JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

Computational Methods for Neuroimaging in R, Hemorrhagic Stroke and Neuroconductor

John Muschelli, PhD - Johns Hopkins Bloomberg School of Public Health
http://johnmuschelli.com/Penn_2017.html
@StrictlyStat
https://github.com/muschellij2

January 19, 2017

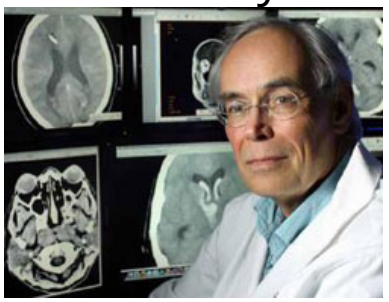

BS - 2008
ScM - 2010
Consulting 2012
PhD 2016
Assistant Scientist
The Office
I HAVE NO IDEA
WHAT I'M DOING
MMM, YEAH. OKAY
THAT'D BE GREAT.
I'M ANALYZING BRAINS!
YOU'RE STILL HERE?

The MISTIE Stroke Trial

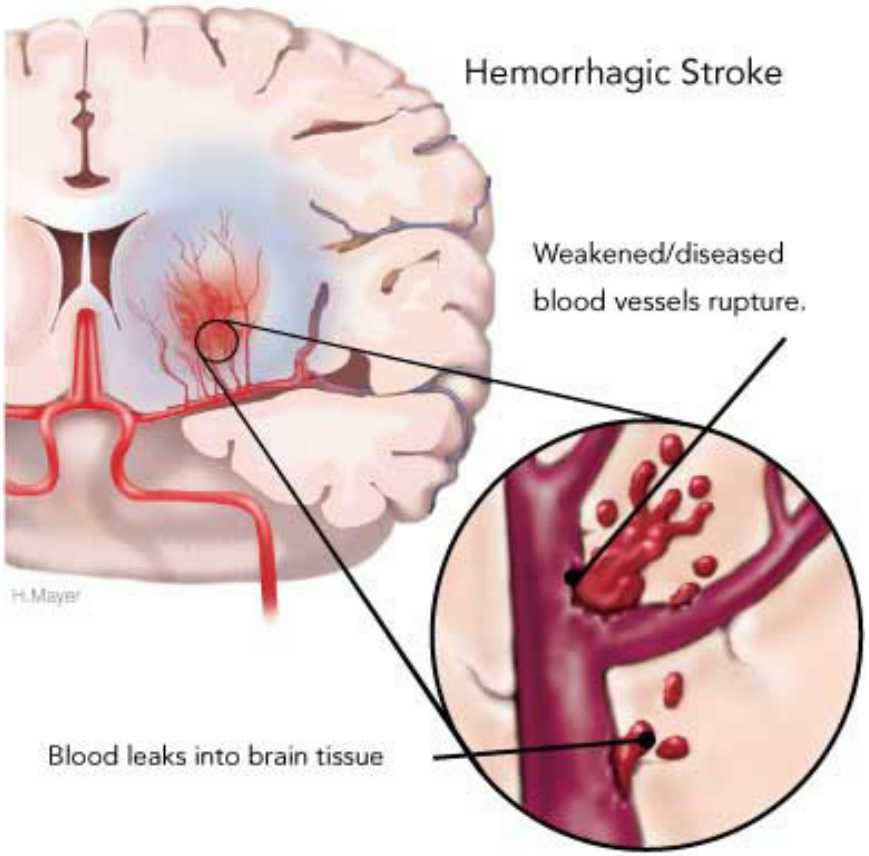
- Minimally Invasive Surgery plus r-tPA for Intracerebral Hemorrhage Evacuation (**MISTIE**)
  - Multi-center, multi-national Phase II clinical trial
  - Alteplase (donated by Genentech)
- MISTIE III

http://braininjuryoutcomes.com/mistie-about

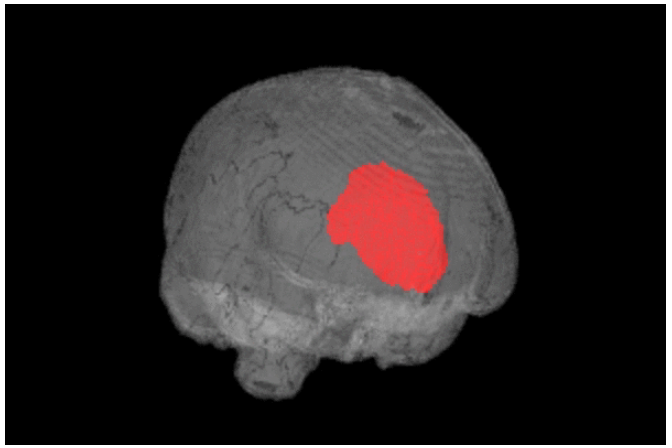
PI: Dr. Dan Hanley



Intracranial/Intracerebral Hemorrhage (ICH)



- When a blood vessel ruptures into tissue
- ≈ 13% of strokes



http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3484153/k.7675/Stroke__Hemorrhagic_stroke.htm

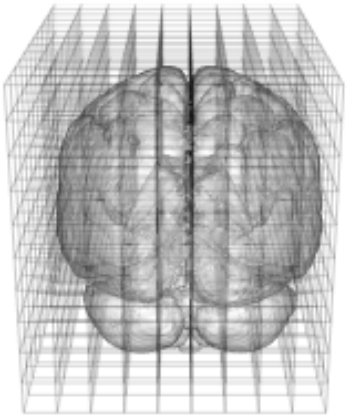
Larger Hemorrhage Volume ⇒
Worse Outcome

Goal:
Automatic Hemorrhage Volume Estimation

Images are acquired from an X-ray scanner.
x-ray goes around object and detector the other side of the object determines how many x-rays are recovered - fancy transform - Image!

Image Representation: voxels (3D pixels)

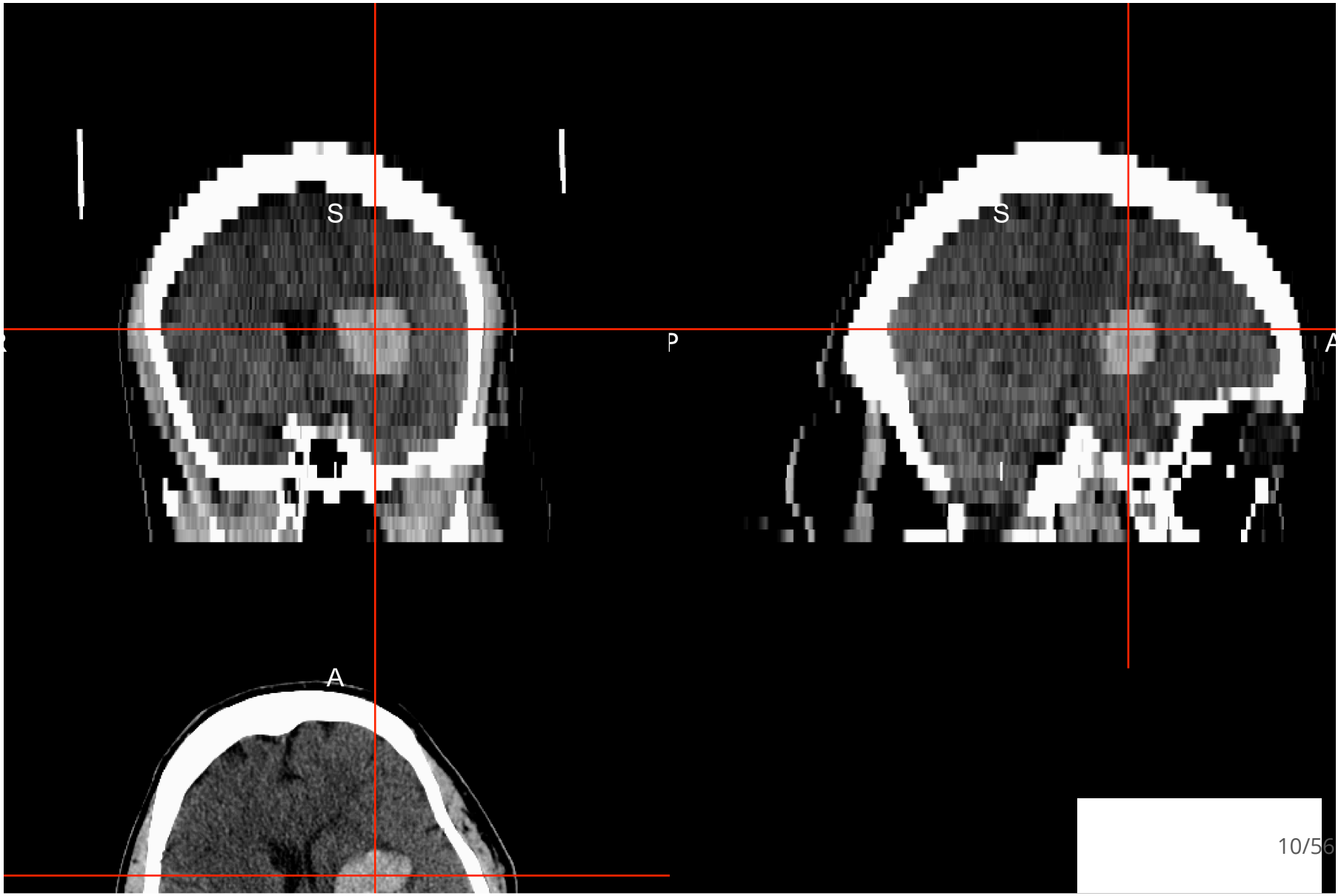
Typical CT has $512 \times 512 \times 30 \approx 7.8$ million voxels



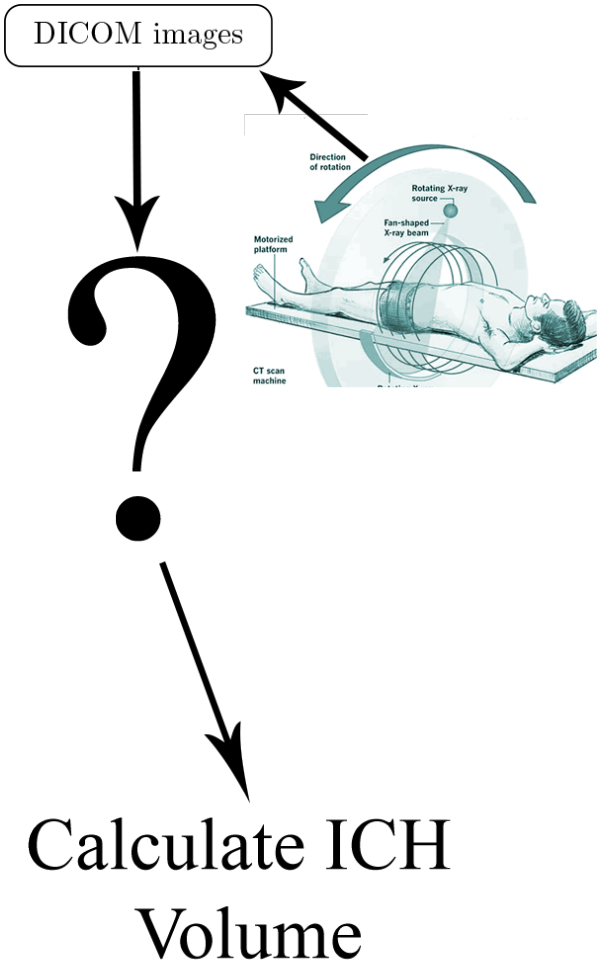
Muschelli, John, Elizabeth Sweeney, and Ciprian Crainiceanu. "brainR: Interactive 3 and 4D Images of High Resolution Neuroimage Data." R JOURNAL 6.1 (2014): 42-48.

How do we measure volume (currently)?

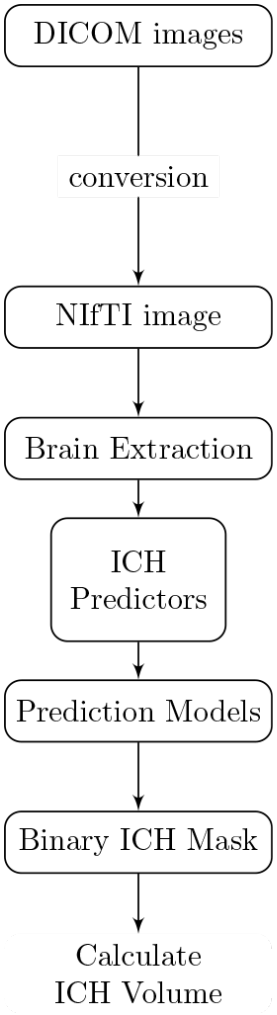
Manual Segmentation



Workflow for the Analysis

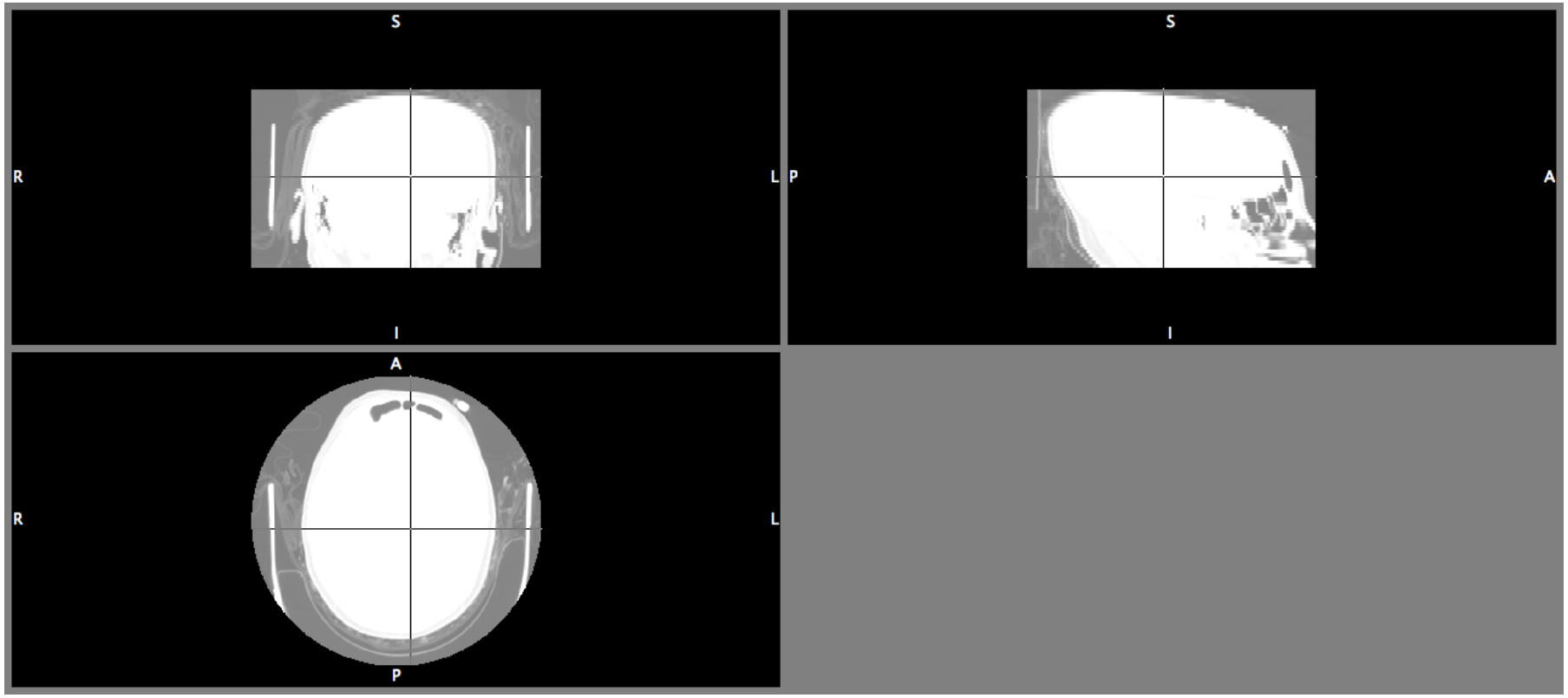


Workflow for the Analysis



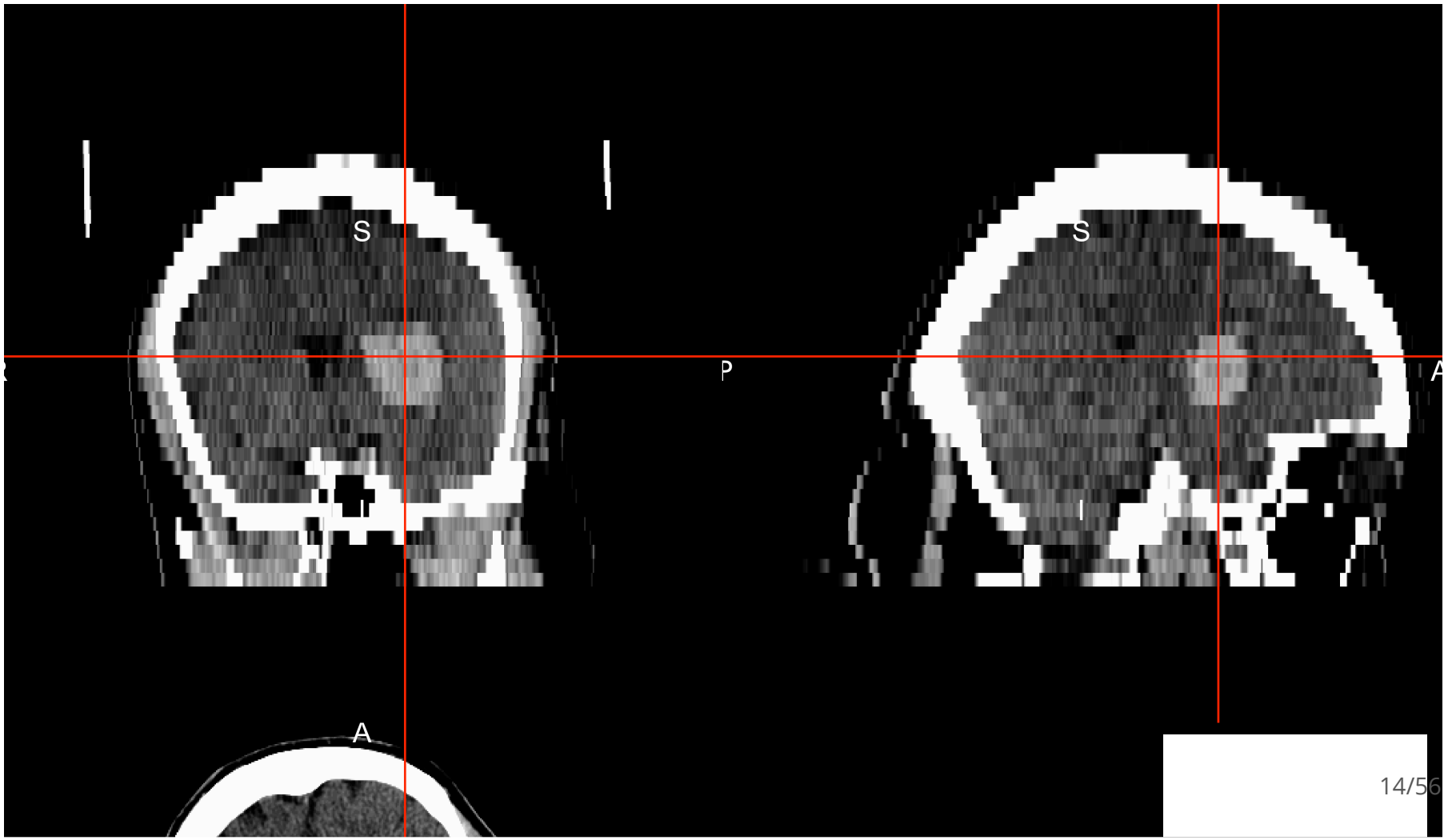
Problem: CT Scans Capture **Everything**

Also has negative values

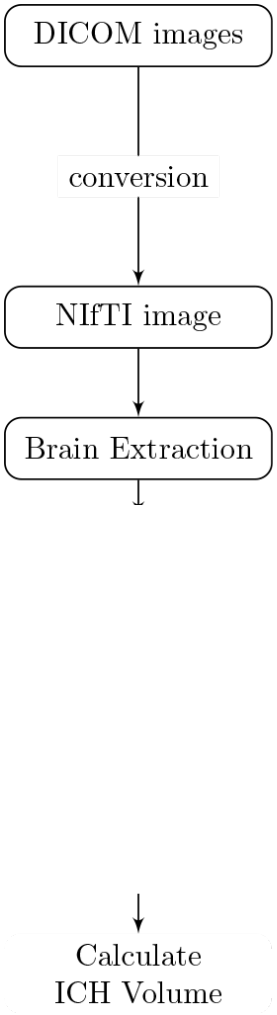


Brain Segmentation of CT Scans (uses BET)

- Muschelli, John, et al. "Validated automatic brain extraction of head CT images." NeuroImage 114 (2015): 379-385. http://bit.ly/CTBET_RCODE



Workflow for the Analysis



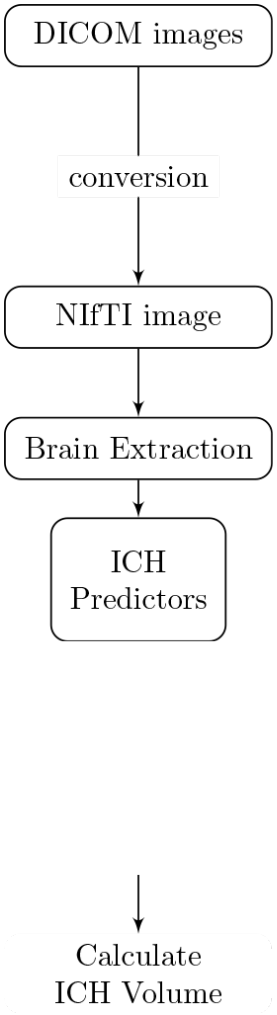
Hemorrhage Segmentation

Subject Data used: 111 scans (1 Per Patient)

	Overall
Age in Years: Mean (SD)	60.8 (11.2)
Male: N (%)	76 (68.5%)
Reader-Based Clot Location (%)	
Putamen	68 (61.3)
Lobar	33 (29.7)
Globus Pallidus	6 (5.4)
Thalamus	4 (3.6)
ICH Volume in mL: Mean (SD)	37.4 (20.1)

- Adults (inclusion criteria 18-80 years old)
- Mostly males
- Different sites, scanners, and locations in the brain

Workflow for the Analysis

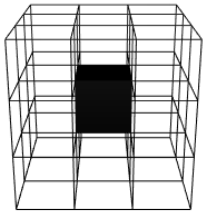


Predictors of ICH

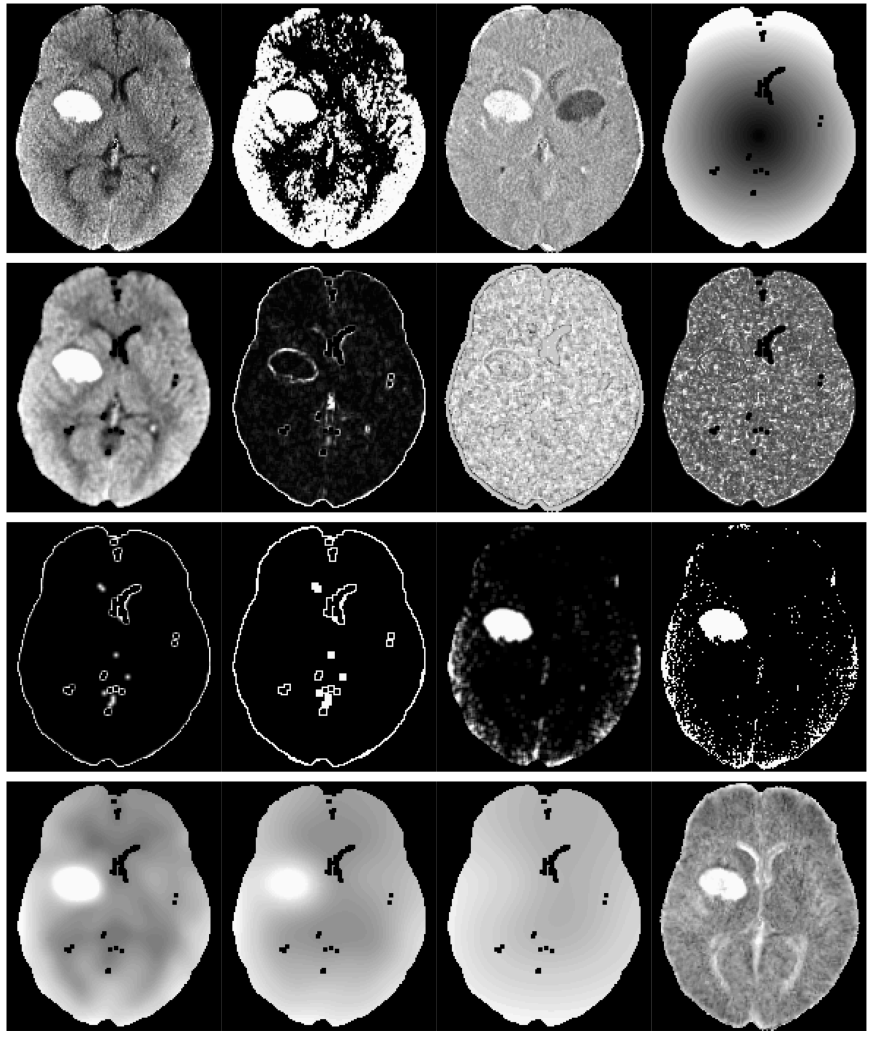
- Local "neighborhood" moments (mean, sd, skew, kurtosis)

Local Mean:

$$\bar{x}(v) = \frac{1}{27} \sum_{k}^{27} x_k(v)$$

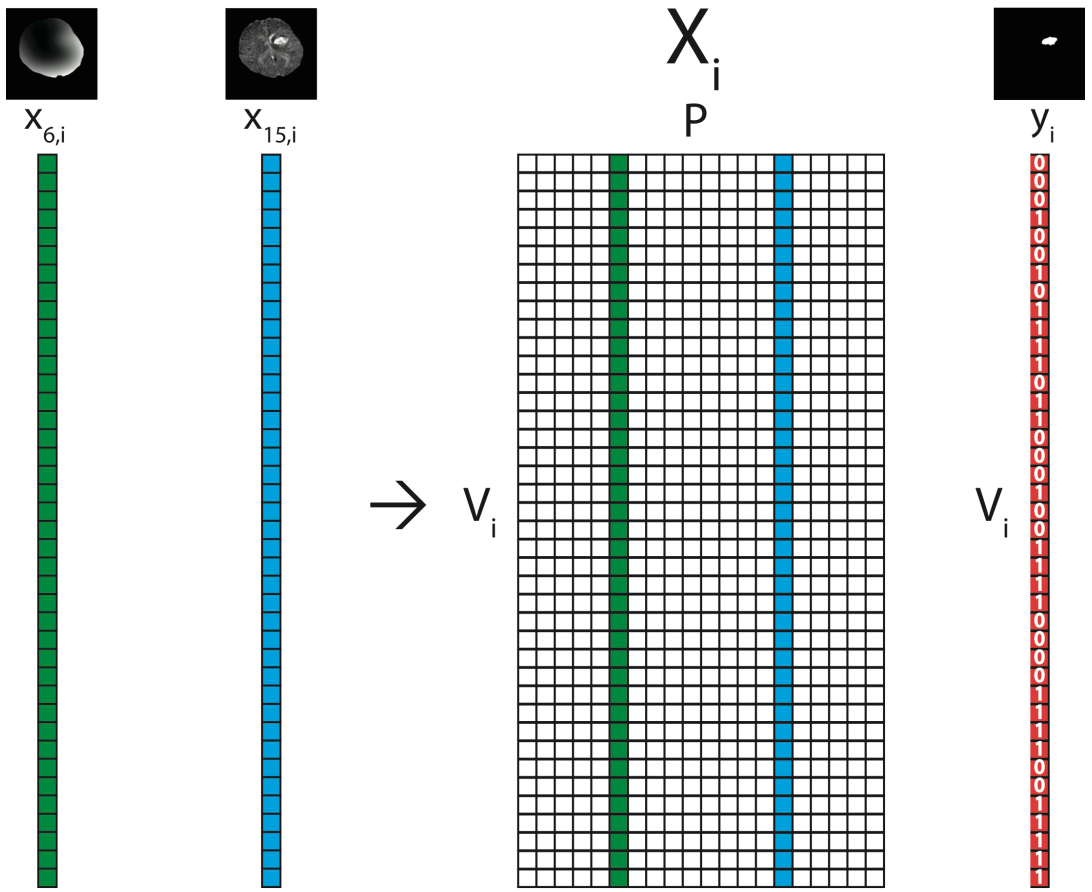


- Threshold intensity
- Gaussian Smoother (**big** neighborhood)



Data Structure for One Patient

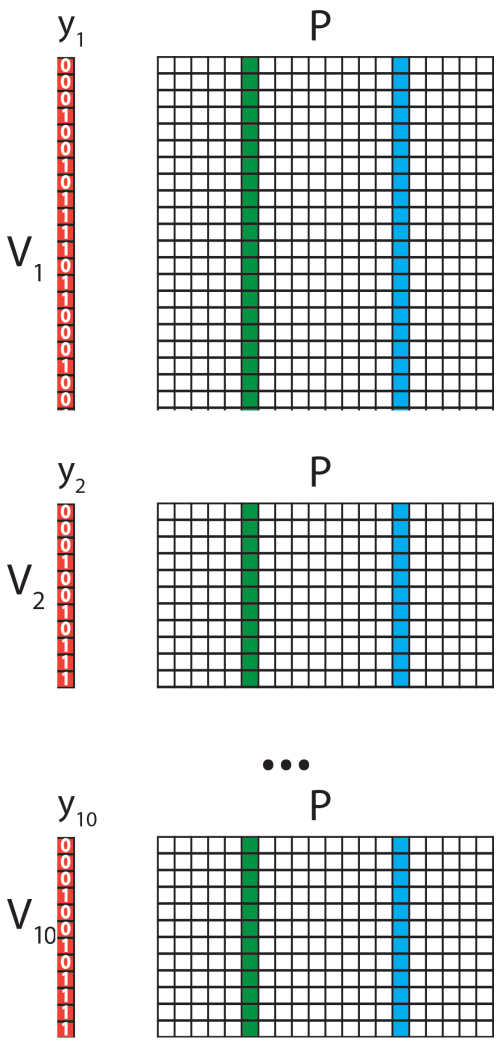
- Each subject has matrix X_i
- V_i - voxels per person
- P - number of predictors
- y_i - manual segmentation



Aggregate Data

Training Data Structure

- Stack together 10 randomly selected patients
- Train model/classifier on this design matrix



Fit Models / Classifier

Again, $y_i(v)$ is the presence / absence of ICH for voxel v from person i.

General model form:

$$P\{y_i(v) = 1\} \propto f\{X_i(v)\}$$

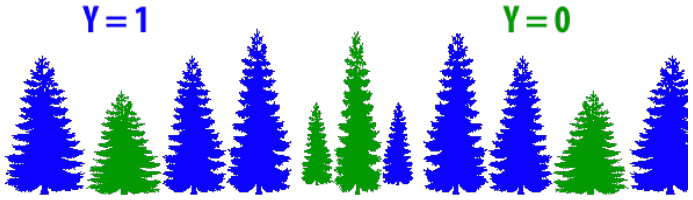
All models fit in R.

Models Fit on the Training Data

- Logistic Regression: $f(X_i(v)) = \text{expit}\left\{\beta_0 + \sum_{k=1}^{p} x_{i,k}(v)\beta_k\right\}$ (`glm` function)
- Generalized Additive Model (Hastie, et al., 1990)
  - fit using penalized thin plate splines (`mgcv` package)
- LASSO (Tibshirani, 1996; Friedman, et al., 2010) (`glmnet` package):

$$\mathcal{L}\left[Y_i(v)|\ f\{X_i(v)\}\right] \propto \beta_0 + \sum_{k=1}^{p} x_{i,k}(v)\beta_k + \lambda \sum_{k=1}^{p} |\beta_k|$$

- Random Forests (Liaw, et al., 2002; Breiman, 2001) (`randomForest` package)

$f(X_i(v)) \propto$ 

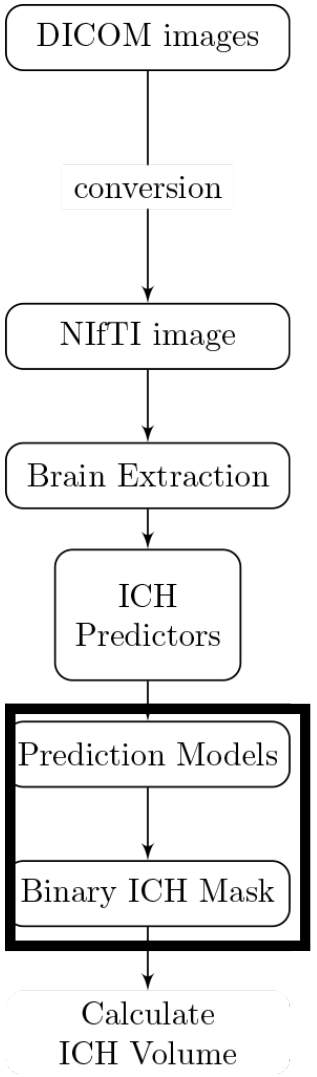
All results are on the 101 scans/patients not in the training data

- Get prediction for each voxel:
  $\hat{p}_i(v) = \hat{P}(y_i(v) = 1)$
- Threshold to get a binary value:
  $\hat{y}_i = \hat{p}_i(v) > 0.5$

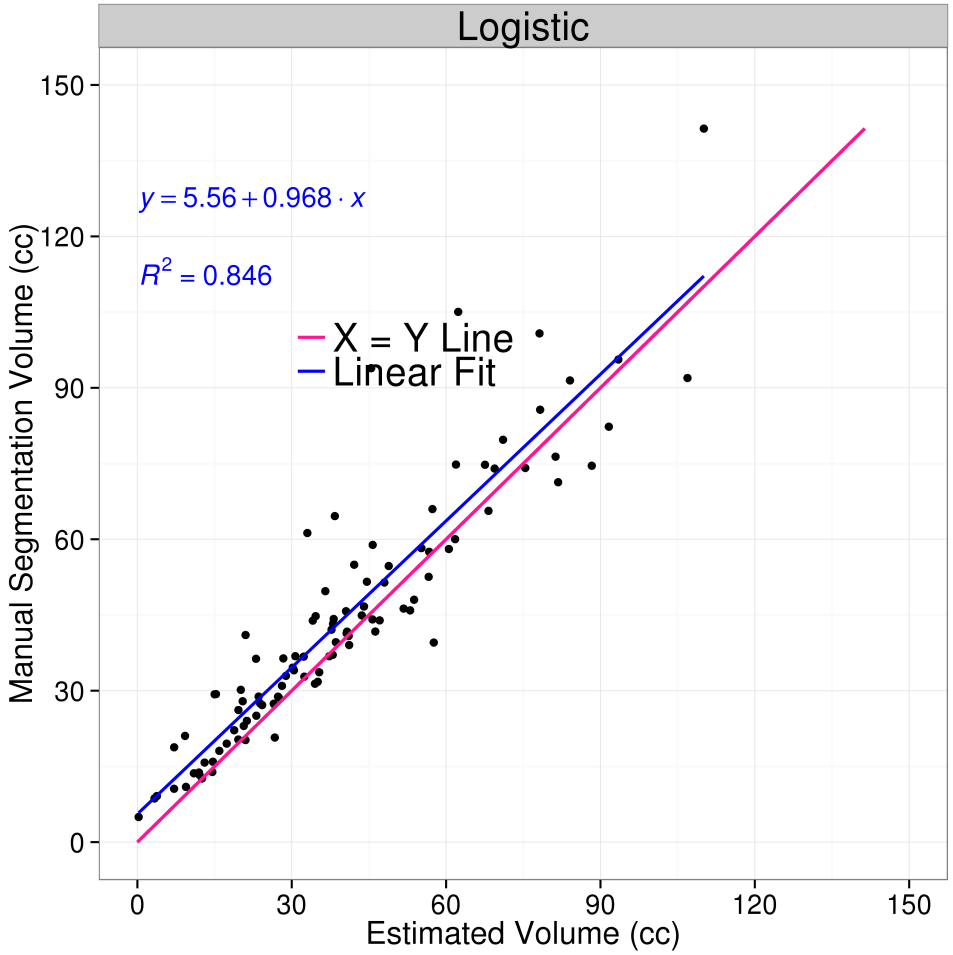
$$\text{Estimated Volume}_i = \text{cc per voxel} \times \sum_{v}^{V_i} \hat{y}_i(v)$$

$$\text{Volume}_i = \text{cc per voxel} \times \sum_{v}^{V_i} y_i(v)$$

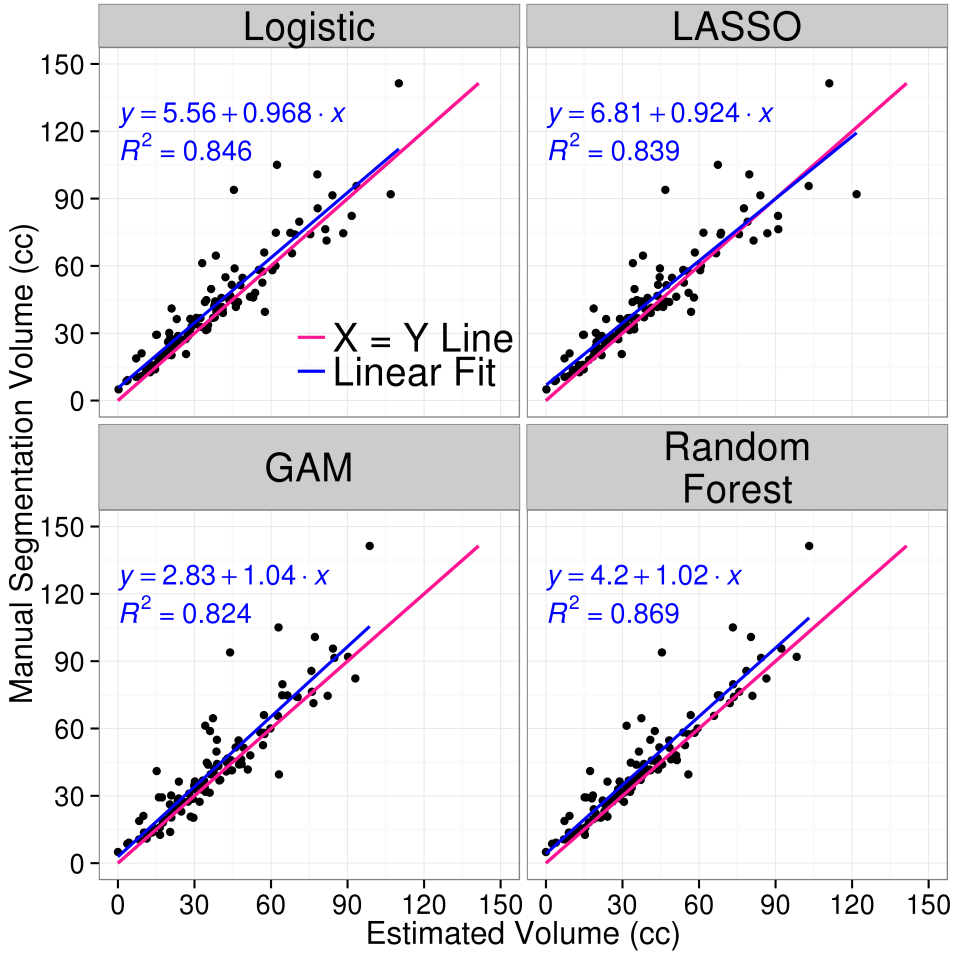
- cc = cubic centimeters
- one milliliter (mL) = 1 cc



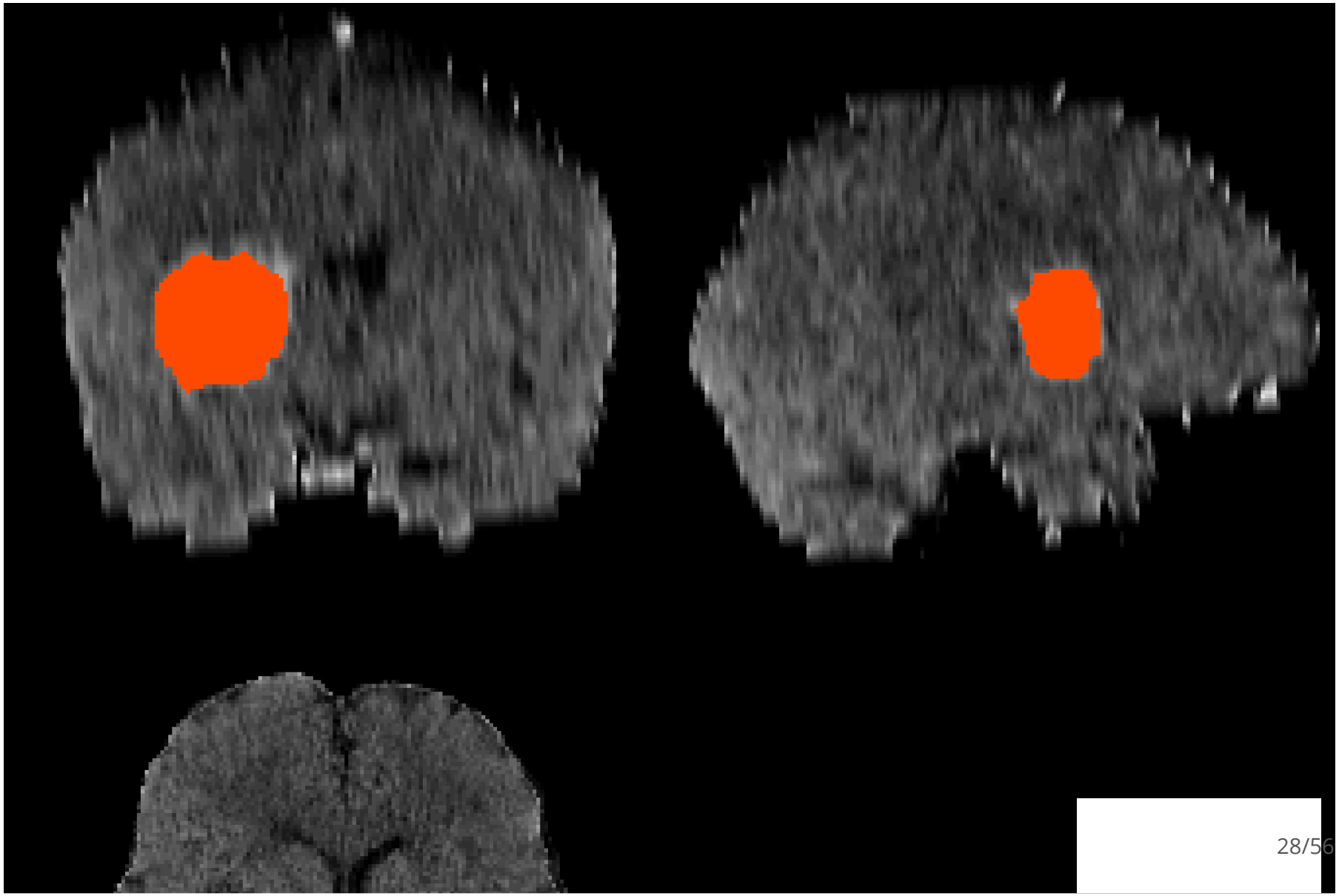
Predicted Volume Estimates True Volume Well



All models predicted volume pretty well

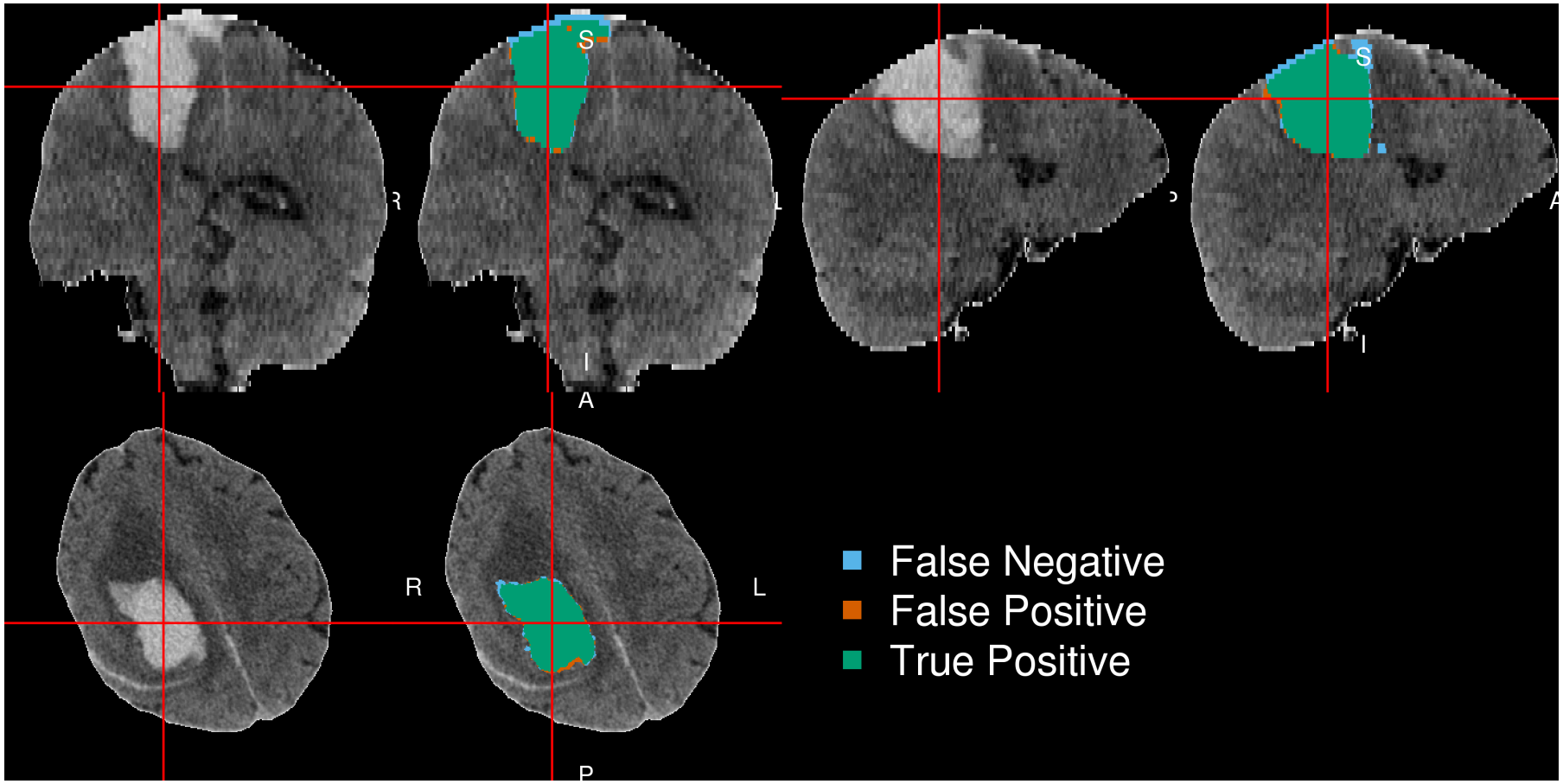


Two Segmentations with the Same Volume

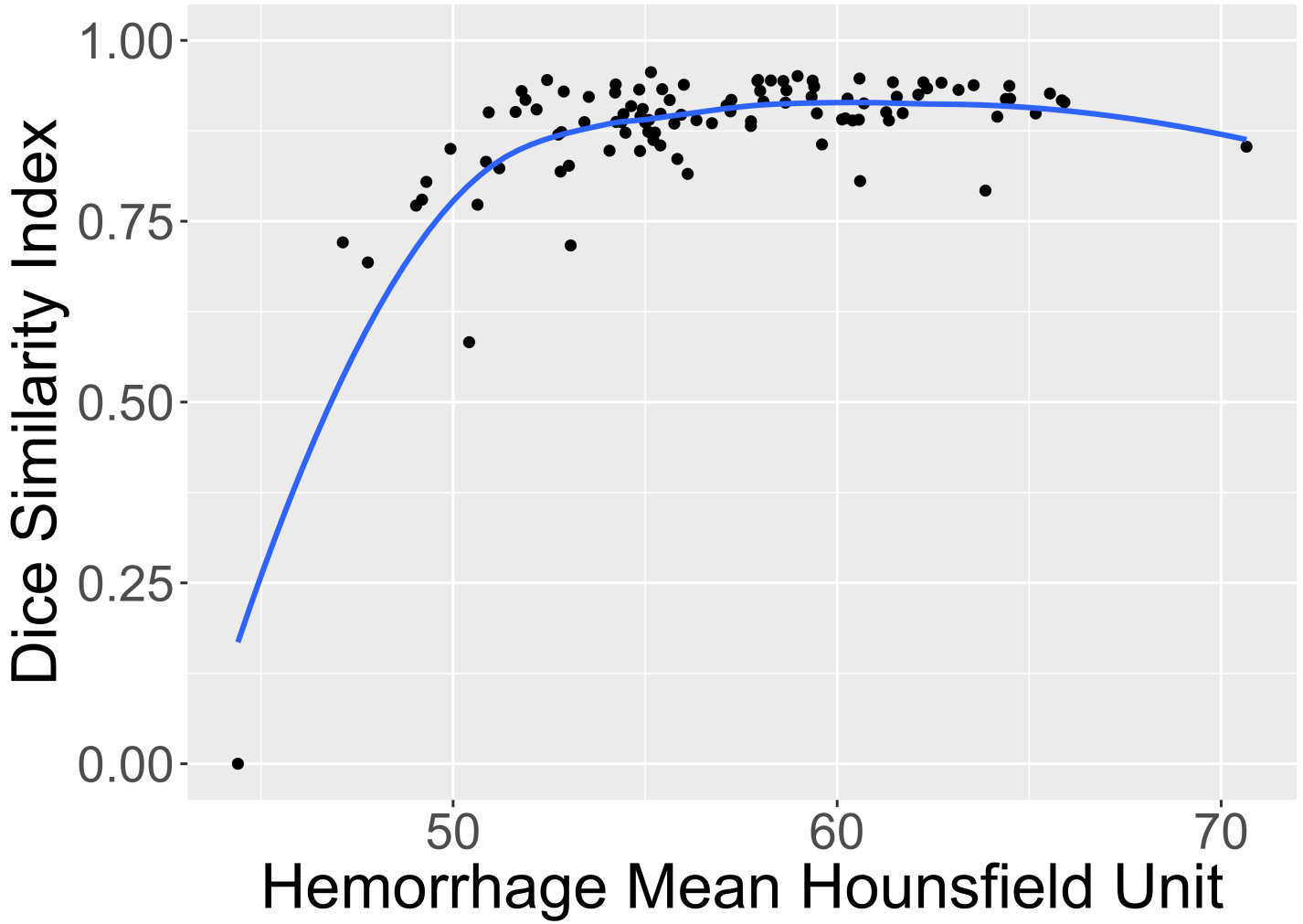


Dice Similarity Index/Overlap by Scanner

Patient with Median Overlap/Dice



Why'd that one fail?



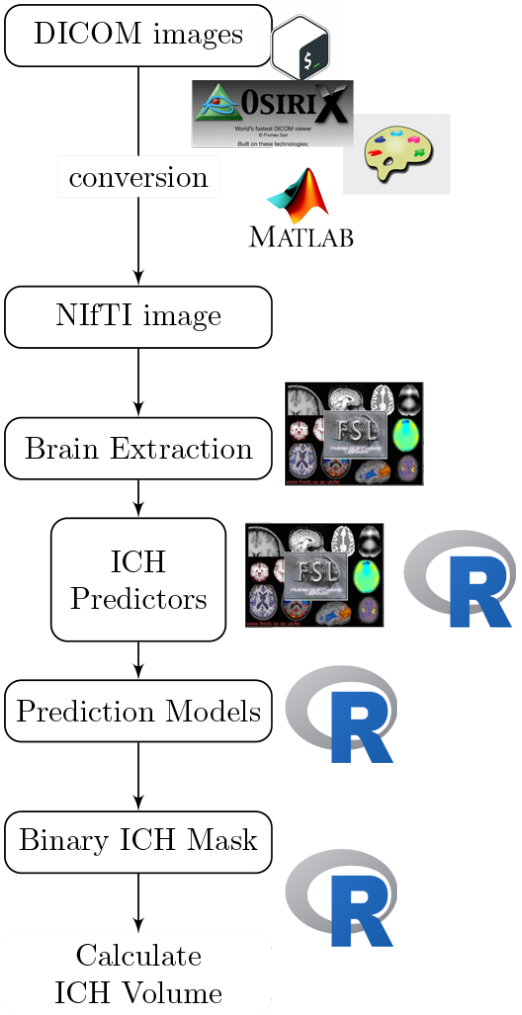
Conclusions of Stroke Analyses

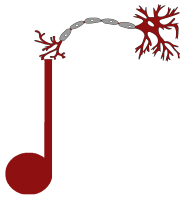
- We can segment ICH volume from CT scans
- The predictors seemed to be the "secret sauce"
  - not the algorithm
- Chose the Random Forest
  - PItcHPERFeCT: Primary Intracranial Hemorrhage Probability Estimation using Random Forests on CT
- R Package: https://github.com/muschellij2/ichseg
- Shiny Application http://johnmuschelli.com/ich_segment.html

Workflow for the Analysis

Multiple pieces of software used

- all different syntax





Neuroconductor: A Framework for Reproducible Neuroimaging Analysis in R

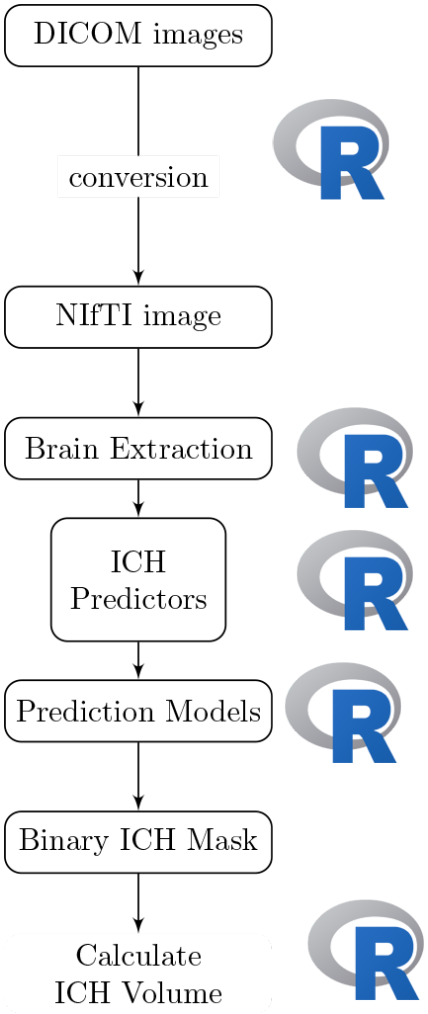
Neuroconductor Goal:

Lower the bar to entry

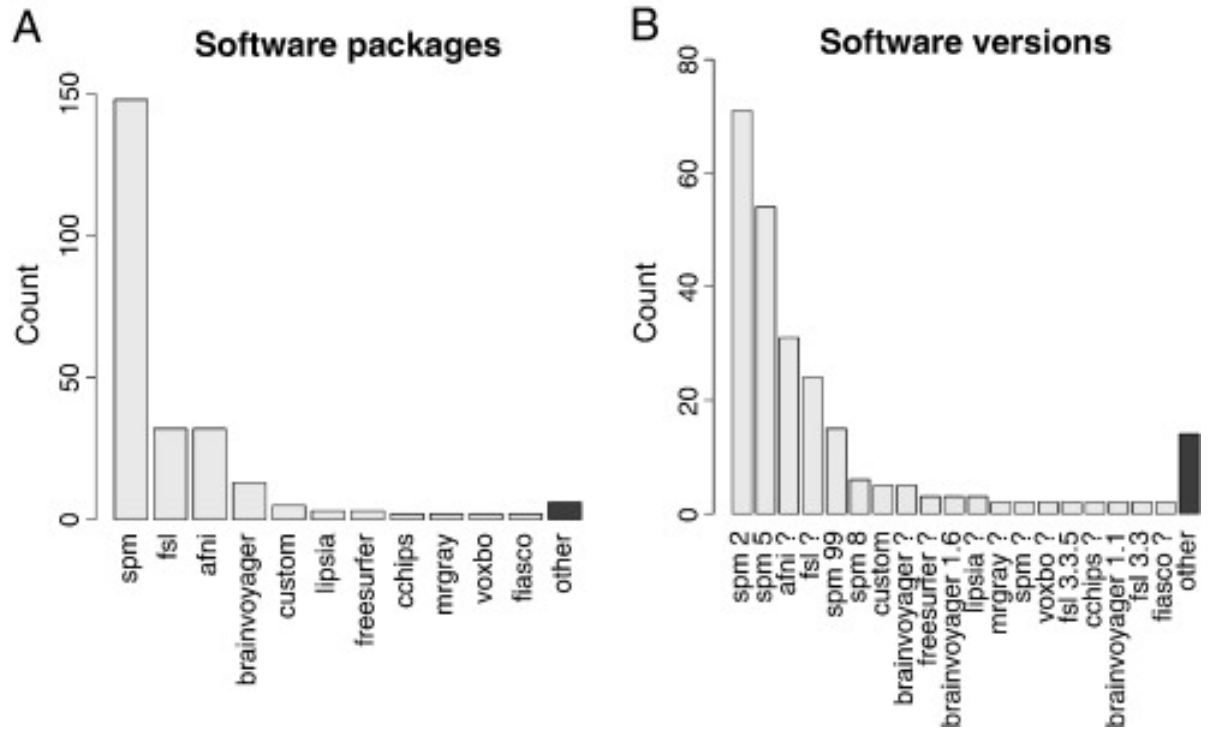
- all R code
  - pipeline tool
  - native R code

Complete pipeline

- pipeline sensitivity analyses



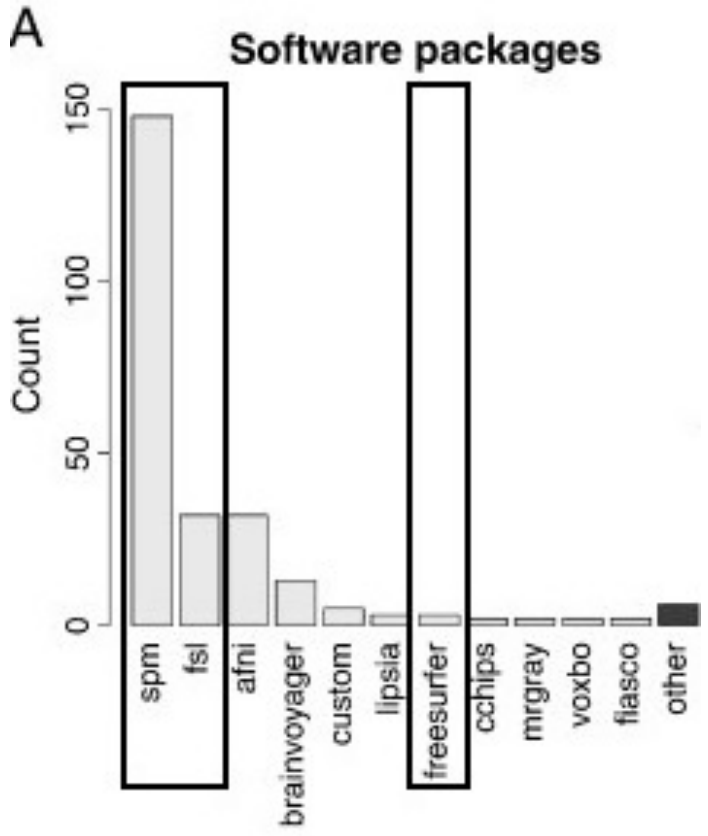
It's typical to have lots of software choices



From Carp, Joshua. "The secret lives of experiments: methods reporting in the fMRI literature." Neuroimage 63.1 (2012): 289-300.

Current Progress (my R packages)

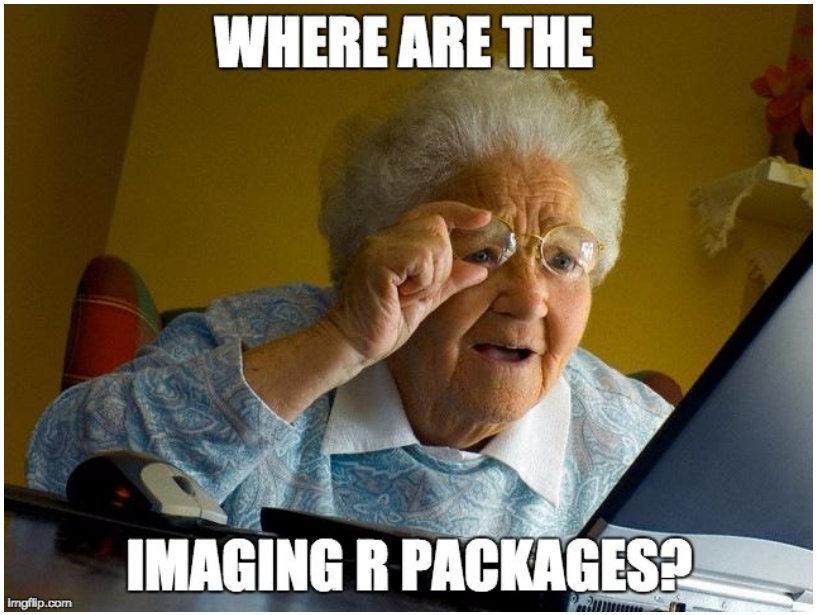
Number of downloads as of January 18, 2017 (`cranlogs` package):



Neuroconductor Goal:

Centralize the packages

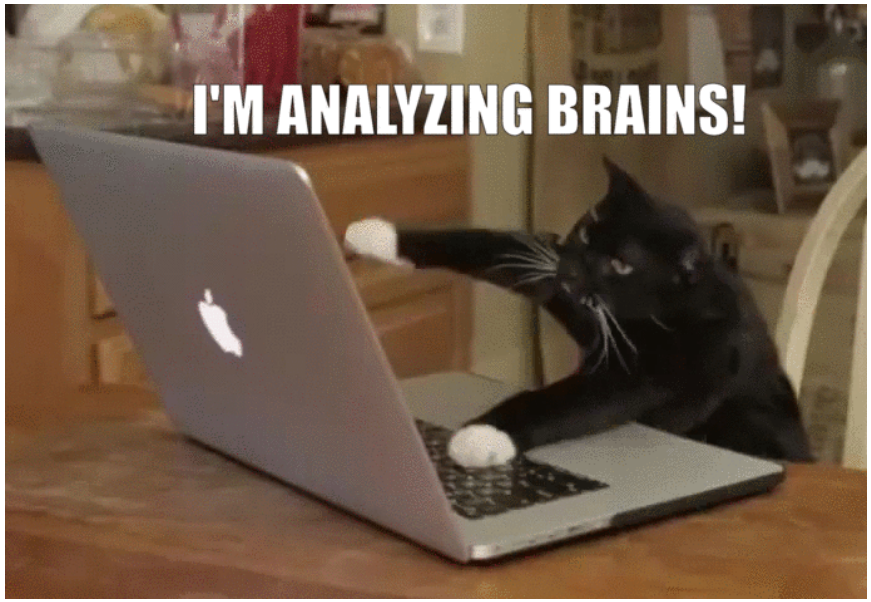
- Medical Imaging Task View
  - no tutorials
- Neuroconductor Repository



From https://imgflip.com/memegenerator/Grandma-Finds-The-Internet.

Neuroconductor Goal:

Detailed **tutorials** on how to actually perform an analysis



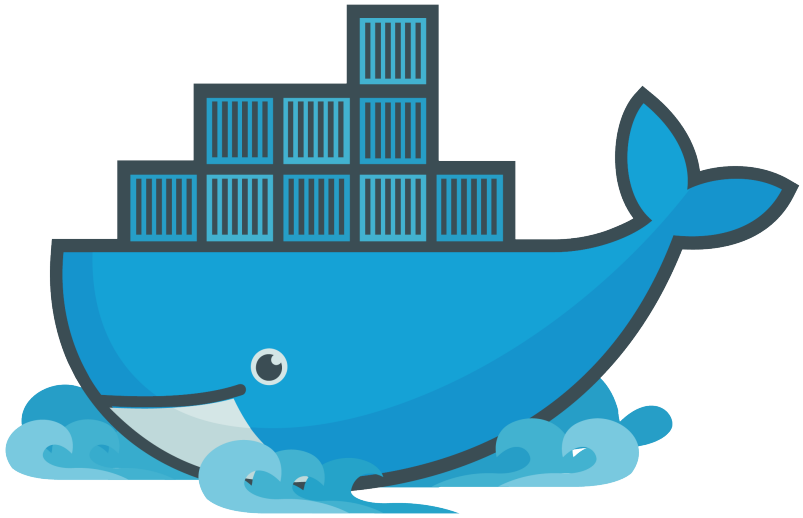
From http://i.imgur.com/0Y1xISa.gifv.

- http://johnmuschelli.com/neuroc/

Neuroconductor Goal:

Provide package checks / rules / **stability**

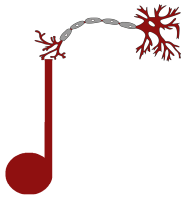
- check against other imaging software (e.g. FSL)



Benefits of Neuroconductor:

Allow neuroimaging to use all R has to offer:

- Statistics and Machine Learning
- Versioning and testing
- Reproducibile reports and analyses
- Shiny (web applications)



Neuroconductor Downsides

1. More control over the workflow = more work
2. Users need external software (versions/installation)
3. No control over external software
   - if maintainer changes something, not much recourse
4. Need the content (buy-in from the community)

Training we are providing

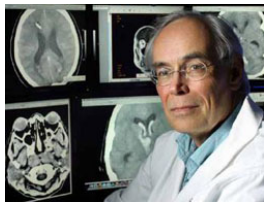
Coursera Course:
Introduction to
Neurohacking In R

https://www.coursera.org/learn/neurohacking/

Short Course: Neuroimaging analysis within R (ISBI, Melbourne, April 2017)

Statistics in Imaging (Pittsburgh, May 2017)

Thanks

Dan Hanley 

Jean-Philippe Fortin 

Ciprian Crainiceanu 

Adi Gherman 

Brian Caffo 

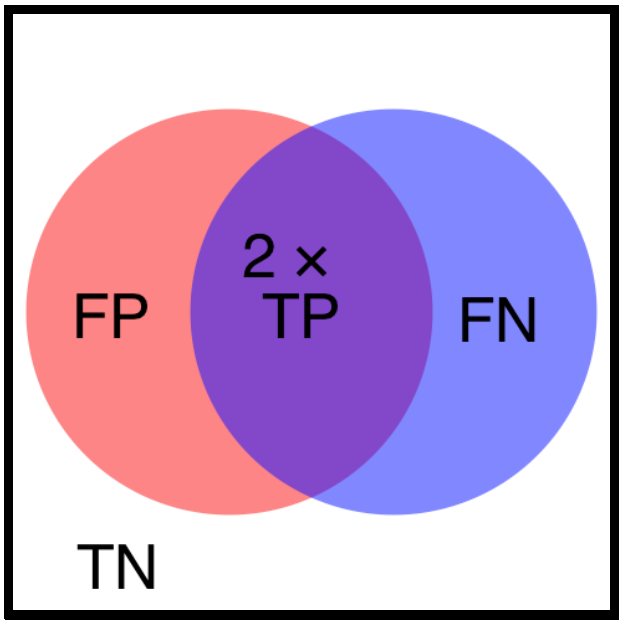
Elizabeth Sweeney 

Questions

Assessing Performance

For each manual and automated segmentation, we can calculate the following 2-by-2 table, where the cells represent number of voxels and a corresponding Venn diagram:

		Manual 0	Manual 1
PitCH	0	TN	FN
	1	FP	TP

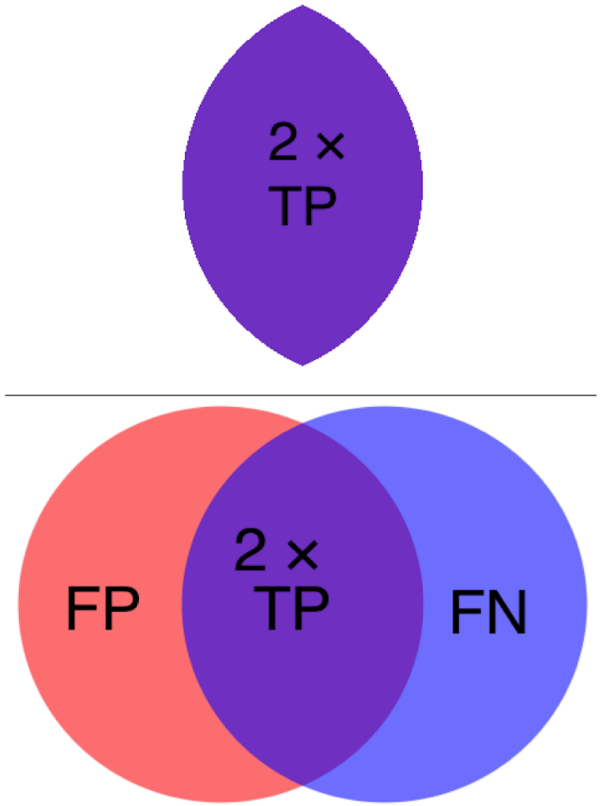


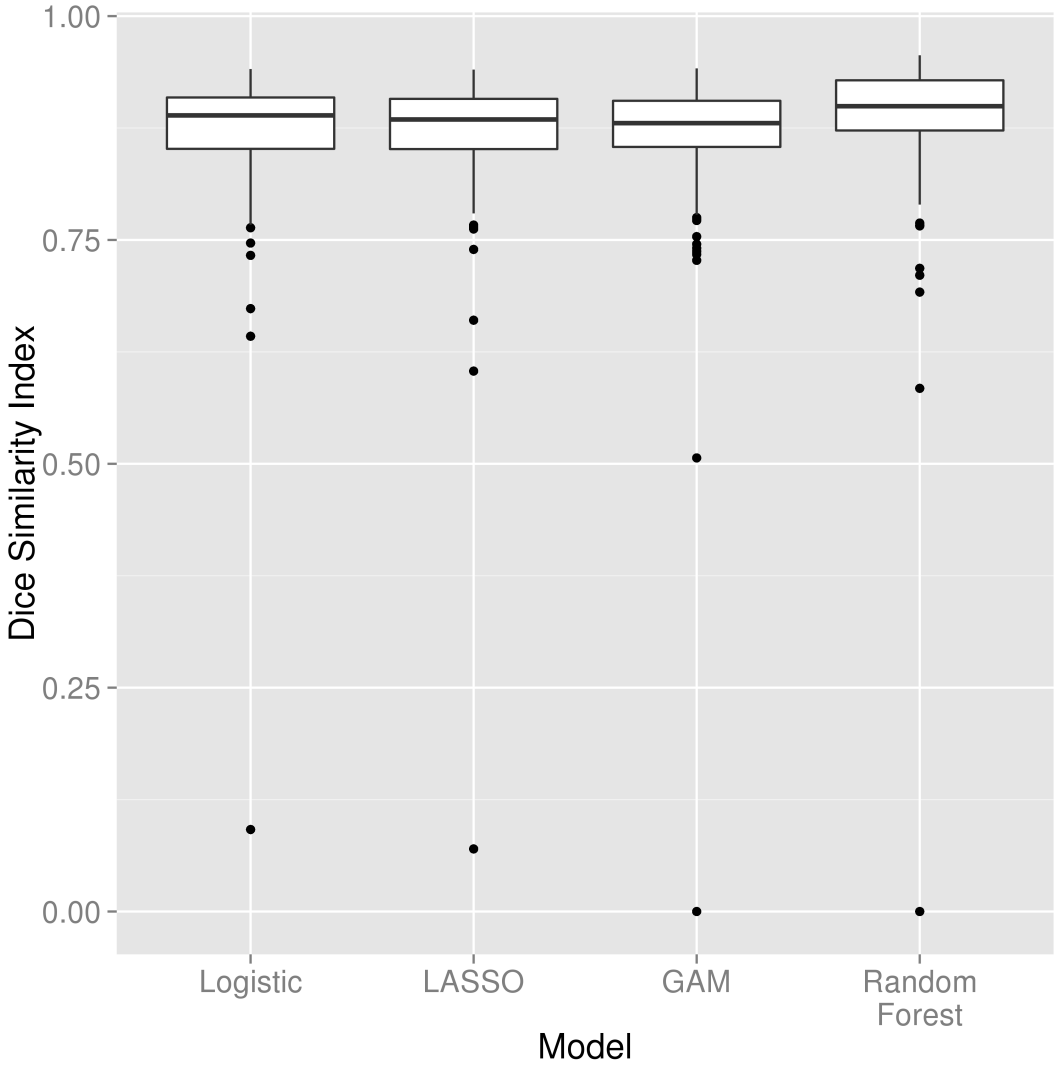
Dice Similarity

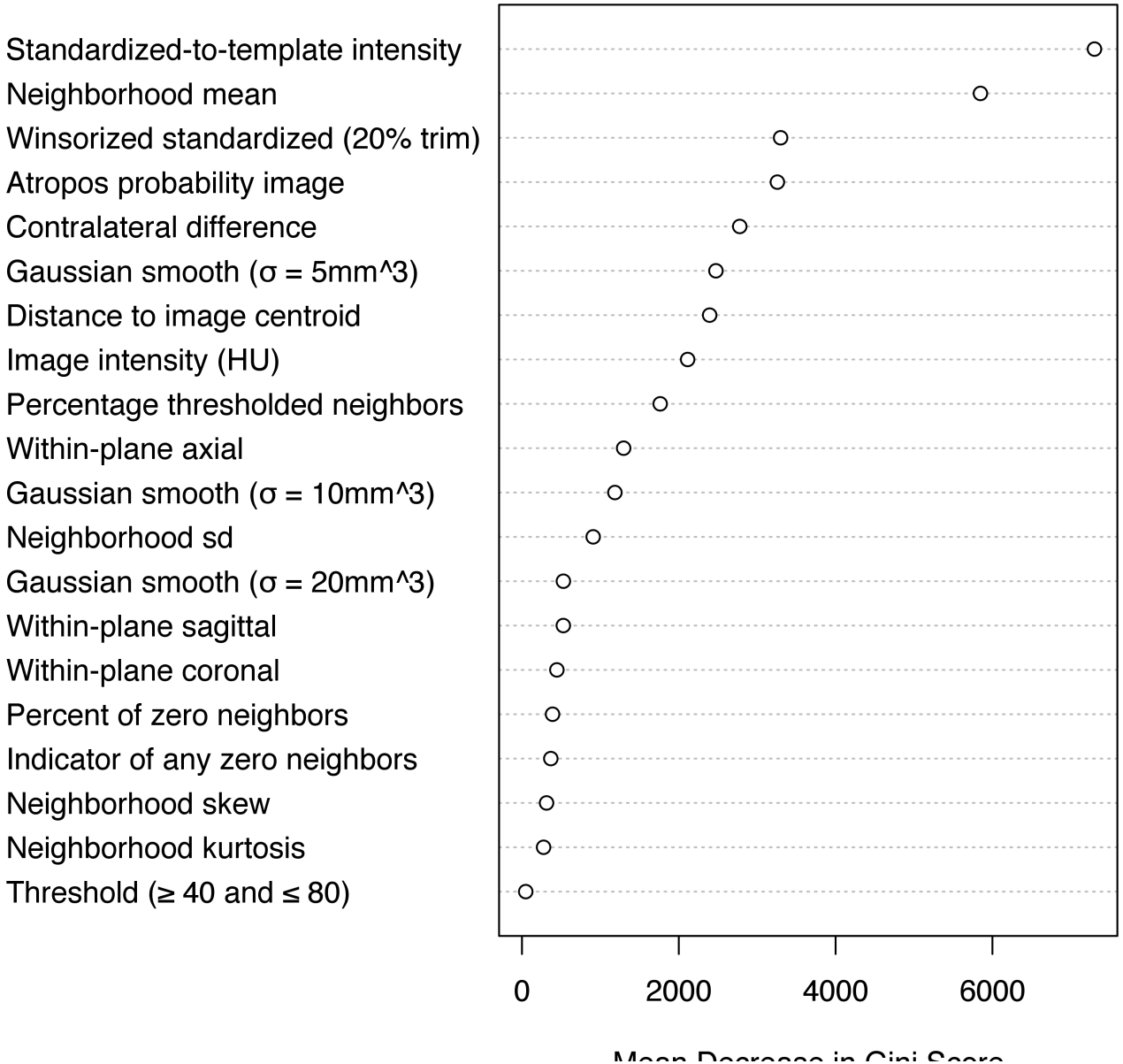
We calculate the Dice Similarity Index (DSI):

$$\frac{2 \times \#TP}{2 \times \#TP + FN + FP}$$

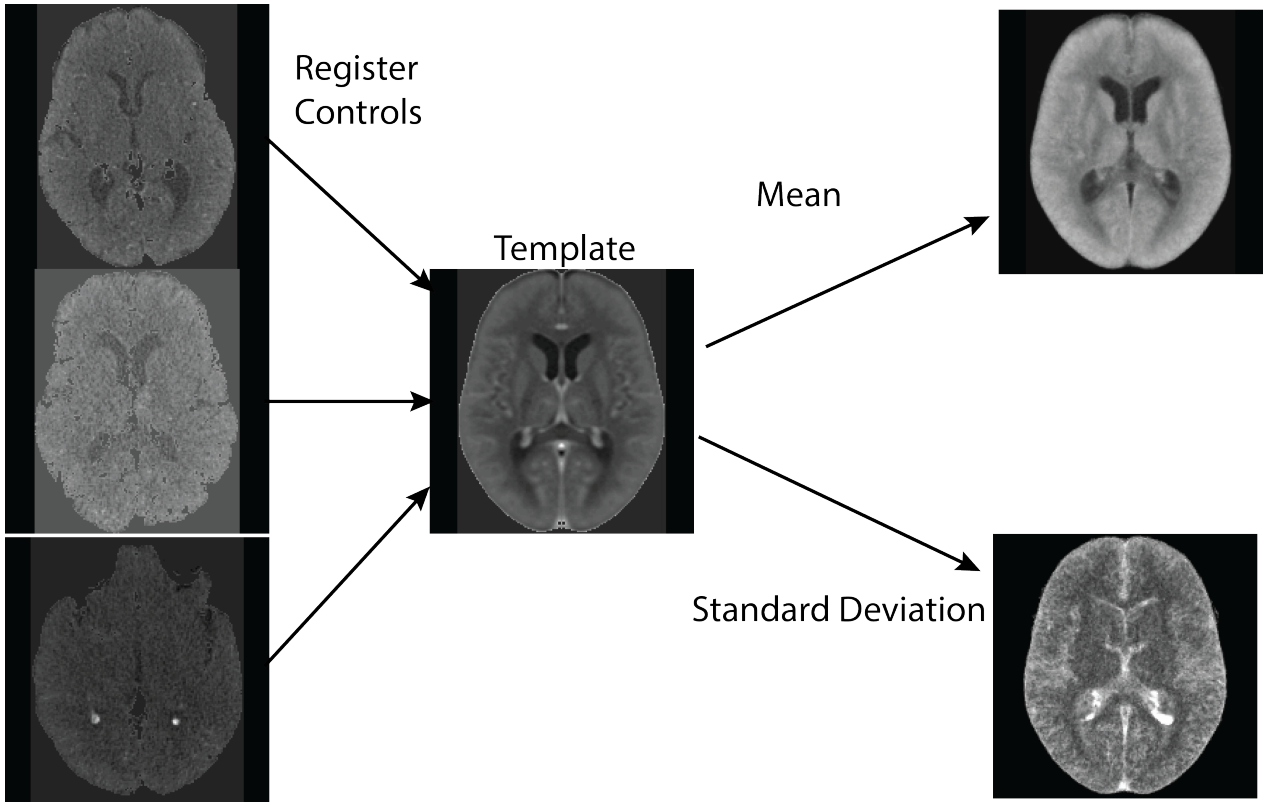
- 0 indicates no overlap
- 1 means perfect agreement

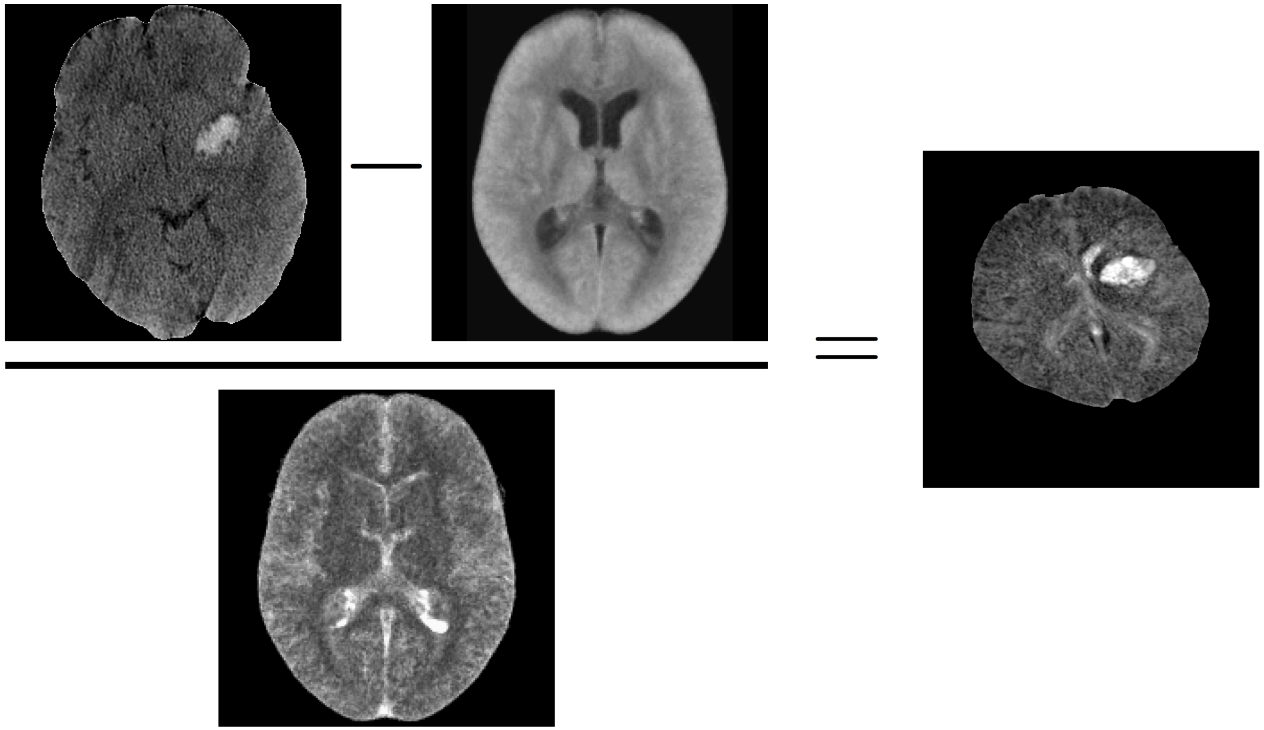



1.00
0.75
0.50
0.25
0.00
Dice Similarity Index
Logistic
LASSO
GAM
Random Forest
Model


Standardized-to-template intensity
Neighborhood mean
Winsorized standardized (20% trim)
Atropos probability image
Contralateral difference
Gaussian smooth (σ = 5mm^3)
Distance to image centroid
Image intensity (HU)
Percentage thresholded neighbors
Within-plane axial
Gaussian smooth (σ = 10mm^3)
Neighborhood sd
Gaussian smooth (σ = 20mm^3)
Within-plane sagittal
Within-plane coronal
Percent of zero neighbors
Indicator of any zero neighbors
Neighborhood skew
Neighborhood kurtosis
Threshold (≥ 40 and ≤ 80)
0
2000
4000
6000
Mean Decrease in Gini Score

Mean Decrease in Gini Score





Under Development R Packages

1. nitrc - download data from the **NITRC repository**
2. MNITemplate* - data of a population-level "template" image
3. EveTemplate* - data of a different template image
4. kirby21 - data package with 2 subjects, 2 visits with multimodal imaging
5. rcamino - interface to analyze DTI data
6. msseg - MS lesion segmentation
7. extrantsr - pipelines for structural imaging analysis

Not started yet

1. hcp - interface with Human Connectome Project
2. afnir - R port of AFNI software (No. 2 on the chart)

* - working with Jean-Philippe Fortin on these

The knitcitations, knitr, pander, plyr, RefManageR, rmarkdown, and tableone packages were used to create this presentation in RStudio.

```
setting  value
version  R version 3.3.2 (2016-10-31)
system   x86_64, darwin13.4.0
ui       X11
language (EN)
collate  en_US.UTF-8
tz       America/New_York
date     2017-01-18
```

```
package       * version     date
backports       1.0.4       2016-10-24
bibtex          0.4.0       2014-12-31
bitops          1.0-6       2013-08-17
class           7.3-14      2015-08-30
devtools        1.12.0.9000 2016-12-08
digest          0.6.11      2017-01-03
DT              0.2         2016-08-09
e1071           1.6-7       2015-08-05
evaluate        0.10        2016-10-11
htmltools       0.3.6       2016-12-08
htmlwidgets     0.8         2016-11-09
```

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httr            1.2.1.9000  2016-11-21
jsonlite        1.2         2016-12-31
knitcitations * 1.0.7.1     2016-02-01
knitr         * 1.15.1      2016-11-22
```


Ischemic Stroke

- Ischemic stroke - clot blocks oxygen/nutrients
- Tissue dies

Neuroconductor Goal:

From https://memegenerator.net/Everywhere-Toy-Story.

R **Data** packages for testing

- getting data is a common problem
- developers can test packages
- Kirby21 Data:
  - https://github.com/muschellij2/kirby21.t1
  - https://github.com/muschellij2/kirby21.t2
  - https://github.com/muschellij2/kirby21.flair
  - https://github.com/muschellij2/kirby21.fmri
  - https://github.com/muschellij2/kirby21.dti

Not Ischemic Stroke

- Ischemic stroke - clot blocks oxygen/nutrients
- Tissue dies