Enabling integrative modeling of human immunological data **in a reproducible manner** with *ImmuneSpace*

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Associate Member
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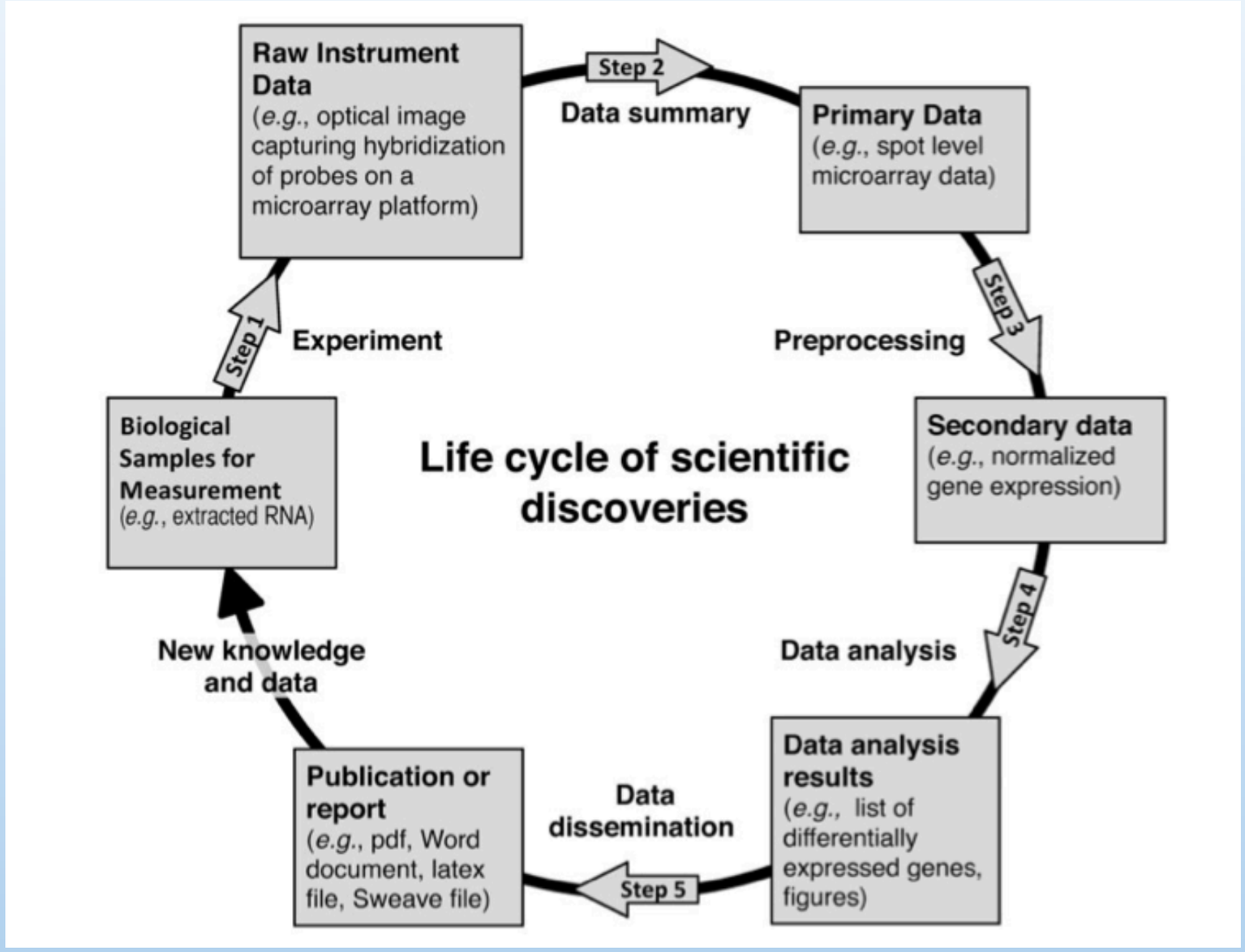
Fred Hutchinson Cancer Research Center

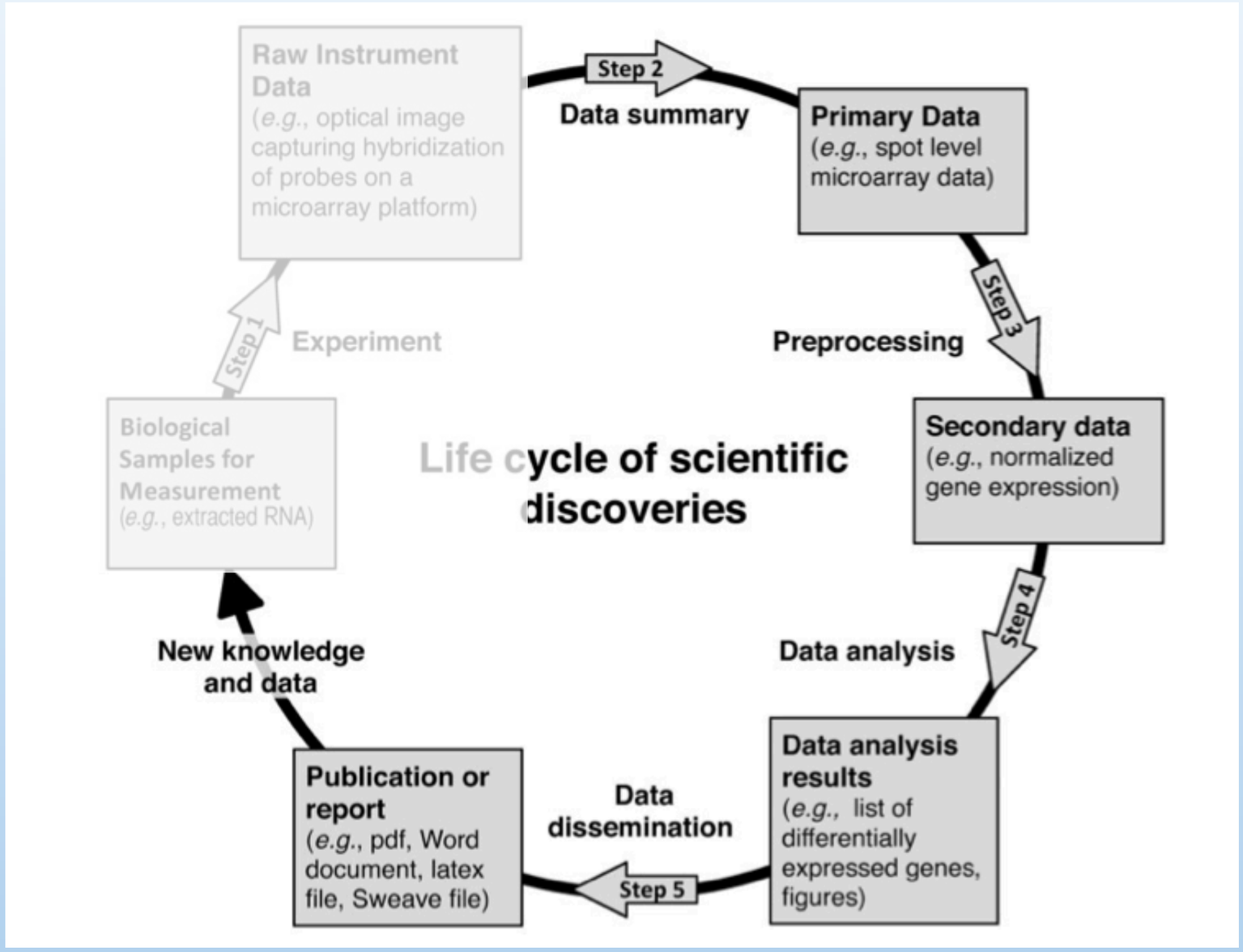
ImmuneSpace
supported by
HIPC Human Immunology Project Consortium

Reproducibility?



Huang, Yunda, and Raphael Gottardo. "Comparability and Reproducibility of Biomedical Data." *Briefings in Bioinformatics* (2012).

Reproducibility?



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Why is it important?

ARTICLES

2006

nature medicine

Genomic signatures to guide the use of chemotherapeutics

Anil Potti[1,2], Holly K Dressman[1,3], Andrea Bild[1,3], Richard F Riedel[1,2], Gina Chan[4], Robyn Sayer[4], Janiel Cragun[4], Hope Cottrill[4], Michael J Kelley[2], Rebecca Petersen[5], David Harpole[5], Jeffrey Marks[5], Andrew Berchuck[1,6], Geoffrey S Ginsburg[1,2], Phillip Febbo[1–3], Johnathan Lancaster[4] & Joseph R Nevins[1–3]

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Using *in vitro* drug sensitivity data coupled with Affymetrix microarray data, we developed gene expression signatures that predict sensitivity to individual chemotherapeutic drugs. Each signature was validated with response data from an independent set of cell line studies. We further show that many of these signatures can accurately predict clinical response in individuals treated with these drugs. Notably, signatures developed to predict response to individual agents, when combined, could also predict response to multidrug regimens. Finally, we integrated the chemotherapy response signatures with signatures of oncogenic pathway deregulation to identify new therapeutic strategies that make use of all available drugs. The development of gene expression profiles that can predict response to commonly used cytotoxic agents provides opportunities to better use these drugs, including using them in combination with existing targeted therapies.

Numerous advances have been achieved in the development, selection and application of chemotherapeutic agents, sometimes with remarkable clinical successes—as in the case of treatment for lymphomas or identifies opportunities for combining chemotherapeutic drugs with targeted therapeutic drugs in a way that best matches the characteristics of the individual.

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Why is it important?

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Correspondence

Nature Medicine **13**, 1276 - 1277 (2007)
doi:10.1038/nm1107-1276b

Microarrays: retracing steps

Kevin R Coombes[1], Jing Wang[1] & Keith A Baggerly[1]

1. Department of Bioinformatics and Computational Biology, University of Texas M.D. Anderson Cancer Center, Houston, Texas 77030, USA. e-mail: kcoombes@mdanderson.org

To the editor:

Recently, Potti *et al.*[1] published an article in *Nature Medicine* reporting an approach predicting whether a tumor will respond to chemotherapy. Using publicly available data, they derived signatures from microarray profiles of the NCI-60 human cancer cell lines with known *in vitro* sensitivity or resistance to a particular drug. They used these profiles to predict *in vivo* chemotherapeutic response to seven different drugs. In order to help investigators at our institution use similar approaches, we tried to reproduce their results. We used the same published data and additional information generously supplied by the authors regarding methods, lists of cell lines called sensitive or resistant, and the software used to perform their analysis.

We report here our inability to reproduce their findings. Details of our methods and results are described in the supplementary information (Supplementary Reports 0-9) and are summarized here.

1. We cannot reproduce their selection of cell lines. The most sensitive and resistant lines should be used to focus on drug effects. However, the GI_{50} (the concentration needed to reduce the growth of treated cells to half that of untreated cells)

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Why is it important?

trail of data handling and statistical analysis. We use Sweave[4, 5], a package that allows analysts to combine source code (in R)[6] and documentation (in LaTeX)[7] in the same file. Our Sweave files are available at (http://bioinformatics.mdanderson.org/Supplements/ReproRsch-Chemo/). Running them reproduces our results and generates figures, tables and a complete PDF manuscript.

The idea of using the NCI-60 cell lines to predict patient response to chemotherapy is exciting. Our analysis, however, suggests that it did not work here.

ARTICLE

Nature Medicine - **12**, 1294 - 1300 (2006)
Published online: 22 October 2006; Corrected online: 27 October 2006; Corrected online: 21 July 2008; Retracted: 07 January 2011 | doi:10.1038/nm1491

There is a Corrigendum (November 2007) associated with this Article.

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[2] Department of Medicine, Duke University Medical Center, Box 31295, Durham, North Carolina 27710, USA

[3] Department of Molecular Genetics and Microbiology, Duke University Medical Center, Box 3054, Durham, North Carolina 27710, USA

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[5] Department of Surgery, Duke University Medical Center, Box 3627, Durham, North Carolina 27710, USA

[6] Department of Obstetrics and Gynecology, Duke University Medical Center, Box 3079, Durham, North Carolina 27710, USA

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Deadline: Jan 31 2014
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ARTICLE

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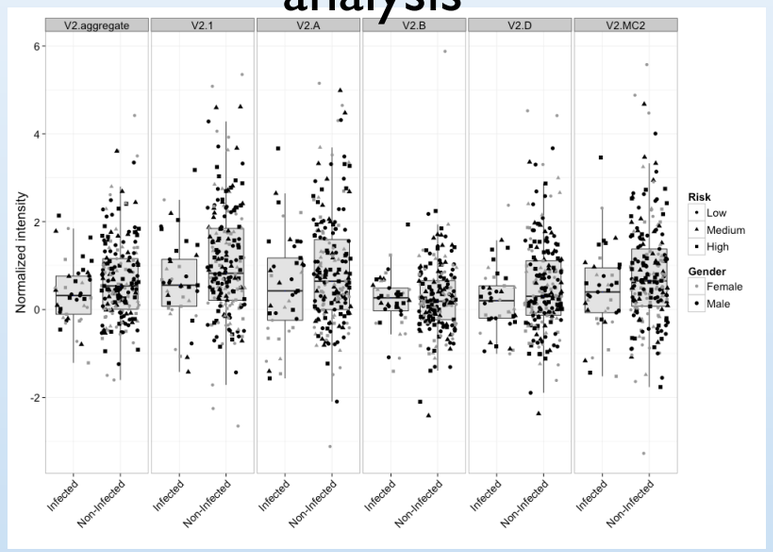
Data analysis workflow

Data management

Data munging

Data analysis



- The workflow can be complex and can involve multiple datasets, people, tools, etc.
- Workflows are (for the most part) poorly documented
- Can be difficult to reproduce even by the same group
- Solution? → LabKey + R

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The R programming language

- Open-source software for statistical computing and graphics
- State-of-the art for data analysis and data visualization
- Community driven, with over 5000 packages available to extend the base functionalities
- Well suited for biological data analysis through the Bioconductor project

R and LabKey

- LabKey provides a flexible R API for running R analysis on data stored in LabKey
- R views
  - Attach an R script to a data view
  - Limited output: a table, figure, text, pdf
  - Very limited control of the output format

Literate programming

- Approach to programming introduced by Donald Knuth
  - An explanation of a program logic in a plain English, interspersed with chunk of computer code.
- Sweave
  - Create dynamic reports by embedding R code in latex documents

knitr *vs.* Sweave

- Sweave is good but …
  - Writing latex is painful
  - Output is limited to pdf
- knitr
  - Transparent engine for dynamic report generation
  - knitr allows any input languages (e.g. R, Python and Awk) and any output markup languages

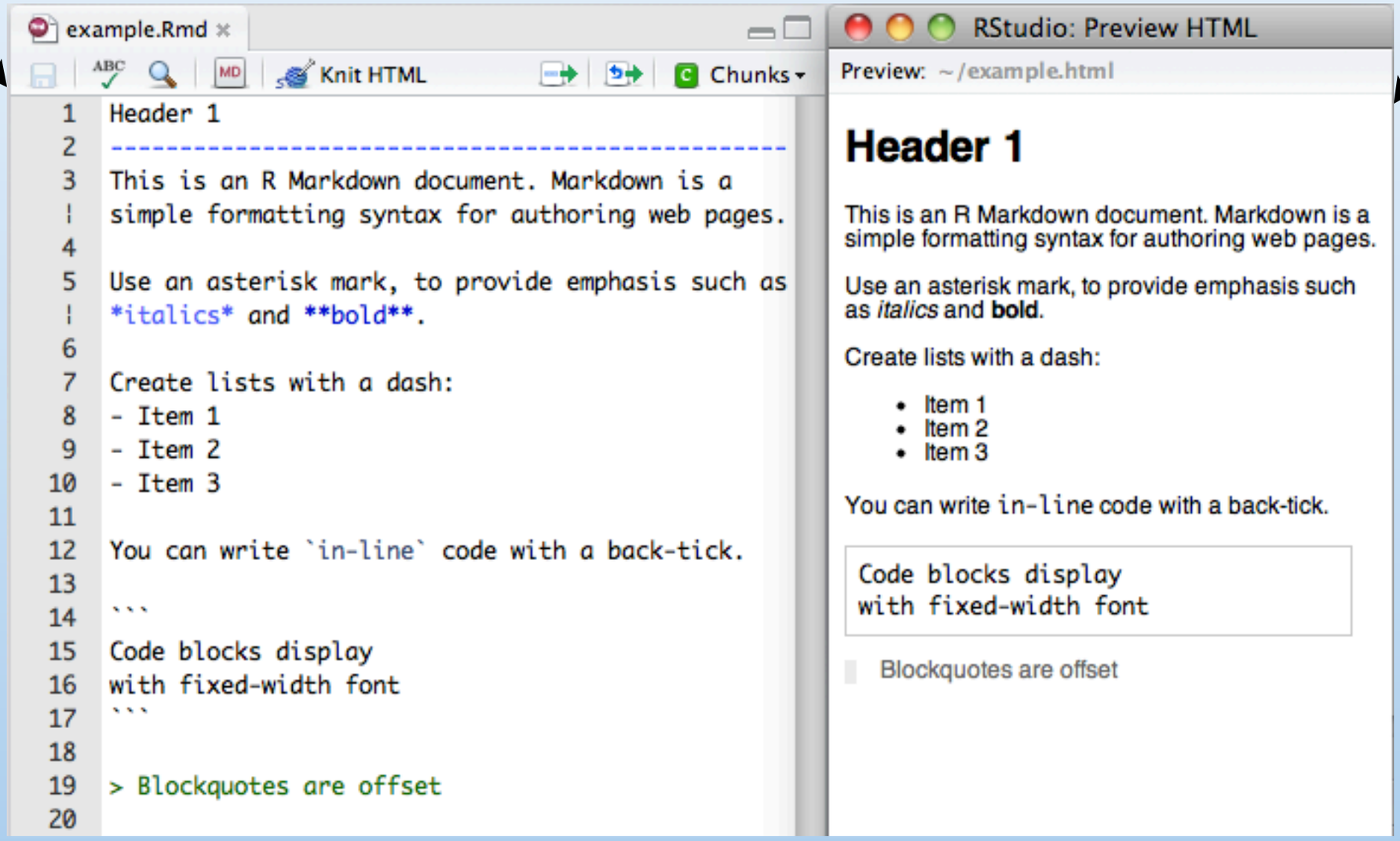
knitr

- Full control of input, code, and output
  - Fine control over how the code is executed and the ouput is displayed
  - knitr can process input files in various formats: latex, html, R markdown
- R markdown
  - markdown: easy-to-read, easy-to-write plain text format that can be converted to html
  - R markdown: markdown + R code chunks

markdown

Input

Output



R markdown

Input

Output

chunks.Rmd

Knit HTML | Chunks

```
1  R Code Chunks
2  ==========
3
4  With R Markdown, you can insert R code
   chunks including plots:
5
6  ```{r qplot, fig.width=4, fig.height=3,
   message=FALSE}
7  # quick summary and plot
8  library(ggplot2)
9  summary(cars)
10 qplot(speed, dist, data=cars) +
11       geom_smooth()
12 ```
13
```

RStudio: Preview HTML

Preview: ~/chunks.html | Save As | Publish

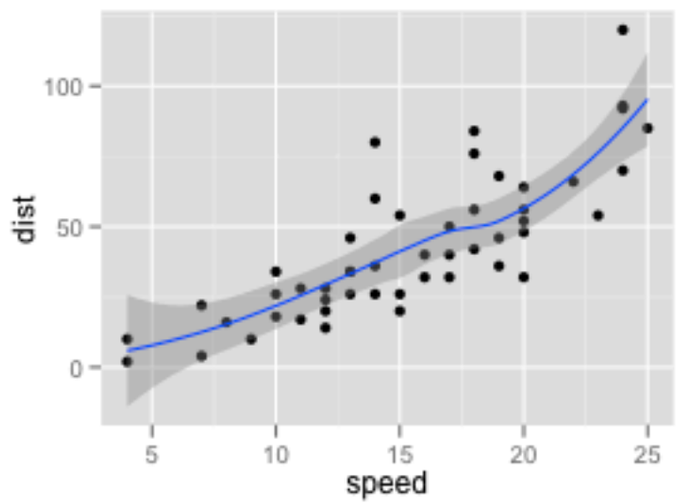
R Code Chunks

With R Markdown, you can insert R code chunks including plots:

```
# quick summary and plot
library(ggplot2)
summary(cars)
```

```
##      speed           dist
##  Min.   : 4.0   Min.   :  2
##  1st Qu.:12.0   1st Qu.: 26
##  Median :15.0   Median : 36
##  Mean   :15.4   Mean   : 43
##  3rd Qu.:19.0   3rd Qu.: 56
##  Max.   :25.0   Max.   :120
```

```
qplot(speed, dist, data = cars) + geom_smooth()
```



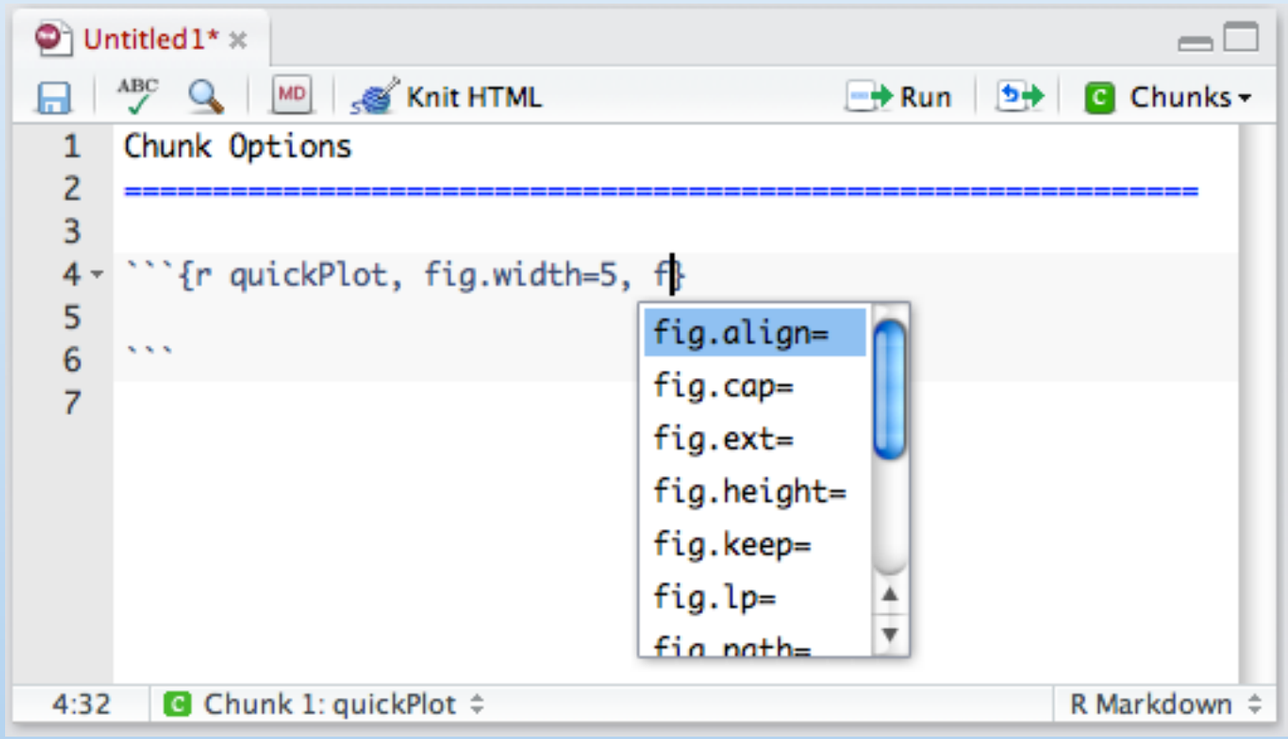
R markdown

Option for code chunks

```
23 ```{r echoExample, eval=TRUE, echo=FALSE}
24 # This code chunk is evaluated,
25 # however the source code is hidden.
26 # Only the result is displayed.
27
28 x <- "Hello World"
29 y <- "!"
30 cat(c(x, rep(y,3)), sep="")
31 ```
```

R markdown

Many chunk options
knitr is fully integrated within RStudio



R markdown

R expression and also be added and evaluated in line

```
1
2  I counted `r 1 + 1` red trucks on the highway.
3
```

Results in this output: "I counted 2 red trucks on the highway."

knitr and caching

- Large data and complex analysis can require significant computing time
  - Not unusual for an analysis to take a few minutes to an hour
    - This can result in some performance issues when viewing a report → User frustration
- Why rerun a script when nothing has changed?
- The solution is caching

knitr and caching

- cache can be turned on/off for each code chunk
- If caching is on, knitr will check if the code has changed when rerunning a report
- Chunks can be made dependent
- The caching mechanism is flexible can be attached to an R version an input dataset (e.g. labkey.data), a date, etc.

Some references

- www: http://yihui.name/knitr/
- RStudio (rstudio.com)

knitr in LabKey

View | Data | Source | Help

Download input data?

SUBJECT ACCESSION	Description	Phenotype	Age Reported	Age Unit	Age Event	Strain	Gender	Ethnicity	Race	Species	Cohort
SUB112827	Healthy human control for in-vitro RT-PCR analysis of PBMCs	healthy adult	32.0	Years	Age at enrollment		Male	Not Hispanic or Latino	Asian	Homo sapiens	CamKIV Humans
SUB112828	Healthy human control for in-vitro RT-PCR analysis of PBMCs	healthy adult	35.0	Years	Age at enrollment		Male	Not Hispanic or Latino	Asian	Homo sapiens	CamKIV Humans
SUB112829	Age at Trial 2	healthy adult	26.0	Years	Age at enrollment		Male	Not Hispanic or Latino	White	Homo sapiens	LAIV group
SUB112830	Age at Trial 1; only in Trial 1	healthy adult	31.0	Years	Age at enrollment		Female	Hispanic or Latino	White	Homo sapiens	TIV Group
SUB112831	Age at Trial 2	healthy adult	40.0	Years	Age at enrollment		Male	Not Hispanic or Latino	Black or African American	Homo sapiens	LAIV group
SUB112832	Age at Trial 2	healthy adult	26.0	Years	Age at enrollment		Male	Not Hispanic or Latino	White	Homo sapiens	TIV Group
SUB112833	Age at Trial 1; only in Trial 1	healthy adult	22.0	Years	Age at enrollment		Female	Not Hispanic or Latino	White	Homo sapiens	TIV Group
SUB112834	Age at Trial 2	healthy adult	27.0	Years	Age at enrollment		Male	Not Hispanic or Latino	White	Homo sapiens	TIV Group
SUB112835	Age at Trial 1; only in Trial 1	healthy adult	46.0	Years	Age at enrollment		Male	Not Hispanic or Latino	White	Homo sapiens	TIV Group
SUB112836	Age at Trial 2	healthy adult	28.0	Years	Age at enrollment		Female	Not Hispanic or Latino	White	Homo sapiens	LAIV group
SUB112837	Age at Trial 1; only in Trial 1	healthy adult	26.0	Years	Age at enrollment		Female	Hispanic or Latino	White	Homo sapiens	TIV Group
SUB112838	Age at Trial 2	healthy adult	39.0	Years	Age at enrollment		Male	Not Hispanic or Latino	White	Homo sapiens	LAIV group
SUB112839	Age at Trial 2	healthy adult	23.0	Years	Age at enrollment		Female	Not Hispanic or Latino	White	Homo sapiens	LAIV group
SUB112840	Age at Trial 2	healthy adult	22.0	Years	Age at enrollment		Female	Not Hispanic or Latino	White	Homo sapiens	LAIV group
SUB112841	Age at Trial 2	healthy adult	28.0	Years	Age at enrollment		Female	Not Hispanic or Latino	White	Homo sapiens	TIV Group

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knitr in LabKey

View | Data | Source | Help

```
55
56```{r filter-subject, cache.extra=digest::digest(labkey.data)}
57ds_cohort <- labkey.data
58dt_cohort <- data.table(ds_cohort)
59subject_selected <- dt_cohort[,subject_accession]
60subject_filter <- makeFilter(c("SUBJECT_ACCESSION","IN",paste(subject_selected,collapse=";")))
61```
62
63
64### HAI titers in plasma after vaccination
65Figure 1 shows that there are strong differences between vaccine groups in terms of HAI responses.
66
67```{r hai, hfig.cap=TRUE, fig.cap="Figure 1. HAI titers in plasma on day 28 after vaccination with TIV or LAIV, relative to baseline (day 0).", dependson="filter-subject
68study_filter <- makeFilter(c("study_accession","IN","SDY61"))
69ds_biosample <- labkey.selectRows(baseUrl=labkey.url.base, schemaName="hipcdb", folderPath=labkey.url.path, queryName ="biosample", colNameOpt='rname', colFilter=study_f
70dt_biosample <- data.table(ds_biosample)
71
```

- [x] Make this view available to all users
  - [ ] Show source tab to all users
- [ ] Make this view available in child folders ?
- [ ] Run this view in the background as a pipeline job

Knitr Options

- ( ) None ?
- ( ) Html ?
- (•) Markdown ?

Report Thumbnail

- (•) Auto-generate ?
- ( ) None ?

Shared Scripts

You can execute any of the following scripts as part of your current script by calling: source('<Script Name>.r') after checking the box next to the <Script Name> you plan to use.

https://www.immunespace.org/study/Emory/SDY61/dataset.view?Dataset.reportId=db%3A60&datasetId=5001#

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knitr in LabKey

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knitr in LabKey

View | Data | Source | Help

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knitr in LabKey

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Overview of antibody responses induced by TIV and LAIV

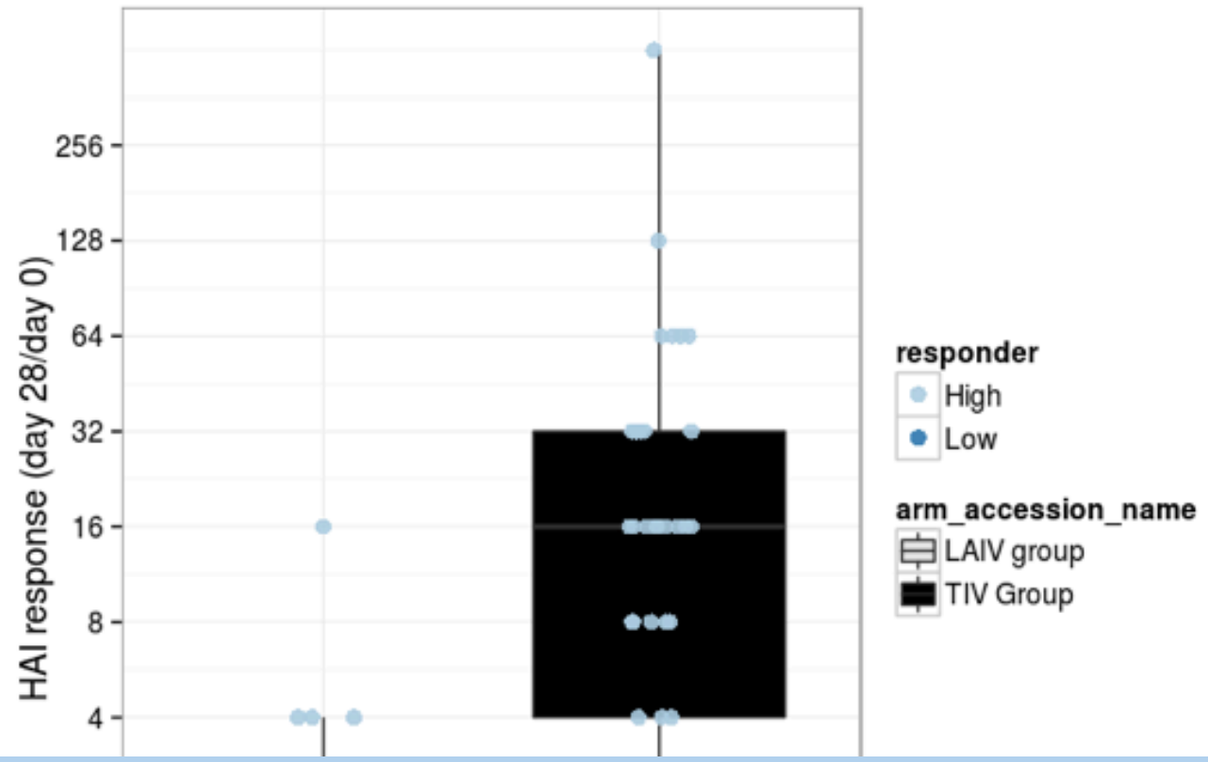
Report generated by rgottard@fhcrc.org

Summary

This report reproduces all figures related to antibody data presented in the original study (Nakaya et al., 2011), namely Figures 1- a, b and d. Unfortunately, Figure 1-c cannot be reproduced due to the missing gate definitions for the flow cytometry data (e.g. GatingML).

HAI titers in plasma after vaccination

Figure 1 shows that there are strong differences between vaccine groups in terms of HAI responses.



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Demo: Overview of the knitr environment in LabKey

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HIPC

- The human immunology project consortium
  - Collaborative effort across 7 centers
  - Established in 2010 by the NIAID Division of Allergy, Immunology, and Transplantation
  - Characterize the status of the immune system in diverse populations under both normal conditions and in response to stimuli
  - Use systems biology approaches
  - Generate large amount of data

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HIPC → ImmuneSpace

- Wide range of data types
  - Flow cytometry, Luminex, Antibody titers, gene expression, next generation sequencing, etc.
- Ultimate goal: combine data across assay and centers
- Need for central data management and analysis
  - Database an analysis engine using LabKey and R
  - ImmuneSpace.org

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Demo

- Using knitr to query PubMed
- Using knitr to predict antibody response from gene expression

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Other additions to LabKey server

- Rserve (TCP/IP interface to R): consistent R session, session management, remote server, etc.
- API

Acknowledgments

- Greg Finak, Renan Sauteraud, Lev Dashevkiy
- Matthew Bellew, Cory Nathe, Avital Sadot and LabKey team
- Adam Asare and ITN
- Funding
  - VISC/CAVD (Gates Foundation)
  - HIPC Consortium (NIAID)

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