Discovery and Visualization of Latent Structure
with Applications to the Microbiome

Kris Sankaran
Department of Statistics

March 9, 2018

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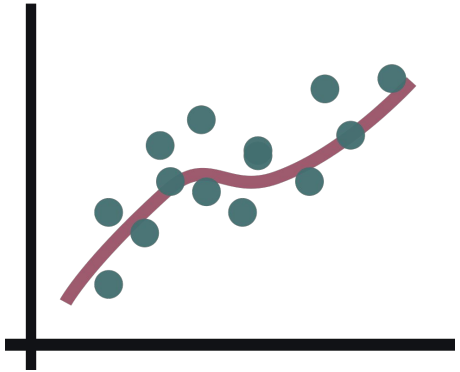
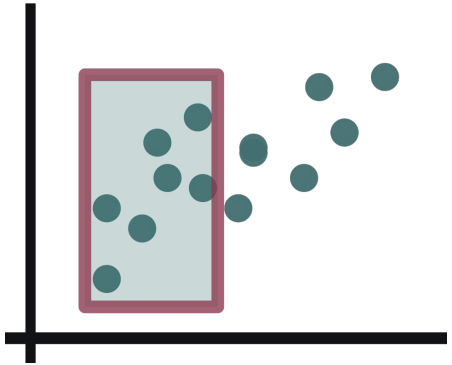
Approaches

Modeling Workflows



Visualization Packages



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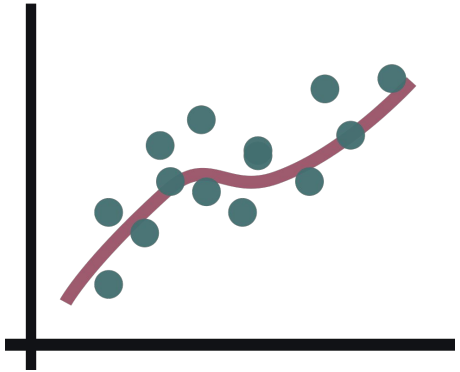

- Compute reductions in data
- Characterize uncertainty in reductions
- Sufficiency provides summaries

$$X \rightarrow \hat{\theta}$$

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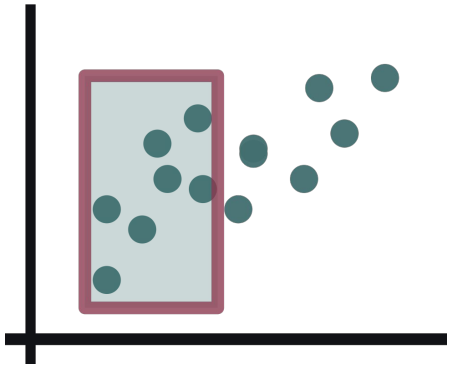

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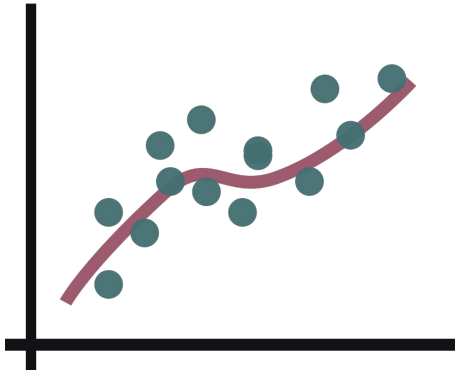

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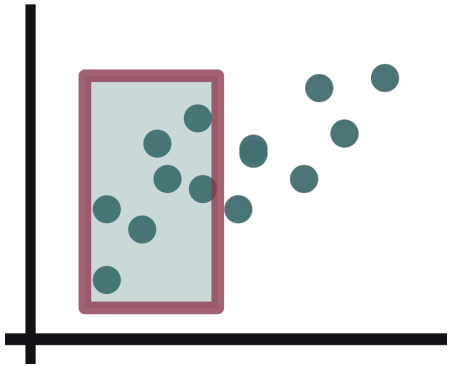
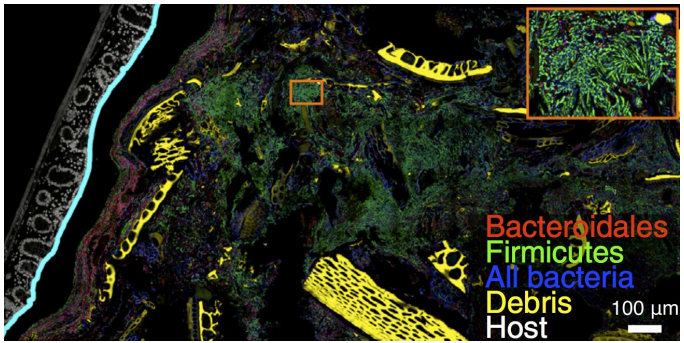


- Simplify navigation across data
- Suggest simple models + hypotheses
  - Motivate reductions

$$\Theta?$$

Microbiome Studies

- **Microbiome**: All the bacteria living together in some place (e.g., the human gut)
  - Quantification enabled by advances in 16S rRNA and metagenomics sequencing technologies
- **Typical goal**: Characterize variation in community profiles across conditions
- Intersection of several sciences
  - **Ecology + Medicine**: Bacterial communities can have medical implications
  - **Evolution + Microbiology**: A data-rich setting for studying evolutionary principles



Imaging the microbiome. Figure from [Earle et. al 2015].

Data Sources

- 16S Sequencing: Marker gene allows quantification of variants
- Size: Typically 10 - 1000 samples, 500 - 2000 bacteria

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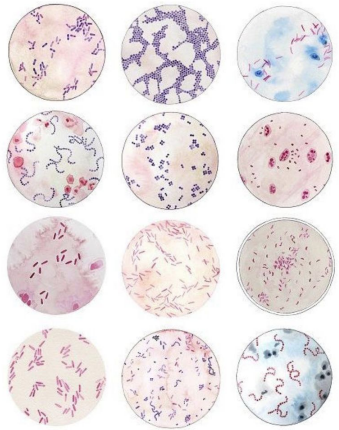
- Size: Typically 10 - 1000 samples, 500 - 2000 bacteria
- Contextual data are available
  - Samples → subject characteristics
  - Bacteria → taxonomic information

Probabilistic Latent Variable Modeling for the Microbiome

Motivating Idea

- Schloss and Handelsman [2007] noted parallels between text and microbiome data
  - Limited application of text models in microbiome studies
  - Probability models are useful in studies with complex structure
- **Contribution**: In the spirit of [Callahan 2016, Fukuyama 2017], describe a workflow, provide code, and compare existing methods, focusing on interpretation, usability, and visualization



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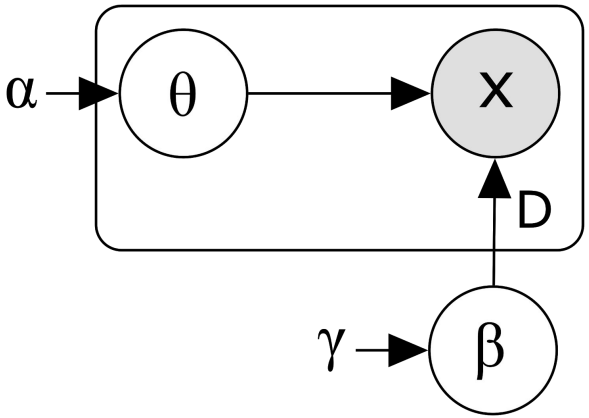
index	book	eliza.	darcy	bennet	miss	jane
0	P&P	0	0	4	0	1
1	P&P	1	0	5	0	1
2	P&P	0	0	6	0	0
3	P&P	1	4	5	1	0
4	P&P	3	3	5	4	4

time	subject	sp_1	sp_2	sp_3	sp_4	sp_5
0	D	791	0	79	108	11
1	D	1616	0	1413	192	31
2	D	1323	0	915	165	23
3	D	1846	0	1366	170	31
4	D	2314	0	689	135	26

Models Considered: Latent Dirichlet Allocation



- Latent Dirichlet Allocation (LDA) is an alternative to Multinomial Mixture Modeling that assumes samples have mixed memberships across topics [Pritchard et. al 2000, Blei et. al. 2003]
  - Posterior inference can be done with variational approximations or (collapsed) Gibbs sampling
- Observed microbiomes ≈ mixtures of underlying community types

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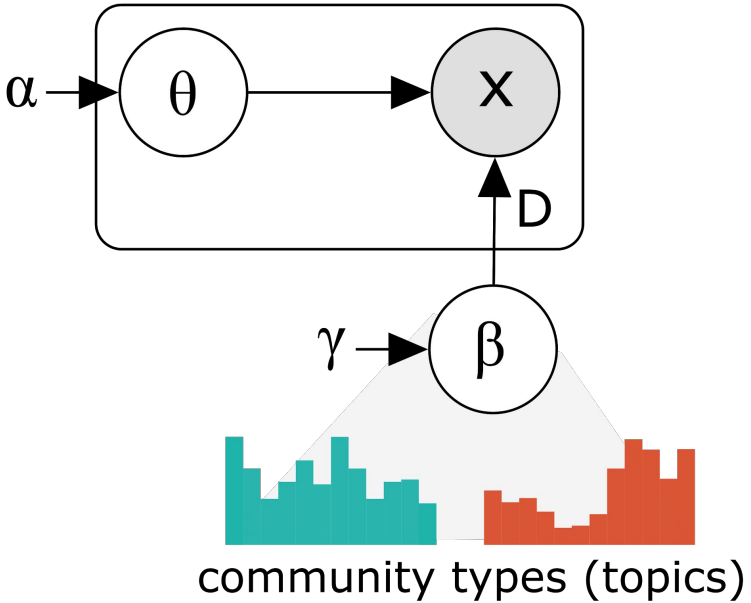

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$$\theta_d \overset{iid}{\sim} \text{Dir}(\alpha) \text{ for } d = 1, \ldots, D$$

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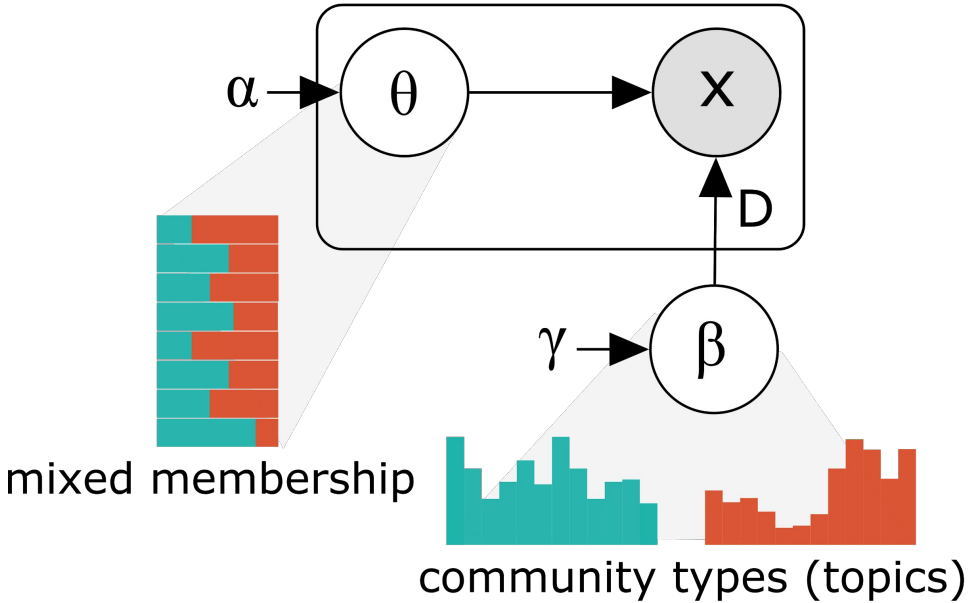

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$$x_{d\cdot} \,|\, (\beta_k)_1^K \overset{iid}{\sim} \text{Mult}\,(N_d, B\theta_d) \;\text{ for } d = 1, \ldots, D$$

$$\theta_d \overset{iid}{\sim} \text{Dir}\,(\alpha) \;\text{ for } d = 1, \ldots, D$$

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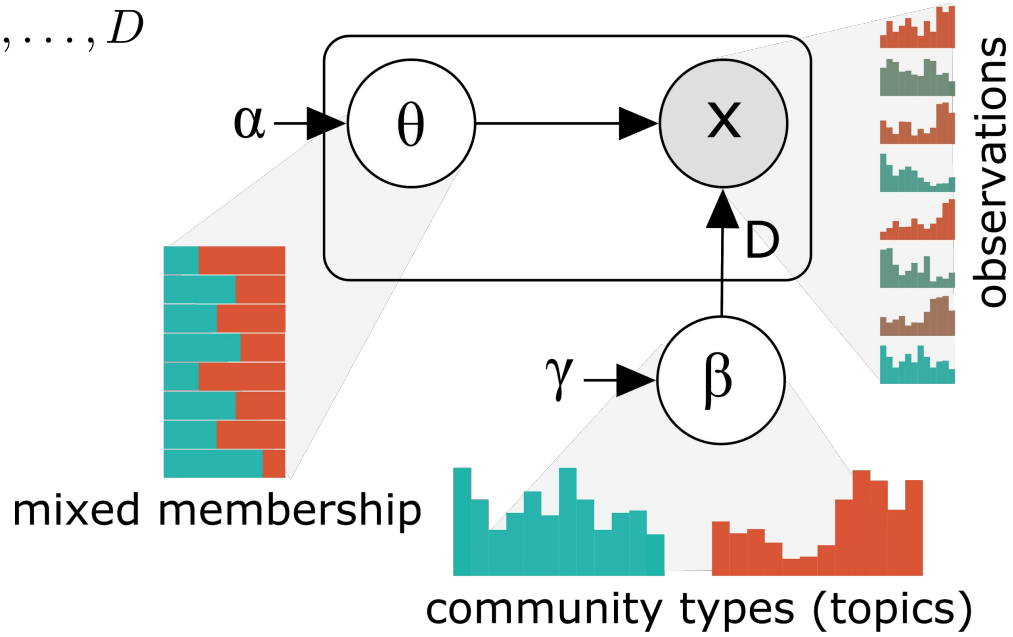

Models Considered: Gamma-Poisson Factorization

- Nonnegative Matrix Factorization using a low-rank Gamma-Poisson model [Canny 2004]
- Mixture and topic vectors are no longer required to sum to one
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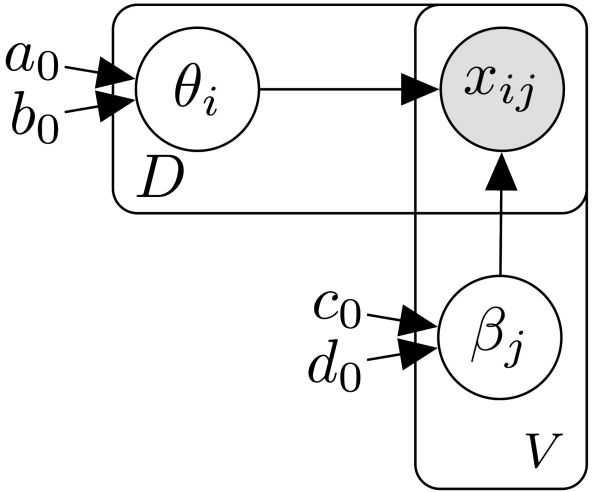

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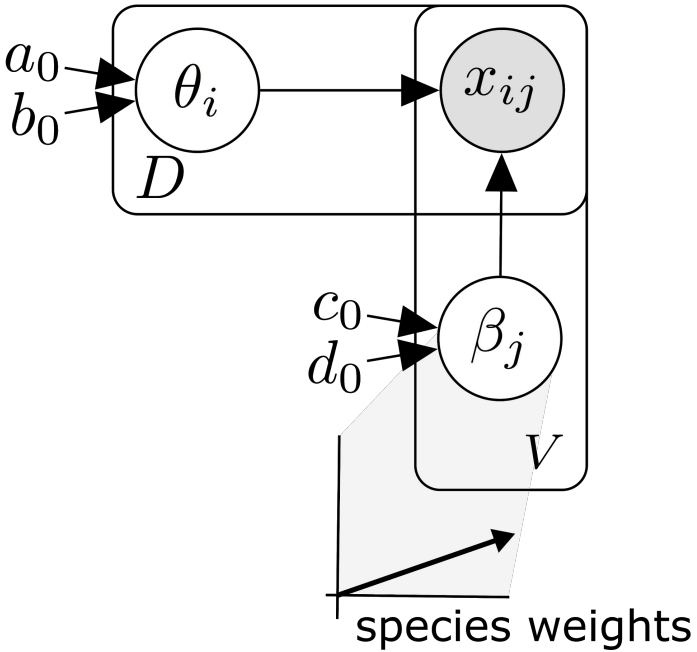

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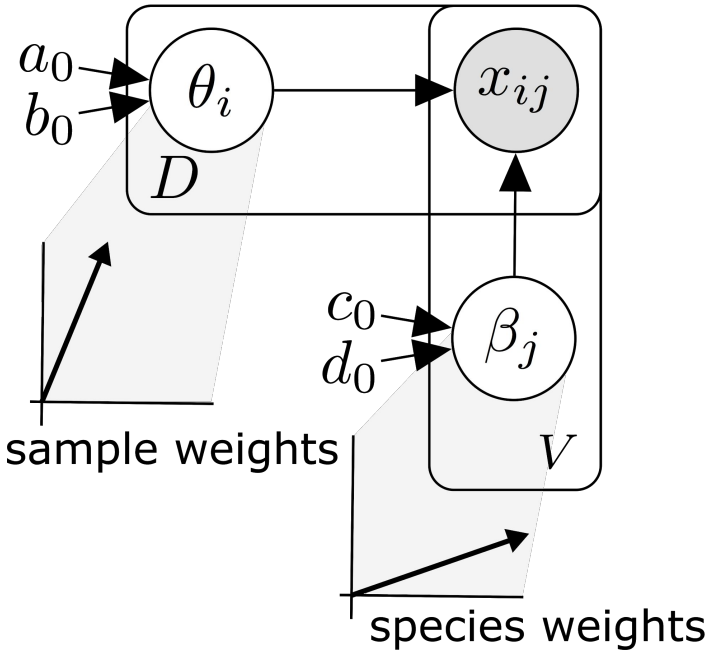

Models Considered: Gamma-Poisson Factorization

$$x_{dv} \overset{iid}{\sim} \text{Poi}\left(\theta_d^T \beta_v\right) \text{ for } d = 1, \ldots, D \text{ and } v = 1, \ldots V$$

$$\theta_d \overset{iid}{\sim} \text{Gam}\left(a_0, b_0\right) \text{ for } d = 1, \ldots, D$$

$$\beta_v \overset{iid}{\sim} \text{Gam}\left(c_0, d_0\right) \text{ for } v = 1, \ldots, V$$

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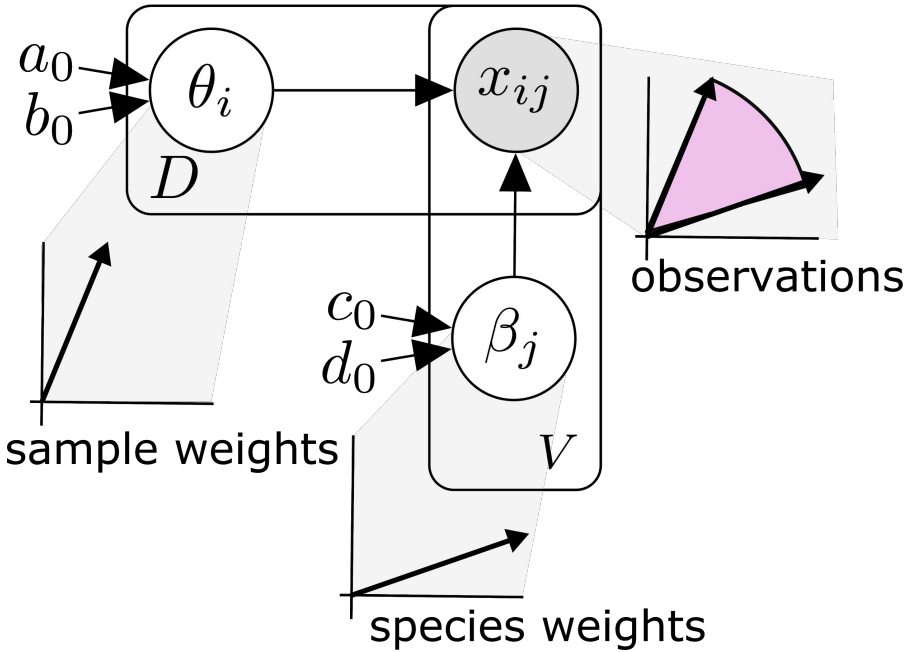
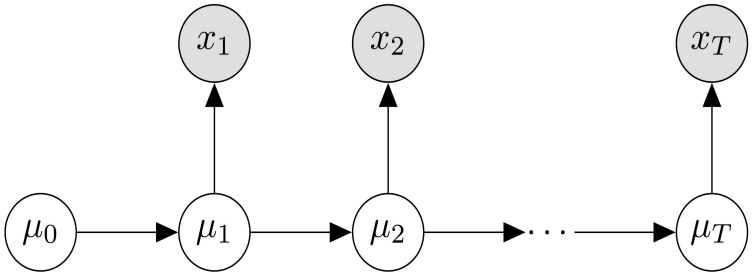


Models Considered: Dynamic Unigrams

- The Dynamic Unigram Model supposes the distribution of species within a sample evolves smoothly over time
- This is accomplished by passing a Gaussian random walk through a multilogit link
- The factorized version is the Dynamic Topic Model [Blei and Lafferty 2006]



Models Considered: Dynamic Unigrams

$$\mu_t|\mu_{t-1} \overset{iid}{\sim} \mathcal{N}\left(\mu_{t-1}, \sigma^2 I_V\right) \text{ for } t = 1, \ldots, T$$

$$\mu_0 \overset{iid}{\sim} \mathcal{N}\left(0, \sigma^2 I_V\right)$$

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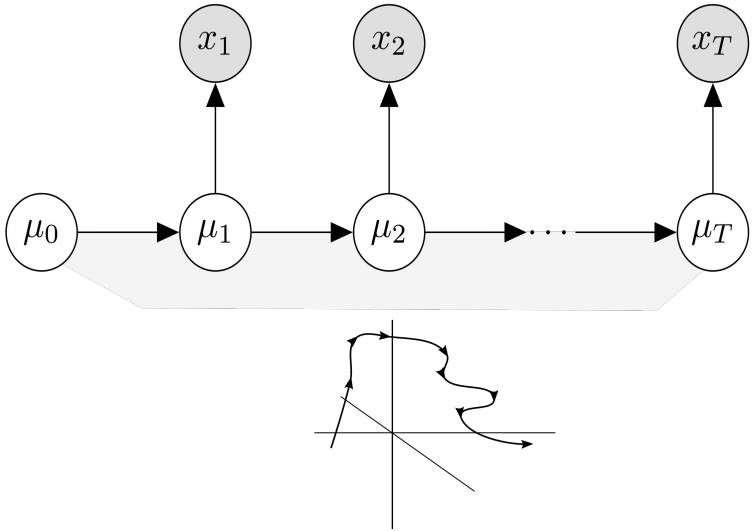

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$$x_{d\cdot}|\mu_{t(d)} \overset{iid}{\sim} \text{Mult}\left(N_d, S\left(\mu_{t(d)}\right)\right) \text{ for } d = 1, \ldots, D$$

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$$[S(\mu)]_v = \frac{\exp \mu_v}{\sum_{v'} \exp \mu_{v'}}$$

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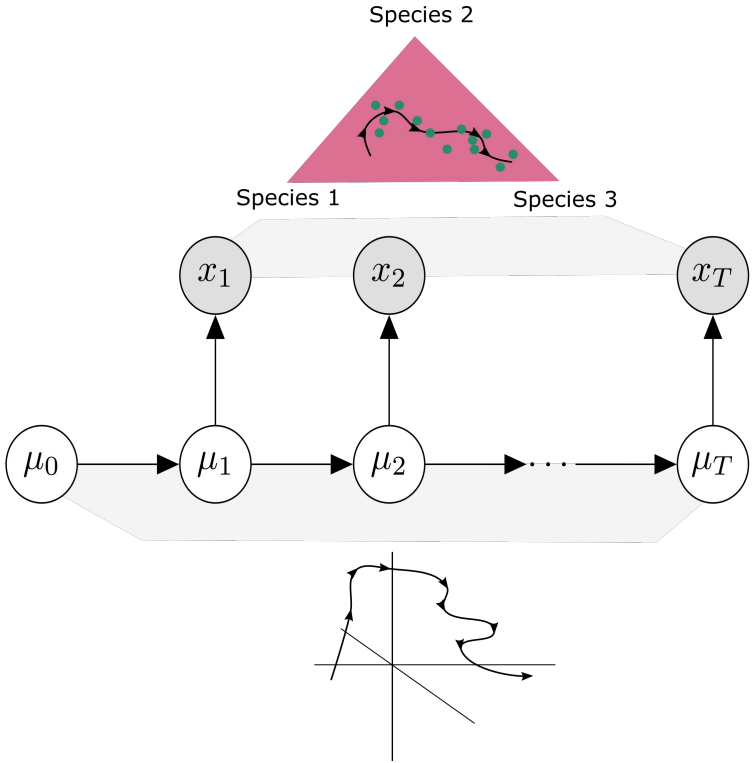


Bacterial Dynamics and Antibiotic Time Courses

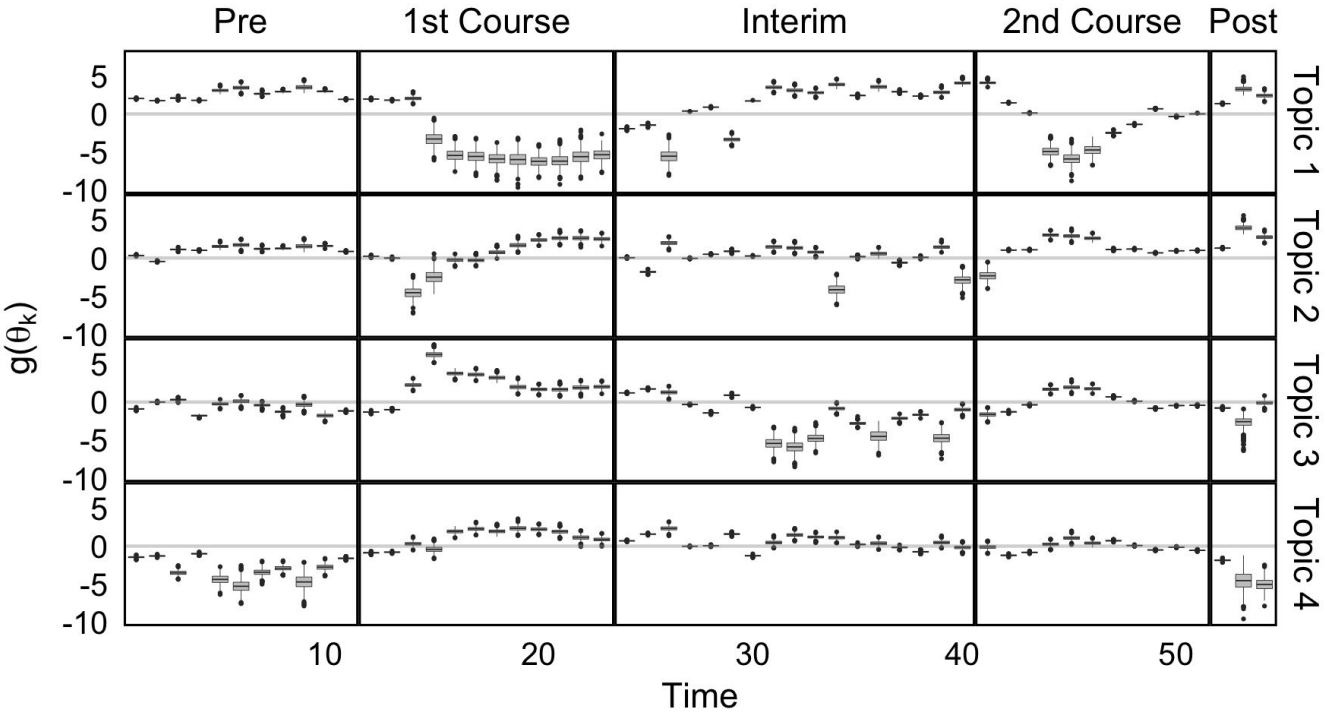
- Revisiting the study [Dethlefsen and Relman, 2011]
- Study Goal: How does the microbiome respond to antibiotics, keeping in mind typical day-to-day variation? ["Wildfire" analogy]

Bacterial Dynamics and Antibiotic Time Courses

- Revisiting the study [Dethlefsen and Relman, 2011]
- Study Goal: How does the microbiome respond to antibiotics, keeping in mind typical day-to-day variation? ["Wildfire" analogy]
- Data: 3 subjects, across ~ 50 timepoints, with two antibiotic time courses introduced in-between
- We study one subject at a time

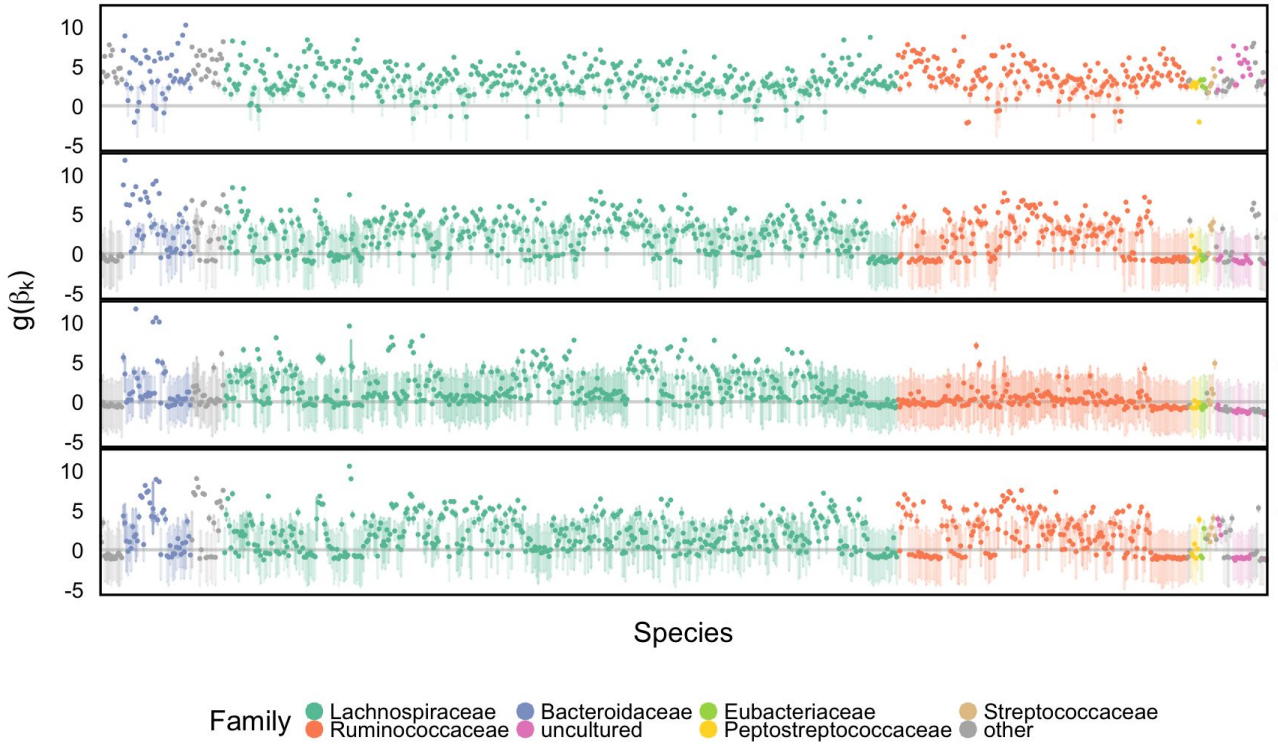
Estimated Mixed-Memberships: θ_{dk}

- Boxplots represent approximate posteriors for θ_{dk} and their evolution
- A centered log transform has been applied
- Interpretations
  - Slow recovery
  - Fast recovery
  - Relatively increase
  - No effect



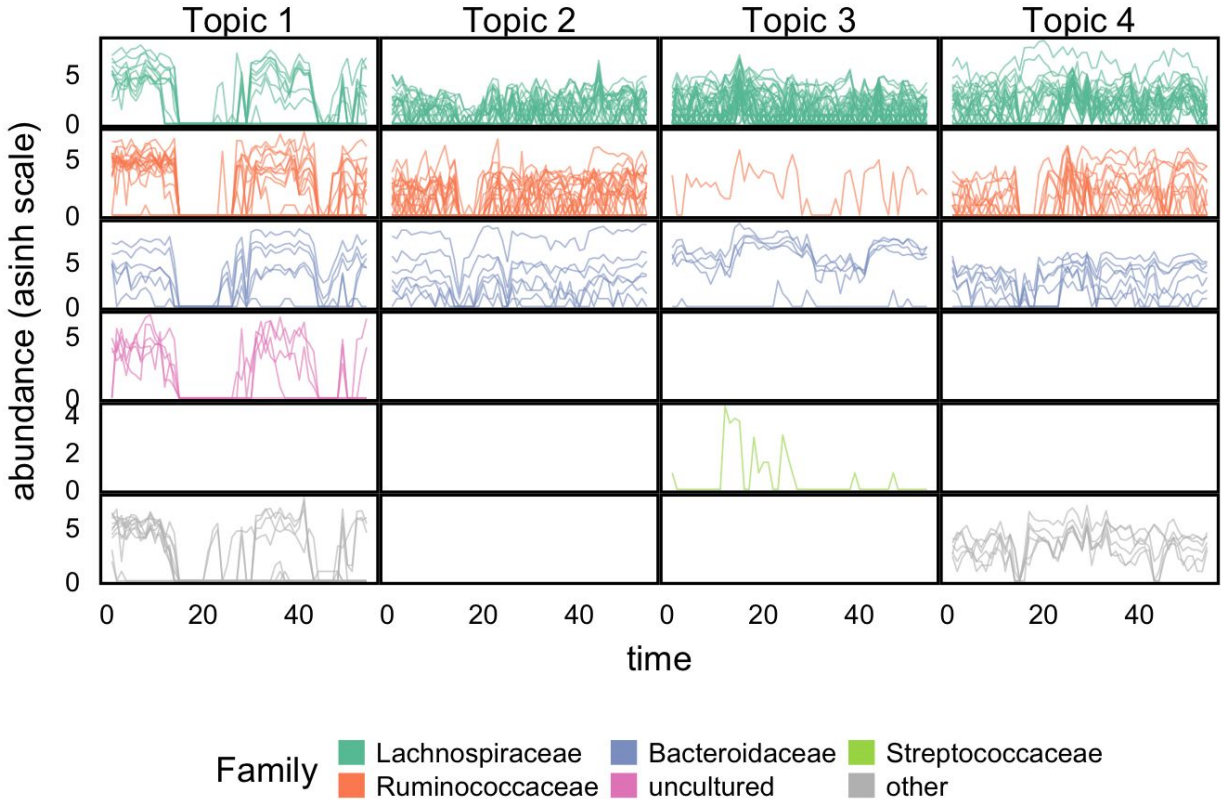
Estimated Topics: β_{vk}

- Intervals represent approximate β_{vk} posteriors
- Each row is a topic, each interval is a species, colors are taxonomic groups
- A centered log transform has been applied
- The third topic is noticeably less diverse, corresponding to the community during antibiotics time courses



Topic Prototypes

- Prototypes are species representative of individual topics
  - 50 species with large $\beta_{kv} - \sum_{k' \neq k} \beta_{k'v}$
- Rows are taxonomic groups, columns are topics
- Each trajectory gives the abundance of a single species over time

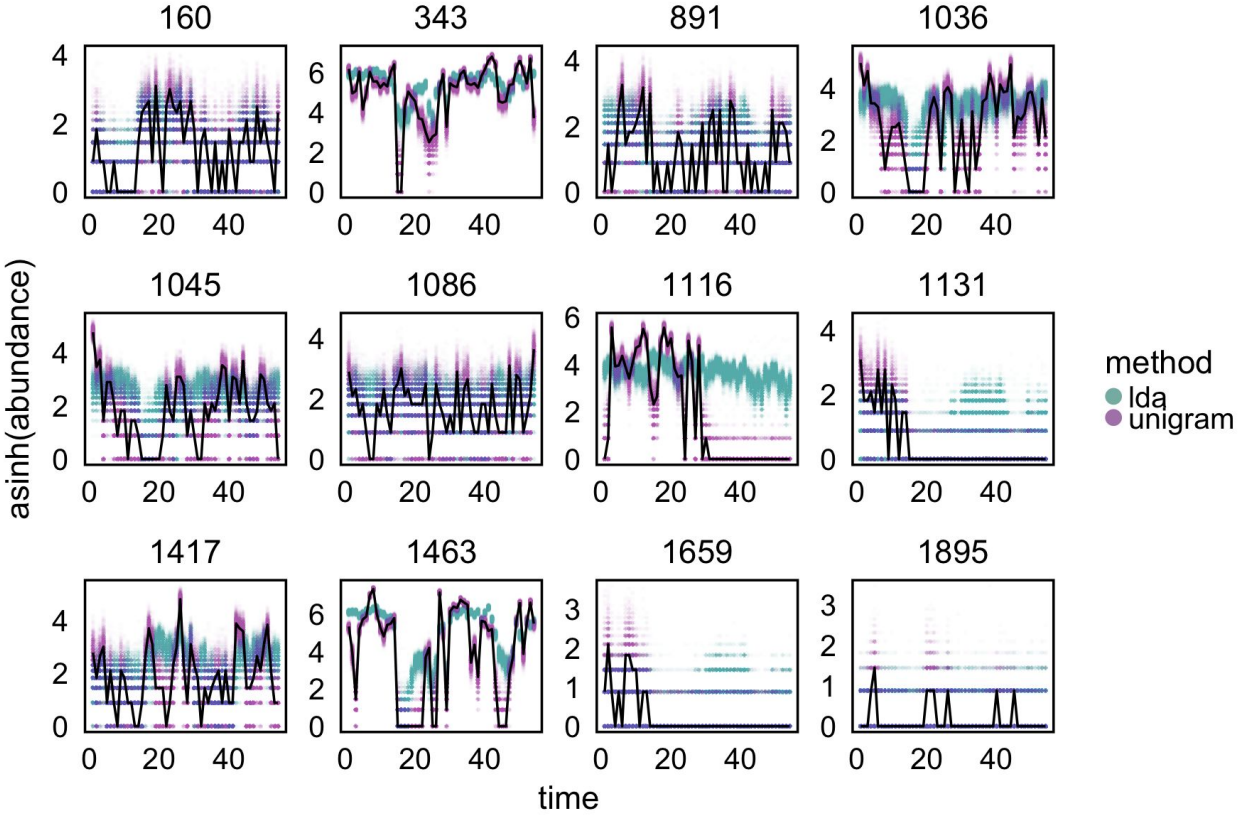


Model Criticism

- We simulate data from the posterior predictive,

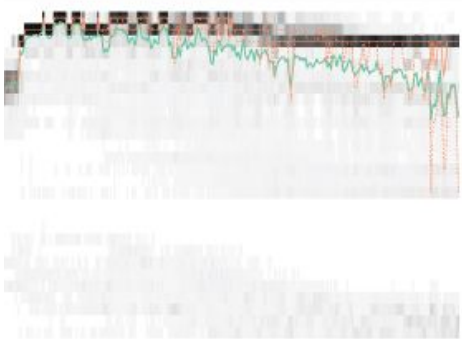
$$p\left(x^{*}|x\right)=\int p\left(x^{*}|\theta\right)p\left(\theta|x\right)d\theta$$

- Each panel represents one species, the black lines are observed species trajectories
- The blue and purple lines are LDA and unigram posterior predictive samples
  - The unigram model overfits
  - Species 1116 is an interesting outlier



Other Workflow Guides

- Distill, critique, and compare existing approaches
- Guide for turning raw reads into abundance matrices



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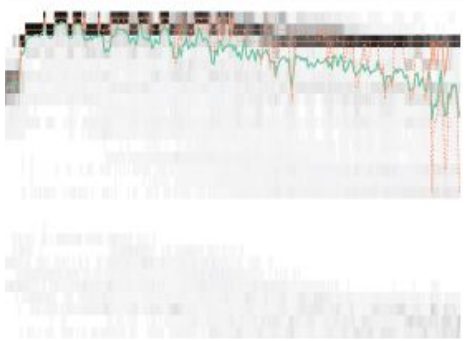
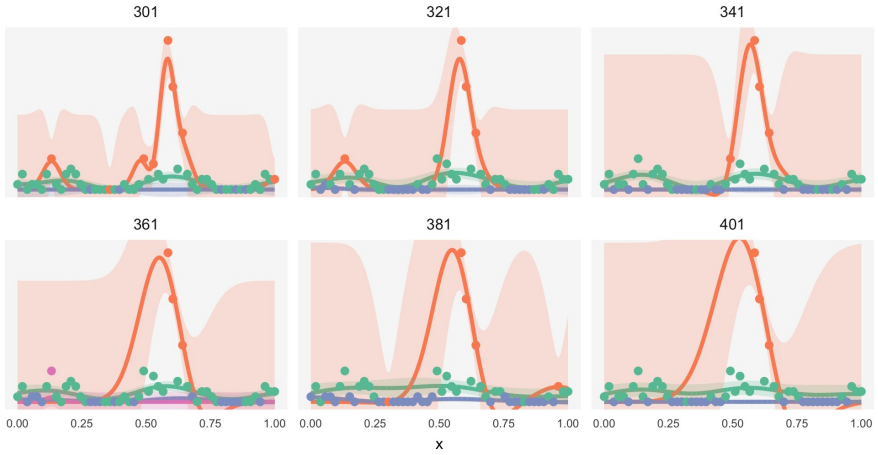
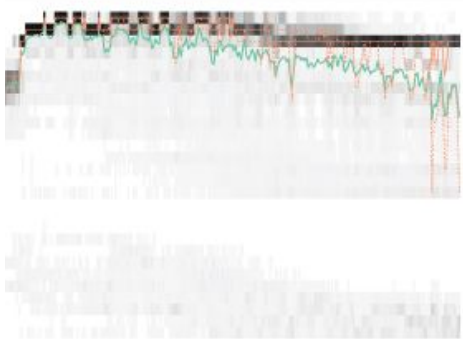
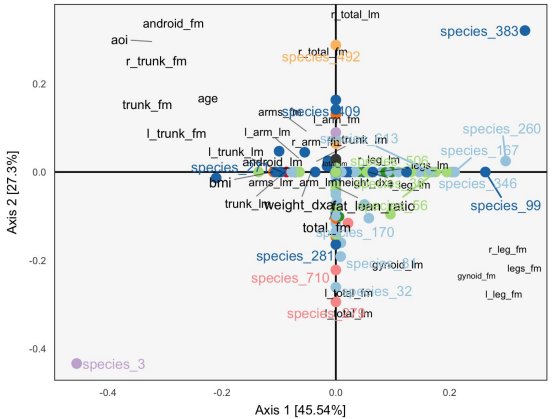


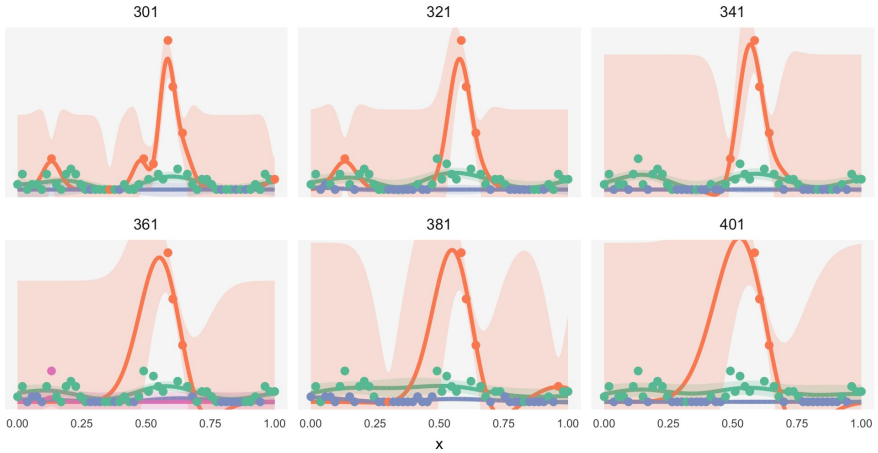


Other [Workflow Guides]

- Distill, critique, and compare existing approaches
- Guide for turning raw reads into abundance matrices
- Methods for segmenting dynamic regimes
- A survey of multitable modeling techniques





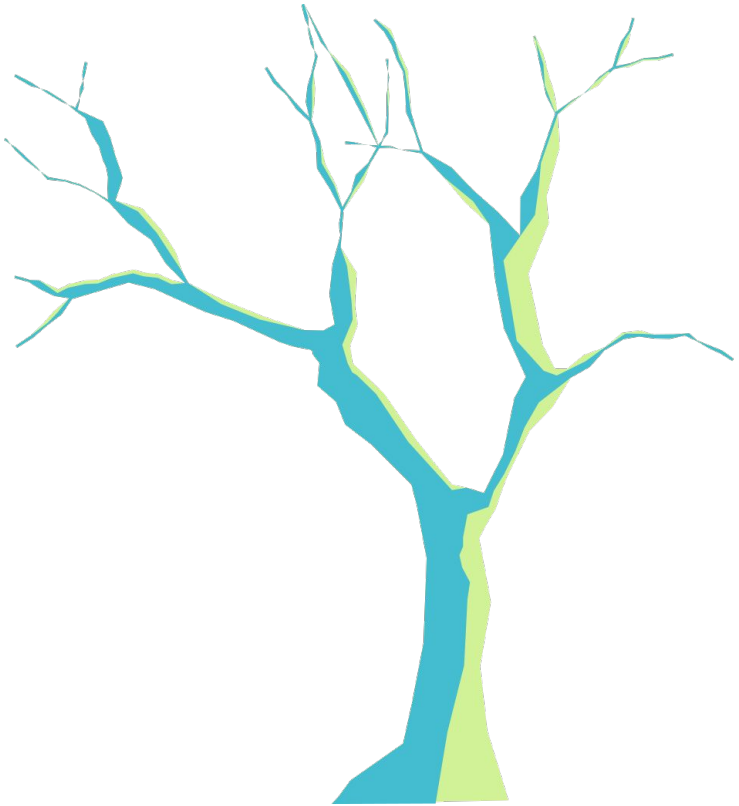


treelapse = trees + timelapse

Visualizing Hierarchies of Time Series

Tree-Structured Statistical Problems

- Differential Abundance
  - Compare bacterial abundances across conditions, for different species
  - Identify the taxonomic subtrees whose bacteria are differentially abundant

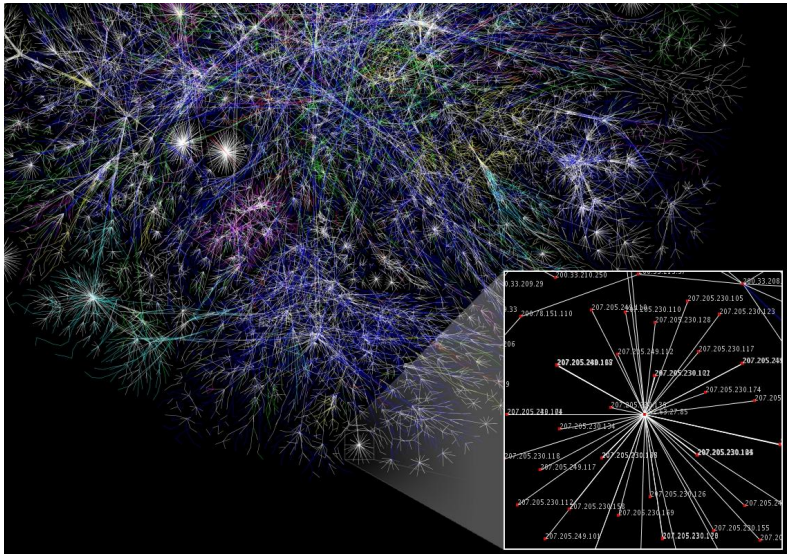


Tree-Structured Statistical Problems

- Differential Abundance
  - Compare bacterial abundances across conditions, for different species
  - Identify the taxonomic subtrees whose bacteria are differentially abundant
- Differential Dynamics
  - Describe changes in bacterial abundances, at the largest subtree where the pattern appears
  - Has an ecological flavor, with emphases on role of niches and environmental changes

Visualization Principles: Focus + Context

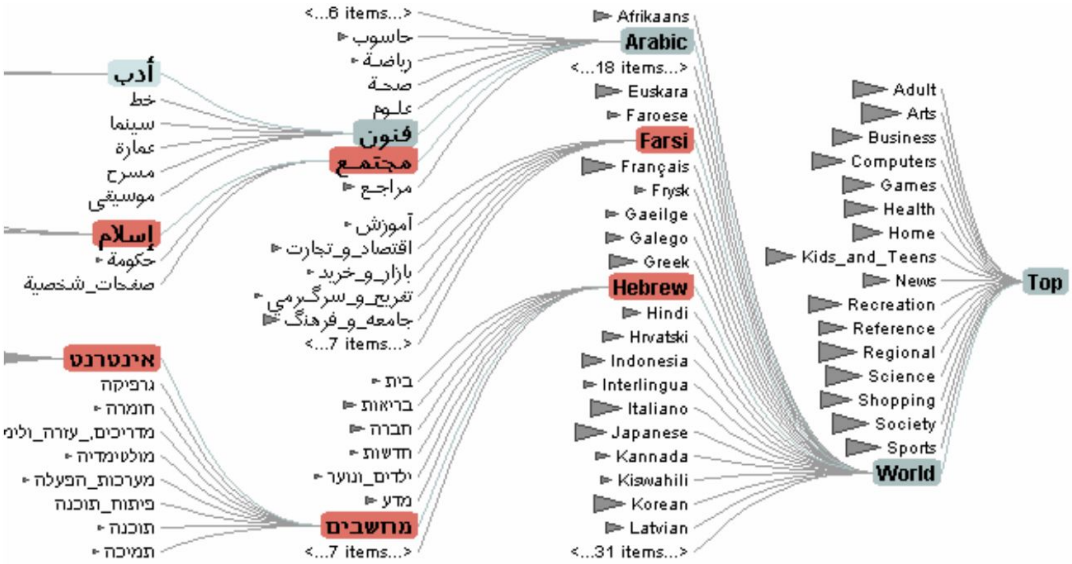
- Study a dataset across scales
  - Full network vs. neighborhood of a node
  - Full time series vs. short time window
- Interactivity allows transitions across scales
- *Focusing* on elements of interest while retaining *context*



A partial map of the internet, from The Opte Project, distributed under a Creative Commons license.

Degree-of-Interest (DOI) Trees

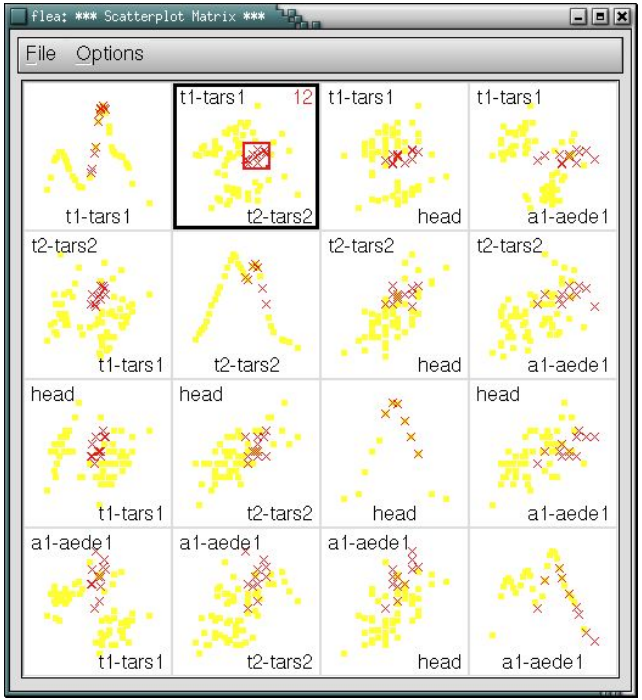
- An application of the focus + context idea to tree structured data
- Easily navigate the tree across different scales (e.g., species vs. phylum)



Screenshot of a DOI tree, from [Heer and Card 2004].

Visualization Principles: Linking

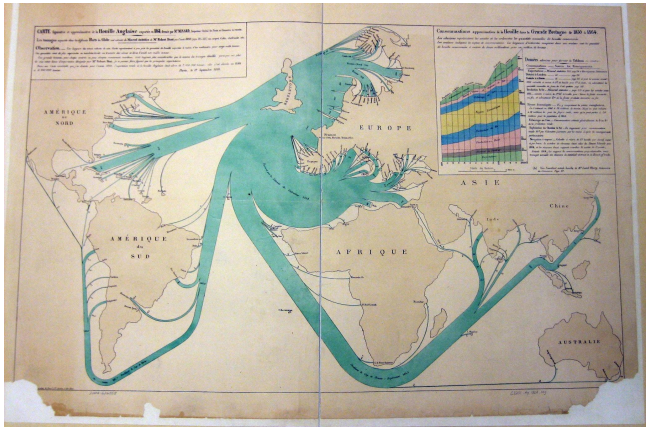
- Alternative representations reveal covariation [Becker and Cleveland 1987, Buja et. al. 1996]
- Can be useful in high-dimensional settings
- Conditional probability and database query interpretations
    - What are values other variables, conditional on constraints for some of them?



Linked scatterplot brushing, as implemented in GGobi [Voigt 2002].

Visualization Proposals

- Differential Abundance
    - DOI Tree: Usual DOI, but node sizes reflect species abundances
    - DOI Sankey: Extension to multiple groups, distinguished by color
    - Instead of separate trees, split branches into several groups



A sankey diagram of British coal exports, made in 1868 by Charles Joseph Minard.

Visualization Proposals

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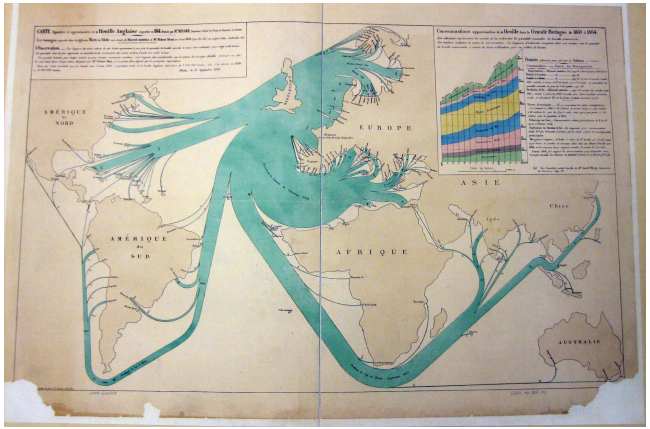
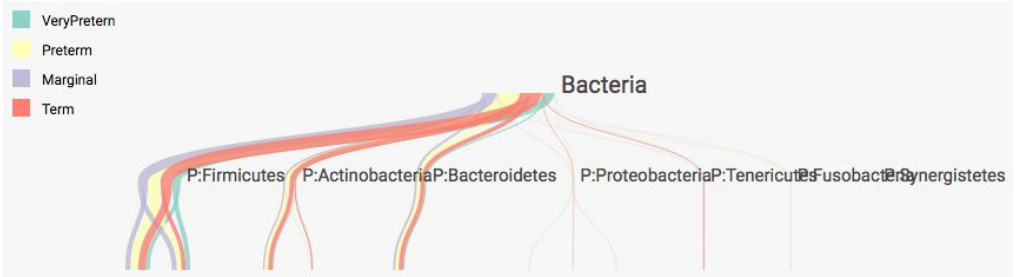


A sankey diagram of British coal exports, made in 1868 by Charles Joseph Minard.

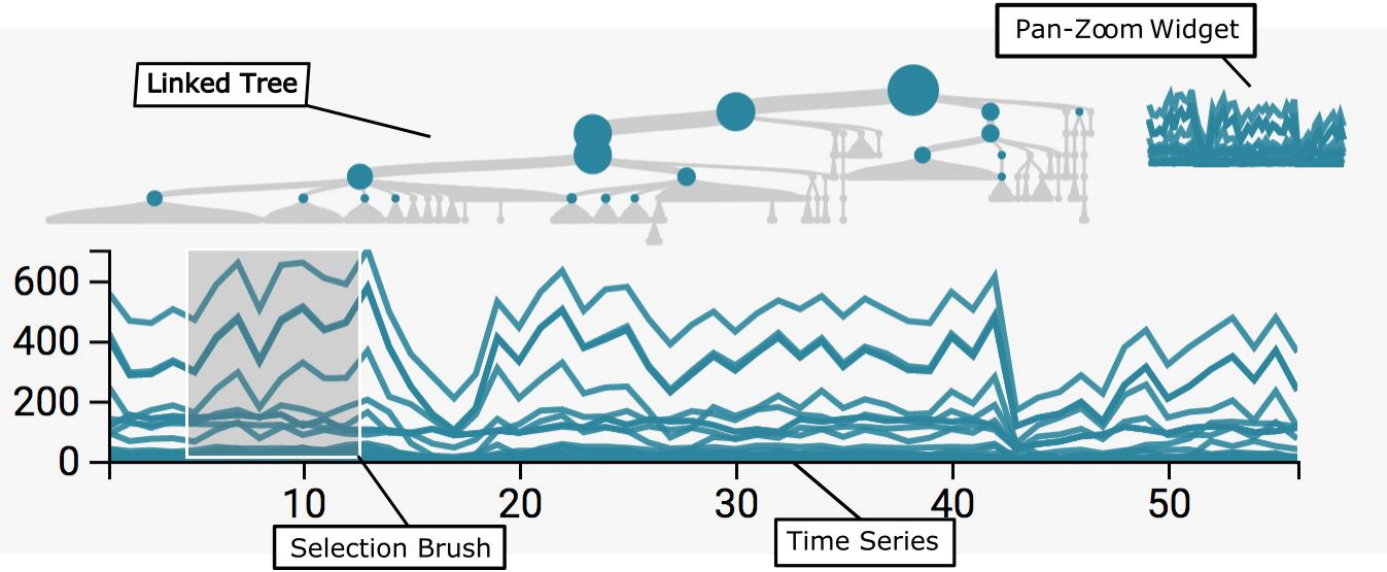
[Demo]



An example DOI Sankey, applied to a microbiome taxonomy.

Visualization Proposals

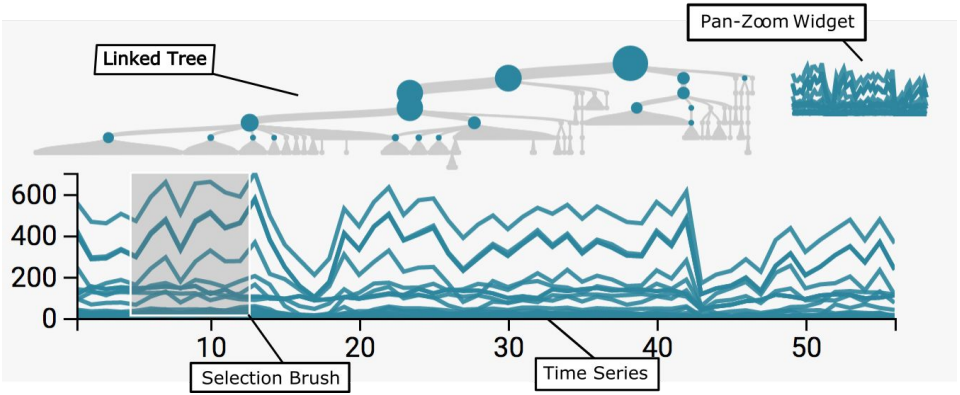
- Differential Dynamics
  - One-to-one mapping between nodes and time series
  - Timebox Trees: Link timeboxes and the tree, with selections over the time series
  - Treeboxes: Link timeboxes and the tree, with selections over the tree



Antibiotics revisited

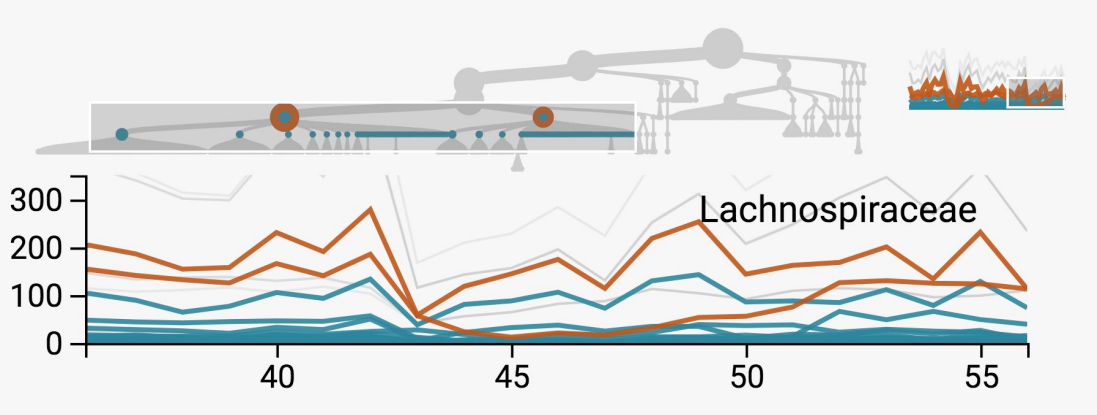
- We apply these methods to the data of [Dethlefsen and Relman 2011], which we analyzed earlier using latent variable models
- In contrast to that work, our goal here is interactive visualization of species abundance trajectories

Demo



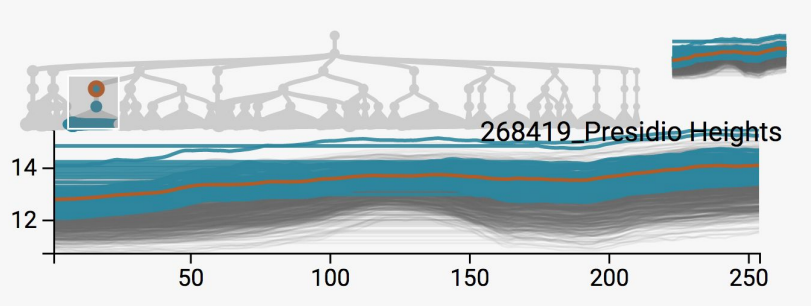
Differential Response among Firmicutes

- Drawing boxes over the tree and searching across suborders of Firmicutes suggests a differential responses between Lachnospiraceae and Ruminococcaceae
- Note that we are focusing on the time window surrounding the second antibiotic time course

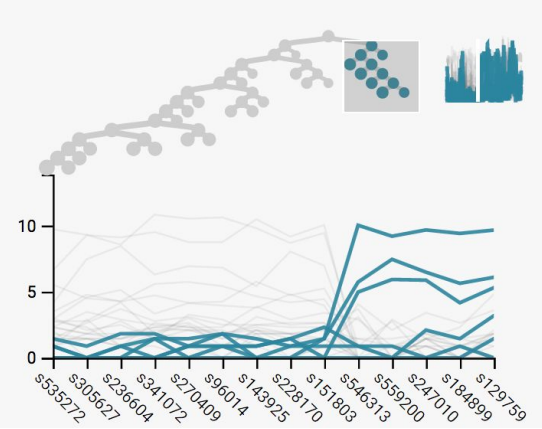


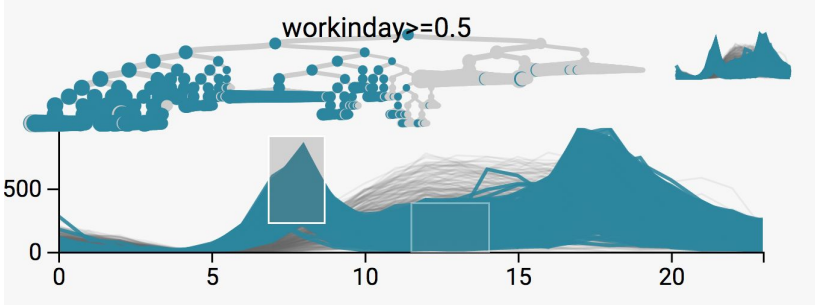
Beyond Phylogenies

Hierarchical structure is present in many contexts



Spatial Hierarchies: Nodes / series are geographic regions





Regression Trees: Nodes / series are averages of samples on one side of a split

Hierarchical Clustering: Nodes / series are centroids within clusters

Other Visualization Projects

- **centroidview**: Combine differential dynamics with differential abundance
  - Demo
  - Package: github.com/krisrs1128/centroidview

Other Visualization Projects

- **centroidview**: Combine differential dynamics with differential abundance
  - Demo
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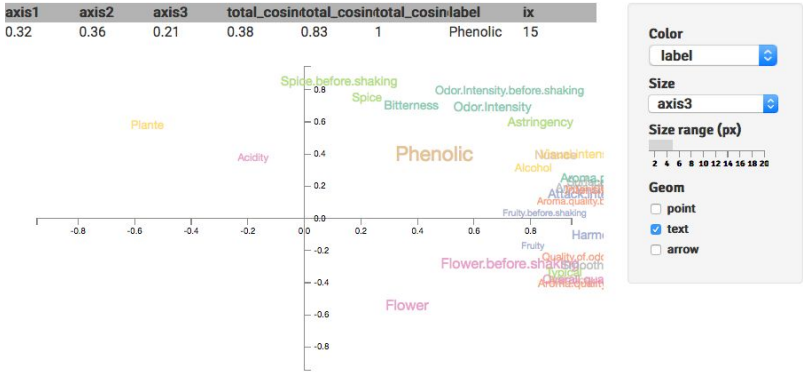
- **mvarVis**: Streamline interpretation of multivariate analysis results
  - Demo
  - Package: github.com/krisrs1128/mvarVis



Conclusion

- Microbiome studies are a source of richly structured, high-dimensional data
- Interactive data visualization and probabilistic modeling can guide the discovery and representation of latent structure

treelapse
- https://krisrs1128.github.io/treelapse/
- Interactive Visualization of Hierarchically Structured Data (Sankaran and Holmes 2017)

Latent variable modeling:
- https://github.com/krisrs1128/microbiome_plvm
- Latent Variable Modeling for the Microbiome (Sankaran and Holmes 2017 (arXiv))

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- Stanford Weiland Graduate Fellowship

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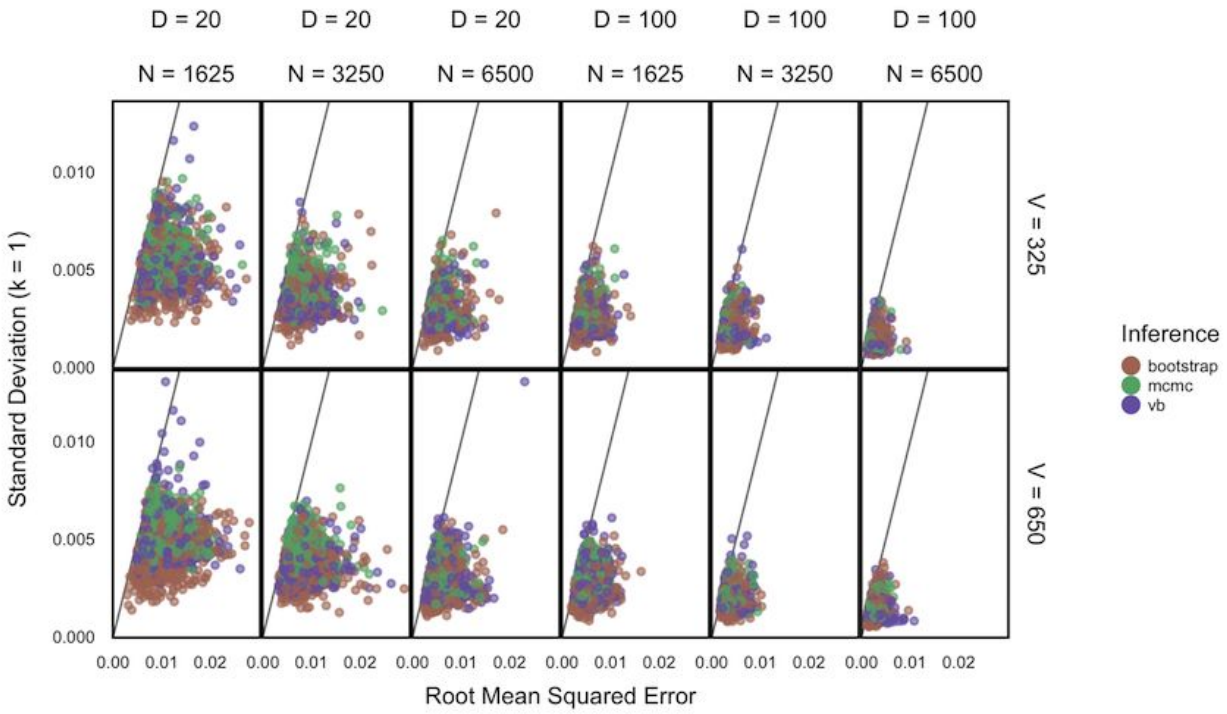
Thank you friends -- Joey A., Jessy, Subhabrata, Zhou, Mona, Stephen, Keli, Pragya, Gene, Robin, Wanning, Chris, Ling, Prof. Zerlang, ... -- for making life here so interesting.

And finally thank you to my family for teaching me everything that was important, besides just statistics.

Simulation Study

- We perform a simulation study to better understand algorithms
  - D: Number of samples
  - V: Number of species
  - N: Sequencing depth
- Colors are inference techniques
- Variational Bayes and the Bootstrap generally underestimate posterior uncertainty, but all become precise with large N



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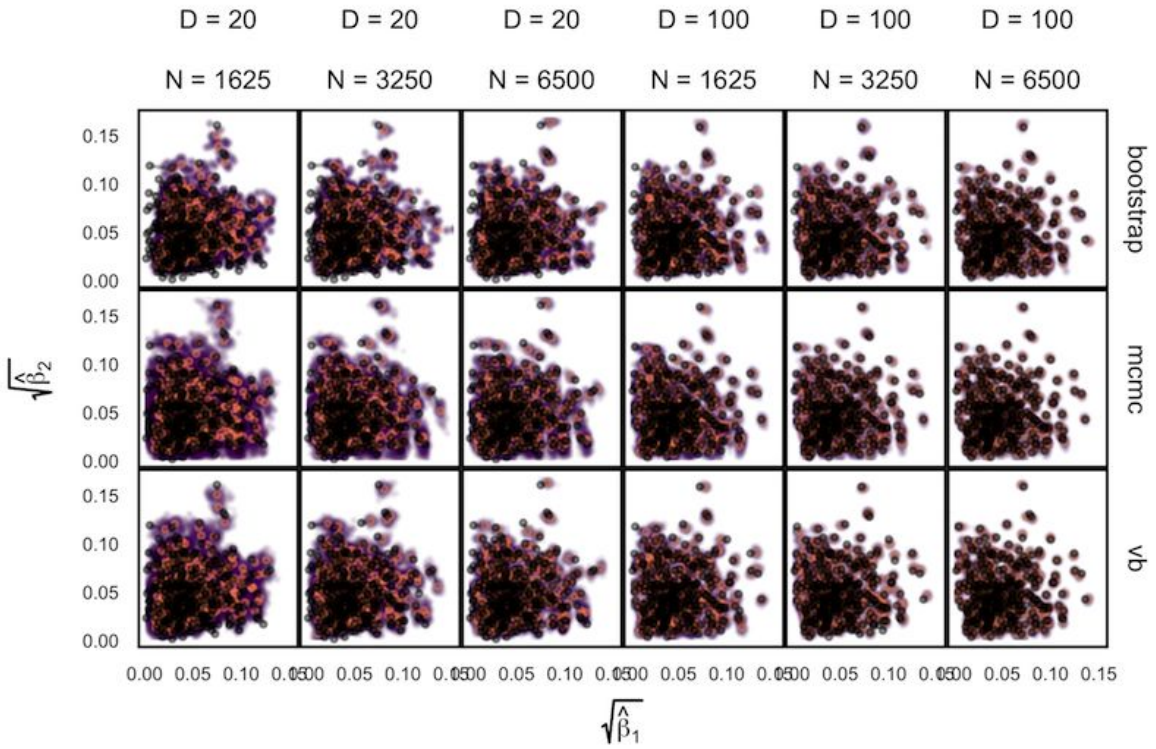
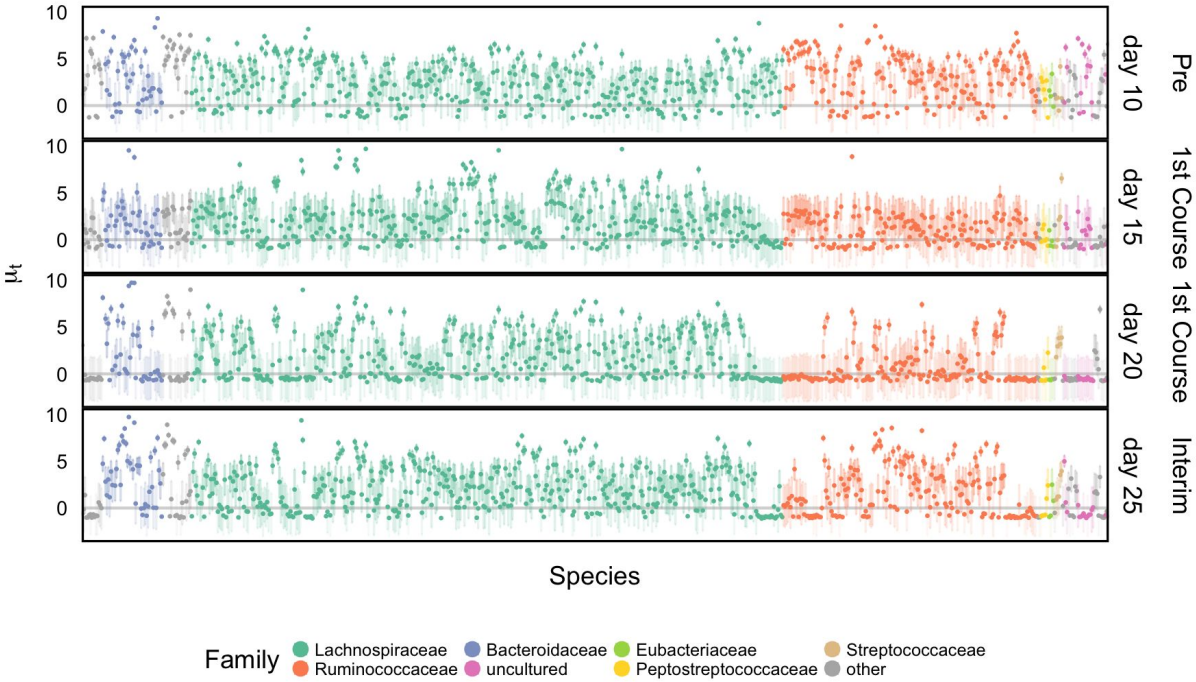


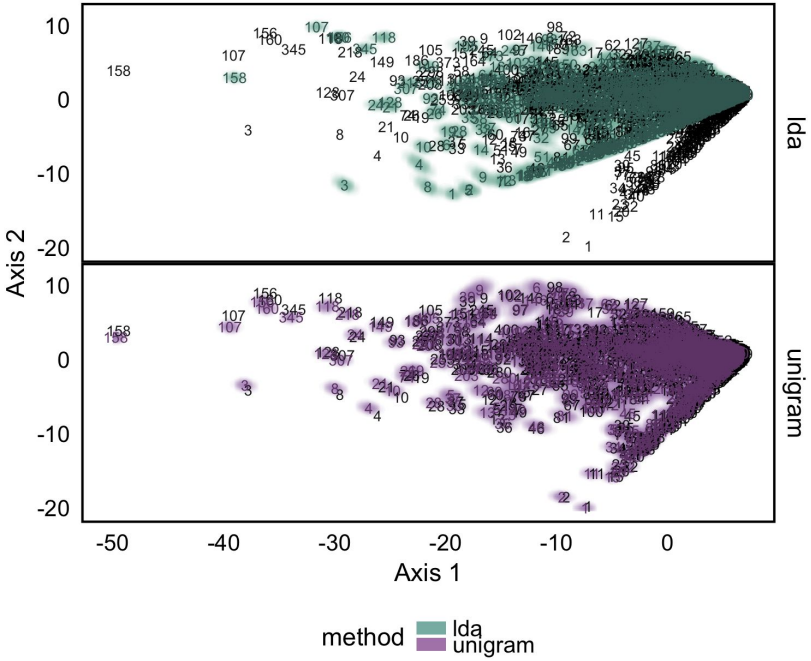
Unigram Smoothed Means: $\mu_{t(d)v}$

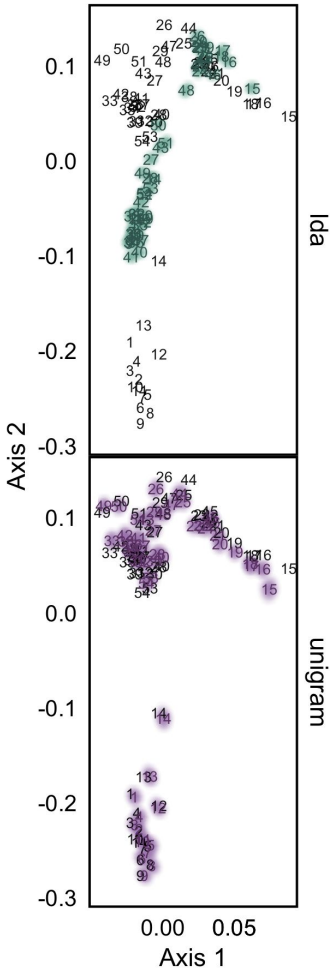
- Intervals represent posteriors for the smoothed means
- Each row is a timepoint, each interval is a species, colors are taxonomic groups
- The third panel down is the first one where antibiotics has been applied, note the drop in diversity



Model Criticism

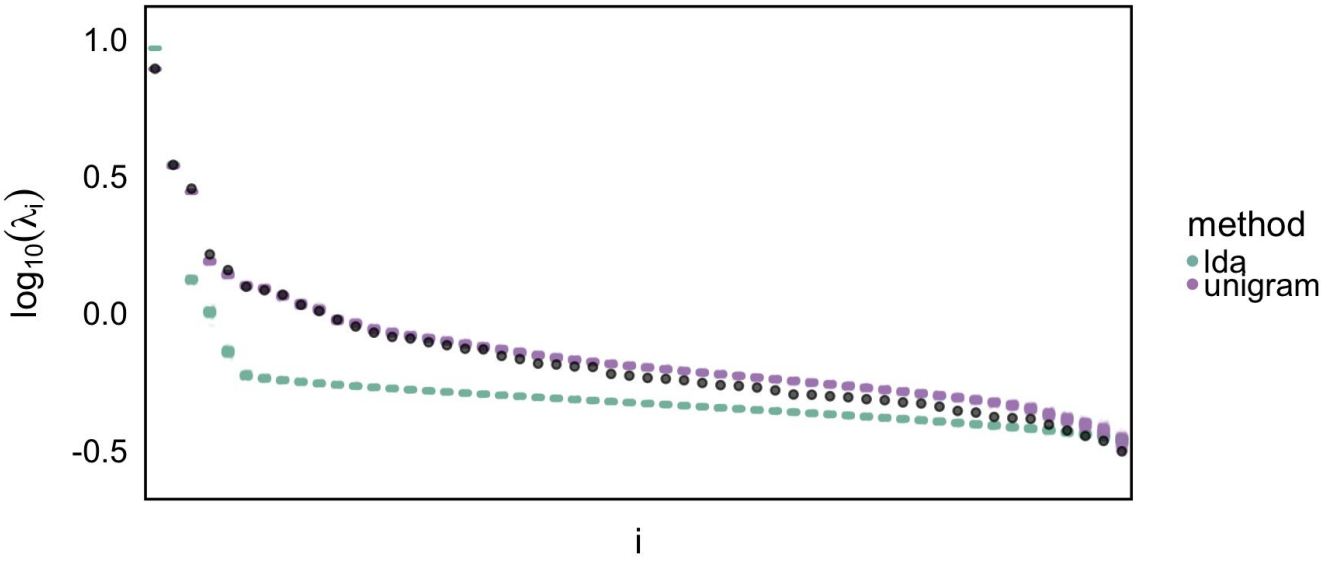
- We can perform PCA on the posterior predictive samples
- Loadings (species) are given on the left, while scores (samples) are given on the right
- Black text are observed scores / loadings, blue and purple clouds are posterior predictive samples
- Scores and loadings have been aligned using a procrustes rotation





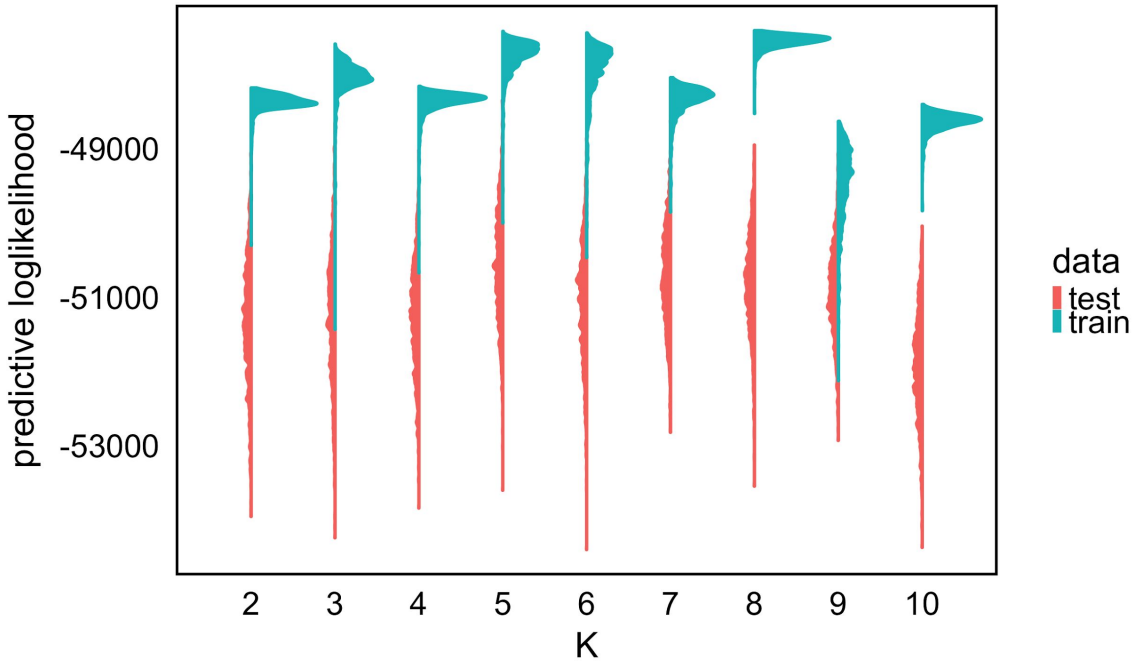
Model Criticism

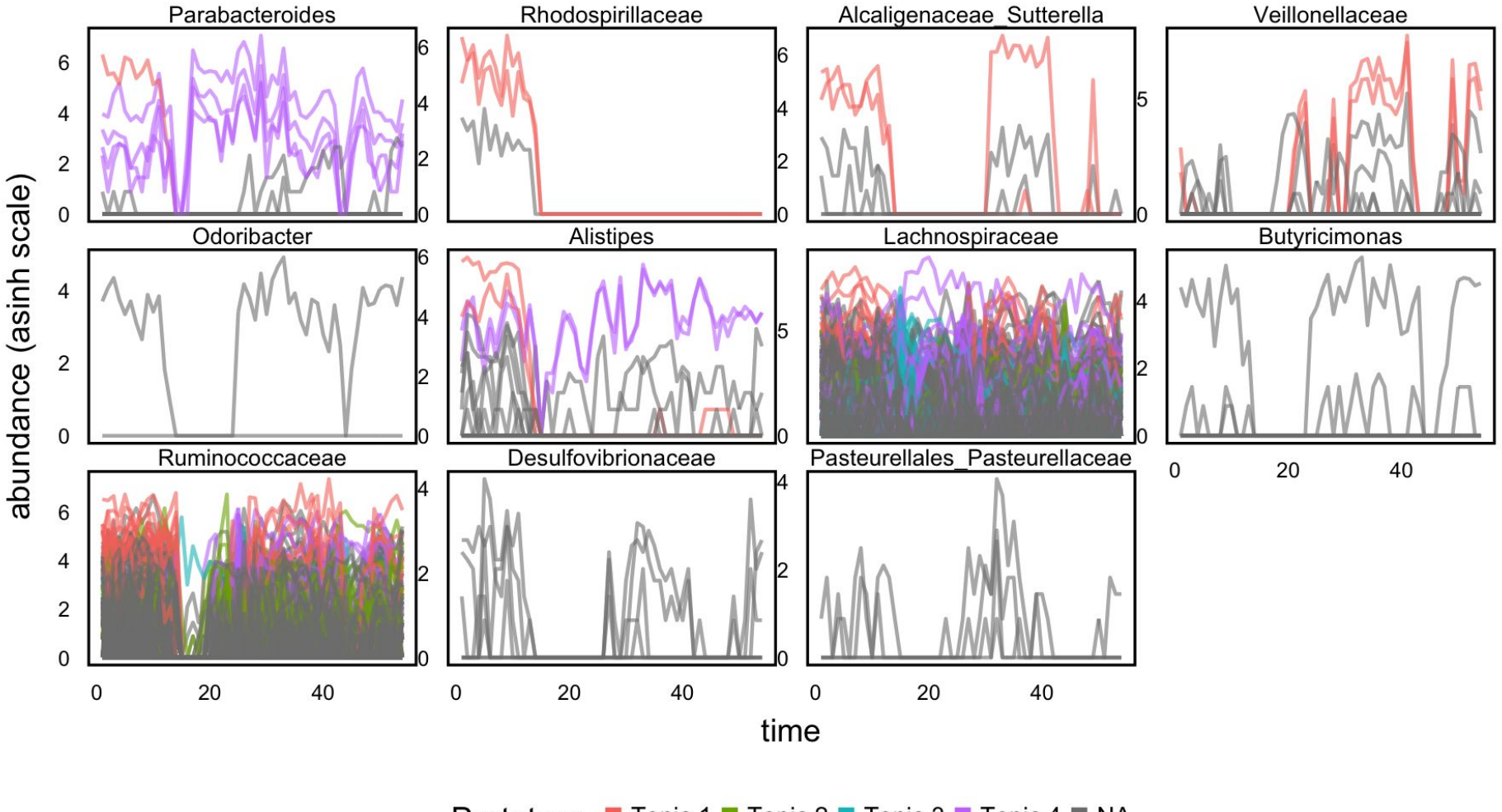
- Eigenvalues from real and posterior predictive samples
- Can be used to guide choice of tuning parameters



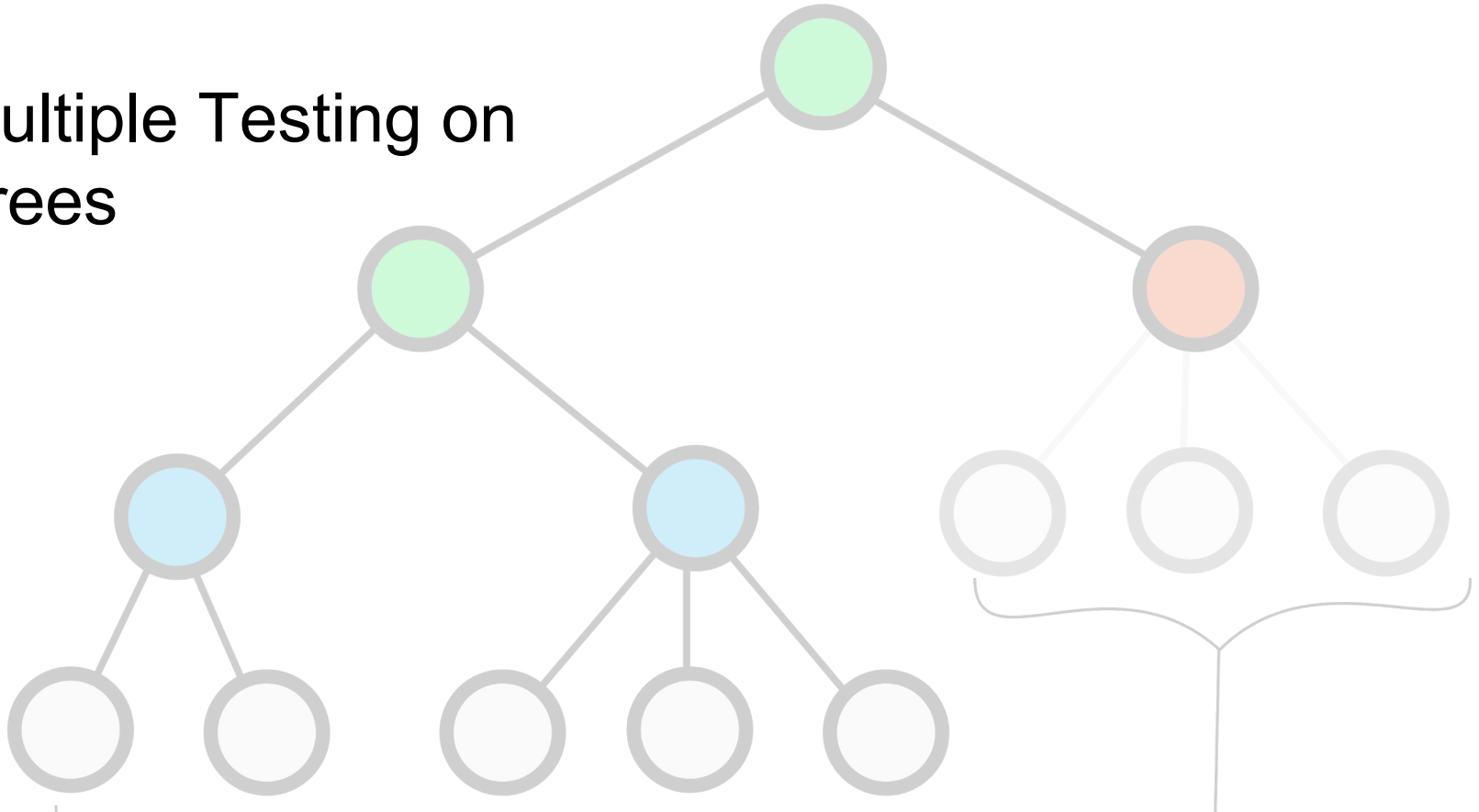
Train / Test log-likelihood

- We can choose k by evaluating the log-likelihood on test data
- Approximate predictive log-likelihoods by sampling the posterior
- Occam's razor effect: larger K don't necessarily increase training log-likelihoods




Parabacteroides
Rhodospirillaceae
Alcaligenaceae_Sutterella
Veillonellaceae
Odoribacter
Alistipes
Lachnospiraceae
Butyricimonas
Ruminococcaceae
Desulfovibrionaceae
Pasteurellales_Pasteurellaceae
abundance (asinh scale)
time
Prototype
Topic 1
Topic 2
Topic 3
Topic 4
NA

Multiple Testing on Trees

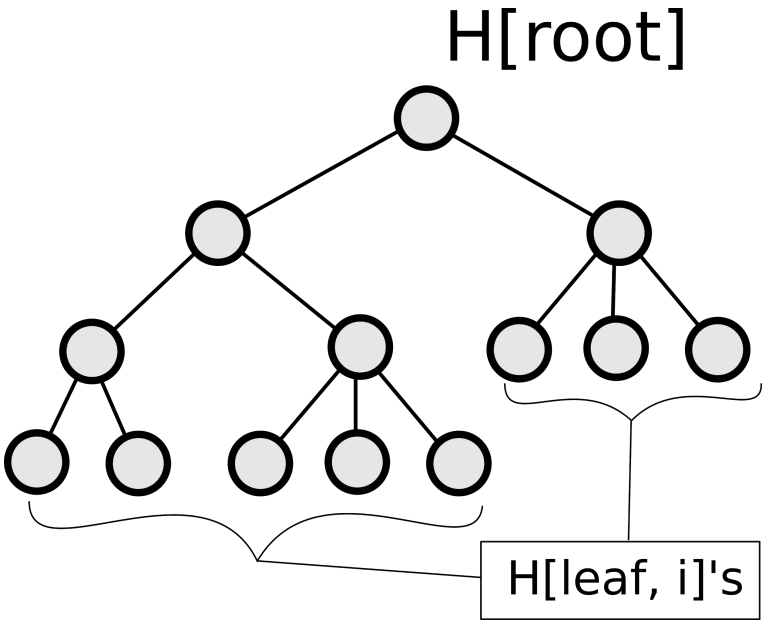


Problem and Approaches

- What is an inferential approach to tree-structured differential abundance?
  - FDR control only applies at the level of individual hypothesis
  - How can we leverage indirect evidence across the tree?
- This question is related to a few recent research programs
  - Testing groups of hypothesis: Group BH, p-filter, Multilayer Knockoffs
  - Hierarchical search: TreeQTL, DAGGER
  - Isolated proposals from bioinformatics: HALLA, OiMAT, StructFDR

A simple algorithm and its properties

A proposal of Yekutieli [2008] is to proceed top-down through a hierarchy, using an FDR controlling procedure for each collection of sibling nodes.



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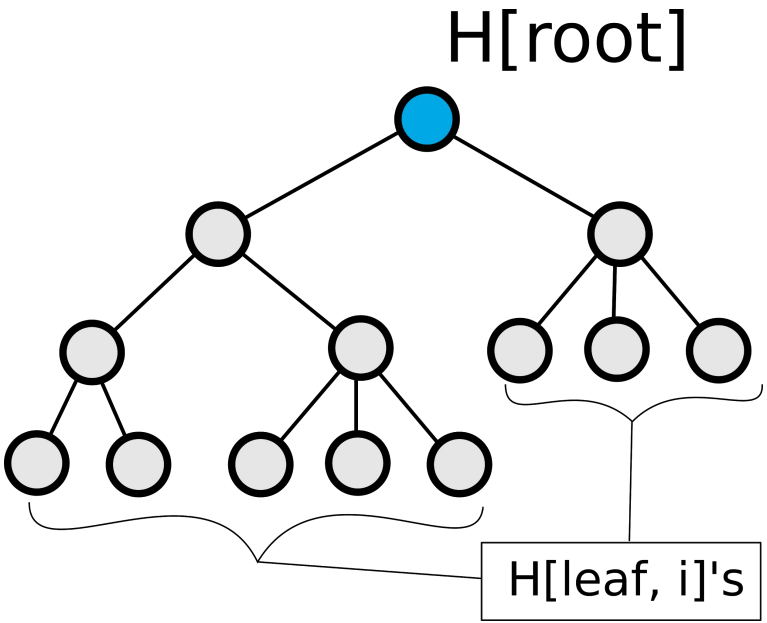

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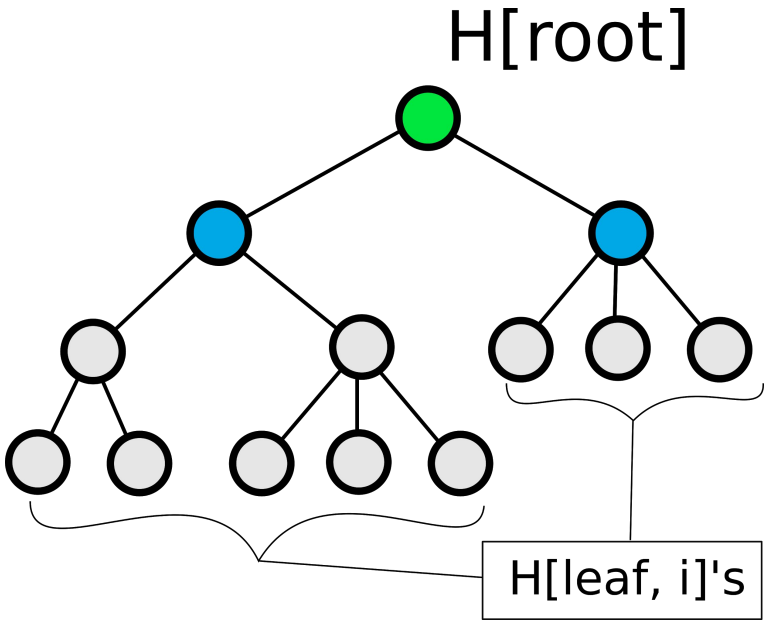

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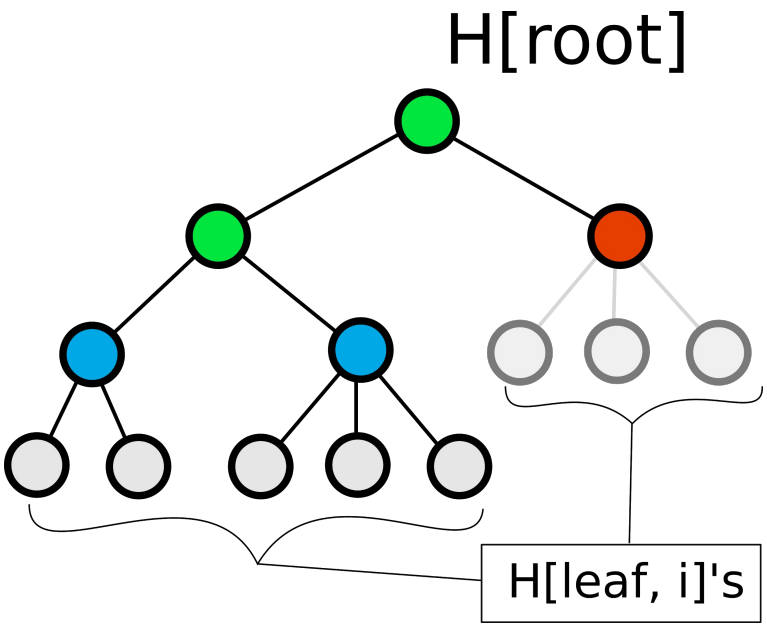

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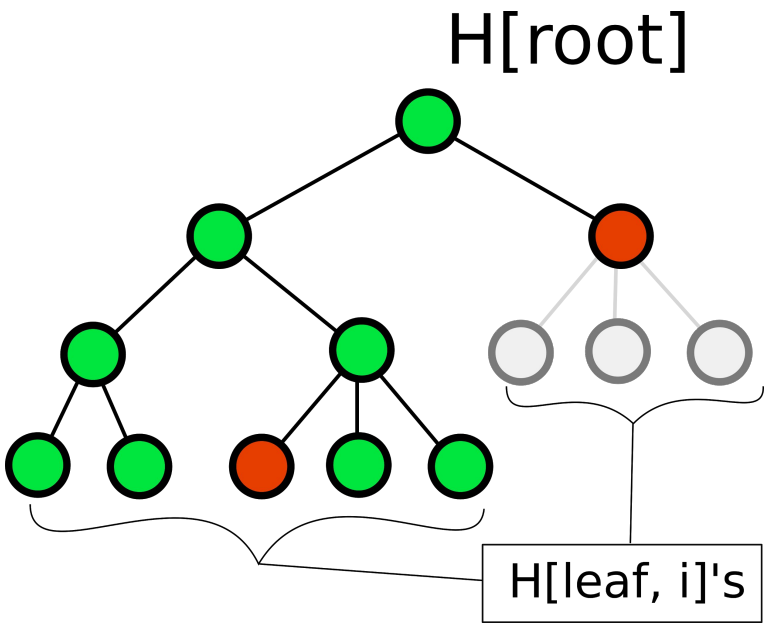

- Test the root. If this fails to reject, report no discoveries.
- If it is rejected, test the children hypothesis with BH.
- If it fails to reject, don't test any of the descendant hypothesis
- Continue testing in this fashion down to the leaves

A simple algorithm and its properties

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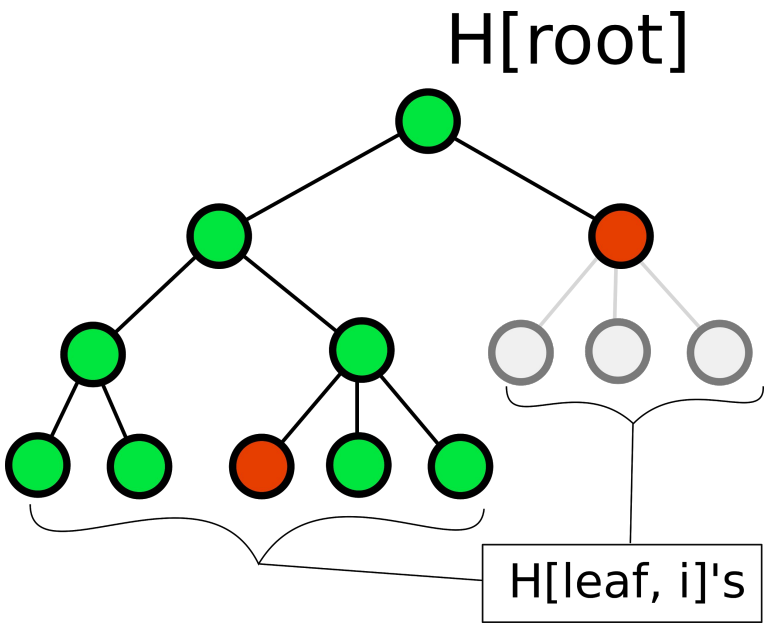


- This procedure was shown to guarantee different types of false discovery rates
- Tree FDR $\leq 2\delta^* q$
- Level-L FDR $\leq 2\delta^* Lq$

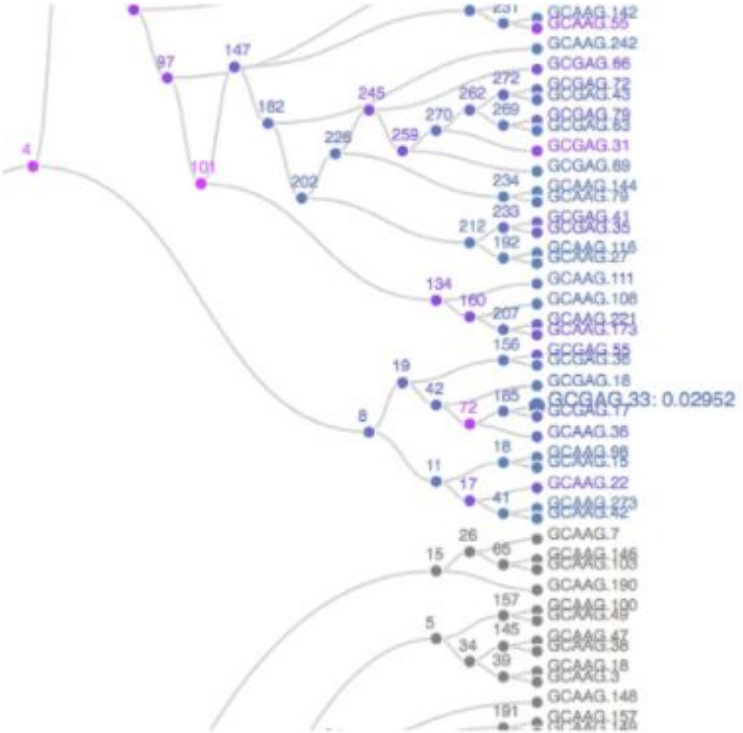
q Sibling-wise BH level

L Depth in the tree

δ^* Universal constant (< 1.44)

Implementation

- We designed and implemented the structSSI (“structured simultaneous and selective inference”) R package [Sankaran and Holmes 2014], implementing this method and a group testing procedure
- Includes utilities for
  - Computing statistics along the tree
  - Interactively inspecting results of confirmatory analysis is better than printing tables of p-values



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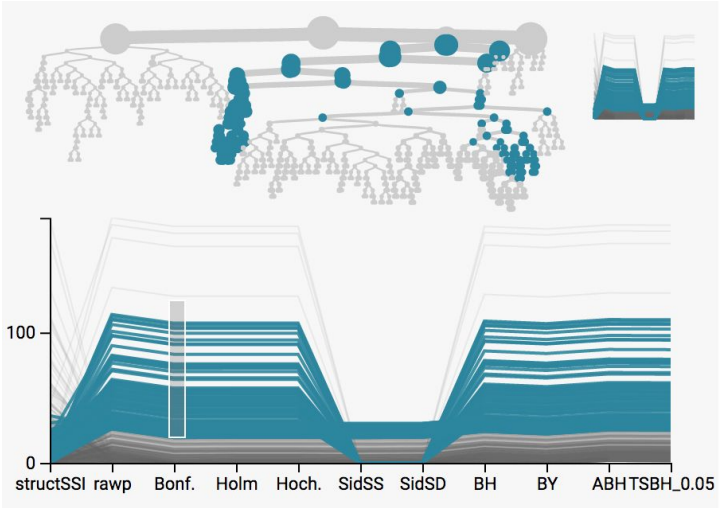

Developments

- Since our work on structSSI, alternative approaches for testing along trees have been proposed
- Petersen et. al. [2016] (TreeQTL), Bogomolov et. al [2017], and Ramdas et. al [2017] (p-filter) describe variations of Yekutieli [2008] that control a selective version of FDR
- Barber and Ramdas [2017] (DAGGER) and Katsevich and Sabatti [2017] (Multilayer Knockoff Filter) describe multilayer approaches to FDR control in the multiple testing and knockoff settings

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