BIO390: Introduction to Bioinformatics

Lecture II: What is Bioinformatics?

Michael Baudis | 2023-09-26

Course Information BIO390

- Tuesdays at 08:00; 2x45min
- 13 presentations by different lecturers
- (unchecked) homework / preparation exercises w/ focus on test topics
- course language is English
- course slides may/should be made available through the website
- written exam at end of course (== 14th course - December 19)
- Organizer:

Prof. Dr. Michael Baudis

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CH-8057 Zurich

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Please use website & OLAT for additional course information

https://compbiozurich.org/courses/UZH-BIO390/

compbiozurich.org/courses/UZH-BIO390/

BIO390 - Introduction to Bioinformatics

Summary

The handling and analysis of biological data using computational methods has become an essential part in most areas of biology. In this lecture, students will be introduced to the use of bioinformatics tools and methods in different topics, such as molecular resources and databases, standards and ontologies, sequence and high performance genome analysis, biological networks, molecular dynamics, proteomics, evolutionary biology and gene regulation. Additionally, the use of low level tools (e.g. Programming and scripting languages) and specialized applications will be demonstrated. Another topic will be the visualization of quantitative and qualitative biological data and analysis results.

Practical Information

- Autumn semesters
- 1 x 2h / week
- Tue 08:00-09:45
- UZH Irchel campus, **Y03-G-85**
- OLAT lecture recordings
- Course language is English

Some very approximate learning goals may provide you with additional guidance - but plese be aware that those may not be particularly adjusted to a given course edition.

Upcoming

September 20, 2022

What is Bioinformatics? Introduction and Resources

BIO390 UZH HS22 - INTRODUCTION TO BIOINFORMATICS

What is Bioinformatics? Introduction and Resources

BIO390 UZH HS22 - Introduction to Bioinformatics

Michael Baudis

The first day of the "Introduction to Bioinformatics" lecture series starts with a general introduction into the field and a description of the lecture topics, timeline and procedures.

Topics covered in the lecture are e.g.:

- a term definition for *bioinformatics*
- the relation of hypothesis driven and data driven science, with respect to bioinformatics
- categories of bioinformatics tools and data
- research areas and topics
- the varying emphasis on "bio" and "informatics"
- databases (primary vs. derived) and data curation
- data collection & curation
- file Formats, ontologies & APIs ass areas/topics (w/o details)
- "not-bioinformatics"

At the end of the lecture, a - very - brief introduction into the relevance of different aspects of bioinformatics for human genome variation is being given.

Q & A[1]

WHAT IS MEANT WITH PROSE IN BIOINFORMATICS?

Prose refers to written text, e.g. the body of scientific publications or descriptions of experimental procedures, which may contain much

1. Thanks to Katja W. in HS21 for starting some questions!
2. One shouldn't write in MS Word, IMO. Use LaTex, Markdown, OpenOffice ...

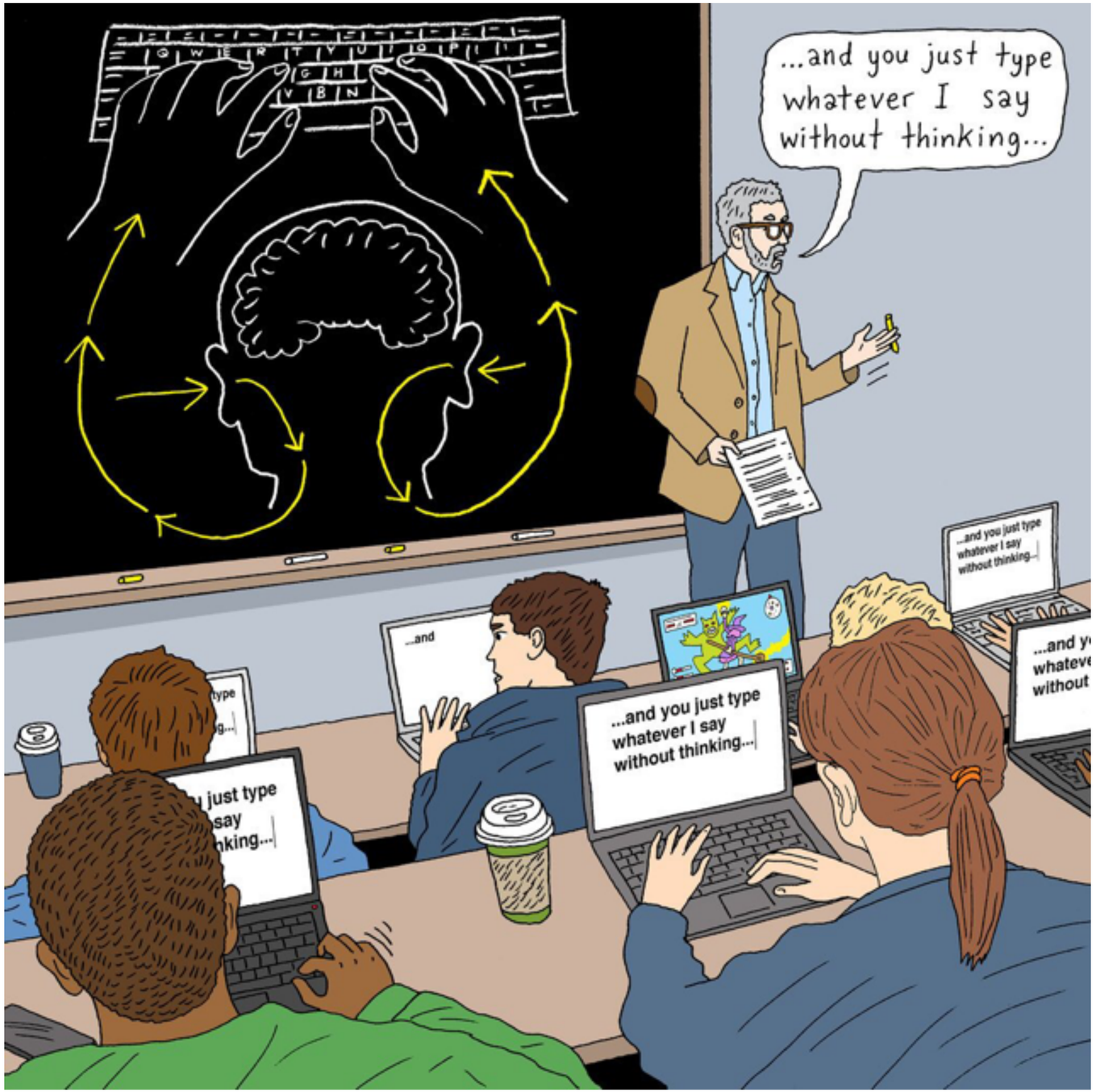
Links

- [2021 lecture slides] (PDF)

September 20, 2022

BIO390: Course Schedule

- 2022-09-19: Christian von Mering - Sequence Bioinformatics
- 2022-09-26: Michael Baudis - What is Bioinformatics? Introduction and Resources
- 2022-10-03: Mark Robinson - Statistical Bioinformatics
- 2022-10-10: Shinichi Sunagawa (ETHZ) - Metagenomics
- 2022-10-17: Izaskun Mallona - Regulatory Genomics and Epigenomics
- 2022-10-24: Valentina Boeva (ETHZ) - Machine Learning for Biological Use Cases
- 2022-10-31: Katja Baerenfaller (SIAF) - Proteomics
- 2022-11-07: Pouria Dasmeh - Biological Networks
- 2022-11-14: Patrick Ruch - Text mining & Search Tools
- 2022-11-23: Ahmad Aghaebrahimian (ZHAW) - Semantic Web
- 2022-11-28: Michael Baudis - Building a Genomics Resource
- 2022-12-05: Valérie Barbie (SIB) - Clinical Bioinformatics
- 2022-12-12: Michael Baudis - Genome Data & Privacy | Feedback
- 2022-12-19: Exam (Multiple Choice)



Source: New York Times | SUSAN DYNARSKI NOV. 22, 2017

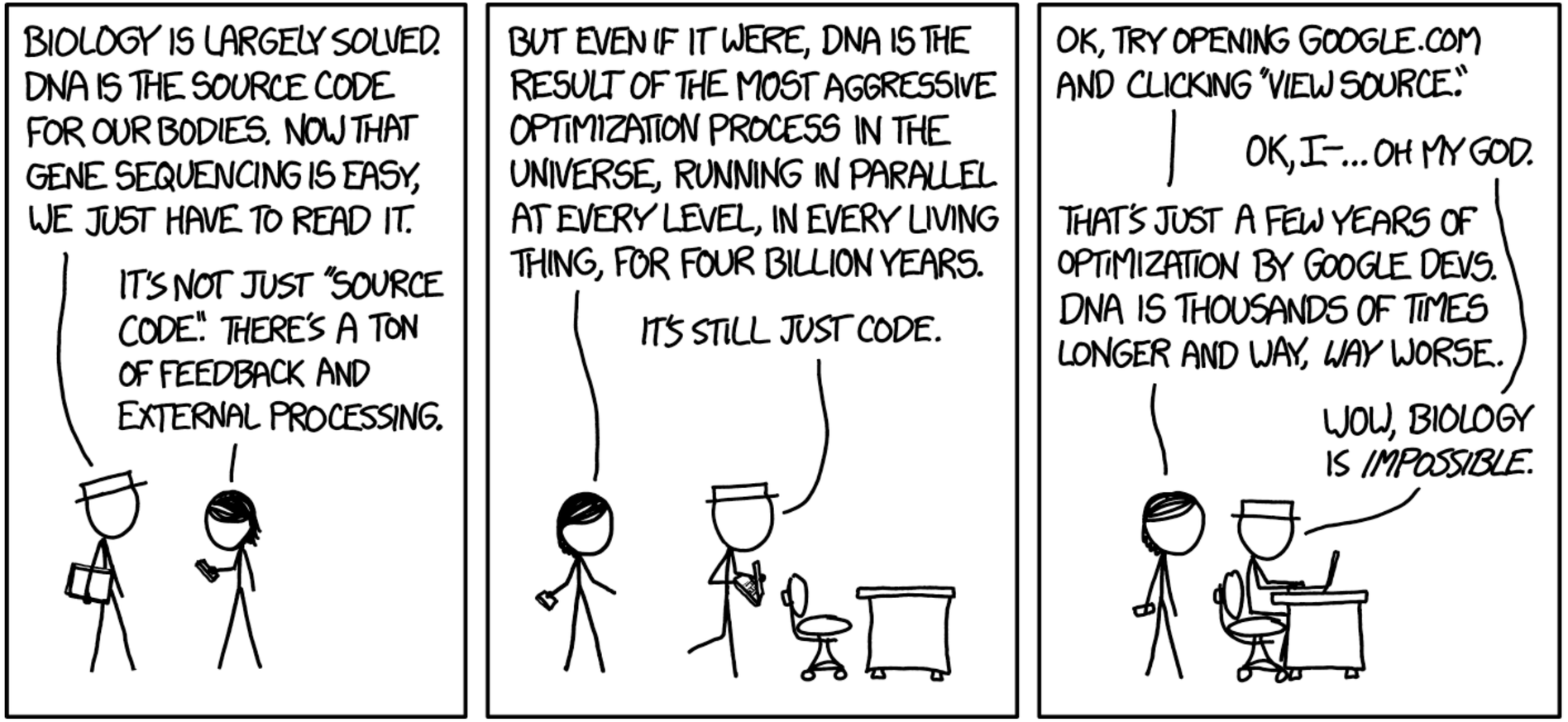
Some Recommended Books

- Anna Tramontano: Introduction to Bioinformatics
- Susan Holmes and Wolfgang Huber: Statistics for Biology
- Robert Gentleman: R Programming for Bioinformatics
- John Maindonald & W. John Braun: Data Analysis and Graphics Using R
- Andy Hector: The New Statistics with R
- Neil C. Jones & Pavel A. Pevzner: Bioinformatics Algorithms
- Edward Tufte: The Visual Display of Quantitative Information (& other works by Tufte)

Why Bioinformatics?

- **hypotheses** are the basis of biological experiments
- biological experiments produce **data**, the quantitative and/or qualitative read-outs of experiments
- both quantitative as well as qualitative data need to be **processed** for
  - **statistical significance**
  - **categorisation**
  - **communication**
- many datatypes are **beyond** the proverbial "**intuitive** understanding”
- analysis of data **confirms** or **refutes** initial **hypotheses** - or requires new hypotheses and new data

Biology is *impossibly complex* - But bioinformatics might help



Randall Munroe: https://xkcd.com/1605/

So, What is Bioinformatics?

- Bioinformatics is "the science that uses the instruments of informatics to analyze biological data in order to formulate hypotheses about life." (Anna Tramontano)

What is Bioinformatics?

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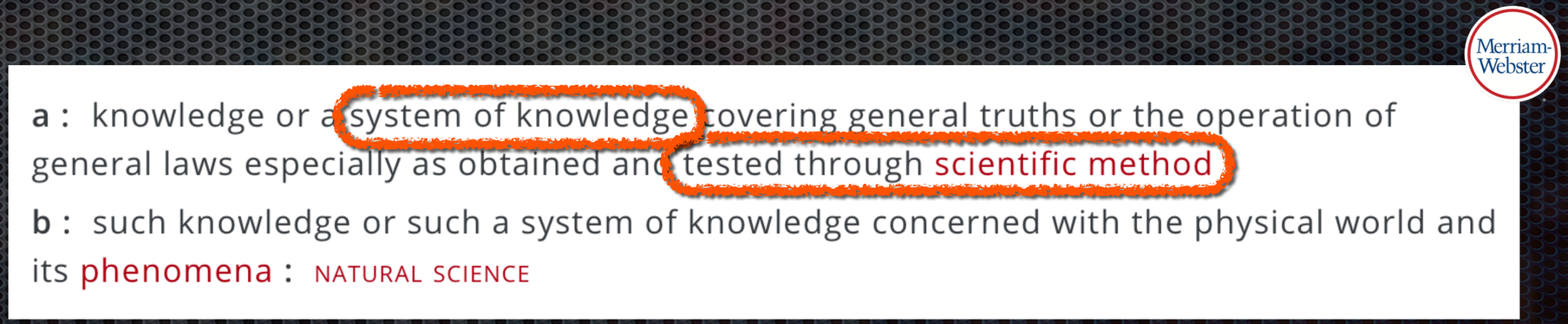

What is Bioinformatics?

Bioinformatics **uses** informatics tools for analyses

- Bioinformatics is "the science that **uses** the instruments of informatics to analyze biological data in order to formulate hypotheses about life." (Anna Tramontano)

➡ **software** (programming languages, statistics & visualisation, program and web APIs, databases, hardware drivers)
➡ **hardware** (HPC, data storage, signal measurement & processing)
➡ **algorithms** (modeling, encryption...)

What is Bioinformatics?

Bioinformatics **develops** informatics tools for analyses

- Bioinformatics is "the science that uses the **instruments of informatics** to analyze biological data in order to formulate hypotheses about life." (Anna Tramontano)

➡ **software** (statistics & visualisation packages, program and web APIs, file formats)
➡ **hardware** (drivers and procedures...)
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What is Bioinformatics?

biological data

- Bioinformatics is "the science that uses the instruments of informatics to analyze **biological data** in order to formulate hypotheses about life." (Anna Tramontano)

sequences, graphs, high-dimensional data, spatial/geometric information, scalar and vector fields, patterns, constraints, images, models, prose, declarative knowledge ... *

adapted from "Catalyzing Inquiry at the Interface of Computing and Biology"; John C Wooley and Herbert S Lin. National Research Council (US) Committee on Frontiers at the Interface of Computing and Biology. Washington (DC): National Academies Press (US); 2005.

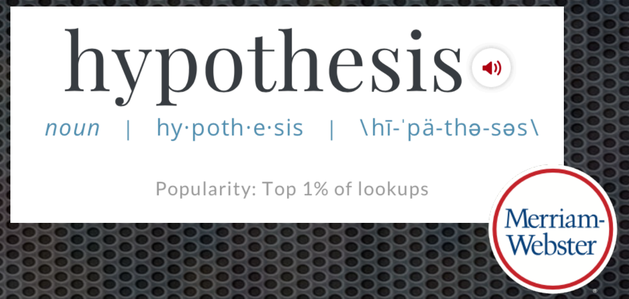
What is Bioinformatics?

Bioinformatics **analyzes**

- Bioinformatics is "the science that uses the instruments of informatics to **analyze** biological data in order to formulate hypotheses about life." (Anna Tramontano)

1 : to study or determine the nature and relationship of the parts of (something) by analysis

What is Bioinformatics?



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b : an interpretation of a practical situation or condition taken as the ground for action

What is Bioinformatics?

hypothesis driven science

data driven science

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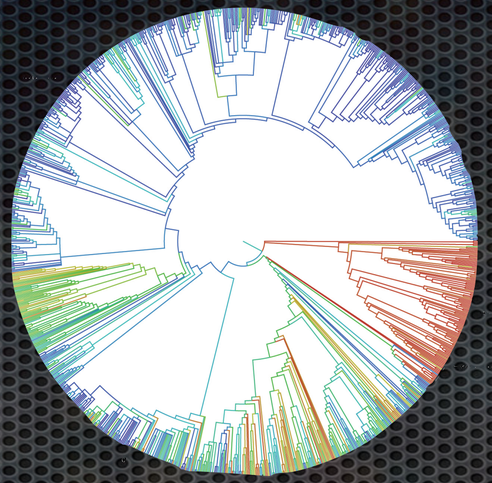
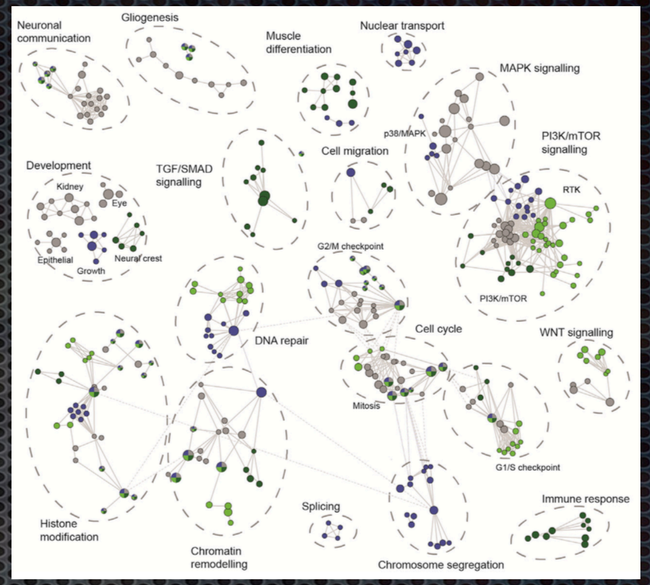
b : an interpretation of a practical situation or condition taken as the ground for action





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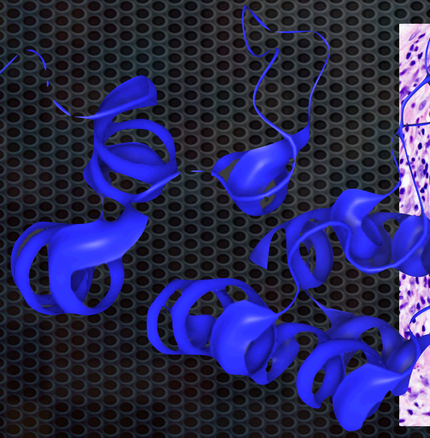
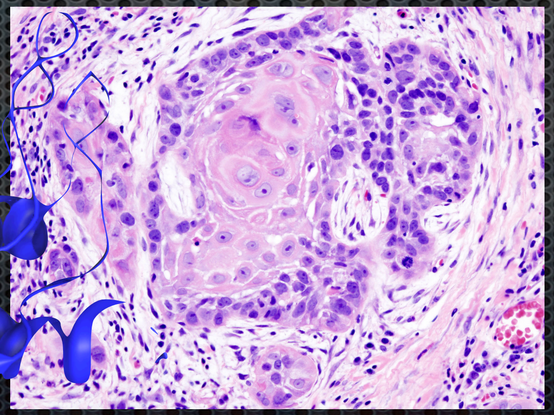
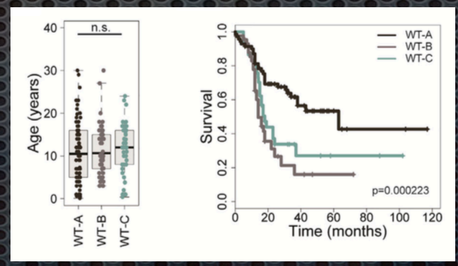
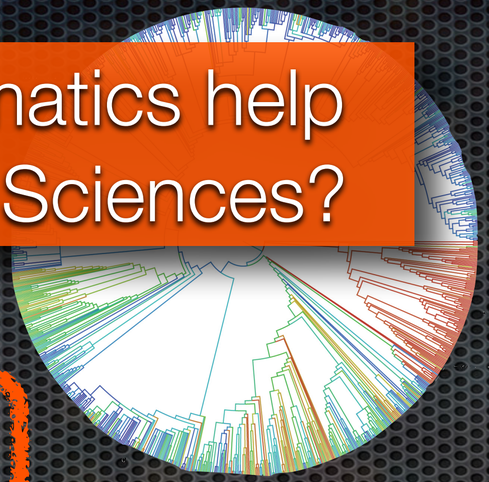






Sources: nextprot | opentreeoflife | wikipedia | MacKay et al., Cancer Cell (2017) | original photos

How can Bioinformatics help with the *42* of Life Sciences?



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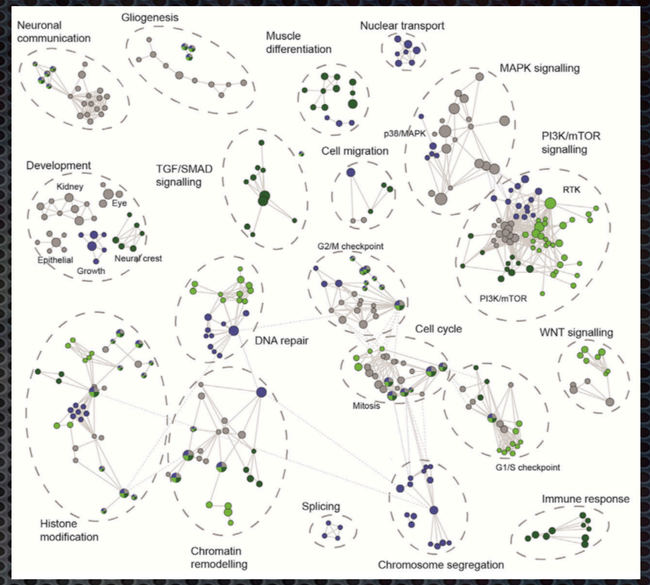

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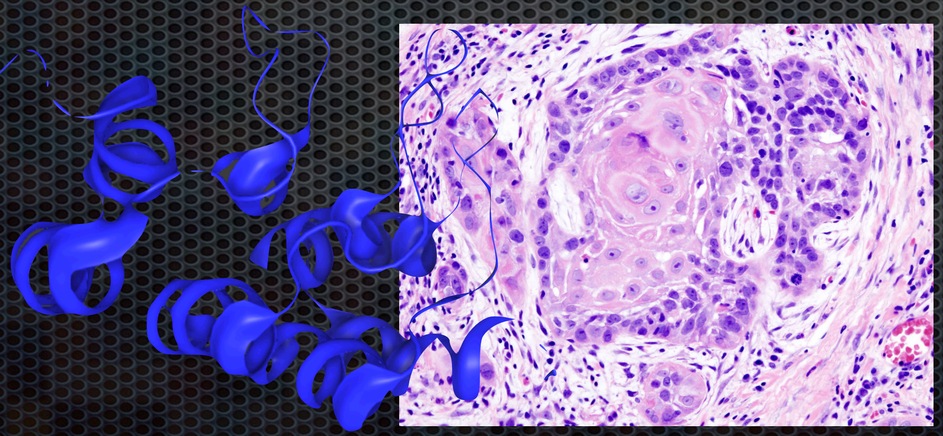

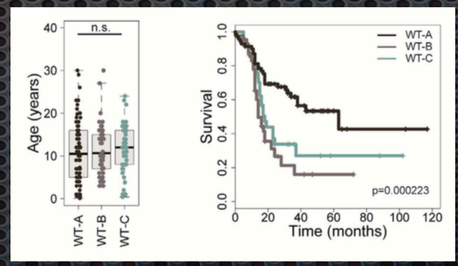

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{bio_informatics_science}

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    $probefile    = $pgx->{samples}->[0]->{paths}->{probefile} }
  else {
    my $seriesId  = (split('::', $pgx->{samples}->[0]->{id}))[1];
    my $arrayId   = (split('::', $pgx->{samples}->[0]->{id}))[2];
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  }
  $probefile  =~ s/^\///;
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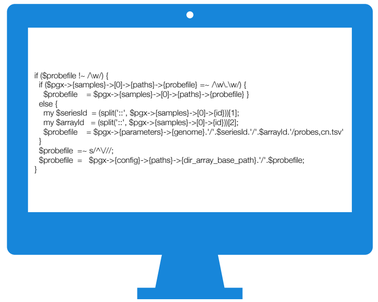
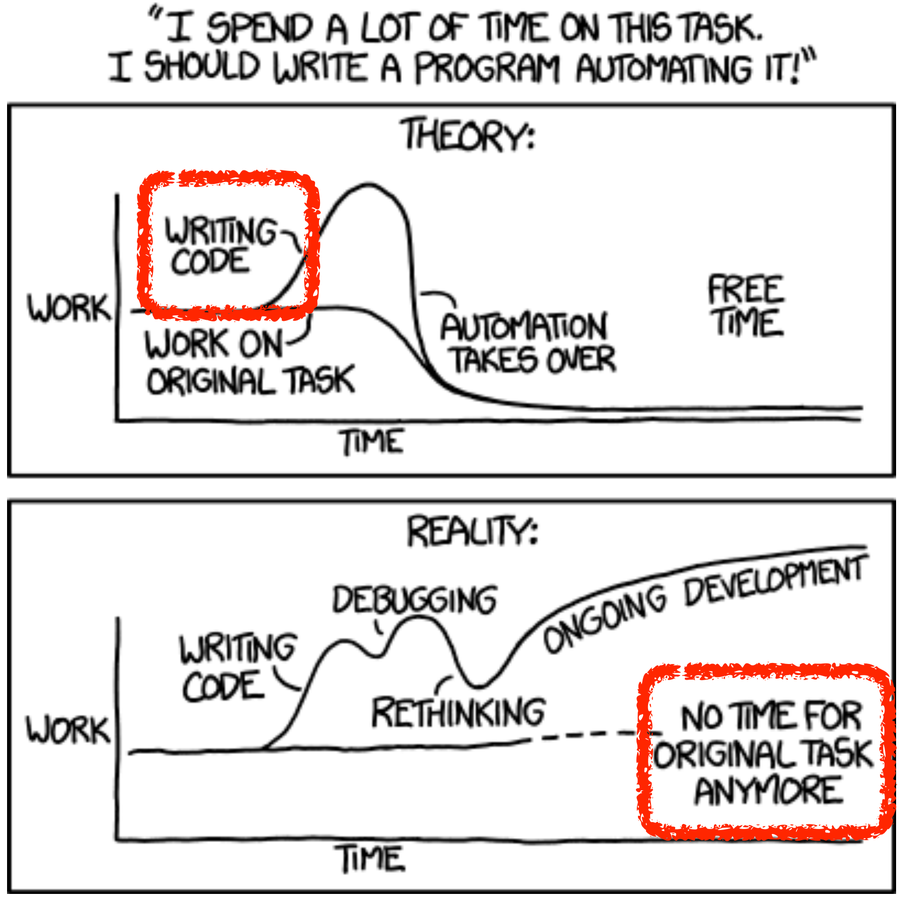
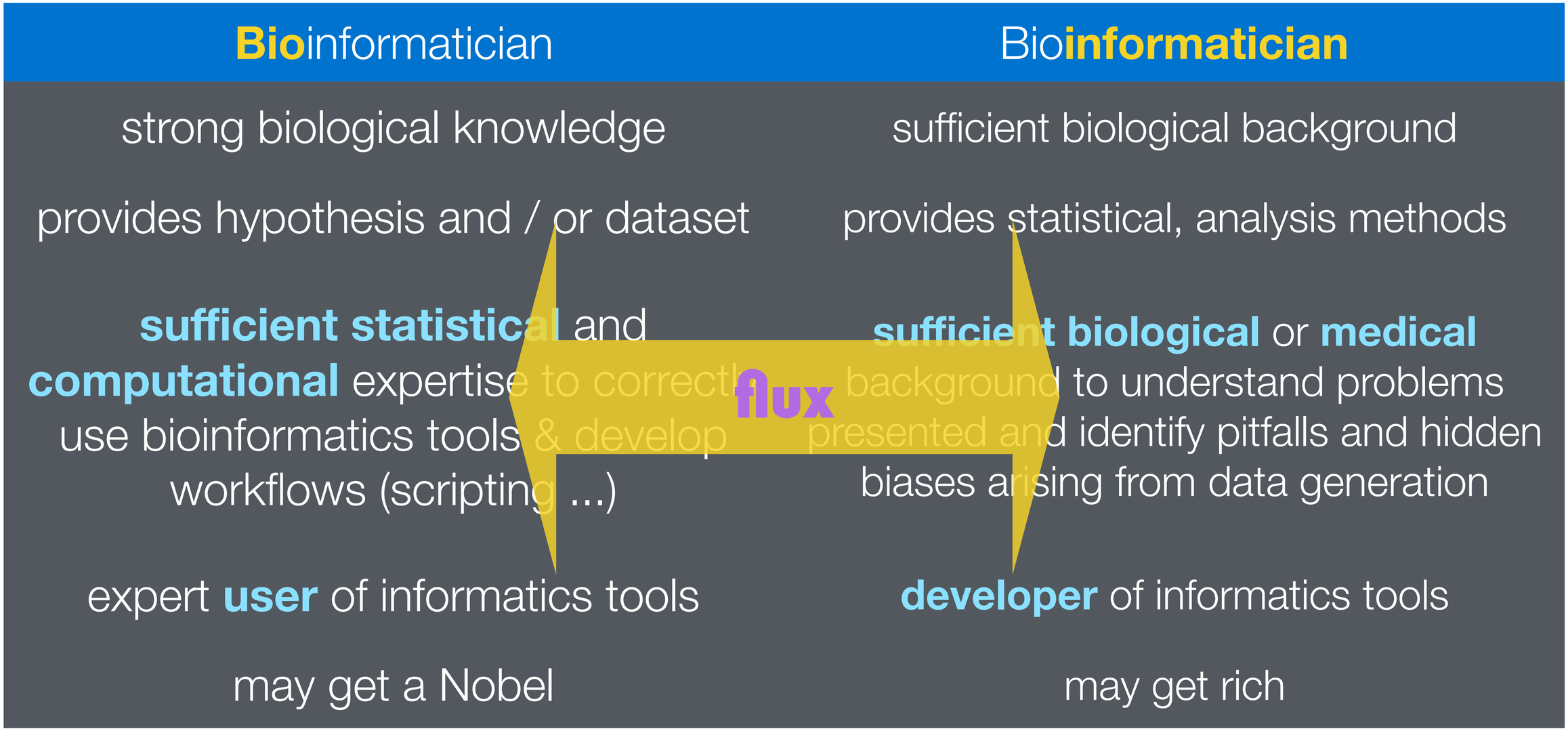
{bio_informatics_science}





Randall Munroe - XKCD
https://xkcd.com/1319/

Bioinformatician	Bio**informatician**
strong biological knowledge	sufficient biological background
provides hypothesis and / or dataset	provides statistical, analysis methods
sufficient statistical and **computational** expertise to correctly use bioinformatics tools & develop workflows (scripting ...)	**sufficient biological** or **medical** background to understand problems presented and identify pitfalls and hidden biases arising from data generation
expert **user** of informatics tools	**developer** of informatics tools
may get a Nobel	may get rich


Bioinformatician
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strong biological knowledge
sufficient biological background
provides hypothesis and / or dataset
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sufficient statistical and computational expertise to correctly use bioinformatics tools & develop workflows (scripting ...)
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What do Bioinformaticians work on?

Hypothesis & Data Driven Approaches to Biological Topics

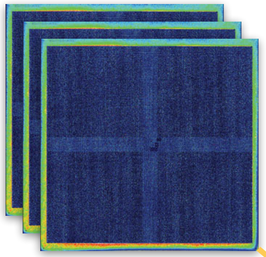
- protein **structure** definition
- DNA/RNA/protein **sequence** analysis
- **quantitative** analysis of "-omics" and cytometry data
- **functional** enrichment of target data (e.g. genes, sequence elements)
- **evolutionary** reconstruction and "tree of life" questions
- **image processing** for feature identification and spatial mapping
- **statistical** analysis of measurements and observations
- **protocols** for efficient storage, annotation and retrieval of biomedical data
- **information extraction** from prose & declarative knowledge resources (think publications & data tables)
- **clinical** bioinformatics - risk assessment and therapeutic target identification
- ...

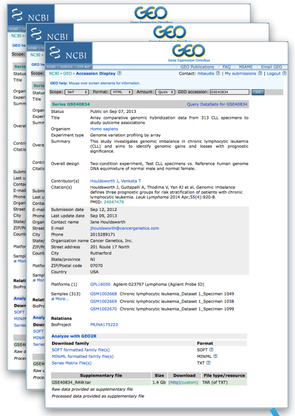

EVER
CLEANING
THE DATA
FITTING
THE MODEL
@kareem_carr

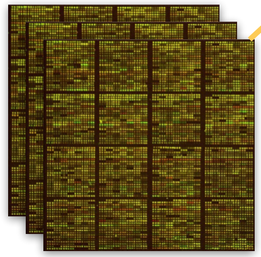
Data sets in tutorials

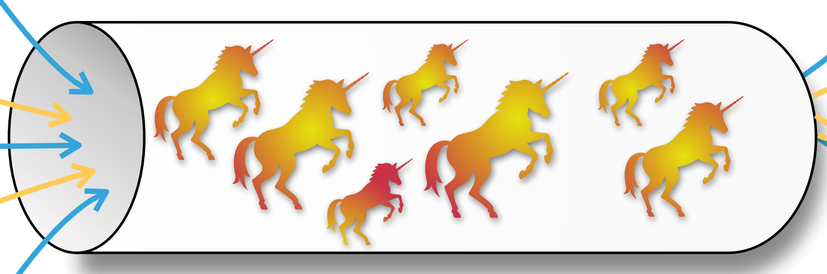
Data sets in the wild

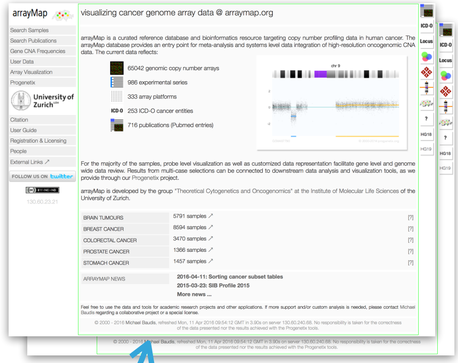
DATA PIPELINE

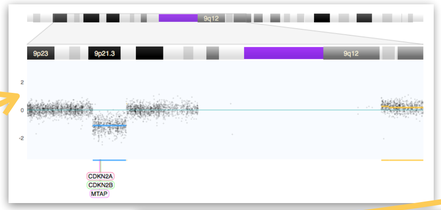


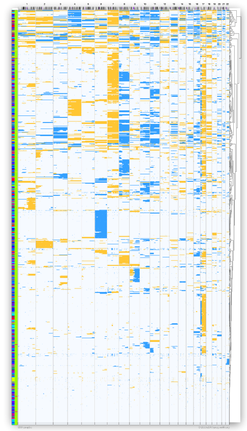


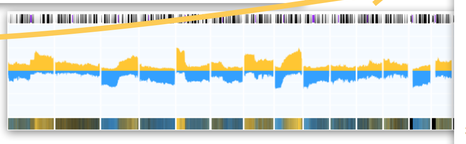


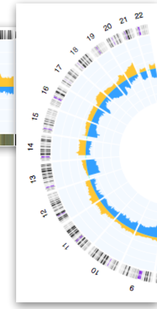


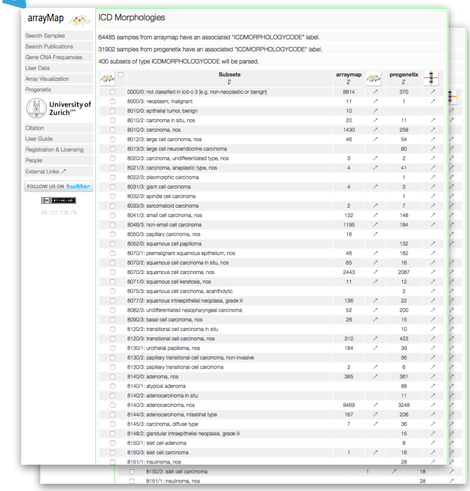












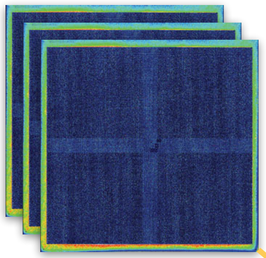
arrayMap

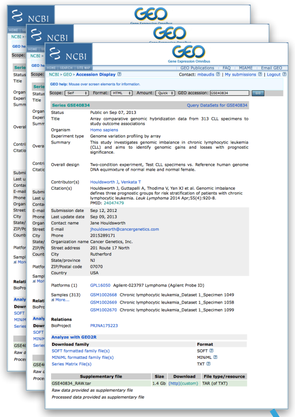
progenetix

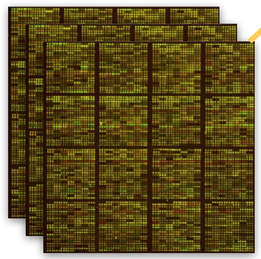
DATA PIPELINE

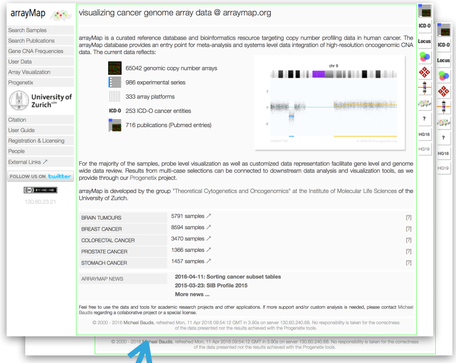
BIOCURATION

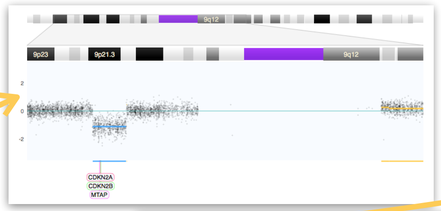
BIOINFORMATICS

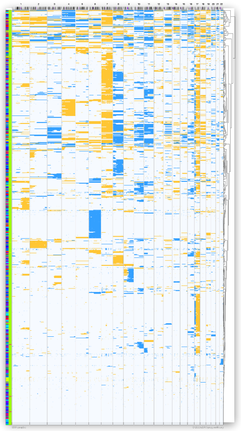


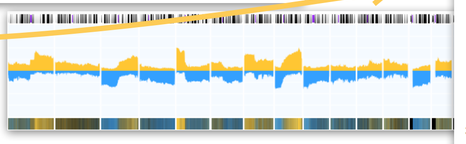


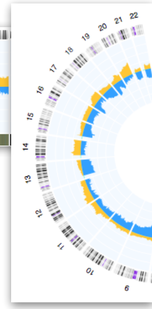


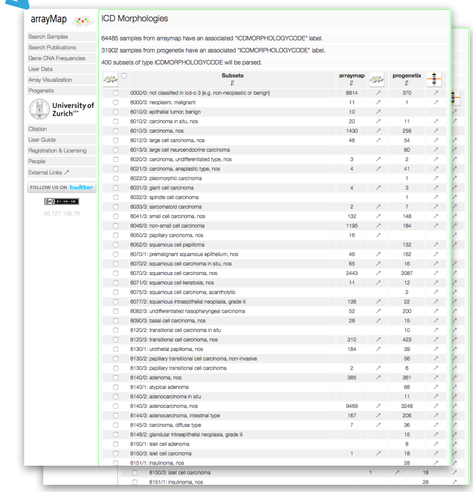












arrayMap

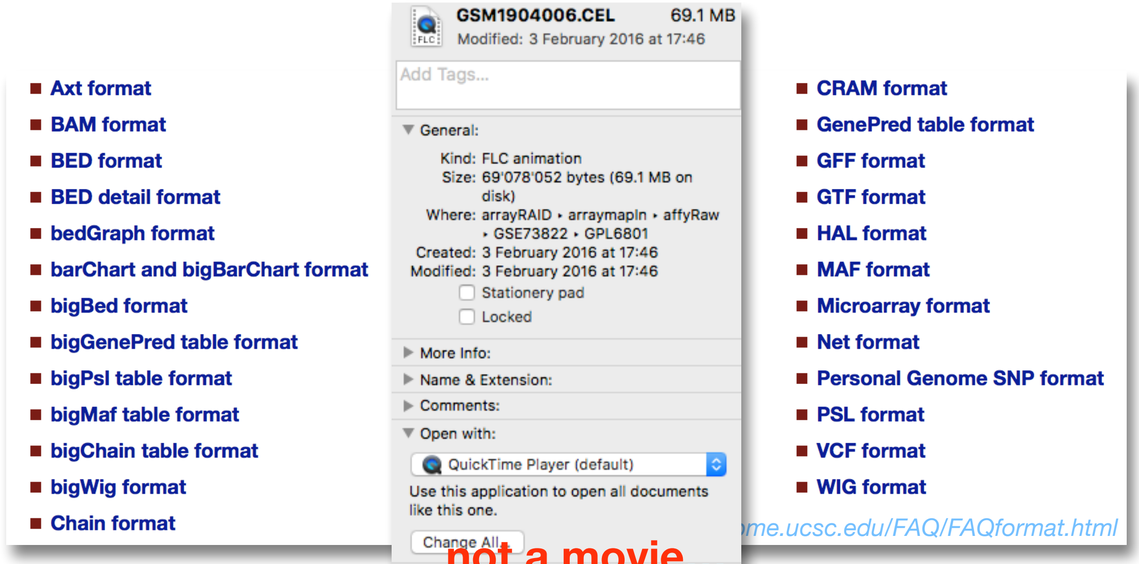
progenetix

Bioinformatics: Data Categories & Databases

- biological data comes in **3 main categories**:
  - **sequence** data (nucleic acids, aminoacids)
  - **structural** data (DNA, RNA, proteins; intracellular organisation, tissues ...)
  - **functional** data (interactions in time and space)
- data storage & retrieval: importance of local and connected **databases**
  - **primary databases** - for deposition of original, raw data (e.g. SRA - sequence read archive; ENA - European Nucleotide Archive; GEO - NCBI Gene Expression Omnibus; EBI arrayExpress...)
  - **derived databases / resources** - information resources providing agglomerated & **curated** data derived from primary sources (e.g. UniprotKB, nextProt, String, KEGG, Progenetix...)

Bioinformatics: File Formats, Ontologies & APIs

- **text** or **binary** file formats, optimised for specific types of biological data
- examples from genomics:
  - **BAM** - compressed binary version of Sequence Alignment/ Map (SAM)
  - **BED** (Browser Extensible Data) -flexible way to define the data lines in an genome browser annotation tracks
  - **VCF** (Variant Call Format)

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browser position chr7:127471196-127495720
browser hide all
track name="ItemRGBDemo" description="Item RGB                                    itemRgb="On"
chr7    127471196  127472363  Pos1  0  +  127                                    
chr7    127472363  127473530  Pos2  0  +  127472363  127473530  255,0,0
chr7    127473530  127474697  Pos3  0  +  127473530  127474697  255,0,0
chr7    127474697  127475864  Pos4  0  +  127474697  127475864  255,0,0
chr7    127475864  127477031  Neg1  0  -  127475864  127477031  0,0,255
chr7    127477031  127478198  Neg2  0  -  127477031  127478198  0,0,255
chr7    127478198  127479365  Neg3  0  -  127478198  127479365  0,0,255
chr7    127479365  127480532  Pos5  0  +  127479365  127480532  255,0,0
chr7    127480532  127481699  Neg4  0  -  127480532  127481699  0,0,255
```

BED file example

File Formats: VCF

Genomic variant storage standard

- The VCF Variant Call Format is an example for a widely used file format with "built-in logic"
- has been essential to master the "genomics data deluge" through providing "logic compression" for genomic annotations which rely on the notion of "assessed variant in a population"
- very expressive, but complex interpretation
- mix of "observed" and "population" variant concepts confusing for some use cases
- no replacement in sight (but new versions)

The Variant Call Format (VCF) Version 4.2 Specification

25 Jun 2020

The master version of this document can be found at `https://github.com/samtools/hts-specs`.
This printing is version 09fbcec from that repository, last modified on the date shown above.

1 The VCF specification

VCF is a text file format (most likely stored in a compressed manner). It contains meta-information lines, a header line, and then data lines each containing information about a position in the genome. The format also has the ability to contain genotype information on samples for each position.

1.1 An example

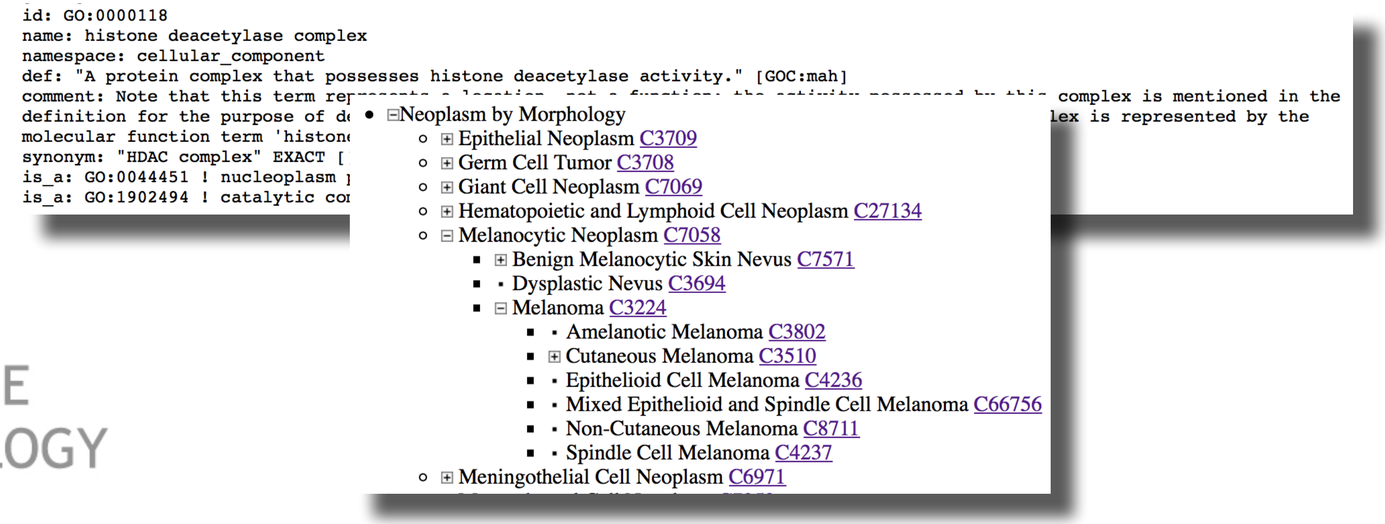
```
##fileformat=VCFv4.2
##fileDate=20090805
##source=myImputationProgramV3.1
##reference=file:///seq/references/1000GenomesPilot-NCBI36.fasta
##contig=<ID=20,length=62435964,assembly=B36,md5=f126cdf8a6e0c7f379d618ff66beb2da,species="Homo sapiens",taxonomy=x>
##phasing=partial
##INFO=<ID=NS,Number=1,Type=Integer,Description="Number of Samples With Data">
##INFO=<ID=DP,Number=1,Type=Integer,Description="Total Depth">
##INFO=<ID=AF,Number=A,Type=Float,Description="Allele Frequency">
##INFO=<ID=AA,Number=1,Type=String,Description="Ancestral Allele">
##INFO=<ID=DB,Number=0,Type=Flag,Description="dbSNP membership, build 129">
##INFO=<ID=H2,Number=0,Type=Flag,Description="HapMap2 membership">
##FILTER=<ID=q10,Description="Quality below 10">
##FILTER=<ID=s50,Description="Less than 50% of samples have data">
##FORMAT=<ID=GT,Number=1,Type=String,Description="Genotype">
##FORMAT=<ID=GQ,Number=1,Type=Integer,Description="Genotype Quality">
##FORMAT=<ID=DP,Number=1,Type=Integer,Description="Read Depth">
##FORMAT=<ID=HQ,Number=2,Type=Integer,Description="Haplotype Quality">
#CHROM POS     ID        REF    ALT     QUAL FILTER INFO                              FORMAT      NA00001        NA00002        NA00003
20     14370   rs6054257 G      A       29   PASS   NS=3;DP=14;AF=0.5;DB;H2           GT:GQ:DP:HQ 0|0:48:1:51,51 1|0:48:8:51,51 1/1:43:5:.,.
20     17330   .         T      A       3    q10    NS=3;DP=11;AF=0.017               GT:GQ:DP:HQ 0|0:49:3:58,50 0|1:3:5:65,3   0/0:41:3
20     1110696 rs6040355 A      G,T     67   PASS   NS=2;DP=10;AF=0.333,0.667;AA=T;DB GT:GQ:DP:HQ 1|2:21:6:23,27 2|1:2:0:18,2   2/2:35:4
20     1230237 .         T      .       47   PASS   NS=3;DP=13;AA=T                   GT:GQ:DP:HQ 0|0:54:7:56,60 0|0:48:4:51,51 0/0:61:2
20     1234567 microsat1 GTC    G,GTCT  50   PASS   NS=3;DP=9;AA=G                    GT:GQ:DP    0/1:35:4       0/2:17:2       1/1:40:3
```

Bioinformatics: File Formats, Ontologies & APIs

- ontologies in information sciences describe concrete and abstract **objects**, there precisely defined **hierarchies** and **relationships**
- ontologies in bioinformatics support the move from a descriptive towards an **analytical science** in describing biological data and relations among it

> "The widest use of ontologies within biology is for conceptual annotation – a representation of stored knowledge **more computationally amenable than natural language**."*

- Gene ontology (GO)
- NCIt Neoplasm Core
- UBERON anatomical structures
- Experimental Factor Ontology (EFO)
- Disease Ontology (DO)



Ontologies in bioinformatics. R Stevens, C Wroe, P Lord and C Goble, Department of Computer Science, University of Manchester. Retrieved from http://homepages.cs.ncl.ac.uk/phillip.lord/download/publications/handbook.pdf

Standardized Data

Data re-use depends on standardized, machine-readable metadata

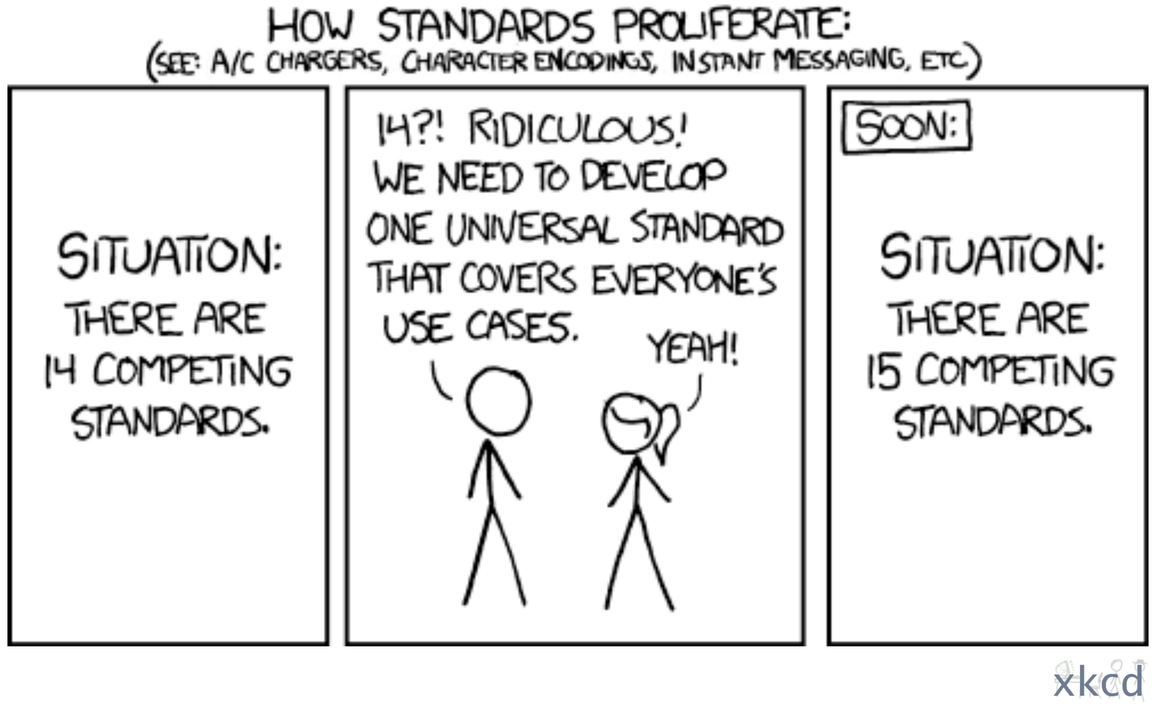
- Multiple international initiatives (ELIXIR, GA4GH, MONARCH...) and resource providers (EBI, NCBI ...) work on the generation and implementation of data annotation standards
- emerging / established principles are the use of **hierarchical** coding systems where individual codes are represented as CURIEs
- other formats for non-categorical annotations based on international standards, e.g.
  - ISO (ISO 8601 time & period, ISO 3166 country codes ...)
  - IETF (GeoJSON ...)
  - W3C (CURIE ...)
- these standards become pervasive throughout GA4GH's ecosystem (e.g. Phenopackets ...)


```
    "label" : "no restriction",
    "id" : "DUO:0000004"
  },

  "provenance" : {
    "material" : {
      "type" : {
        "id" : "EFO:0009656",
        "label" : "neoplastic sample"
      }
    },
    "geo" : {
      "label" : "Zurich, Switzerland",
      "precision" : "city",
      "city" : "Zurich",
      "country" : "Switzerland",
      "latitude" : 47.37,
      "longitude" : 8.55,
      "geojson" : {
        "type" : "Point",
        "coordinates" : [
          8.55,
          47.37
        ]
      },
      "ISO-3166-alpha3" : "CHE"
    }
  },
  {
    "age": "P25Y3M2D"
```

Standardized Data

Data re-use depends on standardized, machine-readable metadata




```
    "label" : "no restriction",
    "id" : "DUO:0000004"
  },

  "provenance" : {
    "material" : {
      "type" : {
        "id" : "EFO:0009656",
        "label" : "neoplastic sample"
      }
    },
    "geo" : {
      "label" : "Zurich, Switzerland",
      "precision" : "city",
      "city" : "Zurich",
      "country" : "Switzerland",
      "latitude" : 47.37,
      "longitude" : 8.55,
      "geojson" : {
        "type" : "Point",
        "coordinates" : [
          8.55,
          47.37
        ]
      },
      "ISO-3166-alpha3" : "CHE"
    }
  },
  {
    "age": "P25Y3M2D"
```

Schemas for Data & APIs - Standardization & Documentation!

BeaconAlleleRequest beacon ↗

{S}[B] Status [i]	**implemented**
Provenance	○ Beacon API
Used by	○ Beacon ○ Progenetix database schema (Beacon+ backend)
Contributors	○ Marc Fiume ○ Michael Baudis ○ Sabela de la Torre Pernas ○ Jordi Rambla ○ Beacon developers...
Source (v1.1.0)	○ raw source [JSON] ○ Github

Attributes

Type: object
Description: Allele request as interpreted by the beacon.

Properties

Property	Type
alternateBases	string
assemblyId	string
datasetIds	array of string
end	integer
endMax	integer
endMin	integer
mateName	https://schemablocks.org/schemas/beacon/v1.1.0/Chromosome.json [SRC] [HTML]
referenceBases	string
referenceName	https://schemablocks.org/schemas/beacon/v1.1.0/Chromosome.json [SRC] [HTML]
start	integer (int64)
startMax	integer
startMin	integer
variantType	string

alternateBases

- type: string

The bases that appear instead of the reference bases. Accepted values: [ACGTN]*. N is a wildcard, that denotes the position of any base, and can be used as a standalone base of any type or within a partially known sequence. For example a sequence where the first and last bases are known, but the middle portion can exhibit countless variations of [ACGT], or the bases are unknown: ANNT the Ns can take take any form of [ACGT], which makes both ACCT and ATGT (or any other combination) viable sequences.

Symbolic ALT alleles (DEL, INS, DUP, INV, CNV, DUP:TANDEM, DEL:ME, INS:ME) will be represented in `variantType`.

Optional: either `alternateBases` or `variantType` is required.

`alternateBases` **Value Example**

assemblyId

- type: string

Assembly identifier (GRC notation, e.g. GRCh37).

`assemblyId` **Value Example**

Curie sb-vr-spec ↗

{S}[B] Status [i]	
Provenance	
Used by	
Contributors	
Source (v1.0)	

Attributes

Type: string
Pattern: ^\w[^:]+:.+$
Description: A string that refers
sender.

VR does not impose any contrair
data, the VR Specification RECOM

String CURIEs are represented a
`namespace:accession` or `name`

The VR specification also RECOM

The `reference` component is ar

A CURIE is a URI. URIs may *locat*
VR uses CURIEs primarily as a na

Implementations MAY provide C

Using internal ids in public mess

`Curie` **Value Examples**

```
"ga4gh:GA.01234abcde"
```

```
"DUO:0000004"
```

```
"orcid:0000-0003-3463-0775"
```

```
"PMID:15254584"
```

Biosample sb-phenopackets ↗

{S}[B] Status [i]	**implemented**
Provenance	○ Phenopackets
Used by	○ Phenopackets
Contributors	○ GA4GH Data Working Group ○ Jules Jacobsen ○ Peter Robinson ○ Michael Baudis ○ Melanie Courtot ○ Isuru Liyanage
Source (v1.0.0)	○ raw source [JSON] ○ Github

Attributes

Type: object
Description: A Biosample refers to a unit of biological material from which the substrate molecules (e.g. genomic DNA, RNA, proteins) for molecular analyses (e.g. sequencing, array hybridisation, mass-spectrometry) are extracted.

Examples would be a tissue biopsy, a single cell from a culture for single cell genome sequencing or a proteir fraction from a gradient centrifugation.

Several instances (e.g. technical replicates) or types of experiments (e.g. genomic array as well as RNA-seq experiments) may refer to the same Biosample.

FHIR mapping: Specimen.

Properties

Property	Type
ageOfIndividualAtCollection	https://schemablocks.org/schemas/sb-phenopackets/v1.0.0/Age.json [SRC] [HTML]
ageRangeOfIndividualAtCollection	https://schemablocks.org/schemas/sb-phenopackets/v1.0.0/AgeRange.json [SRC] [HTML]
description	string
diagnosticMarkers	array of https://schemablocks.org/schemas/sb-phenopackets/v1.0.0/OntologyClass.json [SRC] [HTML]
histologicalDiagnosis	https://schemablocks.org/schemas/sb-phenopackets/v1.0.0/OntologyClass.json [SRC] [HTML]
htsFiles	array of https://schemablocks.org/schemas/sb-phenopackets/v1.0.0/HtsFile.json [SRC] [HTML]
id	string
individualId	string
isControlSample	boolean
phenotypicFeature	array of https://schemablocks.org/schemas/sb-phenopackets/v1.0.0/PhenotypicFeature.json [SRC] [HTML]
procedure	https://schemablocks.org/schemas/sb-phenopackets/v1.0.0/Procedure.json [SRC] [HTML]
sampledTissue	https://schemablocks.org/schemas/sb-

Checksum sb-checksum ↗

{S}[B] Status [i]	**proposed**
Provenance	○ GA4GH DRS (`develop` branch)
Used by	○ GA4GH DRS ○ GA4GH TRS
Contributors	○ Susheel Varma
Source (v0.0.1)	○ raw source [JSON] ○ Github

Attributes

Type: object
Description: Checksum

Properties

Property	Type
checksum	string
type	string

checksum

- type: string

The hexadecimal encoded (Base16) checksum for the data

`checksum` **Value Example**

```
"77af4d6b9913e693e8d0b4b294fa62ade6054e6b2f1ffb617ac955dd63fb0182"
```

type

- type: string

The digest method used to create the checksum. The value (e.g. `sha-256`) SHOULD be listed as `Hash Name String` in the GA4GH Hash Algorithm Registry. Other values MAY be used, as long as implementors are aware of the issues discussed in RFC6920.

GA4GH may provide more explicit guidance for use of non-IANA-registered algorithms in the future.

`type` **Value Example**

```
"sha-256"
```

Bioinformatics: File Formats, Ontologies & APIs

- databases can be accessed through **A**pplication **P**rogramming **I**nterfaces
- ***API*** *: set of routines, protocols, and tools that specifies how software components interact, to exchange data and processing capabilities*
- web API example: implementing geographic maps, with parameters provided by the client (e.g. location coordinates, quantitative payload)
- web APIs provide a *machine readable* response to queries over HTTP
- bioinformatic applications frequently make use of web APIs for **data retrieval** or genome browser APIs for **data display**
- bioinformatics software libraries for API functionality are usually implemented in **Perl**, **Python** and/or **R**

Bioinformatics: File Formats, Ontologies & APIs


```
{
    "$schema":"https://raw.githubusercontent.com/ga4gh-beacon/
beacon-v2/main/framework/json/requests/beaconRequestBody.json",
    "meta": {
        "apiVersion": "2.0",
        "requestedSchemas": [
            {
                "entityType": "genomicVariation",
                "schema:": "https://raw.githubusercontent.com/
ga4gh-beacon/beacon-v2/main/models/json/beacon-v2-default-
model/genomicVariations/defaultSchema.json"
            }
        ]
    },
    "query": {
        "requestParameters": {
            "g_variant": {
                "referenceName": "NC_000017.11",
                "start": [ 5000000, 7676592 ],
                "end": [ 7669607, 10000000 ],
                "variantType": "DEL"
            }
        }
    },
    "requestedGranularity": "record",
    "pagination": {
        "skip": 0,
        "limit": 5
    }
}
```

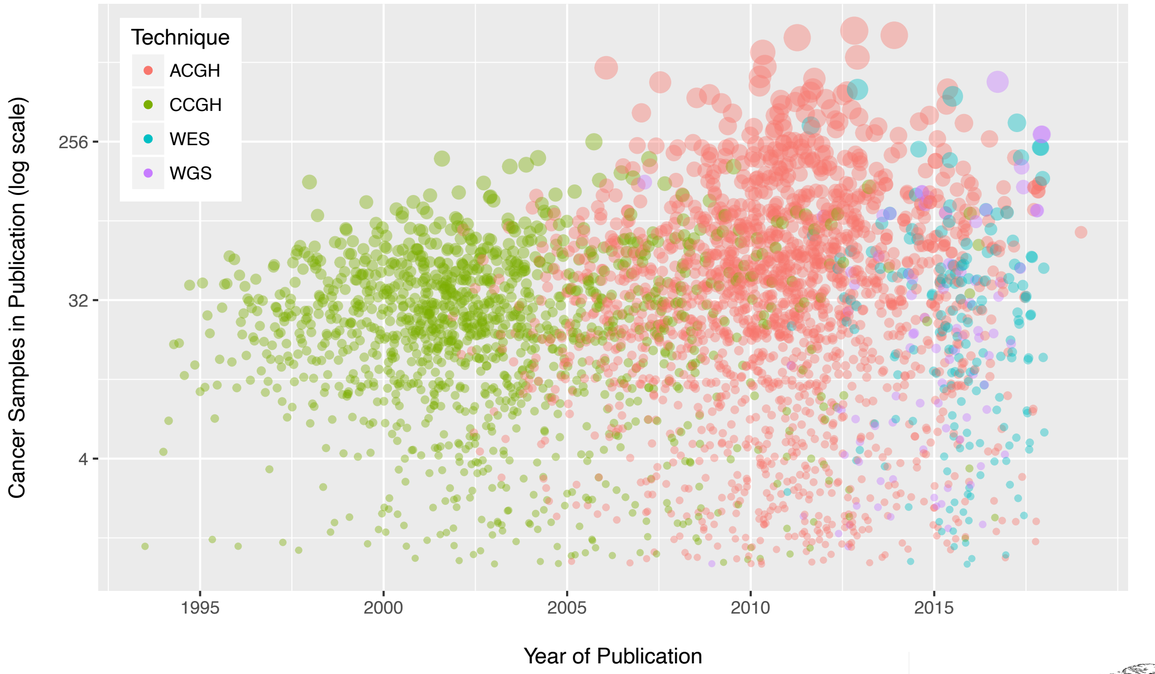


```
{
  "meta": {
    "apiVersion": "v2.0.0",
    "beaconId": "org.progenetix.beacon",
    "createDateTime": "2015-11-13 00:00:00",
    "receivedRequestSummary": {
      "apiVersion": "v2.0.0",
-------------------------------------------------------------
  "response": {
    "resultSets": [
      {
        "exists": true,
        "id": "progenetix",
        "info": {
          "counts": {
            "callCount": 525,
            "sampleCount": 515,
            "variantCount": 247
          }
        },
        "paginatedResultsCount": 247,
        "results": [
          {
            "caseLevelData": [
              {
                "analysisId": "pgxcs-kftwbzza",
                "biosampleId": "pgxbs-kftviv0x",
                "id": "pgxvar-5c86619f09d374f2dc3bbfcd"
              },
```


http://docs.genomebeacons.org/variant-queries/

Data Science: Meta-Studies of Metadata

Publication Landscape of Cancer CNV Profiling

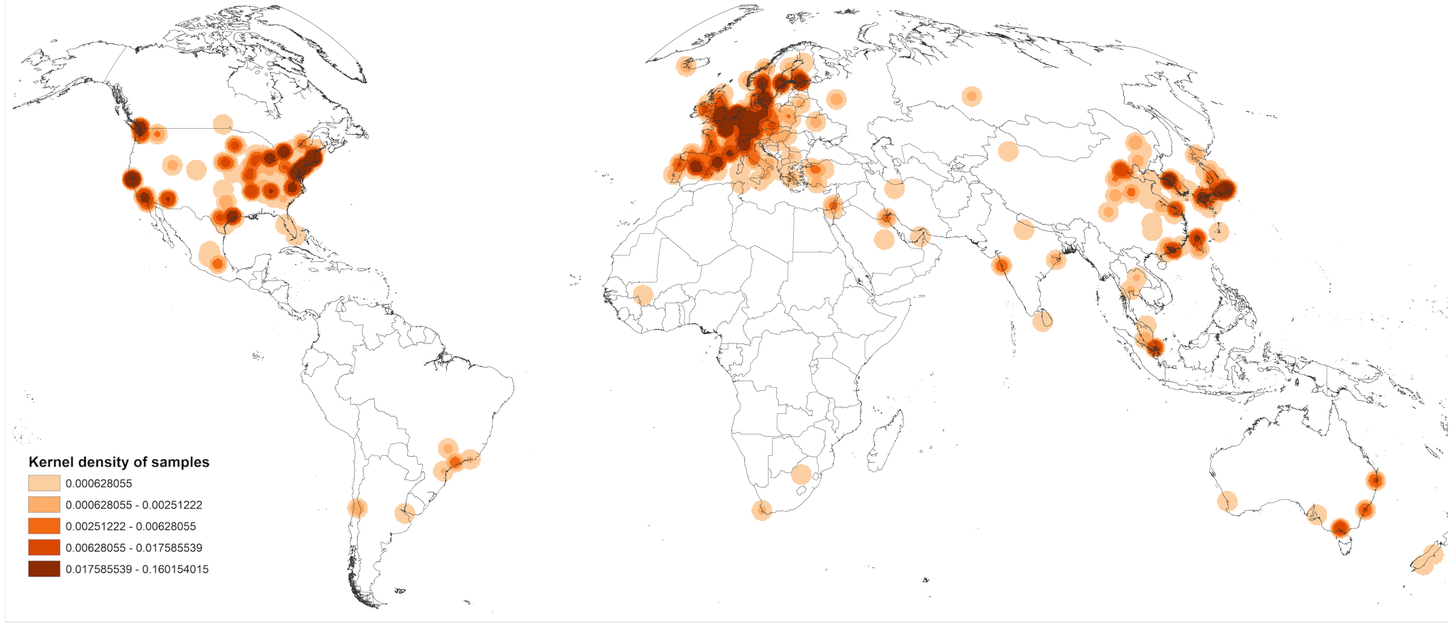


Publication statistics for cancer genome screening studies. The graphic shows our assessment of publications reporting whole-genome screening of cancer samples, using molecular detection methods (chromosomal CGH, genomic array technologies, whole exome and genome sequencing).

For the years 1993-2018, we found 3'229 publications reporting 174'530 individual samples in single series from 1 to more than 1000 samples. Y-axis and size of the dots correspond to the sample number; the color codes indicate the technology used.

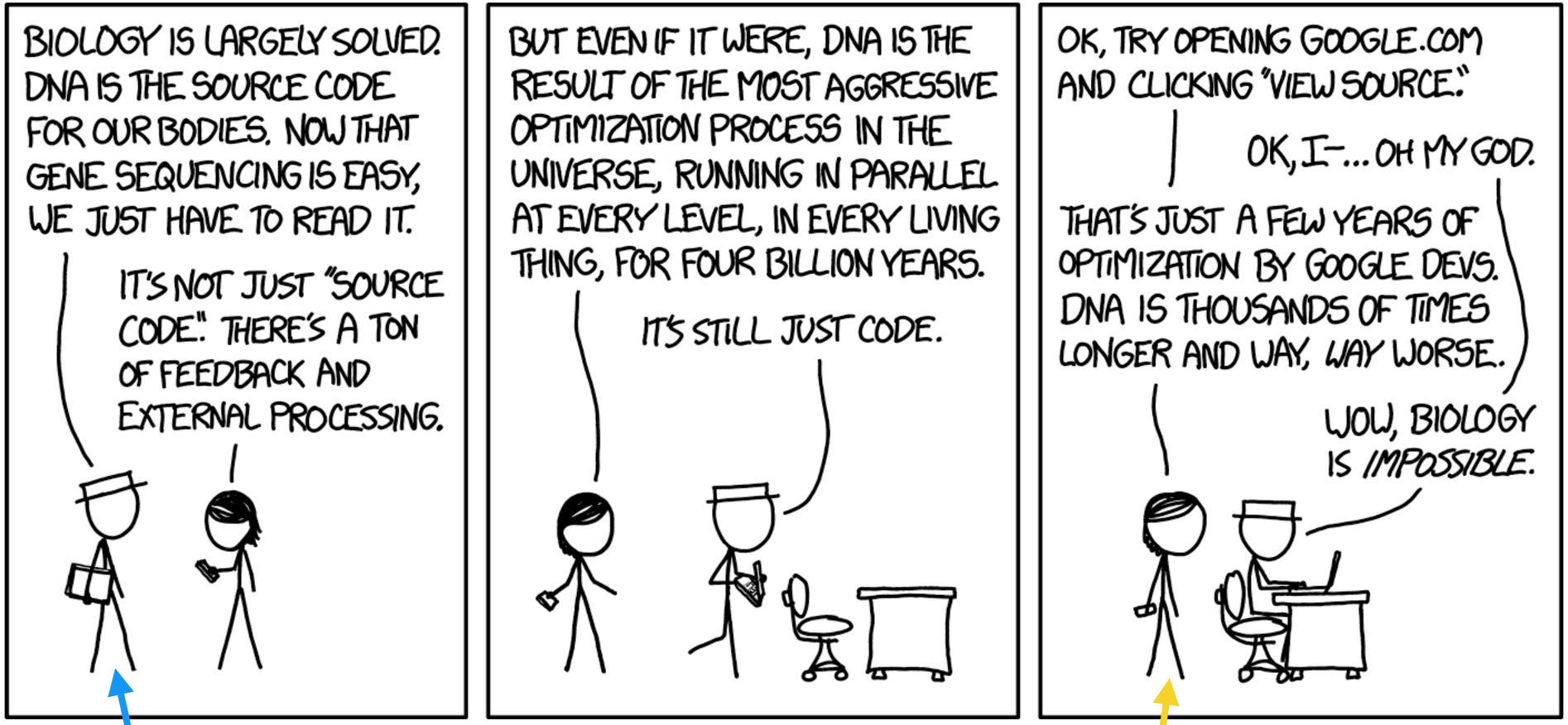
Map of the geographic distribution (by first author affiliation) of the 104'543 genomic array, 36'766 chromosomal CGH and 15'409 whole genome/exome based cancer genome datasets.

The numbers are derived from the 3'240 publications registered in the Progenetix database.



progenetix

Who is a Bioinformatician?



Randall Munroe: https://xkcd.com/1605/

bioinformatician

bioinformatician

But: What is not bioinformatics, though being "bio" and using computers?

- *"I do not think all biological computing is bioinformatics, e.g. **mathematical modelling** is not bioinformatics, even when connected with biology-related problems. In my opinion, bioinformatics has to do with management and the subsequent use of biological information, particular genetic information."* (Richard Durbin)
- **biologically-inspired computation** (neural networks etc.) - though their application may be part of bioinformatics
- **computational & systems biology**, where the emphasis is on **modelling** rather than on **data interpretation**

Bioinformatics OR **Computational / Systems Biology?**

- **Bioinformatics**

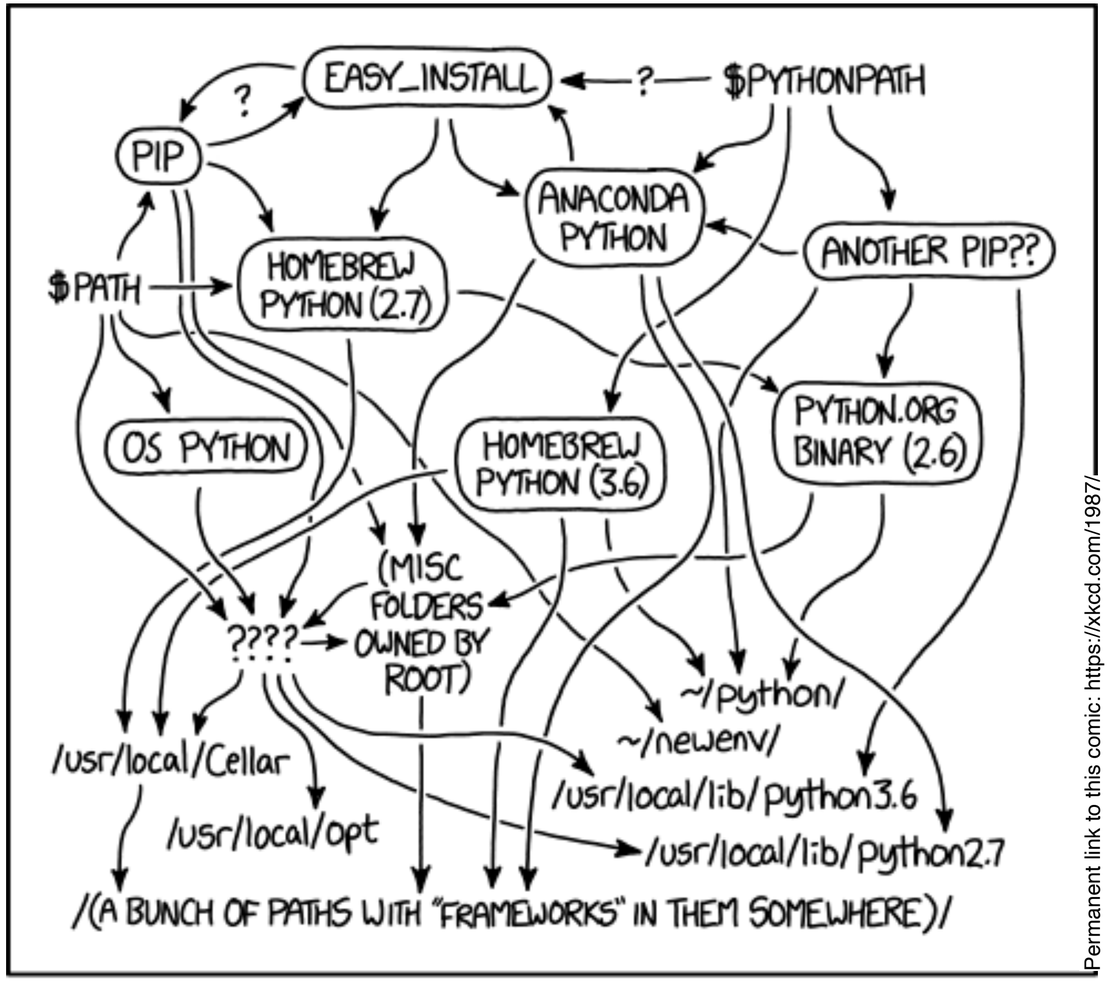
  Research, development, or **application** of computational **tools** and approaches to make the vast, diverse and complex **life sciences data** more understandable and useful

- **Computational Biology**

  The development and application of **mathematical** and computational **approaches** to address **theoretical** and experimental questions in biology

source: Colin Dewey (UWisc): "Introduction to Bioinformatics Fall 2016"

But in reality that is what bioinformaticians do...



xkcd


ESC
F1
F2
F3
F4
~ `
! 1
@ 2
# 3
$ 4
% 5
^ 6
& 7
TAB
Q
W
E
R
T
Y
CAPSLK
A
S
D
F
G
H
SHIFT
Z
X
C
V
B

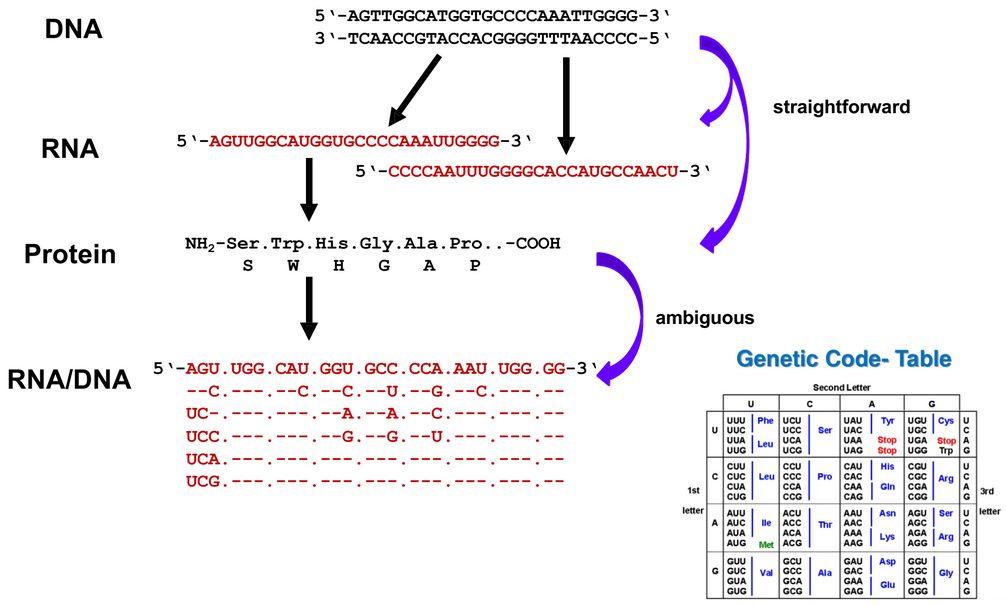
BIO390: Course Schedule

- 2022-09-19: Christian von Mering - Sequence Bioinformatics
- 2022-09-26: Michael Baudis - What is Bioinformatics? Introduction and Resources
- 2022-10-03: Mark Robinson - Statistical Bioinformatics
- 2022-10-10: Shinichi Sunagawa (ETHZ) - Metagenomics
- 2022-10-17: Izaskun Mallona - Regulatory Genomics and Epigenomics
- 2022-10-24: Valentina Boeva (ETHZ) - Machine Learning for Biological Use Cases
- 2022-10-31: Katja Baerenfaller (SIAF) - Proteomics
- 2022-11-07: Pouria Dasmeh - Biological Networks
- 2022-11-14: Patrick Ruch - Text mining & Search Tools
- 2022-11-23: Ahmad Aghaebrahimian (ZHAW) - Semantic Web
- 2022-11-28: Michael Baudis - Building a Genomics Resource
- 2022-12-05: Valérie Barbie (SIB) - Clinical Bioinformatics
- 2022-12-12: Michael Baudis - Genome Data & Privacy | Feedback
- 2022-12-19: Exam (Multiple Choice)

Biological Sequence Informatics

Christian von Mering

Sequences can be interconverted computationally



Genetic Code- Table

1st letter	Second Letter: U	C	A	G	3rd letter
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U
	UUC Phe	UCC Ser	UAC Tyr	UGC Cys	C
	UUA Leu	UCA Ser	UAA Stop	UGA Stop	A
	UUG Leu	UCG Ser	UAG Stop	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC Leu	CCC Pro	CAC His	CGC Arg	C
	CUA Leu	CCA Pro	CAA Gln	CGA Arg	A
	CUG Leu	CCG Pro	CAG Gln	CGG Arg	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC Ile	ACC Thr	AAC Asn	AGC Ser	C
	AUA Ile	ACA Thr	AAA Lys	AGA Arg	A
	AUG Met	ACG Thr	AAG Lys	AGG Arg	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC Val	GCC Ala	GAC Asp	GGC Gly	C
	GUA Val	GCA Ala	GAA Glu	GGA Gly	A
	GUG Val	GCG Ala	GAG Glu	GGG Gly	G

Sequence Similarity

Many possible definitions of “similarity”: length, character content, character distribution,…..

Biological definition: (interrupted) stretches of **identical** or **similar** characters

E.g. search identical sequence segments for assembly of long sequences from short, overlapping fragments

```
AAGCTTACCAAAATTGAAGGGACGTTGACGTAGGGGGACGCTTTAG
                                  GACGCTTTAGTTTAGCCACCGGTATTTAGC
```

Similar characters: physico-chemical characteristics, functional characteristics, evolutionary relation……

Comparison of two (or more) sequences: **Alignment** of identical and similar sequence segments

```
AAGCTTACCAAAATTGAAGGGACGTTGACGTAGGGGGACGCTTTAG
    AATCTAGCAATTATTGAAGGGACGTTGACGAAGGGGTTCGCTACCG
```

Challenge: Find the best possible alignment **(and do it fast)**

```
AAGCTTACCAAAATTGAAGGGACGTTGACGTAGGGGGACGCTTTAG
AATCTAGCAATTATTGAAGGGACGTTGACGAAGGGGTTCGCTACCG
```

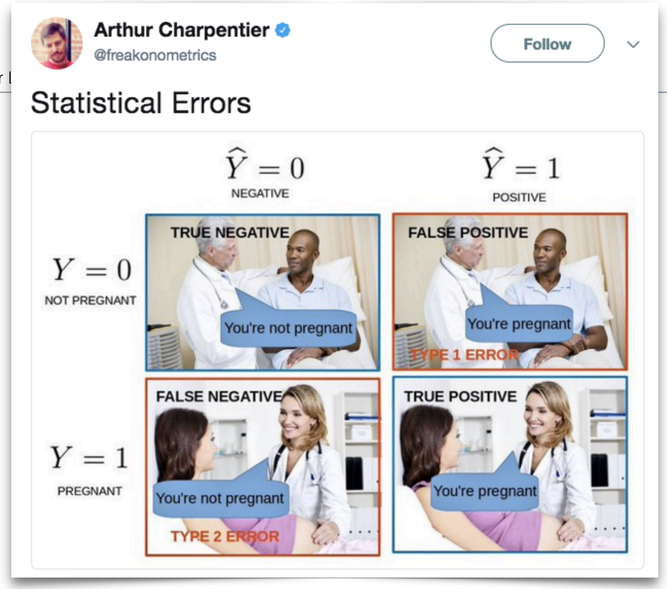
Statistical Bioinformatics

Mark Robinson

False positives /
false negatives

Most statistical testing regimes set an error rate (5%)

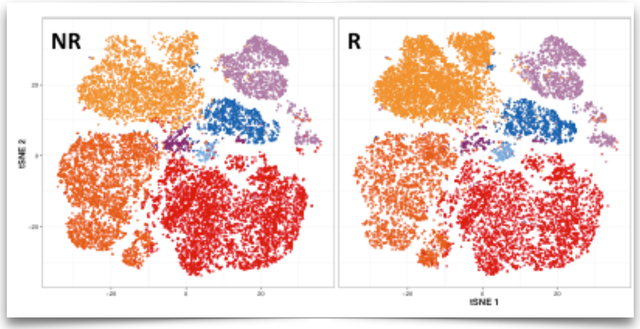
Type I error = false positive
Type II error = false negative



https://twitter.com/freakonometrics/status/779060142239260672

Differential abundance of cell populations

tSNE projection
(each dot = cell,
cells from multiple
patients)



NR: non-responders
R: responders

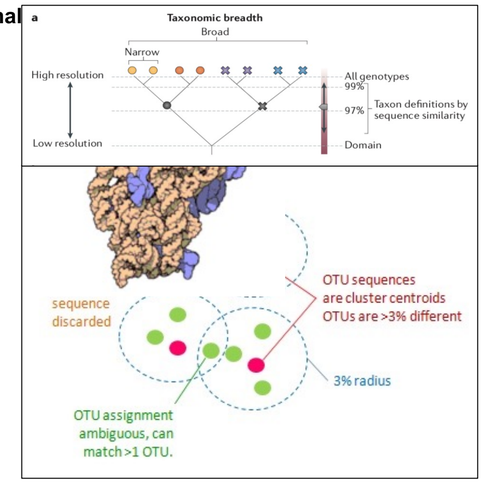
Under the hood: Generalized linear mixed model to assess the change in relative abundance of subpopulations.

Metagenomics

Shinichi Sunagawa (ETHZ)

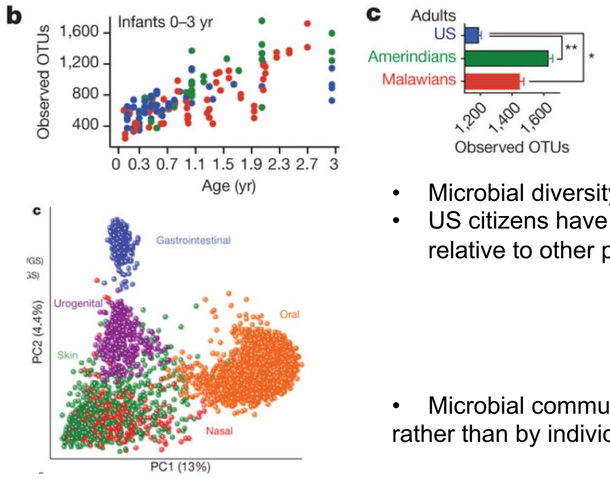
Review: 16S rRNA-based Operational Taxonomic Units (OTUs)

- 16S rRNA
  - present in all prokaryotes
  - conserved function as integral part of the protein synthesis machinery
  - similar mutation rate: → molecular clock
- Proxy for phylogenetic relatedness of organisms
- Owing to lack of prokaryotic species definition, 97% sequence similarity is often used to define ‘species’-like:
  “**Operational Taxonomic Units” (OTUs)**



Hanson et al., Nat Rev Microbiol, 2012

Applied examples I



- Microbial diversity in human gut increases with age
- US citizens have harbor less diverse gut microbiota relative to other populations

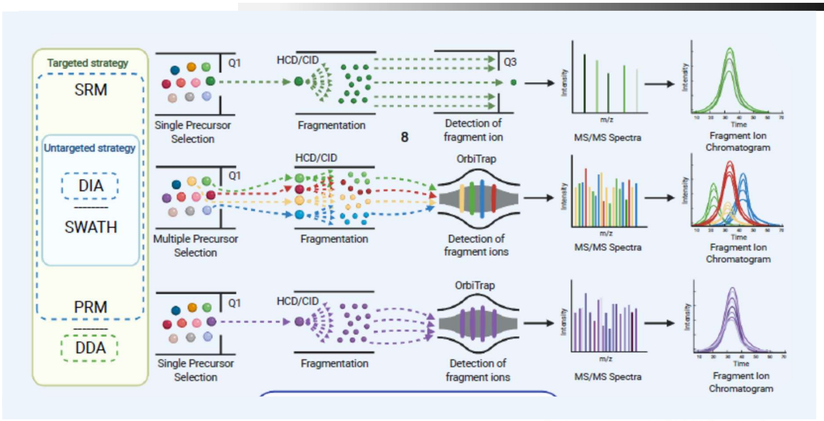
- Microbial communities cluster by human body site rather than by individual

Top: Yatsunenko *et al. Nature* (2012); Bottom: C Huttenhower *et al. Nature* (2012)

Proteomics

Katja Bärenfaller (SIAF)

Hypothesis-driven, targeted bottom-up proteomics approaches



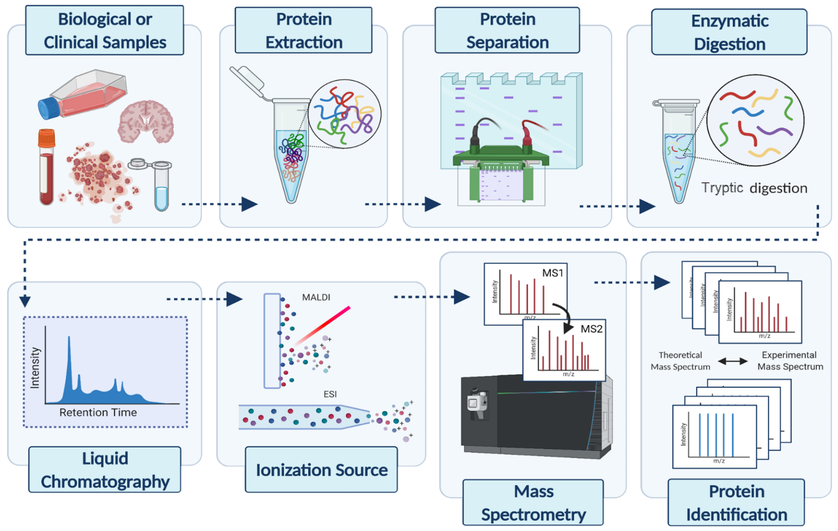
Radzikowska et al., *EAACI Position Paper,* in revision

S/MRM: Selected/Multiple Reaction Monitoring; the proteins are pre-selected and provide information on the characteristic peptide precursor and fragment ion signals (transitions)

DIA/SWATH: Data Independent Acquisition/Sequential Windowed Acquisition of All Theoretical Mass Spectra

fragment ion signals from a precursor ion

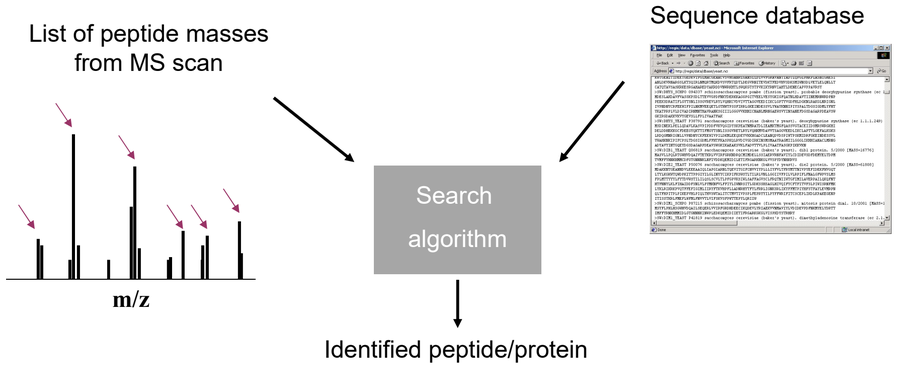
Generic mass spectrometry-based proteomics experiment



Mass spectrometry

Peptide Mass Fingerprint

Identifying peptides using an MS spectrum:



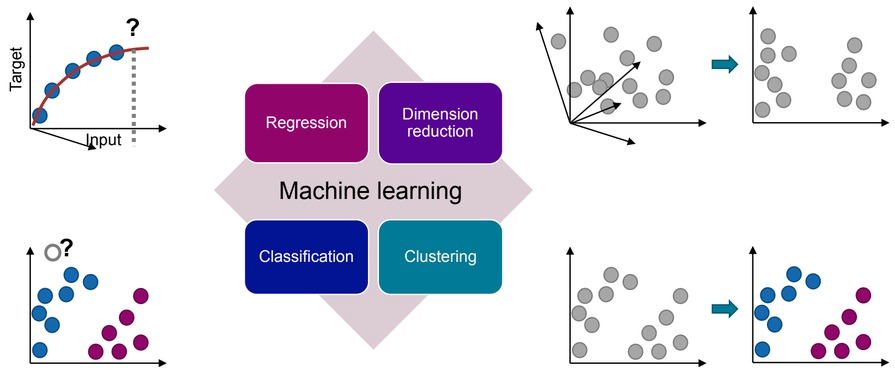
- Peptide spectrum assignment with Peptide Mass Fingerprinting is only advisable with samples of low complexity and small sequence databases, as the number of all possible peptides with a given mass over charge is huge in large sequence databases.

Mass spectrometry

Machine Learning for Biological Use Cases

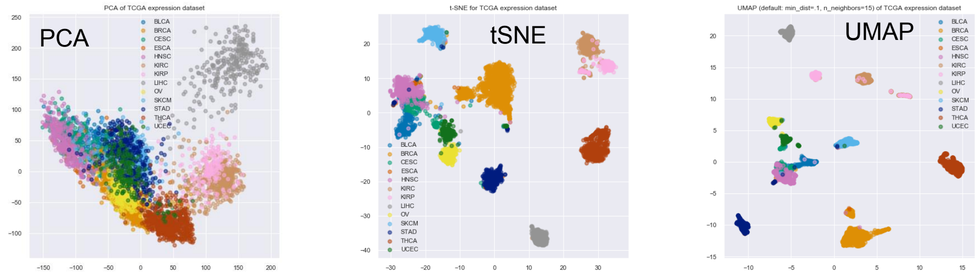
Valentina Boeva (ETHZ)

Map of classical machine learning methods



Uniform Manifold Approximation and Projection (UMAP)

- UMAP: nonlinear dimensionality reduction technique. Idea is similar to tSNE, but
  - Much faster
  - Not limited to the first 2-3 dimensions
  - Uses binary cross-entropy as a cost function instead of the KL-divergence
  - Preserves global structure
  - Uses the number of nearest neighbors instead of perplexity



First introduced by McInnes, L, Healy, J, ArXiv e-prints 1802.03426, 2018

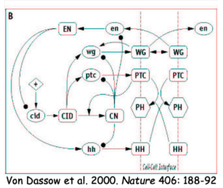
Biological Networks

Pouria Dasmeh / Andreas Wagner

Cell-biological networks

1. Small networks dedicated to a specific task
(up to dozens of gene products)

Chemotaxis
Cell-cycle regulation
Fruit fly segmentation
Flower development
...



Von Dassow et al. 2000. Nature 406: 188-92

Mathematical characterization based on detailed, quantitative biochemical information

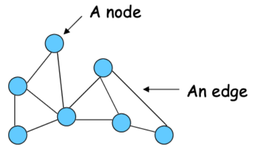
Cell-biological networks

2. Genome-scale networks
(hundreds to thousands of gene products)

Protein interaction networks
Metabolic networks
Transcriptional regulation networks
Genetic interaction networks
...

Mathematical characterization based on qualitative understanding of network topology

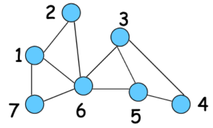
Graphs



A graph G=(V,E) comprises
a set V of nodes (vertices)
a set E of edges

$$V = \{V_1, \ldots, V_n\}$$
$$E = \{(V_i, V_j), \ldots, (V_k, V_l)\}$$

Protein interaction networks are undirected graphs
(Individual node pairs in *E* are unordered.)



The degree (connectivity) k_i of a node V_i is the number of edges incident with the node (e.g., k_1=3, k_6=5).

$$k_i = \sum_j a_{ij}$$

Graphs can be characterized according to their degree distribution P(k), the fraction of nodes having degree k.

Text Mining

Patrick Ruch (HES-SO Genève)

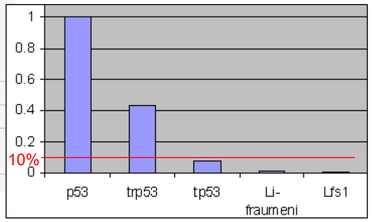
Features

- Words
- Subwords (character N-grams)
- Stems
- Word N-grams
- Syntactic entities (noun phrases, verb phrases, …),
- Semantic entities (gene names, chem. compounds, diseases, …)

Term normalization: database & ontology vs. reality !

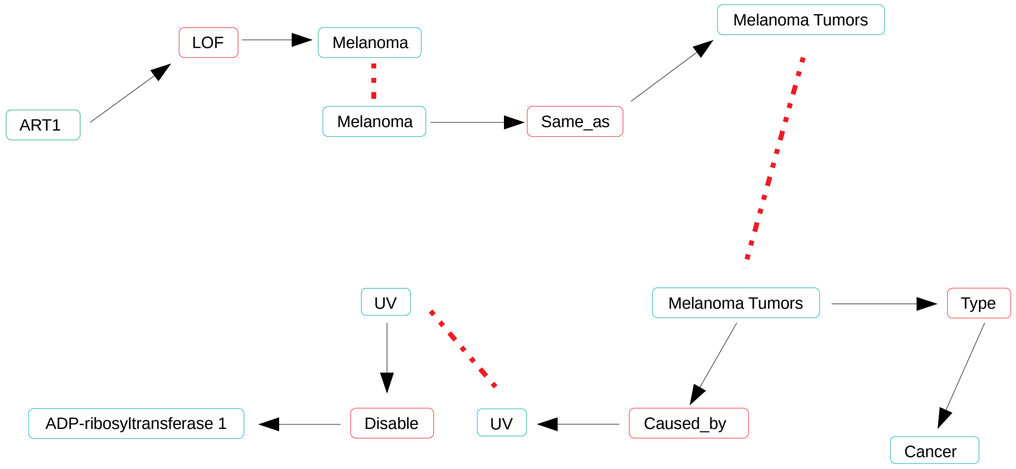
Antigen NY-CO-13	Protein	SwissProt:P04637
Cellular tumor antigen p53	Protein [preferred]	SwissProt:P04637
FLJ92943	Gene	EntrezGene:7157
LFS1	Gene	EntrezGene:7157
		HGNC:11998
Li-Fraumeni syndrome	Gene	HGNC:11998
p53	Gene	EntrezGene:7157
		HGNC:11998
P53	Gene	OMIM:191170
		SwissProt:P04637
p53 antigen	Gene	EntrezGene:7157
p53 transformation suppressor	Gene	EntrezGene:7157
p53 tumor suppressor	Gene	EntrezGene:7157
phosphoprotein p53	Gene	EntrezGene:7157
Phosphoprotein p53	Protein	SwissProt:P04637
TP53	Gene [preferred]	HGNC:11998
		SwissProt:P04637
	Gene	EntrezGene:7157
		OMIM:191170
transformation-related protein 53	Gene	EntrezGene:7157
TRANSFORMATION-RELATED PROTEIN 53	Gene	OMIM:191170
TRP53	Gene	EntrezGene:7157
		OMIM:191170
tumor protein p53	Gene [preferred]	HGNC:11998

Synonyms	#
p53	53362
trp53	23364
tp53	4156
li-fraumeni	775
lfs1	431



Semantic Web

Ahmad Aghaebrahimian (ZHAW)



Semantic Web Standards

RDF:

RDF is a **graph-based data model** and the set of **syntax** that allows us to write **description** about the resources on the web and to exchange them. It presents data in the **triple format** and gives it structures and unique identifiers so that data can be easily linked.

Principles:

Triple structure: (subject, predicate, object)

- subject → a URI resource
- predicate → binary type URI
- object → a URI resource or literal

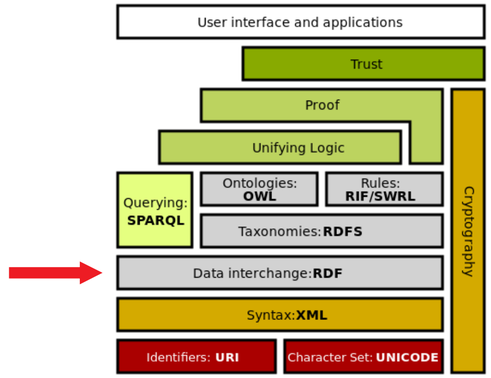
Predicates are labeled

Predicates are directed

RDF is a graph model

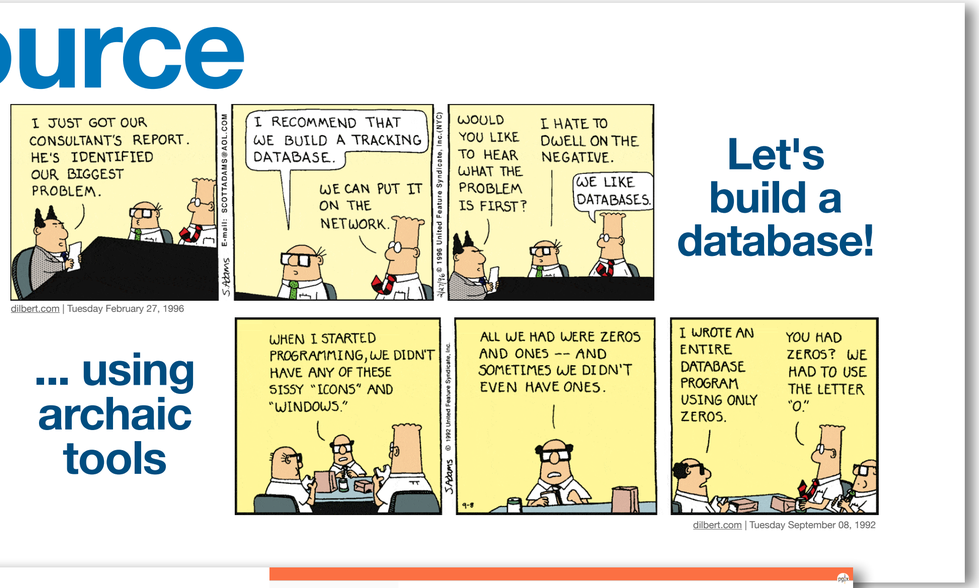
RDF serialization:

XML, N-triple, Turtle, TriG, JSON-LD



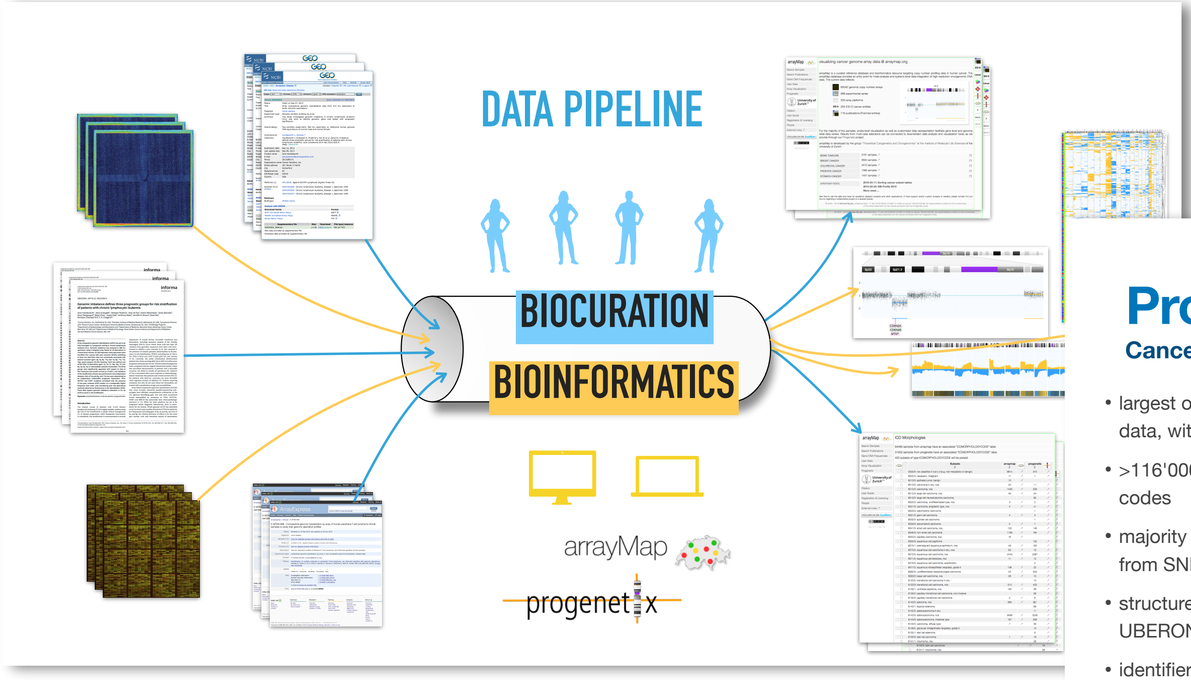
Building a Genomics Resource

Michael Baudis



Let's build a database!

... using archaic tools



Progenetix in 2021

Cancer Genomics Reference Resource

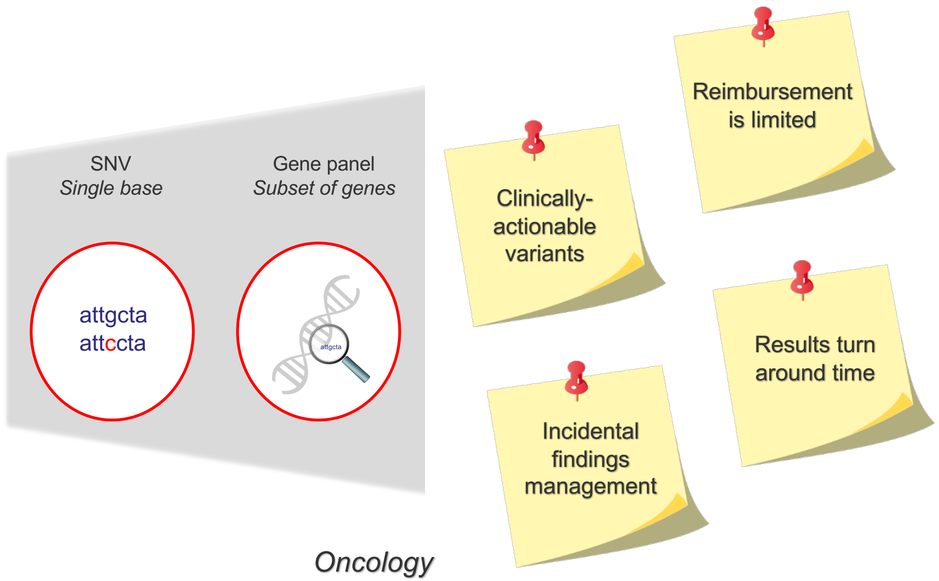
- largest open resource for curated cancer genome profiling data, with focus on copy number variations (CNV)
- >116'000 cancer CNV profiles, mapped to >800 NCIt codes
- majority of data from genomic arrays with ~50% overall from SNP platforms with original data re-processing
- structured diagnostic encodings for NCIt, ICD-O 3, UBERON
- identifier mapping for PMID, GEO, Cellosaurus where appropriate
- core biosample and technical metadata annotations where accessible (TNM, genotypic sex, survival ...)
- publication database and code mapping services

progenetix

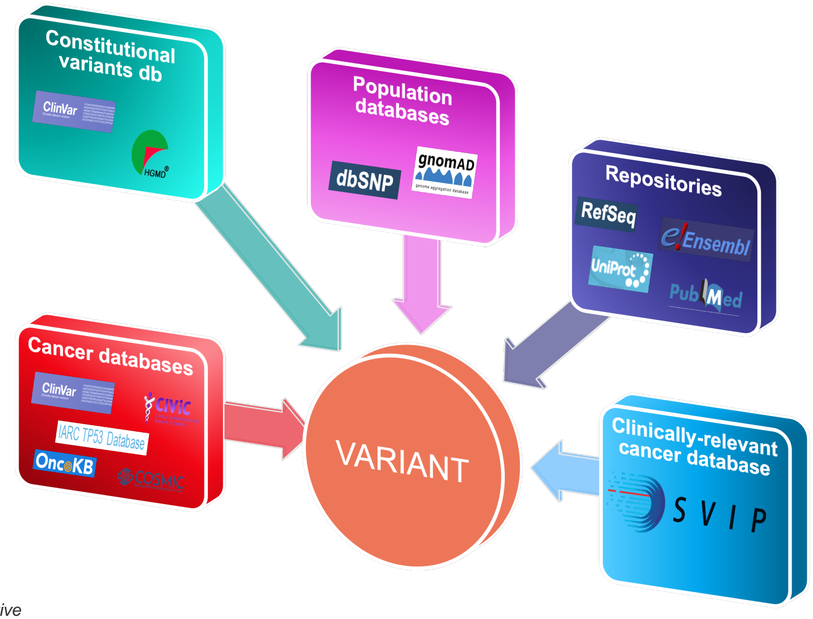
Clinical Bioinformatics

Valérie Barbié (Director SIB Clinical Bioinformatics)

Scale matters



Knowledge bases



Non exhaustive

Genomic Data & Privacy: Risks & Opportunities

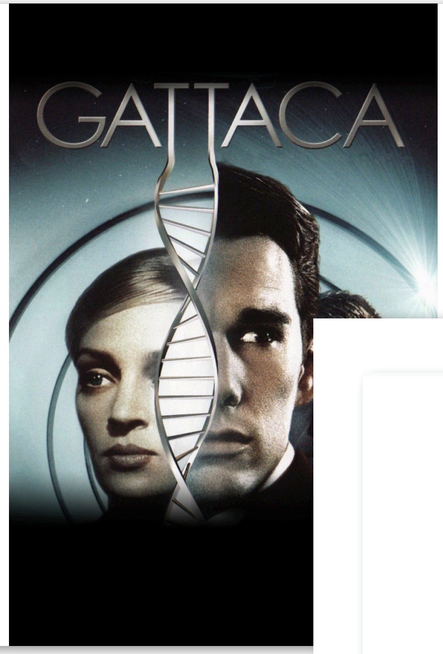
Michael Baudis

Gattaca (1997)

A genetically inferior man assumes the identity of a superior one in order to pursue his lifelong dream of space travel.

- genetic determinism
  - main character has been determined to be unsuitable for complex jobs based on genetic analysis
- genetic identification
  - the use of genetic sampling for personal identification is daily routine

With information from https://www.imdb.com/title/tt0119177/



Genome *Beacons* Compromise Security?

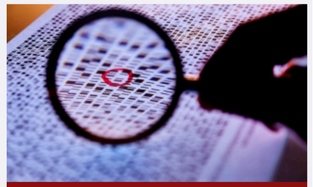
Querying for thousands of specific SNV occurrences in a genomic data pool can identify individuals in an anonymized genomic data collection

Stanford researchers identify potential security hole in genomic data-sharing network

Hackers with access to a person's genome might find out if that genome is in an international network of disease databases.

OCT 29 **2015**

Sharing genomic information among researchers is critical to the advance of biomedical research. Yet genomic data contains identifiable information and, in the wrong hands, poses a risk to individual privacy. If someone had access to your genome sequence — either directly from your saliva or other tissues, or from a popular genomic information service — they could check to see if you appear in a database of people with certain medical conditions, such as heart disease, lung cancer or autism.



Stanford researchers are working with the Global Alliance for Genomics and Health to make genomic information in the Beacon Project more secure.
Science photo/Shutterstock

Work by a pair of researchers at the Stanford University School of Medicine makes that genomic data more secure. Suyash Shringarpure, PhD, a postdoctoral scholar in genetics, and Carlos Bustamante, PhD, a professor of genetics, have
genomic databases and how to prevent it.
e for Genomics and Health on implementing

an Genetics, also bears importantly on the
h as those from different people at a crime

Rapid re-identification of human samples

...

We developed a rapid, inexpensive, and portable strategy to re-identify human DNA using the MinION. Our strategy requires only ~60 min preparation and 5-30 minutes of MinION sequencing, works with low input DNA, and enables familial searches using Direct-to-Consumer genomic reference datasets. This method can be implemented in a variety of fields:

Forensics

Identification of abandoned meterial using DNA fingerprinting is a common practice. The main challange currently being: time. Our method allows rapid sample preparation at the crime scene (see movie). We envision that the method can be adopted in the field for rapid checks, after a mass disaster, and can be adopted in border control to fight human traffacking.

Clinic

Clinics procces many samples, either for analysis or, for example, organ donations. These samples are DNA fingerprinted to prevent sample mix-up mistakes. Our method can be implemnted in the clinic for rapid sanitiy-check of all incoming samples.

Cell line identification

Cross contamination of cell lines in science is a major problem. It results in unreproducible data, and clinical trails based on inaccurate findings. This problem costs billions of dollars per year. We envision labs can adopt our identification method to ensure the purity of the cell line, and detect contamination.

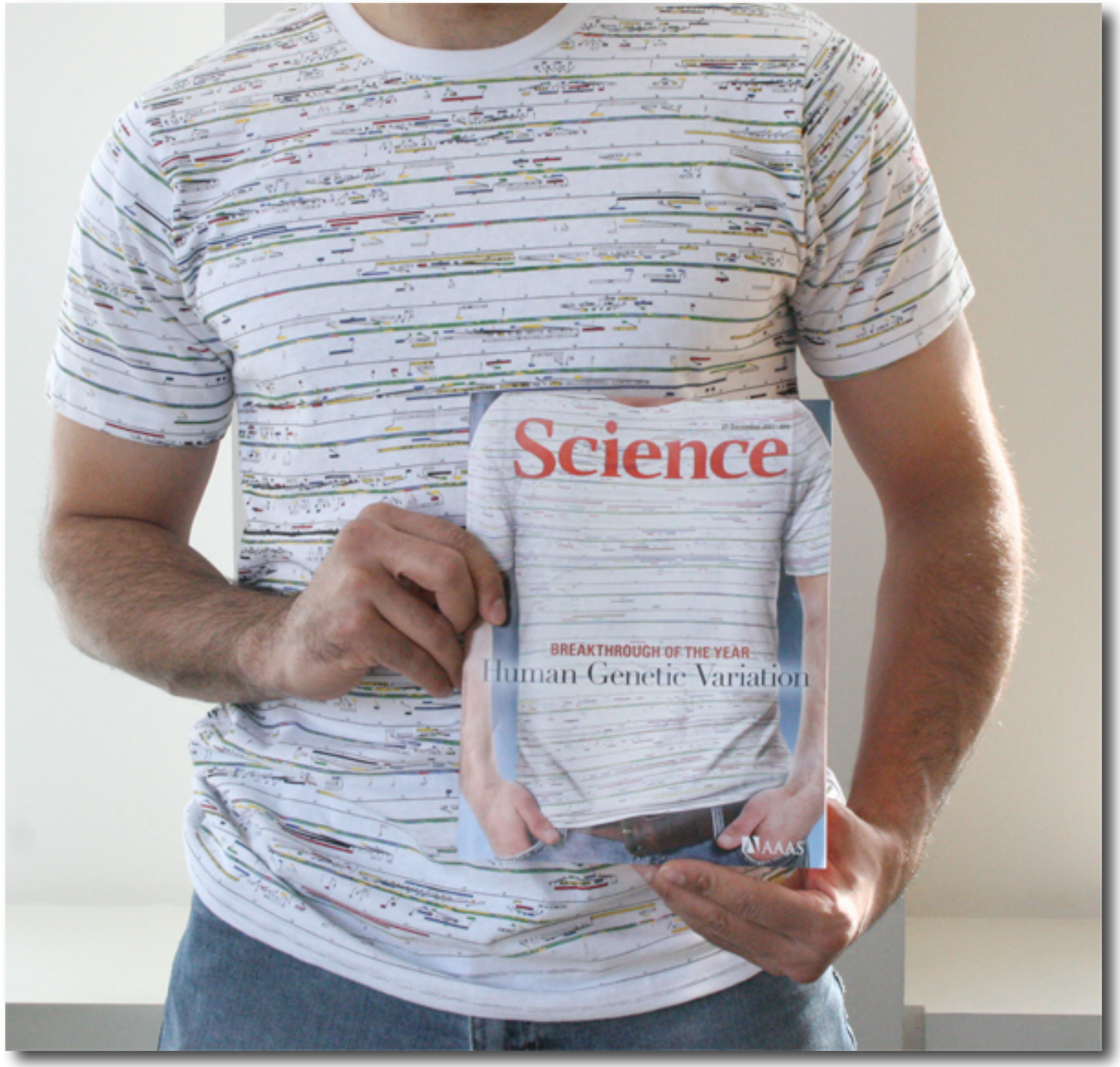
The MinION (Oxford Nanopore)
Source: Sophie Zaaijer
https://medium.com/neodotlife/nanopore-6443c81d76d3

BIO390: Introduction to Bioinformatics

Lecture I: What are Bioinformaticians doing? Example of Developing "Federated Human Data" concepts

Michael Baudis | 2023-09-26

The trouble with human genome variation



Conclusions from the analysis of variation in the human genome

- 1. Humans are all very similar to each other
  - Two humans will show about 99.9% sequence identity with each other. In other words, only about 1 in 1’000 bp is different between two individuals.
  - Humans show about 98% sequence identity to chimps. So two humans are still much more similar to each other than either is to the monkey.

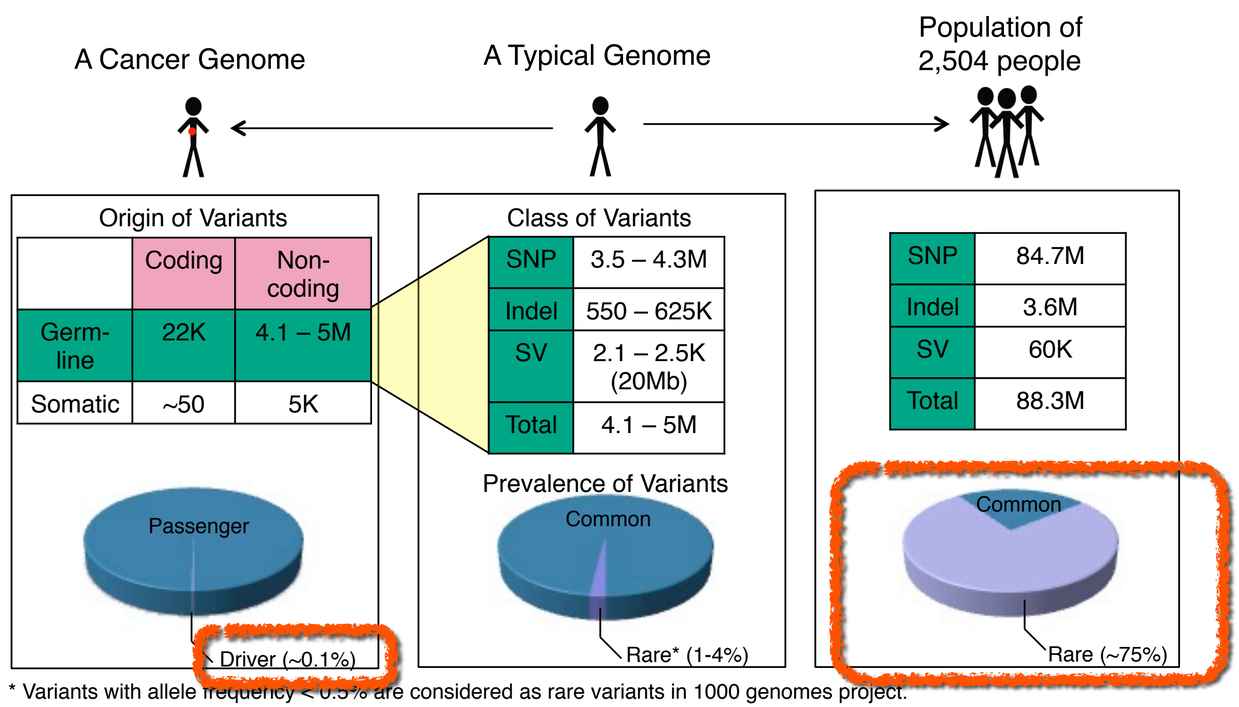
- 2. Humans are very different from each other
  - Two typical humans will likely have over 1’000’000 independent sequence differences in their genomes.

Slide from Michael Hengartner’s Human Genome Lecture

Finding Somatic Mutations In Cancer

Many Needles in a Large Haystack

- a typical humen genome (~3 billion base pairs) has ~5 million variants
- most of them are "**rare**"; i.e. can only be identified as recurring when sequencing thousands of people
- cancer cells accumulate additional variants, only **few** of which ("**drivers**") are relevant for the disease

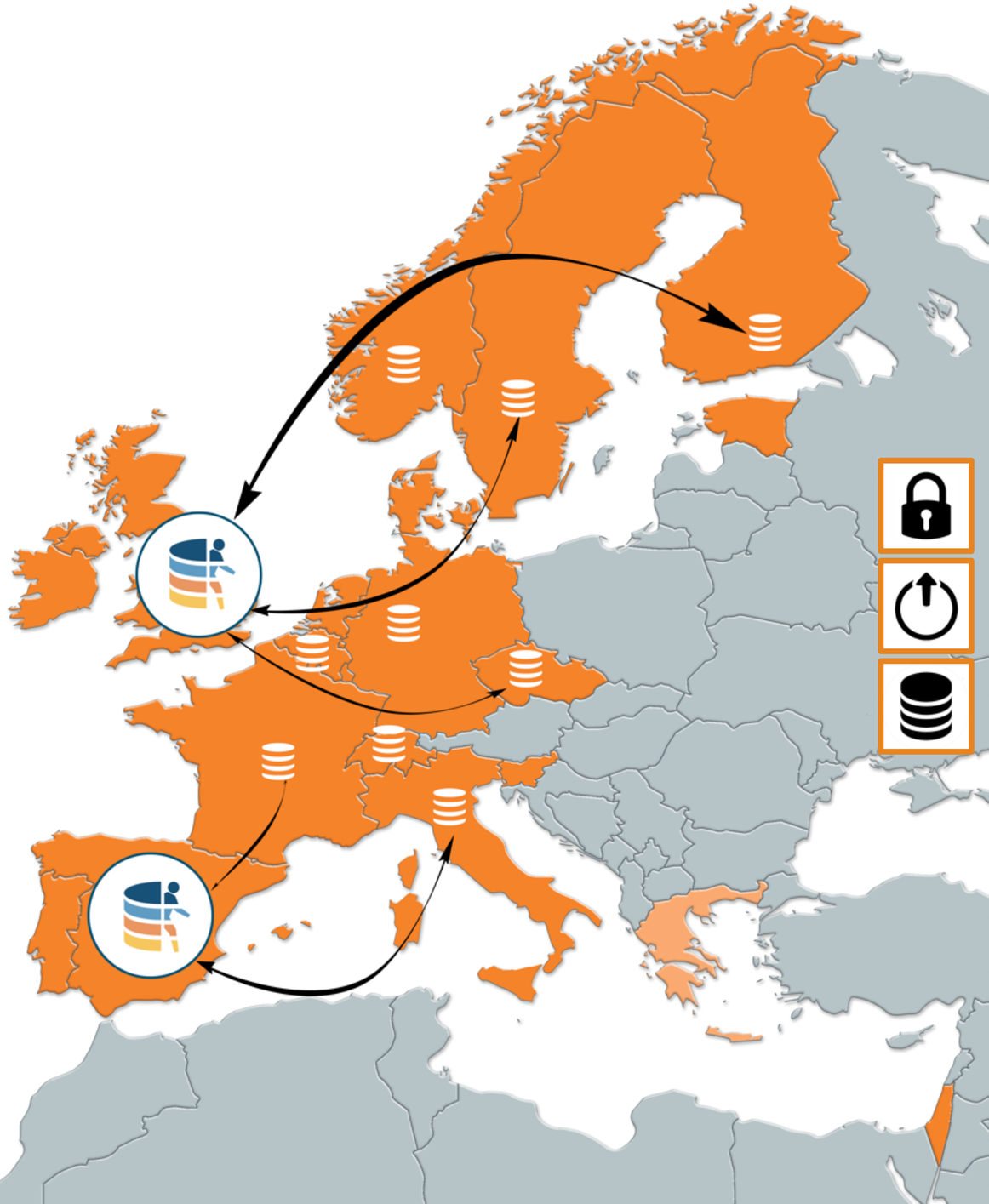


The 1000 Genomes Project Consortium, Nature. 2015. 526:68-74
Khurana E. et al. Nat. Rev. Genet. 2016. 17:93-108

Graphic adapted from Mark Gerstein (GersteinLab.org; @markgerstein)

Federation of human genome data

- Many national datasets from human research participants needs to be stored locally
- ELIXIR developing a federation with shared metadata (FAIR) and local data store (secure)
- Linking local EGA to national clouds – and international access (ELIXIR-AAI)



GENOMICS

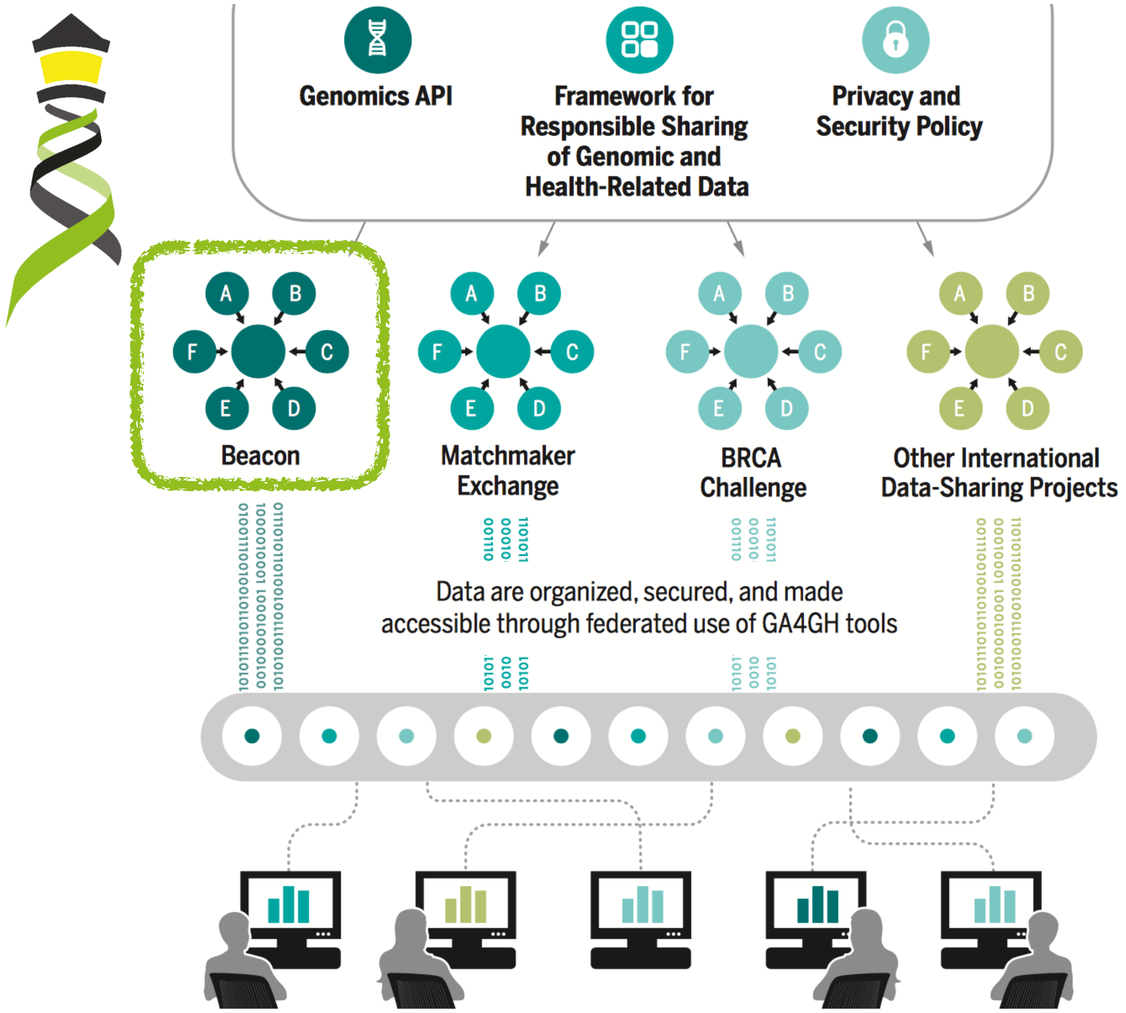
A federated ecosystem for sharing genomic, clinical data

Silos of genome data collection are being transformed into seamlessly connected, independent systems

The Global Alliance for Genomics and Health*

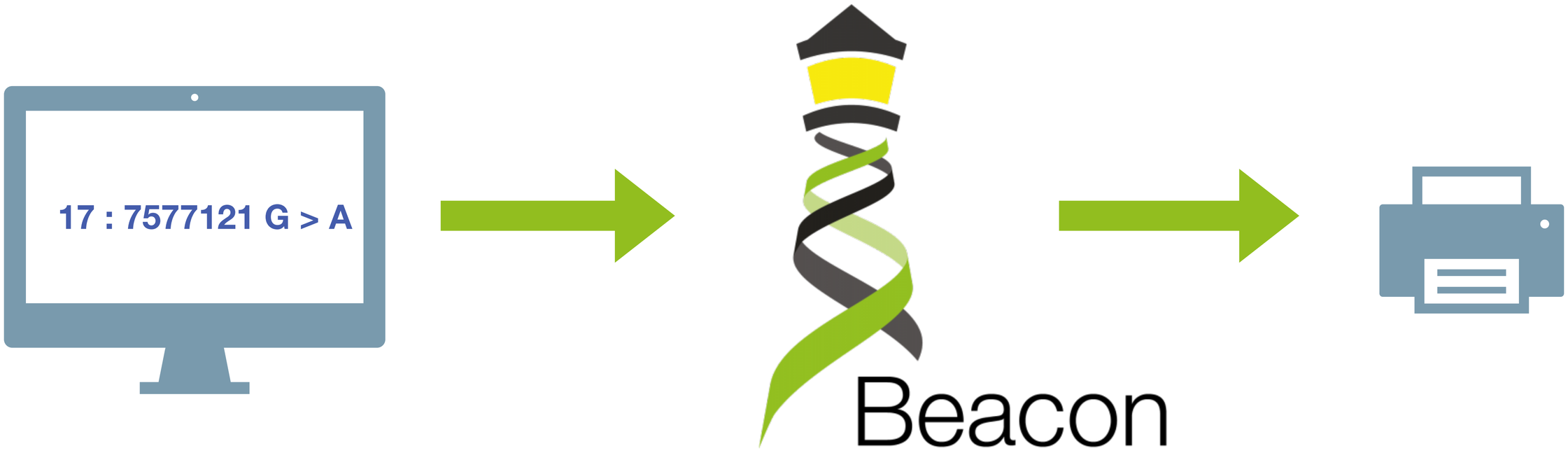
SCIENCE 10 JUNE 2016 • VOL 352 ISSUE 6291

A federated data ecosystem. To share genomic data globally, this approach furthers medical research without requiring compatible data sets or compromising patient identity.



DNASTACK

Global Alliance for Genomics & Health



A ***Beacon*** answers a query for a specific genome variant against individual or aggregate genome collections

YES | **NO** | **\0**

Beacon v2 Requests

POSTing Queries

- Beacon v2 supports a mix of dedicated endpoints with REST paths
- POST requests using JSON query documents
- final syntax for core parameters still in testing stages

```
{
    "$schema":"beaconRequestBody.json",
    "meta": {
        "apiVersion": "2.0",
        "requestedSchemas": [
            {
                "entityType": "individual",
                "schema": "https://progenetix.org/services/schemas/Phenopacket/"
            }
        ]
    },
    "query": {
        "requestParameters": {
            "datasets": {
                "datasetIds": ["progenetix"]
            }
        },
        "filterLogic": "OR"
    },
    "pagination": {
        "skip": 0,
        "limit": 10
    },
    "filters": [
        { "id": "NCIT:C4536" },
        { "id": "NCIT:C95597" },
        { "id": "NCIT:C7712" }
    ]
}
```

Progenetix & Beacon v1->2

Handover elements in Beacon responses

- Progenetix utilizes handovers to deliver data matched by the Beacon queries
- These handovers are interpreted by the front end to populate different parts of the UI, w/o the need of active selection
- Handovers are either standard Beacon v2 paths or dedicated custom functions

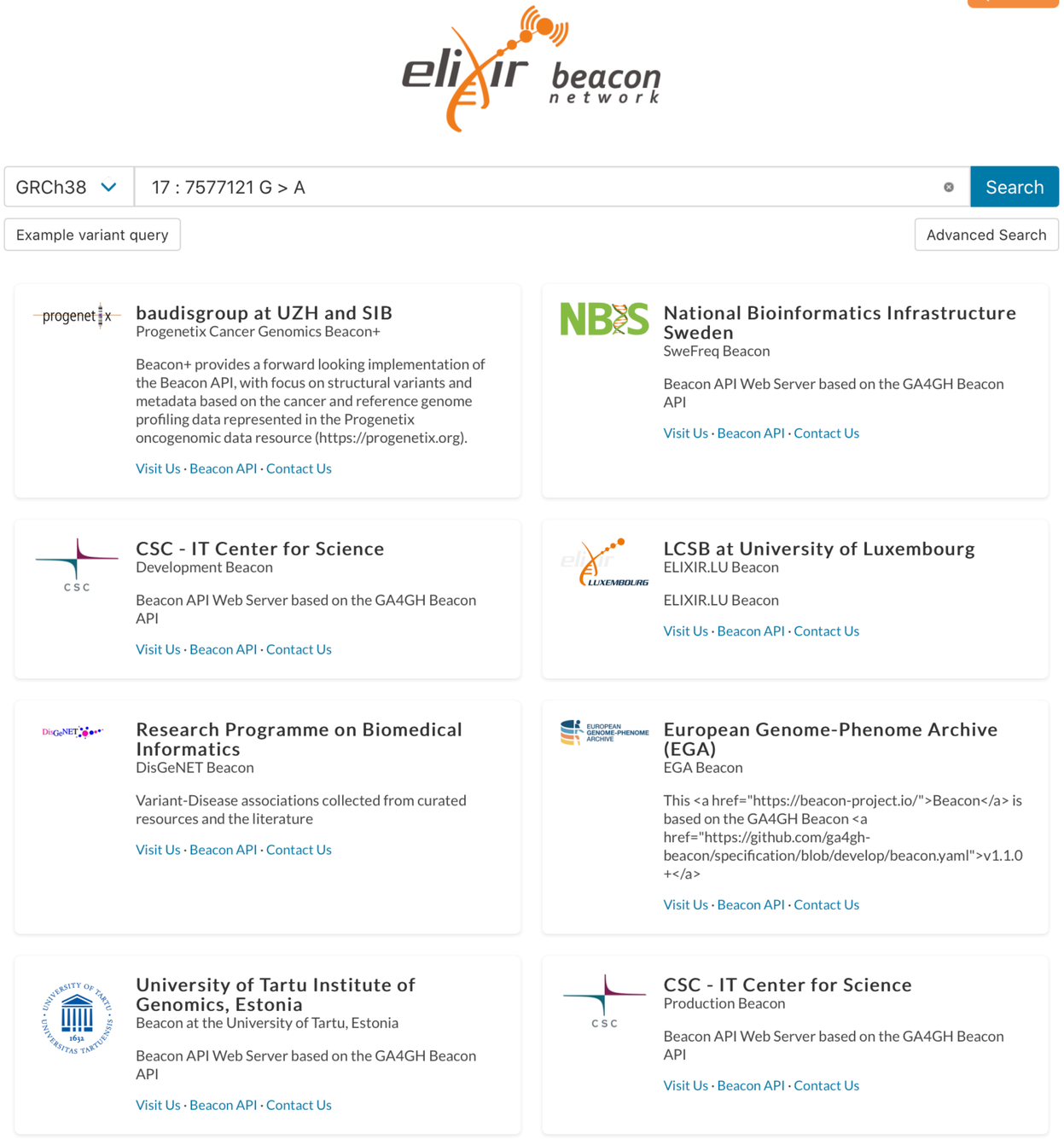

```
  "results_handovers": [
    {
      "description": "create a CNV histogram from matched callsets",
      "handoverType": {"id": "pgx:handover:cnvhistogram", "label": "CNV
Histogram"},
      "url": "https://progenetix.org/cgi-bin/PGX/cgi/samplePlots.cgi?
method=cnvhistogram&accessid=aff0f73f-6dbf-45e5-91ba-04f19e3621bb"
    },
    {
      "description": "retrieve data of the biosamples matched by the query",
      "handoverType": {"id": "pgx:handover:biosamples", "label":
"Biosamples"},
      "url": "https://progenetix.org/beacon/biosamples/?
accessid=61b68a59-2160-41e4-a17d-0cf128841a57"
    },
    {
      "description": "retrieve variants matched by the query",
      "handoverType": {"id": "pgx:handover:variants", "label": "Found
Variants (.json)"},
      "url": "https://progenetix.org/beacon/variants/?
method=variants&accessid=5cced529-3acf-4156-b121-6ae7e5e63d0c"
    },
    {
      "description": "Download all variants of matched samples - potentially
huge dataset...",
      "handoverType": {"id": "pgx:handover:callsetsvariants", "label": "All
Sample Variants (.json)"},
      "url": "https://progenetix.org/beacon/variants/?
method=callsetsvariants&accessid=61b68a59-2160-41e4-a17d-0cf128841a57"
    },
    {
      "description": "map variants matched by the query to the UCSC
browser",
      "handoverType": {"id": "pgx:handover:bedfile2ucsc", "label": "Show
Variants in UCSC"},
      "url": "http://genome.ucsc.edu/cgi-bin/hgTracks?
org=human&db=hg38&position=chr9:21531306-22492891&hgt.customText=https://
progenetix.org/tmp/5cced529-3acf-4156-b121-6ae7e5e63d0c.bed"
    }
  ]
```

ELIXIR Beacon Network

- developed under lead from ELIXIR Finland
- **authenticated access** w/ ELIXIR AAI
- **incremental extension**, starting with ELIXIR Beacon resources adhering to the **latest specification** (contrast to legacy networks)
- service details provided by individual Beacons, using **GA4GH service-info**
- **registration service**

➡**integrator** throughout ELIXIR Human Data

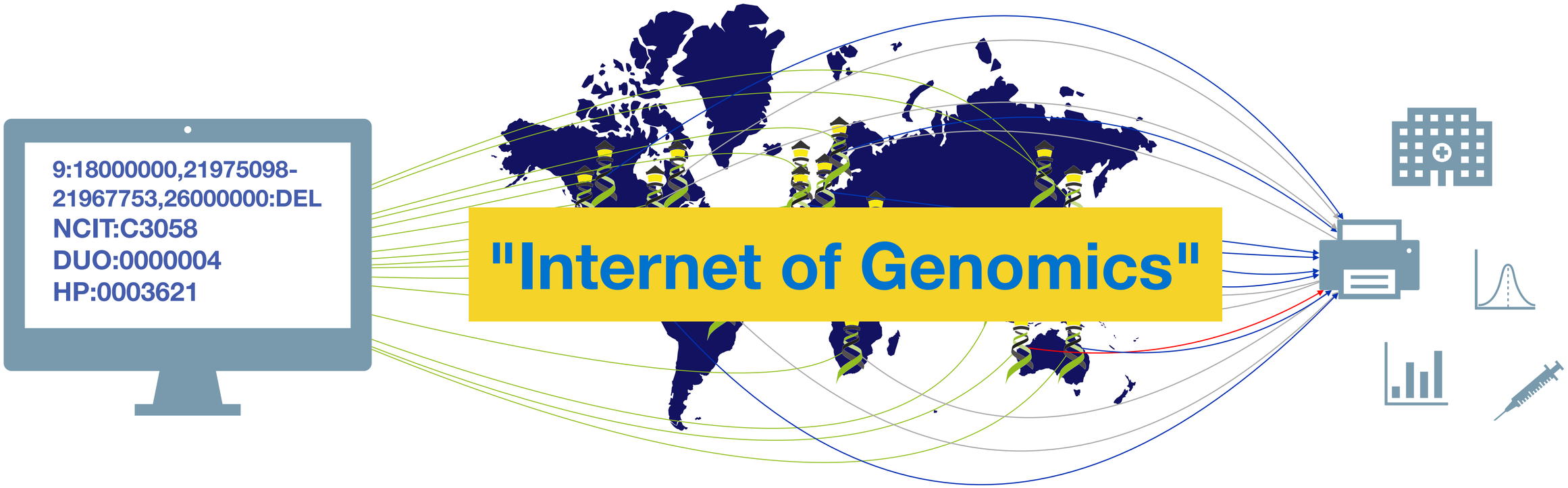
➡starting point for "**beyond ELIXIR**" **feature rich** federated Beacon **services**



Have you seen deletions in this region on chromosome 9 in Glioblastomas from a juvenile patient, in a dataset with unrestricted access?

Beacon *v2* API

The Beacon API v2 proposal opens the way for the design of a simple but powerful "**genomics API**".



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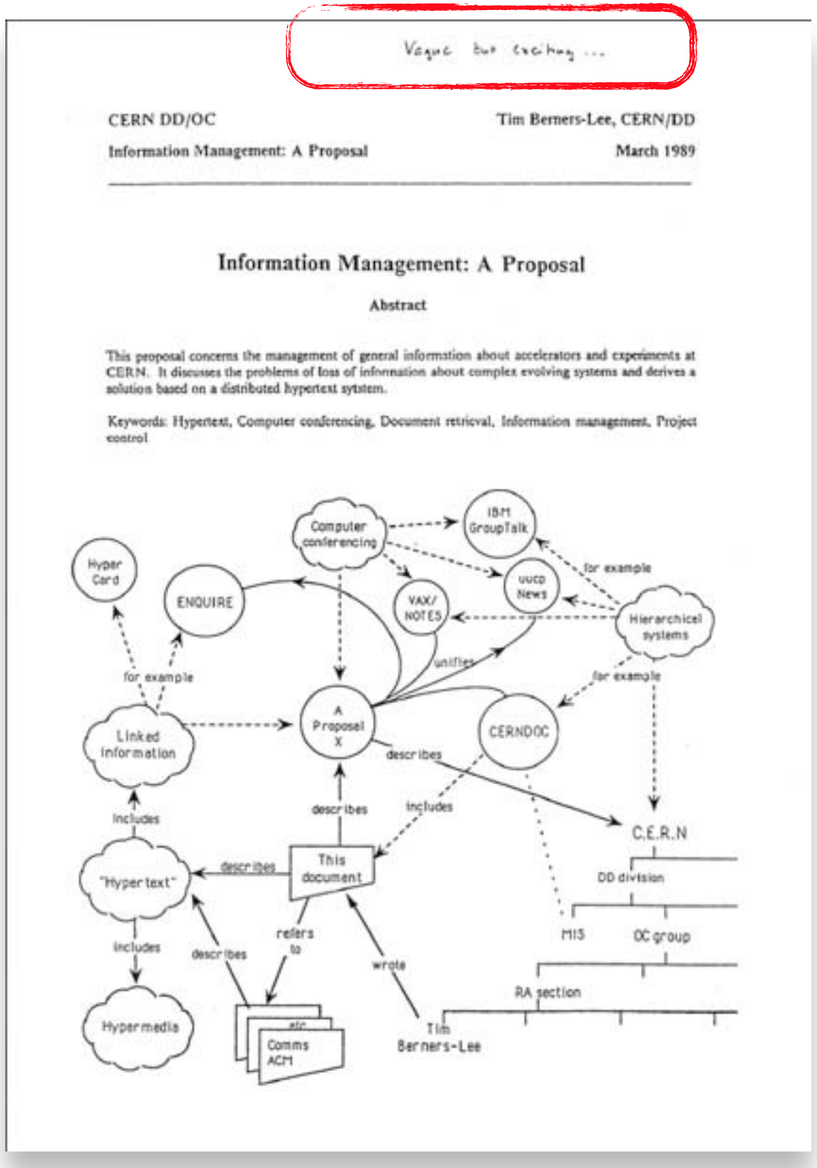

Vague but exciting ...

CERN DD/OC — Tim Berners-Lee, CERN/DD

Information Management: A Proposal — March 1989

Information Management: A Proposal

Abstract

This proposal concerns the management of general information about accelerators and experiments at CERN. It discusses the problems of loss of information about complex evolving systems and derives a solution based on a distributed hypertext sytstem.

Keywords: Hypertext, Computer conferencing, Document retrieval, Information management, Project control

Tim Berners-Lee: Information Management: A Proposal (CERN 1989) & WWW: First Page (1990)

World Wide Web

The WorldWideWeb (W3) is a wide-area hypermedia information retrieval initiative aiming to give universal access to a large universe of documents.

Everything there is online about W3 is linked directly or indirectly to this document, including an executive summary of the project, Mailing lists , Policy , November's W3 news , Frequently Asked Questions .

What's out there?
: Pointers to the world's online information, subjects , W3 servers, etc.

Help
: on the browser you are using

Software Products
: A list of W3 project components and their current state. (e.g. Line Mode ,X11 Viola , NeXTStep , Servers , Tools , Mail robot , Library)

Technical
: Details of protocols, formats, program internals etc

Bibliography
: Paper documentation on W3 and references.

People
: A list of some people involved in the project.

History
: A summary of the history of the project.

How can I help ?
: If you would like to support the web..

Getting code
: Getting the code by anonymous FTP , etc.

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