Connecting the Dots from Image Analysis to Health Outcomes

Alexandria Jensen, MS

UC Denver Anschutz Medical Campus - Department of Biostatistics and Informatics

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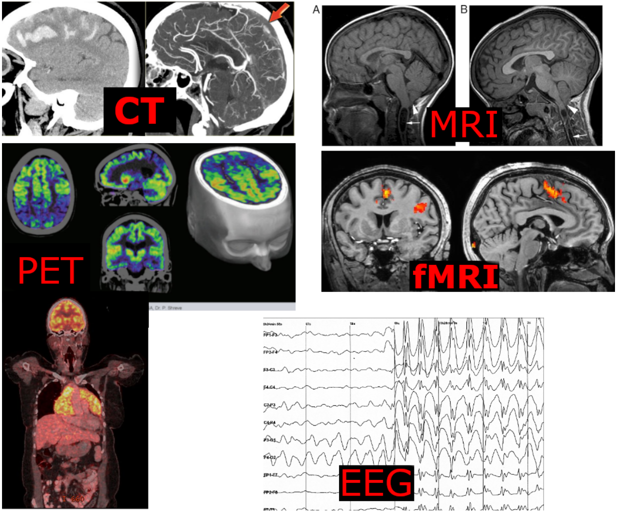
Outline

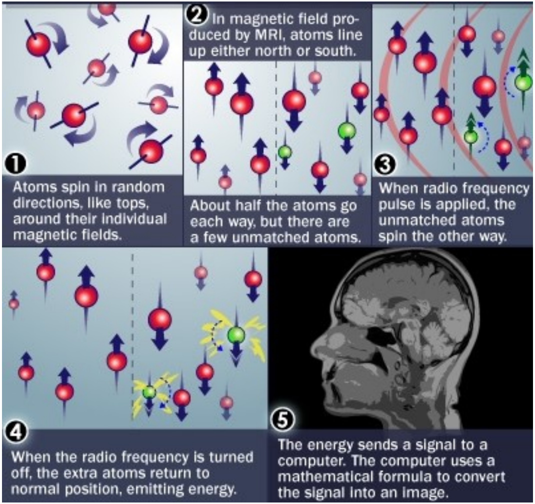
About Me

- BS in Mathematics and BA in Economics from Colorado State University (2011)
- MS in Biostatistics from CU Anschutz (2018)
- PhD candidate in the Department of Biostatistics & Informatics at CU Anschutz
- Graduate research assistant in CIDA, working in the Colorado Aging Brain Lab as well as the Translational Outcomes in Radiology Research (TORR) Lab.

An Introduction to Neuroimaging



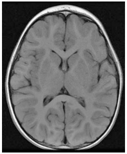
How MRI Works - Infographic



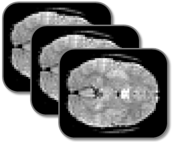
MRI Sequences

An MRI sequence is a number of radiofrequency pulses and field gradients that result in a particular image appearance.

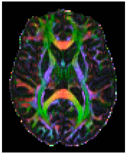
Sequences can be thought of in three broad buckets:



(a) Anatomical MR Image



(b) Functional MR Image



(c) Diffusion MR Image

Common Analysis Objectives

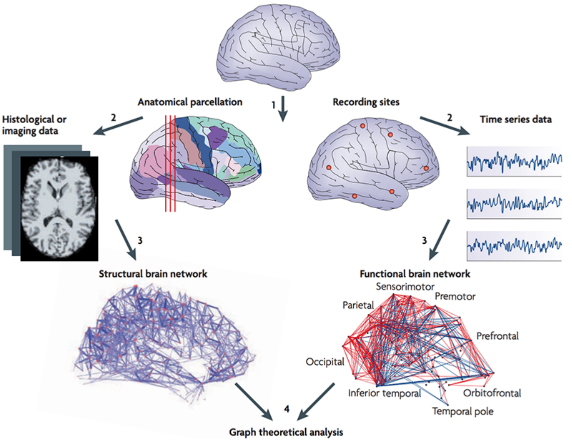
Research objectives

- Insights about normal brain function and structure and how these vary between indviduals and within an individual over time
- Manifestations and progression of neurological and psychiatric disorders
- Neural plasticity associated with stimuli or treatment response

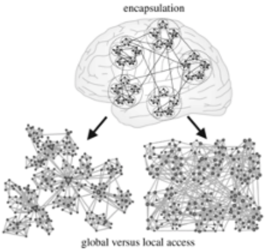
Statistical objectives

- Volume quantification
- Targeting localization
- Brain connectivity
- Prediction/classification

Brain Graphs



Modular and Hierarchical Organization of the Brain



Modular (or community) organization of the brain is thought to be a method of minimizing energy consumption in the development and maintenance of connections.

The brain has an intrinsic hierarchical structure - from neurons to entire brain regions and systems. Specialized cognitive sub-modules exist within large communities and can dynamically change their coupling with each other based on the cognitive process.

The Spinglass Algorithm

First introduced by Reichardt and Bornholdt in 2006, relies on the analogy between the Potts model and community detection, where the optimal community configuration is akin to the groud state of the Potts model.

$$
\begin{aligned}
\mathcal{H}(\{C\}) = &- \sum_{i \neq j} a_{ij} \underbrace{W_{ij}\delta(C_i, C_j)}_{\text{internal links}} + \sum_{i \neq j} b_{ij} \underbrace{(1 - W_{ij})\,\delta(C_i, C_j)}_{\text{internal non-links}} \\
&+ \sum_{i \neq j} c_{ij} \underbrace{W_{ij}(1 - \delta(C_i, C_j))}_{\text{external links}} - \sum_{i \neq j} d_{ij} \underbrace{(1 - W_{ij})(1 - \delta(C_i, C_j))}_{\text{external non-links}}
\end{aligned}
$$

Rewriting the Spinglass Hamiltonian

The algorithm can be simplified to only consider internal links and non-links, with $a_{ij} = 1 - \gamma p_{ij}$ and $b_{ij} = \gamma p_{ij}$, where p_{ij} is the probability that a non-zero edge exists between nodes i and j normalized to the total weight of the graph.

$$\mathcal{H}(\{C\}) = -\sum_{i \neq j} (W_{ij} - \gamma p_{ij})\, \delta(C_i, C_j)$$

Girvan-Newman modularity can be written as a special case of the Potts spinglass model by choice of p_{ij} and normalization of the Hamiltonian.

Semi-Supervised Spinglass

Extending on the work of Reichardt and Bornholdt, in 2012 Eaton and Mansbach incorporated external guidance into the community search, creating a semi-supervised spinglass algorithm.

$$\mathcal{H}'(C) = \mathcal{H}(C) + \mu \sum_{i \neq j} (u_{ij} - (u_{ij} - \bar{u}_{ij})\,\delta(C_i, C_j))$$

where u_{ij} is the penalty for violating guidance that nodes v_i and v_j belong to the same community, $\bar{u}_{ij}$ is the penalty for violating guidance that v_i and v_j belong to different communities, and $\mu \geq 0$ controls the balance between inherent community structure and external guidance.

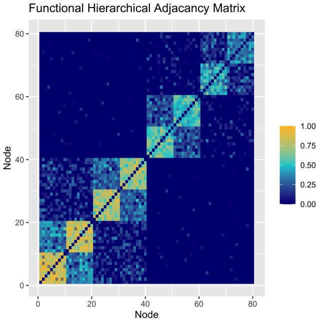
Hierarchical, Multimodal Spinglass

Adopting Eaton and Mansbach's semi-supervised methodology for multimodal community detection in the human brain, our modified Hamiltonian takes the following form:

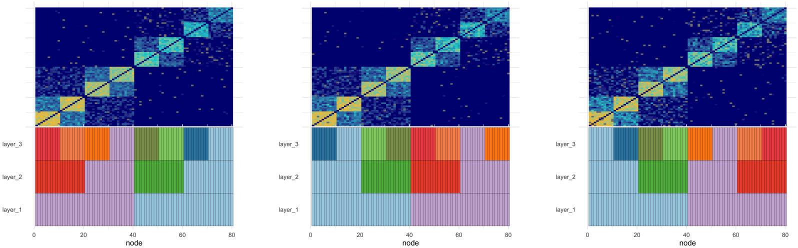
$$\mathcal{H}'(C) = -\sum_{i \neq j} M_{ij}\delta(C_i, C_j) - \alpha \sum_{i \neq j} S_{ij}\delta(C_i, C_j),$$

where M_{ij} is the modularity matrix associated with functional connectivity, S_{ij} is the structural connectivity matrix, and $\alpha \geq 0$ controls the balance between the community structure determined solely by functional connectivity and being informed by the structural connectivity via white matter fiber tract information.

Simulating Functional and Structural Connectivity



Simulation Results




Rx

Administrative Databases

Also known as claims data or secondary data, administrative data was collected for non-research purposes (often billing) that can be analyzed retrospectively for research.

These datasets typically contain limited, deidentified information regarding hospitals, clinicians, and patients (including demographics and clinical information) as these pertain to specific clinical encounters.

Major Administrative Databases - CMS

Medicare Limited Data Set Standard Analytical Files

- Represent national fee-for-service data for $\approx 70\%$ of beneficiaries enrolled in traditional fee-for-service Part A and B coverage.
- Each year, distinct files are created, aggregating claims for outpatient, inpatient and ambulatory care, and patient demographics.

Medicare Physician Supplier/Procedure Summary

- Represents Medicare claims data that is aggregated from CMS designated public use files.
- Comprehensively capture all Part B billing claims submitted by both physicians and other providers nationally.

Major Administrative Databases - HCUP

National Inpatient Sample

- Largest publicly available capture of claims from hospital admissions across the United States, yielding national estimates of hospital inpatient stays.

Nationwide Emergency Department Sample

- The largest all-payer emergency department (ED) database in the United States, yielding national estimates of hospital-owned ED visits.

State Inpatient Databases / State Emergency Department Databases

- State-specific files that capture all inpatient (or ED) records in participating states. These represent the largest capture of longitudinal hospital care data that is inclusive of all payers and ages.

Pros and Cons

Pros

- Large sample sizes
- Information on diagnoses, treatments, and outcomes
- Uniformity of coding
- Available on local, state, regional, and national levels

Cons

- Documentation and coding for clinical or reimbursement purposes, not research
- Lack of clinical detail
- Lag time of data
- Selection bias concerns

Statistical Considerations

- Data management
- Uncontrolled confounding due to lack of clinical data
- Left- and right-censored nature of data collection
- Accounting for clustering
- Survey weights
- Challenges inferring causation
- Statistical versus clinical significance

Ethnoracial Disparities in Management of Acute Variceal Bleeding

(1) Determine if black patients treated with TIPS for variceal bleeding have a higher odds of mortality due to higher baseline disease severity.

(2) Determine if there are differences in treatment utilization for variceal bleeding by patient race.

(3) Determine if time-to-treatment with TIPS following admission with variceal bleeding is associated with hospital survival and if patient race is a confounding factor.

Specific Aim 1

A hierarchical logistic regression was fit for the outcome of inpatient mortality, with a random intercept included for hospital ID. Patient demographics (age, sex, race/ethnicity, etc.), measures of comorbid burden (APR-DRG risk mortality), and clinical risk factors (ascites, hepatic encephalopathy, etc.) were included in the model.

Black race was found to be significantly associated with inpatient mortality (OR: 3.01; 95% CI: $(1.55, 3.84)$; $p=0.001$).

A sensitivity analysis looking only at patients without ascites found Black race to no longer be significantly associated with the outcome (OR: 1.25; 95% CI: $(0.43, 3.63)$; $p=0.682$).

Specific Aim 2

Parallel hierarchical logistic regressions were fit for the outcomes of receiving at least one endoscopy and receiving TIPS, respectively, with random intercepts included for hospital ID. Patient demographics (age, sex, race/ethnicity, etc.), measures of comorbid burden (APR-DRG illness severity), and encounter details (length of stay, weekend admission) were included in the model.

Black race was found to be significantly associated both with receiving endoscopy (OR: 0.845; 95% CI: $(0.755, 0.946)$; $p=0.003$) and receiving TIPS (OR: 0.541; 95% CI: $(0.413, 0.708)$; $p < 0.001$).

Specific Aim 3

A Cox proportional hazards model was fit for the outcome of time-to-TIPS with a frailty term for hospital ID and stratified by inpatient mortality. Similar patient demographics and comorbid burden metrics from aims 1 and 2 were included as covariates.

Black race was found to be significantly associated with time-to-TIPS (HR: 0.676; 95% CI: $(0.503, 0.910)$; p=0.010)

Modeling the Hospital Care Process

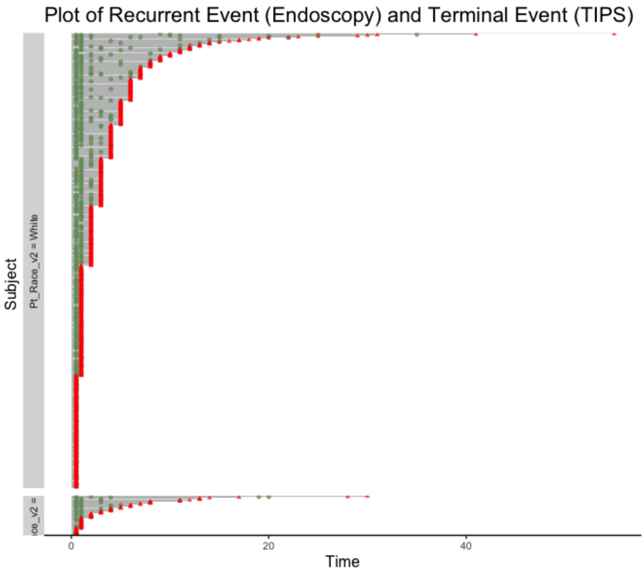
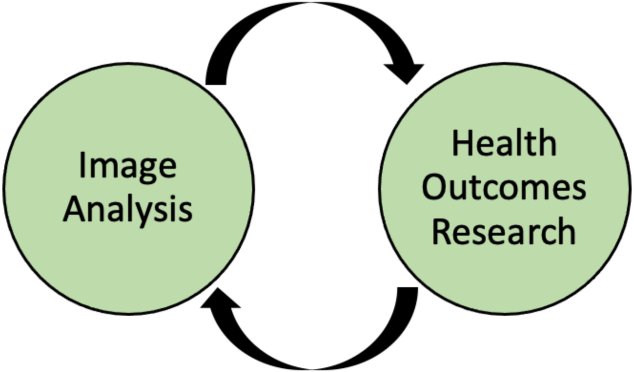


Image Analysis and Health Outcomes

Imaging in the age of precision medicine

- The increasing role of imaging in the management of complex, genetically heterogenous diseases.
  - Guiding the application of particular treatments
  - Availability of open source imaging software and large imaging databases - building common tools for processing a preclinical analysis, harmonization across industry standards
- Radiogenomics: the correlation of genetic information with information from imaging and, often, other patient metrics, with the ultimate purpose of improving classifier models.

Feedback Loop



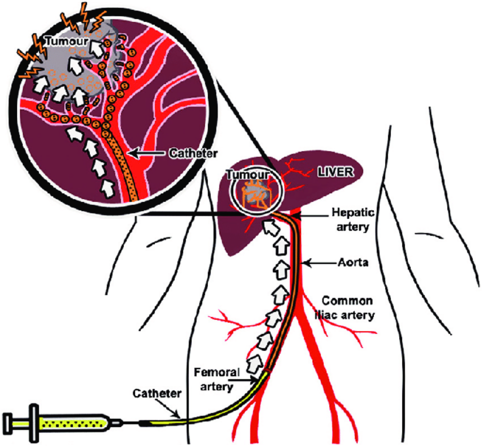
Future Directions: Image Analysis

- Extending the semiparametric kernel regression framework
  - If omnibus test is statistically significant, where in the structure (network, tree) are these differences localized?
  - Accommodate longitudinal data to look at within- and between-subject changes over time
- Continue exploring multimodal sources of information in network analysis
- Bayesian and functional data approaches to network analysis

Future Directions: Health Outcomes

- Spatial analysis of screening mammography recall
- Incorporation of mental health conditions in comorbidity indices
- Build flexible models to analyze the process of care (e.g., acute variceal bleeding)

Future Directions: Integrating Imaging and Health Outcomes



Thank You

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