Modeling High-Dimensional Functional and Image Data

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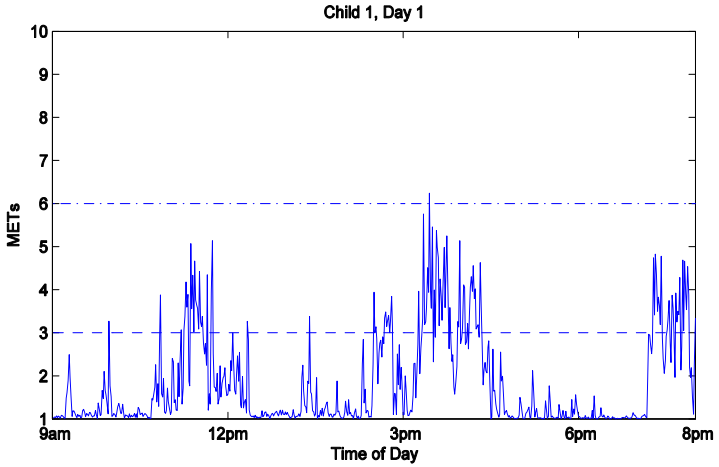
Object Data

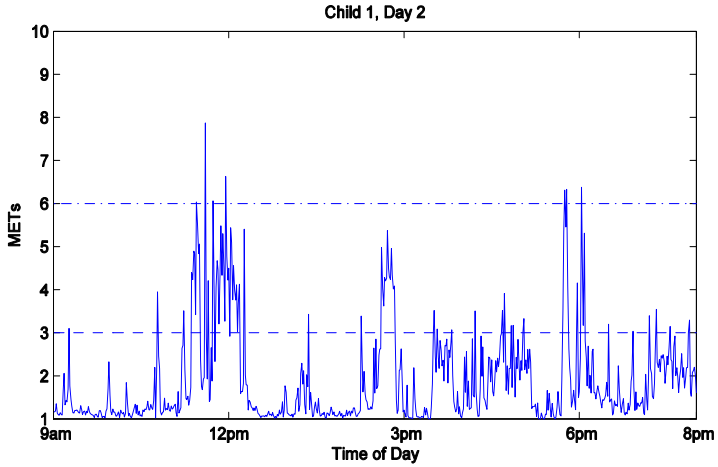
- Technological innovations have produced modern biomedical data that are increasingly complex and high-dimensional
- Object Data: data consisting of multiple (often many) measurements on some type of structured space.
  - **Functional Data**: Time series, measurements on spatial grids, spectral data; e.g. accelerometers, copy number, mass spectra
  - **Quantitative Image Data**: pixel intensities represent some quantitative measure; e.g. fMRI, 2DGE proteomics, LC-MS/GC-MS
  - **Functions on other Manifolds**: spheres or closed surfaces; e.g. ophthalmological data; corticol surface thickness
  - **Other Objects**: shapes, trees, graphs (pathways)
  - **Multi-way Objects**: time-space data, spatial functional data, longitudinal functional data; e.g. ERP, fMRI
  - **Genomic Data**: View entire genome as single structured object
- Internal structure can be simple and driven by basic geometry (space/time proximity), or can be more complex and driven by underlying biology (functional connectivity/pathways)
  - Efficient statistical methods should account for this structure in the modeling. (structure~correlation)

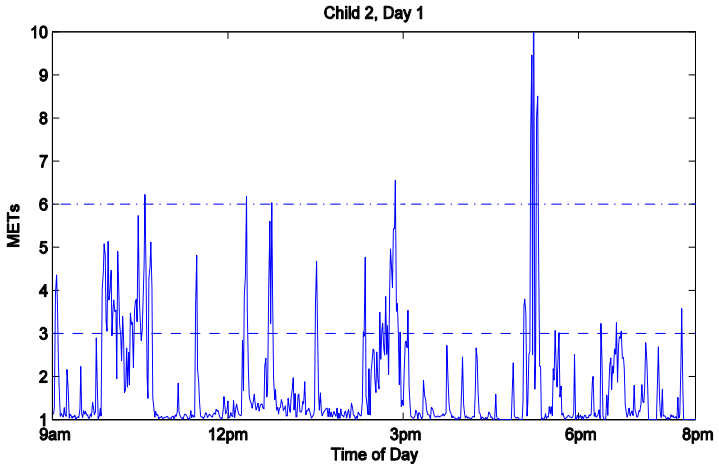
2-D Gel Electrophoresis (2dGE)

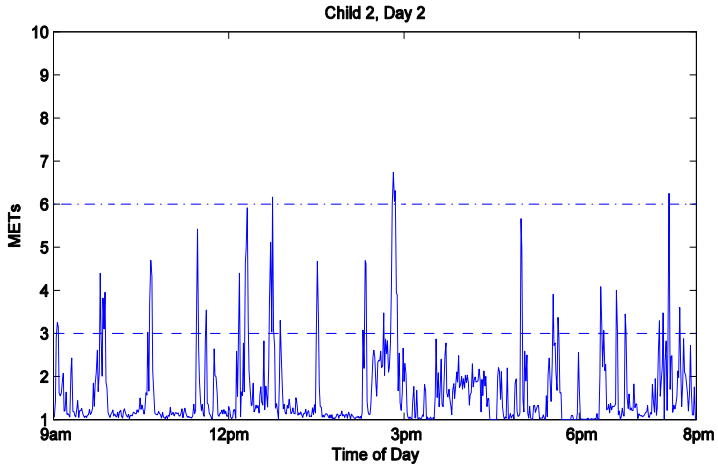
- Each gel scanned, resulting in 2d image (1 MP)
- Frequently have multiple gels per individual
- **Goal**: Associate proteins with factors of interest
- Other assays: MS, lipids + metabolites

Accelerometer Data









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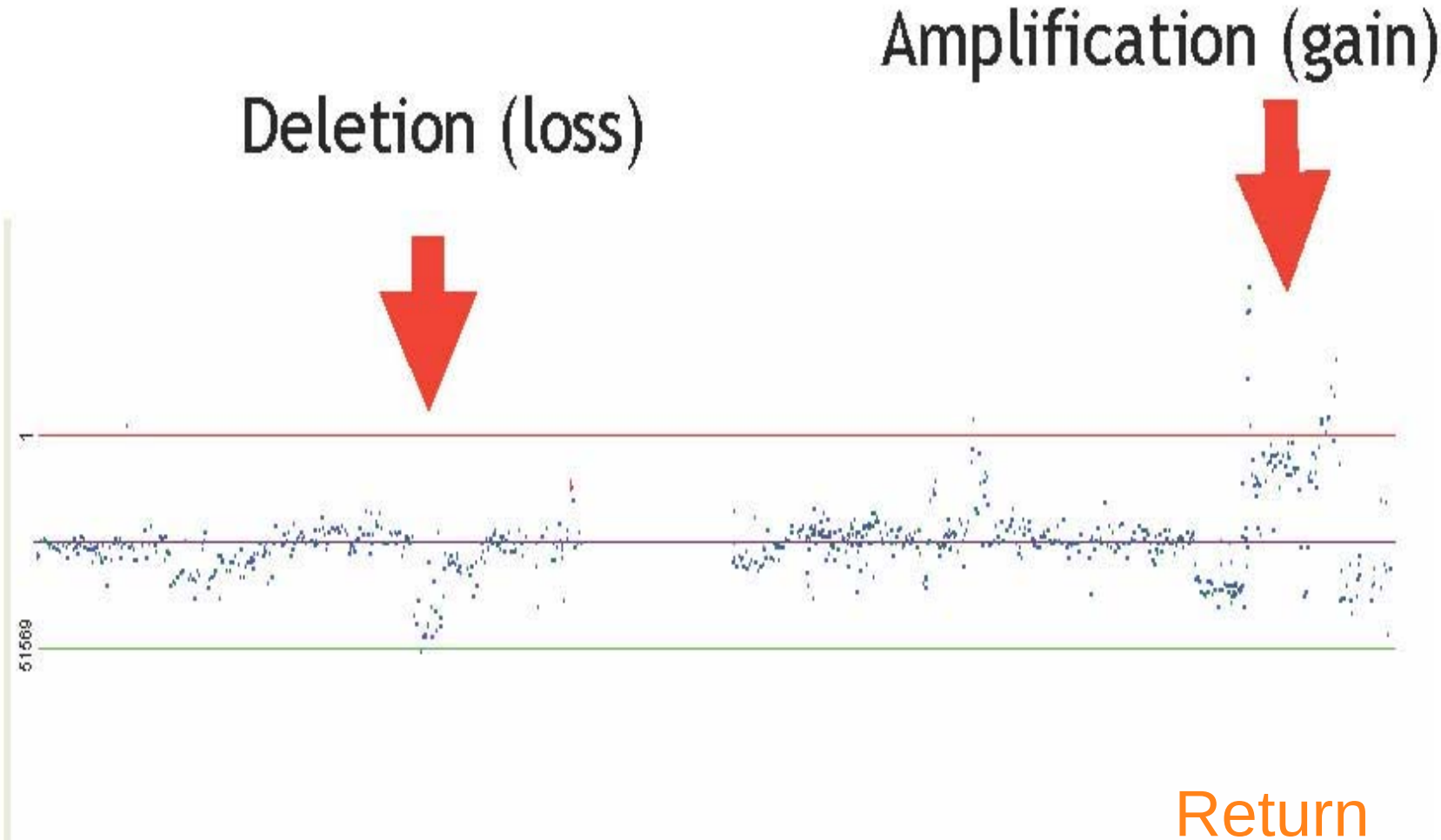
DNA Copy Number Cancer Genomics Study



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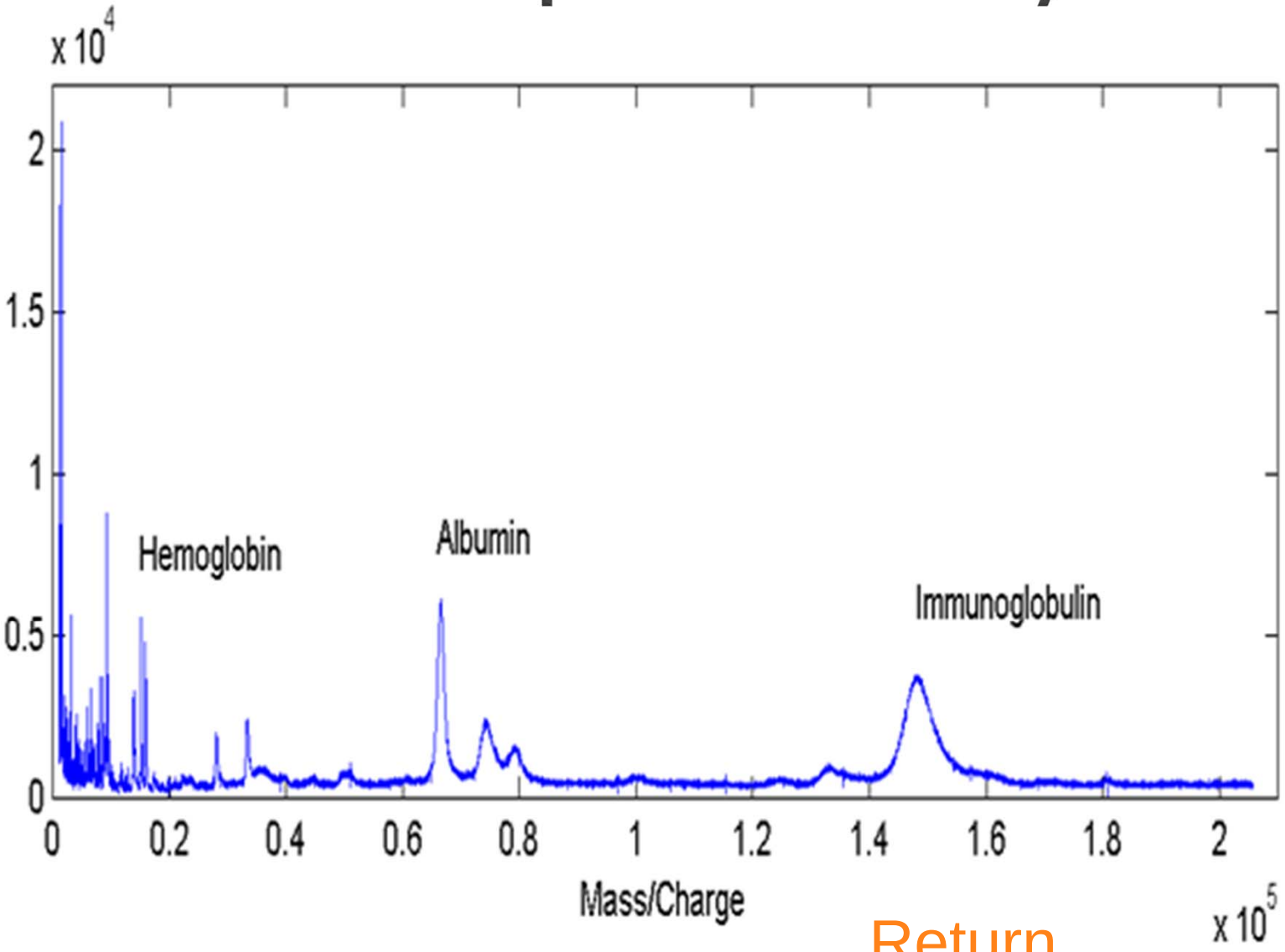
Mass Spectrometry



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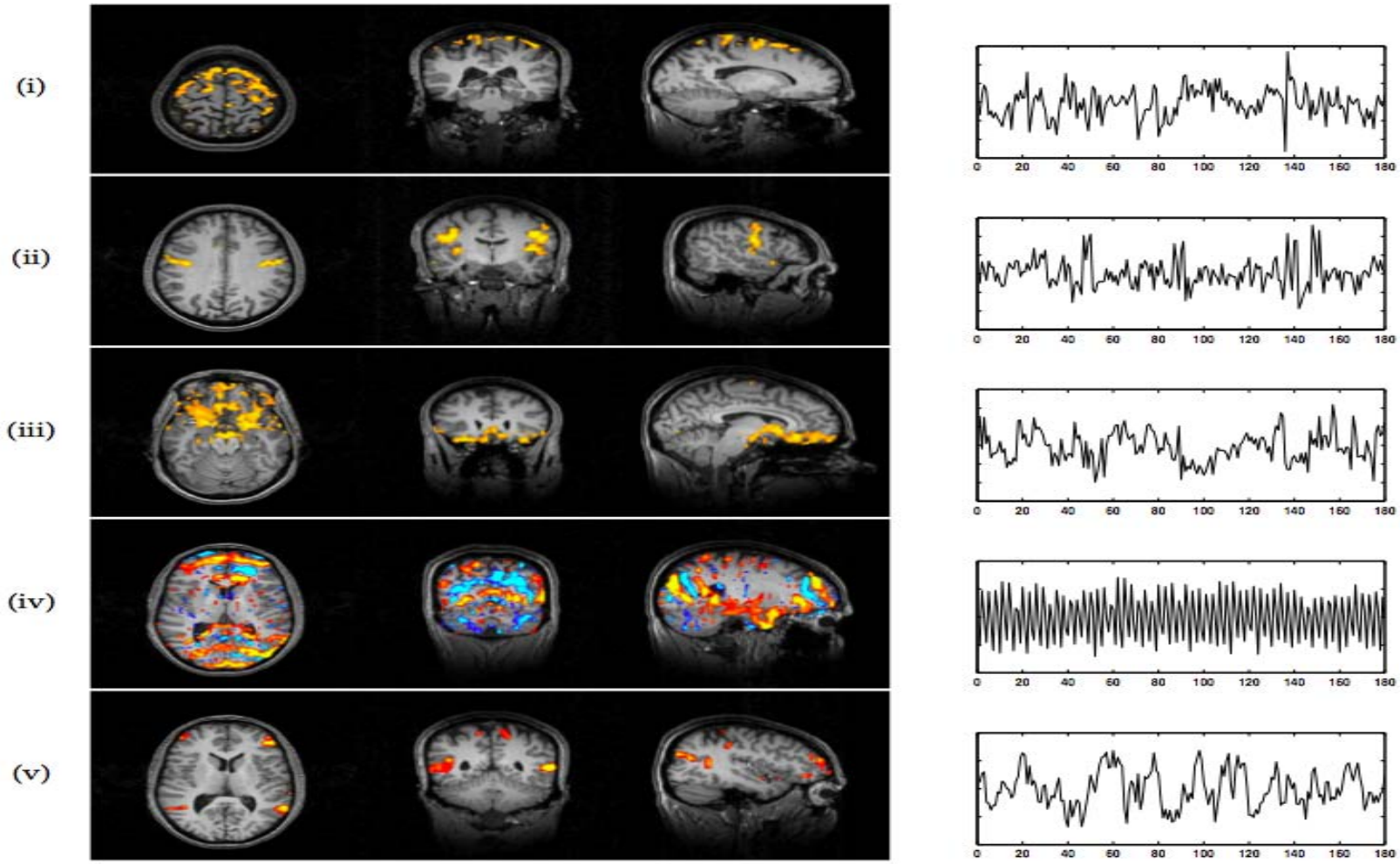
fMRI



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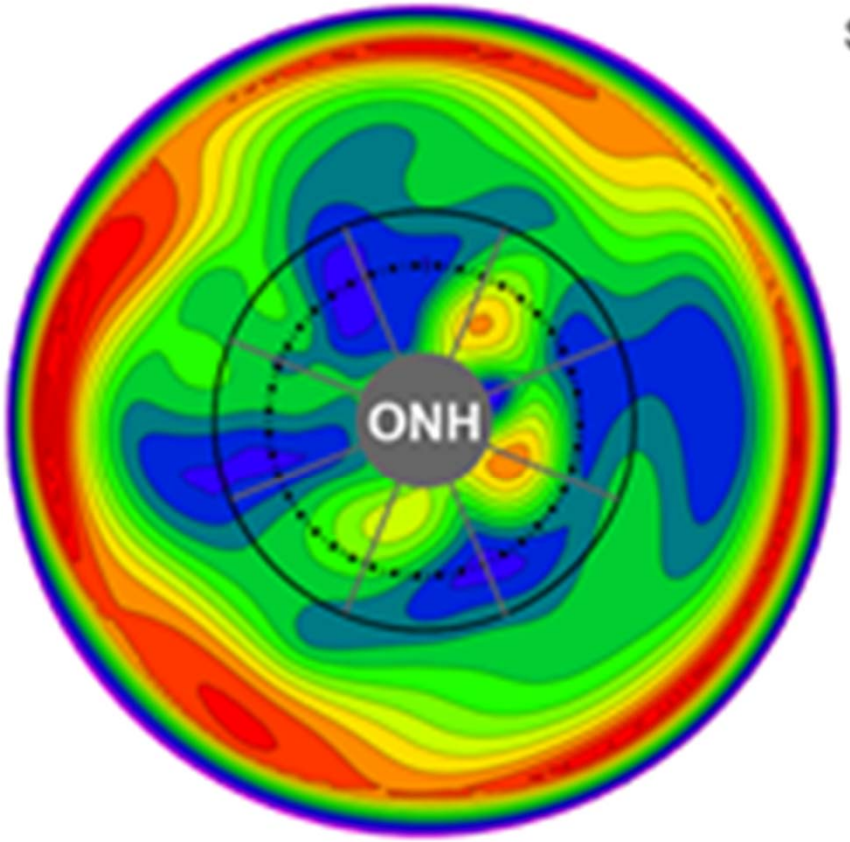
Ophthalmological Data: Scleral Surface Tension



Max. Principal Strain

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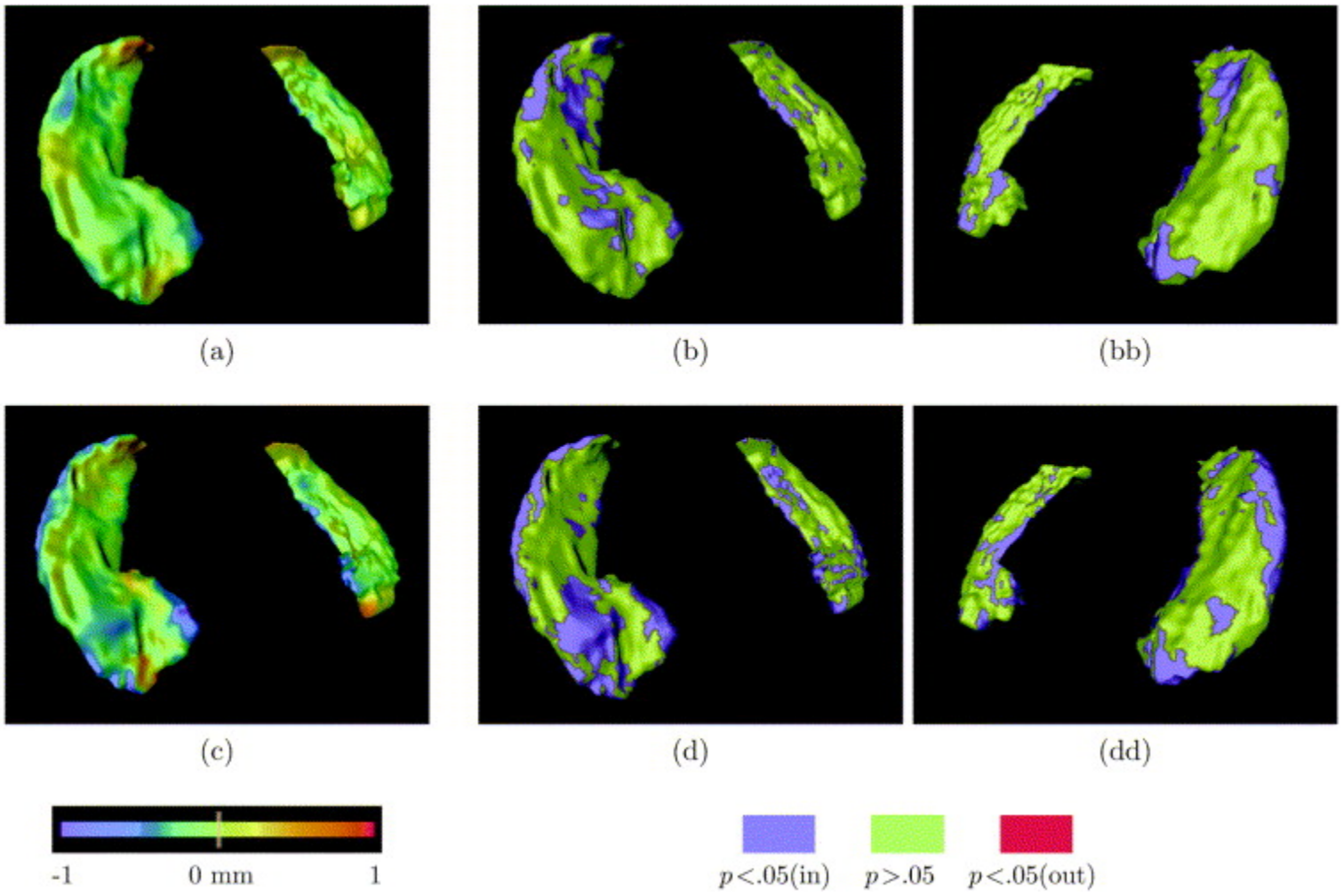
Fazio MA, et al. (2012). Age-related changes in Human Peripapillary Scleral Stiffness. Submitted.

Longitudinal Shape Data



- Wei L, et al. (2003). Changes in hippocampal volume and shape across time distinguish dementia of the Alzheimer type from healthy Aging. Neuroimage 20(2): 667-682.

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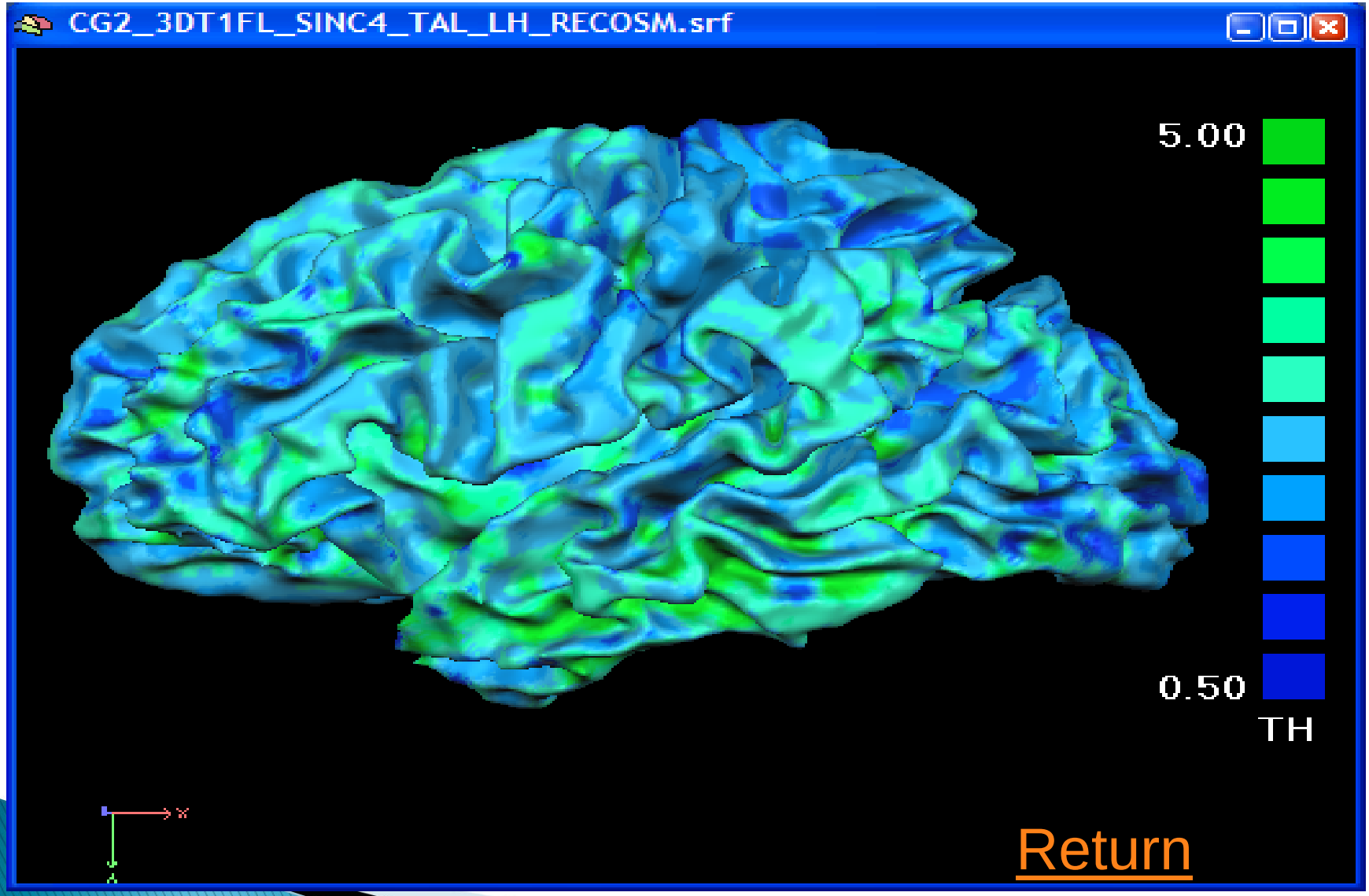
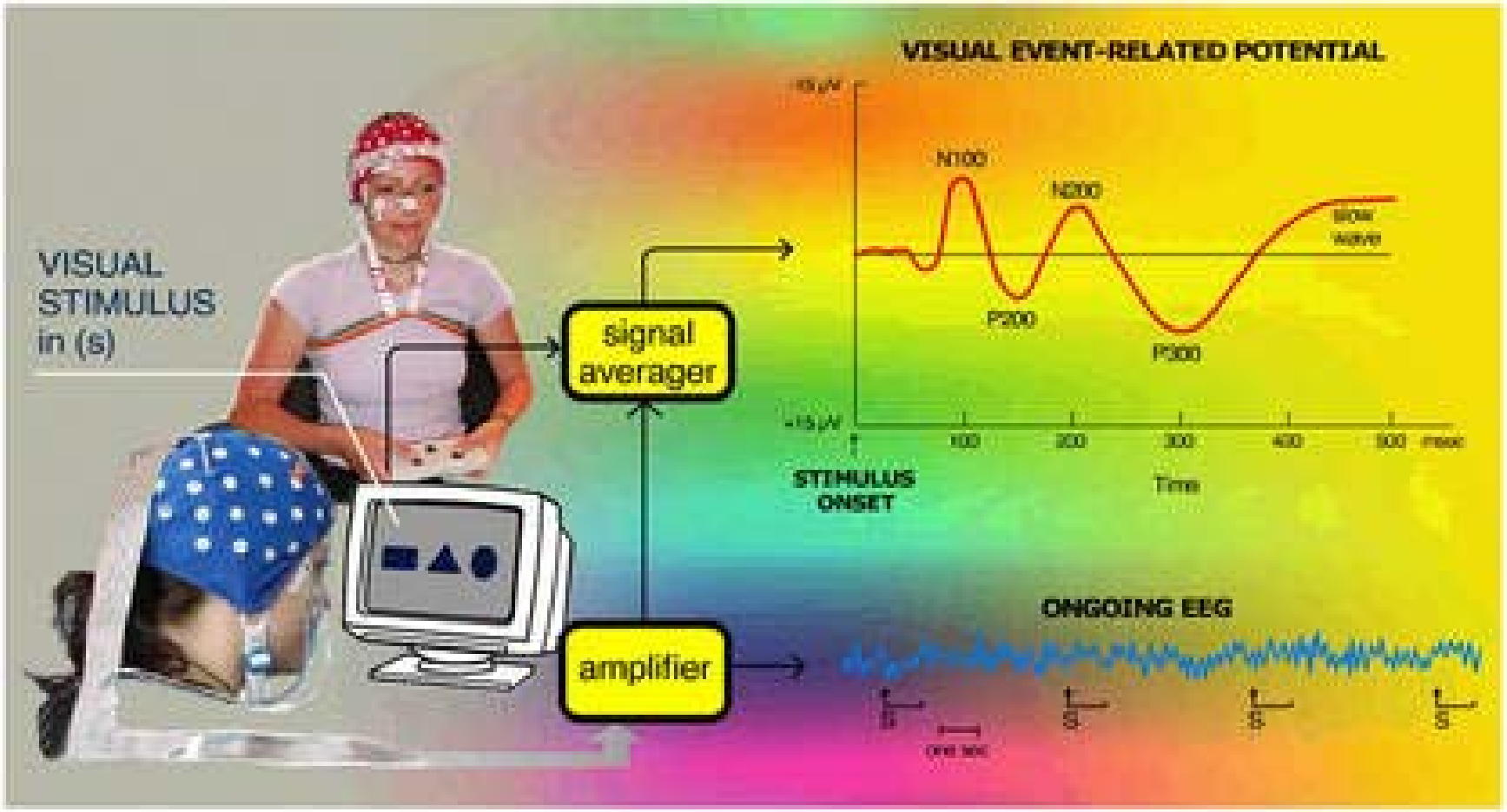
Corticol Surface Thickness



Event-related Potentials (ERP/EEG)



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Key Questions of Interest in Object Data Analysis

1. **Group Comparison**: regression of objects on scalar class predictors to assess which "parts" of the object differ across groups

   Object ~ Class + Covariates

2. **Group Discrimination**: classify subjects into groups based on their object data; e.g. by regressing class on object.

   Class ~ Object + Covariates

3. **Clustering**: unsupervised clustering of subjects based on their object data.

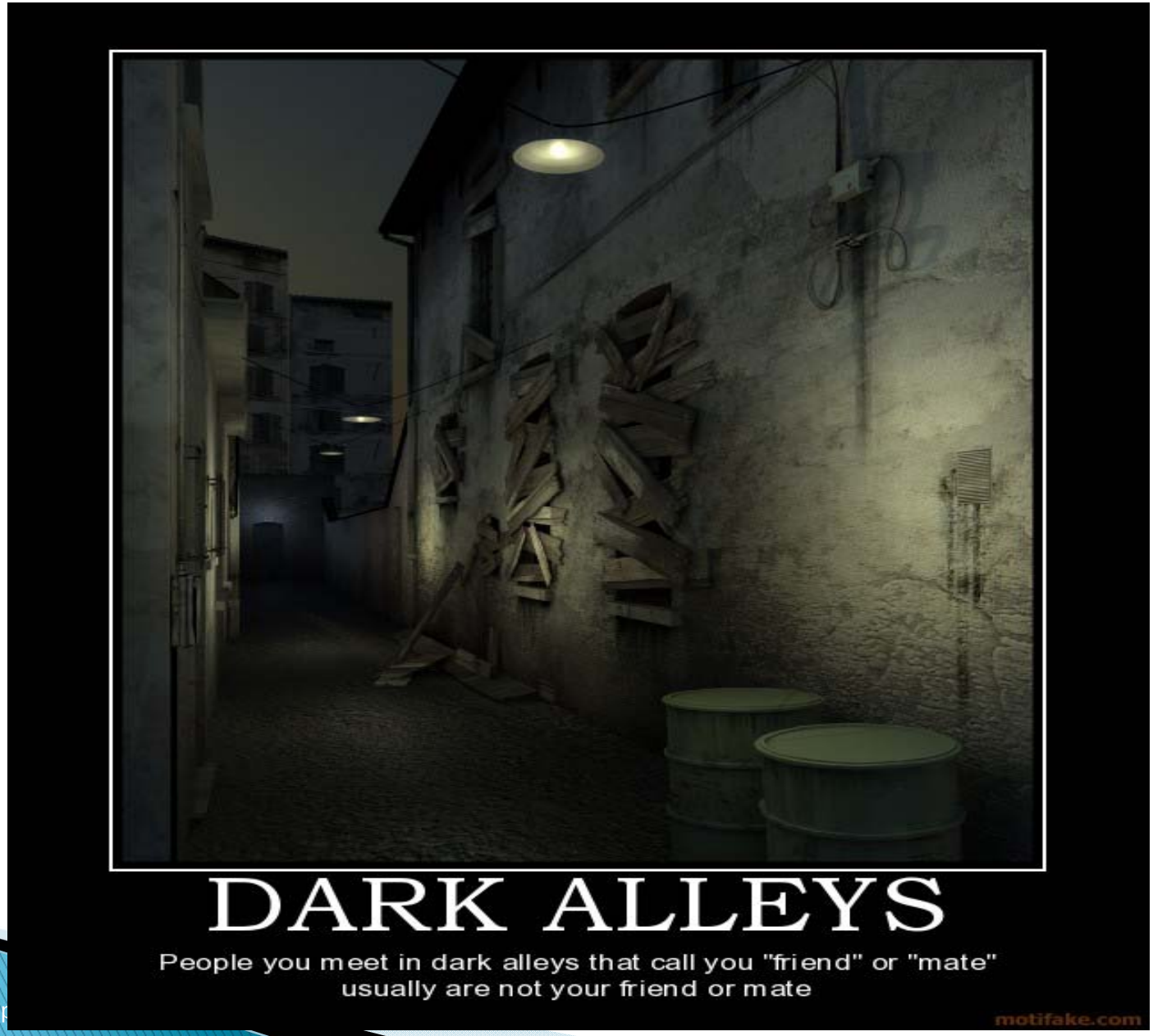
Standard Approach 1: Feature Extraction

- Compute summary statistics from object and then perform standard analyses on the summaries
- **Examples**:
  - *Accelerometers*: average daily levels, % above threshold
  - *Mass spectra*: detect peaks, then analyze by peak
  - *2dGE*: detect spots, then analyze by spot
  - *fMRI*: integrate within known brain regions (ROI)
  - *Copy number*: segments of gain/loss on individual array
- **Benefits**: reduces dimensionality, can incorporate biological information about objects, easy to use
- **Drawbacks**: loses information not in summaries

Looking under the Lamp Post

"I'm searching for my keys."

Complex Data are Scary!!!



Standard Approach 2: Element-wise Modeling

- Apply standard statistical tests on each element of the object, treating them as independent
- **Examples**:
  - *Time series*: separate analyses at each time point
  - *fMRI*: separate analyses for each voxel in the brain
  - *ERP*: separate analyses for each EEG sensor
- **Benefits**: retains all information, easy to implement
- **Drawbacks**: doesn't borrow strength across measurements within an object; ignores internal structure; inefficient; may give misleading inference

Element-wise Modeling

- "No object element is an island"
- They have neighbors, and should be allowed to share with and borrow from their neighbors

Approach 3:
Statistical Modeling of Object Data

- Increasingly, statisticians are developing innovative statistical models to account for internal structure in objects, e.g. functional data analysis (FDA).
- **Note**: Dimensionality typically precludes modeling within-object correlation in unstructured fashion
- Alternative: use **basis functions**/**frames** to parsimoniously capture the local (splines, kernels, wavelets) or global (PCA) internal structure within the objects.
- **Challenges:** Scale up to extremely large data sets
  - Provide unified inference that accounts for sources of var.
  - Handle multiple types of objects with different structure
  - Be able to model common types of between-object structure from experimental design (subsamples; nested designs; longitudinal objects)

MaTaDOR: MulTi-Domain Object Regression

General suite of methods for object data analysis

- Flexible enough for broad class of objects
- Models object~scalar, scalar~object, object~object
- Can account for various types of between-object structure induced by experimental design
- Yields unified Bayesian inference, including pointwise and joint intervals and FDR thresholds
- Automated code that scales up to EXTREMELY large data sets (up to 100s of GBs)
- Can incorporate **biological knowledge** as well as uncover **unknown structure**
- Modular approach: extendible in many ways as we keep building on the core method/code

Model 1: GLOMM
Generalized Linear Object Mixed Models

$$g\{E(X_i)\} = \sum_{a=1}^{p_Y} \int_{\mathrm{T}} Y_{ia}(t) B_a(t) dt + V_i \boldsymbol{\beta} + \sum_{h=1}^{H} Z_{ih} \mathbf{U}_h + \varepsilon_i$$

- X_i: exponential family response, g: link function
- $Y_{ia}(t)$: object predictor of type a, subject i
- t: index for elements w/in object (may be multi-dim)
- $B_a(t)$: object regression coefficient for type a
- V_i and β: vectors of scalar predictors and coeffs.
- Z_{ih} and $\mathbf{U}_h$: random predictors/coeffs at level h
- ε_i: residual error in latent space

Model 2: ORMM
Object Response Mixed Models

$$Y_i(t) = \sum_{a=1}^{p_X} X_{ia} B_a(t) + \sum_{h=1}^{H} \sum_{b=1}^{p_h} Z_{hib} U_{hb}(t) + E_i(t)$$

- $Y_i(t)$: object response for subject i for element t
- X_{ia} and $B_a(t)$: predictor and fixed effect object a
- Z_{hib} and $U_{hb}(t)$: predictor and random effect objects
- $E_i(t)$: residual for subject i at object element t
- $\mathrm{Cov}\{U_{hb}(t_1), U_{hb'}(t_2)\} = \boldsymbol{P_{(h)bb'}} \boldsymbol{Q_h(t_1,t_2)}$; $\mathrm{Cov}\{E_i(t_1), E_{i'}(t_2)\} = \boldsymbol{R_{ii'}} \boldsymbol{S(t_1,t_2)}$
- $\boldsymbol{P_{(h)}}$, $\boldsymbol{R}$: between-object covariance matrices
- $\boldsymbol{Q_h(t_1,t_2)}$, $\boldsymbol{S(t_1,t_2)}$: within-object covariance surfaces (form reflects internal structure of objects)

Multi-Domain Modeling of Object Data

- $\boldsymbol{Y}$=matrix ($N \times T$) of object data, on same T elements
- Write out basis function expansion: $Y=Y^*\phi$
  - ϕ =matrix ($T^* \times T$) of basis functions on grid of size T
  - Y^*=matrix ($N \times T^*$) of basis coefficients (T^* coefficients)
- Compute basis coefficients $Y^*=Y\phi^-$
- ϕ^-= ***transformation matrix*** (data space Y to basis space Y^*)
- ϕ = ***inverse transform matrix*** (basis space Y^* to data space Y)
- Multi-Domain Modeling Approach

1. Transform objects into alternative domain ($Y \rightarrow Y^*$)
2. Fit alternative-domain object regression models (ORMM/GLOMM)
3. Transform object coefficients back to data domain $\{B^* \rightarrow B(t)\}$
4. Perform Bayesian inference in data domain

Basis Function Modeling

- Types of Basis Functions
  - Local: splines, Fourier, wavelets, needlets (sphere)
  - Empirical: PC, fPC, sPC, gPC, IC, PLS, GLRAM
  - Biological: ROI, peak templates, pathway bases
- For many basis functions, special fast algorithms exist for computing Y^* from Y or Y from Y^*
  - E.g., wavelets O(T), Fourier O($T \log T$), PC, IC
- For many other basis functions, the transform and inverse transform matrices ϕ and ϕ^- are sparse, and only need be computed once.
- Many bases yield parsimonious representations , i.e. $T^* \ll T$, greatly reducing dimensionality while retaining most all information in data

Alternative Domain ORMM

$$Y^*_{ik} = \sum_{a=1}^{p_X} X_{ia} B^*_{ak} + \sum_{h=1}^{H} \sum_{b=1}^{p_h} Z_{hib} U^*_{hbk} + E^*_{ik}, k = 1, \ldots, T^*$$

- Y^*_{ik}: basis coefficient k for subject i
- B^*_{ak}, U^*_{hbk}, E^*_{ik} : basis space fixed, random, residual
- $\mathrm{Cov}\{U_{hbk}, U_{hb'k}\} = P^h_{bb'} q_{hk}$ $\mathrm{Cov}\{E_{ik}, E_{i'k}\} = R_{ii'} s_k$
- Computing is parallelizable and linear in T^*
- Form of $Q_h(t_1,t_2)$ and $S(t_1,t_2)$ defined by T^* dimensional manifold: $Q_h(t_1,t_2) = \phi' Q^*_h \phi$ and $S(t_1,t_2) = \phi' S^* \phi$ $Q^*_h = \mathrm{diag}_k\{q_{hk}\}$ $S^* = \mathrm{diag}_k\{s_k\}$
- Covariance of dimension T^* but flexibly capturing internal structure of object given suitably choice of basis
- Random effects U^*_{hbk} and residuals E^*_{ik} assumed Gaussian or for robust regression, heavier tailed distribution (DE)

Why Bayesian Modeling?

- Could fit ORMM without using Bayesian modeling
  - Mixed model (perhaps with penalty for regularization)
- So why do we use a Bayesian approach?
  - Our Bayesian approach does not require subjective priors
  - Automatically obtain pointwise/joint inference all model quantities
    - Posterior probabilities of effect sizes: connection to FDR
  - Unified modeling approach integrates over all variability
  - MCMC can be challenging in some high dimensional contexts, but here we have stable, automated algorithm.
  - Straightforward approach to handle measurement error and missing data. *(Morris, et al. 2006 JASA)*
  - Natural way classification.*(Zhu, Brown, Morris, 2012 Biom)*
  - Extendability: can make other distributional assumptions and sparsity priors and get improved performance (e.g, robust FMM; *Zhu, Brown, Morris 2011 JASA*)

Sparsity priors for fixed effects B^*_{ak}

- Spike_0/Gaussian, DE, Spike_0/DE, NG, NEG, NMIG, HShoe
- Performs variable selection/nonlinear shrinkage on B^*_{ak}
  - E.g. Gaussian = ridge regression, DE = Lasso
  - Induces **structured regularization** of $B_a(t)$, which is a type of smoothing within manifold defined by basis functions that should take internal structure of the object into account.
- Amount of regularization depends on set of **sparsity hyperparameters**, which can be estimated from data or given their own hyperpriors.
- This regularization should lead to improved estimation and inference on fixed effect functions $B_a(t)$

Model Fitting and Inference

- Model fit by automated MCMC (MH w/in Gibbs)
  - Parallelizable in MCMC iterations and/or basis coeffs. k
- Inverse transform ϕ used to transform posterior samples back to data space, e.g. $B_a(t)$, for inference
- Useful types of Bayesian Inference
  - Pointwise posterior credible intervals
  - Joint posterior credible intervals
  - Posterior probability (*pp*) of minimal effect size δ (posterior probability maps on object space)
  - Can find threshold on *pp* that corresponds to average Bayesian FDR of α. This approach takes both statistical and practical significance into account (Morris, et al. 2008 *Biometrics*)

Brain proteomics addiction study (Gutstein, MDACC)

- **Goal:** Find brain proteins related to cocaine addiction
- **Animal Model:**
  - Mice trained to obtain cocaine by pressing lever.
  - 21 mice, 6 short access (1hr), 7 long access (12hr), 8 ctrl
  - Mice euthanized, brain tissue harvested, microdissected
- **2d Gels**
  - Total of 53 gels from 21 rats, run on central nucleus of amygdala region (CeA) of brain
- **Analysis objective:**
  - Find proteins that are overexpressed/underexpressed in cocaine exposure group relative to controls.

Brain proteomics addiction study

- Standard analysis approach: **Spot-based**
  - Detect spots, quantify spot volumes, then analyze
  - Many flaws in existing commercial spot detection algorithms (*Gutstein and Clark 2009*)
  - *Pinnacle*: improved spot detection/quantification (*Morris, Clark, Gutstein 2008*, *Morris, et al. 2010*)
- Still limited in ability to detect and resolve all protein spots; e.g., **co-migrating proteins**
- Can we build models suitable for the scanned images themselves and flag significant regions?
- Would such an approach find more proteins and better separate effects of co-migrating proteins?
  - Morris (2011 Statistics and Its Interface): summary of work in statistics for proteomics data

Brain proteomics addiction study

- 53 gels, 21 mice, 3 groups (C/SA/LA), run in blocks
- (*Morris, et al. 2011 AOAS*): with Gutstein, Baladan.
- MODEL:

$$\underbrace{\log_2\{Y_i(t_1,t_2)\}}_{\text{response images}} = \sum_{j=0}^{2} \underbrace{X_{ij}}_{\text{group indicators}} \overbrace{B_j(t_1,t_2)}^{\text{group } j \text{ mean image}} + \sum_{k=1}^{21} \underbrace{Z_{ik}}_{\text{rat indicators}} \overbrace{U_k(t_1,t_2)}^{\text{Rat } k \text{ random effect image}} + \underbrace{E_i(t_1,t_2)}_{\text{residual error images}}$$

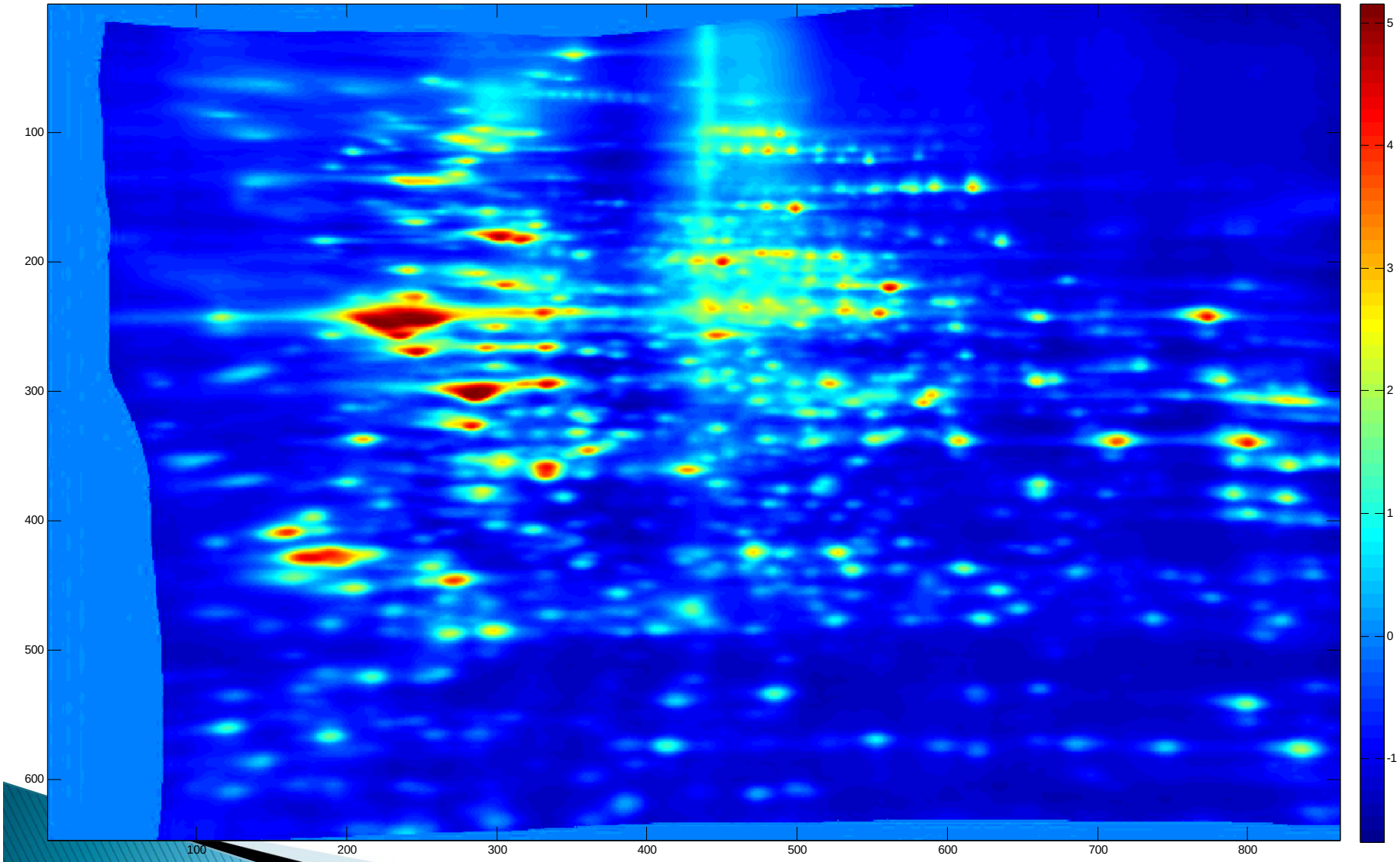
- Construct overall mean, case-control images:

  Mean Image: $M(t_1,t_2)=1/3\ \{B_0(t_1,t_2) + B_1(t_1,t_2) + B_2(t_1,t_2)\}$

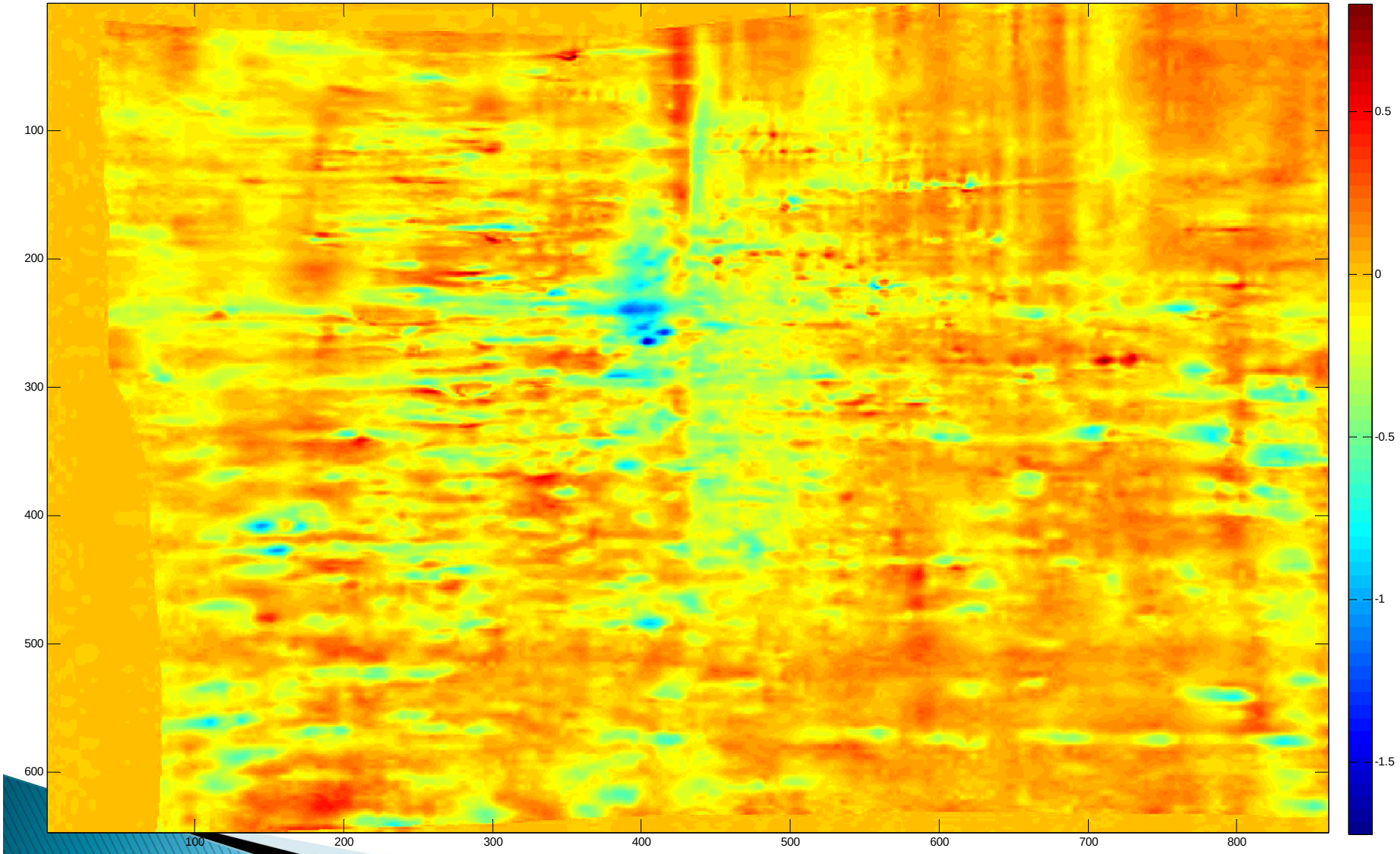
  Case-Control : $C(t_1,t_2)= B_1(t_1,t_2) - B_0(t_1,t_2)$

- **Goal**: Find regions of gel for which $C(t_1,t_2)$ is "significant" (significant evidence of at least 1.5-fold case/control ratio)

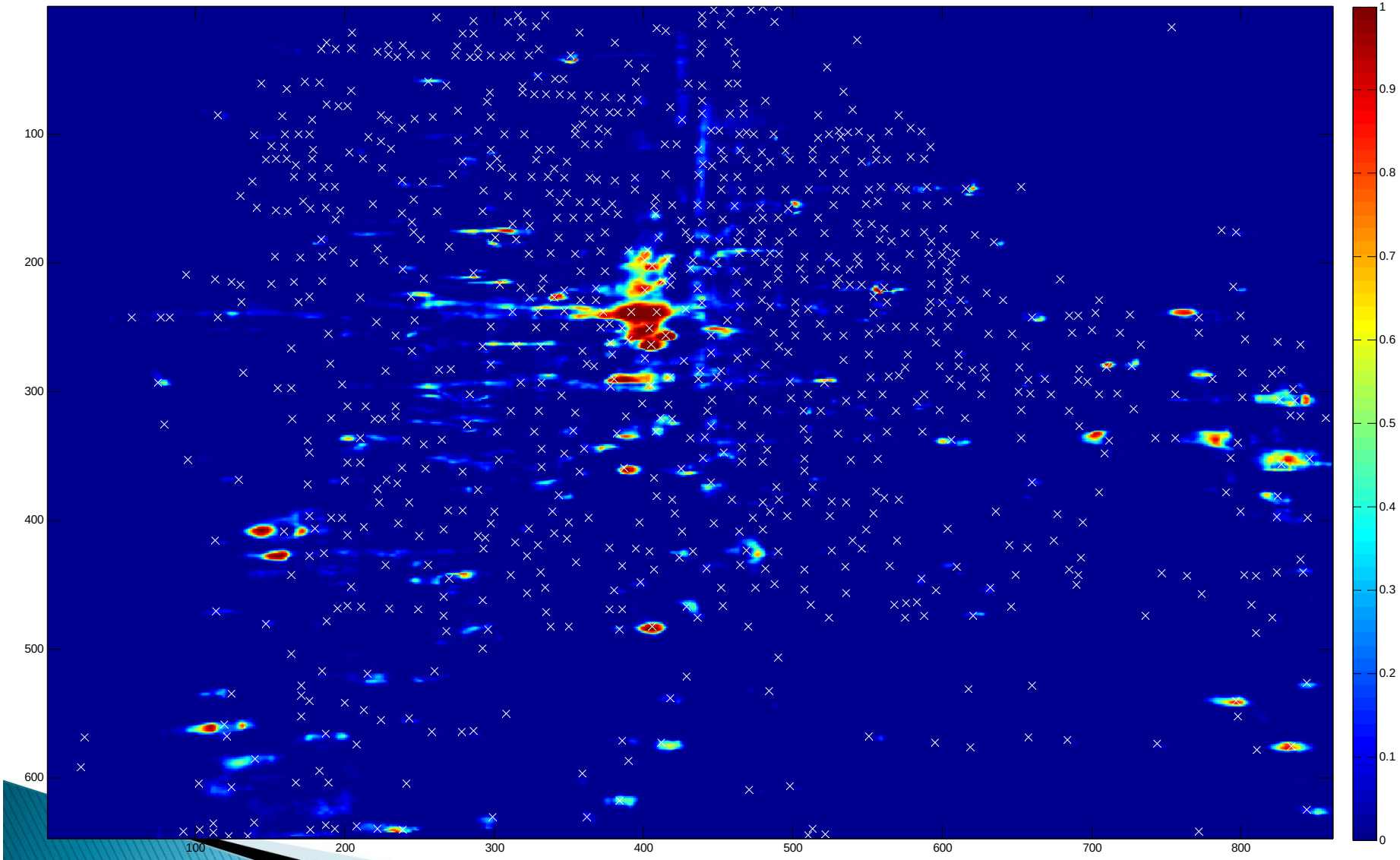
Model-Based Mean Gel : $M(t_1,t_2)$



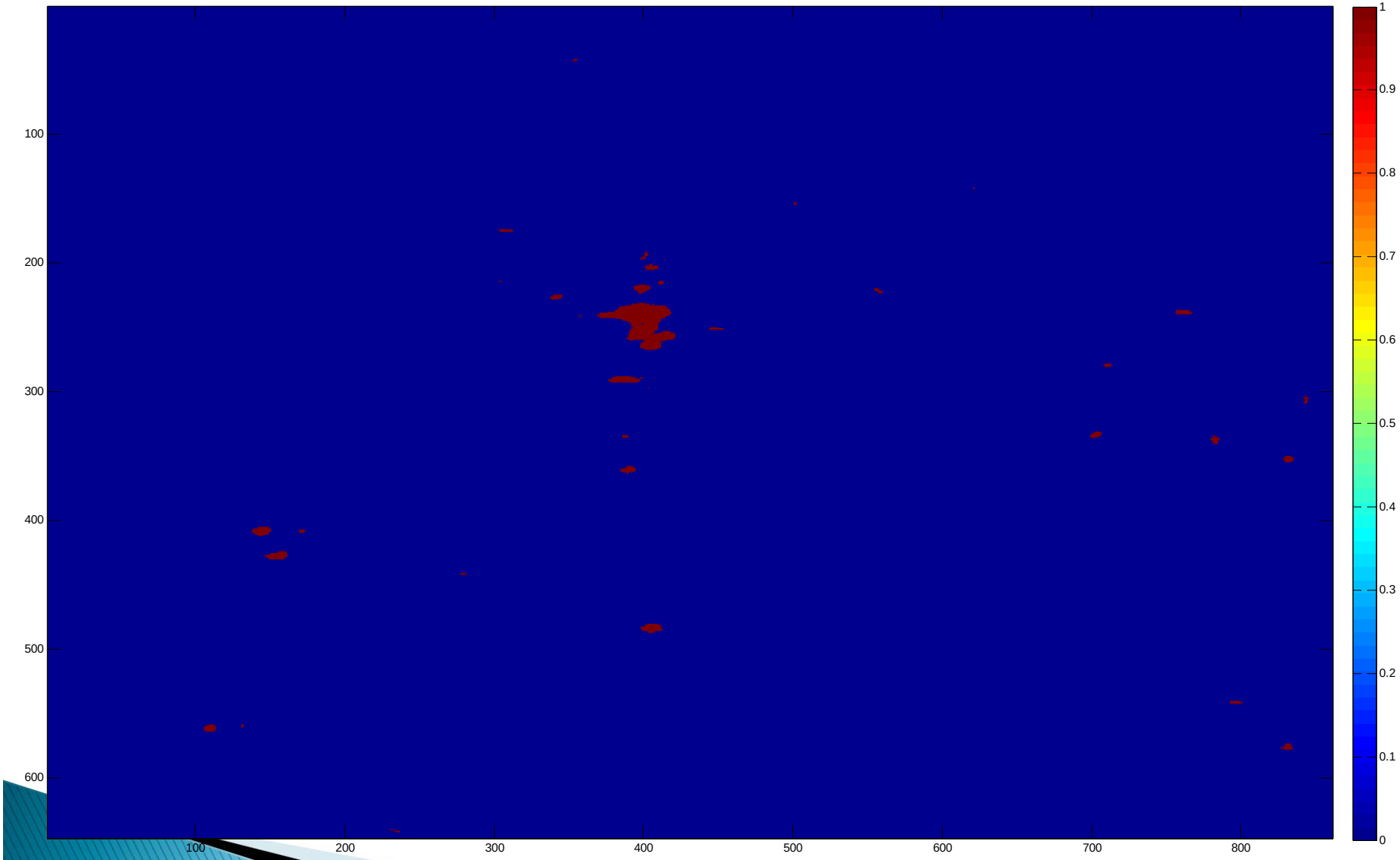
Case-Control Effect Image : $C(t_1,t_2)$



$p(t_1,t_2)$, with spots



Regions 1.5-fold different (FDR=0.10)

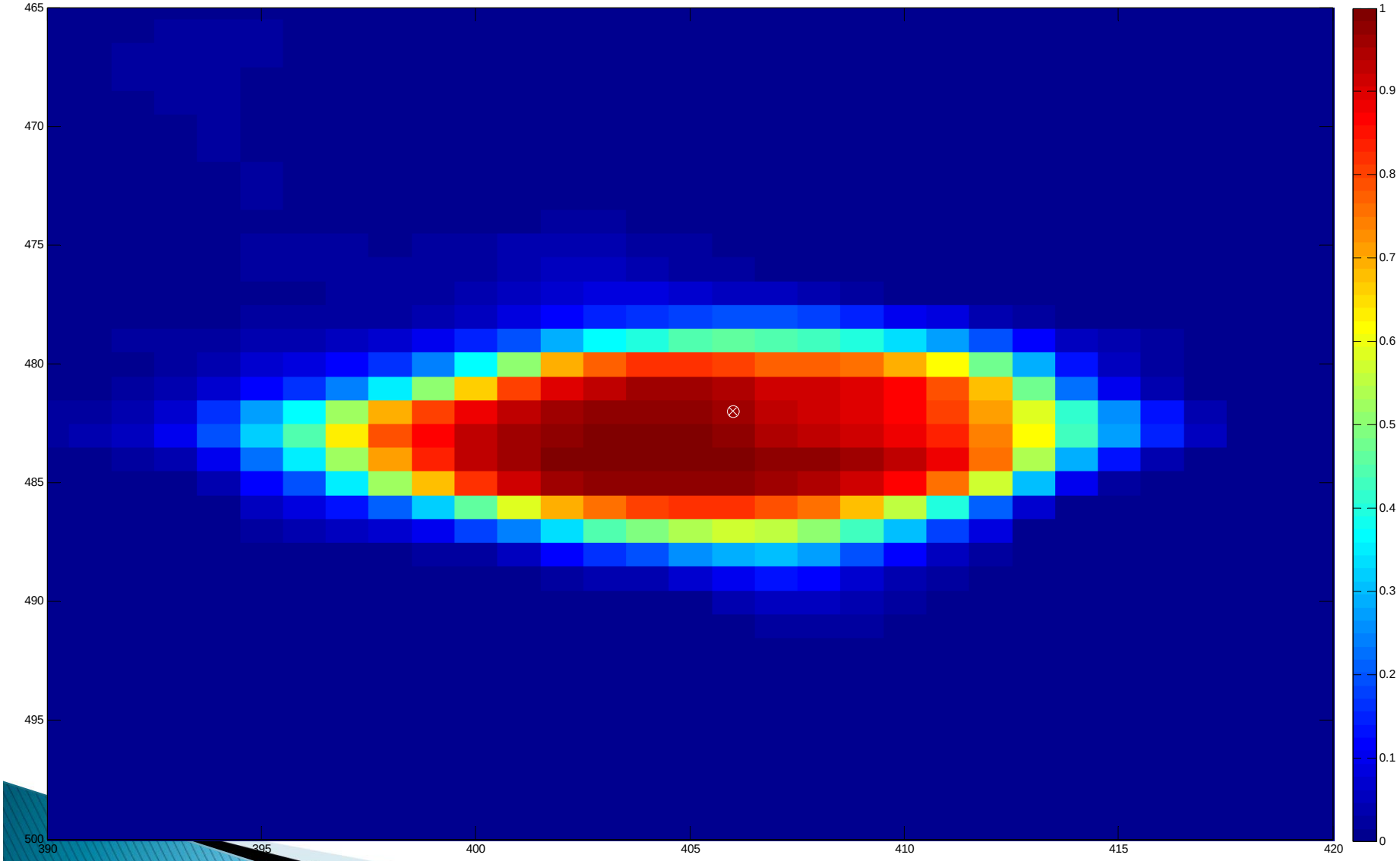


Brain proteomics addiction study

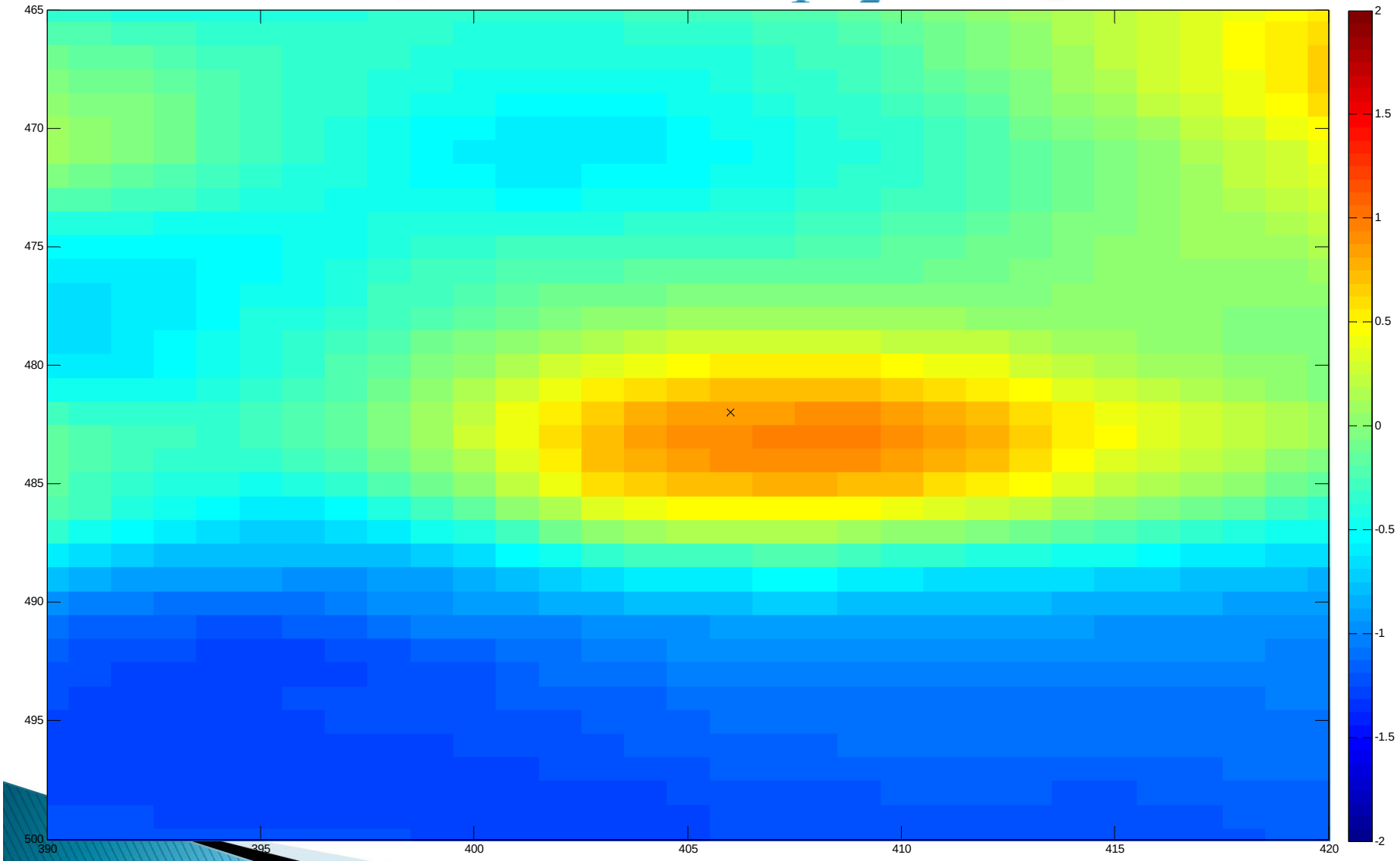
- **Results**:
  - WFMM Flagged a total of 27 contiguous regions as significant for cocaine vs. control
  - Spot-based method (*Pinnacle*) found only 17 spots.
- It appeared that WFMM was able to find essentially all results found by spot-level analysis, plus many additional results
  - Many of these were found in the tail of an abundant spot, and may correspond to co-migrating proteins
  - This suggests that perhaps there is more measurable proteomic information on 2D gels than thought, and image-based analyses can extract more of that information than spot-based approaches

Jump

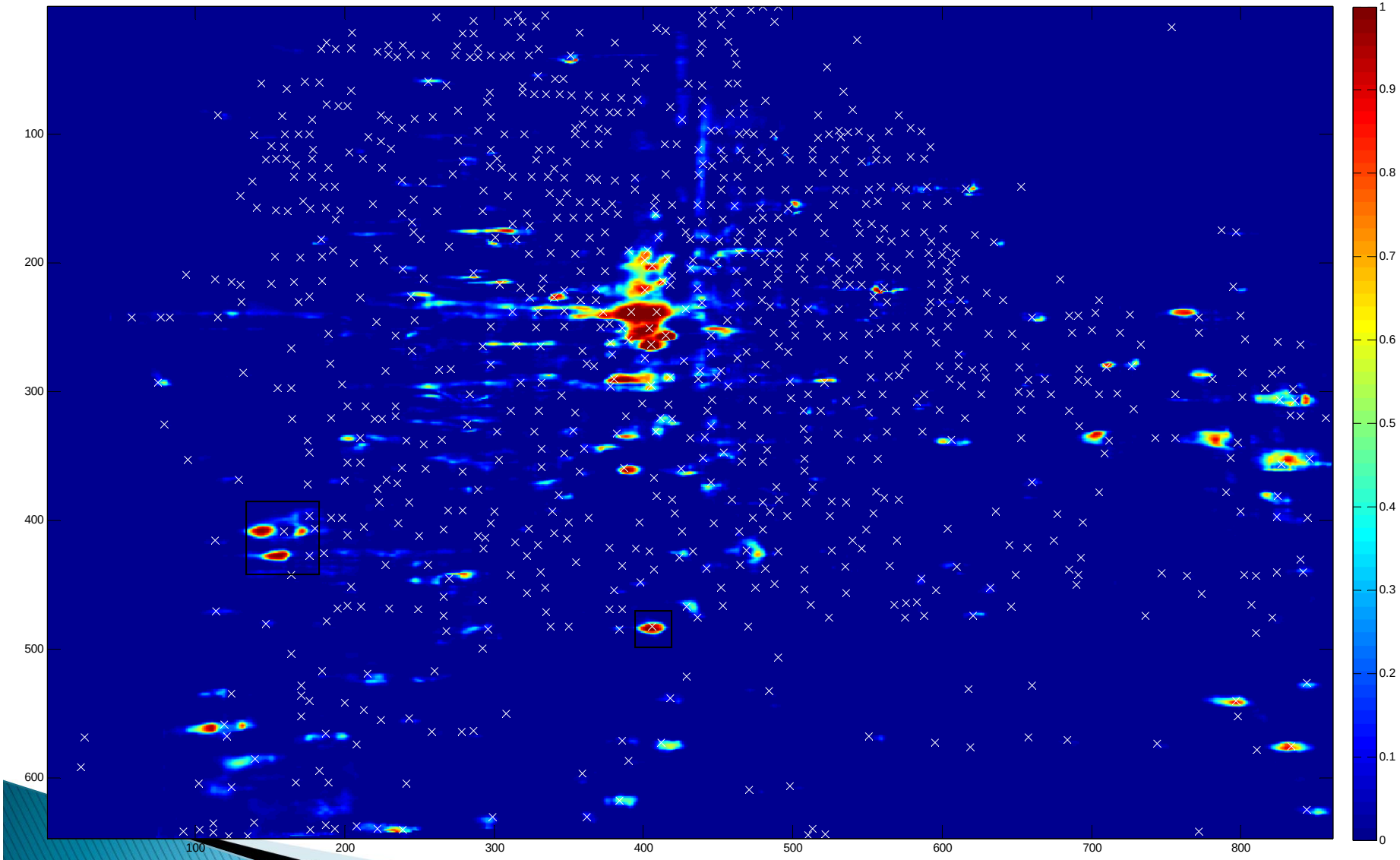
$p(t_1,t_2)$, region 1



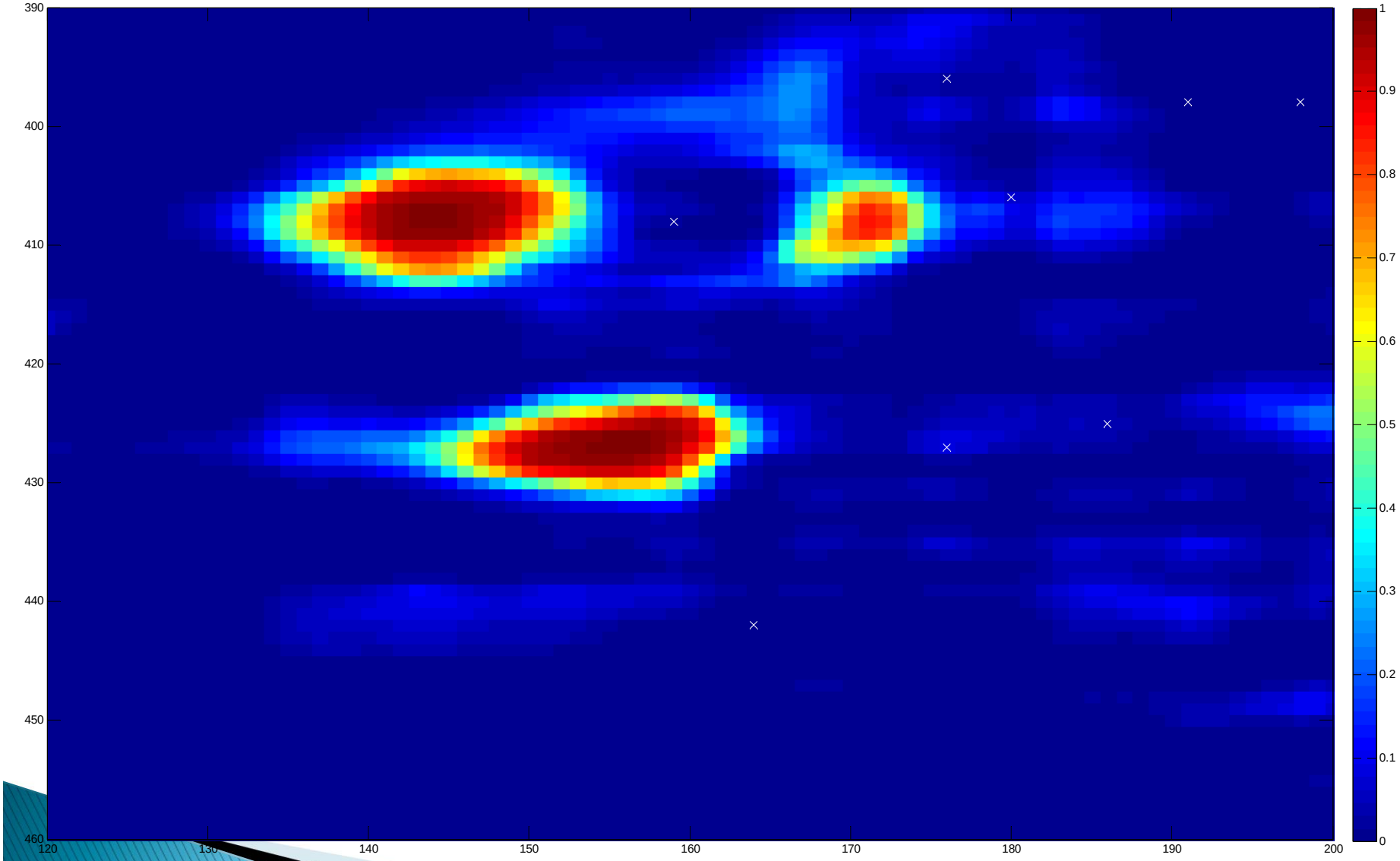
Average Gel $M(t_1,t_2)$, region 1



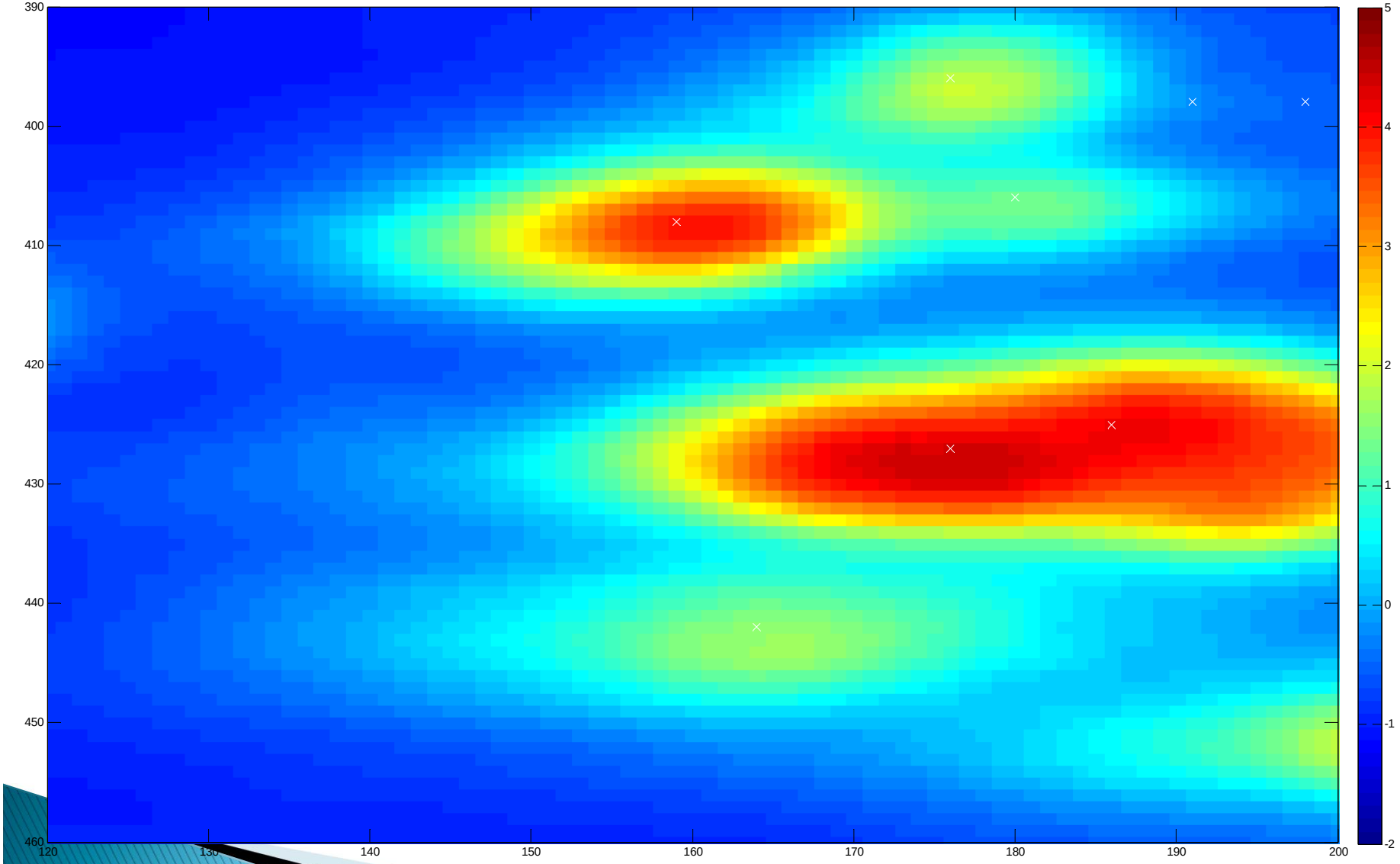
$p(t_1,t_2)$, with spots



$p(t_1,t_2)$, region 2



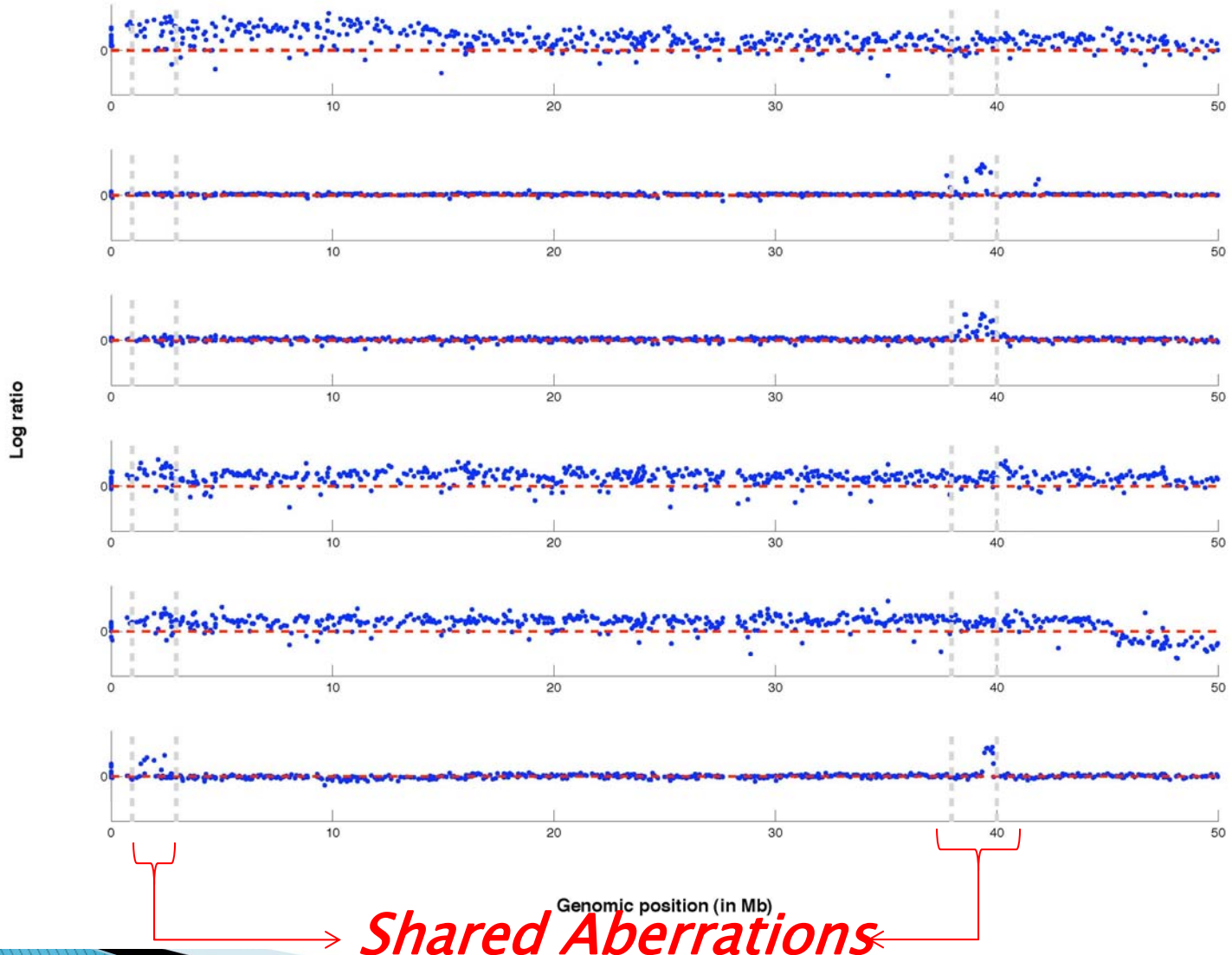
Average Gel $M(t_1,t_2)$, region 2



DNA Copy Number Cancer Genomics Study

- Cancer is characterized by various types of genomic instabilities, including in copy number
  - Discovery of prevalent copy number changes in given cancer can help better characterize a given cancer, and potentially provide markers for detection, prognosis, and prediction of response
- **Lung cancer array CGH data set** (*Coe, et al. 2006*)
  - Copy number arrays from 39 lung cancer cell lines, 4 types: small cell classical (SC) and variant (SV), non-small cell adenocarcinoma (NA) and squamous (NS)
  - **Goal**: Find ***shared aberrations*** within each of 4 lung cancer types, and assess differences between subtypes
  - ***Shared aberrations***: genomic regions with copy number changes that characterize a population

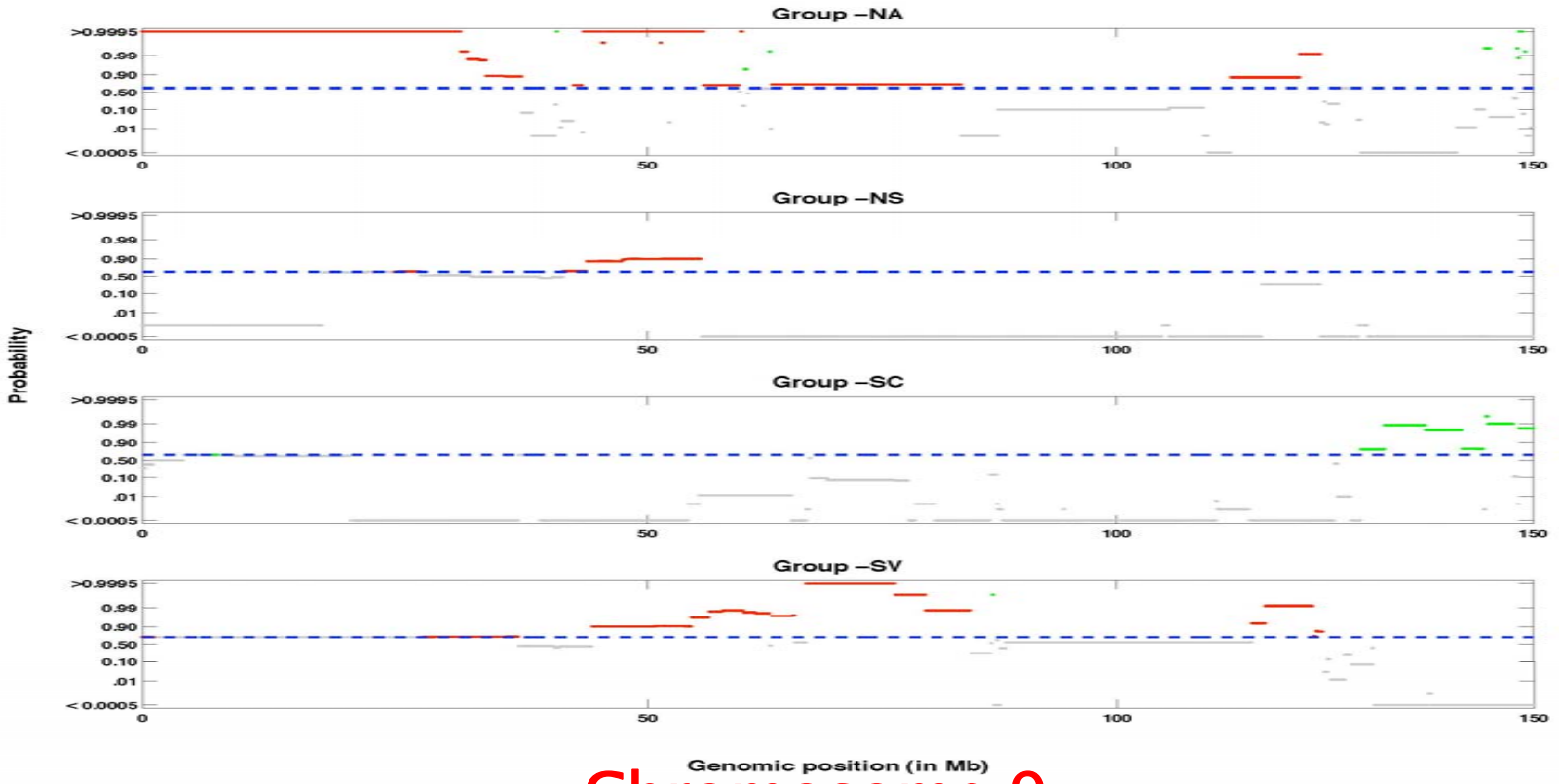
DNA Copy Number Cancer Genomics Study



DNA Copy Number Cancer Genomics Study

- Modeled using FMM with constant basis functions; prior: mixture with non-local alternatives
  - Baladandayuthapani, et al. (2010 JASA)
  - RJMCMC involving stochastically varying cut points defining regions of shared aberration
  - Unified model that borrows strength across/within arrays
  - Computed posterior probability of gain or loss for each group, and posterior probabilities of group differences
- Results:
  - Simulation study showed significant gains in sensitivity & specificity for detecting shared aberrations over alternative multi-step methods
  - Relative improvement was greater as:
    - Number of arrays in group increased
    - Noise level increased

DNA Copy Number Cancer Genomics Study



Chromosome 9

- Found 34 genes in flagged regions known to be related to lung cancer, many more than found in original multi-step analysis.

Hybrid Basis Functions

- Each type of basis has strengths/weaknesses
  - Empirical: adaptive, global, may be inconsistent
  - Local: flexible for local structure, not global
  - Biological: based on science, may lose information
- Hybrid basis functions can be constructed that combine strengths and mitigate weaknesses of different bases
  - Sequential hybrids: Fit one type of basis, take null space of projection, then apply another basis transform to the null space
  - Composite hybrids: Fit one type of basis, apply second basis transform to basis coefficients from first transform
  - E.g., fMRI brain volumes: ROI+wavelets; PC(ROI)+wavelets
- Hybrid basis functions can be used on genomic data to simultaneously perform pathway/gene/exon level analyses while accounting for local, functional, and interactive structure in genome

Works with existing GLOMM and ORMM code

Nonparametric Additive Terms

- All regression terms in ORMM (and GLOMM) assume linear relationship between object $Y_i(t)$ and scalar X_{ia}

$$X_{ia}\, B_a(t)$$

- This linearity assumption can easily be relaxed to allow additive nonparametric relationships between $Y_i(t)$ & X_{ia}

$$\boldsymbol{f_a(x,t)}$$

- This is done in straightforward fashion using the existing ORMM code by specifying a design matrix $\boldsymbol{X}$ and specific sparsity priors on $\boldsymbol{B_a}$ that correspond to O'Sullivan splines (smoothing splines are special case).
- We can do any desired Bayesian inference on $\boldsymbol{f_a(x,t)}$
- A similar approach can be used with object predictor (GLOMM) model

Object-on-Object Regression

- The ORMM can also be straightforwardly extended to regress object type 1 $Y_i(t)$ on object type 2 $X_{ia}(s)$

$$Y_i(t) = \int X_{ia}(s)\, B_a(s,t)\, ds$$

- The multi-domain modeling approach is applied by transforming both $Y_i(t)$ and $X_{ia}(s)$ using respective bases and then fitting the alternative domain ORMM.
- Again, existing code can be used for the model fitting
- This approach allows us to investigate the relationships between different types of objects on same subject, e.g. *fMRI* and *ERP* data or different types of *genomics* data.
- Many other extensions of this framework are possible, e.g. to model complex multi-way object data in unprecedentedly flexible and efficient ways

ORMM Software: Current state

- Freely available standalone executable

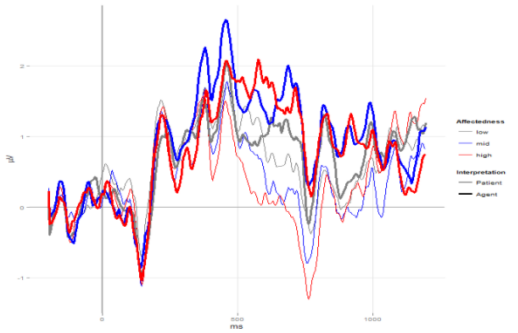
  https://biostatistics.mdanderson.org/SoftwareDownload

  - *Herrick and Morris (2006):* paper on computational issues
  - Automated: Can just specify $\boldsymbol{Y}$, $\boldsymbol{X}$, $\boldsymbol{Z}$ and method will run if happy with default choices of basis, levels, priors
  - Produces posterior samples for all model parameters, plus standard summary statistics, including posterior means, variances, quantiles, probabilities of effect sizes
  - Can be used to flag regions of object related to outcomes of interest with effect size δ and FDR α
  - R wrapper for code, with plotting functions under development
  - Wavelet bases built in, can input trans. data Y^*; others to be added
- Our methods have been used for various object data types
  - Our analyses: colon carcinogenesis, accelerometer, MS, 2DGE, sonic data, copy number
  - Outside researchers: fMRI, ERP, tiling arrays, forestry data, ophthalmology data

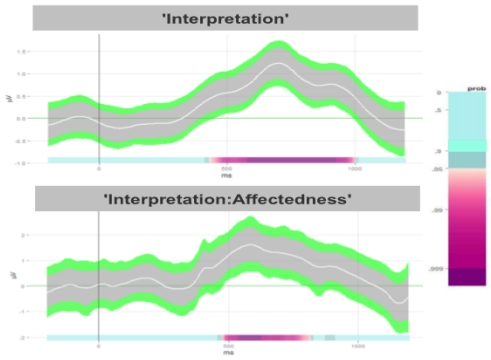
wrapfmm R package

wrapfmm

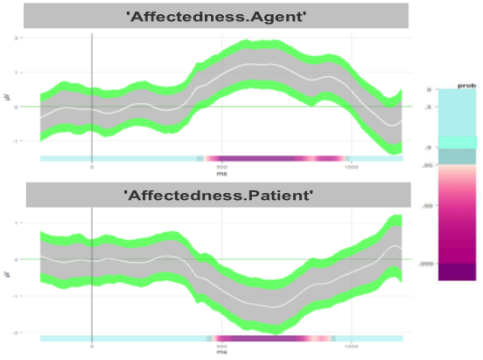
Data @ Fz split by 'Interpretation' levels & 3 'Affectedness' levels



Posterior fixed effect curves @ Fz (95% pointwise & simultaneous credible intervals)



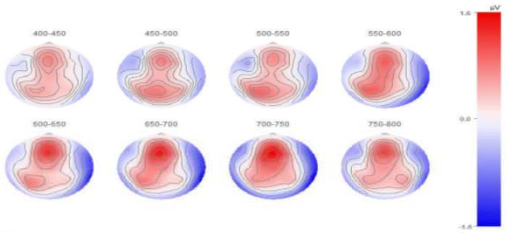
Simple effects of 'Affectedness' by 'Interpretation' (95% pointwise & simultaneous credible intervals)



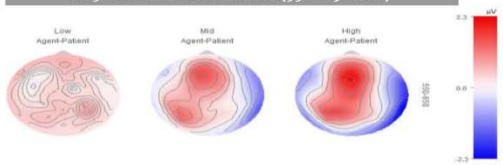
stepmom

Data plots

Difference maps for 'Interpretation' levels (400-800 ms)

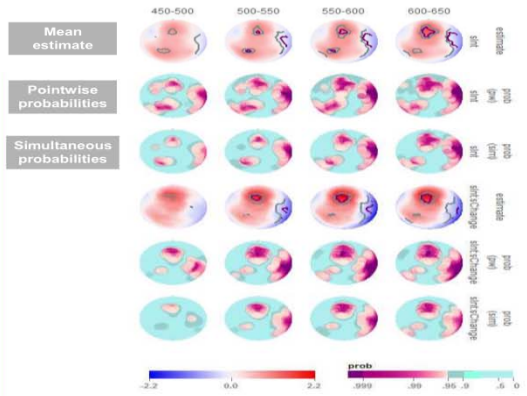


Difference maps for 'Interpretation' factor at 3 'Affectedness' levels (550-650 ms)



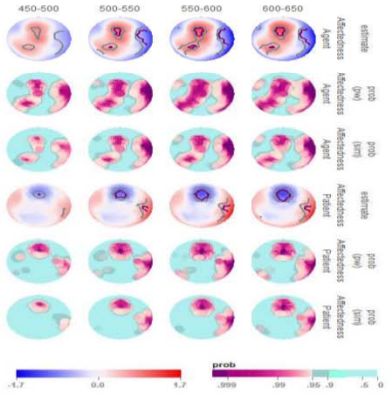
Model summaries

Model maps for 'Interpretation' & 'Interpretation:Affectedness' fixed effects (450-650 ms)



Custom posteriors

Model maps for simple effects of 'Affectedness' by 'Interpretation' levels (450-650 ms)



Conclusion

- Biomedical research experiencing an explosion of complex, high-dimensional data.
- **Object data**: general term encompassing many of these types of structured data.
- **MaTaDOR**: suite of object regression methods using multi-domain modeling approach
  - Handles object responses and/or predictors
  - Can capture *between-object structure* induced by design
  - Applies to a *broad class of object data*
  - Various internal structure captured by basis functions, local, empirical, biological, and hybrid basis functions
  - *Automated, parallelizable code*, linear in T^* (# of bases), and yields various types of unified Bayesian inference

    Framework *modular*, extendible in many ways.

The alley is much less scary in the light!

Key References

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Key References

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A number of papers describing both feature extraction and functional mixed model methods, plus papers giving overviews of proteomics and proteomic data analysis are available on my website (http://works.bepress.com/jeffrey_s_morris)

Code for fitting Bayesian multi-domain FMM is also available on the web
http://biostatistics.mdanderson.org/SoftwareDownload/

Code will continue to be updated to make it more user friendly in the future, and to contain features from recent publications.

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