIAAVPR 60

Query: 159 FPIXXXXXXXXXLVRYLQNVPGVRRVVVAGSFRRGRDTVGDLD.....................
       FPI     LVRYLQNVPGVRRVVVAGSFRRGRDTVGDLD.................
Sbjct: 61  FPIAVAAPYAAALVRYLQNVPGVRRVVVAGSFRRGRDTVGDLD.....................


.....................LIGSREPMDVDMPRIIRHARERGCFLEIDAQPERLDLVDIHARTA 518
       .............LIGSREPMDVDMPRIIRHARERGCFLEIDAQPERLDLVDIHARTA
.....................LIGSREPMDVDMPRIIRHARERGCFLEIDAQPERLDLVDIHARTA 420

Query: 519 KEEGVLLAVNSDAHSIHDFDNLRFGLQQAQRGWLEMKDVLNTRTLEELRPLLAATMSR 576
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Sbjct: 421 KEEGVLLAVNSDAHSIHDFDNLRFGLQQAQRGWLEMKDVLNTRTLEELRPLLAATMSR 478
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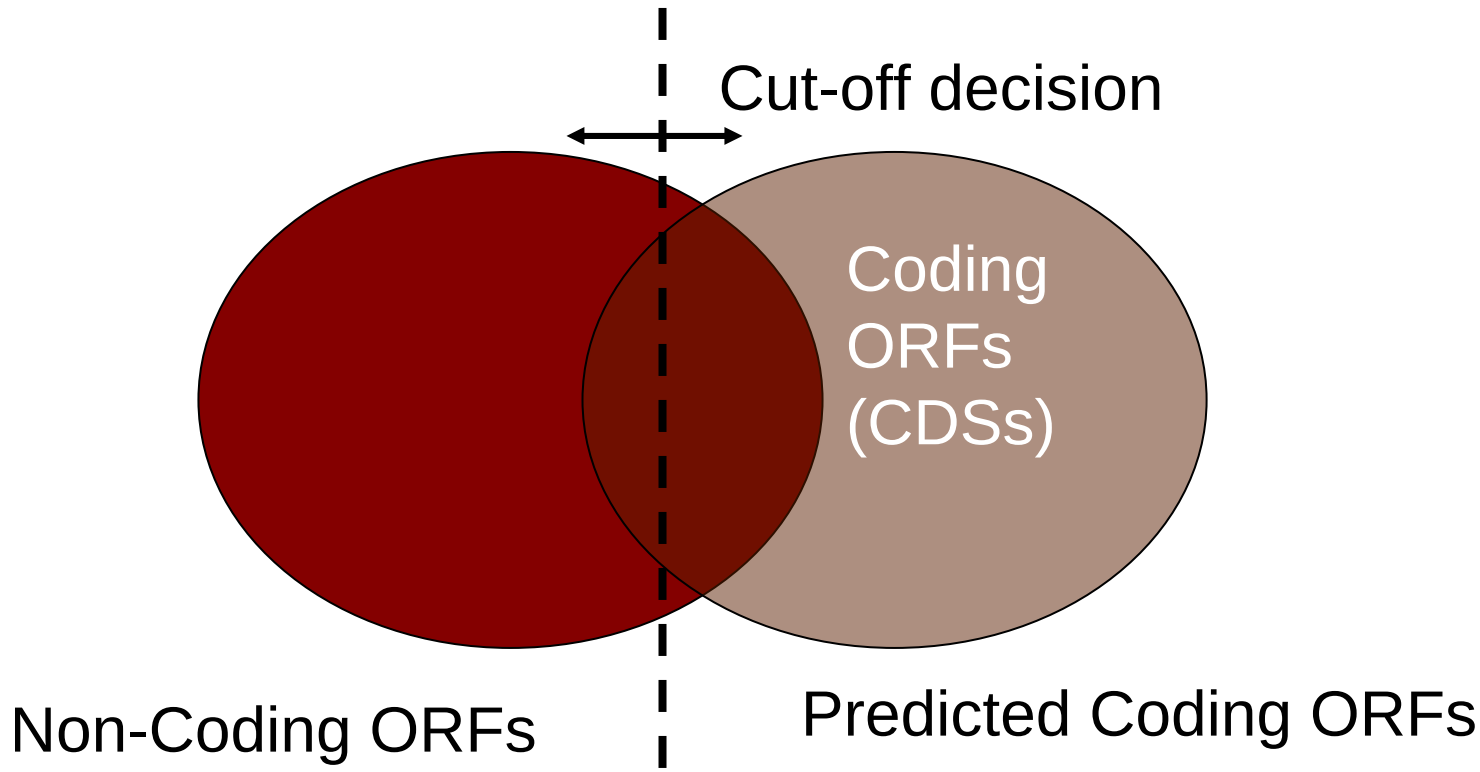
Extrinsic Methods (CDSs)

- Search against gene or protein DBs.
  - Sequence Alignments (Blasts, etc)
  - Position weighted matrices (Pfam, etc)

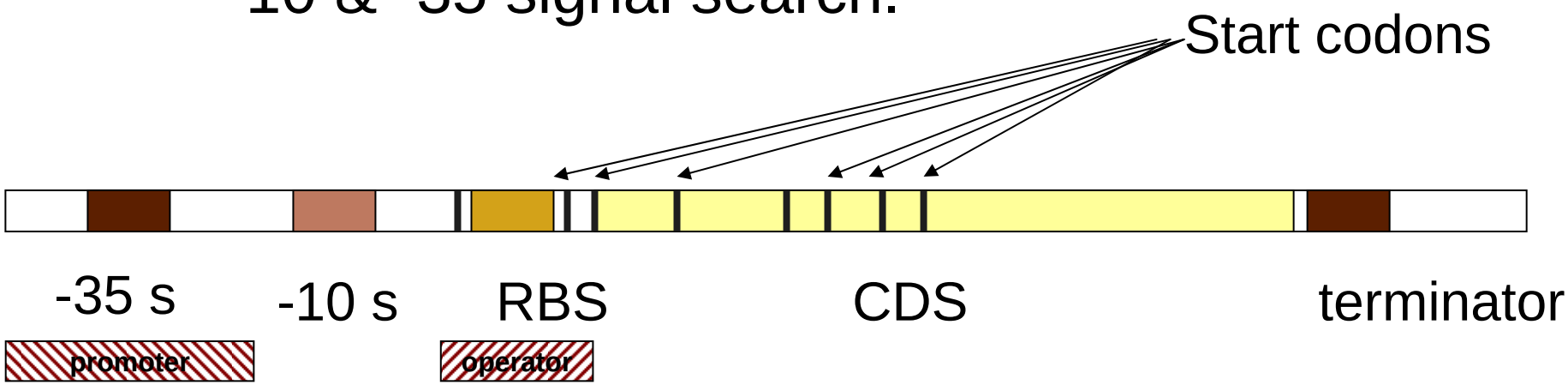
Class overlap



Glimmer: Up to 18% false pos.

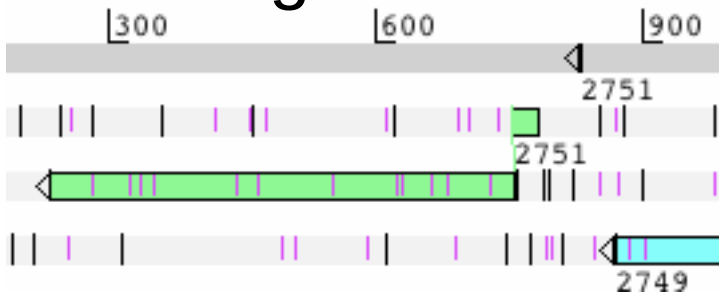
Start codon issue

- Difficult problem.
- Integrate up-stream signal search.
  - RBS.
  - -10 & -35 signal search.



Frame shift issue

- One gene, more than one reading frame.
- Manual Joining.
- Sequence correction needed.
  - Compare against sequence quality.
  - Re-sequence some short tags.



CDS Marking Software

- Glimmer (1997 - 2004)
  - Variable Order Markov models.
- Critica (1999 - 2000)
  - Codon statistics of known coding sequences.
- ProKoV (2002)
  - Markov models/Bayes

CDS Marking Software

- ZCurve (2003)
  - Sequence transformation.
- AMIGene (2003)
  - Prokov, heuristic to select CDSs from ORFs.
- Priam (2003)
  - Position-weighted matrix from known E.C. classes.
- FrameD (2003)
  - DAG, designed for frame shifts and overlaps.

Other Seq. Features Markers

- TRNAscan SE (2000)
- RBSfinder (2001)
  - Markov Model for consensus RBSs.
- Search for RNAs(1999)
- GSFinder (2004)
  - Z-Curve method.
- TermIt (1990)
  - Single cistron or polycistron statistics.
- TransTerm (2000)
  - Whole genome statistics.


>gi|16127994|ref|NC_000913.1| Escherichia coli K12, complete genome
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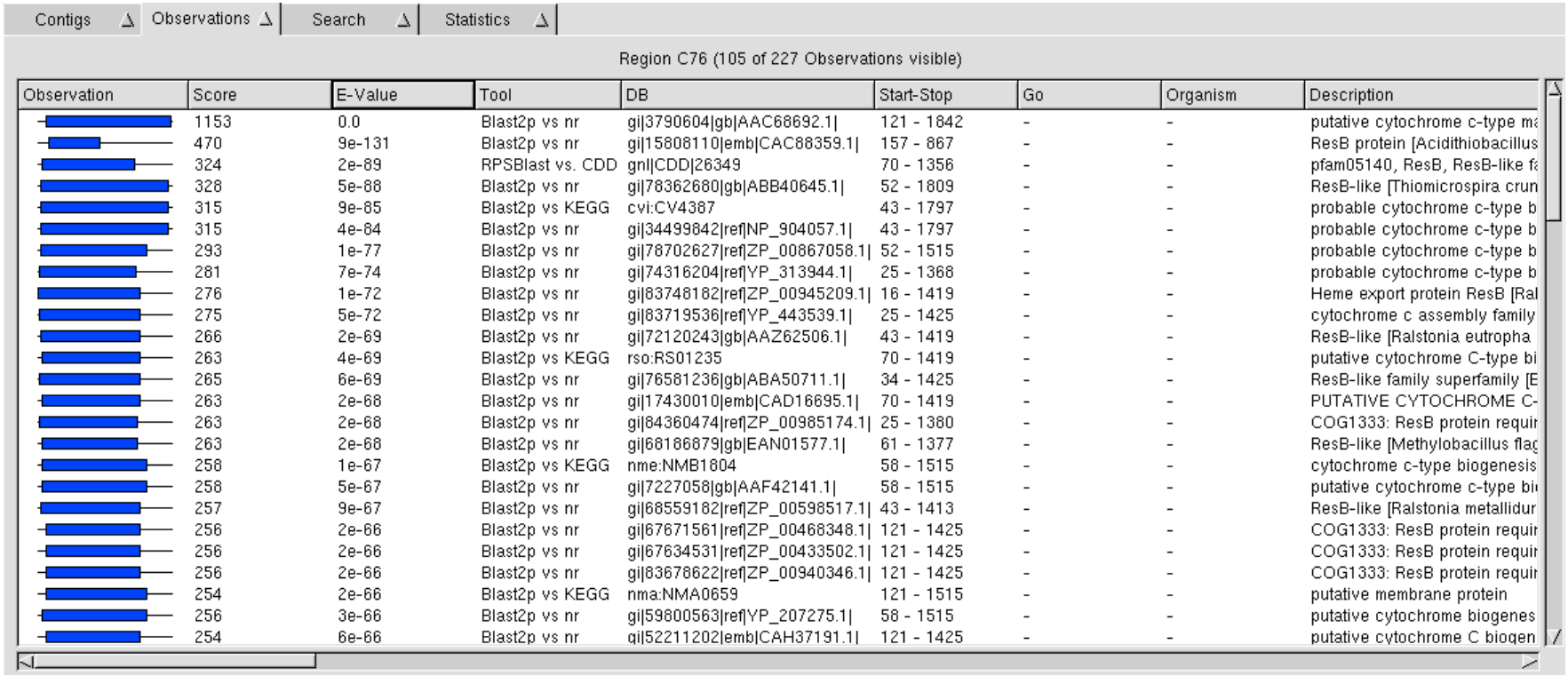
TCAC
0,06 % of E. coli complete genome seq.
LABORATORIO DE BIOINFORMÁTICA Y MATEMÁTICA DE GENOMAS UNIVERSIDAD DE CHILE

CDSs to Functions

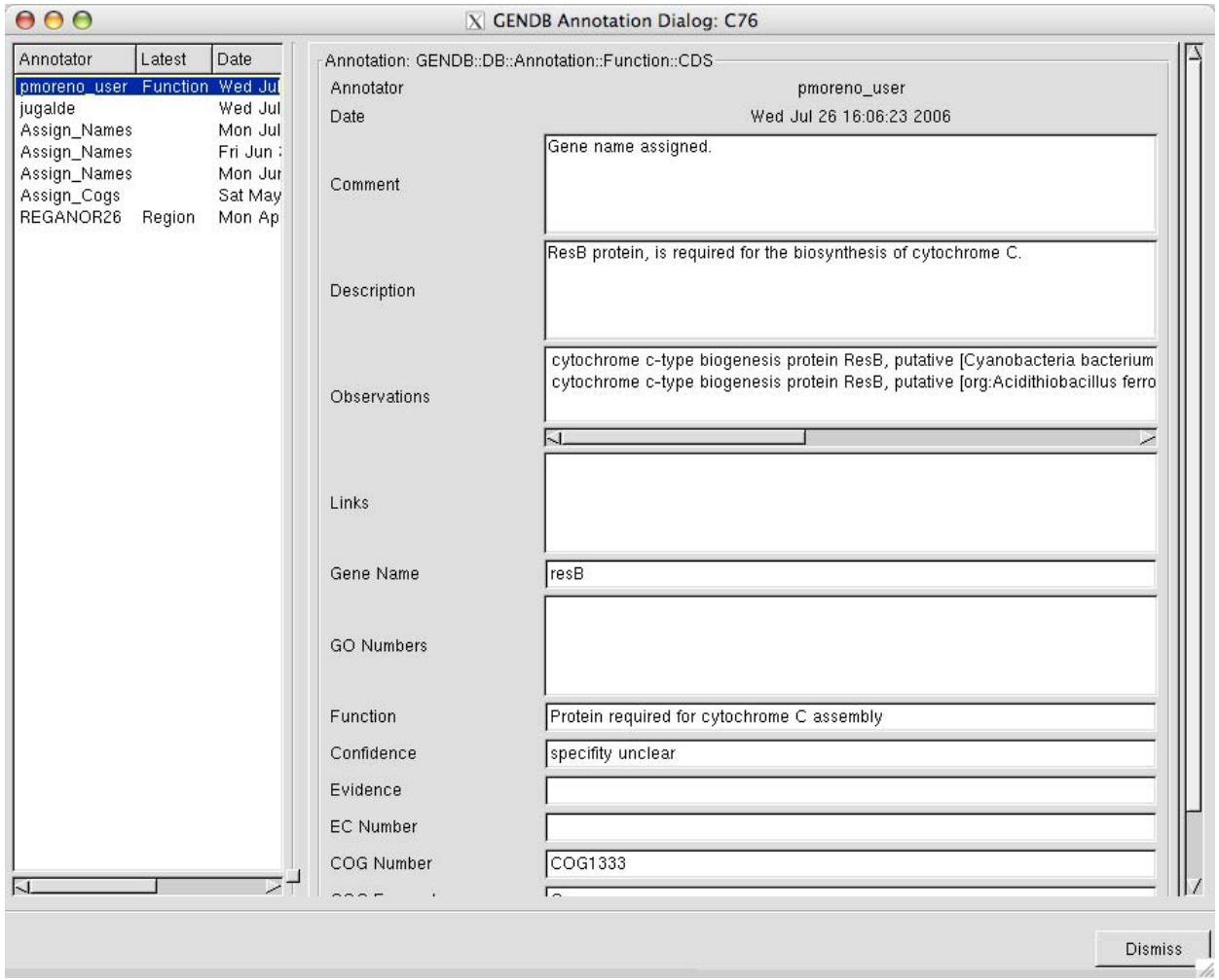
- “Black” CDSs say nothing
- Search Tools
  - Blast (t-n, -x, -p)
  - Emboss
  - InterProScan (pfam, hmmer)
- Sequence Databases & Controlled Vocabularies
  - COG, KOG.
  - NCBI, Swiss-Prot, etc.
  - GO, EC.
- Assignment Method!!

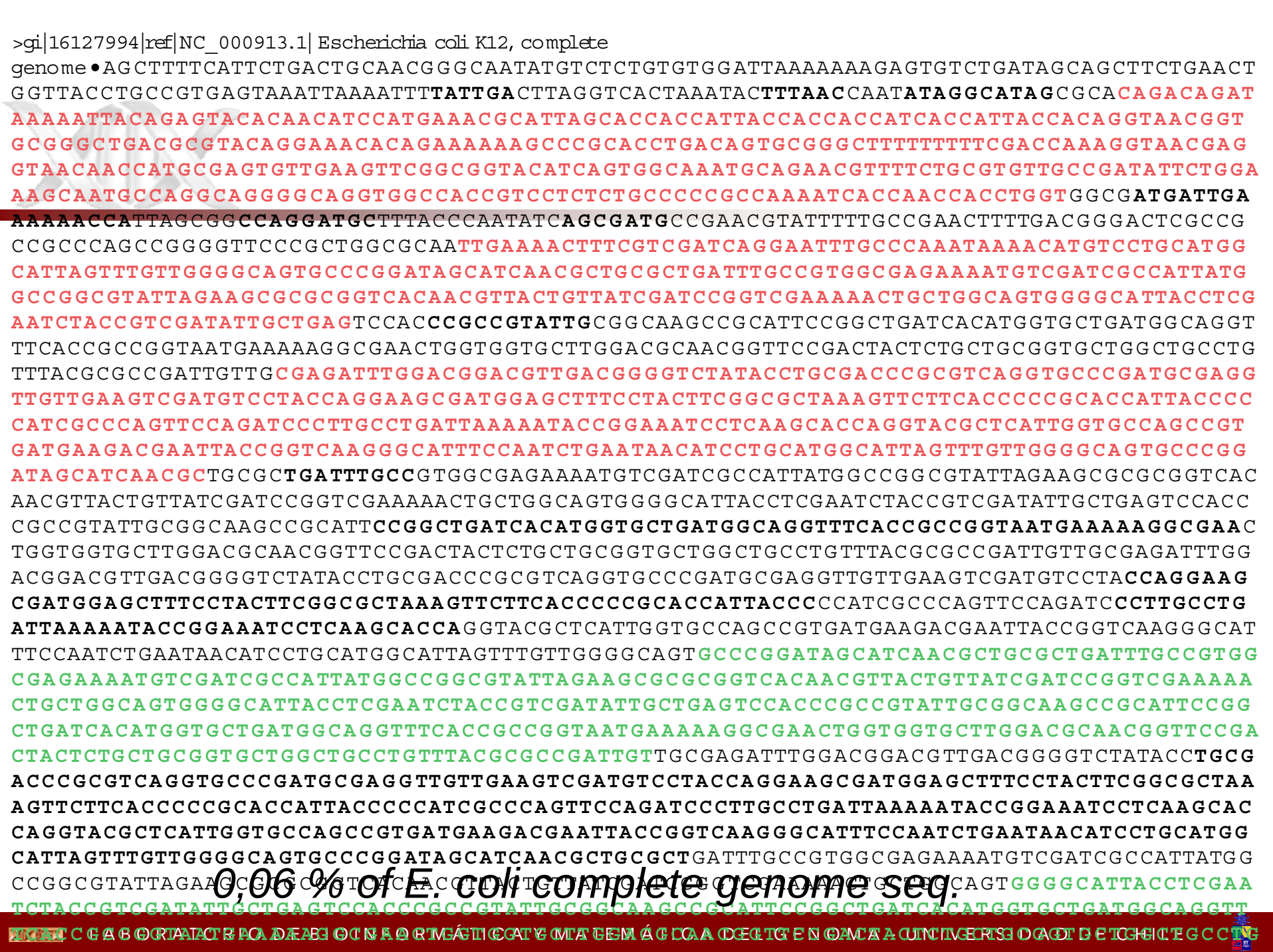
Observations



Observation	Score	E-Value	Tool	DB	Start-Stop	Go	Organism	Description
	1153	0.0	Blast2p vs nr	gi|3790604|gb|AAC68692.1|	121 - 1842	-	-	putative cytochrome c-type ma
	470	9e-131	Blast2p vs nr	gi|15808110|emb|CAC88359.1|	157 - 867	-	-	ResB protein [Acidithiobacillus
	324	2e-89	RPSBlast vs. CDD	gnl|CDD|26349	70 - 1356	-	-	pfam05140, ResB, ResB-like fa
	328	5e-88	Blast2p vs nr	gi|78362680|gb|ABB40645.1|	52 - 1809	-	-	ResB-like [Thiomicrospira crun
	315	9e-85	Blast2p vs KEGG	cvi:CV4387	43 - 1797	-	-	probable cytochrome c-type b
	315	4e-84	Blast2p vs nr	gi|34499842|ref|NP_904057.1|	43 - 1797	-	-	probable cytochrome c-type b
	293	1e-77	Blast2p vs nr	gi|78702627|ref|ZP_00867058.1|	52 - 1515	-	-	probable cytochrome c-type b
	281	7e-74	Blast2p vs nr	gi|74316204|ref|YP_313944.1|	25 - 1368	-	-	probable cytochrome c-type b
	276	1e-72	Blast2p vs nr	gi|83748182|ref|ZP_00945209.1|	16 - 1419	-	-	Heme export protein ResB [Ral
	275	5e-72	Blast2p vs nr	gi|83719536|ref|YP_443539.1|	25 - 1425	-	-	cytochrome c assembly family
	266	2e-69	Blast2p vs nr	gi|72120243|gb|AAZ62506.1|	43 - 1419	-	-	ResB-like [Ralstonia eutropha
	263	4e-69	Blast2p vs KEGG	rso:RS01235	70 - 1419	-	-	putative cytochrome C-type bi
	265	6e-69	Blast2p vs nr	gi|76581236|gb|ABA50711.1|	34 - 1425	-	-	ResB-like family superfamily [E
	263	2e-68	Blast2p vs nr	gi|17430010|emb|CAD16695.1|	70 - 1419	-	-	PUTATIVE CYTOCHROME C-
	263	2e-68	Blast2p vs nr	gi|84360474|ref|ZP_00985174.1|	25 - 1380	-	-	COG1333: ResB protein requir
	263	2e-68	Blast2p vs nr	gi|68186879|gb|EAN01577.1|	61 - 1377	-	-	ResB-like [Methylobacillus flag
	258	1e-67	Blast2p vs KEGG	nme:NMB1804	58 - 1515	-	-	cytochrome c-type biogenesis
	258	5e-67	Blast2p vs nr	gi|7227058|gb|AAF42141.1|	58 - 1515	-	-	putative cytochrome c-type bi
	257	9e-67	Blast2p vs nr	gi|68559182|ref|ZP_00598517.1|	43 - 1413	-	-	ResB-like [Ralstonia metallidur
	256	2e-66	Blast2p vs nr	gi|67671561|ref|ZP_00468348.1|	121 - 1425	-	-	COG1333: ResB protein requir
	256	2e-66	Blast2p vs nr	gi|67634531|ref|ZP_00433502.1|	121 - 1425	-	-	COG1333: ResB protein requir
	256	2e-66	Blast2p vs nr	gi|83678622|ref|ZP_00940346.1|	121 - 1425	-	-	COG1333: ResB protein requir
	254	2e-66	Blast2p vs KEGG	nma:NMA0659	121 - 1515	-	-	putative membrane protein
	256	3e-66	Blast2p vs nr	gi|59800563|ref|YP_207275.1|	58 - 1515	-	-	putative cytochrome biogenes
	254	6e-66	Blast2p vs nr	gi|52211202|emb|CAH37191.1|	121 - 1425	-	-	putative cytochrome C biogen

Annotations

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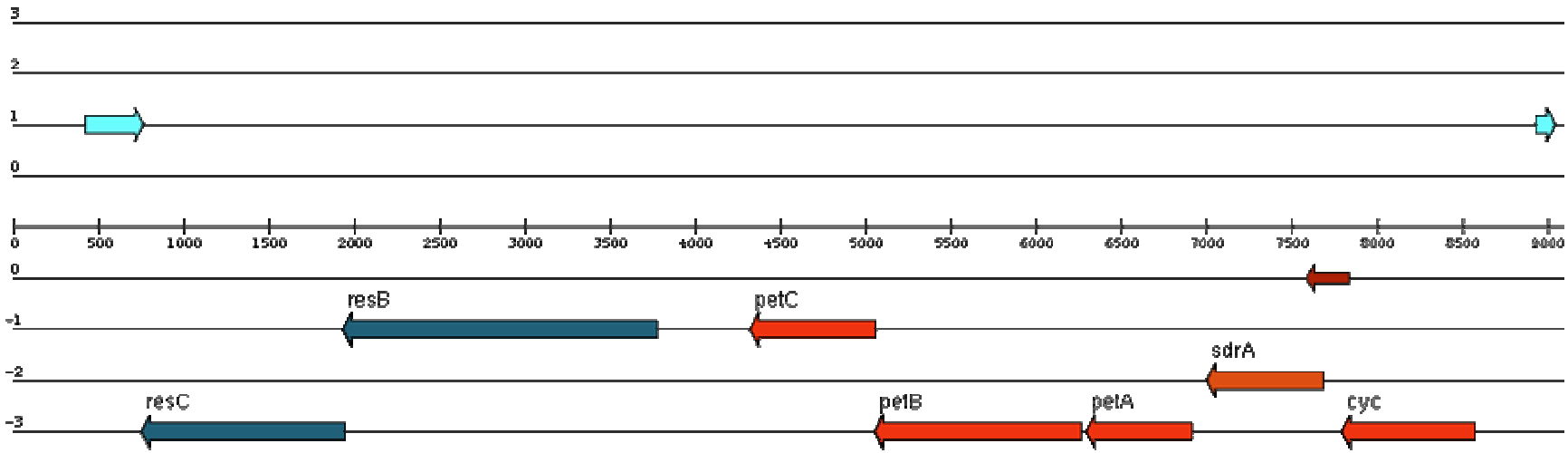
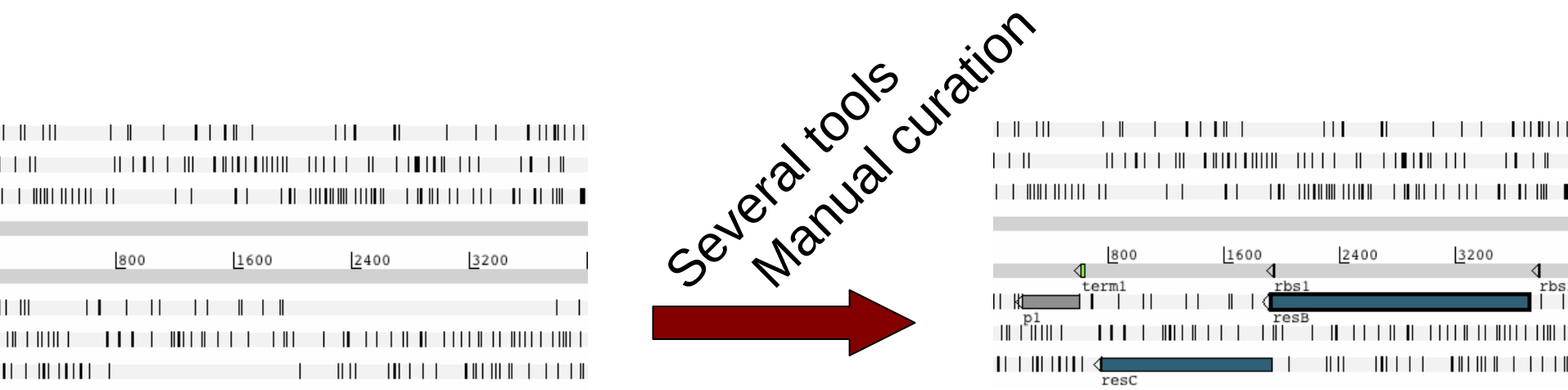
0,06 % of E. coli complete genome seq.

Real genome view



Environments & Pipelines

- Need to integrate several tools.
- Need to automate this integration.
- Avoid file storage, migrate data to a relational database.



Annotation Pipeline

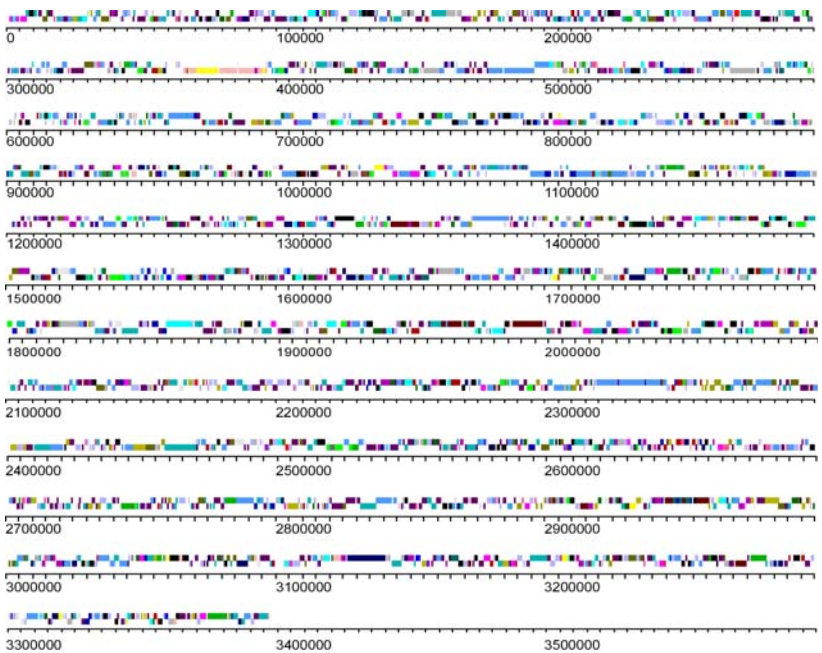
- Integrates several annotation tools.
- Perl, C++, Python plug-ins
- SQL Database backend
- Client-Server
- Grid Job Submission

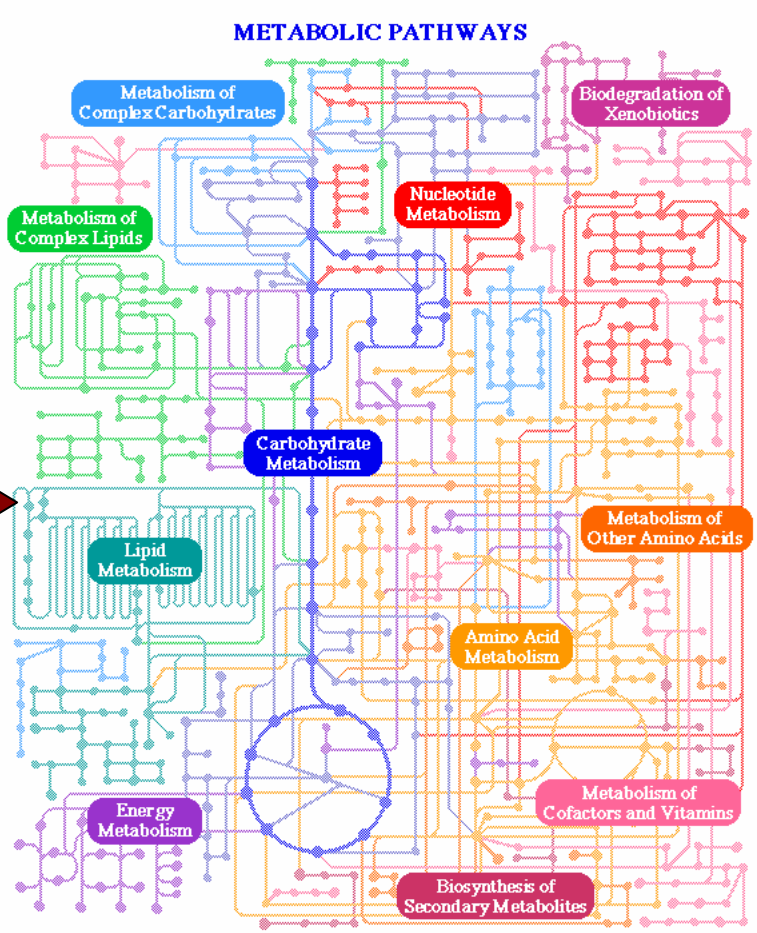
Systems Biology

Systems Biology

- *"Systems biology is an academic field that seeks to integrate high-throughput biological studies to understand how biological systems function. By studying the relationships and interactions between various parts of a biological system (e.g. metabolic pathways, organelles, cells, physiological systems, organisms etc.) it is hoped that eventually an understandable model of the whole system can be developed."* -Wikipedia

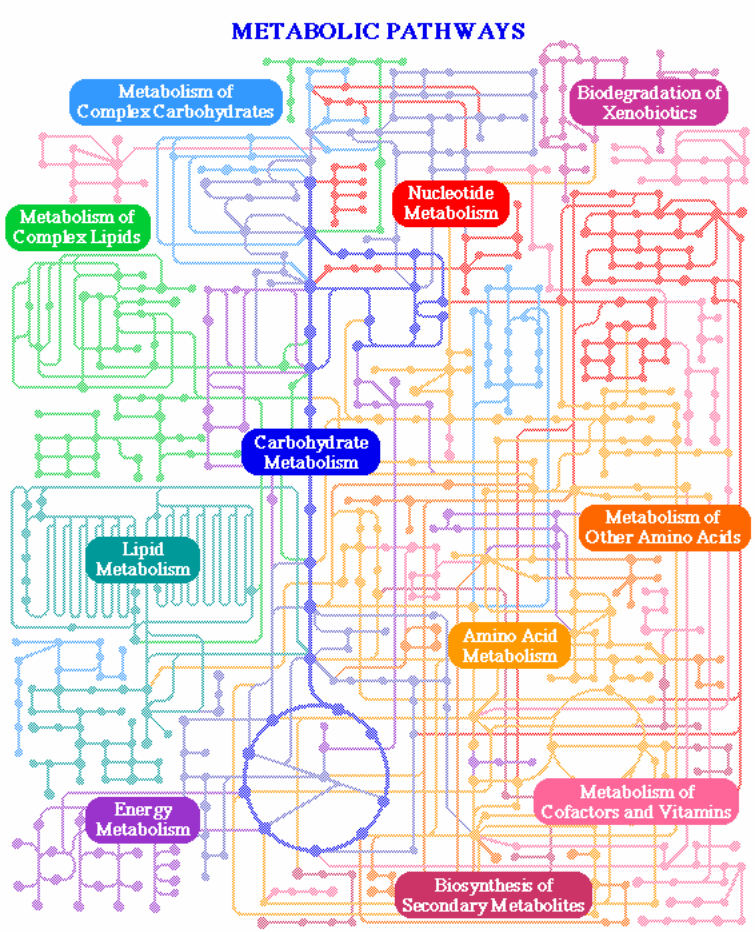
Gene Reg. & Metabolic Pathways





Populating the network

- Kinetics Data.
- Stationary Fluxes.
- Gene Expression.
- Protein-DNA Interactions.
- Physical constraints.
- *New pathways inferences.*



Simulating “the Cell”

- Dynamic.
- Stationary.
- As an Optimization LP problem.
- Parameter Estimation.