Medical Image Analysis with R

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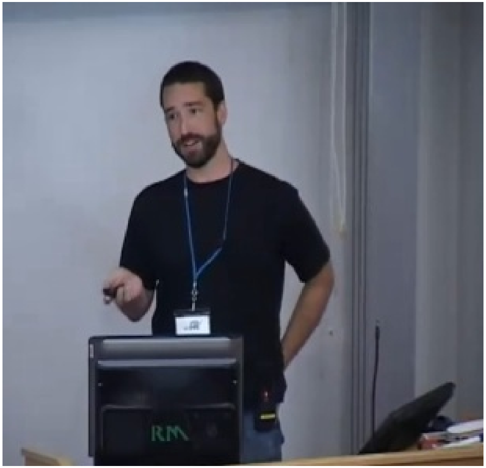
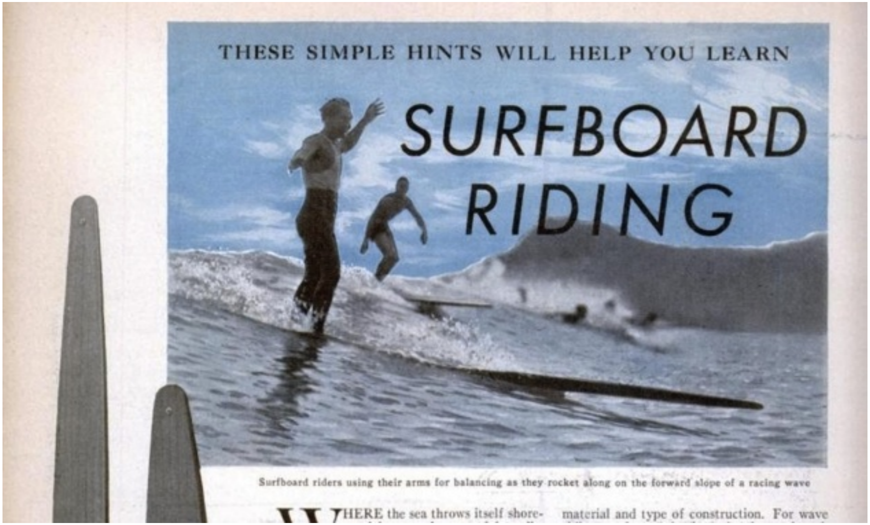
[1] Thank you for participating!

Many Thanks for Contributions from:

Brandon Whitcher, Ph.D.
Pfizer
Cambridge, MA, USA



How much *R* experience in the room?



THESE SIMPLE HINTS WILL HELP YOU LEARN

SURFBOARD RIDING

Surfboard riders using their arms for balancing as they rocket along on the forward slope of a racing wave

WHERE the sea throws itself shore- material and type of construction. For wave

Schedule

- Introduction
- Basic Examples
- 1/2 Hour Break
- Longitudinal Analysis and Model Selection (P. Thomas Fletcher)
- Wrap-up / discussion

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- Learn about *R* in general (operations, dataframes, models)
- Understand basics of *R* image-based statistics (I/O, accessing values, structure, function)
- Practice some example reproducible studies ...
- Identify opportunities for innovation/future work
- A good source on data analysis with *R* examples: "Advanced Data Analysis from an Elementary Point of View" here.

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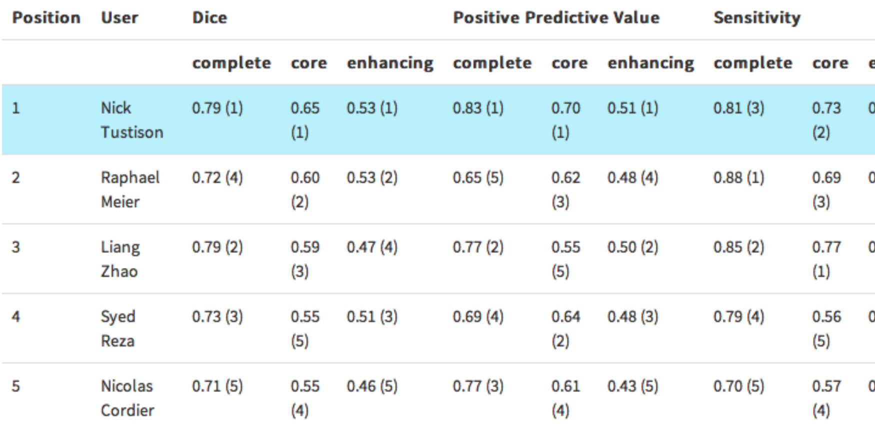
R is Relevant to Your Success

We entered a competition with R in our holster.



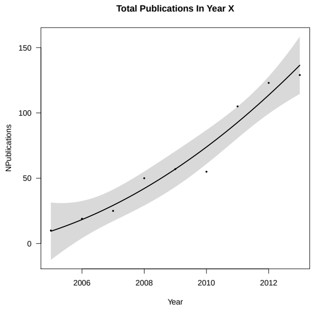
Position	User	Dice			Positive Predictive Value			Sensitivity		
		complete	core	enhancing	complete	core	enhancing	complete	core	e
1	Nick Tustison	0.79 (1)	0.65 (1)	0.53 (1)	0.83 (1)	0.70 (1)	0.51 (1)	0.81 (3)	0.73 (2)	0
2	Raphael Meier	0.72 (4)	0.60 (2)	0.53 (2)	0.65 (5)	0.62 (3)	0.48 (4)	0.88 (1)	0.69 (3)	0
3	Liang Zhao	0.79 (2)	0.59 (3)	0.47 (4)	0.77 (2)	0.55 (5)	0.50 (2)	0.85 (2)	0.77 (1)	0
4	Syed Reza	0.73 (3)	0.55 (5)	0.51 (3)	0.69 (4)	0.64 (2)	0.48 (3)	0.79 (4)	0.56 (5)	0
5	Nicolas Cordier	0.71 (5)	0.55 (4)	0.46 (5)	0.77 (3)	0.61 (4)	0.43 (5)	0.70 (5)	0.57 (4)	0

The first 3 rules of statistics: 'Draw a picture, Draw a picture, Draw a picture.'—Michael Starbird.

R in medical imaging?

Search "r-project.org + medical + imaging"

```r
dd <- read.csv("data/RMI.csv")
mdl <- lm(NPublications ~ Year + I(Year^2), data = dd)
visreg(mdl, main = "Total Publications In Year X")
```



R contains virtually all popular statistical and machine learning algorithms, including Boosting, the LASSO, and random forests, often contributed by the inventors.

Why use *R* in medical imaging?

- It's free — not "free" like Matlab/SPM but really free
  - It is the *de facto* standard for statistical computing
  - a New York Times article from 2009 estimated that there are at least 250,000 active R users
- Why not use Python?
  1. IMHO, *R* is easier to compile/maintain/install
  2. Visualization in *R* is as good or better than Python
  3. Most importantly—*statisticians contribute directly to R*
  4. Because of this, many Python users rely on *R*
- *R* facilitates reproducible research:
  1. CRAN Task View (link)
  2. *Biostatistics (link)*
  3. *jstatsoft.org*
- *R* assists reproducible medical image analysis but it's still effortful to do it correctly. See our comments in Frontiers.

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Set up for Medical Image Analysis

Let's assume you downloaded the latest 3.x version of *R* from CRAN.
We now open *R* and install MIA-relevant packages.

```
pkgnames <- c("visreg", "boot", "rgl", "knitr", "ggplot2", "oro.nifti",
    "candisc", "pheatmap")
k <- length(pkgnames)
```

Next actually install the packages.

```
install.packages(pkgnames)
```

We installed 8 packages. (knitr lets us use `\Sexpr{}` to refer to *R* variables in LaTeX.)

Install *ANTsR*

ANTs + *R*

- Operating System: Linux, OSX
- See: Install ANTsR (link)
- Will install ⋆everything⋆ you need if you want it to, including R .... otherwise will just intall *ANTsR* dependencies/utils.

OSX NOTES

- Requires: Xcode (link) and its command line tools (google install instructions)
- Requires: a clean Homebrew ("brew doctor" does not complain)
- you may want to comment out lines like: brew install ...X... if you already have software X around.

What is *knitr* ?

- Yihui Xie's system *knitr* for making documents that compute
- *knitr* lets you write a document that employs *R* directly
- *R* evaluates code when the document is compiled
- The user controls when this does / does not happen ...
- Creates, figures, statistics etc that are embedded in rst, html, latex, pretty much any common document format is doable.

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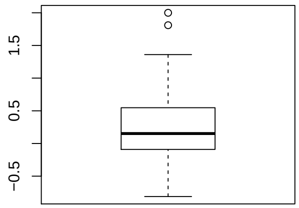
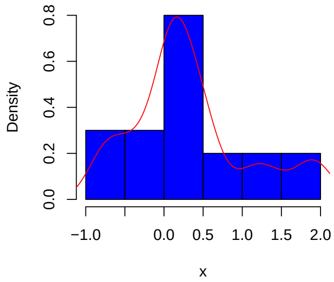
Simple knitr Example

Use knitr to make a couple of plots in our code "chunk":

```
x <- rnorm(20)
boxplot(x)
hist(x, main = "", col = "blue", probability = TRUE)
lines(density(x), col = "red")
```





R ⋆Very⋆ Basics

R organizes data with dataframes, vectors, matrices and arrays (matrices with $\geq$ 3 dimensions).
These can contain missing variables - but you must be careful about type!

```
as.numeric(as.character(c("0.5", 0.1, 0.6, "A")))

## Warning:  NAs introduced by coercion

## [1] 0.5 0.1 0.6  NA
```

A data frame is used for storing data tables. It is a list of vectors of equal length.

R ⋆Very⋆ Basics 2

mtcars is a built-in *R* dataframe

```
mtcars[c(1, 13, 28), 1:6]

##                 mpg cyl  disp  hp drat    wt
## Mazda RX4      21.0   6 160.0 110 3.90 2.620
## Merc 450SL     17.3   8 275.8 180 3.07 3.730
## Lotus Europa   30.4   4  95.1 113 3.77 1.513
```

We analyze the relationship between MPG and other variables.

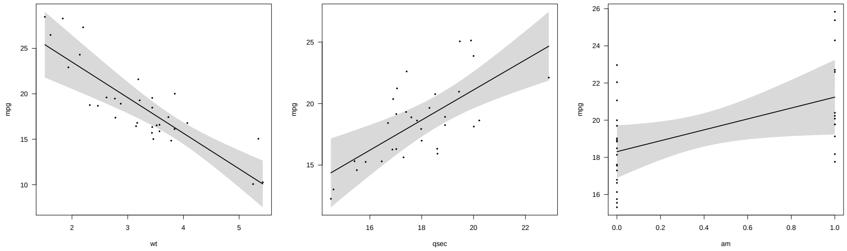
```
myform <- paste(colnames(mtcars)[2:ncol(mtcars)], collapse = "+")
myform <- as.formula(paste("mpg~", myform))
mdl <- lm(myform, data = mtcars)
mdla <- stepAIC(mdl, direction = c("both"))
```

R ⋆Very⋆ Basics 3

```
##
## Call:
## lm(formula = mdla$call$formula, data = mtcars)
##
## Residuals:
##    Min     1Q Median     3Q    Max
## -3.481 -1.556 -0.726  1.411  4.661
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept)    9.618      6.960    1.38  0.17792
## wt            -3.917      0.711   -5.51    7e-06 ***
## qsec           1.226      0.289    4.25  0.00022 ***
## am             2.936      1.411    2.08  0.04672 *
## ---
## Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
##
## Residual standard error: 2.46 on 28 degrees of freedom
## Multiple R-squared:  0.85, Adjusted R-squared:  0.834
## F-statistic: 52.7 on 3 and 28 DF,  p-value: 1.21e-11
```

R ⋆Very⋆ Basics: Draw a Picture

```
mdl <- lm(mdla$call$formula, data = mtcars)
visreg(mdl, xvar = "wt")
visreg(mdl, xvar = "qsec")
visreg(mdl, xvar = "am")
```

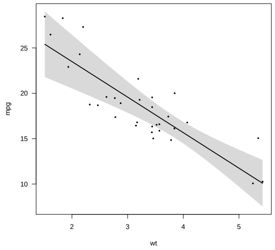


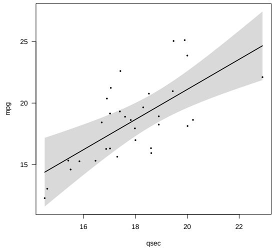
Oops!

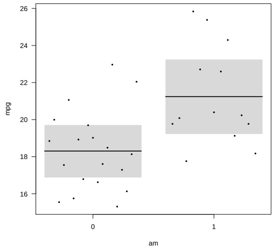
Transmission type should be a factor.

R ⋆Very⋆ Basics: Draw a Picture Fix

```
mtcars$am <- as.factor(mtcars$am)
mdl <- lm(mdla$call$formula, data = mtcars)
visreg(mdl, xvar = "wt")
visreg(mdl, xvar = "qsec")
visreg(mdl, xvar = "am")
```







This is better ...

R ⋆Very⋆ Basics: Draw a Picture 3

```r
coplot(mpg ~ wt | qsec, data = mtcars, panel = panel.smooth,
    rows = 1)
```

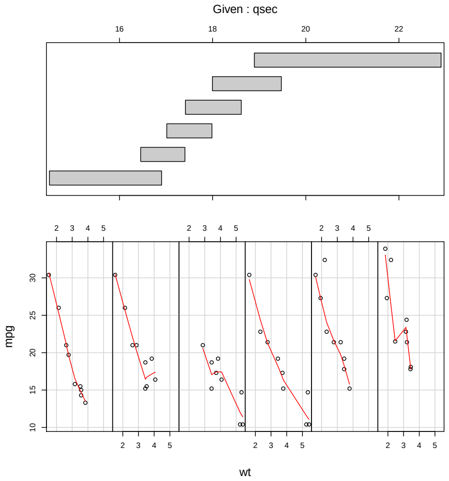
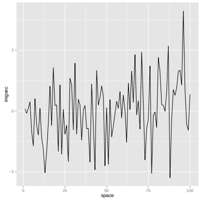


Image Input/Output in *R*

Data Representation in *R*

Represent an image as a *vector* (more on this later). This vector may be derived from a 2 or 3D array of spatially related voxels.

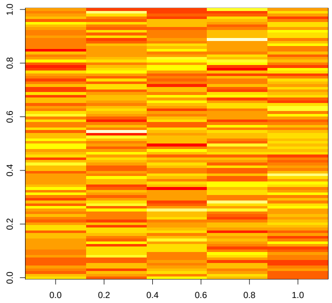
```r
nvox <- 100
imgvec <- rnorm(nvox)
mydat <- data.frame(space = 1:nvox, imgvec = imgvec)
ggplot(data = mydat, aes(x = space, y = imgvec, group = 1)) +
    geom_line()
```



Data Representation in *R*

Represent an image set as a *matrix*.

```
nSubjectsOrTimePoints <- 5
imgmat <- matrix(rep(NA, nSubjectsOrTimePoints * nvox), ncol = nvox)
for (i in 1:nSubjectsOrTimePoints) {
    imgmat[i, ] <- rnorm(nvox)
}
image(imgmat)  # try antsImageWrite( as.antsImage( imgmat ), imgmat.mha )
```



Reading Images

Read em and weep

```
fn <- getANTsRData("ch2", usefixedlocation = FALSE)

## [1] "checksum failure"

print(fn)

## NULL

# oro.nifti
colin <- readNIfTI(fn)

## Error:  File(s) not found!

# antsr
colina <- antsImageRead(fn, 3)

## [1] "filename argument must be of class character and have length 1"
```

Quickly Show Images by oro.nifti

```
orthographic(as.array(colina), oma = rep(2, 4))

## Error:  error in evaluating the argument 'x' in selecting a
method for function 'orthographic':  Error in
as.array.default(colina) :  attempt to set an attribute on NULL
## Calls:  as.array -> as.array -> as.array.default
```

Quickly Show Images w/ANTsR

```r
fn <- "figure/antsrviz.jpeg"
plotANTsImage(as.antsImage(colin), slices = "50x140x5", outname = fn)

## Error:  error in evaluating the argument 'object' in selecting a
method for function 'as.antsImage':  Error:  object 'colin' not
found
```

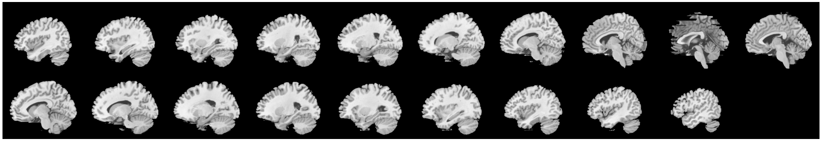


Figure : The *ANTsR* multi-slice output.

Convert an Image to a Vector

Use *ANTsR* to convert an image to a vector.

```r
imgvec <- colina[colina > 50]
print(length(imgvec))
```

Use oro.nifti to convert an image to a vector.

```r
imgvec <- colin[colin > 50]

## Error:  object 'colin' not found

print(length(imgvec))
```

Both packages enable similar functionality in terms of accessing / converting images to vectors. *ANTsR* allows I/O to files other than nifti such as meta, jpg, dicom, etc, anything ITK reads/writes.

Quantifying Images in *R*

Image Quantification with *R*

It is possible to implement full processing pipelines with *R* for submission to distributed computing systems ...
My knowledge is limited to *ANTsR* .

ANTsR based image quantification

- antsRegistration example (link)
- Atropos segmentation (link)
- phantom population study (link)

The Basic Toolset from outside *R*

Registration: Data is in Examples/Data

```
ANTS 2 -m  CC[r16slice.nii.gz,r64slice.nii.gz,1,4]

 -t SyN[0.25]  -r Gauss[3,0] -o TEST -i 50x40x30
```

Segmentation

```
Atropos -d 2 -a r16slice.nii.gz -x r16mask.nii.gz

-m [0.1,1x1]   -c [10,0]  -i kmeans[3]

-o [Output.nii.gz,Output_prob_%02d.nii.gz]
```

Template building

```
 bash buildtemplateparallel.sh -d 3 -m 30x50x20

-t GR  -s CC -c 1 -o OutPrefix  *ImageName*T1x.nii.gz
```

R Statistical Methods for Imaging

Basic Linear Regression

This is a simple regression study that associates diagnosis (dx) with a local Jacobian-based volume measurement.
We also look at global volume.

```r
predictor <- as.factor(read.csv("data/phantpredictors.csv")$dx)
gvol <- read.csv("data/globalvols.csv")
attach(gvol)
mdl <- lm(vol ~ predictor)
```

This is simulated data ....

Basic Linear Regression Output

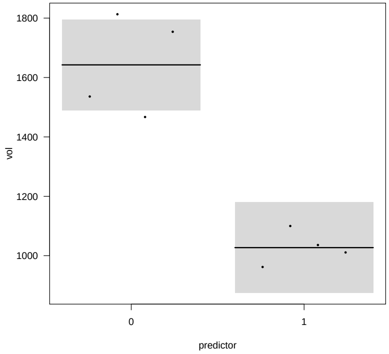
```
summary(mdl)

##
## Call:
## lm(formula = vol ~ predictor)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -175.50  -75.56   -3.75   82.44  170.50
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept)   1642.5       62.4   26.31    2e-07 ***
## predictor1    -615.2       88.3   -6.97  0.00043 ***
## ---
## Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
##
## Residual standard error: 125 on 6 degrees of freedom
## Multiple R-squared:  0.89, Adjusted R-squared:  0.872
## F-statistic: 48.6 on 1 and 6 DF,  p-value: 0.000434
```

Basic Linear Regression Visualization

visreg has easy to use "natural" visualizations for regression ...

```
visreg(mdl)
```



Next apply the global test to the voxelwise morphometry case.

.... voxel-wise statistics in R

```r
mask <- antsImageRead("data/phantmask.nii.gz", 2)
logjac <- read.csv("data/phantomGlogjacs.csv")  # a population of images

attach(logjac)
nvox <- ncol(logjac)
pvals <- rep(NA, nvox)
for (x in c(1:nvox)) {
    voxels <- logjac[, x]
    lmres <- summary(lm(voxels ~ predictor))
    coeff <- coefficients(lmres)
    pval <- coeff[2, 4]
    pvals[x] <- pval
}
qvals <- p.adjust(pvals, method = "BH")
print(min(qvals))
pvali <- antsImageClone(mask)
pvali[mask > 0] <- 1 - qvals
plotANTsImage(mask, functional = list(pvali), threshold = "0.99x1",
    outname = "figure/lmreg.jpeg")
```

Exercise: What happens when you include globalvol as a covariate?

Visualizing voxel-wise statistics in R

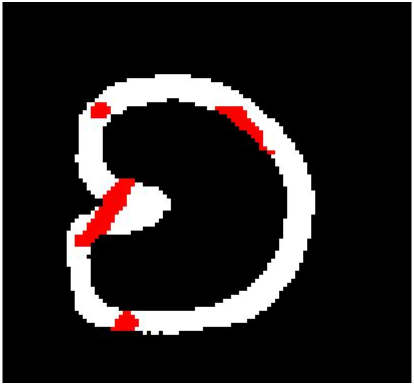


Figure : The regression solution p-values thresholded at 0.01 FDR-corrected.

.... multivariate statistics in R

```r
continuousDX <- 1 - as.numeric(predictor)
continuousDX2 <- gvol
mypreds <- as.matrix(cbind(continuousDX, continuousDX2))
sccan <- sparseDecom2(inmatrix = list(as.matrix(logjac), mypreds),
    inmask = c(mask, NA), sparseness = c(0.25, -1), nvecs = 1,
    its = 2, smooth = 1, perms = 200)
sccansol <- sccan$eig1[[1]]
sccansol[mask > 0] <- sccansol[mask > 0]/max(sccansol[mask >
    0])
plotANTsImage(mask, functional = list(sccansol), threshold = "0.05x1",
    outname = "figure/mvarreg.jpeg")
```

Exercise: What happens when you include globalvol as a covariate?

Visualizing multivariate statistics in R

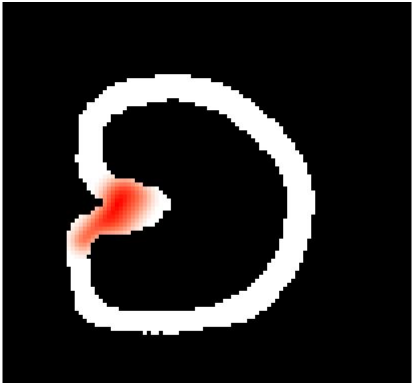


Figure : The sccan solution with p-value 0.

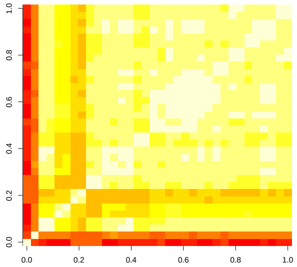
ANOVA 1

How do we assess the importance of multiple predictors acting together within classic regression?

```
nki <- read.csv("data/labelresultsN.csv")
print(names(nki)[1:8])

## [1] "ID"      "SITE"    "SEX"     "AGE"     "VOLUME"
## [6] "LABEL_1" "LABEL_2" "LABEL_3"

image(cor(as.matrix(nki[, 4:37])))
```



ANOVA 2

How do we assess the importance of multiple predictors acting together within classic regression?

```
mdl1 <- lm(LABEL_14 ~ SEX + VOLUME, data = nki)
mdl2 <- lm(LABEL_14 ~ SEX + VOLUME + AGE + I(AGE^2), data = nki)
print(anova(mdl1, mdl2))

## Analysis of Variance Table
##
## Model 1: LABEL_14 ~ SEX + VOLUME
## Model 2: LABEL_14 ~ SEX + VOLUME + AGE + I(AGE^2)
##   Res.Df  RSS Df Sum of Sq    F  Pr(>F)
## 1    183 44.8
## 2    181 34.9  2       9.9 25.7 1.5e-10 ***
## ---
## Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
## pdf
##   2
```

How do we assess the importance of multiple predictors acting together within classic regression?

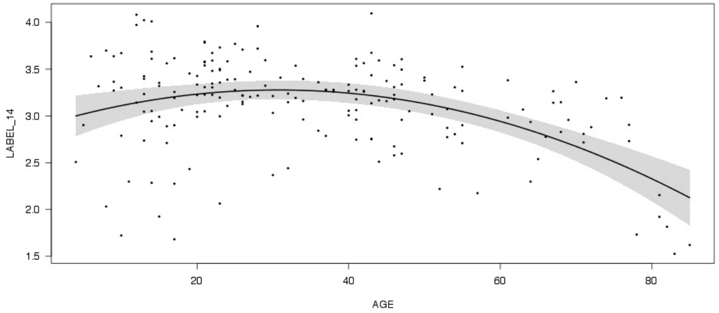


Figure : The quadratic regression of age against thickness while controlling for gender and brain volume

R Multivariate Methods for "Big Data"

first: some brief theory

What is multiple regression?

The solution to a quadratic minimization problem:

Multiple Regression

$$\|y - X\beta\|^2 + \lambda\|\beta\|^2$$

Solved by ordinary least squares methods:

$$\hat{\beta} = (X^T X)^{-1} X^T y$$

with theory for turning β entries into "significance" measurements.

The "ridge" penalty is useful if $p >> n$.

Principal Component Analysis

Also the solution to a quadratic minimization problem:

PCA: U, V minimize reconstruction error:

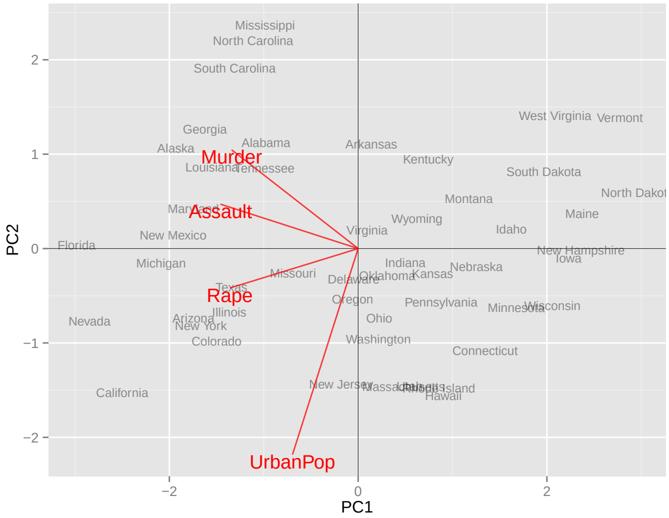
$$\|X - UV^T\|^2 + \sum_k \lambda_k \|V_k\|_1$$

Each of the columns of X is a linear combination of the columns of U. Easy solution in *R* (w/o penalties):

```
mysolution = svd(X)  # or prcomp(X) if X not centered
```

The ℓ_1 penalty is useful if $p >> n$.

Principal Component Analysis Example



Canonical Correlation Analysis

CCA Generalizes Multiple Regression

$$YV + \sum_k \lambda_k \|V_k\|_1 \propto XW + \sum_k \gamma_k \|W_k\|_1$$

where Y, V, X, W are matrices and V, W are canonical variates (the CCA solutions). Also easy in *R* (SVD used internally):

```
enginedata <- mtcars[, c(2, 3, 4, 11)]
outputdata <- mtcars[, c(1, 7)]
mycca <- cancor(enginedata, outputdata)
```

CCA is "symmetric" in that the sets X and Y have equivalent status. A truly multivariate multiple regression.

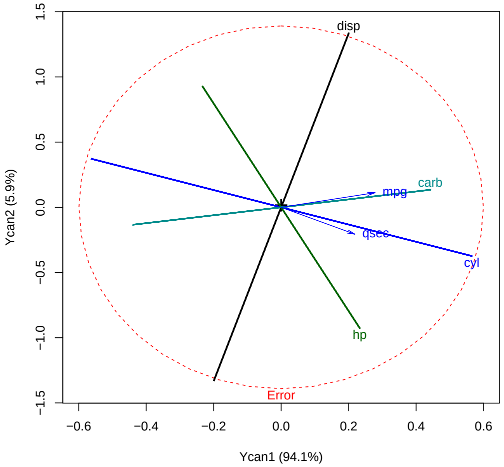
Canonical Correlation Analysis Visualization 1

```
print(mycca)

##
## Canonical correlation analysis of:
##   4   X  variables:  cyl, disp, hp, carb
##   with  2   Y  variables:  mpg, qsec
##
##     CanR CanRSQ  Eigen percent    cum                scree
## 1 0.9319 0.8684 6.5988   94.13  94.13 ********************
## 2 0.5399 0.2915 0.4115    5.87 100.00 *
##
## Test of H0: The canonical correlations in the
## current row and all that follow are zero
##
##    CanR WilksL    F df1 df2 p.value
## 1 0.932  0.093 14.8   8  52  0.0000
## 2 0.540  0.708  3.7   3  27  0.0237
```

Canonical Correlation Analysis Visualization 2

```
heplot(mycca, xpd = TRUE, scale = 0.3)
```



Sparse multiple regression/PCA/CCA

Any of the methods can be made sparse by enforcing the penalties previously highlighted in blue.

Sparse Optimization

- Formulate the problem as a constrained optimization.
- Identify the gradient descent solution—*without sparseness*.
- Use projected gradient descent to solve the optimization—*with sparseness*.
- In imaging, other constraints are valuable too.

PBAC: R ready medical imaging data.

We have training (90084)/testing (90084) data images + psychometrics and analyze the relationship between gray matter and cognition.

```
pbacTRcog[c(1, 13, 28), 1:6]

##    age edu mmse fluency_adj dig_fwd_adj dig_bwd_adj
## 1   72  18   24         4.5         2.5           4
## 13  55  17   29         5.0         2.0           3
## 28  51  16   16         3.0         0.5           1

# also pbac imaging data comes from this mask
mask <- antsImageRead(list.files(path = "./data", pattern = glob2rx("gmask_
    full.names = T), 3)
# with anatomical labels
pbacaal <- antsImageRead(list.files(path = "./data", pattern = glob2rx("pba
    full.names = T), 3)
data("aal", package = "ANTsR")  # description of aal
```

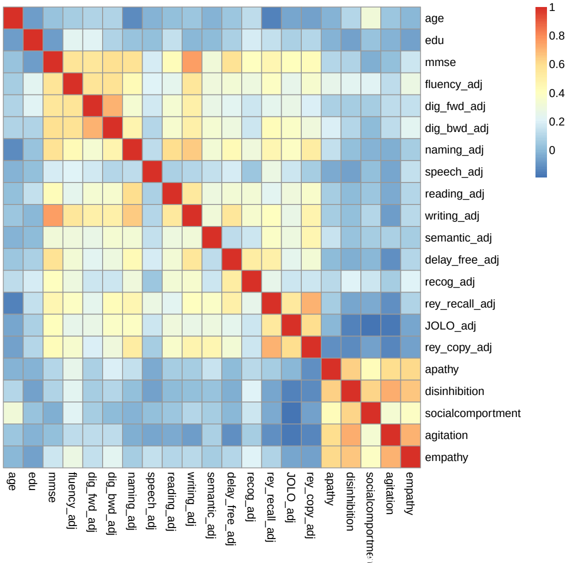
R Multivariate - PBAC ROIs

```
inmask <- mask > 0.5
mylabs <- sort(unique(pbacaal[inmask & pbacaal > 0.5 & pbacaal <
    91 & pbacaal != 51 & pbacaal != 52 & pbacaal != 53 & pbacaal !=
    54]))
roimatrix <- matrix(rep(NA, length(mylabs) * nrow(pbacTRimg)),
    ncol = length(mylabs))
for (i in 1:length(mylabs)) {
    # get vector for this label
    labelVec <- as.numeric(pbacaal[inmask] == mylabs[i])
    roimatrix[, i] <- pbacTRimg %*% (labelVec/sum(labelVec))
}
colnames(roimatrix) <- aal$label_name[mylabs]
mydf <- data.frame(pbacTRcog, roimatrix)
```

Next we will analyze these ROIs and their relationship with demographics.

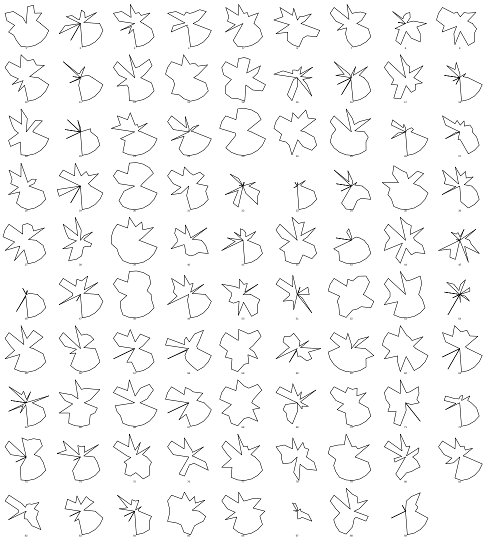
R Multivariate: Inspect Data - PBAC cog

```
pheatmap(cor(pbacTRcog), cluster_rows = F, cluster_cols = F)
```



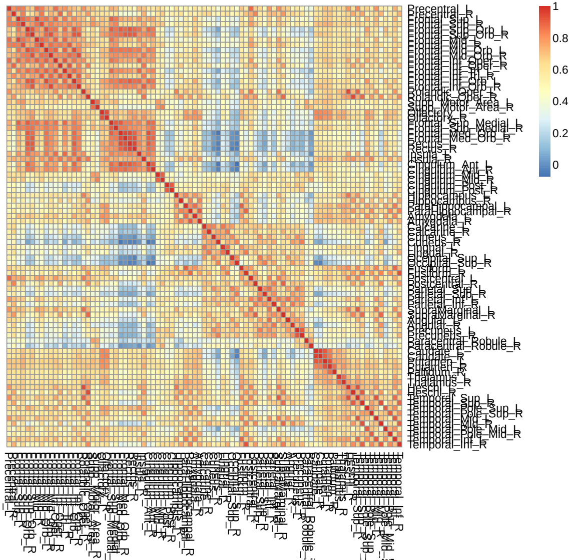
R Multivariate: Inspect Data - PBAC Cog Constellation Plot

Brain Constellation Map of PBAC Cognition

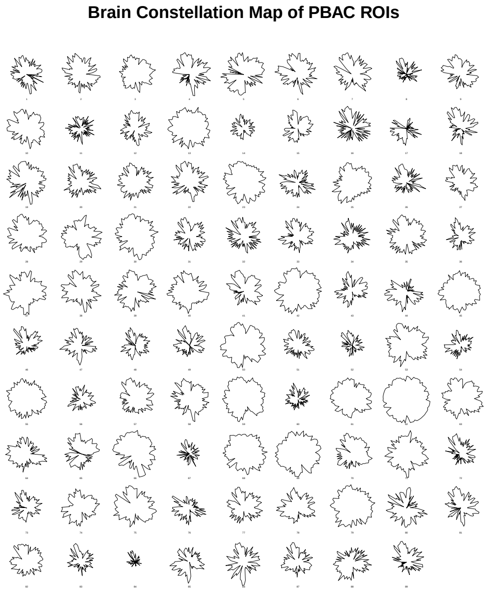


R Multivariate: Inspect Data - PBAC ROI

```r
pheatmap(cor(roimatrix), cluster_rows = F, cluster_cols = F)
```



R Basics: Inspect Data - PBAC ROI Constellation Plot



1200 Subject Constellation Plot

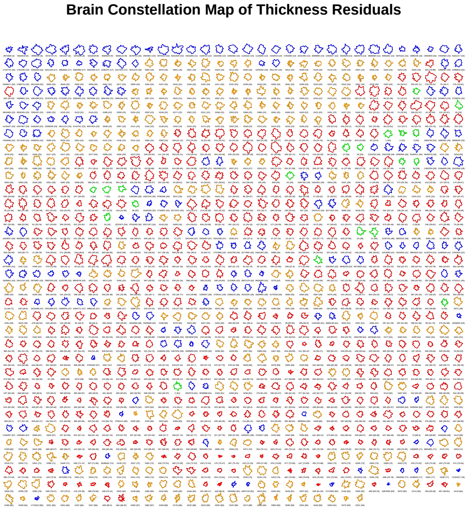
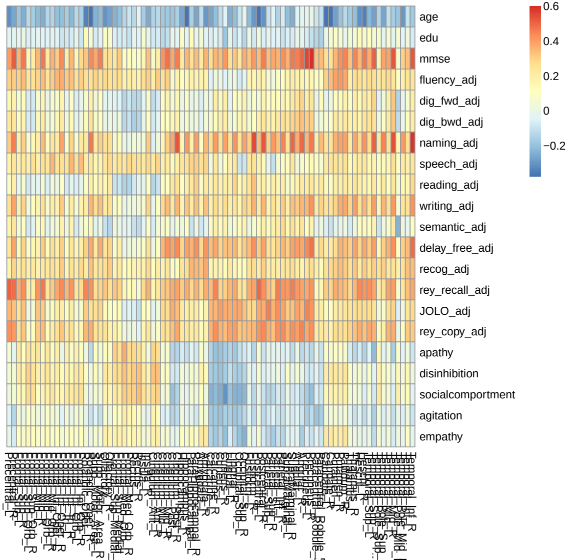


Figure : Data-inspection for a large-scale study.

R Multivariate: Inspect Data - PBAC cog ↔ ROI

```r
pheatmap(cor(pbacTRcog, roimatrix), cluster_rows = F, cluster_cols = F)
```



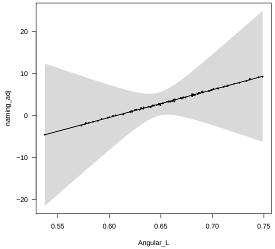
R Multivariate - PBAC ROI Study

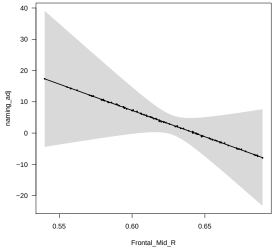
```
myform <- paste(colnames(roimatrix), collapse = "+")
myform <- as.formula(paste("naming_adj~", myform, "+edu"))
mydf <- data.frame(pbacTRcog, roimatrix)
row.names(mydf) <- paste(c(1:nrow(pbacTRcog)), "_", as.character(pbacTRcog$
    sep = "")
mdl <- lm(myform, data = mydf)
mdla <- stepAIC(mdl, direction = c("forward"), k = 20, steps = 20)
ageregions <- gsub("_", "", as.character(mdla$call$formula)[3])
```

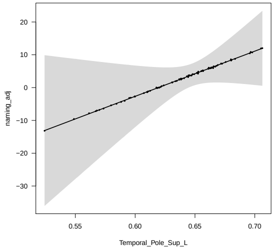
Various brain regions, together, predict naming_adj ... PrecentralL + PrecentralR + FrontalSupL + FrontalSupR + FrontalSupOrbL + FrontalSupOrbR + FrontalMidL + FrontalMidR + FrontalMidOrbL + FrontalMidOrbR + FrontalInfOperL + FrontalInfOperR + FrontalInfTriL + FrontalInfTriR + FrontalInfOrbL + FrontalInfOrbR + RolandicOperL + RolandicOperR + SuppMotorAreaL + SuppMotorAreaR + OlfactoryL + OlfactoryR + FrontalSupMedialL + FrontalSupMedialR + FrontalMedOrbL + FrontalMedOrbR + RectusL + RectusR + InsulaL + InsulaR + CingulumAntL + CingulumAntR + CingulumMidL +

R Multivariate: Draw a Picture - PBAC

```r
visreg(mdla, xvar = "Angular_L")
visreg(mdla, xvar = "Frontal_Mid_R")
visreg(mdla, xvar = "Temporal_Pole_Sup_L")
```

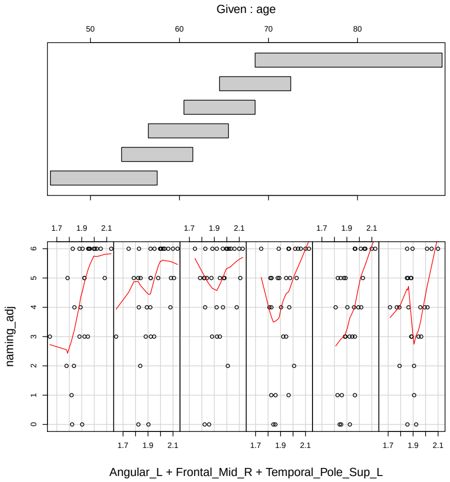






R Multivariate: PBAC Draw a Picture 2

```
coplot(naming_adj ~ Angular_L + Frontal_Mid_R + Temporal_Pole_Sup_L |
    age, data = mydf, panel = panel.smooth, rows = 1)
```



R Multivariate: PBAC SCCAN

Run SCCAN between raw GM data and cognition

```
mysccan <- sparseDecom2(inmatrix = list(as.matrix(pbacTRcog),
    pbacTRimg), inmask = c(NA, mask), smooth = 1, sparseness = c(-0.07,
    0.2), nvecs = nv, its = 3, perms = 0, cthresh = c(0, 250))
```

```
## gm ~ mmse + rey_recall_adj
## [1] "Train Correlation: 1 0.664181703317975"
## gm ~ rey_recall_adj + rey_copy_adj
## [1] "Train Correlation: 2 0.571539338864852"
## gm ~ naming_adj + delay_free_adj
## [1] "Train Correlation: 3 0.586114213255158"
## gm ~ writing_adj + JOLO_adj
## [1] "Train Correlation: 4 0.500195314403038"
## gm ~ delay_free_adj
## [1] "Train Correlation: 5 0.486444226824085"
```

R and Prediction

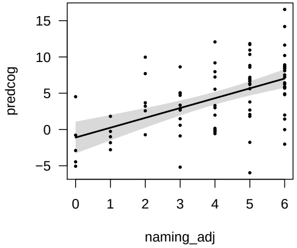
Prediction: PBAC—Cognition from ROIs

Get the testing data ROIs (code hidden).

Predict the naming from test ROI data w/ ordinary regression.

```
predcog <- predict(mdla, newdata = testdf)
print(paste("Test Correlation:", cor.test(pbacTEcog$naming_adj,
    predcog)$est))

## [1] "Test Correlation: 0.522830279263574"
```



Prediction: PBAC—Cognition from Brain

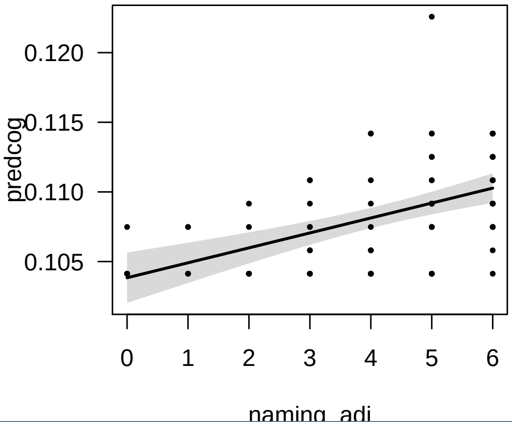
Predict the test voxel data from cognition id'd by SCCAN.

```
## gm ~ mmse + rey_recall_adj
## [1] "Test Correlation: 1 0.607638630247478"
## gm ~ rey_recall_adj + rey_copy_adj
## [1] "Test Correlation: 2 0.450943295749685"
## gm ~ naming_adj + delay_free_adj
## [1] "Test Correlation: 3 0.446546448383557"
## gm ~ writing_adj + JOLO_adj
## [1] "Test Correlation: 4 0.307284063558776"
## gm ~ delay_free_adj
## [1] "Test Correlation: 5 0.504171777768369"
```

The SCCAN model is equally predictive but much more specific.

Prediction: PBAC—Cognition from Brain

```r
predmdl <- lm(predcog ~ 1 + naming_adj, data = pbacTEcog)
visreg(predmdl)
```



Cross-Validation of Diagnosis

boot

```
dx <- as.factor(pbacTRcog$mmse < 26)
dx <- as.factor(pbacTRcog$fluency_adj < 2.6)
traindata <- data.frame(dx = dx, roimatrix)
myform <- paste("dx~", paste(colnames(roimatrix)[1:20], collapse = "+"))
mdl <- glm(as.formula(myform), data = traindata, family = "binomial")
dd <- 0
ntests <- 20
for (i in 1:ntests) dd <- dd + cv.glm(traindata, mdl, K = 5)$delta[1] *
    (1/ntests)
```

Reasonable classification rates.

```
## [1] "prediction % misclassification 6.87711587597379"
```

Prediction: BRATS Challenge

fMRI

fMRI Helper Functions 1

A function for averaging a list of images voxel-wise. Note: It's dimension-free.

```r
avgimg <- function(mylist, mask) {
    avg <- antsImageClone(mylist[[1]])
    avg[mask == 1] <- 0
    for (i in 1:length(mylist)) {
        avg[mask == 1] <- avg[mask == 1] + mylist[[i]][mask ==
            1] * 1/length(mylist)
    }
    return(avg)
}
```

fMRI Helper Functions 2

A function for computing the voxel-wise absolute difference of an image list from its average.

```r
sdimg <- function(mylist, mask) {
    avg <- avgimg(mylist, mask)
    sdi <- antsImageClone(avg)
    sdi[mask == 1] <- 0
    for (i in 1:length(mylist)) {
        sdi[mask == 1] <- sdi[mask == 1] + abs(mylist[[i]][mask ==
            1] - avg[mask == 1]) * 1/length(mylist)
    }
    return(sdi)
}
```

fMRI Helper Functions 3

A function to interleave two R numeric vectors.

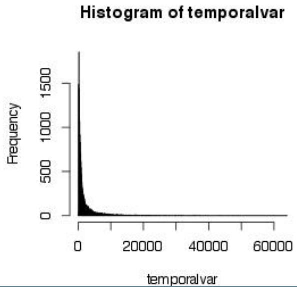
```r
interleave <- function(v1, v2) {
    ord1 <- 2 * (1:length(v1)) - 1
    ord2 <- 2 * (1:length(v2))
    c(v1, v2)[order(c(ord1, ord2))]
}
```

Why might we want this?

BOLD fMRI Motor Tasks 1

"A test-retest fMRI dataset for motor, language and spatial attention functions" — Gigascience, 2013.
Subject: 08143633

```r
fmri <- antsImageRead(fn, 4)
hrf <- hemodynamicRF(scans = dim(fmri)[4], onsets = blockfing,
    durations = rep(12, length(blockfing)), rt = 2.5)
hrf[1:4] <- NA  # first few frames are junk
myvars <- getfMRInuisanceVariables(fmri, moreaccurate = FALSE,
    maskThresh = 100)
```



BOLD fMRI Motor Tasks 2

The previous functions compute *R* friendly variables for fMRI processing: Nuisance, mean, mask, matrix. + the HRF.

```r
mat <- myvars$matrixTimeSeries
avg <- myvars$avgImage
mask <- myvars$mask
nuis <- (myvars$nuisancevariables)
print(colnames(nuis))
antsImageWrite(avg, paste(pre, "avg.nii.gz", sep = ""))
plotANTsImage(myantsimage = avg, functional = list(mask), slices = "12x20x3
    axis = 3, threshold = "0.5x1.5")
```

BOLD fMRI Motor Tasks 3

Use multiple regression to relate a task-design (convolved with HRF) to BOLD activation.

```r
globsig <- myvars$globalsignal
betas <- rep(NA, ncol(mat))
for (i in 1:ncol(mat)) {
    vox <- mat[, i]
    mdl <- lm(vox ~ hrf + globsig + motion1 + motion2 + motion3 +
        compcorr1 + compcorr2 + compcorr3, data = data.frame(nuis))
    betas[i] <- coefficients(summary(mdl))[2, 3]  # probably better way
}
betaimg <- antsImageClone(mask)  # put beta vals in image space
betaimg[mask > 0.5] <- betas
print(max(abs(betas)))  # around 10 or so
# much much faster but i havent figured out how to get
# results out easily
fastResults <- lm(mat[, 1:2] ~ hrf + myvars$globalsignal + motion1 +
    motion2 + motion3 + compcorr1 + compcorr2 + compcorr3, data = data.fram
antsImageWrite(betaimg, paste(pre, "betas.nii.gz", sep = ""))
```

BOLD fMRI Motor Tasks 4

```
gcoords <- getTemplateCoordinates(list(avg, clust), mymni, convertToTal = T
    outprefix = ofn)
print(gcoords$templatepoints)
myregion <- sub("_", "", gcoords$templatepoints$AAL[1])
```

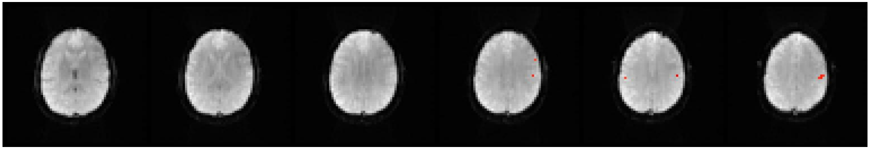


Figure : Univariate results for fingertapping include CentralSulcus.

Is that the "right" location?

BOLD fMRI Motor Tasks 5

We can look at the code for this if it is of interest ...

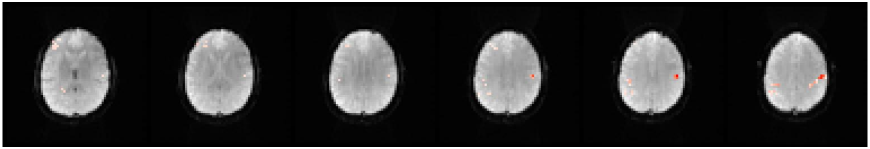


Figure : Multivariate results for fingertapping.

Exercise: Fingertapping repeatability

Repeat with subjects fmri_motor_sub1_s2.nii.gz and fmri_motor_sub2_s1.nii.gz
Evaluate overlap of signal.

BOLD fMRI Processing Inspection

Use multivariate decomposition to help understand both the data and the nuisance variables.

```r
nvecs <- 11
ff <- sparseDecom(rmat[!is.na(hrf), ], mask, 1.25/nvecs, nvecs,
    its = 5, cthresh = 5, smooth = 1, z = -0.9)
for (i in 1:nvecs) {
    print(paste("Test", i))
    mdl <- lm(ff$projections[, i] ~ cblock + myvars$globalsignal[!is.na(hrf
        motion1 + motion2 + motion3 + compcorr1 + compcorr2 +
        compcorr3, data = data.frame(nuis[!is.na(hrf), ]))
    print(summary(mdl))
}
dat <- data.frame(time = ((1:length(hrf[!is.na(hrf)])) * 2.5),
    signal = ff$projections[, 2], nuis = ff$projections[, 3],
    hrf = hrf[!is.na(hrf)])
```

BOLD Decomposition with Regression-Task

Use multivariate decomposition to help understand both the data and the nuisance variables.

```
mdl <- lm(ff$projections[, 2] ~ cblock + myvars$globalsignal[!is.na(hrf)] +
    motion1 + motion2 + motion3 + compcorr1 + compcorr2 + compcorr3,
    data = data.frame(nuis[!is.na(hrf), ]))

##                       (Intercept)
##                         0.8970783
##                            cblock
##                         0.0002709
## myvars$globalsignal[!is.na(hrf)]
##                         0.2735748
##                           motion1
##                         0.6876208
##                           motion2
##                         0.9173405
##                           motion3
##                         0.2948914
##                         compcorr1
##                         0.4551018
##                         compcorr2
```

BOLD Decomposition with Regression-Nuisance

Use multivariate decomposition to help understand both the data and the nuisance variables.

```
mdl <- lm(ff$projections[, 3] ~ cblock + myvars$globalsignal[!is.na(hrf)] +
    motion1 + motion2 + motion3 + compcorr1 + compcorr2 + compcorr3,
    data = data.frame(nuis[!is.na(hrf), ]))

##                        (Intercept)
##                          1.127e-03
##                             cblock
##                          7.895e-01
## myvars$globalsignal[!is.na(hrf)]
##                          2.129e-72
##                            motion1
##                          1.206e-02
##                            motion2
##                          1.652e-16
##                            motion3
##                          1.509e-03
##                          compcorr1
##                          4.179e-06
##                          compcorr2
```

BOLD Decomposition with Regression-Task in the Brain

Use multivariate decomposition to help understand both the data and the nuisance variables.

```r
eigimg <- ff$eigenanatomyimages[[2]]
```

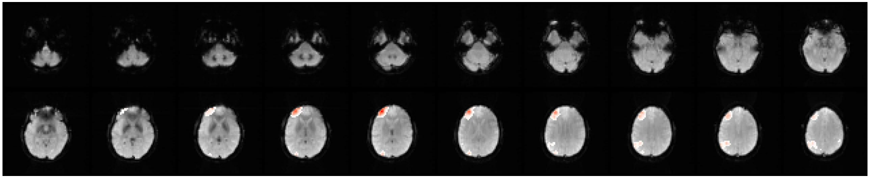


Figure : Multivariate results for fingertapping... task areas

BOLD Decomposition with Regression-Nuis in the Brain

Use multivariate decomposition to help understand both the data and the nuisance variables.

```
eigimg <- ff$eigenanatomyimages[[3]]
```

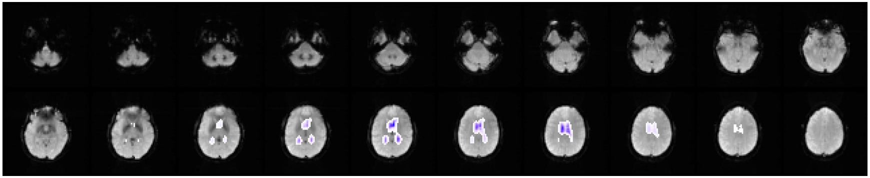


Figure : Multivariate results for fingertapping... nuis areas

BOLD fMRI Signals

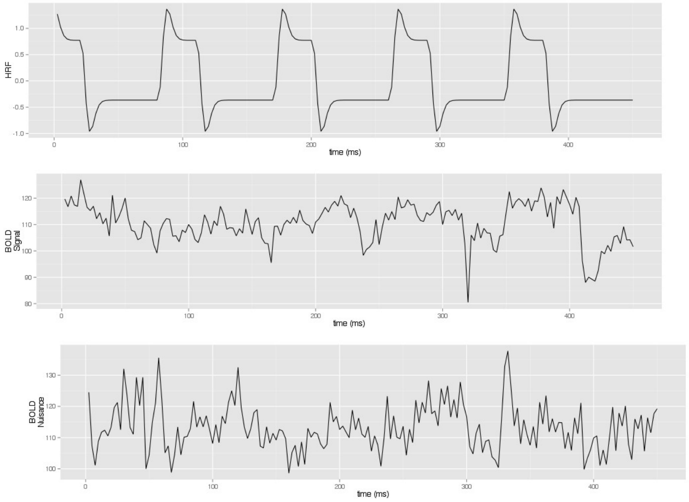


Figure : BOLD signals.

BOLD fMRI Language Tasks

Exercise: Check the code below and run the language task studies from the Gigascience article.

```
if (FALSE) {
    fmri <- antsImageRead("data/fmri_covert_verb_generation_sub1_s2.nii.gz"
        4)
    blocko = c(1, 24, 48, 72, 96, 120, 144)
    hrf <- hemodynamicRF(scans = dim(fmri)[4], onsets = blocko,
        durations = rep(12, length(blocko)), rt = 2.5)
    hrf[1:4] <- NA  # first few frames are junk
    myvars <- getfMRInuisanceVariables(fmri, moreaccurate = TRUE,
        maskThresh = 100)
    avg <- myvars$avgImage
    antsImageWrite(avg, "avg_lang.nii.gz")
    mask <- myvars$mask
    mat <- myvars$matrixTimeSeries
    # fmri2<-antsImageClone(fmri) SmoothImage(4,fmri,1,fmri2)
    # mat<-timeseries2matrix( fmri2, mask ) #
    nuis <- (myvars$nuisancevariables)
    print(colnames(nuis))
    plotANTsImage(myantsimage = avg, functional = list(mask),
        slices = "12x20x3", axis = 3, threshold = "0.5x1.5")
```

Simple ASL CBF

Arterial spin labeling (ASL) can measure cerebral blood flow (CBF) non-invasively and more directly than BOLD. It requires specialized processing techniques not widely available.

```
fns <- Sys.glob(file.path("./data/eld*nii.gz"))
asl <- antsImageRead(fns[1], 4)
perf <- aslPerfusion(asl, maskThresh = 300, moreaccurate = FALSE)
param <- list(sequence = "pcasl", m0 = perf$m0)
cbf <- quantifyCBF(perf$perfusion, perf$mask, param)

## Loading required package:  extremevalues

plotANTsImage(cbf$meancbf, slices = "5x17x3", axis = 3, outname = "figure/a
```

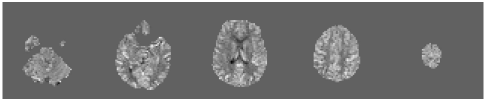


Figure : The *ANTsR* simple CBF estimate with standard regression.

fMRI Boot-Strapping

Load some data already processed.

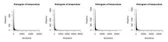
```r
fns <- Sys.glob(file.path("./data/eld*nii.gz"))
asl <- antsImageRead(fns[1], 4)
seg <- antsImageRead(fns[3], 3)
mask <- antsImageClone(seg)
mask[seg > 0] <- 1
mat <- timeseries2matrix(asl, mask)
cbflist <- list()
```

ASL-CBF estimates are unstable and subject to motion artifact.
Idea: We can try resampling methods to estimate both uncertainty and a "true" mean CBF value per voxel.

fMRI Boot-Strapping 2

Luckily, this is easy to implement in *R* .

```
for (i in 1:4) {
    timeinds <- sample(2:nrow(mat), round(nrow(mat)) * 0.3)
    timeinds <- (timeinds%%2) + timeinds
    timeinds <- interleave(timeinds - 1, timeinds)
    aslarr <- as.array(asl)
    aslarr2 <- aslarr[, , , timeinds]
    aslsub <- as.antsImage(aslarr2)
    antsCopyImageInfo(aslsub, asl)
    proc <- aslPerfusion(aslsub, mask = mask, moreaccurate = FALSE,
        dorobust = 0)
    param <- list(sequence = "pcasl", m0 = proc$m0)
    cbf <- quantifyCBF(proc$perfusion, mask, param)
    antsImageWrite(cbf$meancbf, "temp1.nii.gz")
    cbflist <- lappend(cbflist, cbf$meancbf)
}
```



fMRI Boot-Strapping 3

```
avgcbf <- avgimg(cbflist, mask)
sdi <- sdimg(cbflist, mask)
avgcbft <- antsImageClone(avgcbf)
avgcbft[sdi > 25] <- 0
plotANTsImage(avgcbft, slices = "5x17x3", axis = 3, outname = "figure/antsr
plotANTsImage(avgcbft, functional = list(sdi), color = "red",
    slices = "5x17x3", axis = 3, threshold = "20x55", outname = "figure/ant
```

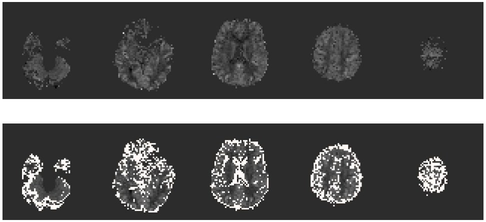


Figure : The *ANTsR* bootstrapped CBF with estimated CBF variance.

Review So Far ...

What Have We Ignored?

- More general linear models: e.g. multinomial, logit ...
- LDA, SVM, advanced visualization, etc.
- functions/packages: *pairs, glmnet, PMA, igraph* ...
- simulation — very valuable.
- too many *R* ⋆tricks⋆ to remember w/o practice.

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Example github projects for reproducible research

Example Papers based on R: SCCAN

Example Papers based on R: Eigenanatomy

Example Papers based on R: ASL-CBF

Three steps in an ASL imaging study.

- Normalization / segmentation
- Data inspection
- Analysis
- Visualization See github VisDemo

Resources for Building *R* Packages

Discussion + Future Work