Kapitel 4: Genom-Datenbanken

- Nukleotidsequenz-Datenbanken
  - Ausgangsproblematik
  - Beispieldatenbanken
- Kartierungs-Datenbanken
  - Genomkarten
  - Beispieldatenbanken
- Genexpressions-Datenbanken
  - Ausgangsproblematik
  - Beispieldatenbanken
  - Projekt GeWare, Universität Leipzig (E. Rahm et al.): Data warehouse design and implementation to support gene expression analysis

Nukleotidsequenz: Rohdaten

- Daten über den Sequenzierprozess
  - Geräterohdaten (Spektren, Sequenzen)
  - Benutzte Programme
  - Labordaten (Maschinen, Personal, Datum, ...)
- NCBI Trace File Archive
- Viele Sequenzier-Center
  - Sanger
  - University of Washington
  - Celera
  - ...

Sequenzdaten

- Technische Herkunft: Wer, wann, wie, Methode, ...
- Biologische Herkunft: Clone, Organismus, Linie, ...
- Literaturreferenzen
- Fehlerraten
- Sequenz als Kerninformation
- Informationen (Features) zu Sequenzteilen
  - Location: Start -Ende, Genau -Ungenau
  - Key: CDS (Coding Sequence(s)) , Repeat, RNA-Strukturen, homologe Sequenzen, Marker, Exon/ Intron Boundaries, Funktion, Motiv, Polymorphismus, ...
  - Qualifier: Ergänzungen, z.B. kodiertes Protein, Regulationsmechanismen, ...

Nukleotidsequenz-Datenbanken: Beispiel-Datenbanken

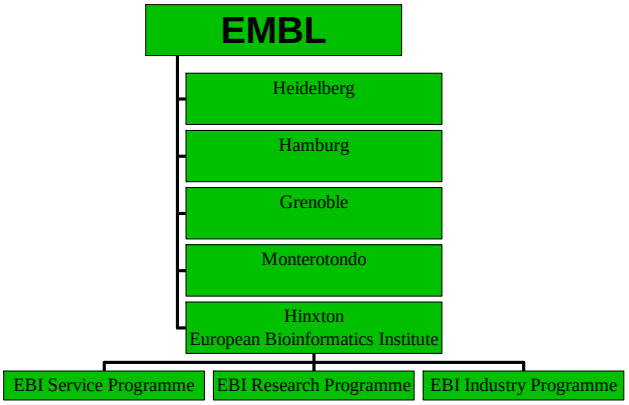
- European Molecular Biology Laboratory (EMBL) am European Bioinformatics Institute (EBI)
- Los Alamos National Laboratory seit 1979; GenBank am NCBI (National Center f Biotech. Information)
- DNA Data Bank of Japan: 1986; DDBJ am NIG (National Inst. of Genetics)
- Zusammenschluss in der "International Nucleotide Sequence Database Collaboration" (seit 1988)
  - Täglicher Datenaustausch
  - Lokale Datenbank jeweils verantwortlich für eingebrachte Sequenzen

EMBL-Datenbank

- Erste (seit 1982) und derzeit größte europäische DNA-Sequenzdatenbank (am European Molecular Biology Laboratory in Hinxton, England)*

- Datenquellen
  - Lokale Forschergruppen
  - Überregionale Sequezierungsprojekte

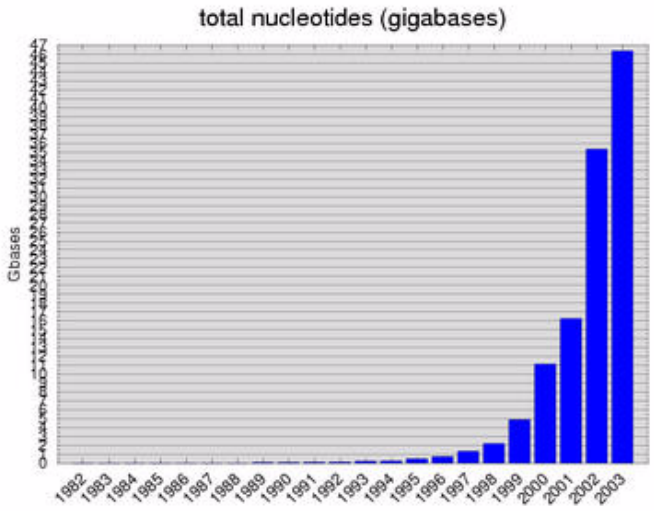
- Verfügbarkeit (als vierteljährlich publizierte Releases)
  - Flatfile
  - SRS (Sequence Retrieval System mit proprietärem EBML-Format)
  - XML (BSML = Bioinformatic Sequence Markup Language)
  - Oracle Dump Files



* http://www.ebi.ac.uk/embl/

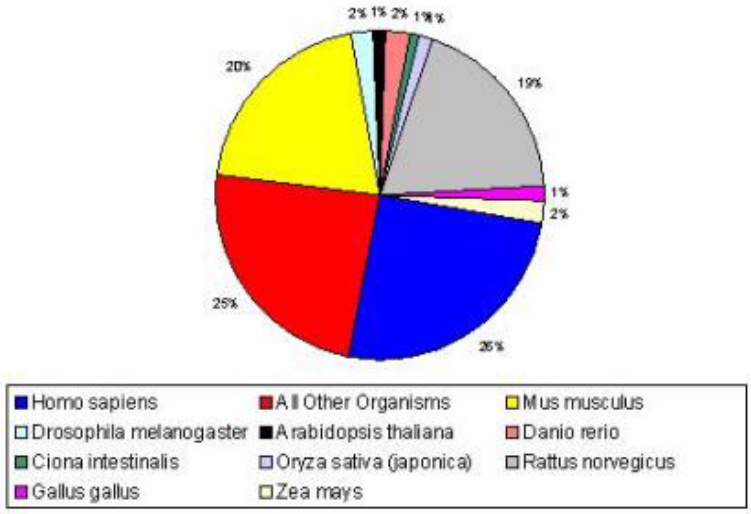
EMBL: Größe

- Release 76 (Sep. 2003)
- Stand Nov. 2003
  - 46,389,602,205 Basen in 32,049,770 Records
  - Über 100 000 Spezies vertreten

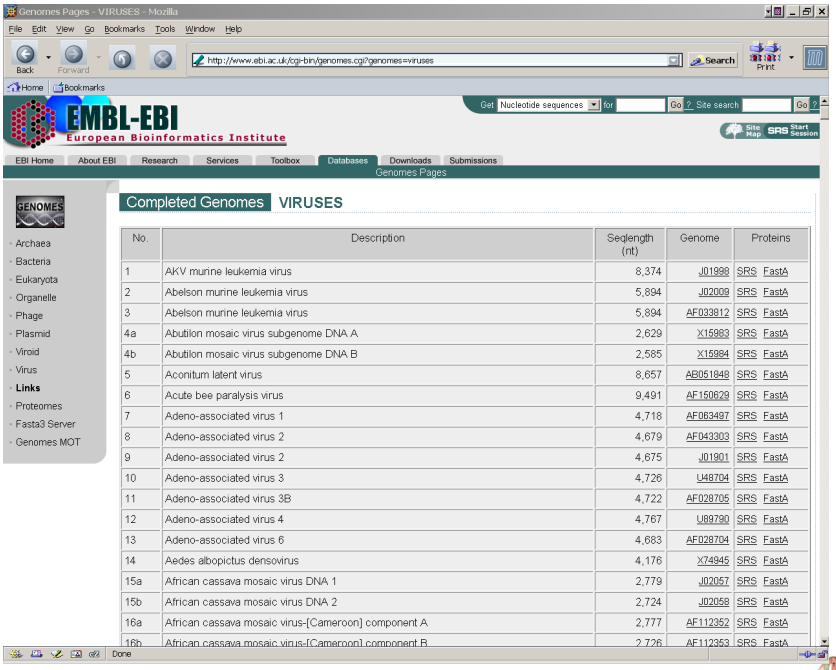


http://www3.ebi.ac.uk/Services/DBStats/ (Gigabase = 10^9 Basen)

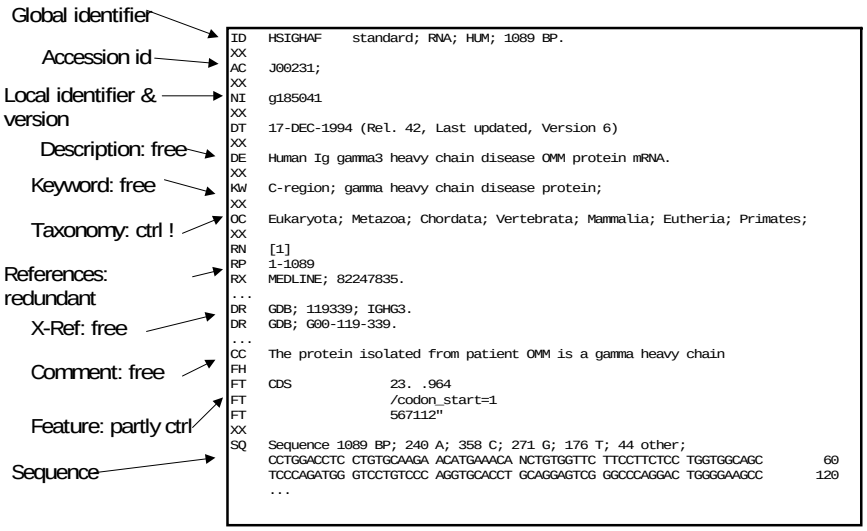
EMBL: Spezies (Verteilung)



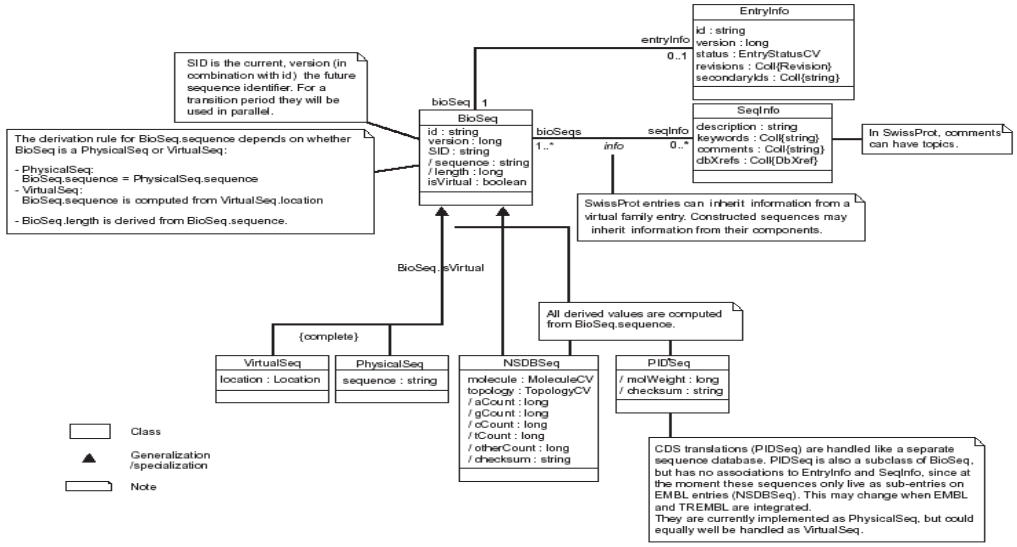
EMBL: Spezies (Beispiele)



EMBL: Beispieleintrag (Entry-Model)

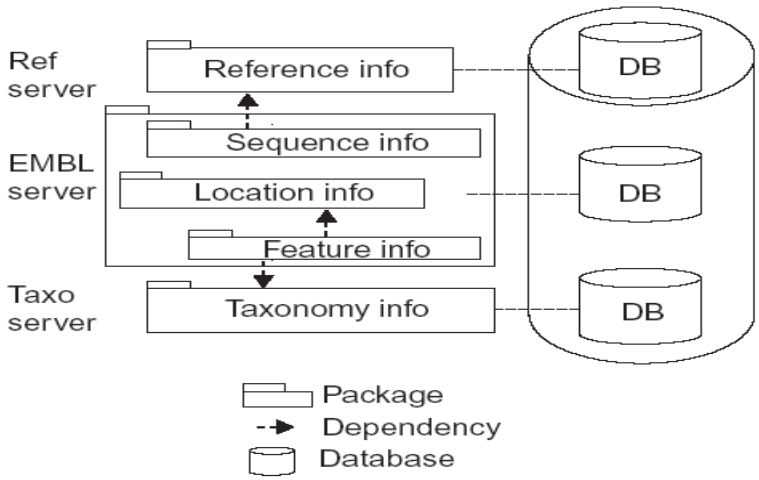


EMBL: UML-Modell (Ausschnitt)



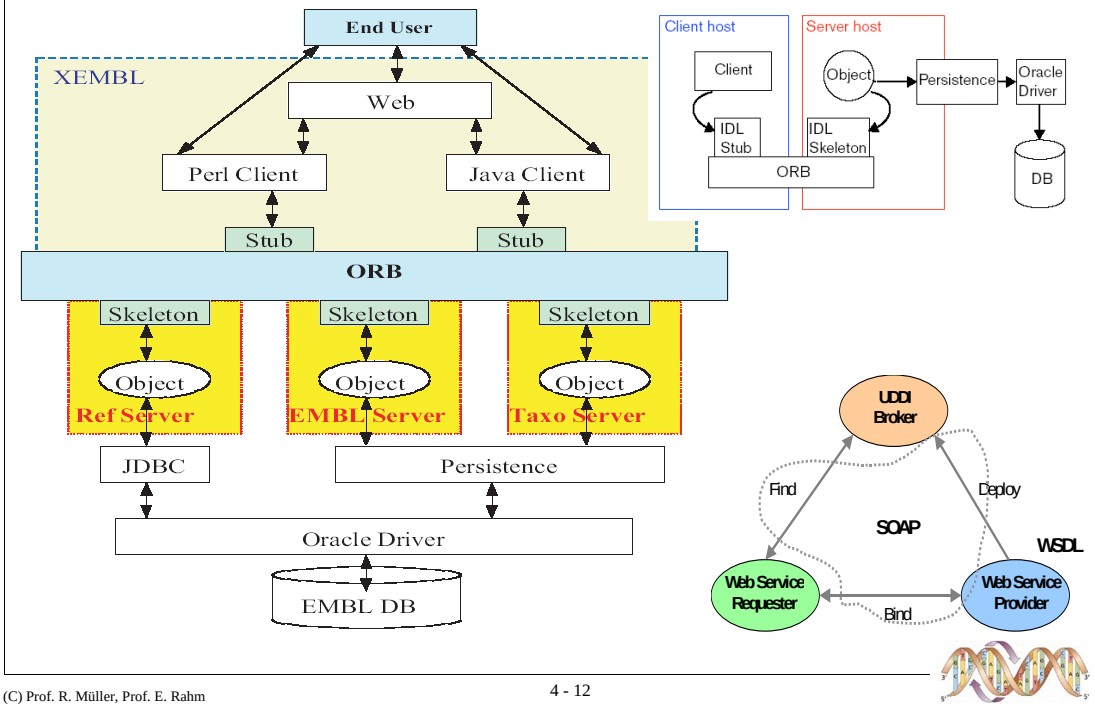
Sequence Info. This package defines class *BioSeq*, which represents biological sequences, and class *SeqInfo*, which describes general information about these sequences. The administrative data associated with database entries are defined in *EntryInfo*. The biological classes of sequence *NSDBSeq*, which is for nucleotide sequences, and *PIDSeq*, which is for protein sequences, are subclasses of *BioSeq*. *VirtualSeq* and *PhysicalSeq* are storage classes of sequence, that is, virtual or literal.

EMBL: Architektur

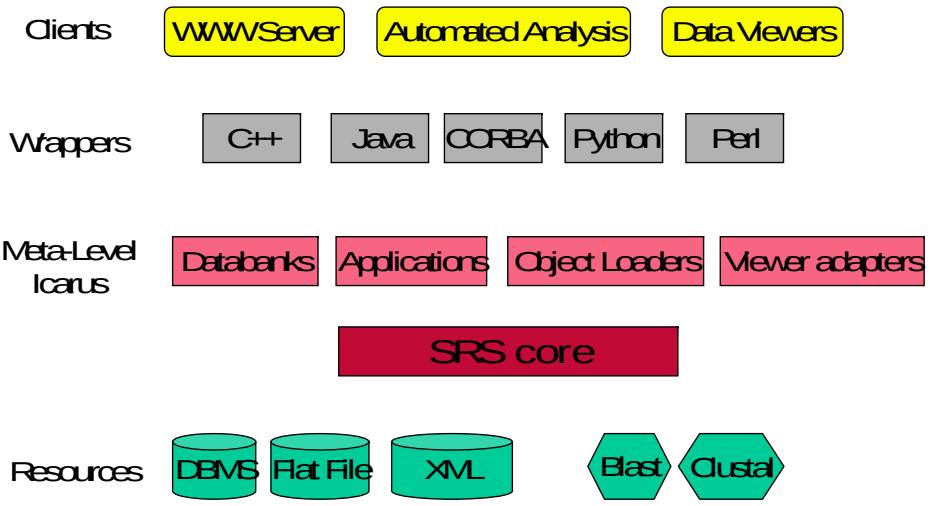


The database partitioning. The database is divided into five main packages: *Sequence Info*, all general information about sequences; *Feature Info*, detailed sequence annotation; *Reference Info*, bibliographic references; *Taxonomy Info*, the taxonomy of the organisms from which the sequences were obtained; *Location Info*, representing locations on sequences.

EMBL: E-Service-Architektur



EMBL: Sequence Retrieval System



GenBank

- NCBI-Datenbank
- Derzeit (Nov. 2003) über $20 * 10^9$ Basen
- Modell in ASN.1
- Zugriff über "Entrez"
  - Ähnlich SRS bei EBML
  - Keine Joins
  - "Neighbours" – "Related Documents"
  - Click-And-Browse

Entrez is the text-based search and retrieval system used at NCBI for the major databases, including PubMed, Nucleotide and Protein Sequences, Protein Structures, Complete Genomes, Taxonomy, and others.

GenBank: Beispieleintrag

```
LOCUS       AE009950             1908256 bp    DNA     circular CON 27-FEB-2002
DEFINITION  Pyrococcus furiosus DSM 3638, complete genome.
ACCESSION   AE009950
VERSION     AE009950.1  GI:18980902
KEYWORDS    .
SOURCE      Pyrococcus furiosus DSM 3638
  ORGANISM  Pyrococcus furiosus DSM 3638
            Archaea; Euryarchaeota; Thermococci; Thermococcales;
            Thermococcaceae; Pyrococcus.

 <<<<< deleted for brevity >>

REFERENCE   4  (bases 1 to 1908256)
  AUTHORS   Weiss,R.B.
  TITLE     Direct Submission
  JOURNAL   Submitted (12-FEB-2002) Human Genetics, University of Utah, 20
            South 2030 East, Salt Lake City, UT 84112, USA
FEATURES             Location/Qualifiers
     source          1..1908256
                     /organism="Pyrococcus furiosus DSM 3638"
                     /strain="DSM 3638"
                     /db_xref="taxon:186497"
CONTIG       join(AE010126.1:1..14559,AE010127.1:61..8666,AE010128.1:21..11327,
             AE010129.1:61..8659,AE010130.1:61..8716,AE010131.1:61..11112,
             AE010132.1:61..11093,AE010133.1:61..11664,AE010134.1:61..3717,
             AE010135.1:61..13488,AE010136.1:61..6244,AE010137.1:61..11952,
             AE010138.1:61..10516,AE010139.1:61..10851,AE010140.1:61..14818,

 <<<<< deleted for brevity >>

             AE010288.1:61..12641,AE010289.1:61..11338,AE010290.1:61..11204,
             AE010291.1:61..11397,AE010292.1:61..13064,AE010293.1:61..9294,
             AE010294.1:61..12888,AE010295.1:61..10029,AE010296.1:61..11091,
             AE010297.1:61..13483,AE010298.1:61..2120)
//
```

Figure 2: A GenBank CON entry for a complete bacterial genome. The information toward the *bottom* of the record describes how to generate the complete genome from the pieces.

Weitere Nukleotid-Datenbanken

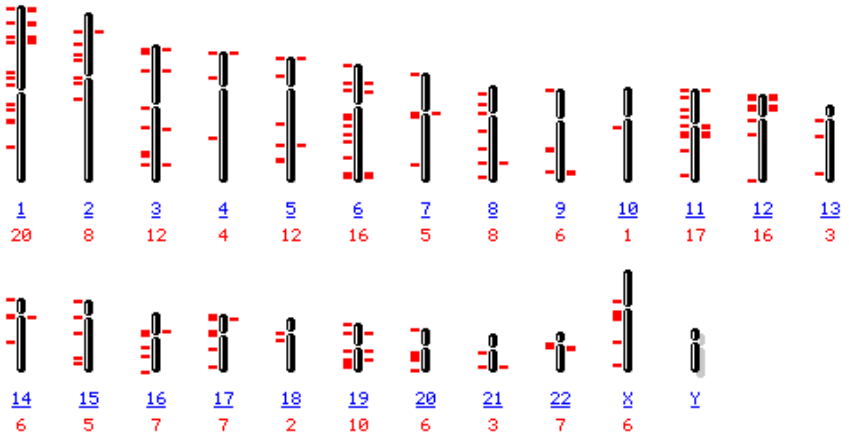
- UniGene, dbEST, RZPD, ...
- Vielzahl von Datenbanken für spezifische Aspekte
  - Organismen (Hefe, Fliege, Maus, HIV, ...)
  - Ribosomen, Immunsystem
  - Motifs: Transskriptionsfaktoren, Promotoren, ...
- Terminologie-Datenbanken
  - GeneOntology (> 7000 Begriffe: Funktion, Prozess, Zelllokation)
  - NCBI TaxonomyDatabase (119000 Organismen)

Kartierungs-Datenbanken

- Motivation
- The Genome Database (GDB)
- eGenome
- LocusLink
- dbSNP

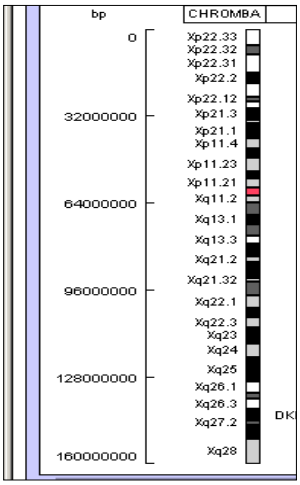
Motivation

- Bestimmung der Gen-Loci: Welches Gen liegt an welcher Position (in welchen Modifikationen) auf welchem Chromosom?
- Medizinische Relevanz: Numerische und strukturelle Chromosomen-Abberationen, Lokalisation von medizinisch relevanten Punktmutationen



Gen-Loci

- Gen-Locus: Ein "Ort" auf einem Chromosom
- Enthält z.B.
  - Gene oder Genfragmente
  - DNA-Marker (Eindeutige Gen-identifizierende Sequenzen mit durchschnittlicher Länge von 300-500 Basenpaare)
  - Polymorphe Strukturen (Unterschiedliche Allele vorhanden)



Telomer

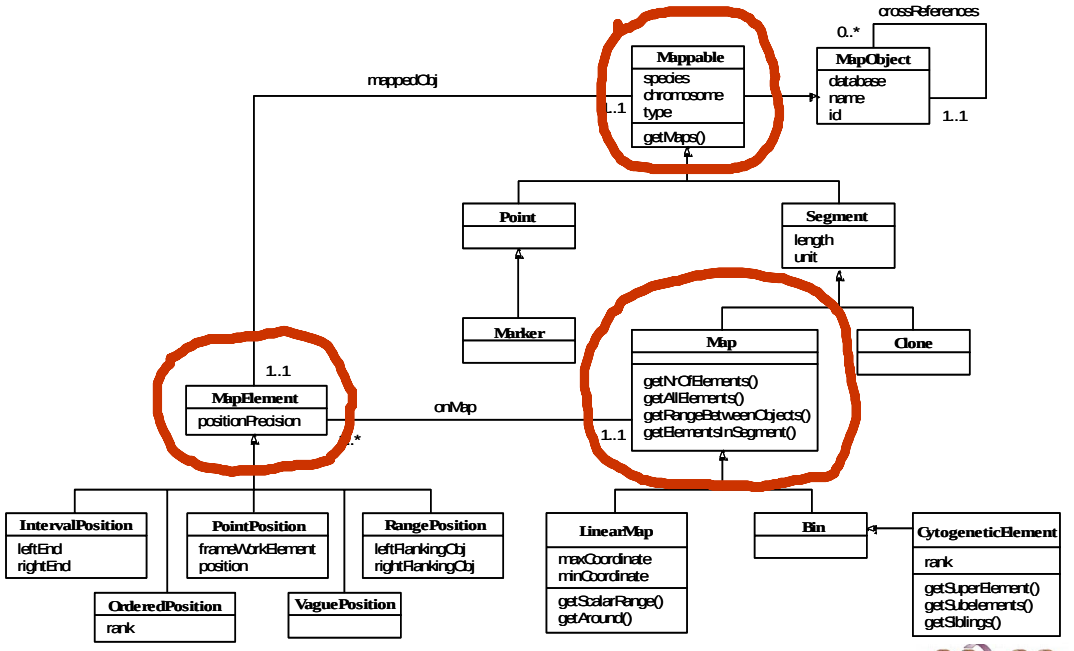
p – der kurze Arm

Centromere

q – der lange Arm

Telomer

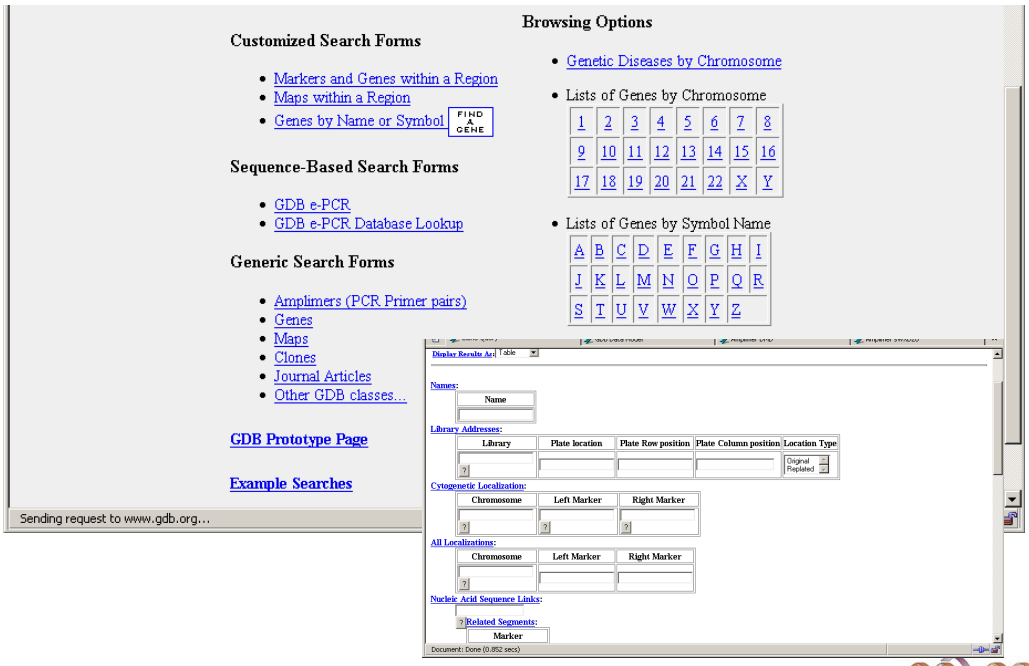
OMG Standard für Genome Maps



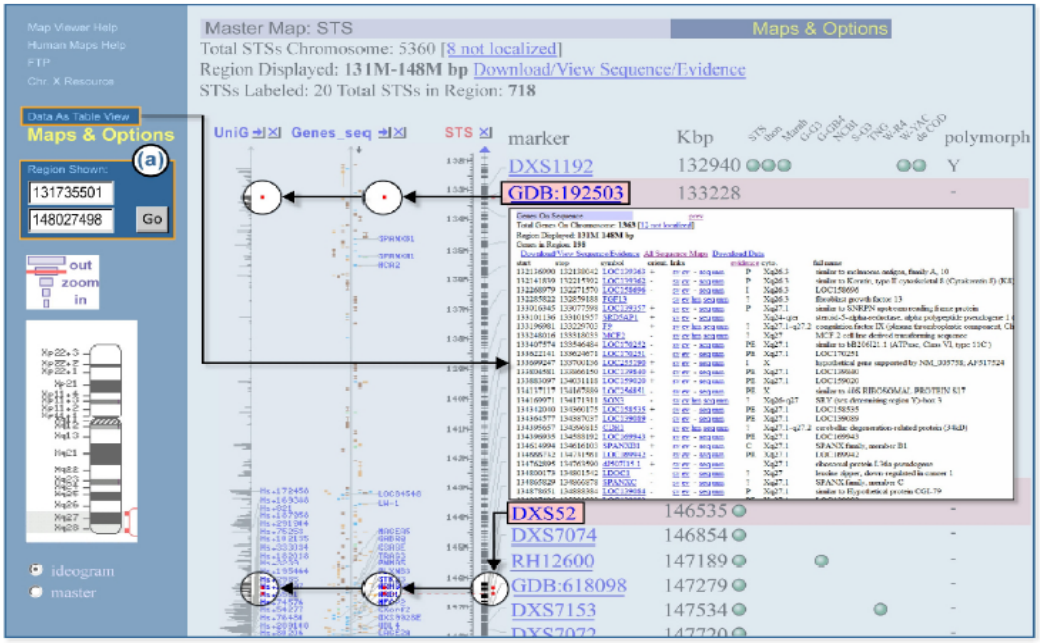
Genome Database: GDB

- Jahrelang Standarddatenbank für Kartierungs-Daten des Humane Genome Projects
- Anzahl Objekte
  - 14.000 Gene mit Position
  - 150.000 DNA-Marker
- Verfahren der Integration
  - Submission-based
  - Idee der "Community Curation"
  - Chromosome Editors
- Implementierung
  - OPM, Sybase
  - OPM-Datenschema mit ca. 75 Klassen
  - Sybase-Implementierung mit ca. 140 Tabellen

GDB: Interface



GDB: MapViewer



GDB: Bewertung

- Sehr technisch orientiert
- Modell ähnlich zu OMG-Standard (OPM)
- Komplizierte Search-Forms kaum benutzt
- Community Curation kaum benutzt
- Relativ langsam

eGenome

- Kartierungsdatenbank
- Z.Z. mehr als 135.000 DNA-Marker (Nov. 2003)
- Technische Realisierung
  - Abpspeicherung der Daten in CompDB, einer Oracle-Datenbank
  - Export als Flatfiles verfügbar

eGenome: Beispiel

eGenome QUICK SEARCH ADVANCED SEARCH INFO DATA INDEX HELP HOME
Site index What's new Acknowledgements

1pter-1qter

1 to 245,203,898 bp from 1pter
0 cR from 1pter
12,469 markers, 1,303 polymorphisms, 241,277 SNPs, 261 bundles

Map of region

■ - SNP ★ - Marker & polymorphism **Bold text** - RH/GL framework element

Markers | Polymorphisms | SNPs | Bundles | Help

Name	Bundle	Status	Sequence position	RH position	Cytolocation
D0S2577 ■		Unknown	0.052 Mb		1p36.3
D0S2578 ■		Unknown	0.053 Mb		1p36.3
G54113 ■		Unknown	0.054 Mb		1p36.3
A071 ■		Unknown	0.076 Mb		1p36.3
GDB:229298		Unknown	0.09 Mb		1p36.3
L31440		Unknown	0.123 Mb		1p36.3
WI-4202 ■		Unknown	0.13 Mb		1p36.3
sV		Unknown	0.194 Mb		1p36.3
GDB:1318434		Unknown	0.272 Mb		1p36.3
WI-4202 ■		Unknown	0.276 Mb		1p36.3
L31440		Unknown	0.491 Mb		1p36.3
GDB:229285		Unknown	0.506 Mb		1p36.3
L28245		Unknown	0.514 Mb		1p36.3
WI-4202 ■		Unknown	0.553 Mb		1p36.3
GDB:1318434		Unknown	0.558 Mb		1p36.3
G01853 ■		Unknown	0.641 Mb		1p36.3
L28277		Unknown	0.649 Mb		1p36.3
L28245		Unknown	0.651 Mb		1p36.3
RH98513 ■		Transcribed	0.658 Mb	1pter to 1qter	1p36.3
stSG144		Unknown	0.658 Mb		1p36.3
GDB:229285		Unknown	0.664 Mb		1p36.3
L31440		Unknown	0.679 Mb		1p36.3
RH37473 ■		Transcribed	0.716 Mb		1p36.3
sV		Unknown	0.78 Mb		1p36.3
AL033601 ■		Unknown	0.811 Mb		1p36.3

First Prev **Page 1 of 513** Records 1 - 25 Next Last All

eGenome: Beispiel (2)

RH98513
1p36.3

Map of region
List of region

Position | Description | Clones & Sequences | Help

Sequence position Help

Base pairs 657,800 to 657,927 from 1pter (UCSC)

RH map position(s) Help

1pter to 1qter
0 to 3613.7 cR from 1pter
RH positions 1pter to 1qter

Cytogenetic position(s) Help

1p36.3 (for sequence 657,800 to 657,927 bp from 1pter)
1pter-1qter (for RH position 0 to 3613.7 cR from 1pter)

RH score Help

Genebridge4
1200202010 2210001010 1011111110 0000000000 0100100000
1110000201 1001100012 0000100002 0100011101 111

RHdb entry Help

RH98513

Primer sequences Help

AAAAAGTCATGGAGGCCATG
CTATATGGATGCCCCCCAC

Neighboring elements Help

Elements within 50 kb GO

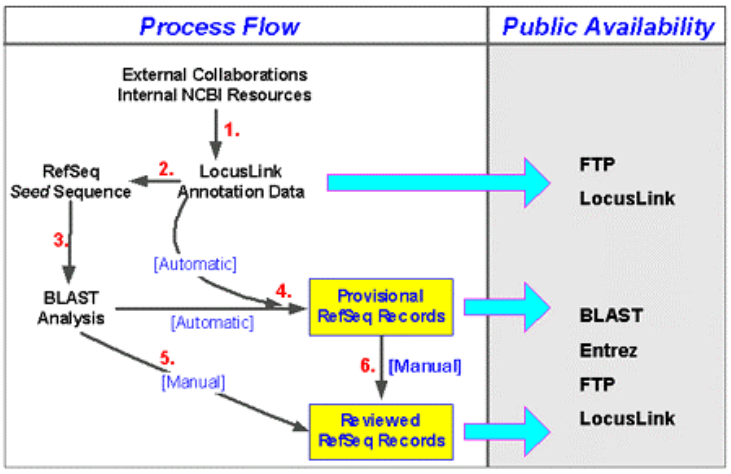
Element	Distance	Orientation
G01853	16,225 bp	pterminal to RH98513
L28277	8,326 bp	pterminal to RH98513
L28245	7,034 bp	pterminal to RH98513
stSG144	509 bp	qterminal to RH98513
GDB:229285	6,472 bp	qterminal to RH98513
L31440	20,780 bp	qterminal to RH98513

LocusLink [http://www.ncbi.nlm.nih.gov/LocusLink]

- Repository von Genen und "some non Genes"
  - Vielfältige Informationen über Position hinaus
  - Proteine, Funktionen, RNA, Phänotypen, ...
  - 32.000 Gene
- Technische Implementierung
  - NCBI: Entrez Search Interface
  - Tab-delimited Files

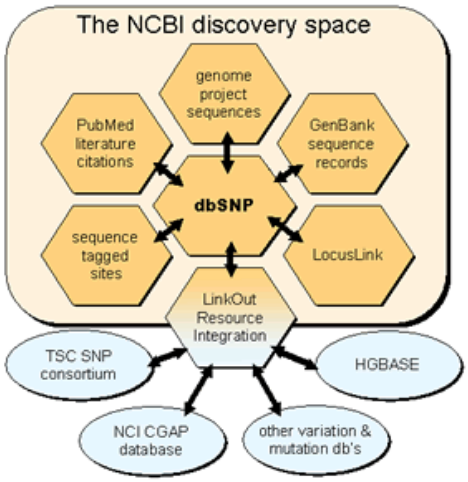
LocusLink: Integrationsworkflow

- Mischung aus manueller und automatischer Bearbeitung
- Objektstatus: Provisional - Reviewed
- Kein Releasekonzept, keine Versionierung



dbSNP

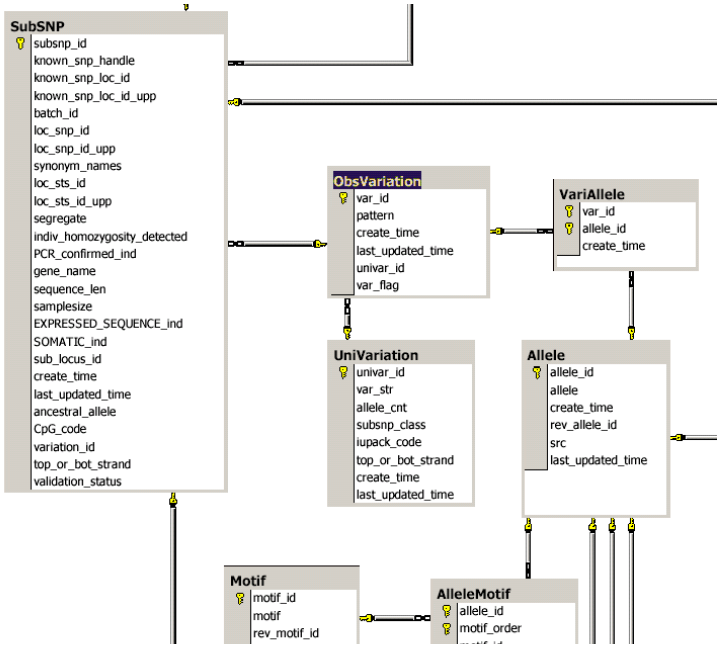
- Single Nucleotide Polymorphism Database*
- SNP ("snip"): Kleinste genetische Variation auf dem Level einer einzelnen Base
  - Beispiel: Variation des DNA-Segments von AAGGTTA zu ATGGTTA
  - Ca. 1.000.000 SNP‘s im menschlichen Genom
  - Viele SNP’s ohne phänotypische Auswirkung
- Bestimmte SNPs führen aber zu veränderten Stoffwechselkompetenz ihrer Träger
  - Allergische Reaktionen
  - Langsamerer Abbau von Medikamenten
  - Prädisposition für bestimmte Krankheiten



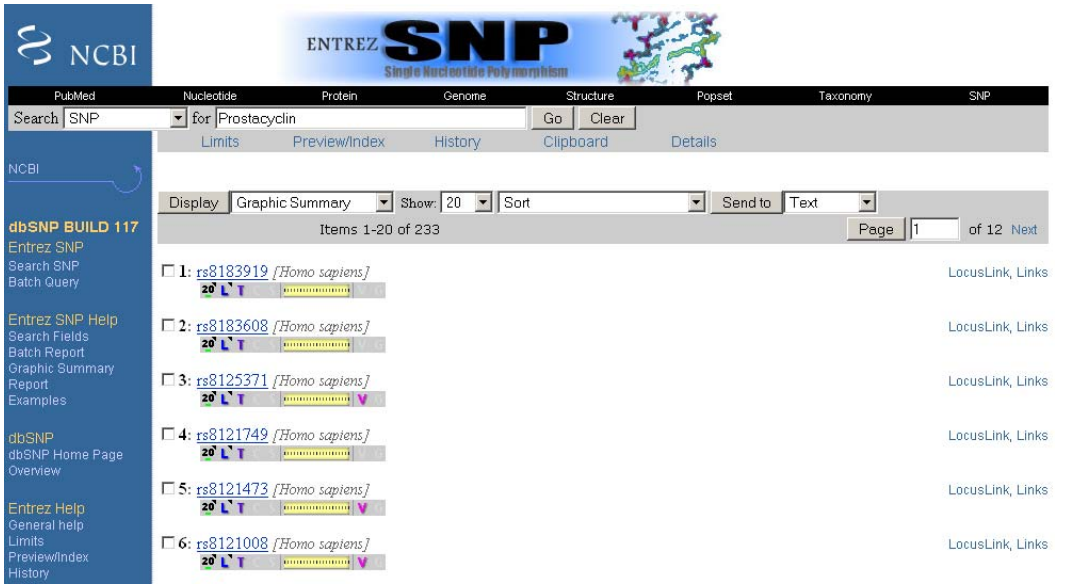
- Zielsetzung von dbSNP: Speicherung aller bekannten "snips", ihrer Genlokalisationen und ggf. medizinischen Relevanz

* http://www.ncbi.nlm.nih.gov/About/primer/snps.html

dbSNP: E/R-Modell (Auszug)



dbSNP: Beispiel



dbSNP: Beispiel (2)

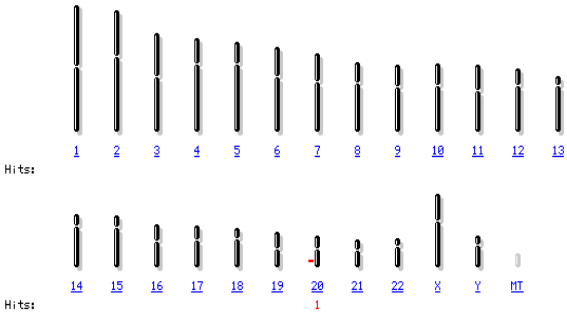
Search for rs8183919 on chromosome(s) assembly All Find

Show linked entries Help FTP MapViewer home Advanced search

Homo sapiens genome view

build 34 version 1 statistics

BLAST search the human genome



Search results for query "rs8183919": 1 hit

Chr	Match	Map element	Type	Maps
20	rs8183919	rs8183919	SNP	Variation

dbSNP: Beispiel (3)