Statistical Modeling for Imaging Studies

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Acknowledgements

Thanks to Nancy Obuchowski and Jeffrey Blume for prior versions of this presentation.

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Goals

- Identify studies when modeling is needed
- Distinguish different types of models
- Interpret models appropriately

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Outline

- When does a study need a model?
- Model basics
- 3 basic types of models:
  - Linear regression
  - Logistic regression
  - Time-to-event analysis

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What is a statistical model?

- Mathematical description of patterns that are of scientific interest.
- The description often consists of two parts:
  - Systematic effects (Pattern)
  - Random error (Noise)
- Statistical models seek to separate systematic effects from noise.

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When does a study need a model?

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- You want to compare two groups of patients and patients were not randomized

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- You want to predict outcome from baseline characteristics

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When does a study need a model?

- You want to compare two groups and patients were not randomized
- You want to test if an outcome differs for patients with different characteristics
- You want to predict outcome from baseline characteristics
- You want to reduce noise

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Example 1

You want to compare two groups of patients and patients were not randomized

- Soccer players known risk for concussions
- Only sport where players head the ball
- Women worse clinical outcomes after concussion

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Example 1

- Study compares Diffusion-tensor imaging (DTI) white matter microstructural alteration in women and men soccer players.
- Use a model to adjust for player age

Rubin et al. *Radiology* 289: 478-486, 2018.

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Example 2

You want to test if an outcome (e.g. sensitivity) differs based on disease characteristics

- Study of CT colonoscopy sensitivity
- Sensitivity of CT may vary based on polyp size, location in colon

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Example 2

- You could stratify by size and location.

	SIZE	
LOCATION	6-9mm	10+mm
rectum	10/20=50%	10/14=71%
cecum	2/7=29%	7/9=78%

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Example 2

- When we stratify, nothing is statistically significant...

	6-9mm	10+mm	p-value
rectum	10/20	10/14	0.212
cecum	2/7	7/9	0.126
p-value	0.408	1.0	

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Example 2

- Stratified analysis has little power…
- Build a model to estimate sensitivity based on characteristics of all 50 polyps

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Example 3

You want to predict outcome from baseline characteristics

- Patients with liver cirrhosis who get a TIPS (Transjugular intrahepatic portosystemic shunt).
- Predict how long until the patient fails (e.g. heart failure, encephalopathy, death) based on type of shunt and pre-TIPS pressures

Can't do stratified analysis-pressures contin.

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Example 3

Right atrial pressure before TIPS	Type of Shunt	# days until failure
6	Naked	70
6	Covered	120
4	Covered	110
5	Covered	Moved on day 50
4	Naked	20
19	Covered	100
11	Naked	80
2	Naked	30
3	Covered	Study ended on day 10 for this patient

- Data on 9 patients
- Staggered entry into study
- Two **censored observations**

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Example 3

- We will build a model to predict the risk of failure over time
- Type of shunts and atrial pressure used to predict
- Must deal with censored observations:
  - Can't omit them … lose statistical power
  - Can't assume failed … introduces bias

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Modeling Basics

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Three parts to every model

Independent Variable(s)

predictors or variables you need to adjust for

Mathematical Function

linear, logistic, time-to-event

Dependent variable

outcome variable

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How do I know which kind of model to use (linear, logistic, time-to-event)??

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The mathematical function depends on the type of outcome variable

Outcome	Type	Function
Brain volume	continuous	linear
CT sensitivity	binary	logistic
Time until TIPS failure	Continuous but there are censored observations	time-to-event

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Types of Models with Examples

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Linear Regression

- We want to compare white matter microstructural alteration for male and female soccer players.
- Age is a predictor of white matter microstructural alteration and may differ between the two groups.

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Unadjusted analysis with t-test

- Use t-test to compare mean volumes between male and female soccer players.

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Unadjusted Model

A t-test is a simple model !

Volume = Mean + Effect_{sex} + error

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Linear Regression

Volume = Mean + Effect_{sex} + error

$Y_i = B_0 + B_1 X_i + \varepsilon_i$

$X_i = 1$ (female) and $X_i = 0$ (male)

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A Better Model

Volume = Mean + Effect_{sex} + Effect_{Age} + error

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A Better Model

Volume = Mean + Effect_{sex} + Effect_{Age} + error

$$Y_i = B_0 + B_1 X_i + B_2 Z_i + \varepsilon_i$$

We are controlling for age by putting an effect for age in the model.

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A Better Model

Volume = Mean + Effect_{sex} + Effect_{Age} + error

$$Y_i = B_o + B_1 X_i + B_2 Z_i + \varepsilon_i$$

After controlling for age, does sex predict brain volume?

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A Better Model

Volume = Mean + Effect_{sex} + Effect_{Age} + error

$$Y_i = B_o + B_1 X_i + B_2 Z_i + \varepsilon_i$$

We test if B_1 is significantly different from zero. Here, p-value < 0.05.

Note: B_2 is also significantly different from zero

- "Women are more sensitive to repetitive subconcussive head impacts at the level of the brain microsctructure."

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Logistic Regression

- We want to see if sensitivity of CT differs based on size and location of polyps.
- A stratified analysis had little power.

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Logistic Regression

$$\log \{Pr(TP) / (1-Pr(TP))\} = Mean + Effect_{location} + Effect_{Size}$$

where Pr(TP) is the Probability of a True Positive

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Example 2

- We estimate B_1 (location) & B_2 (size). Then calculate odds ratios. Odds ratio of 1 means no effect.

Predictor	Odds ratio	P-value
Location	1.4	0.618
Size	3.7	0.035

- Relative to small lesions, the odds of a TP vs FN is 3.7 times better for CT.

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Time-to-Event Analysis

- We want to model time until failure of TIPS
- Can't use a linear model because of censored observations
- For each interval of time, calculate
  - conditional probability of surviving

    # pts surviving / # pts at risk
  - calculate cumulative survival probability

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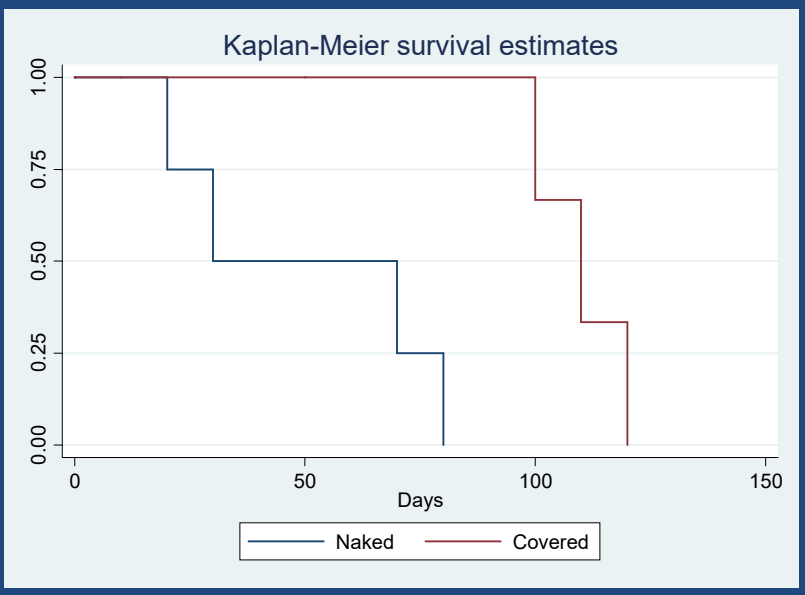

Median survival: Covered 110 days; Naked 30 days

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Cox Proportional Hazards Model

- A model to describe survival as a function of predictors, like stent type and atrial pressure
- It takes into account censored observations
- It can handle time-dependent predictors. For example, atrial pressure may vary over time.

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The Cox Model

Hazard(*t*) = Underlying Hazard(t) X function(predictors)

The Hazard at time *t* = risk of failing at *t*

The Underlying Hazard at time *t* describes how the hazard changes over time irrespective of the predictors

function(predictors) explains how the predictors change the underlying hazard.

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Example 3

Predictor	Hazard Ratio (95% CI)	P-value
Naked stent	1.91 (1.61 – 2.21)	0.038
Atrial pressure	1.05 (0.85 – 1.25)	0.88

- Hazard ratio is the ratio of two hazard rates
- Atrial pressure doesn't predict failure because hazard ratio is near 1.
- The hazard of failing with naked shunt is about twice the hazard of failing with covered shunt.

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Hazard Ratios

- The hazard ratio tells us the chance of failing with a naked stent compared with a covered stent, but it doesn't convey how much longer a patient will survive
- Hazard ratios convey information on risk of failing in the next time period
- Survival curves convey information on magnitude of benefit.

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Prediction Models

- Prediction models are often designed to be very flexible in their mathematical form
- They do not try to compactly mimic the underlying natural process
- Their goal is to provide a good guess on the outcome for the given inputs
- Cross-validation is essential

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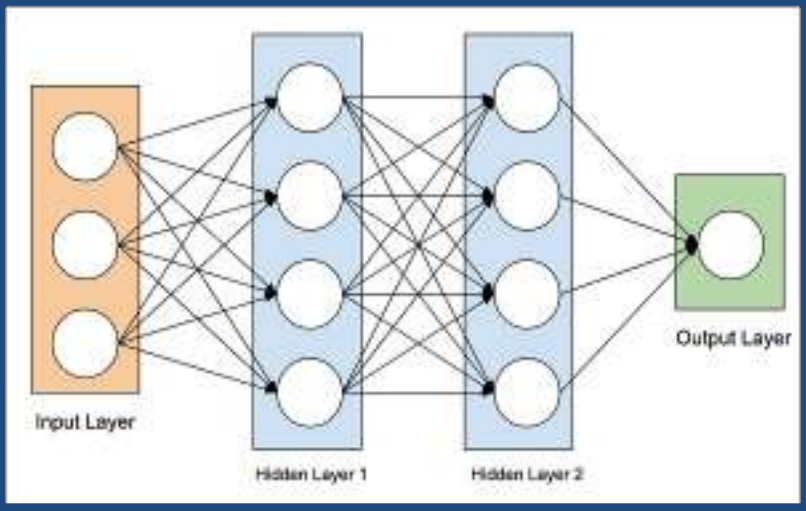
Neural Nets & Deep Learning



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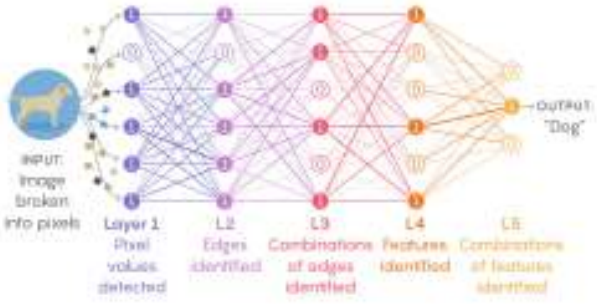
Learning From Experience

Deep neural networks learn by adjusting the strengths of their connections to better convey input signals through multiple layers to neurons associated with the right general concepts.



When data is fed into a network, each artificial neuron that fires (labeled "1") transmits signals to certain neurons in the next layer, which are likely to fire if multiple signals are received. The process filters out noise and retains only the most relevant features.

https://www.quantamagazine.org/new-theory-cracks-open-the-black-box-of-deep-learning-20170921/

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Summary

- Regression models are useful
- Three parts of model:
  - independent variables (variables adjust for)
  - mathematical function
  - dependent variable (outcome variable)
- Mathematical function depends on type of outcome variable
- Interpret regression results appropriately

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