NBIS
NATIONAL BIOINFORMATICS INFRASTRUCTURE SWEDEN

SciLifeLab

Research Data Management

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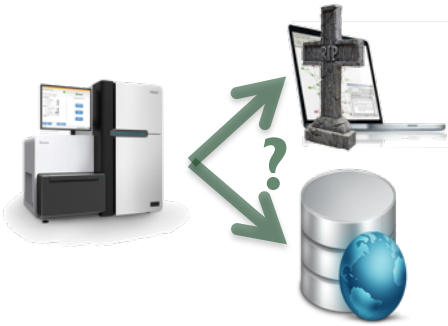
Introduction to NGS course, 2017-05-18

Why manage research data?

- 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

Accusation of fraud

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.

Published online 3 May 2017
10.1126/science.aan5763

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

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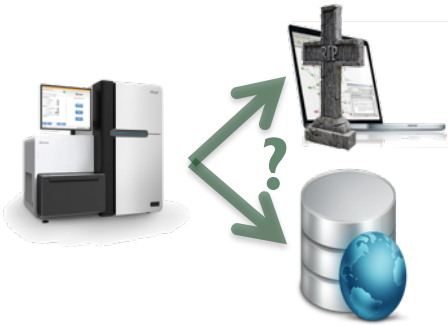
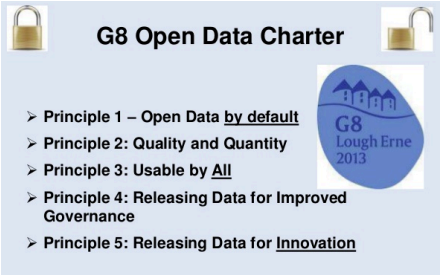


Well-managed data opens up opportunities for re-use, integration and new science

Open Access to research data

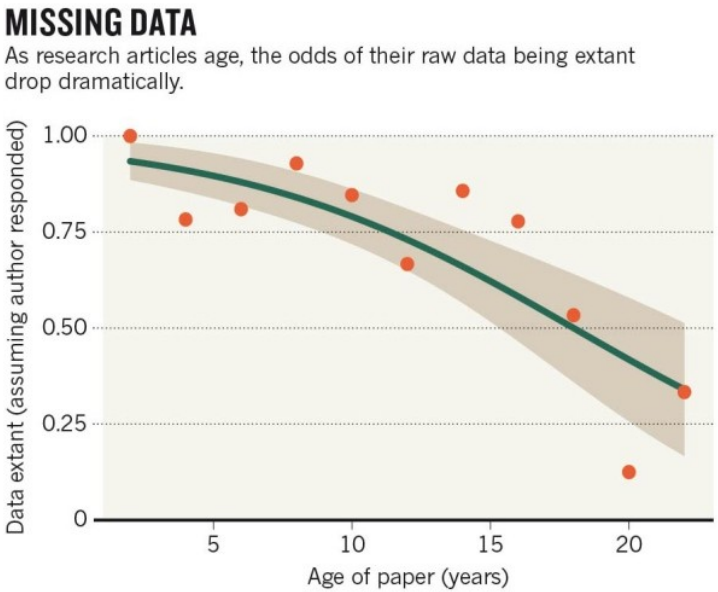
- *The practice of providing on-line access to scientific information that is free of charge to the end-user and that is re-usable.*
  - Does not necessarily mean unrestricted access, e.g. for sensitive personal data
- Strong international movement towards Open Access (OA)
- European Commission recommended 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]



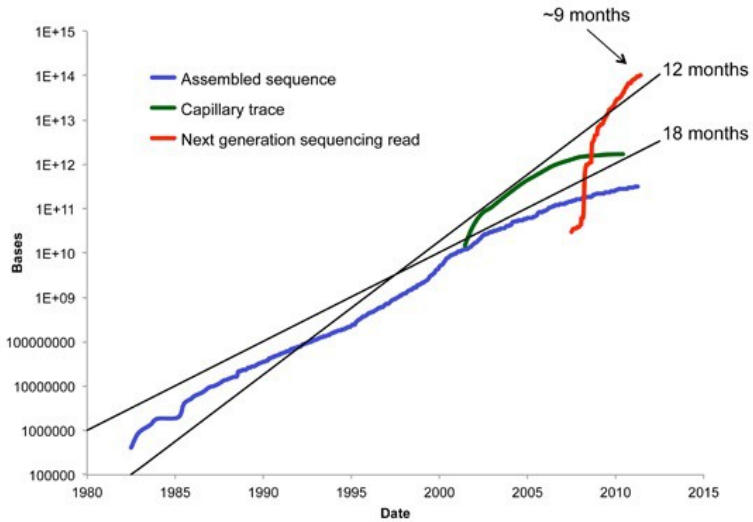
Why Open Access?

- 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



Nature news, 19 December 2013



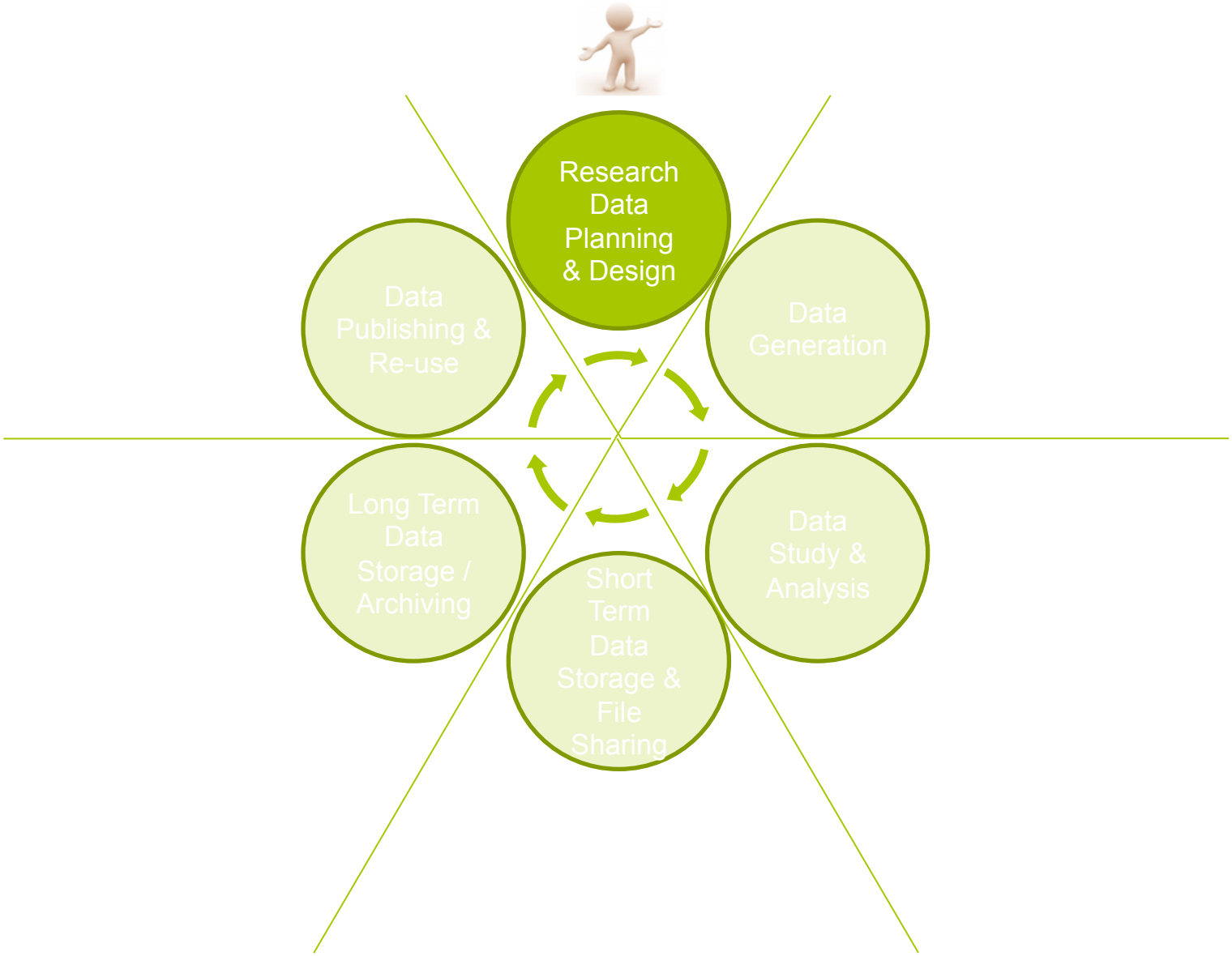
- DNA sequence data is doubling every 6-8 months and looks to continue for this decade
- Projected to surpass astronomy data in the coming decade

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

Slide stolen from Barend Mons

The Research Data Life Cycle

Planning & Design



Planning & Design

- Data Management planning
  - Data types
    - Sizes, were to store, etc
  - **Metadata**
    - Study, Samples, Experiments, etc
    - Use standards!
      - *But not straight-forward...* >600 life science data standards
      - Ontologies & contolled vocabularies
      - http://biosharing.org

biosharing.org
Information Resources

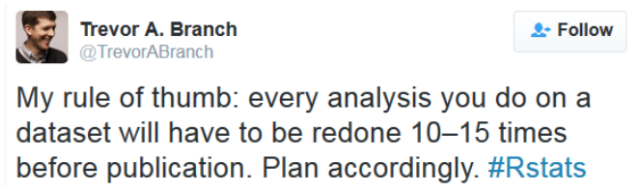
- *Data Management Plans*
  - Will become a standard part of the research funding application process
  - What will be collected?, Size?, Organized?, Documented?, Stored and preserved?, Disseminated?, Policies?, Budget?

Study & Analysis

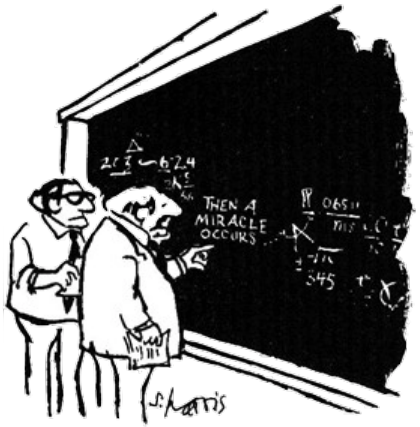
Human derived data

Study & Analysis

- 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

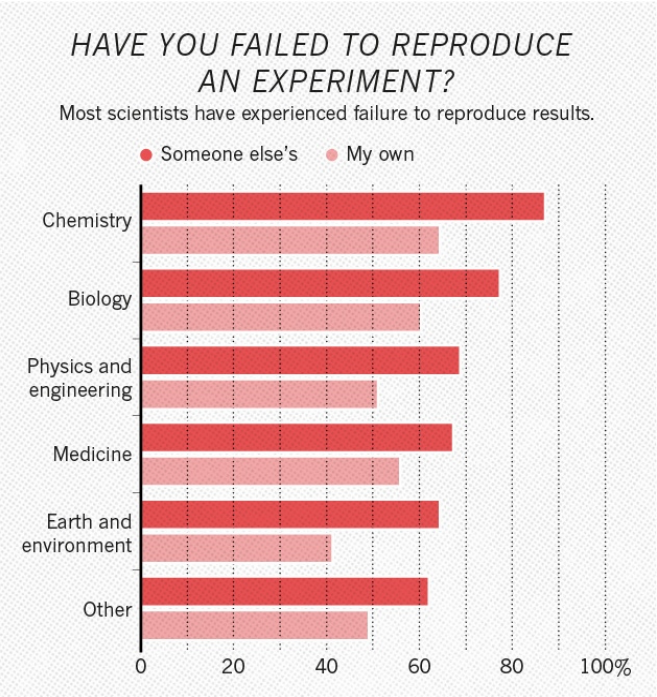


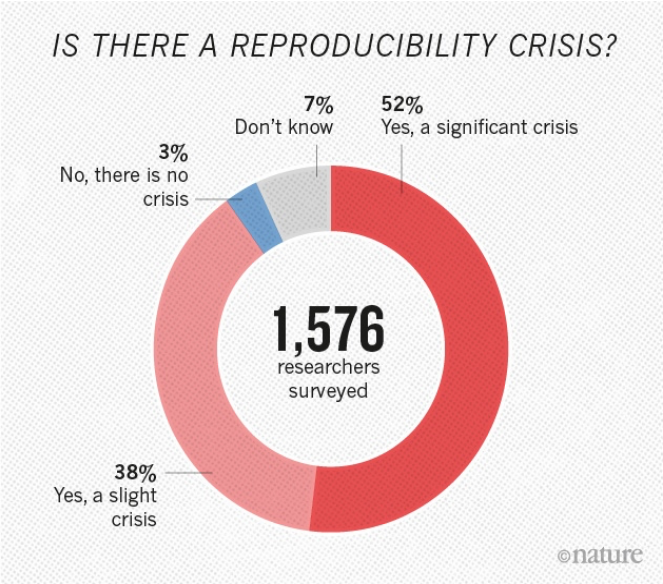
- Structuring data for analysis
  - Poor organizational choices lead to significantly slower research progress.
  - It is critical to make results reproducible.



"I think you should be more explicit here in step two."

A reproducibility crisis





A recent survey in Nature revealed that irreproducible experiments are a problem across all domains of science[1].

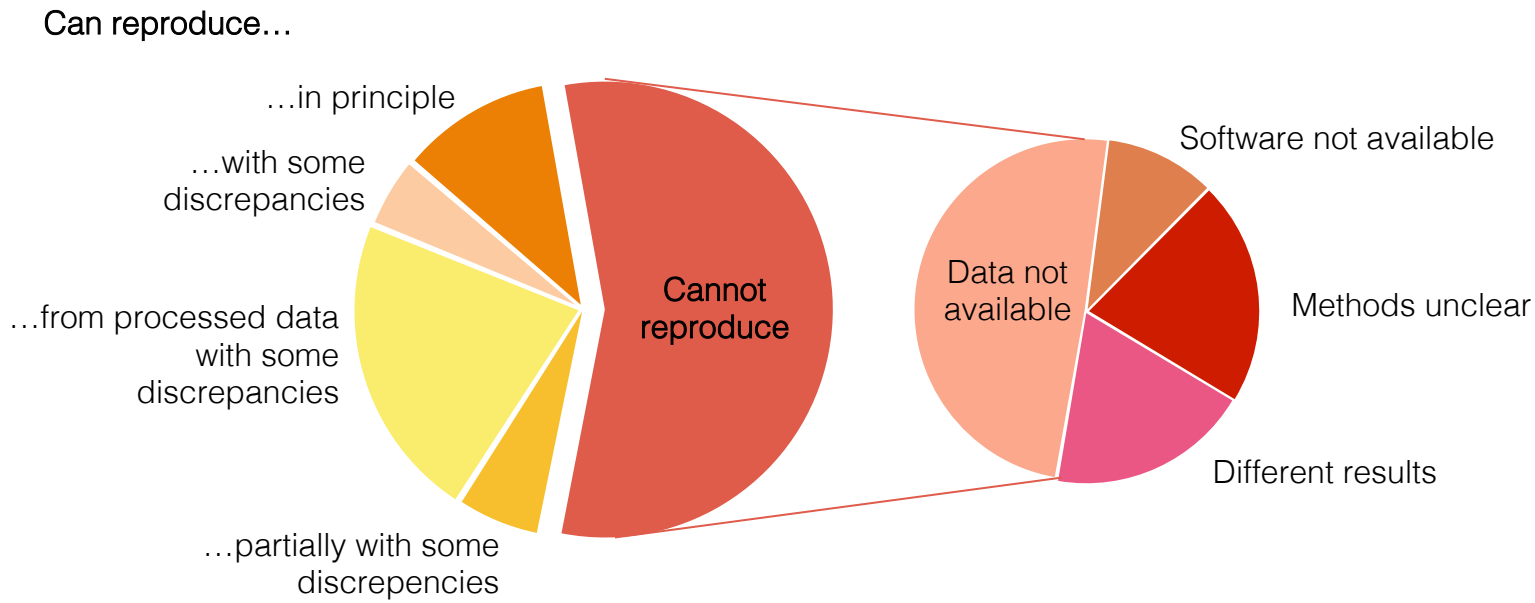
Medicine is among the most affected research fields. A study in Nature found that 47 out of 53 medical research papers focused on cancer research were irreproducible[2].

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:



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

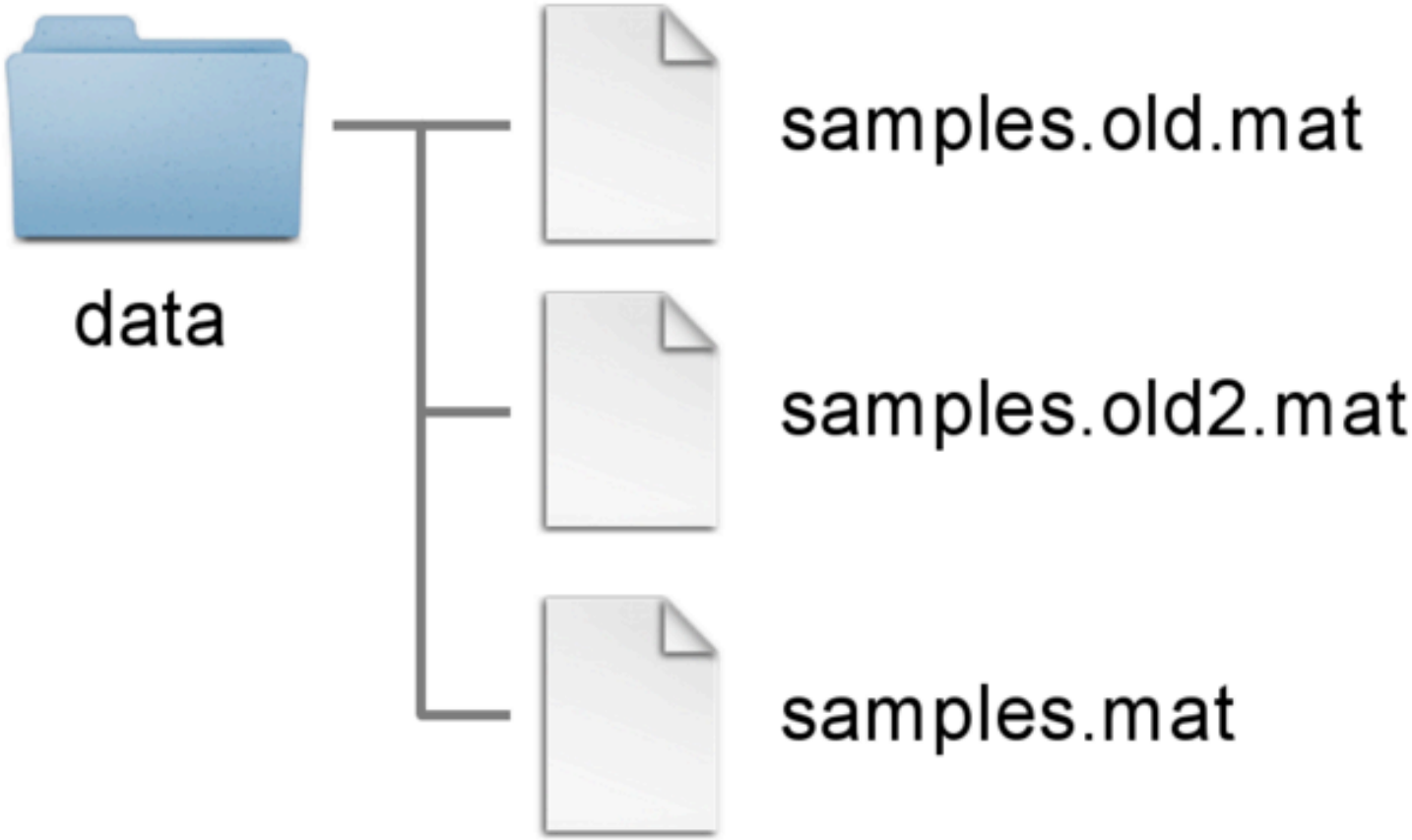
Is it really any point doing this?

- 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.

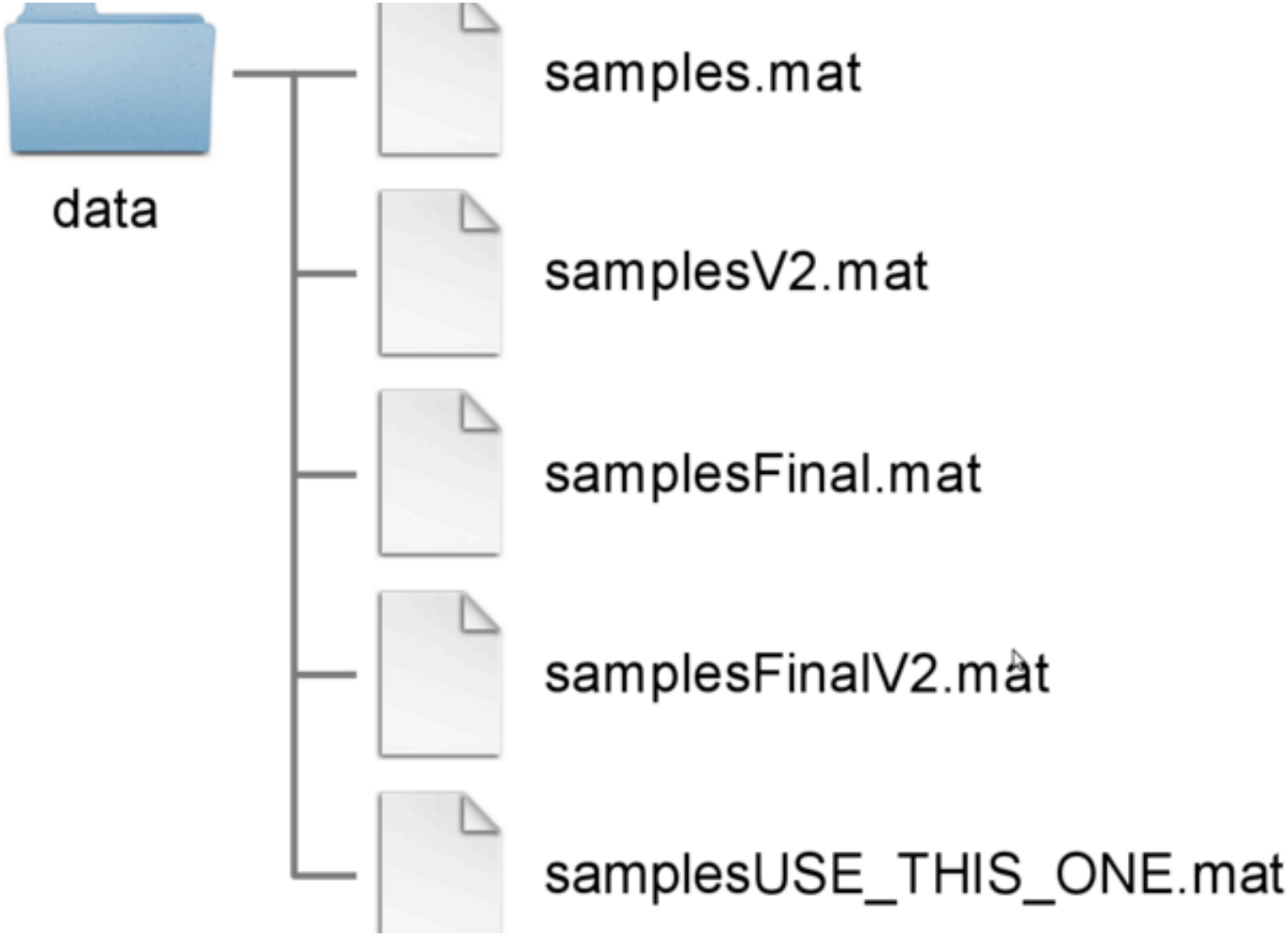
Organization - So far, so good…

Now what?

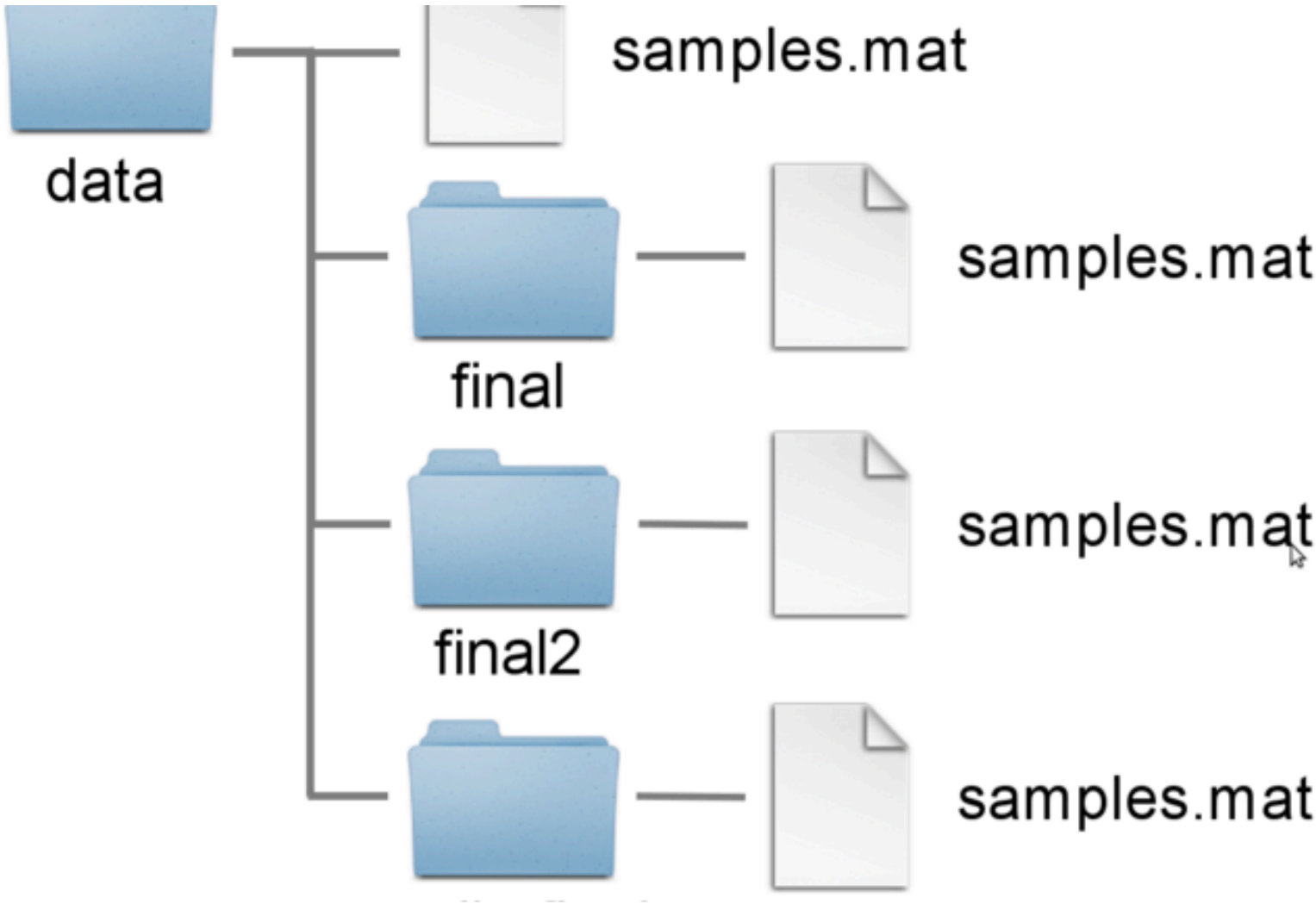
I guess this is alright



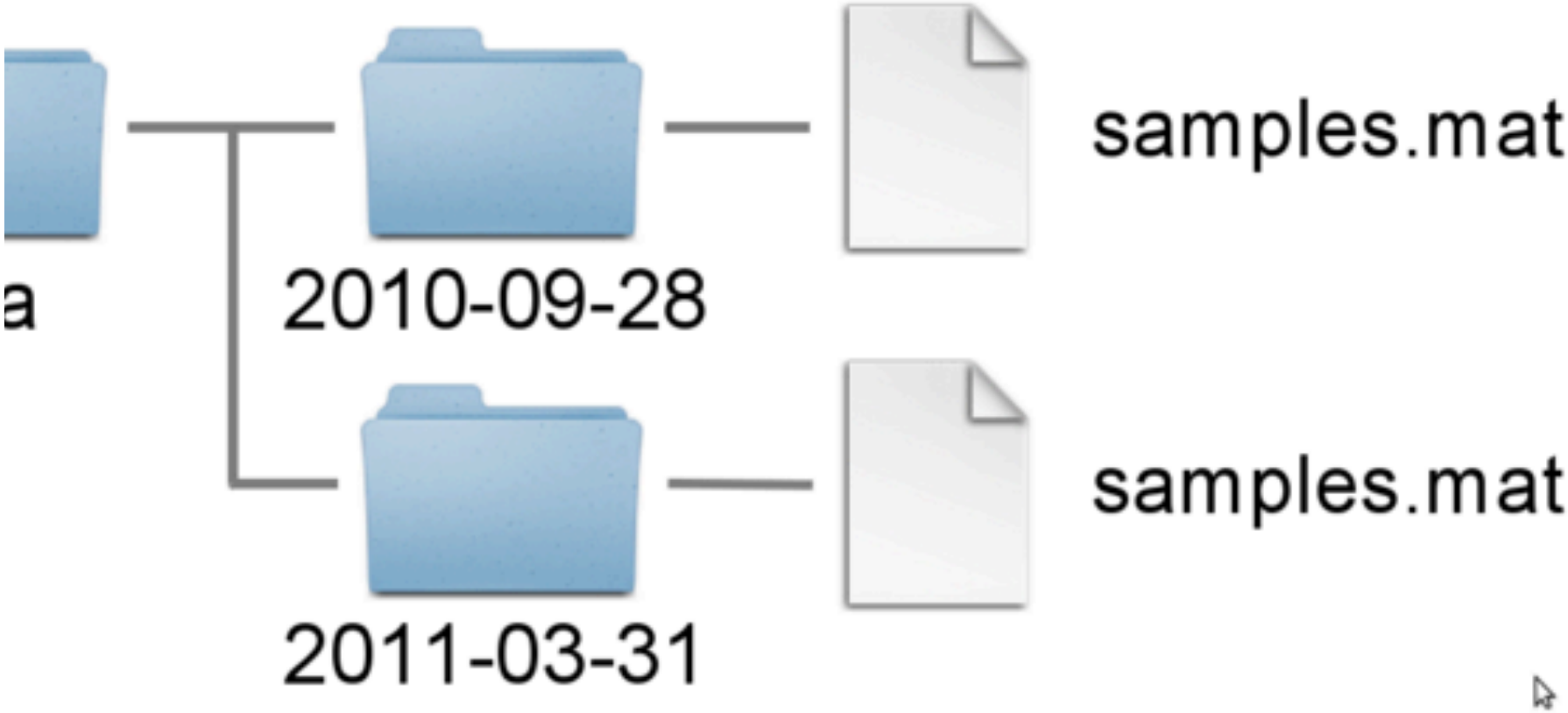
Which one is the most recent?



Another (bad) common approach



A possible solution

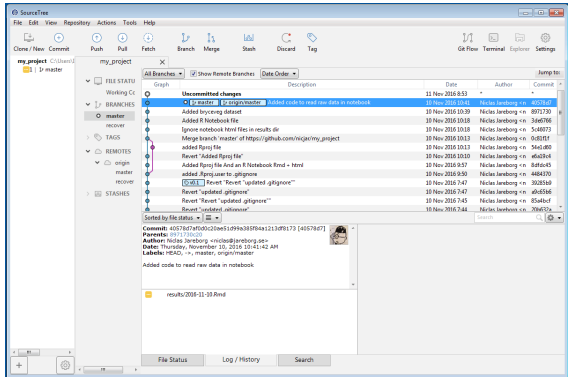


Suggested best practices

- 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…

Version control

- 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



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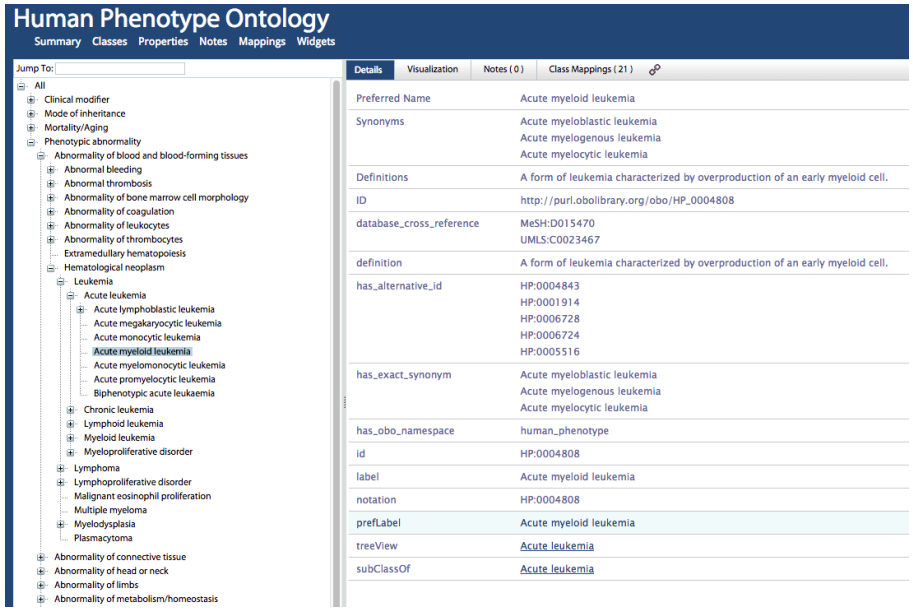
Non-proprietary formats

- 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

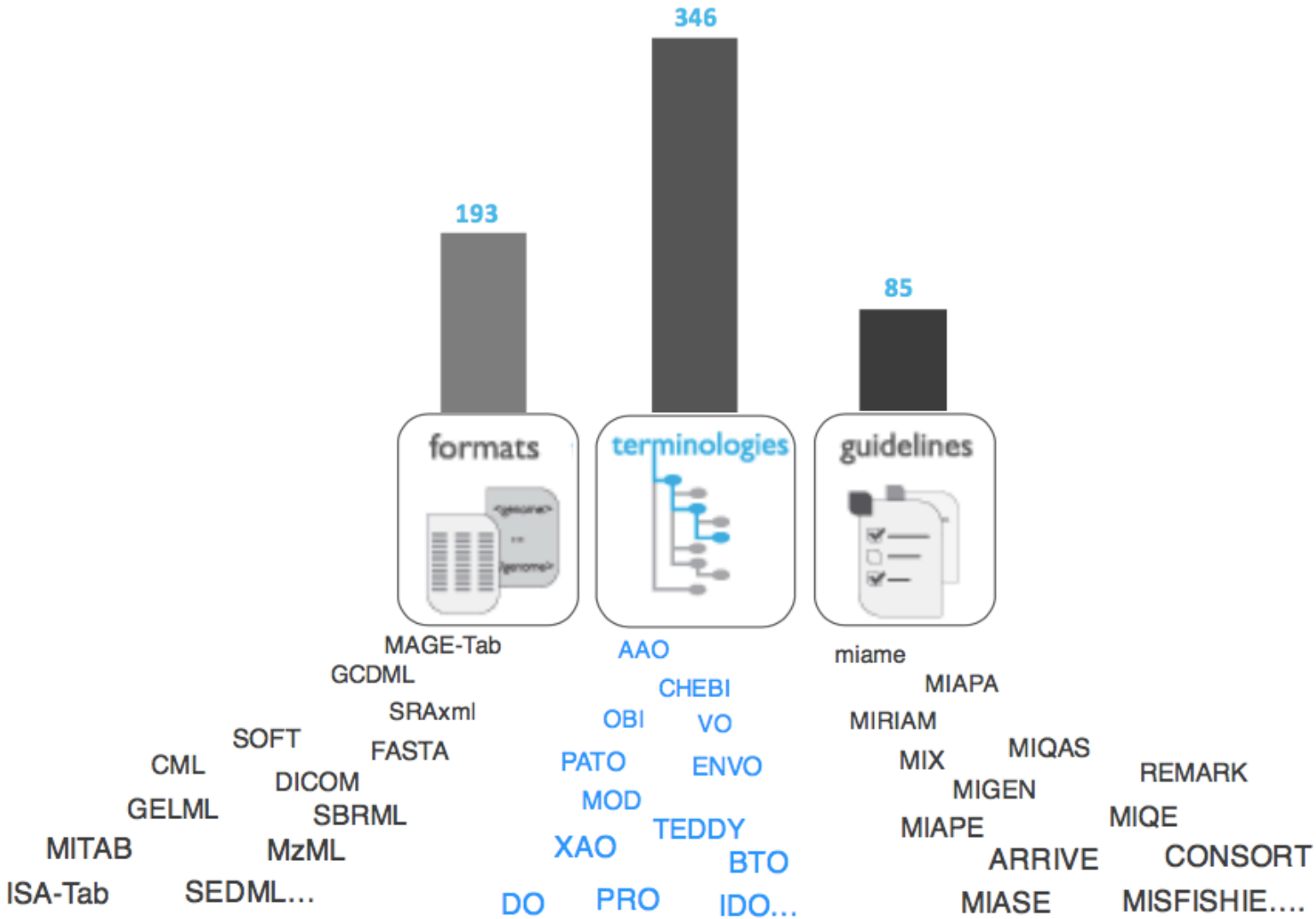
- *Never, never, never use **Excel** for scientific **analysis**!*
  - Script your analysis – bash, python, R, …

Still missing something

- 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…*



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



biosharing.org

biosharing.org
Information Resources

1,379 records and growing

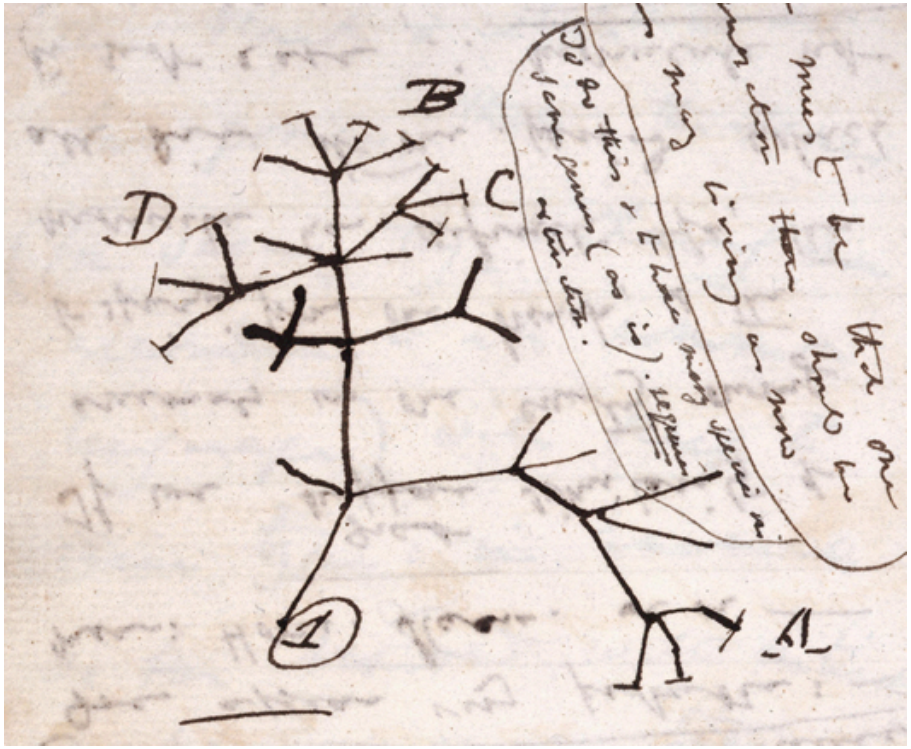
629 Standards		729 Databases		24 Policies	
Terminology Artifact	347	Protein	148	Funder	18
Model/Format	197	Genome	114	Journal	5
Reporting Guideline	85	DNA	75	Society	1
View all		View all		View all	

Mapping the landscape of 'standards' in the life sciences

A **web-based**, **curated** and **searchable registry** ensuring that standards and databases are *registered*, *informative* and *discoverable*; monitoring development and **evolution** of standards, their **use** in databases and adoption of both in data policies

Lab notebooks

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

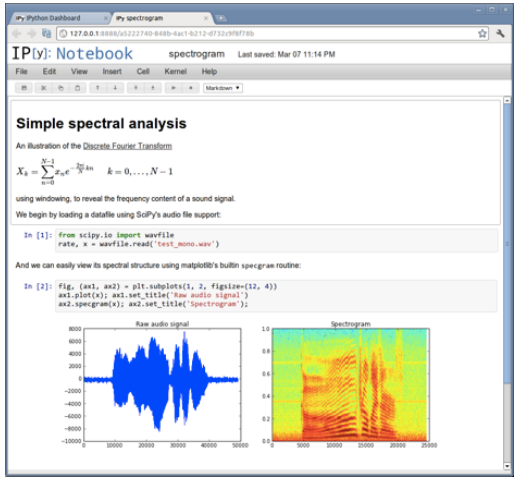


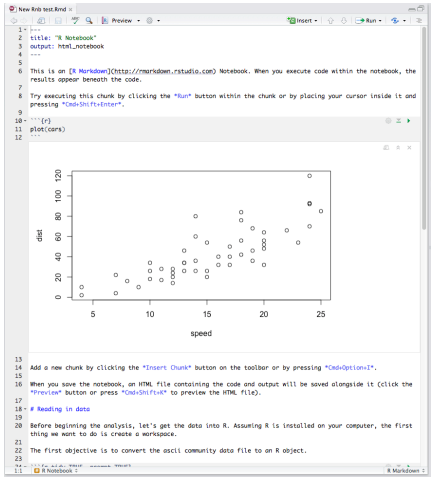
Lab notes – useful practices

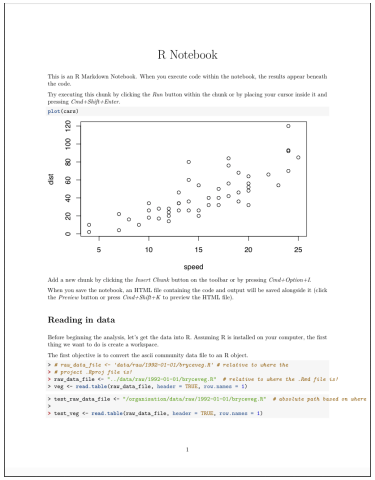
- Put in *results* directory
- *Dated* entries
- Entries relatively verbose
- Link to *data* and *code* (including versions)
    - Point to commands run and results generated
- Embedded images or tables showing results of analysis done
- Observations, Conclusions, and *ideas* for future work
- Also document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

Where to keep notes

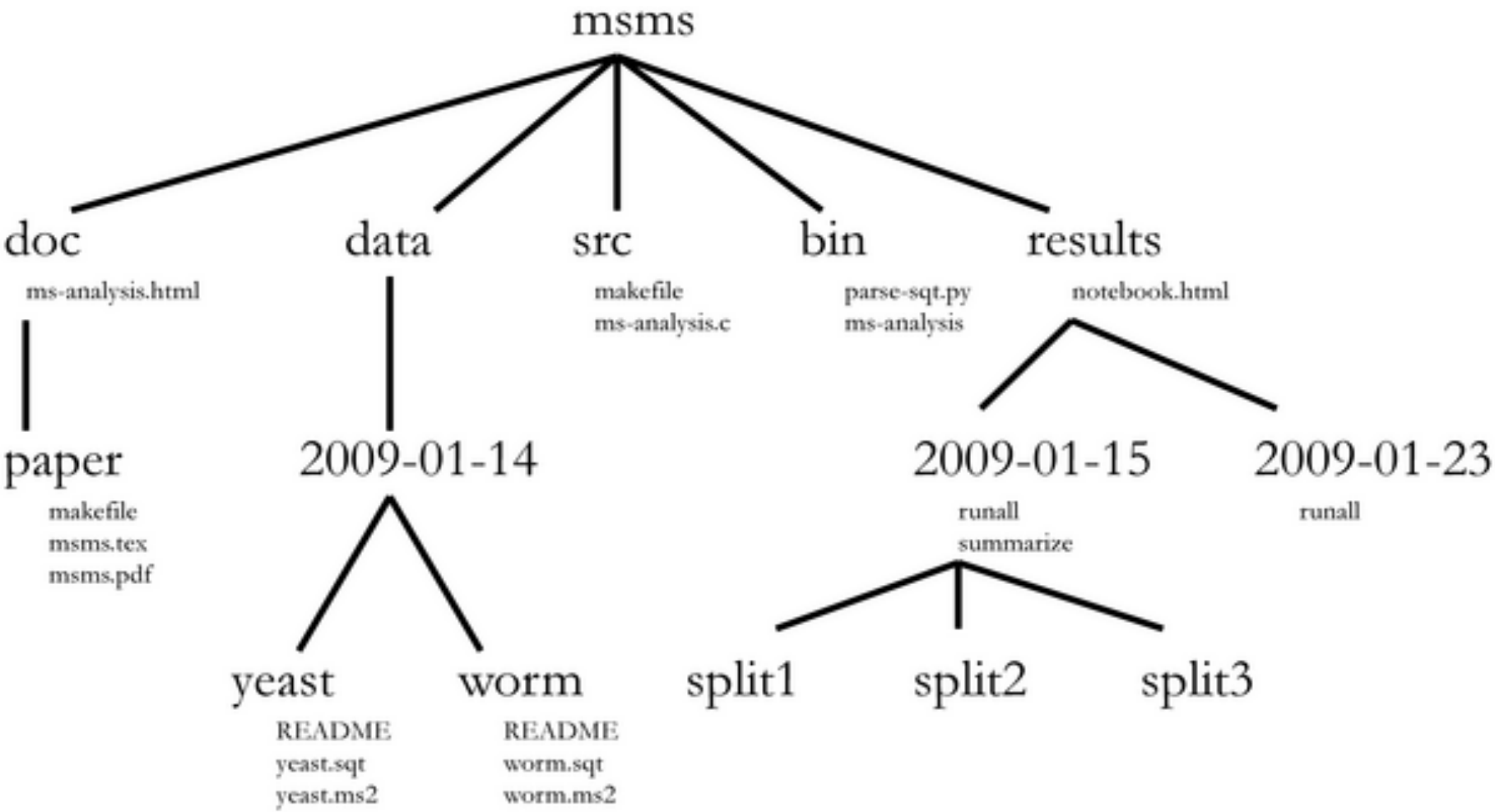
- Paper Notebook
- Word processor program / Text files
- Electronic Lab Notebooks
- 'Interactive' Electronic Notebooks
  - e.g. jupyther, R Notebooks in RStudio
  - Plain text - work well with version control (Markdown)
  - Embed and execute code
  - Convert to other output formats
    - html, pdf, word







Directory structure for a sample project



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

Or like this…

```
├── bin  <---------------# Binary files and executables (jar files & proj-wide scripts etc)
├── conf <---------------# Project-wide configuraiotn
├── doc  <---------------# Any documents, such as manuscripts being written
├── experiments  <-------#  The main experiments folder
│   ├── 2000-01-01-exa <-# An example Experiment
│   │   ├── audit  <-----# Audit logs from workflow runs (higher level than normal logs)
│   │   ├── bin   <------# Experiment-specific executables and scripts
│   │   ├── conf  <------# Experiment-specific config
│   │   ├── data  <------# Any data generated by workflows
│   │   ├── doc   <------# Experiment-specific documents
│   │   ├── log   <------# Log files from workflow runs (lower level than audit logs)
│   │   ├── raw   <------# Raw-data to be used in the experiment (not to be changed)
│   │   ├── results  <---# Results from workflow runs
│   │   ├── run   <------# All files rel. to running experiment: Workflows, run confs/scripts...
│   │   └── tmp   <------# Any temporary files not supposed to be saved
├── raw  <---------------# Project-wide raw data
├── results  <-----------# Project-wide results
└── src  <---------------# Project-wide source code (that needs to be compiled)
```

From Samuel Lampa's blog: http://bionics.it/posts/organizing-compbio-projects

Project organization

- 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

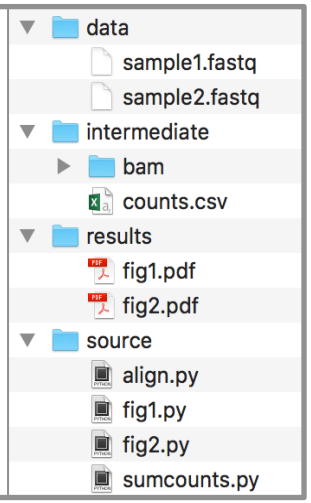
Reproducible research for bioinformatics projects

Leif Väremo (leif.varemo@scilifelab.se)
Rasmus Ågren (rasmus.agren@scilifelab.se)
Bioinformatics long-term support (WABI)

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.



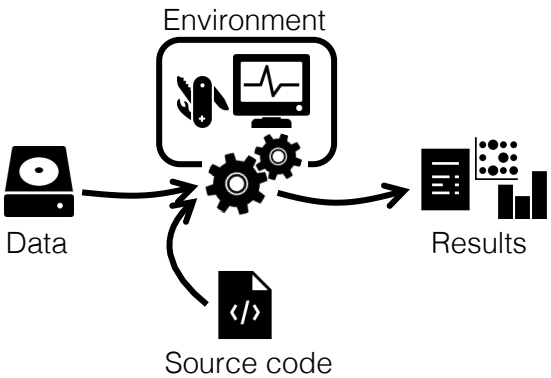
Tip! Learn how to use git, a widely used system (both in academia and industry) for version controlling and collaborating on code.

git
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 reproducible.



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/

jupyter
http://jupyter.org/

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).

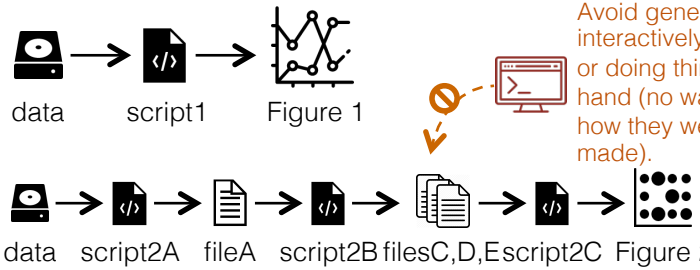
Master your dependencies

- Full reproducibility requires the possibility to recreate the system that was originally used to generate the results.
- Conda is package, dependency, and env-ironment 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

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)



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/

For the advanced

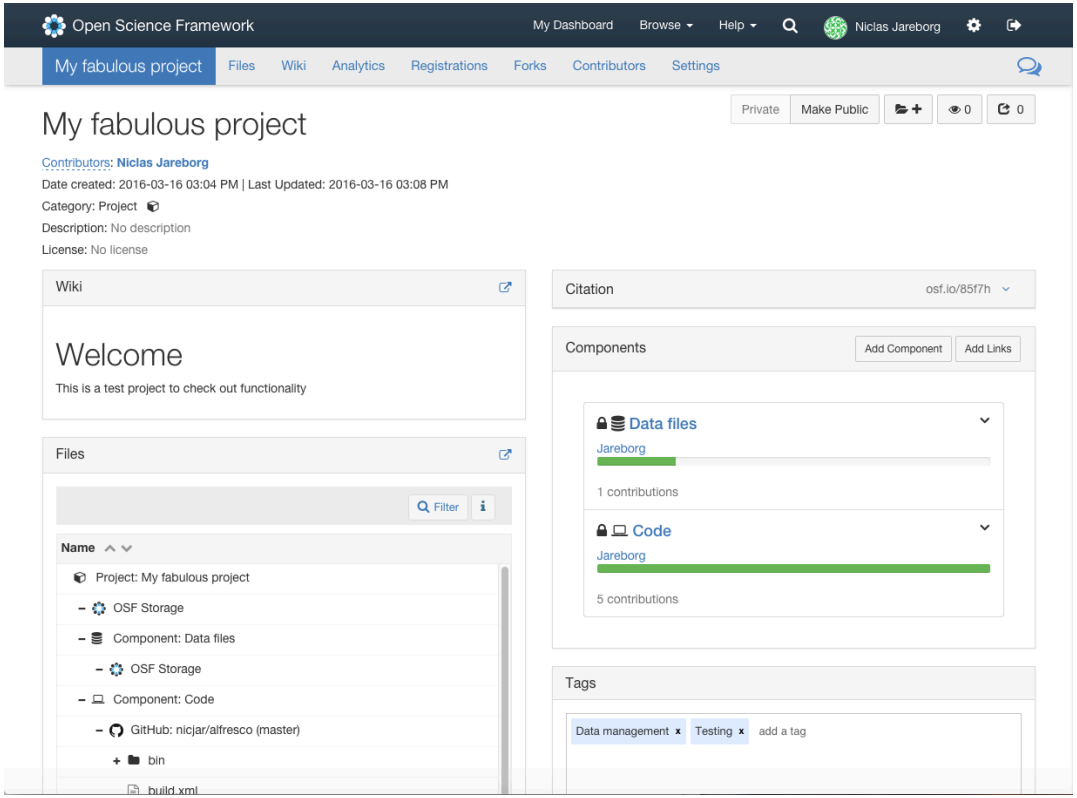
- Conda cannot always *completely* recreate the system, which is required for proper repro-ducibility.
- A solution is to package your project in an isolated Docker container, together with all its dependencies and libraries.
- A vision is that every new bioinformatics publication is accompanied by a 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/

Project collaboration tools

- 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



Personal data

Personal data - Legislation

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

Personal Data Act

- 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

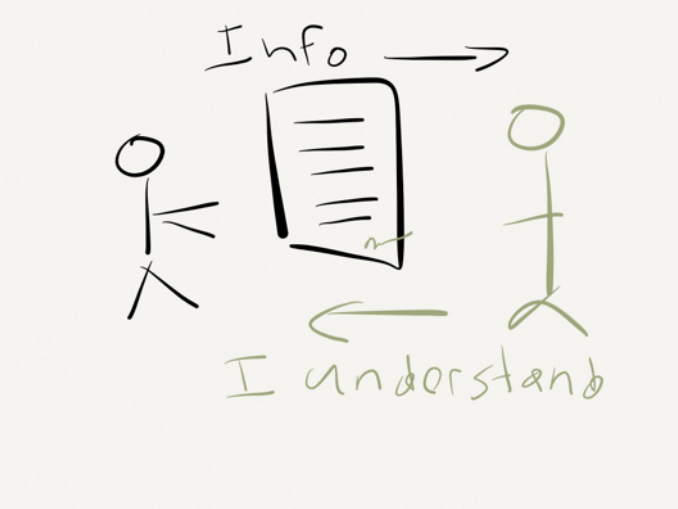
Personal Data Act – cont.

- 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

Act concerning the Ethical Review

- 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



Genetic information

- The genetic information of an individual is personal data
  - **Sensitive** personal data (as it relates to health)
  - 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 an appropriate level of security.”*

Bianca & Mosler

- **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

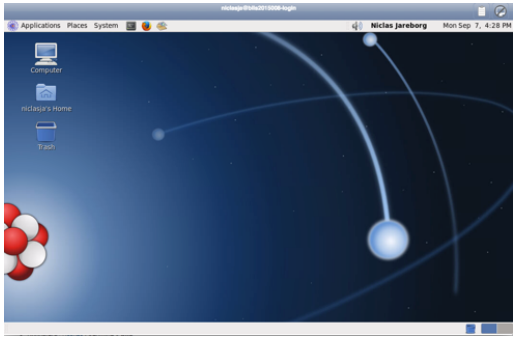
  - Implementation project completed Nov 2015
  - “Pilot-size system”
  - 24 nodes, 270 TB

- Provide users with a compute environment for sensitive data, with an *appropriate level of security*

https://nbis.se/infrastructure/mosler.html

Mosler

- 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



Tryggve – collaboration for sensitive biomedical data

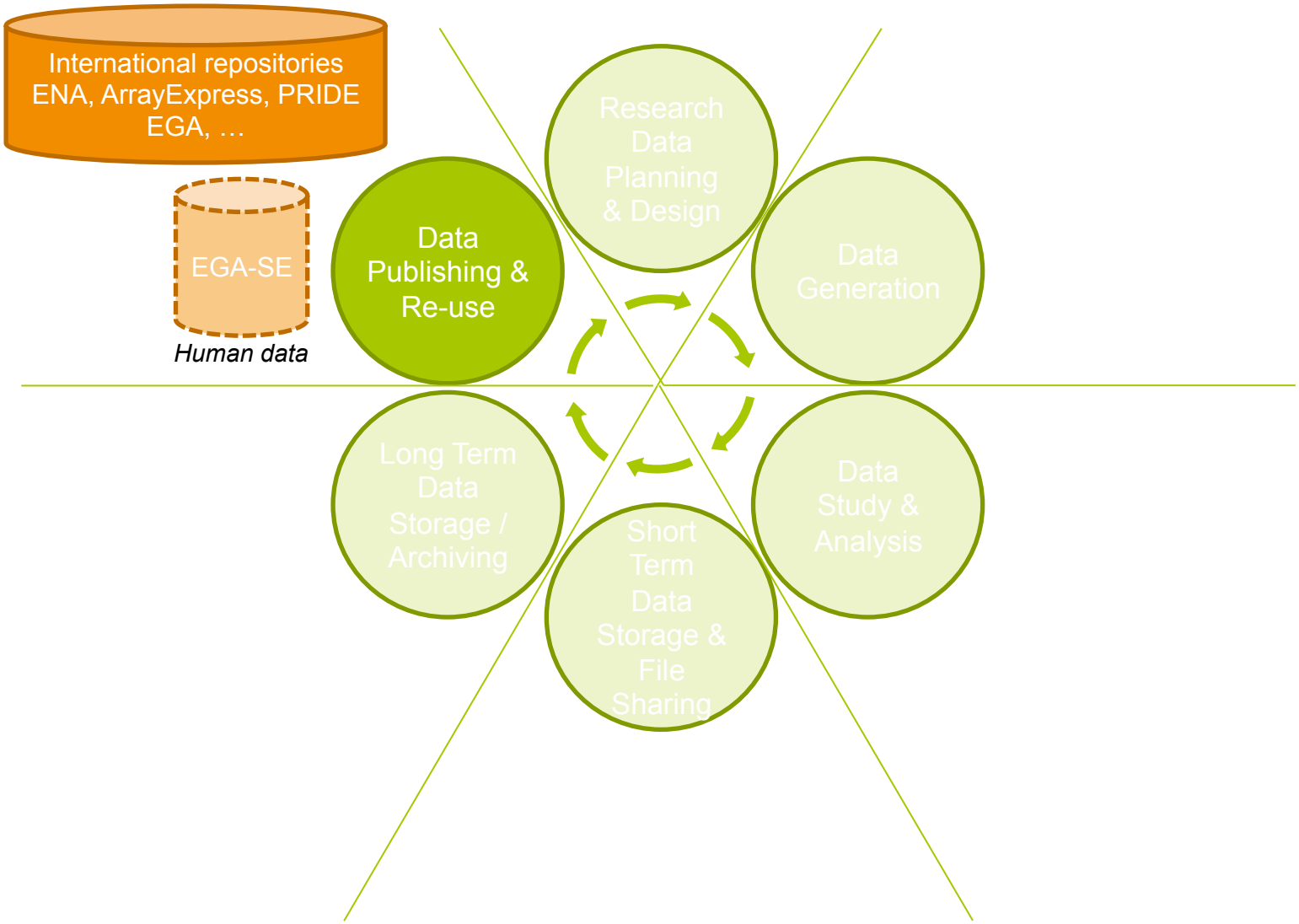
- Project aims to strengthen Nordic biomedical research by facilitating use of **sensitive data in cross-border projects**
- Collaborators and funders are NeIC and ELIXIR Nodes in Denmark, Finland, Norway and Sweden
- Project will build on strong existing capacities and resources in Nordic countries

Tryggve works on 6 themes

1. Technical development
   - Building blocks: Secure systems in Den, Fin, Nor & Swe
2. Interoperability of systems
   - Data transfer service – *sFTP beamer*
   - Portable software installations – *docker containers*
   - Shared computing resources – *Mosler-ePouta*
   - Investigate common authentication and authorization mechanisms
3. Process development
   - Knowledge-sharing (e.g. IT security, administrative processes, harmonizing user agreements)
   - Code of Conduct
4. Legal framework
   - Assessing relevant legislation
   - Analyzing legal requirements in use cases
5. **Use cases**
   - **Implement and support concrete use cases to facilitate cross-border research, and to connect project to actual user demands.**
6. Communication and outreach

https://wiki.neic.no/wiki/Tryggve_Getting_Started

Data Publishing & Re-use

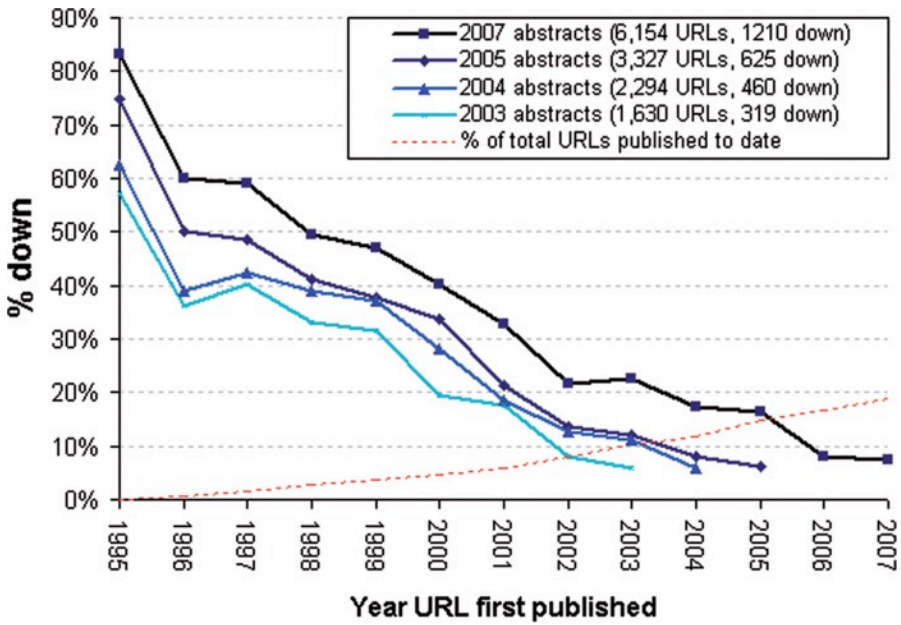


Data persistency issues

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.



Jonathan D. Wren Bioinformatics 2008;24:1381-1385

- 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

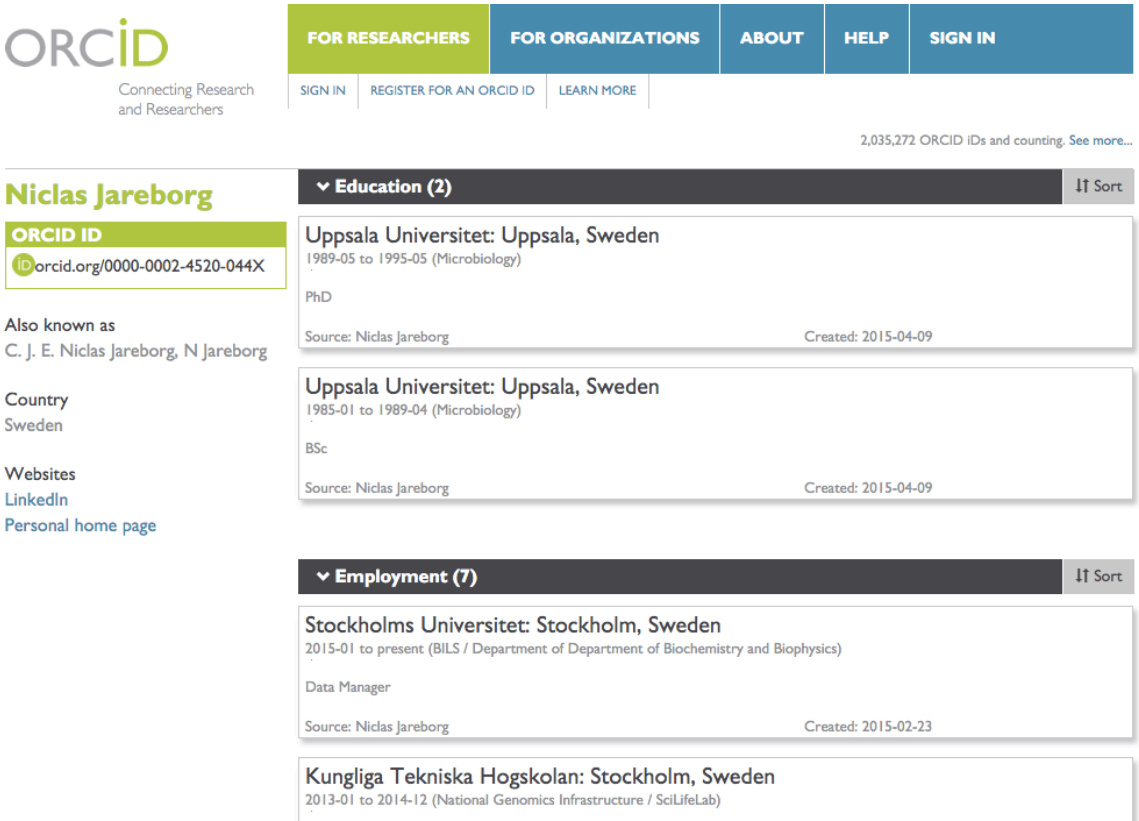
Data Publishing & Re-use

- *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

Who are you?

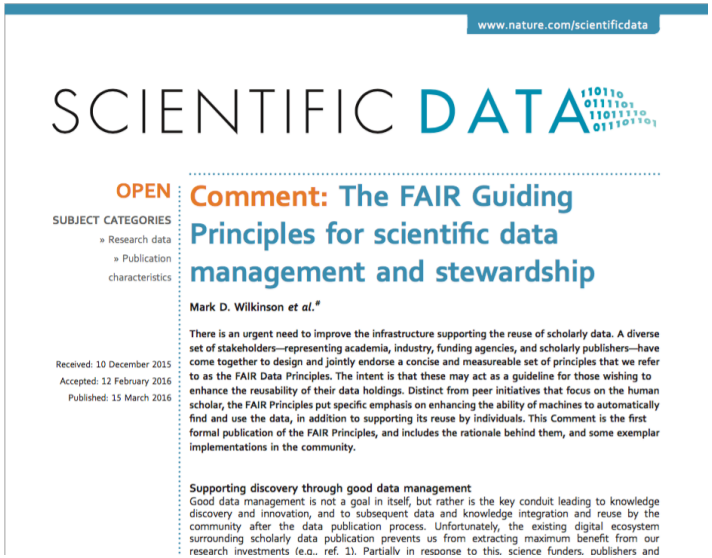
- ORCID is an open, non-profit, community-driven effort to create and maintain a registry of unique researcher identifiers and a transparent method of linking research activities and outputs to these identifiers.
- http://orcid.org
- Persistent identifier for you as a researcher



FAIR

- 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



www.nature.com/scientificdata

SCIENTIFIC DATA

OPEN

SUBJECT CATEGORIES
» Research data
» Publication characteristics

Received: 10 December 2015
Accepted: 12 February 2016
Published: 15 March 2016

Comment: The FAIR Guiding Principles for scientific data management and stewardship

Mark D. Wilkinson *et al.*#

There is an urgent need to improve the infrastructure supporting the reuse of scholarly data. A diverse set of stakeholders—representing academia, industry, funding agencies, and scholarly publishers—have come together to design and jointly endorse a concise and measureable set of principles that we refer to as the FAIR Data Principles. The intent is that these may act as a guideline for those wishing to enhance the reusability of their data holdings. Distinct from peer initiatives that focus on the human scholar, the FAIR Principles put specific emphasis on enhancing the ability of machines to automatically find and use the data, in addition to supporting its reuse by individuals. This Comment is the first formal publication of the FAIR Principles, and includes the rationale behind them, and some exemplar implementations in the community.

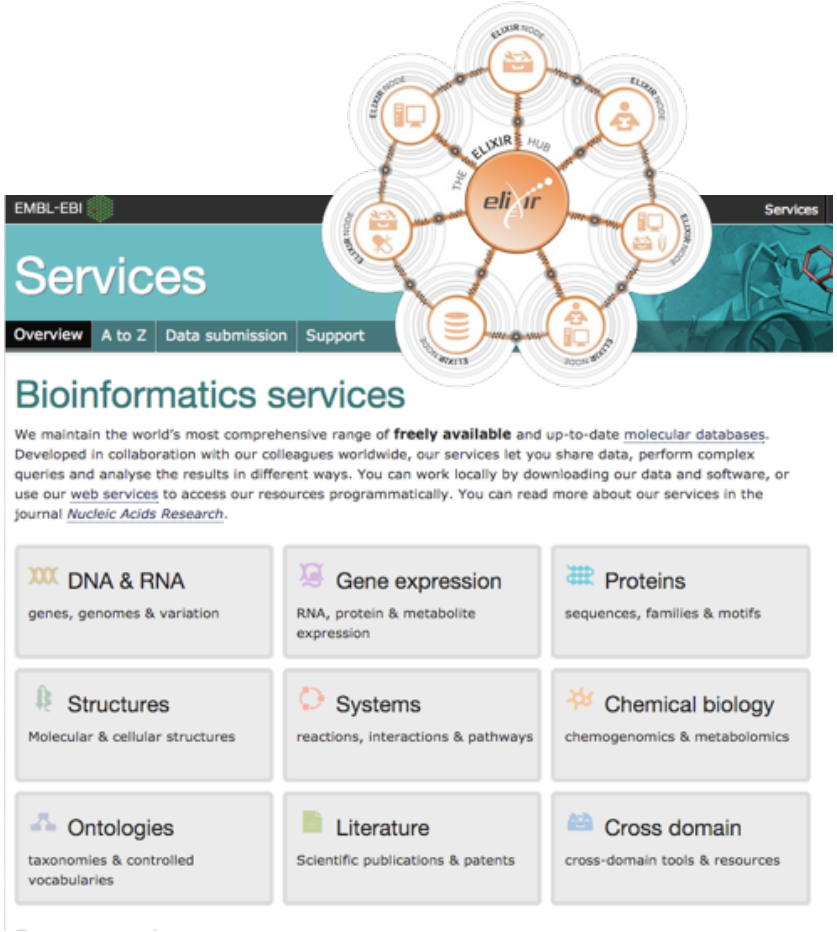
Supporting discovery through good data management
Good data management is not a goal in itself, but rather is the key conduit leading to knowledge discovery and innovation, and to subsequent data and knowledge integration and reuse by the community after the data publication process. Unfortunately, the existing digital ecosystem surrounding scholarly data publication prevents us from extracting maximum benefit from our research investments (e.g., ref. 1). Partially in response to this, science funders, publishers and

DOI: 10.1038/sdata.2016.18

International public repositories

- Best way to make data findable and re-usable
- Domain-specific metadata standards
- *Not always straight-forward!*

- **EBI** databases
  - ENA, Array Express, PRIDE etc



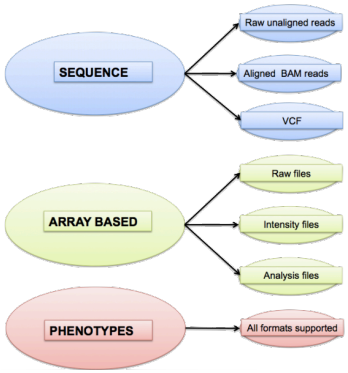
Surprisingly few submit to international repositories

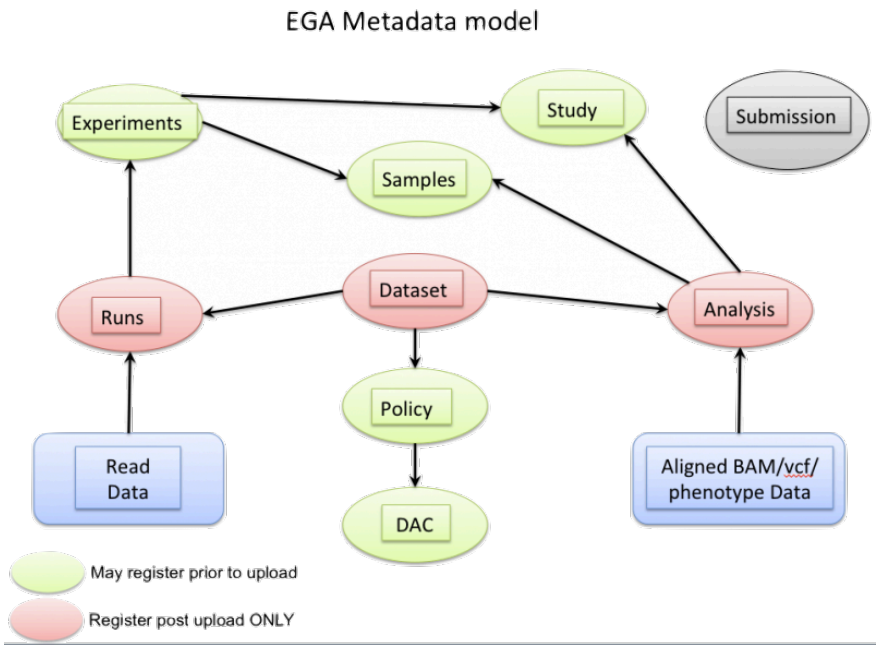
- NIH funded research
  - Only 12% of articles from NIH-funded research mention data deposited in international repositories
  - Estimated 200000+ “invisible” data sets / year

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

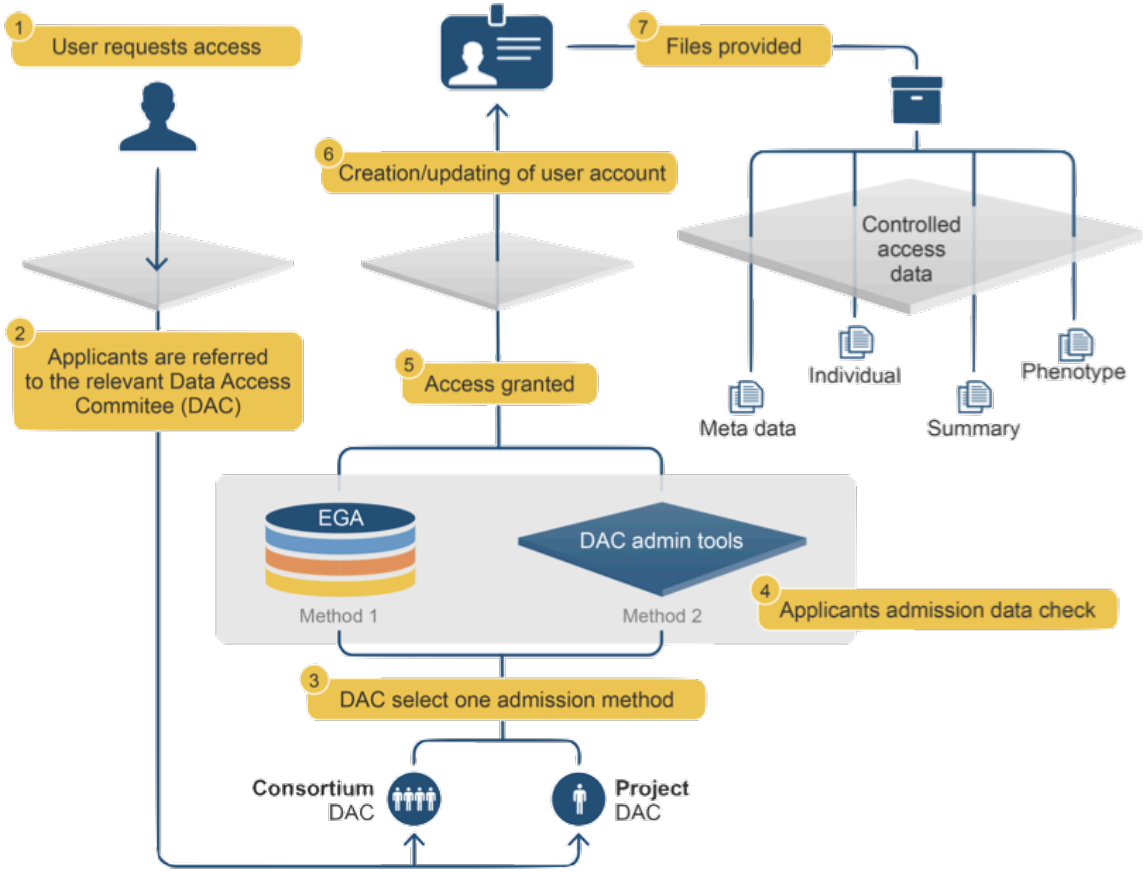
- Repository that promotes the distribution and sharing of **genetic and phenotypic data** consented for specific approved uses but **not fully open, public distribution**.
- All types of sequence and genotype experiments, including case-control, population, and family studies.
- Study & Sample Metadata searchable
- Shares most of the Metadata model with ENA





EGA

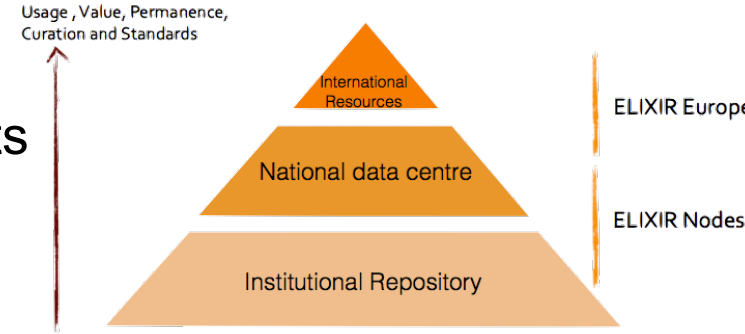
- Data Access Agreement
  - Defined by the dataset owner
- Data Access Committee – DAC
  - Decided by the dataset owner



Local EGA-SE

- Federated EGA
  - Metadata stored centrally
  - Data stored nationally/regionally/locally

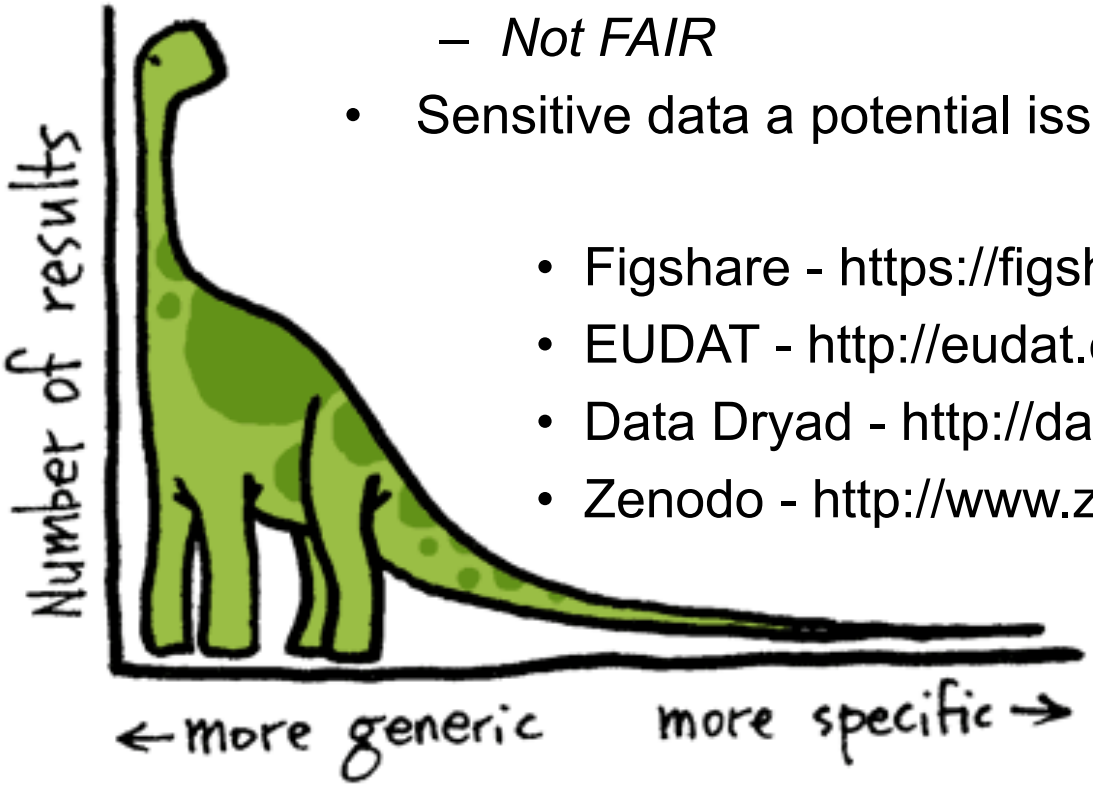
- Part of ELIXIR-Excelerate & Tryggve projects



- Simplify legal situation for Swedish sensitive personal research data
- Establish easy-to-use submission route for human sequence data produced by NGI

“Long-tail data” repositories

- 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/

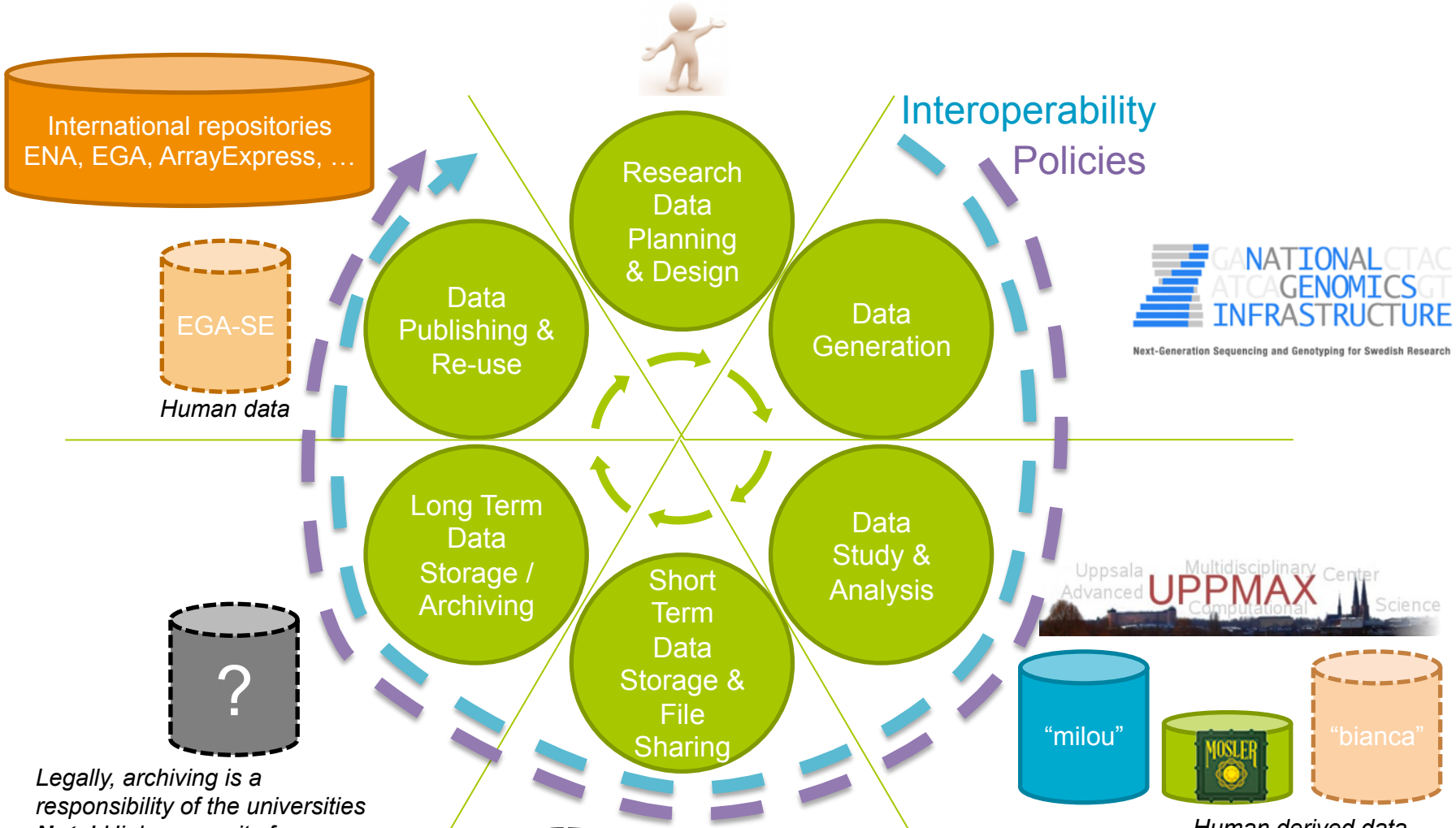
NBIS Data Management support

- Project planning
  - Metadata
  - File formats
  - Licensing
  - *Data Management Plans*

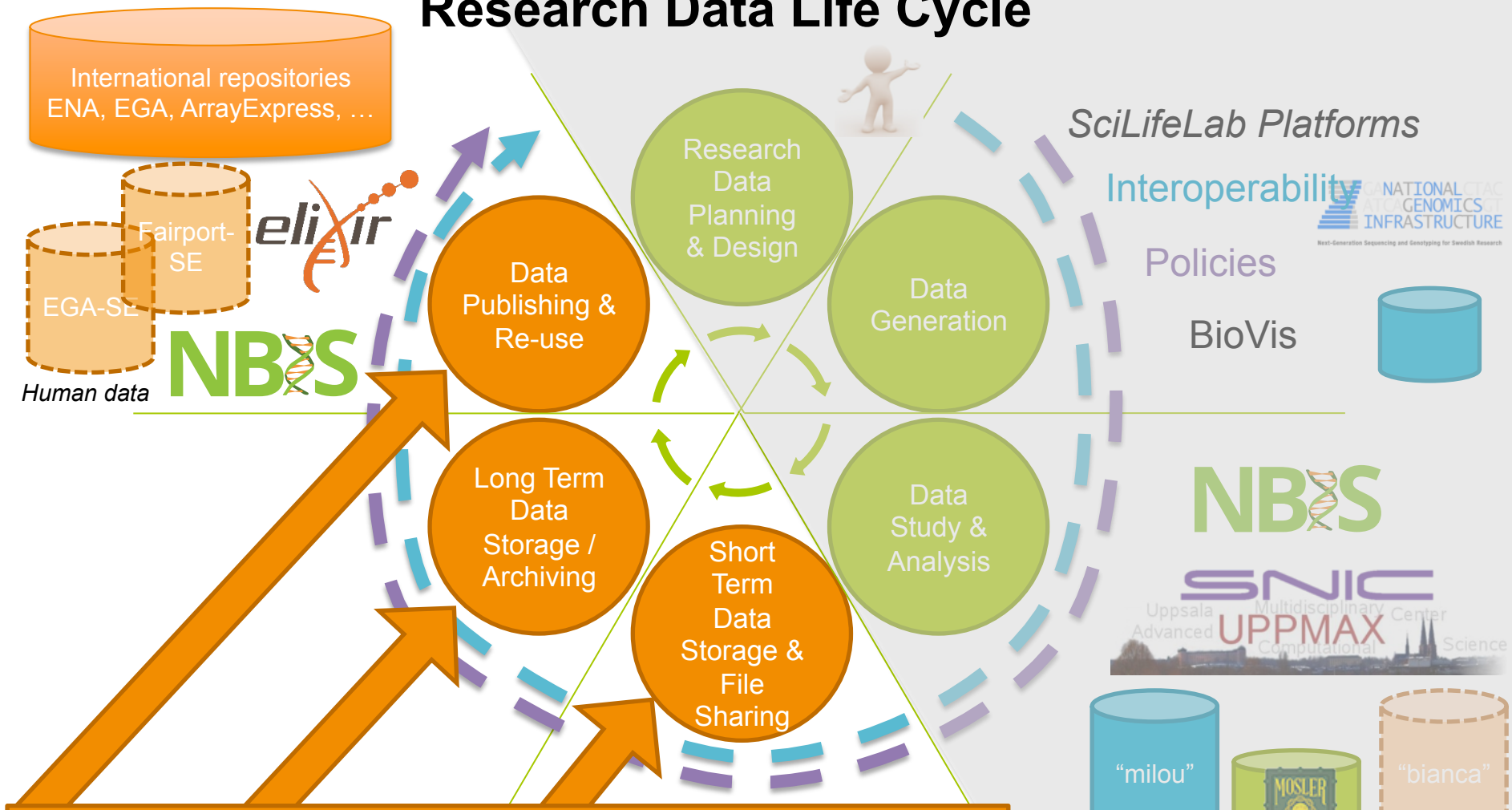
- Data analysis

- Data publication and submission
  - Automate submissions to public repositories
  - Metadata
  - Licensing

Gaps in the NGS Data Life Cycle



Research Data Life Cycle

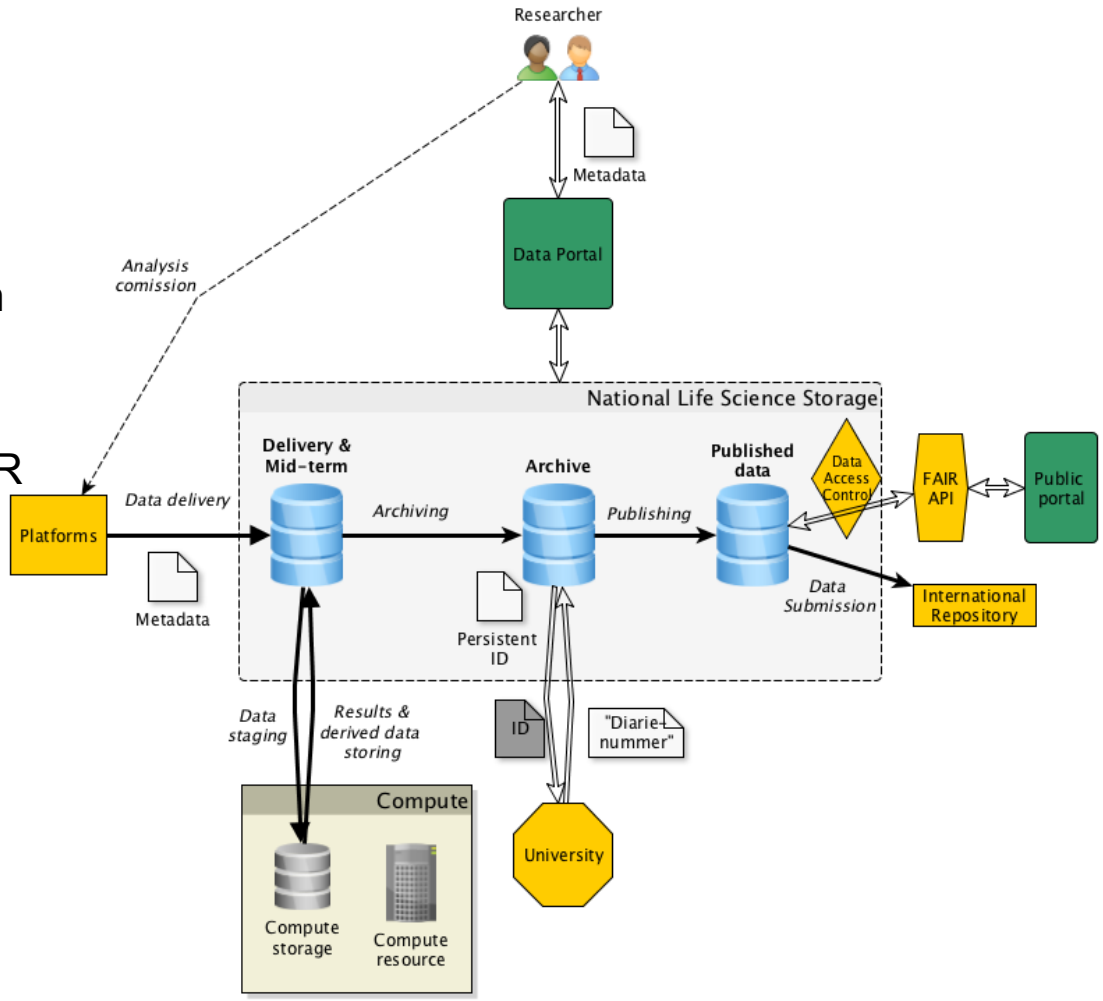


Orange parts to be covered by the *National Life Science Data Storage* that now will be set up by SUNET in collaboration with SciLifeLab

National (Life Science) Data Storage

Components

- "Active Data" storage
- Data staging to HPC resources
- Archiving
  - Offer a solution to the universities' legal obligation (*possible funding stream*)
- Data publication
  - Making SciLifeLab data FAIR
- User-friendly interface to manage the data life cycle process
- Support the SciLifeLab Data Office way of working



Source Acknowledgements

- 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. doi: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 Väremo - https://bitbucket.org/scilifelab-lts/reproducible_research_example/src