

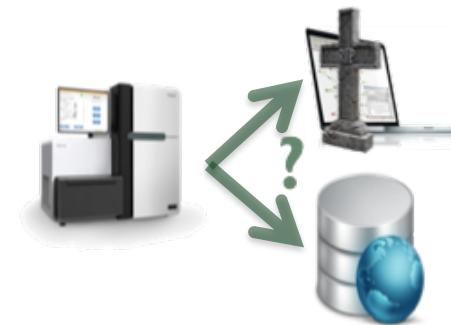
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# Research Data Management

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[niclas.jareborg@nbis.se](mailto:niclas.jareborg@nbis.se)

*Introduction to NGS course*

- To make your research easier!
- To stop yourself drowning in irrelevant stuff
- In case you need the data later
- To avoid accusations of fraud or bad science
- To share your data for others to use and learn from
- To get credit for producing it
- Because funders or your organisation require it



Well-managed data opens up opportunities for re-use, integration and new science

Science

LETTERS

Cite as: J. Berg., *Science*  
10.1126/science.aan5763 (2017).

## Editorial Retraction

Jeremy Berg

Editor-in-Chief

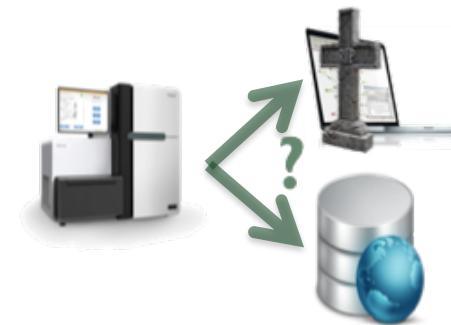
After an investigation, the Central Ethical Review Board in Sweden has recommended the retraction of the Report “Environmentally relevant concentrations of microplastic particles influence larval fish ecology,” by Oona M. Lönnstedt and Peter Eklöv, published in *Science* on 3 June 2016 (1). *Science* ran an Editorial Expression of Concern regarding the Report on 1 December 2016 (2). The Review Board’s report, dated 21 April 2017, cited the following reasons for their recommendation: (i) lack of ethical approval for the experiments; (ii) absence of original data for the experiments reported in the paper; (iii) widespread lack of clarity concerning how the experiments were conducted. Although the authors have told *Science* that they disagree with elements of the Board’s report, and although Uppsala University has not yet concluded its own investigation, the weight of evidence is that the paper should now be retracted. In light of the Board’s recommendation and a 28 April 2017 request from the authors to retract the paper, *Science* is retracting the paper in full.

### REFERENCES

1. O. M. Lönnstedt, P. Eklöv, *Science* **352**, 1213 (2016).
2. J. Berg, *Science* **354**, 1242 (2016); published online 1 December 2016.

- Be able to show that you have done what you say you have done
- Universities want to avoid bad press!

- To make your research easier!
- To stop yourself drowning in irrelevant stuff
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Well-managed data opens up opportunities for re-use, integration and new science

- *The practice of providing on-line access to scientific information that is free of charge to the end-user and that is re-usable.*
    - Does not necessarily mean unrestricted access, e.g. for sensitive personal data
  - Strong international movement towards Open Access (OA)
  - European Commission recommended the member states to establish national guidelines for OA
    - Swedish Research Council (VR) submitted proposal to the government Jan 2015
  - Research bill 2017–2020 – 28 Nov 2016
    - *The aim of the government is that all scientific publications that are the result of publicly funded research should be openly accessible as soon as they are published. Likewise, **research data** underlying scientific publications should be **openly accessible at the time of publication.***  
[my translation]





## G8 Open Data Charter



- Principle 1 – Open Data by default
- Principle 2: Quality and Quantity
- Principle 3: Usable by All
- Principle 4: Releasing Data for Improved Governance
- Principle 5: Releasing Data for Innovation



I presentationen presenterer jeg et utkast til en strategisk utviklingsplan, med målperiode fra 2017 til 2021. Herfor er vi i denne form ikke i behov for konkurransereglementering, og det er ikke ønsket.

Vi oppfordrer også til at vi ikke kan få konkurransereglementering som et mål i seg selv, men vi ønsker at konkurransereglementering skal være et verktøy til å fremme konkurransen i et økende dødt voksende marked.

Hensikten med denne utviklingsplanen er også å sikre at Norges teknologiselskaper kan utvikle seg i en bærekraftig måte, og at de kan konkurrere internasjonalt. Det er ikke tilstrekkelig med å utvikle teknologi, hvis teknologien ikke kan konkurrere med teknologien fra andre land. Det er derfor viktig at konkurransereglementering ikke bare omfatter teknologien, men også markedsordningen.

Begrenslig tilgang til finansiering kan føre til at teknologiene ikke kan utvikles til fulle potensial. Dette er et problem som må løftes ved hjelp av teknologiselskaper. Vi ønsker at teknologiselskaper skal få tilgang til finansiering gjennom bankene, gjennom teknologiselskaper, og gjennom teknologiselskaper.

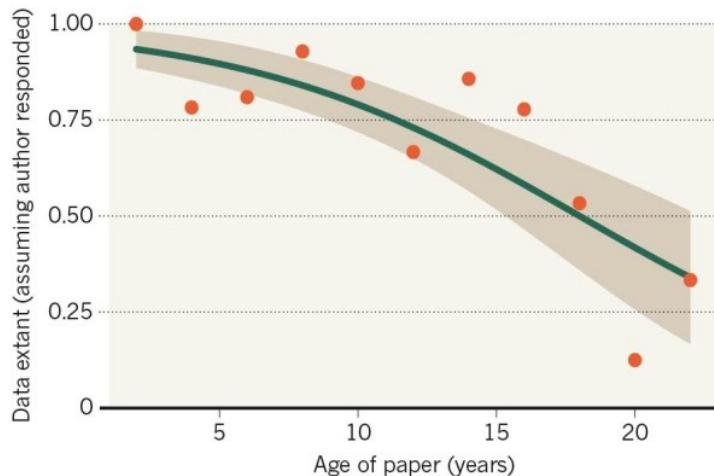
- Democracy and transparency
  - Publicly funded research data should be accessible to all
  - Published results and conclusions should be possible to check by others
- Research
  - Enables others to combine data, address new questions, and develop new analytical methods
  - Reduce duplication and waste
- Innovation and utilization outside research
  - Public authorities, companies, and private persons outside research can make use of the data
- Citation
  - Citation of data will be a merit for the researcher that produced it



# Data loss is real and significant, while data growth is staggering

## MISSING DATA

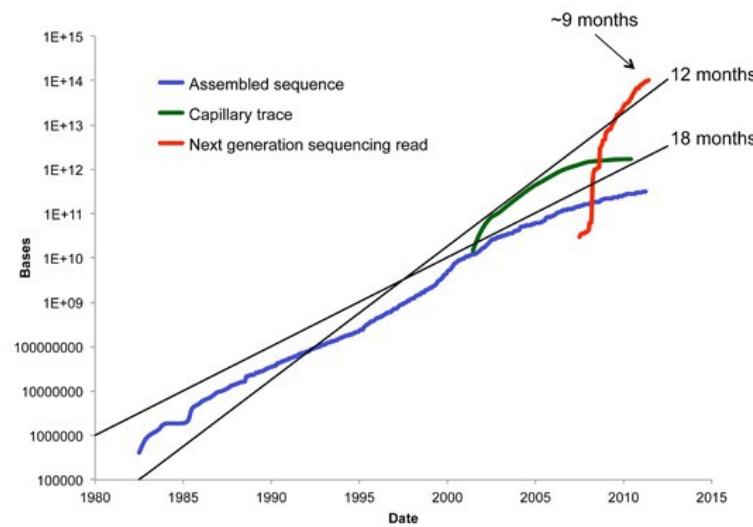
As research articles age, the odds of their raw data being extant drop dramatically.



Nature news, 19 December 2013



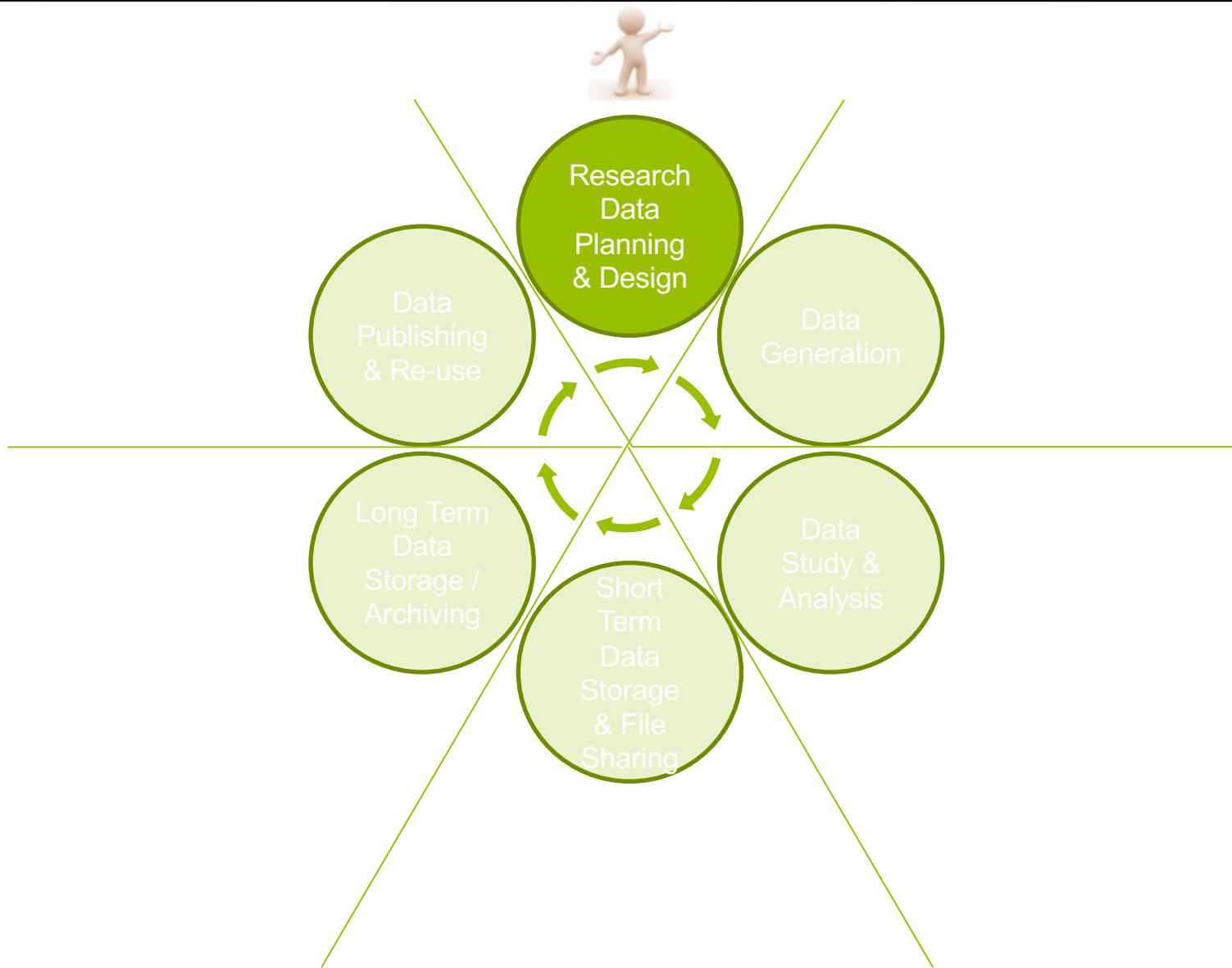
*'Oops, that link was the laptop of my PhD student'*



- DNA sequence data is **doubling every 6-8 months** and looks to continue for this decade
- Projected to surpass astronomy data in the coming decade

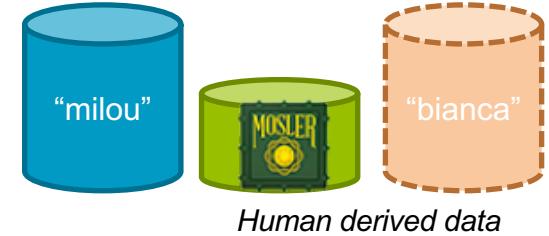
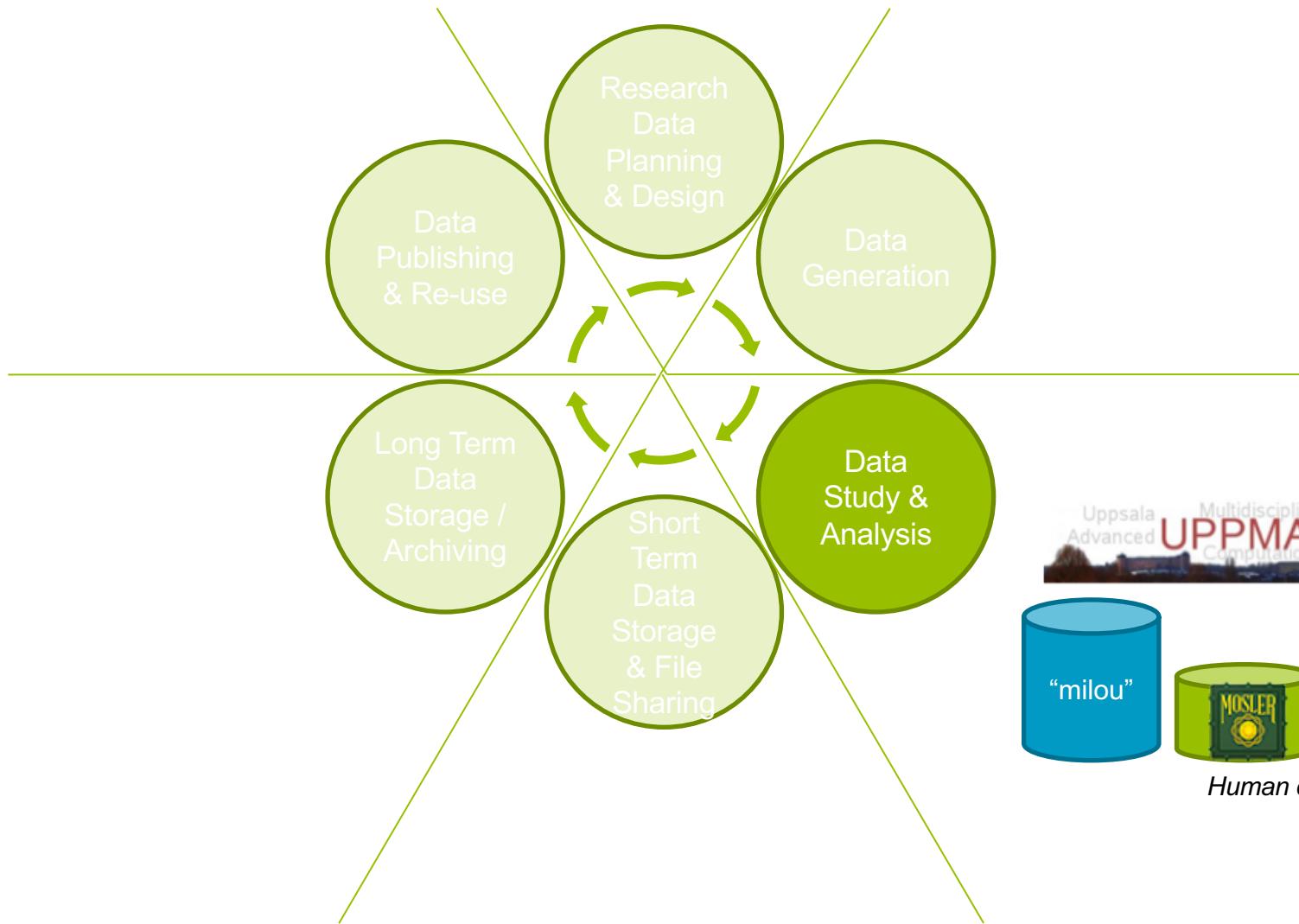
Slide stolen from Barend Mons



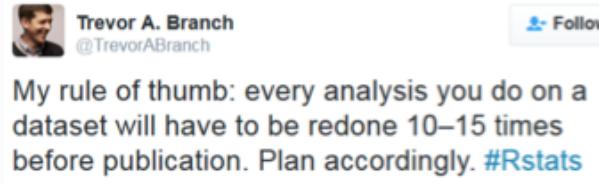


- Data Management planning
  - Data types
    - Sizes, were to store, etc
  - **Metadata**
    - Study, Samples, Experiments, etc
    - Use standards!
- *Data Management Plans*
  - Will become a standard part of the research funding application process
  - What will be collected?, Size?, Organized?, Documented?, Stored and preserved?, Disseminated?, Policies?, Budget?





- Guiding principle
  - “*Someone unfamiliar with your project should be able to look at your computer files and understand in detail what you did and why.*”
- Research reality
  - “*Everything you do, you will have to do over and over again*”
  - Murphy’s law



Trevor A. Branch  
@TrevorABranch

Follow

My rule of thumb: every analysis you do on a dataset will have to be redone 10–15 times before publication. Plan accordingly. #Rstats



- Structuring data for analysis
  - Poor organizational choices lead to significantly slower research progress.
  - It is critical to make results reproducible.



*Retracted*

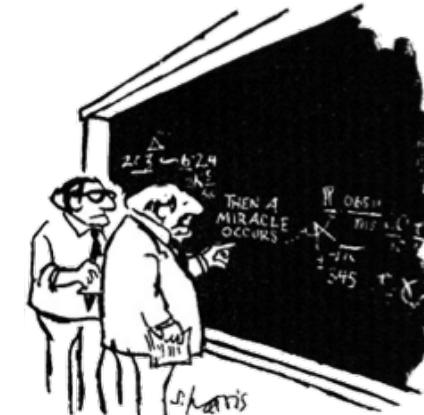
From [bloodjournal.hematologylibrary.org](http://bloodjournal.hematologylibrary.org) by guest on September 2, 2011. For personal use only.

HEMOSTASIS, THROMBOSIS, AND VASCULAR BIOLOGY

Gene-expression patterns predict phenotypes of immune-mediated thrombosis

Antiphospholipid antibody syndrome (APS) is a complex autoimmune disease characterized by recurrent venous thromboembolism (VTE) and/or arterial thrombosis and/or anti-phospholipid antibodies (aPLs). We hypothesized that gene-expression patterns could predict APS phenotype. We analyzed gene-expression profiles in peripheral blood mononuclear cells (PBMCs) from 100 patients with APS and 100 healthy controls. We found that gene-expression profiles in PBMCs from patients with APS were distinct from those of healthy controls. We used a support vector machine to predict APS phenotype based on gene-expression profiles. This model correctly predicted APS phenotype in 87 patients (87%) and 95 healthy controls (95%). We also found that gene-expression profiles in PBMCs from patients with VTE without APS were distinct from those of healthy controls. We used a support vector machine to predict APS phenotype in patients with VTE without APS. Importantly, similar methods identified expression profiles in PBMCs that correctly predicted those patients with APS at high risk for thrombotic events. All profiles were analyzed using a genomic approach that can be applied to other populations of patients with APS and other diseases. Our findings suggest that gene-expression profiles in PBMCs can be used to predict APS phenotype and may be useful for therapeutic decisions. © 2011 American Society of Hematology

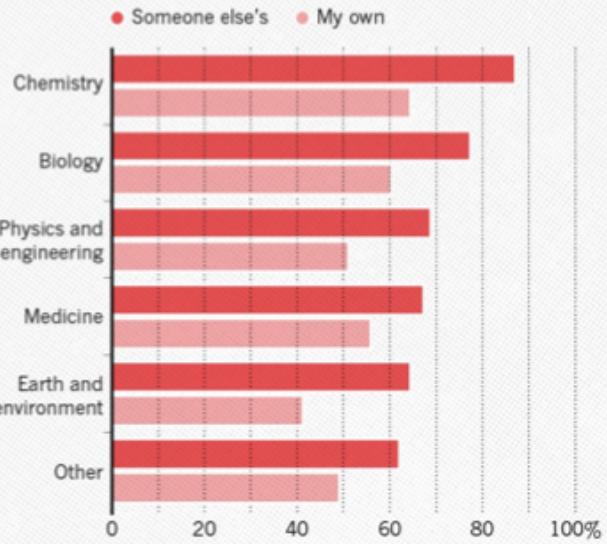
Introduction



# A reproducibility crisis

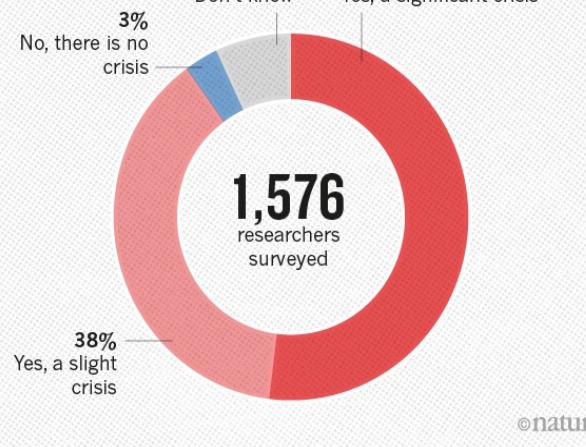
## HAVE YOU FAILED TO REPRODUCE AN EXPERIMENT?

Most scientists have experienced failure to reproduce results.



## IS THERE A REPRODUCIBILITY CRISIS?

7%  
Don't know  
52%  
Yes, a significant crisis  
3%  
No, there is no crisis



A recent survey in Nature revealed that irreproducible experiments are a problem across all domains of science<sup>1</sup>.

Medicine is among the most affected research fields. A study in Nature found that 47 out of 53 medical research papers focused on cancer research were irreproducible<sup>2</sup>.

Common features were failure to show all the data and inappropriate use of statistical tests.

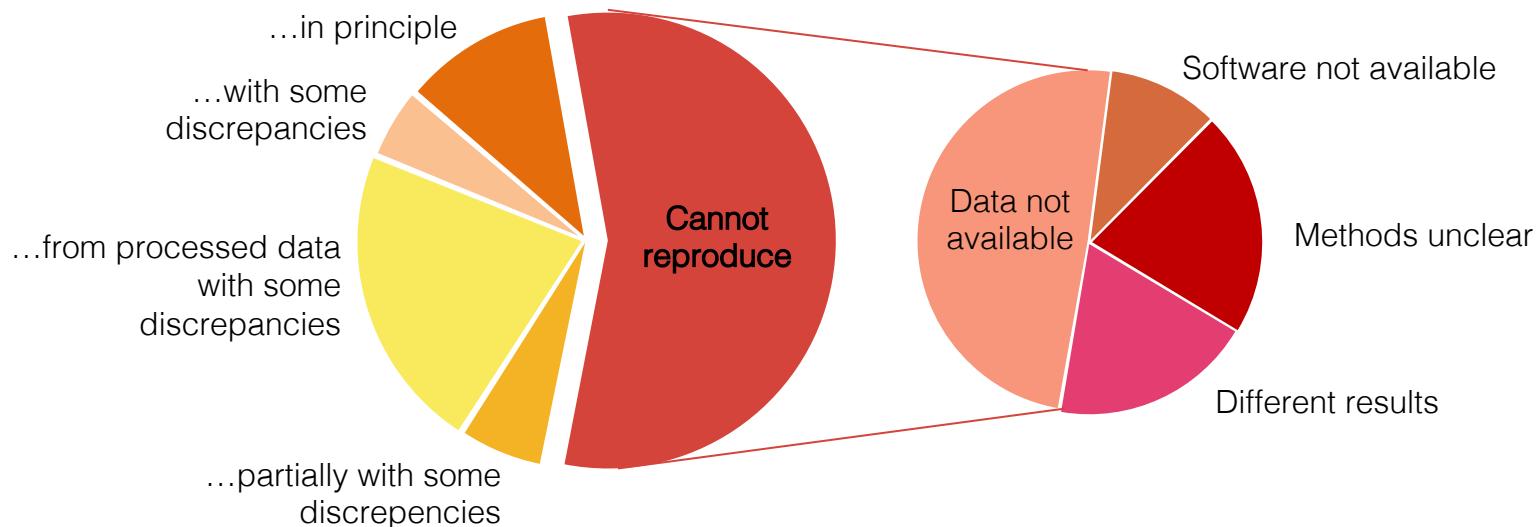
[1] "1,500 scientists lift the lid on reproducibility". Nature. 533: 452–454

[2] Begley, C. G.; Ellis, L. M. (2012). "Drug development: Raise standards for preclinical cancer research". Nature. 483 (7391): 531–533.

# A reproducibility crisis

Reproduction of data analyses in 18 articles on microarray-based gene expression profiling published in *Nature Genetics* in 2005–2006:

Can reproduce...



Summary of the efforts to replicate the published analyses.

Adopted from: Ioannidis et al. Repeatability of published microarray gene expression analyses.  
*Nature Genetics* **41** (2009) doi:10.1038/ng.295

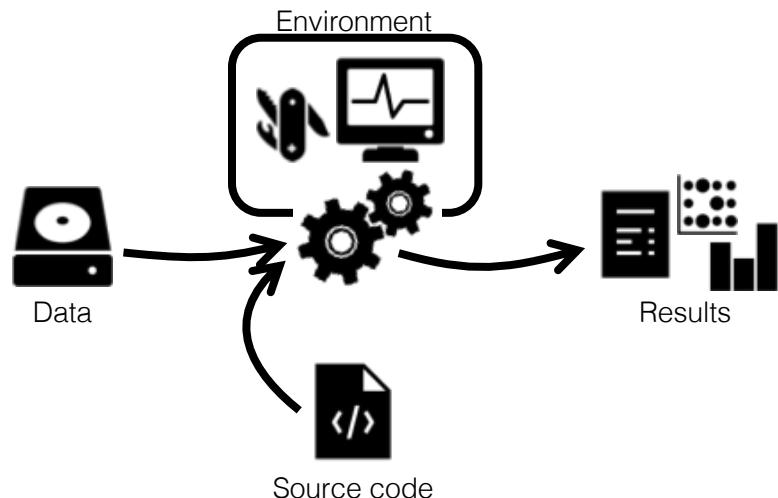
# What do we mean by reproducible research?

		Data	
		Same	Different
Code	Same	Reproducible	Replicable
	Different	Robust	Generalizable

Is it really any point doing this?

- Primarily for ones own benefit!  
Organized, efficient, in control.  
Dynamic team members.
- Transparent what has been done
- Some will be interested in parts of the analysis. Make it easy to redo, then adapt to own data.

All parts of a bioinformatics analysis have to be reproducible:

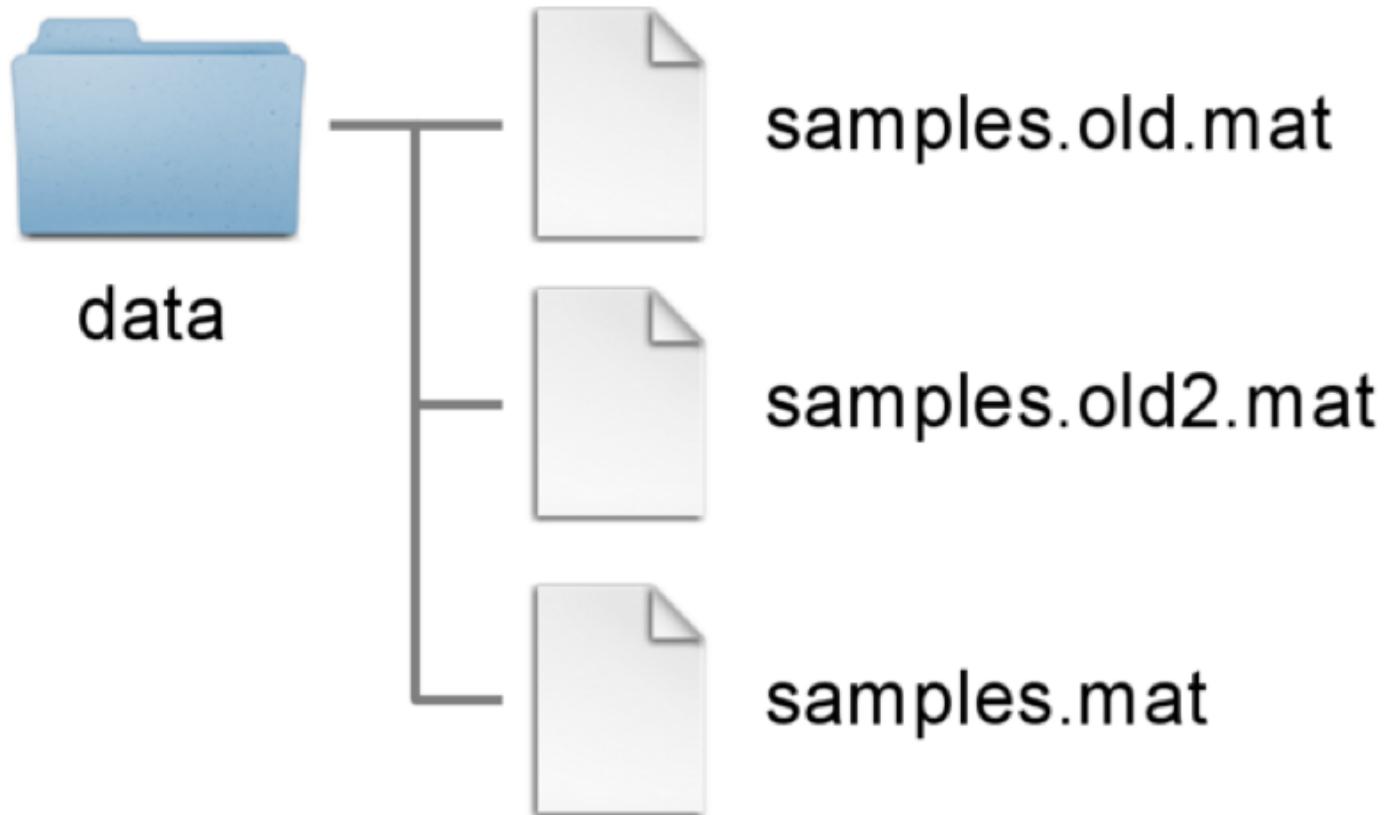


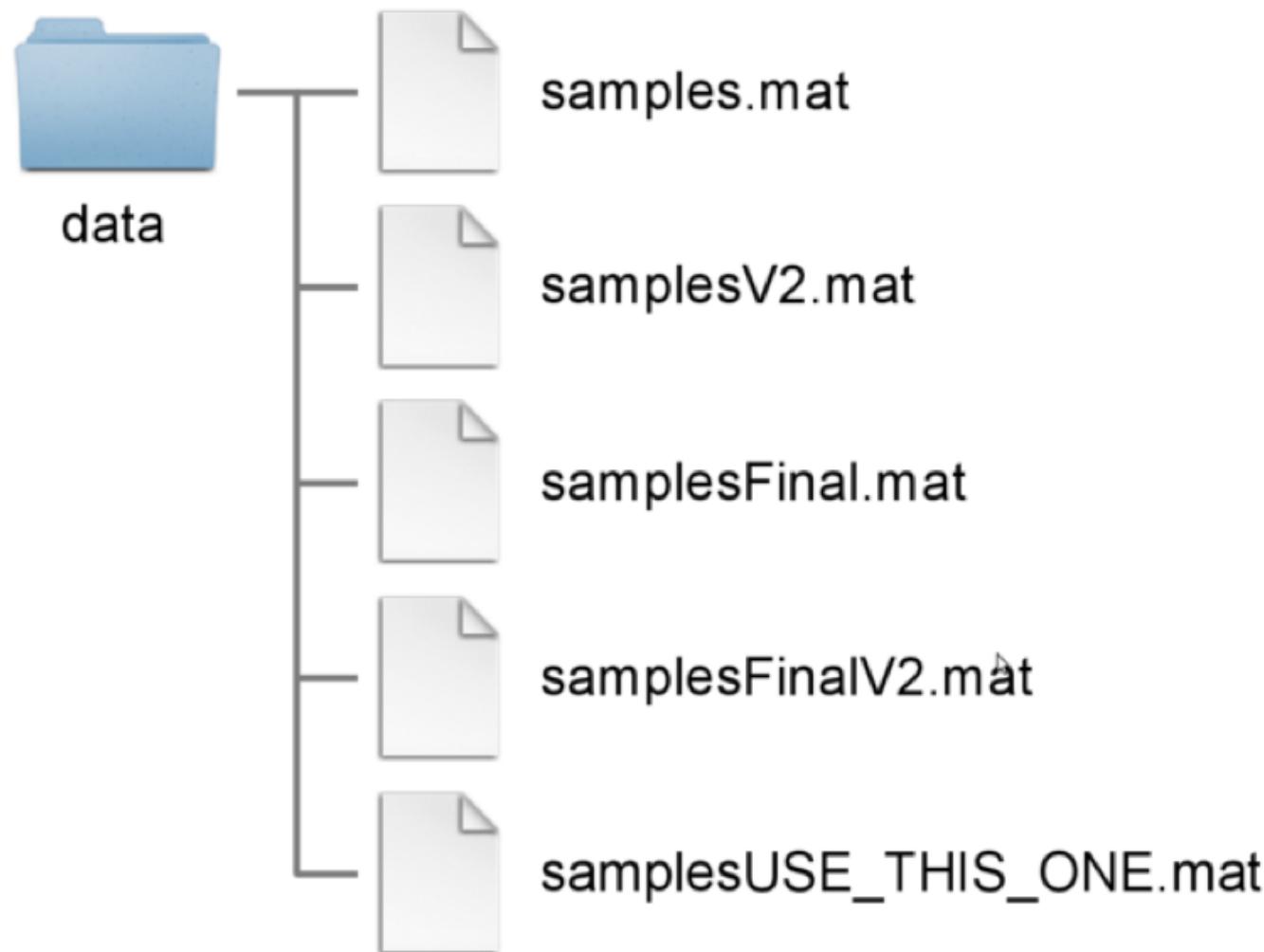


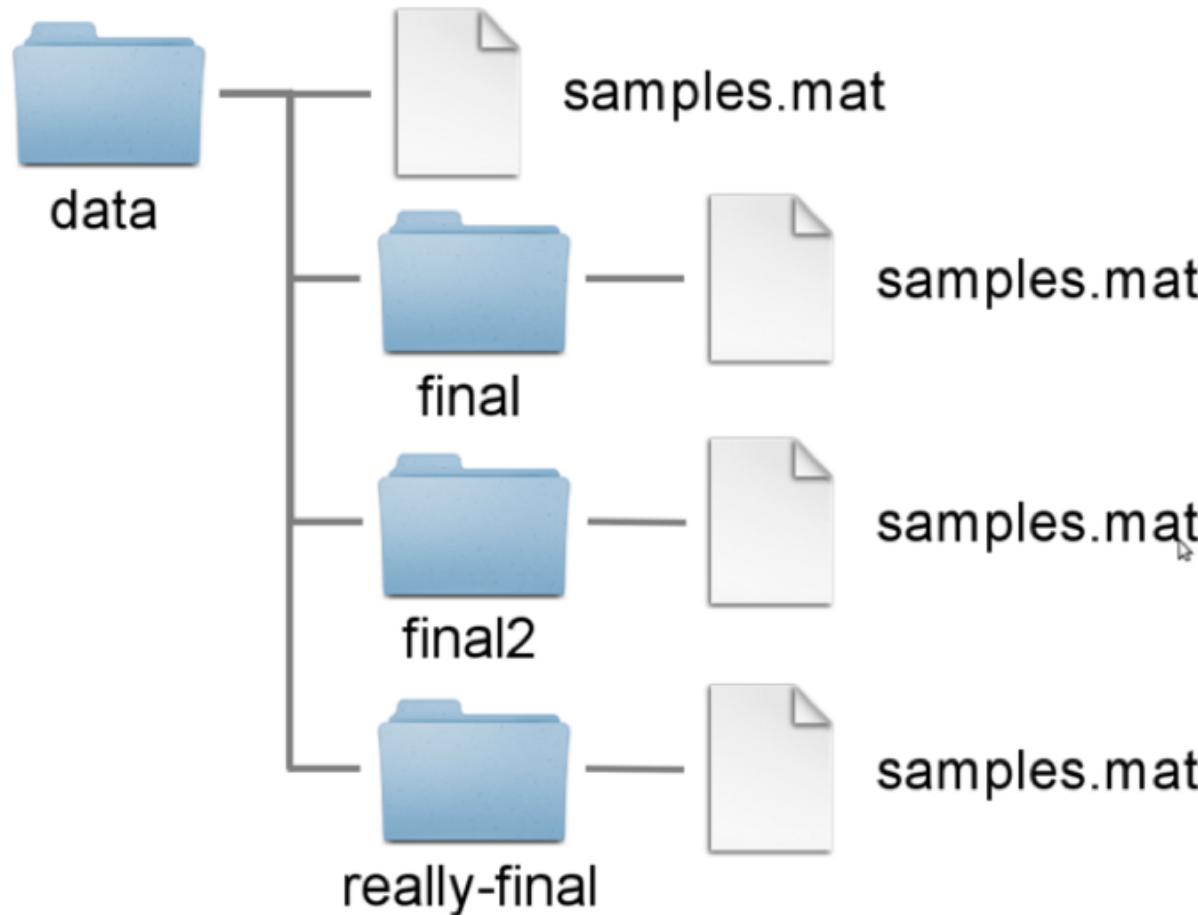
data

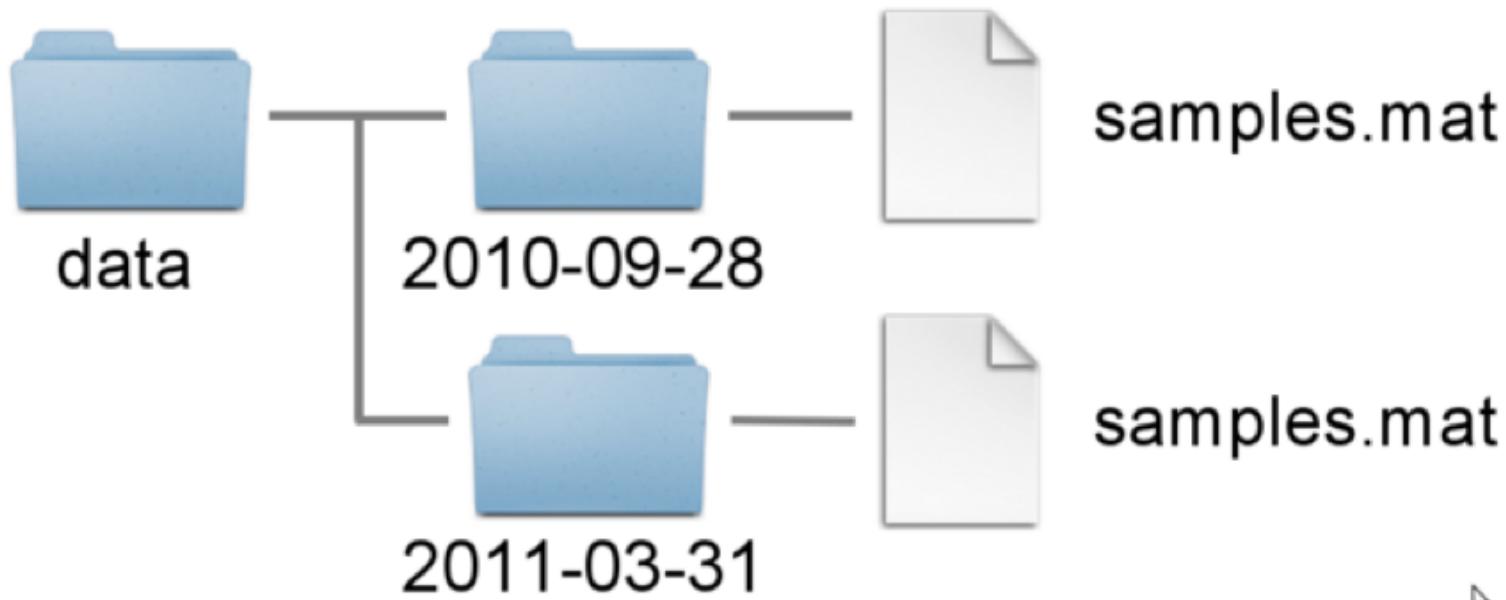
samples.mat





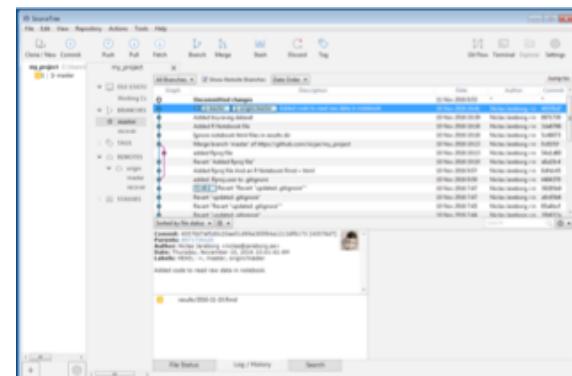






- There is a **folder for the raw data**, which do not get altered, or intermixed with data that is the result of manual or programmatic manipulation. I.e., derived data is kept separate from raw data, and **raw data are not duplicated**.
- **Code is kept separate from data.**
- Use a **version control system** (at least for code) – e.g. **git**
- There is a **scratch directory for experimentation**. Everything in the scratch directory can be deleted at any time without negative impact.
- There should be a **README in every directory**, describing the purpose of the directory and its contents.
- Use **non-proprietary formats** – .csv rather than .xlsx
- Etc...

- What is it?
  - A system that keeps records of your changes
  - Allows for collaborative development
  - Allows you to know who made what changes and when
  - Allows you to revert any changes and go back to a previous state
- Several systems available
  - Git, RCS, CVS, SVN, Perforce, Mercurial, Bazaar
  - Git
    - Command line & GUIs
    - Remote repository hosting
      - GitHub, Bitbucket, etc



- There is a **folder for the raw data**, which do not get altered, or intermixed with data that is the result of manual or programmatic manipulation. I.e., derived data is kept separate from raw data, and **raw data are not duplicated**.
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- Use **non-proprietary formats** – .csv rather than .xlsx
- Etc...

- A text-based format is more future-safe, than a proprietary binary format by a commercial vendor
- ***Markdown*** is a nice way of getting nice output from text.
  - Simple & readable formating
  - Can be converted to lots of different outputs
    - HTML, pdf, MS Word, slides etc
- *Never, never, never use ***Excel*** for scientific ***analysis!****
  - Script your analysis – bash, python, R, ...

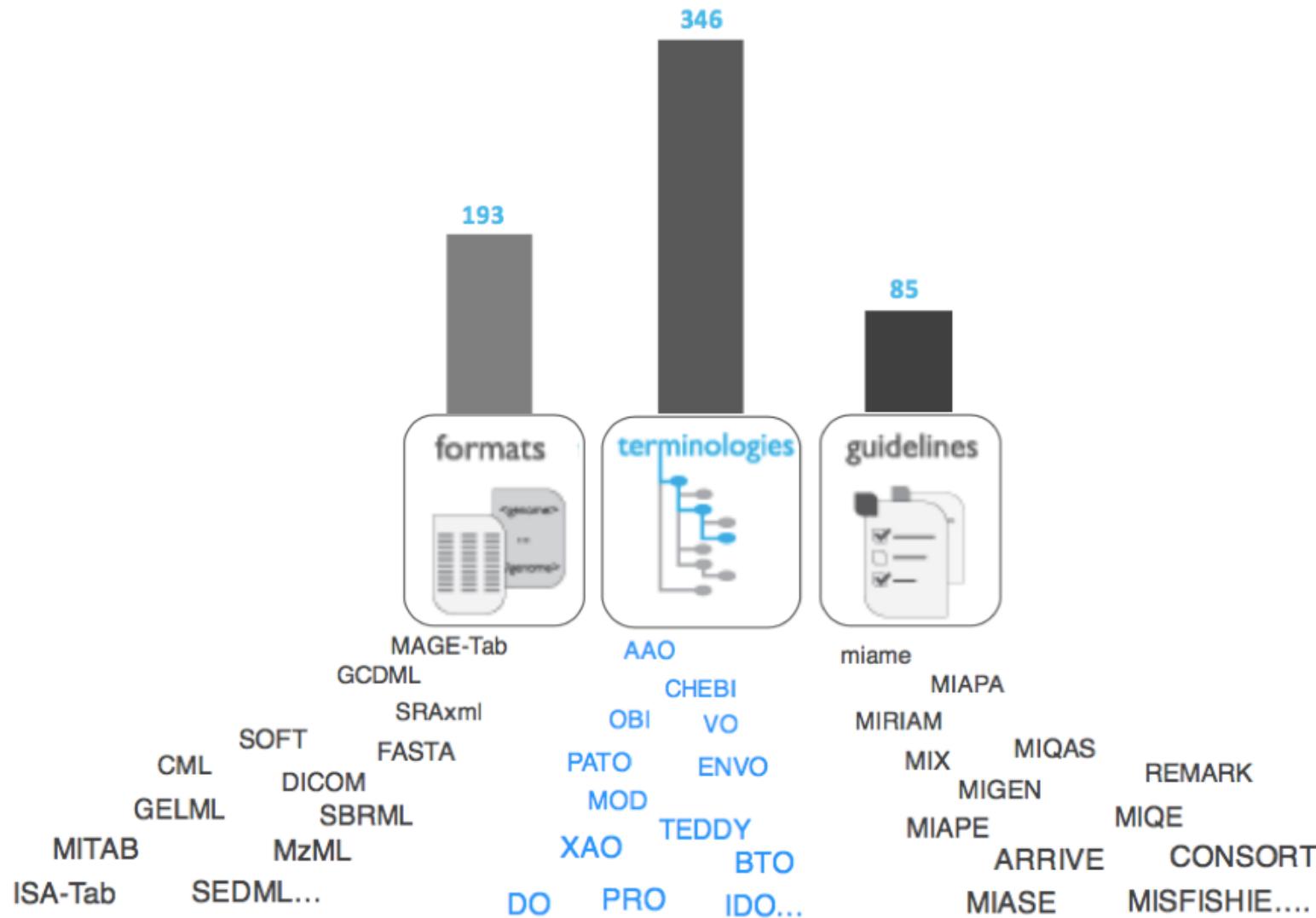


- Need context → document **metadata**
  - How was the data generated?
  - From what was the data generated?
  - What where the experimental conditions?
  - Etc
- Use standards
  - Controlled vocabularies / Ontologies
  - *Not straight-forward...*

Human Phenotype Ontology

Details	Visualization	Notes (0)	Class Mappings (21)
Preferred Name	Acute myeloid leukemia		
Synonyms	Acute myeloblastic leukemia Acute myelogenous leukemia Acute myelocytic leukemia		
Definitions	A form of leukemia characterized by overproduction of an early myeloid cell.		
ID	<a href="http://purl.obolibrary.org/obo/HP_0004808">http://purl.obolibrary.org/obo/HP_0004808</a>		
database_cross_reference	MeSH:D015470 UMLS:C0023467		
definition	A form of leukemia characterized by overproduction of an early myeloid cell.		
has_alternative_id	HP:0004843 HP:0001914 HP:0006728 HP:0006724 HP:0005516		
has_exact_synonym	Acute myeloblastic leukemia Acute myelogenous leukemia Acute myelocytic leukemia		
has_obo_namespace	human_phenotype		
id	HP:0004808		
label	Acute myeloid leukemia		
notation	HP:0004808		
prefLabel	Acute myeloid leukemia		
treeView	Acute leukemia		
subClassOf	Acute leukemia		

In the life sciences there are >600 *content standards*



FAIRsharing.org  
standards, databases, policies

Standards Databases Policies Collections Add/Claim Content Stats Log in or Register

A curated, informative and educational resource on data and metadata *standards*, across all disciplines, inter-related to *databases* and *data policies*.

**Find**

 **Recommendations**  
Standards and/or databases recommended by journal or funder data policies.

**Discover**

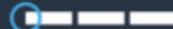
 **Collections**  
Standards and/or databases grouped by domain, species or organization.

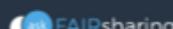
**Learn**

 **Educational**  
About standards, their use in databases and policies, and how we can help you.

Search FAIRsharing

Standards  Databases  Policies  Collections/Recommendations

Advanced Search   
Fine grained control over your search.

Search Wizard   
Let us guide you to your results.



### 699 Standards

Terminology Artifact	343
Model/Format	239
Reporting Guideline	117

[View all](#)



### 974 Databases

Life Science	733
Biomedical Science	181
General Purpose	10

[View all](#)

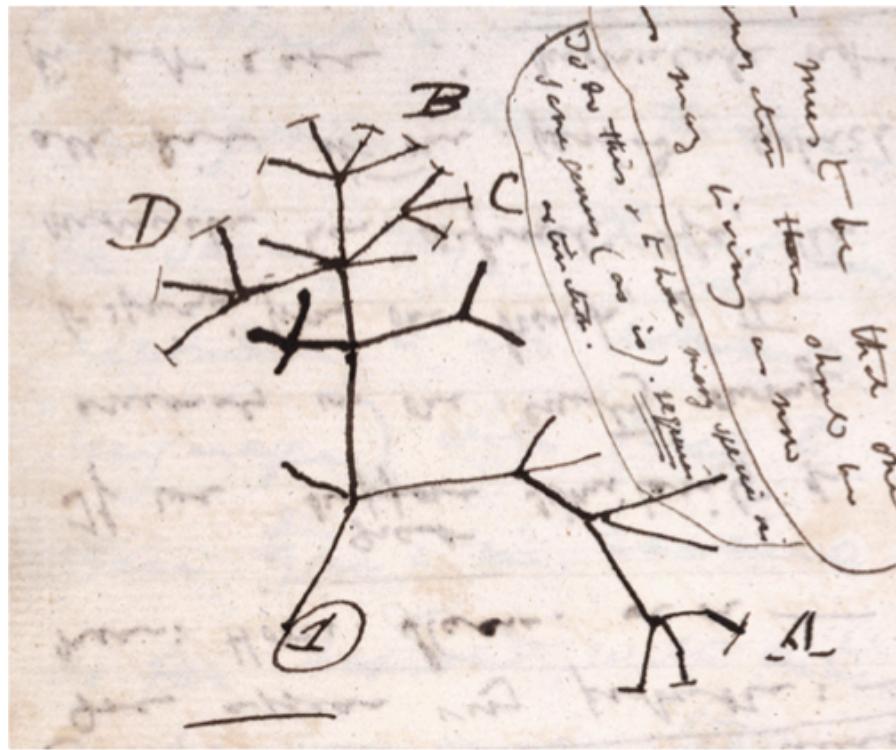


### 97 Policies

Funder	22
Journal	68
Society	3

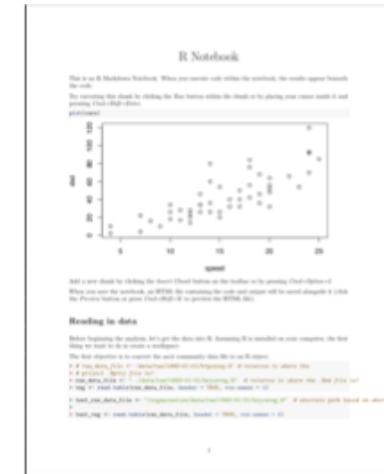
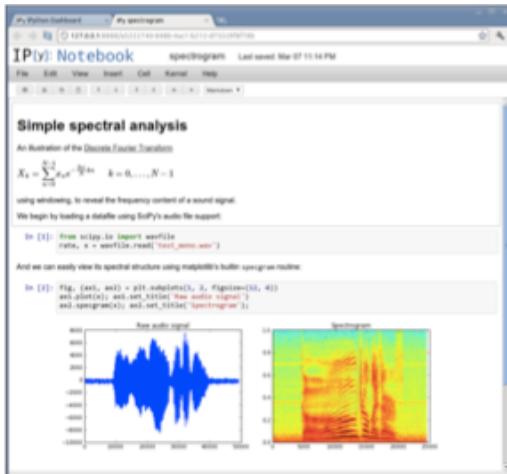
[View all](#)

- Why?
  - You have to understand what you have done
  - **Others should be able to reproduce what you have done**



- 
- Put in *results* directory
  - *Dated* entries
  - Entries relatively verbose
  - Link to *data* and *code* (including versions)
    - Point to commands run and results generated
  - Embedded images or tables showing results of analysis done
  - Observations, Conclusions, and *ideas* for future work
  - Also document analysis that *doesn't* work, so that it can be understood why you choose a particular way of doing the analysis in the end

- Paper Notebook
- Word processor program / Text files
- Electronic Lab Notebooks
- 'Interactive' Electronic Notebooks
  - e.g. [jupyter](#), [R Notebooks](#) in RStudio
  - Plain text - work well with version control (Markdown)
  - Embed and execute code
  - Convert to other output formats
    - html, pdf, word



- R Markdown makes your analysis more reproducible by connecting your code, figures and descriptive text.
- You can use it to make reproducible reports, rather than e.g. copy-pasting figures into a Word document.
- You can also use it as a notebook, in the same way as lab notebooks are used in a wet lab setting

```

1+ ---
2 title: "Differential expression analysis using linear models"
3 output:
4   pdf_document
5 ...
6
7
8+ ```{r setup, echo=FALSE, message=FALSE, warning=FALSE, eval=T}
9 library(knitr)
10 opts_knit$set(root.dir=normalizePath('..'))
11 ...
12+ ```{r, echo=FALSE, message=FALSE, warning=FALSE, eval=T}
13 source("source/rmarkdown_functions.R")
14 ...
15
16+ # Introduction
17 This report and analysis sets out to explore the possibility to use the blood biochemistry
18 factors to predict gene expression.
19
20
21+ # Check which blood biochemistry factors can be used together in linear regression
22
23 First load the biochemistry data (this file has been cleaned up and preprocessed by the `bb_pretreatment.Rmd` script):
24+ ```{r, echo=TRUE, message=FALSE, warning=FALSE}
25 bioch <- read.delim("intermediate/bb_pretreated.tsv", row.names=1, check.names=F)
26 bioch <- na.omit(bioch)
27 sampleAnno <- read.delim("intermediate/sample_annotation.tsv", stringsAsFactors=F)
28 rownames(sampleAnno) <- sampleAnno$Vcode
29 # Remove subjects that are outliers, has iron deficiency, or without blood biochemistry
30 # data (also remove secondary anemia and macrocytic anemia subjects when this info is available...)
31 samplesKeep <- sampleAnno$Vcode[with(sampleAnno, !hasIronDeficiency & !isOutlier &
32                           !hasSecondaryAnemia & !hasMacrocyticAnemia & !is.na(Date))]
33 bb <- bioch[rownames(bioch)%in%samplesKeep,]
34 ...
35
36

```

**Differential expression analysis using linear models**

**Contents**

Introduction	1
Check which blood biochemistry factors can be used together in linear regression	1
VIF scores	1
Pairwise correlation	2
Linear regression using limma	5
Correlate blood biochemistry to PC1 of gene expression	5
Separate linear regression for each factor (Alt. 1)	6
Combining many factors in the same regression (Alt. 2)	16
Differential expression between Hb extreme quantiles	22
Session info	24

**Introduction**

This report and analysis sets out to explore the possibility to use the blood biochemistry factors to predict gene expression.

**Check which blood biochemistry factors can be used together in linear regression**

First load the biochemistry data (this file has been cleaned up and preprocessed by the `bb_pretreatment.Rmd` script):

```

bioch <- read.delim("intermediate/bb_pretreated.tsv", row.names=1, check.names=F)
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samplesKeep <- sampleAnno$Vcode[with(sampleAnno, !hasIronDeficiency & !isOutlier &
                           !hasSecondaryAnemia & !hasMacrocyticAnemia & !is.na(Date))]
bb <- bioch[rownames(bioch)%in%samplesKeep,]

```

**VIF scores**

The Variance Inflation Factor (VIF) score is a way to check if there is a problem of multicollinearity in a regression analysis. This is done by regressing each factor (or predictor) on the remaining ones and calculating the  $R^2$  value. The VIF scores is then calculated as  $VIF = 1/(1 - R^2)$ . A VIF score of 1 means that there is no correlation among a given factor/predictor and the remaining predictor variables. A general rule of thumb is that  $VIF > 4$  need further investigation, while  $VIF > 10$  indicate serious multicollinearity problems.

Below we calculate VIF scores for each blood biochemistry factor, and also including age and gender since these two factors will likely be used in a linear regression model to control for such biases:

1



localhost

File Edit View Insert Cell Kernel Help

Code CellToolbar

**Study of velocity/energy relationship (1722-03-17, W. Gravesande)**

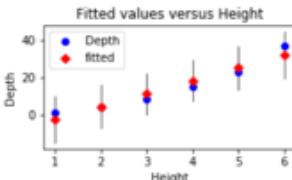
If I drop brass balls from various heights and measure penetration depth in a block of clay, can I settle the dispute regarding conservation of energy?

```
In [146]: import statsmodels as sm; import matplotlib.pyplot as plt; import numpy
plt.rcParams["figure.figsize"] = (4,2)
data = {"Depth": [1.1, 4.3, 8.7, 15.5, 23.2, 37.0], "Height": [1, 2, 3, 4, 5, 6]}
```

Test Bessler's hypothesis that kinetic energy, and thereby penetration depth, is linear with respect to height.

```
In [147]: res = sm.formula.api.ols(formula = 'Depth ~ Height', data = data).fit()
sm.graphics.api.plot_fit(res, 1)
```

Out[147]: Fitted values versus Height

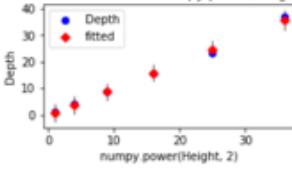


Height	Depth	fitted
1	1.1	~0.5
2	4.3	~1.5
3	8.7	~2.5
4	15.5	~3.5
5	23.2	~4.5
6	37.0	~5.5

Okayish, but maybe Bernoulli's quadratic model fits better?

```
In [148]: res = smf.ols(formula = 'Depth ~ numpy.power(Height,2)', data = data).fit()
sm.graphics.api.plot_fit(res, 1)
```

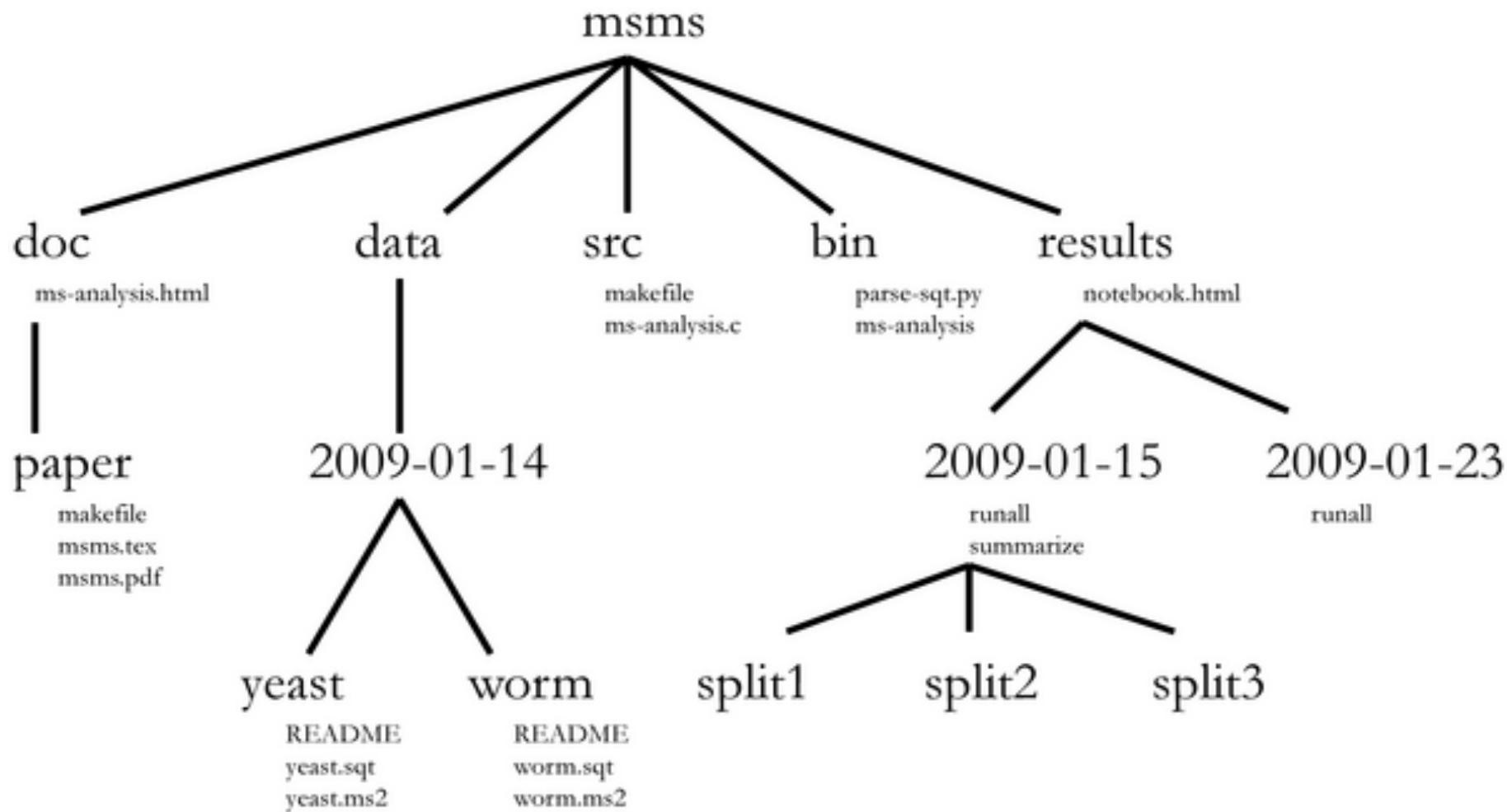
Out[148]: Fitted values versus numpy.power(Height, 2)



numpy.power(Height, 2)	Depth	fitted
1	1.1	~0.5
4	4.3	~1.5
9	8.7	~2.5
16	15.5	~3.5
25	23.2	~4.5
36	37.0	~5.5

Neat!

- In-browser editing for code, with automatic syntax highlighting, indentation, and tab completion/introspection.
- The ability to execute code from the browser, with the results of computations attached to the code which generated them.



Noble WS (2009) A Quick Guide to Organizing Computational Biology Projects. PLoS Comput Biol 5(7): e1000424.  
 doi:10.1371/journal.pcbi.1000424

<http://journals.plos.org/ploscompbiol/article?id=info:doi/10.1371/journal.pcbi.1000424>

---

## The project directory

```
project
|- doc/          documentation for the study
|
|- data/         raw and primary data, essentially all input files, never edit!
|   |- raw_external/
|   |- raw_internal/
|   |- meta/
|
|- code/         all code needed to go from input files to final results
|- notebooks/
|
|- intermediate/ output files from different analysis steps, can be deleted
|- scratch/      temporary files that can be safely deleted or lost
|- logs/         logs from the different analysis steps
|
|- results/      output from workflows and analyses
|   |- figures/
|   |- tables/
|   |- reports/
```

- There's no perfect set-up
  - Pick one! e.g.
    - <https://github.com/chendaniely/computational-project-cookie-cutter>
    - <https://github.com/Reproducible-Science-Curriculum/rr-init>
    - <https://github.com/nylander/pTemplate>
    - ...
- Communicate structure to collaborators
- Document as you go
- Done well it might reduce post-project explaining



# Reproducible research for bioinformatics projects

## Everything can be a project

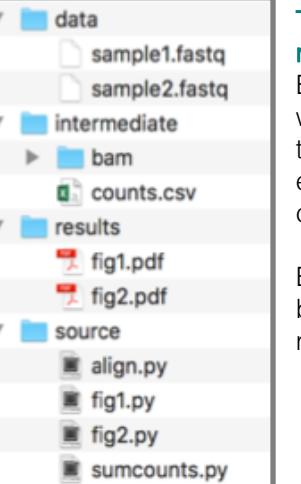
Divide your work into distinct projects and keep all files needed to go from raw data to final results in a dedicated directory with relevant subdirectories (see example).

Many software support the “project way of working”, e.g. Rstudio and the text editors Sublime Text and Atom.

**Tip!** Learn how to use git, a widely used system (both in academia and industry) for version controlling and collaborating on code.



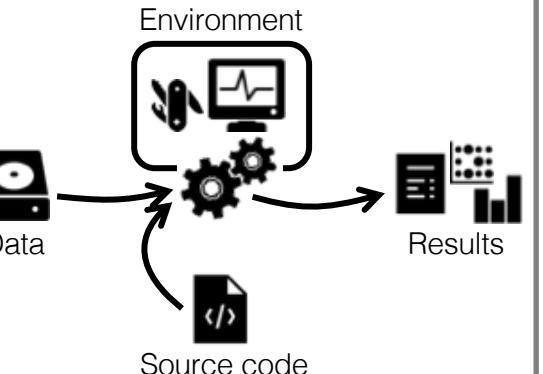
<https://git-scm.com/>



## Take control of your research by making it reproducible!

By moving towards a reproducible way of working you will quickly realize that you at the same time make your own life a lot easier! The added effort pays off by gain in control, organization and efficiency.

Below are all the components of a bioinformatics project that have to be reproducible.



## Treasure your data

- Consider your input data static. Keep it readonly!
- Don't make *different* versions. If you need to preprocess it in any way, script it so you can recreate the steps (see box below).
- Backup! Keep redundant copies in different physical locations.
- Strive towards uploading it to its final destination already at the beginning of a project (e.g. specific repositories such as ENA, or GeneExpress, or general repositories such as Dryad or Figshare).

## Organize your coding

- Write scripts/functions/notebooks for specific tasks (connect raw data to final results)
- Keep parameters separate (e.g. top of file, or input arguments)



Avoid generating files interactively on the fly or doing things by hand (no way to track how they were made).



## For the advanced

As projects grow, it becomes increasingly difficult to keep track of all the parts and how they fit together. Snakemake is a workflow management system that keeps track of how your files tie together, from raw data and scripts to final figures. If anything changes (script code, parameters, software version, etc) it will know what parts to rerun in order to have up to date and reproducible results.



Snakemake

<https://snakemake.readthedocs.io/>

## Connect your results with the code

Rmarkdown and Jupyter notebooks blur the boundaries between code and its output. They allow you to add non-code text (markdown) to your code. This generates a report containing custom formatted text, as well as figures and tables together with the code that generated them.

R Markdown

<http://rmarkdown.rstudio.com/> <http://jupyter.org/>



## Master your dependencies

- Full reproducibility requires the possibility to recreate the system that was originally used to generate the results.
- Conda is package, dependency, and environment manager that makes it easy to install (most) software that you need for your project.
- Your environment can be exported in a simple text format and reinstalled by Conda on another system.

CONDA <https://conda.io>

## For the advanced

- Conda cannot always *completely* recreate the system, which is required for proper reproducibility.
- A solution is to package your project in an isolated Docker container, together with all its dependencies and libraries.
- A vision is that every new bioinformatics publication is accompanied by a publically available Docker container!
- Singularity is an alternative to Docker which runs better on HPC clusters.

Docker

<https://www.docker.com/>

Singularity

<http://singularity.lbl.gov/>

- Open Science Framework – <http://osf.io>
  - Organize research project documentation and outputs
  - Control access for collaboration
  - 3rd party integrations
    - Google Drive
    - Dropbox
    - GitHub
    - External links
    - Etc
  - Persistent identifiers
  - Publish article preprints

The screenshot shows the OSF project dashboard for "My fabulous project". The top navigation bar includes links for My Dashboard, Browse, Help, and Settings. The main content area displays basic project metadata: Contributors: Niclas Jareborg, Date created: 2016-03-16 03:04 PM, Last Updated: 2016-03-16 03:08 PM, Category: Project, Description: No description, and License: No license. Below this, there are four main sections: "Wiki" containing a "Welcome" page with the text "This is a test project to check out functionality"; "Citation" with the URL osf.io/85f7h; "Components" showing contributions for "Data files" (1 contribution by Jareborg) and "Code" (5 contributions by Jareborg); and "Files" listing project files including "Project: My fabulous project", "Component: Data files", "Component: Code", "GitHub: nicjar/alfresco (master)", and "bin/build.xml". A "Tags" section at the bottom lists "Data management" and "Testing".

# Personal data



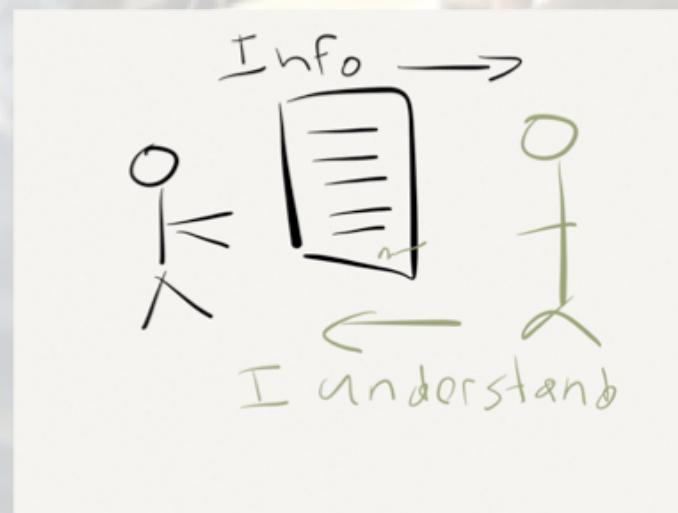
- Personal Data Act (*Personuppgiftslagen (PUL)*)
- Act concerning the Ethical Review of Research Involving Humans (*Lag om etikprövning av forskning som avser människor*)



- All kinds of information that is directly or indirectly referable to a natural person who is alive constitute personal data
- Sensitive data
  - It is **prohibited** to process personal data that discloses *ethnic origin, political opinions, religious or philosophical convictions, membership of trade unions*, as well as personal data relating to **health** or sexual life.
  - Sensitive personal data can be handled for **research purposes** if person has given **explicit consent**
- The Data Inspection Board (*Datainspektionen*) is the supervisory authority under the Personal Data Act
- May 2018: **General Data Protection Regulation (GDPR)**
  - New Swedish laws
    - **Data Protection Act (Dataskyddslag)**
    - **Research Data Act (Forskningsdatalag)**
    - Several other

- The (legal) person that decides why and how personal data should be processed is called the **controller of personal data** (*personuppgiftsansvarig*)
  - e.g. the employing university
- The controller of personal data can delegate processing of personal data to a **personal data assistant** (*personuppgiftsbiträde*)
  - e.g. UPPMAX/Uppsala university
- A **personal data representative** (*personuppgiftsombud*) is a natural person who, on the assignment of the controller, shall ensure that personal data is processed in a lawful and proper manner
- Obligation to report handling of personal data to the Data Inspection Board
  - Or, notify the Board of the named representative

- Research that concerns studies of biological material that has been taken from a living person and that can be traced back to that person may only be conducted if it has been approved subsequent to an ethical vetting
- Informed consent
  - The subject must be informed about the purpose or the research and the consequences and risks that the research might entail
  - The subject must consent



- The genetic information of an individual is personal data
  - **Sensitive** personal data (as it relates to health)
    - Explicitly defining in GDPR
    - Even if *anonymized / pseudonymized*
    - In principle, **no** difference between WGS, Exome, Transcriptome or GWAS data
- Theoretically possible to identify the individual person from which the sequence was derived from the sequence itself
  - The more associated metadata there is, the easier this gets
  - Gymrek et al. “Identifying Personal Genomes by Surname Inference”. Science 339, 321 (2013); DOI:10.1126/science.1229566
- *“The controller is liable to implement technical and organizational measures to protect the personal data. The measures shall attain a suitable level of security.”*

- **Bianca**
  - Swedish Research Council funded - SNIC Sens project
  - Implemented by SNIC/UPPMAX
  - 3200 cores / 1 PB
  - Opened april 2017 <https://uppmax.uu.se/resources/systems/the-bianca-cluster/>
- **Mosler**
  - e-Infrastructure for working with sensitive data for academic research
    - Developed & operated by NBIS
  - Inspired by Norwegian solution (TSD)
  - Designed to look like UPPMAX clusters
    - UPPMAX modules
    - UPPMAX can assist with installing custom tools
  - Implementation project completed Nov 2015
  - “Pilot-size system”
  - 24 nodes, 270 TB
- Provide users with a compute environment for sensitive data, with an *appropriate level of security*



- High-performance computing in a virtualized environment (OpenStack)
  - Each project environment is **isolated** from all other projects
    - Separated private networks and file systems
    - No internet access
    - No root access
- Only accessible over remote Linux desktop (ThinLinc) via a web dashboard
- **2-factor authentication for login**
- **Restricted data transfer in/out**
  - Via a file gateway
  - Project members can transfer IN / only PI allowed to transfer out
  - Not possible to copy/paste out





## TRYGGVE2: NORDIC COLLABORATION ON E-INFRASTRUCTURE FOR SENSITIVE DATA

<https://wiki.neic.no/tryggve>

# TRYGGVE2 VISION AND KEY TARGETS

Tryggve2 develops and facilitates access to secure e-infrastructure for conducting large-scale cross-border biomedical research studies utilizing sensitive data

## Key targets

- Develop state-of-the-art infrastructure
- Support wide range of use cases
- Improve cross-border access and usability of services
- Leverage Nordic secure resources and expertise



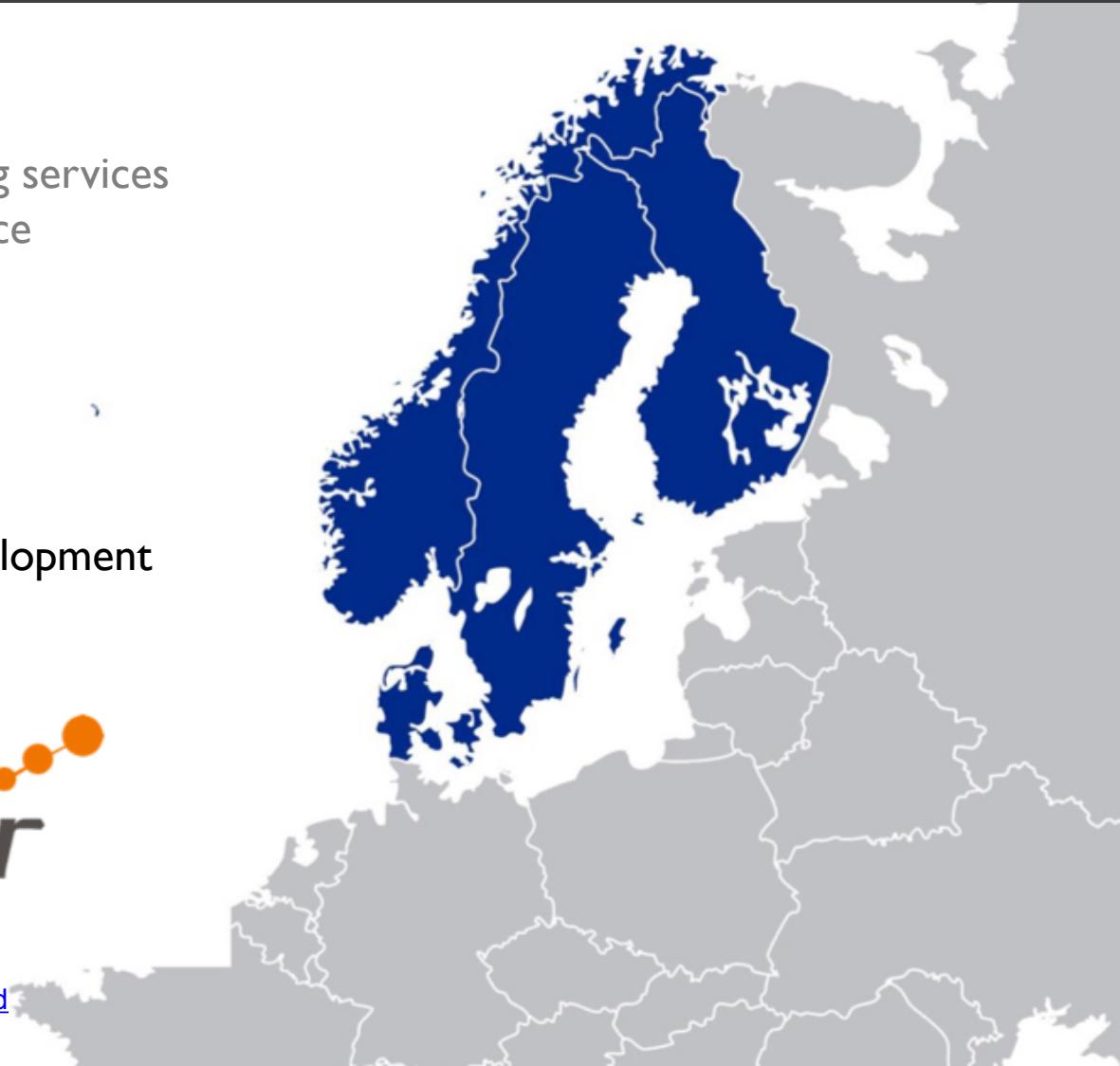
# TRYGGVE2 MAJOR DELIVERABLES

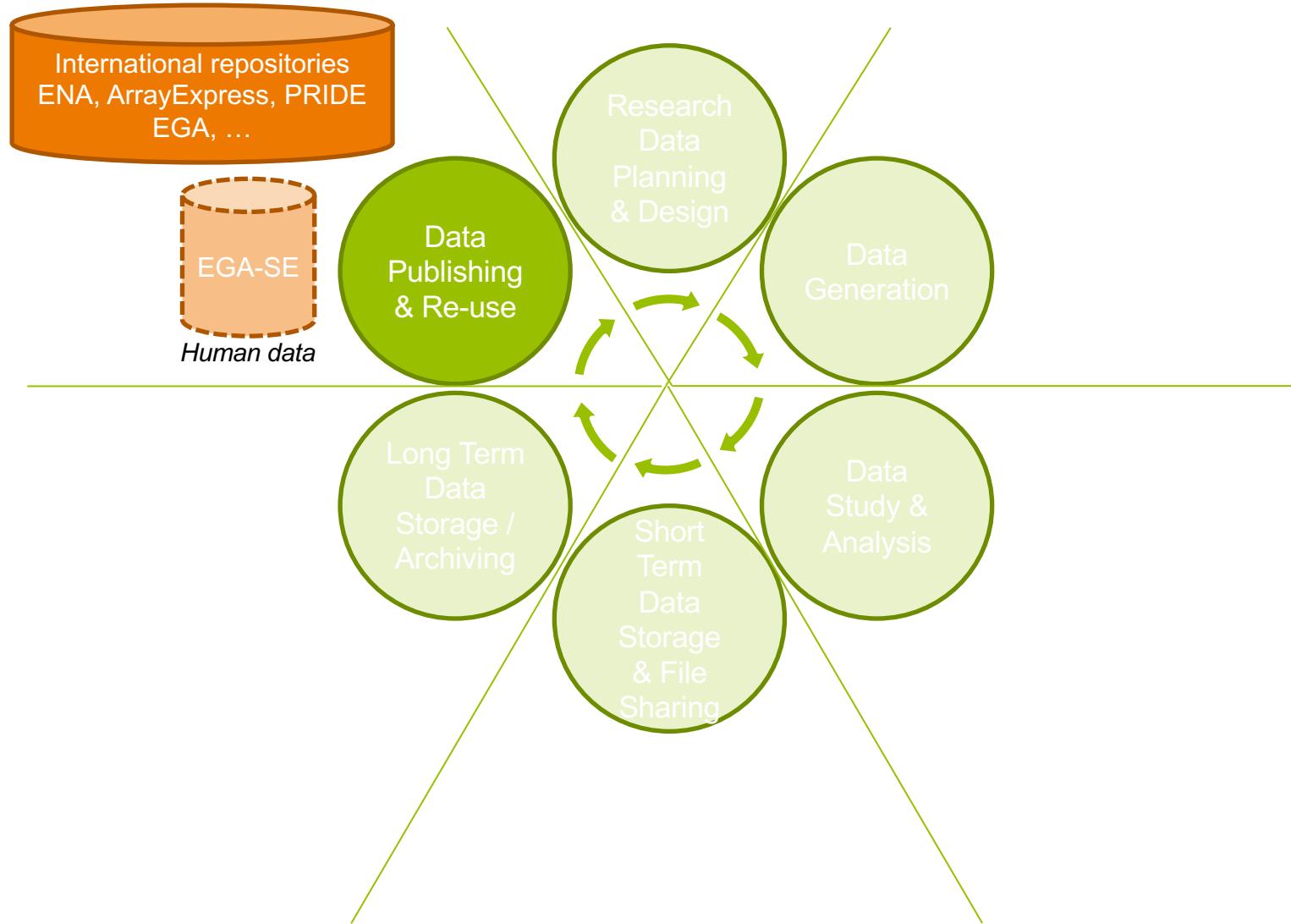
## COLLABORATION FOR SENSITIVE BIOMEDICAL DATA

- 1. Sensitive data archiving
- 2. Production quality processing services
- 3. Homogenized user experience
  - 1. User mobility
  - 2. Workflow mobility
  - 3. Data mobility
- 4. Nordic use cases
  - 1. Research
  - 2. Infrastructure development
- 5. ELIXIR AAI
- 6. IT Security
- 7. ELSI Topics



[https://wiki.neic.no/wiki/Tryggve\\_Getting\\_Started](https://wiki.neic.no/wiki/Tryggve_Getting_Started)





- *Research Data Publishing is a cornerstone of Open Access*
- Long-term storage
  - Data should not disappear
- Persistent identifiers
  - Possibility to refer to a dataset over long periods of time
  - Unique
  - e.g. DOIs (Digital Object Identifiers)
- Discoverability
  - Expose dataset metadata through search functionalities
- *Strive towards uploading data to its final destination already at the beginning of a project*



- DNA sequence databases: *Genbank* and *EMBL db* 1982
- Protein structures: *PDB* 1969

*Proc. Natl. Acad. Sci. USA*  
 Vol. 86, p. 408, January 1989  
 Data Submission

# 1989

## Submission of data to GenBank

CHRISTIAN BURKS AND LAURIE J. TOMLINSON

Theoretical Biology and Biophysics Group T-10, MS K710, Los Alamos National Laboratory, Los Alamos, NM 87545

In response to both the ever-increasing rate of determining nucleotide sequences (1) and the growing trend among journals to allow articles to appear that describe the results of determining a sequence without explicitly presenting the sequence (1), GenBank\* (2-5) and a number of the journals that publish nucleotide sequence data are working together to promote the direct, timely submission of nucleotide sequence data to GenBank. The policy being established by the PROCEEDINGS is described in the editorial on p. 407; here, we will provide a brief summary, in the context of this policy, of

*Electronic file transfer.* Files can be network to the network GenBank submit above. This address—in most cases with can be reached from various networks, ARPANET, USENET, JANET, JUNET, etc. / work or system expert how to send electronic us for help. *Floppy disks.* We can read M or 5½-in diskettes written on MS-DOS so that the submitted data be written as flat t in a format specific to a given word |

Growth of the GenBank Database  
 October 1982 to August 1987

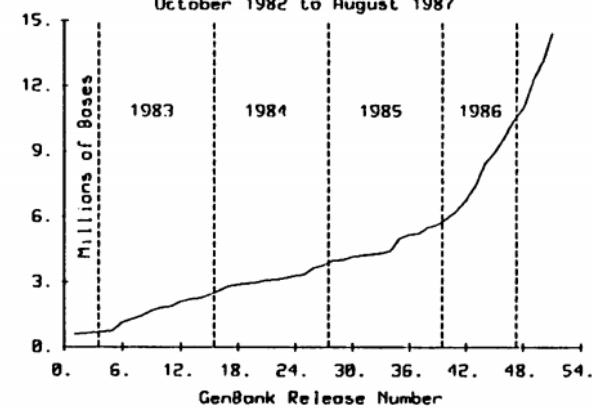


Figure 1.

“The author will provide the accession number to the PROCEEDINGS [PNAS] office to be included in a footnote to the published paper.”

Bilofsky & Burks (1988)  
*Nucleic Acids Research* v16 n5

## Bermuda Principles for sharing DNA sequence data

- Automatic release of sequence assemblies larger than 1 kb (preferably within 24 hours).
- Immediate publication of finished annotated sequences.
- Aim to make the entire sequence freely available in the public domain



# Data persistency issues

## URL decay in MEDLINE—a 4-year follow-up study

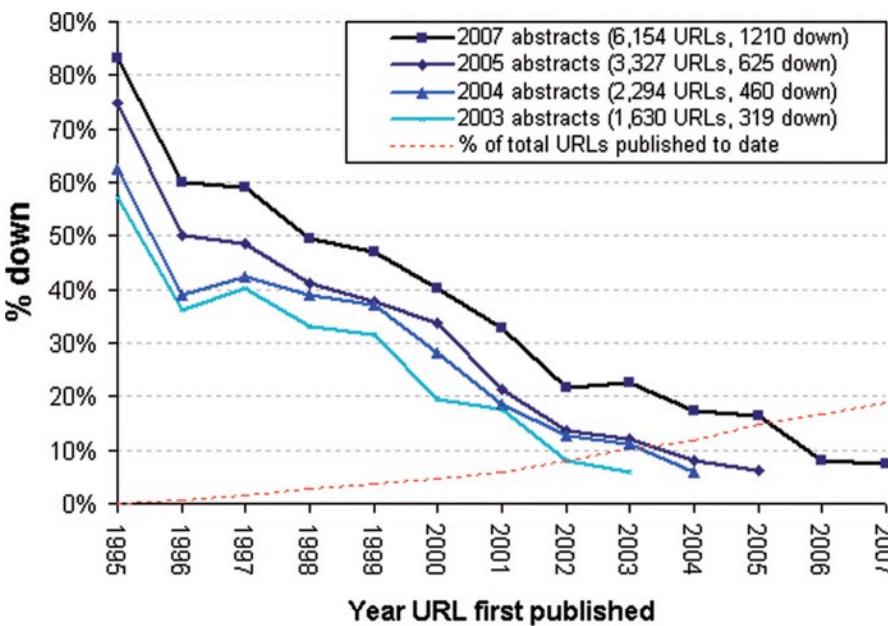


Jonathan D. Wren\*

 Author Affiliations

\*To whom correspondence should be addressed.

Received January 22, 2008.  
 Revision received March 11, 2008.  
 Accepted April 6, 2008.



- Link rot – more 404 errors generated over time
- Reference rot\* – link rot plus content drift i.e. webpages evolving and no longer reflecting original content cited

\* Term coined by Hiberlink <http://hiberlink.org>

- To be useful for others data should be
  - **FAIR** - Findable, Accessible, Interoperable, and Reusable  
*... for both Machines and Humans*

Wilkinson, Mark et al. “*The FAIR Guiding Principles for scientific data management and stewardship*”. *Scientific Data* 3, Article number: 160018 (2016)  
<http://dx.doi.org/10.1038/sdata.2016.18>



The screenshot shows the front page of a scientific article. At the top left, it says "OPEN SUBJECT CATEGORIES" with options like "Research data" and "Publication characteristics". The title "SCIENTIFIC DATA" is prominently displayed. Below the title, there's a section titled "Comment: The FAIR Guiding Principles for scientific data management and stewardship" by Mark D. Wilkinson et al. The text of the comment discusses the need to improve infrastructure for scholarly data reuse. At the bottom left, there are publication details: "Received: 10 December 2015", "Accepted: 12 February 2016", and "Published: 15 March 2016". A small "bioRxiv" logo is also present.

## Box 2 | The FAIR Guiding Principles

### To be Findable:

- I1. (meta)data are assigned a globally unique and persistent identifier
- I2. data are described with rich metadata (defined by R1 below)
- I3. metadata clearly and explicitly include the identifier of the data it describes
- I4. (meta)data are registered or indexed in a searchable resource

### To be Accessible:

- A1. (meta)data are retrievable by their identifier using a standardized communications protocol
- A1.1 the protocol is open, free, and universally implementable
- A1.2 the protocol allows for an authentication and authorization procedure, where necessary
- A2. metadata are accessible, even when the data are no longer available

### To be Interoperable:

- I1. (meta)data use a formal, accessible, shared, and broadly applicable language for knowledge representation.
- I2. (meta)data use vocabularies that follow FAIR principles
- I3. (meta)data include qualified references to other (meta)data

### To be Reusable:

- R1. meta(data) are richly described with a plurality of accurate and relevant attributes
- R1.1. (meta)data are released with a clear and accessible data usage license
- R1.2. (meta)data are associated with detailed provenance
- R1.3. (meta)data meet domain-relevant community standards

# G20 HANGZHOU SUMMIT

**'We support appropriate efforts to promote open science  
and facilitate appropriate access to publicly funded  
research results on findable, accessible, interoperable and reusable  
(FAIR)'**

HANGZHOU, CHINA 4-5 SEPT



- European Open Science Cloud – EOSC

- *Enable trusted access to services, systems and the re-use of shared scientific data across disciplinary, social and geographical borders.*
- FAIR principles are a cornerstone of EOSC



EUROPEAN COMMISSION  
 DIRECTORATE-GENERAL FOR RESEARCH & INNOVATION  
 The Director-General

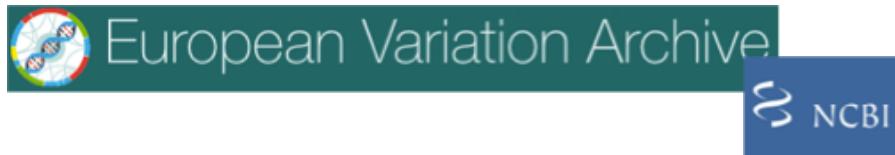
Brussels, 10 July 2017

## EOSC Declaration

RECOGNISING the challenges of data driven research in pursuing excellent science;  
 GRANTING that the vision of European Open Science is that of a research data commons, widely inclusive of all disciplines and Member States, sustainable in the long-term,  
 CONFIRMING that the implementation of the EOSC is a process, not a project, by its nature iterative and based on constant learning and mutual alignment;  
 UPHOLDING that the EOSC Summit marked the beginning and not the end of this process, one based on continuous engagement with scientific stakeholders, the European Commission,  
PROPOSES that all EOSC stakeholders consider sharing the following intents and will actively support their implementation in the respective capacities:

### Data culture and FAIR data

- [Data culture] European science must be grounded in a common culture of data stewardship, so that research data is recognised as a significant output of research and is appropriately curated throughout and after the period conducting the research. Only a considerable cultural change will enable long-term reuse for science and for innovation of data created by research activities: no disciplines, institutions or countries must be left behind.
- [Open access by-default] All researchers in Europe must enjoy access to an open-by-default, efficient and cross-disciplinary research data environment supported by FAIR data principles. Open access must be the default setting for all results of publicly funded research in Europe, allowing for proportionate limitations only in duly justified cases of personal data protection, confidentiality, IPR concerns, national security or similar (e.g. ‘as open as possible and as closed as necessary’).
- [Skills] The necessary skills and education in research data management, data stewardship and data science should be provided throughout the EU as part of higher education, the training system and on-the-job best practice in the industry. University associations, research organisations, research libraries and other educational brokers play an important role but they need substantial support from the European Commission and the Member States.
- [Data stewardship] Researchers need the support of adequately trained data stewards. The European Commission and Member States should invest in the education of data stewards via career programmes delivered by universities, research institutions and other trans-European agents.
- [Rewards and incentives] Rewarding research data sharing is essential. Researchers who make research data open and FAIR for reuse and/or reuse and reproduce data should be rewarded, both



dbSNP  
Short Genetic Variations



- Best way to make data FAIR
- Domain-specific metadata standards

Deposition Database	Data type	International collaboration framework <sup>1</sup>	Deposition Database	Data type	International collaboration framework <sup>1</sup>
ArrayExpress	Functional genomics data. Stores data from high-throughput functional genomics experiments.		PDBe	Biological macromolecular structures.	wwPDB
BioModels	Computational models of biological processes.		PRIDE	Mass spectrometry-based proteomics data, including peptide and protein expression information (identifications and quantification values) and the supporting mass spectra evidence.	The ProteomeXchange Consortium
EGA	Personally identifiable genetic and phenotypic data resulting from biomedical research projects.	European Bioinformatics Institute and the Centre for Genomic Regulation		Pending incorporation into a Node Service Delivery Plan (see <a href="#">How countries join</a> ):	
ENA	Nucleotide sequence information, covering raw sequencing data, contextual data, sequence assembly information and functional and taxonomic annotation.	International Nucleotide Sequence Database Collaboration	BioSamples	BioSamples stores and supplies descriptions and metadata about biological samples used in research and development by academia and industry.	NCBI BioSamples database
IntAct	IntAct provides a freely available, open source database system and analysis tools for molecular interaction data.	The International Molecular Exchange Consortium	BioStudies	Descriptions of biological studies, links to data from these studies in other databases, as well as data that do not fit in the structured archives.	
MetaboLights	Metabolite structures and their reference spectra as well as their biological roles, locations and concentrations, and experimental data from metabolic experiments.		EVA	The European Variation Archive covers genetic variation data from all species.	dbSNP and dbVAR
			EMDB	The Electron Microscopy Data Bank is a public repository for electron microscopy density maps of macromolecular complexes and subcellular structures.	

<https://www.elixir-europe.org/platforms/data/elixir-deposition-databases>

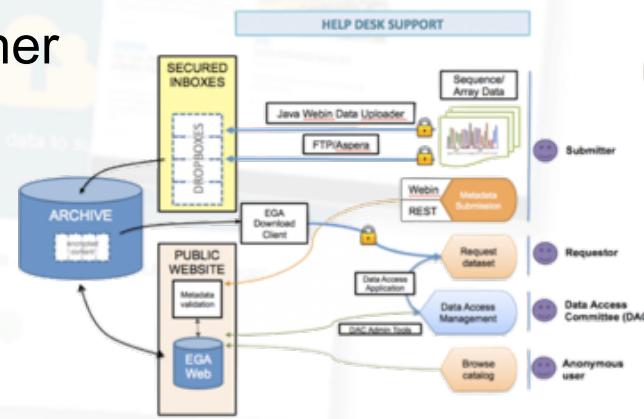
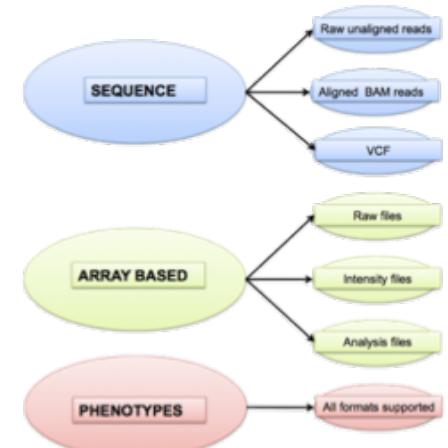
# Surprisingly few submit to international repositories

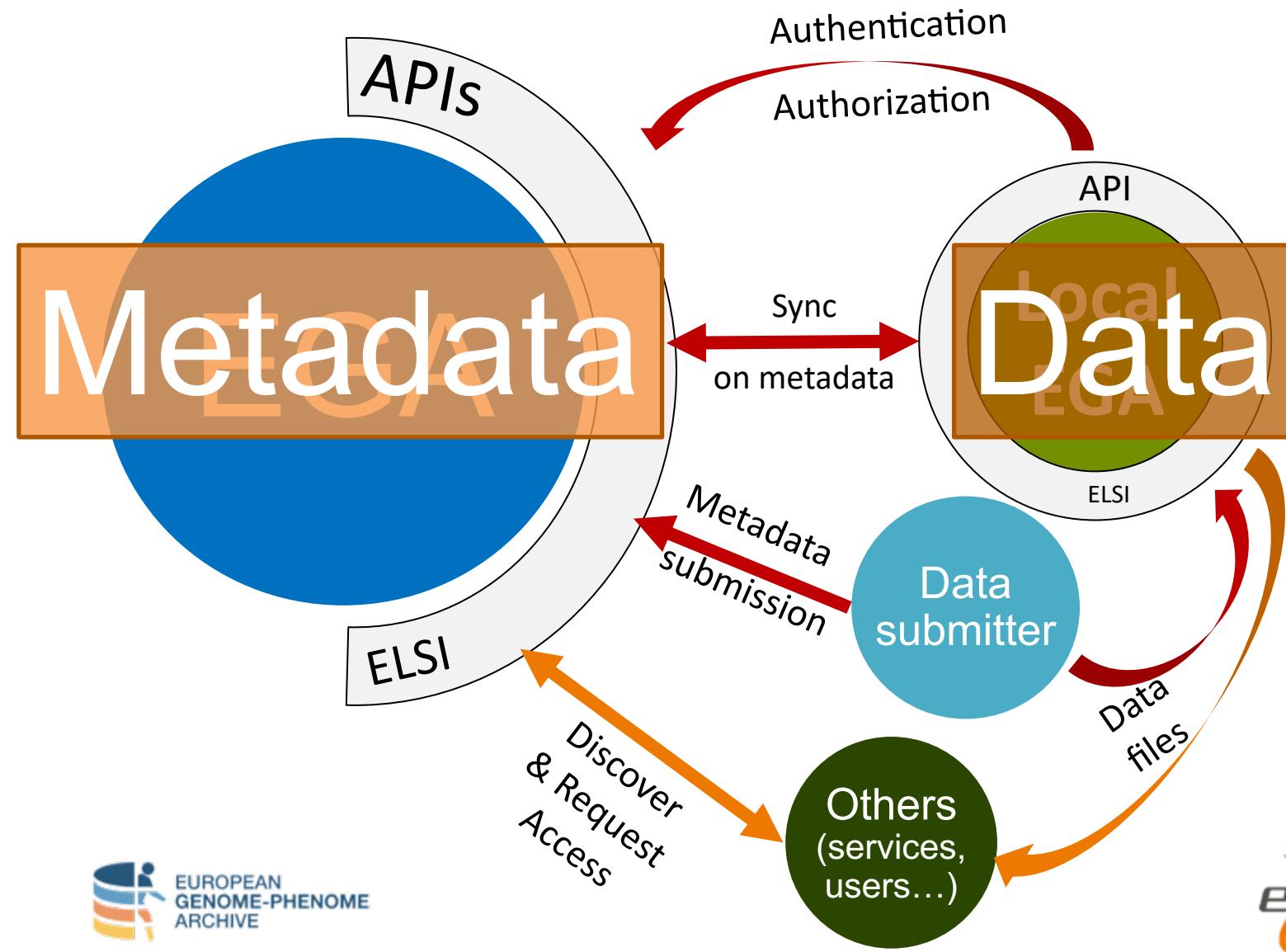
- NIH funded research
  - Only 12% of articles from NIH-funded research mention data deposited in international repositories
  - Estimated 200000+ “invisible” data sets / year

*Read et al. “Sizing the Problem of Improving Discovery and Access to NIH-Funded Data: A Preliminary Study” (2015)*

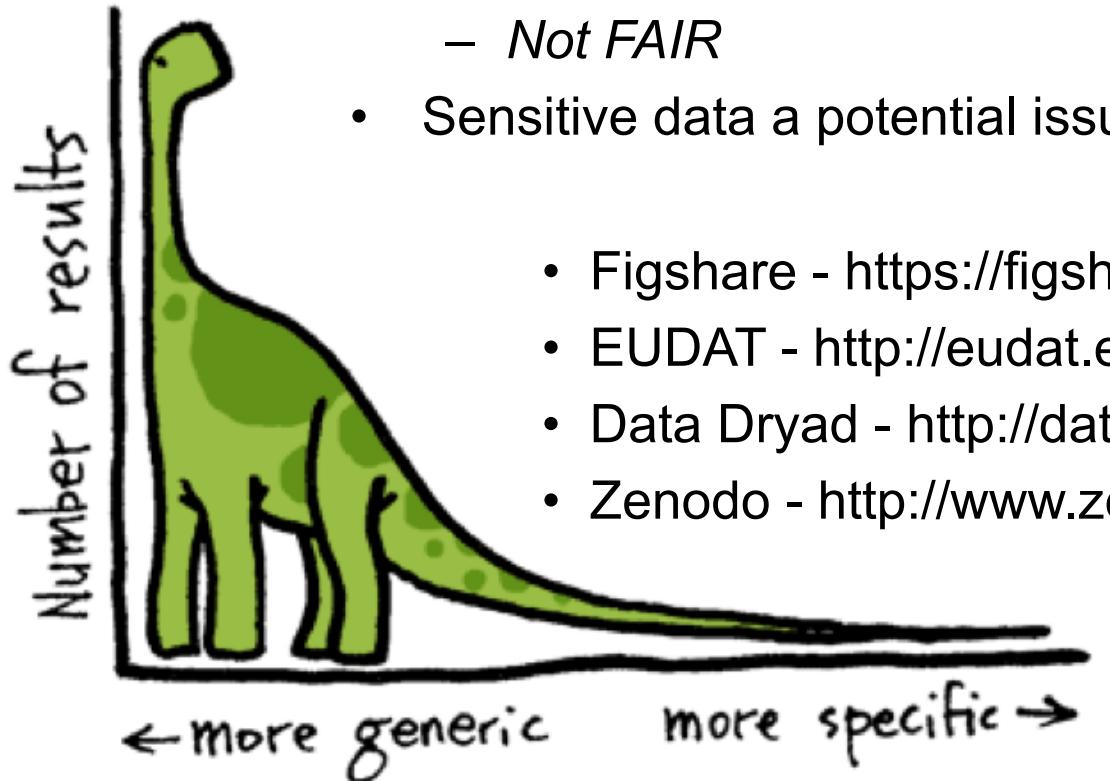
*PLoS ONE 10(7): e0132735. doi: 10.1371/journal.pone.0132735*

- **EGA – European Genome-phenome Archive**
  - Repository that promotes the distribution and sharing of **genetic and phenotypic data** consented for specific approved uses but **not fully open, public distribution.**
  - All types of sequence and genotype experiments, including case-control, population, and family studies.
- Data Access Agreement
  - Defined by the data owner
- Data Access Committee – DAC
  - Decided by the data owner





- Research data that doesn't fit in structured data repositories
- Data publication – persistent identifiers
- Metadata submission – not tailored to Life Science
  - *Affects discoverability*
  - *Not FAIR*
- Sensitive data a potential issue



- Figshare - <https://figshare.com/>
- EUDAT - <http://eudat.eu/>
- Data Dryad - <http://datadryad.org/>
- Zenodo - <http://www.zenodo.org/>

- ORCID is an open, non-profit, community-driven effort to create and maintain a registry of unique researcher identifiers and a transparent method of linking research activities and outputs to these identifiers.
- <http://orcid.org>
- Persistent identifier for you as a researcher

The screenshot shows the ORCID profile page for Niclas Jareborg. At the top, there's a navigation bar with tabs for 'FOR RESEARCHERS' (selected), 'FOR ORGANIZATIONS', 'ABOUT', 'HELP', and 'SIGN IN'. Below the navigation bar, there are links for 'SIGN IN', 'REGISTER FOR AN ORCID ID', and 'LEARN MORE'. A statistic at the top right says '2,035,272 ORCID IDs and counting. See more...'. The main content area displays Niclas Jareborg's profile information, including his ORCID ID (0000-0002-4520-044X) and other details like 'Also known as' (C. J. E. Niclas Jareborg, N Jareborg), 'Country' (Sweden), and 'Websites' (LinkedIn, Personal home page). Below this, there are sections for 'Education' (with two entries for Uppsala Universitet) and 'Employment' (with three entries for Stockholms Universitet and Kungliga Tekniska Högskolan). Each entry includes the institution, period, field (e.g., Microbiology, Biochemistry and Biophysics), title (e.g., PhD, BSc, Data Manager), source (Niclas Jareborg), and creation date (e.g., 2015-04-09, 2015-02-23).

**Niclas Jareborg**

**ORCID ID**  
ID.orcid.org/0000-0002-4520-044X

Also known as  
C. J. E. Niclas Jareborg, N Jareborg

Country  
Sweden

Websites  
LinkedIn  
Personal home page

**Education (2)**

Uppsala Universitet: Uppsala, Sweden  
1989-05 to 1995-05 (Microbiology)  
PhD  
Source: Niclas Jareborg  
Created: 2015-04-09

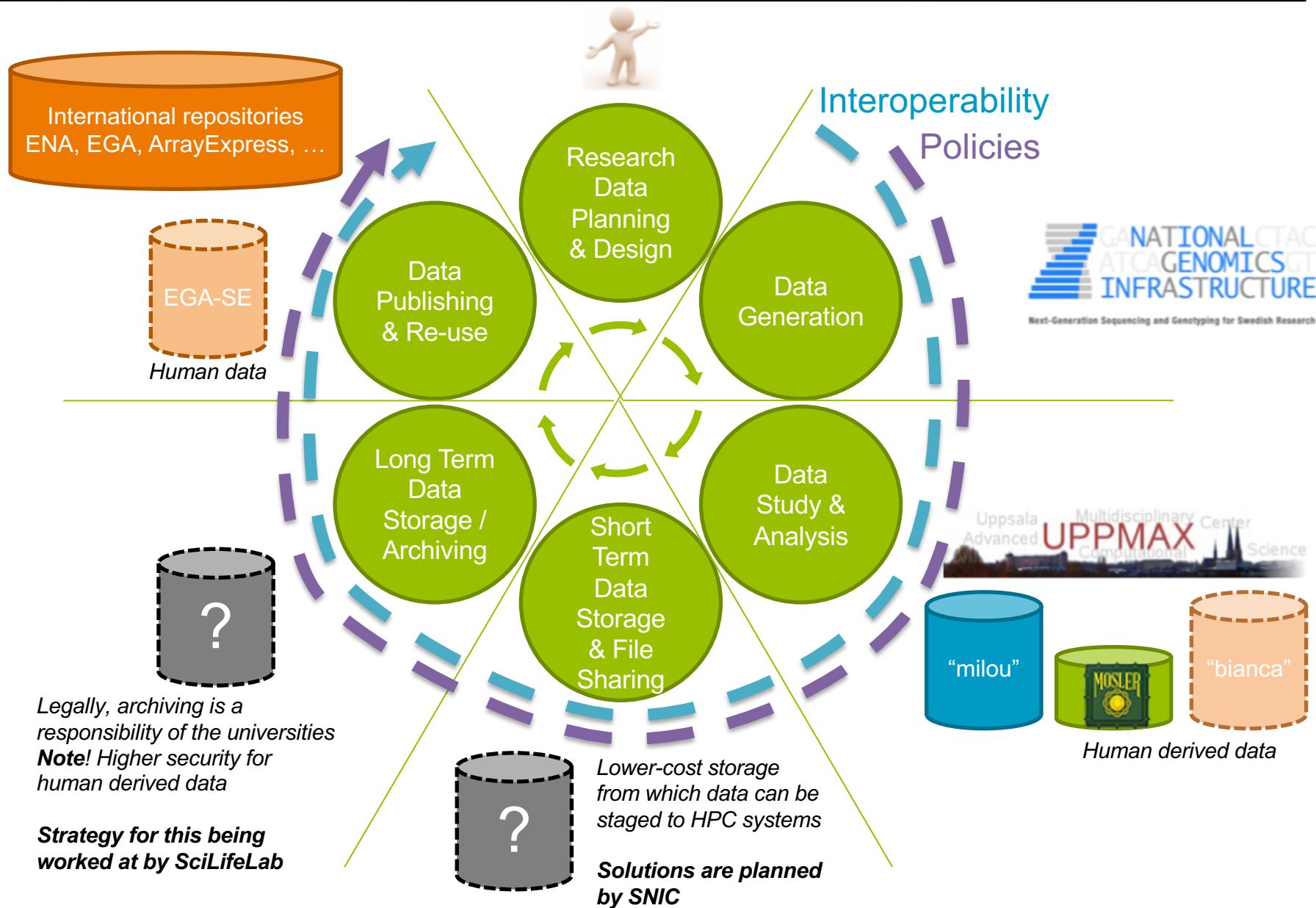
Uppsala Universitet: Uppsala, Sweden  
1985-01 to 1989-04 (Microbiology)  
BSc  
Source: Niclas Jareborg  
Created: 2015-04-09

**Employment (7)**

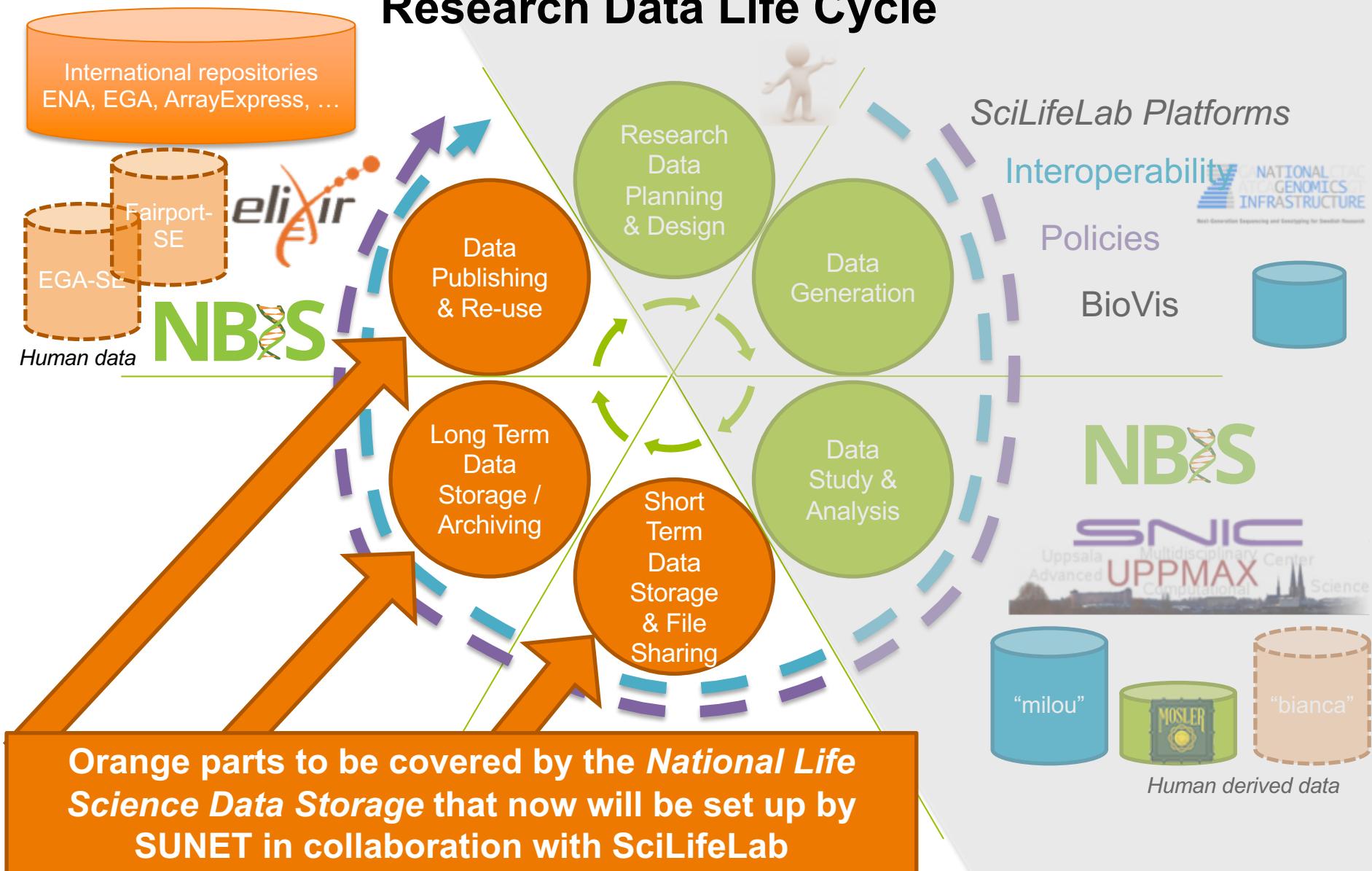
Stockholms Universitet: Stockholm, Sweden  
2015-01 to present (BiLS / Department of Department of Biochemistry and Biophysics)  
Data Manager  
Source: Niclas Jareborg  
Created: 2015-02-23

Kungliga Tekniska Högskolan: Stockholm, Sweden  
2013-01 to 2014-12 (National Genomics Infrastructure / SciLifeLab)

- 
- Project planning
    - Metadata
    - File formats
    - Licensing
    - *Data Management Plans*
  - Data analysis
  - Data publication and submission
    - Automate submissions to public repositories
    - Metadata
    - Licensing



# Research Data Life Cycle



- Research Data Management, EUDAT -  
<http://hdl.handle.net/11304/79db27e2-c12a-11e5-9bb4-2b0aad496318>
- Barend Mons – FAIR Data
- Antti Pursula – Tryggve <https://wiki.neic.no/wiki/Tryggve>
- Noble WS (2009) [A Quick Guide to Organizing Computational Biology Projects. PLoS Comput Biol 5\(7\): e1000424.](https://doi.org/10.1371/journal.pcbi.1000424)  
[doi:10.1371/journal.pcbi.1000424](https://doi.org/10.1371/journal.pcbi.1000424)
- Samuel Lampa - <http://bionics.it/posts/organizing-compbio-projects>
- Reproducible Science Curriculum – <https://github.com/Reproducible-Science-Curriculum/rr-init>
- Leif Wigge - [https://bitbucket.org/scilifelab-lts/reproducible\\_research\\_example/src](https://bitbucket.org/scilifelab-lts/reproducible_research_example/src)