Sparse Functional Data with an Irregular Cyclical Component: An Application to Psychiatric Data

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Bipolar Disorder

- Bipolar Disorder (BP) is a chronic psychiatric illness characterized by a cycle of manic and depressive episodes interspersed with periods of euthymia or normal mood.
- Multiple patterns of symptoms:
  - Bipolar I: Severe mood swings and functional problems
  - Bipolar II: Milder mood swings, depression most prominent
  - Rapid cycling: Switching frequently among mood states. Rapid cyclers have poorer prognoses and are more difficult to treat.
- Interventions:
  - BD is commonly treated with lithium (Li+) and other mood stabilizers.
  - Adherence is a problem as subjects may like manic state.
  - Balancing poles of the disorder is difficult-e.g. antidepressants can trigger manic episodes, side effects can be a problem.

Treatment Refractory BP

- Many BP patients do not respond to standard treatments
- Thyroid irregularities can be both induced by and interfere with standard treatments and are associated with rapid cycling.
- Open label studies have suggested high doses of thyroid hormones as a beneficial treatment supplement in refractory cases.
- We present data from a small randomized double blind thyroid hormone treatment trial in BP patients with rapid cycling. Subjects received a standard Li+ regiment plus one of
  - Placebo
  - Normal dose tri-iodothyronine (T3)
  - High dose levothryroxin (T4)

Study Goals

- The purpose of the study was to determine whether thyroid treatment improved mood outcomes as measured by
  - Rate of treatment response
  - Severity of episodes (amplitude)
  - Time spent manic or depressed (periodicity)
    - Length of episodes
    - Frequency of episodes/pattern of mood state switching
- The expectation was that T4 would be more effective than T3 or placebo

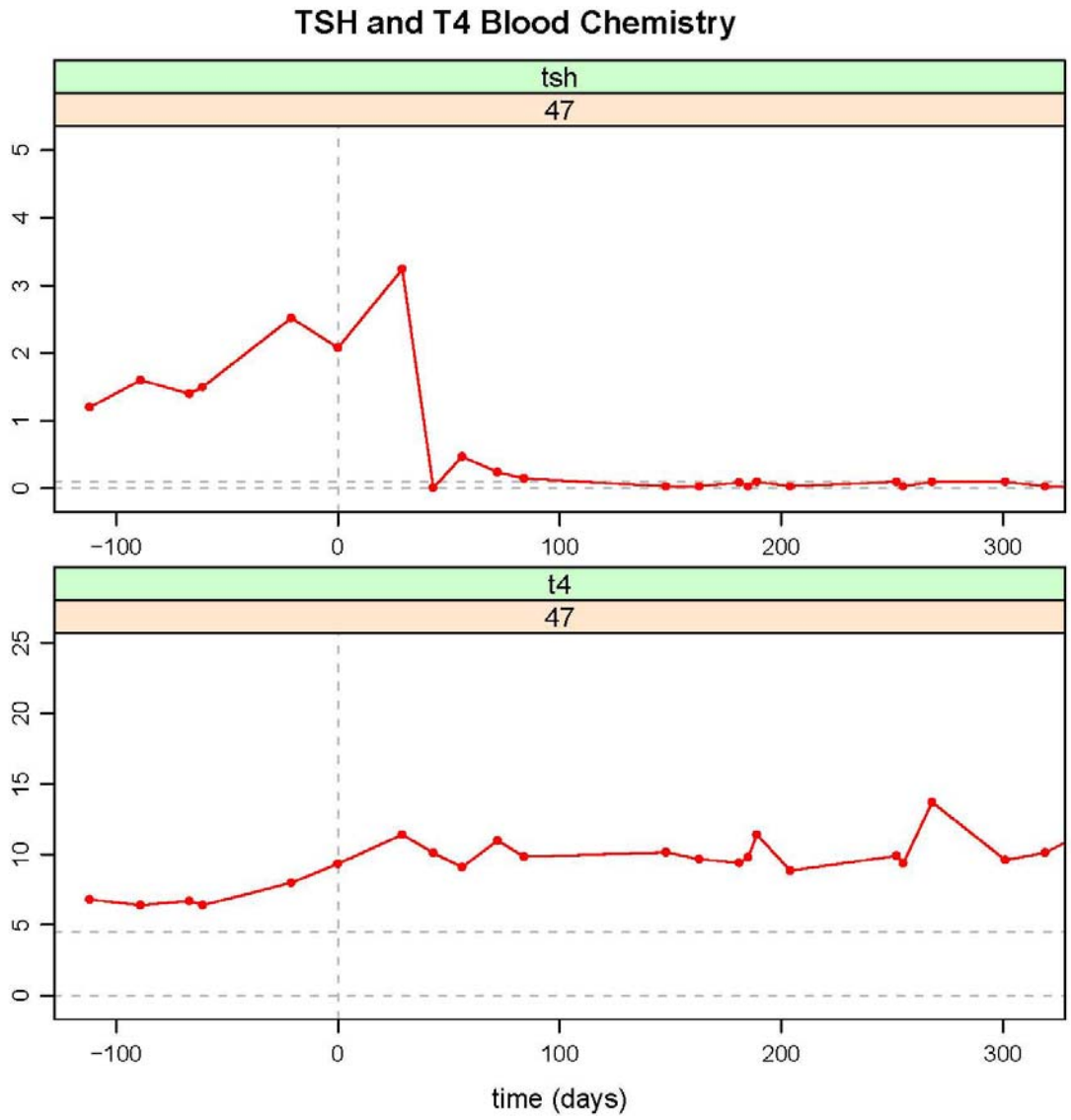
Study Design

- Patients randomized to three treatment arms
  - Li^+ + PL: n = 9
  - Li^+ + T3: n = 10
  - Li^+ + T4: n = 13
- Laboratory measurements to ensure thyroid levels had stabilized and were maintained
- Mood measurements to characterize symptoms
- Time points: Every two weeks both before and after treatment initiation. Follow-up was supposed to be one year but was variable as to length and frequency.

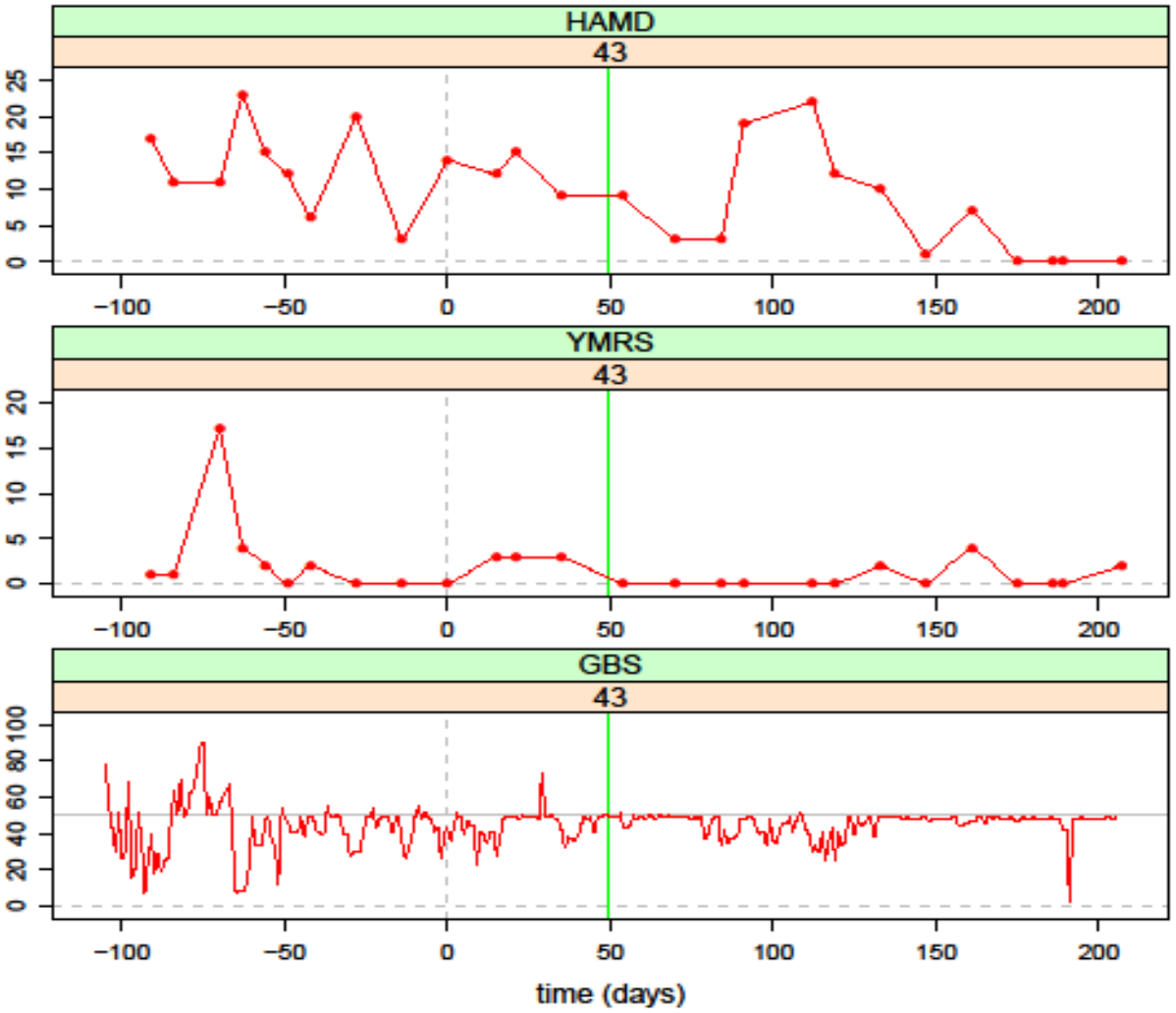
Main Study Variables

- Gold standard measures (approx. every 2 weeks):
  - Lab measures of thyroid hormone levels; it is expected to take 2-4 weeks for the effects of T3 and T4 to stabilize
  - Hamilton Depression Index (HAMD-21); an extended version of a standard depression instrument tailored to BP. Higher values indicate more severe symptoms.
  - Young Mania Rating Scale (YMRS); higher values indicate more severe symptoms.
- Patient self report measures (daily)
  - Chronorecord: Subjects record activities, functioning, medication and a self-rating of mood/energy levels on a scale of 0-100 with 50 representing normal.

Sample Lab Data



Sample Mood Data



Original Study Analysis Plan

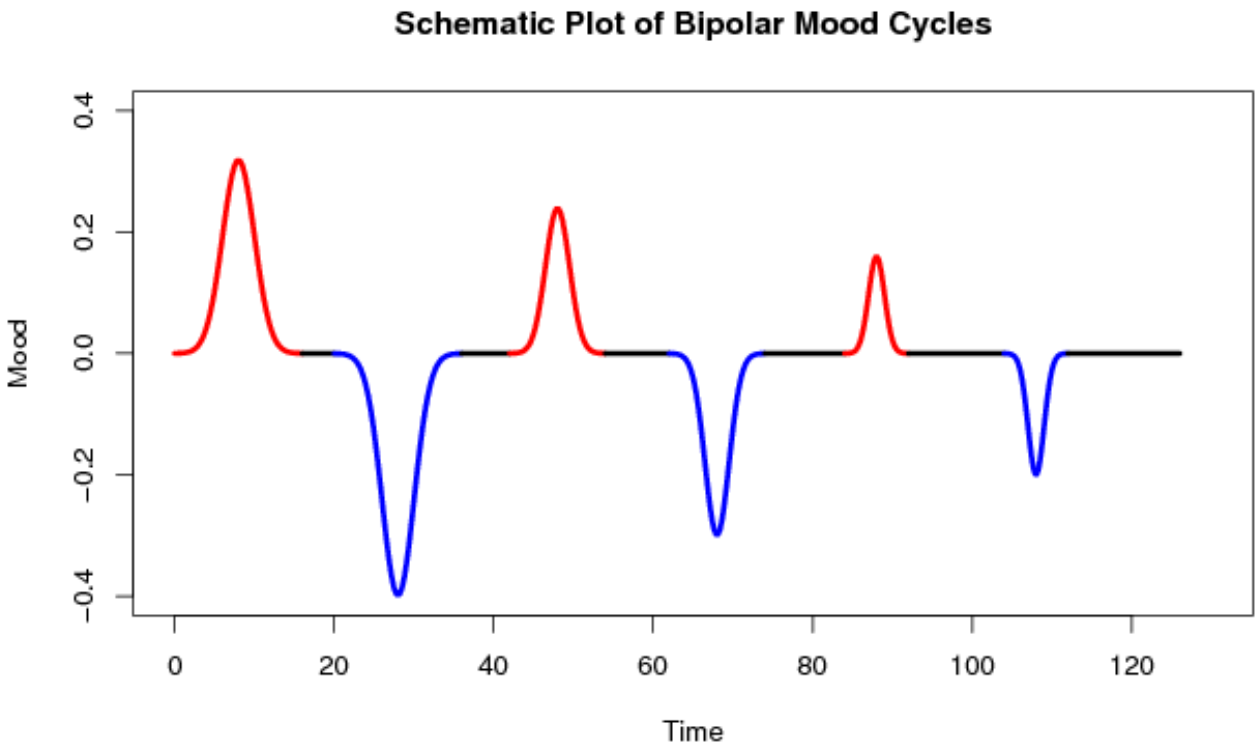
- Compare treatment groups on response rates. To be considered a responder a subject had to have a 50% reduction in both HAMD and YMRS scores plus both scores needed to be below a set threshold.
- Within-group Change: Compare pre- and post-treatment means for HAMD and YMRS with paired t-tests
- Change Across Groups: GLMM with group by time interaction
- Results: Response rates extremely low; no treatment effects except hint of a T4 change in depression.

Problems With Original Analysis

- Unrealistic response criteria
- Low power (especially for categorical analyses)
- Throws away huge amounts of information
- Doesn’t get at key ideas of change in rate, periodicity
- Doesn’t take into account variable amount of available data per subject
- Ignores individual subject characteristics
- This is really……

…A Functional Data Problem

- Mood and hormone levels are measured at multiple time points both pre- and post-treatment.
- Use trajectory patterns to discriminate between treatment groups.



What Is Functional Data Analysis?

- Observational units consist of curves or trajectories rather than finite dimensional vectors.
- Examples of functional data:
  - Growth curves
  - Longitudinal measurements of clinical status
  - Technology evolution
  - Spectra
- In practice: Only get a finite number of observations at possibly sparse or irregularly spaced time points.

Classical Approaches to FDA

- Regularization:
  - Form a grid of equally spaced time points.
  - Evaluate each curve at the time points, giving a finite representation of each curve.
  - Apply a standard finite dimensional method possibly with a regularization constraint
- Filtering:
  - Fit a smooth curve to each subject using a finite set of basis functions (e.g. polynomials)
  - Perform analyses on the basis coefficients (η)

Problems With the Traditional Approaches

- Regularization:
  - Cannot be easily applied when curves are measured at different or unevenly spaced time points or when the data are too sparse
  - Even when it can be used, the resulting data vectors are high-dimensional and auto-correlated
- Filtering:
  - Measurements may be too sparse to fit a curve for each subject
  - Requires fitting many parameters
  - If subjects are measured at different time points, the basis coefficients will not have a common covariance

More Recent Approaches

- Let $g_i(t), Y_i(t)$ and $\varepsilon_i(t)$ respectively be the true value, observed value and error for *i*th curve at time t. i.e.

$$Y_i(t) = g_i(t) + \varepsilon_i(t), \quad i = 1, \ldots, n$$

- Represent g(t) using a spline basis:

$$g_i(t) = s(t)^T \eta_i$$

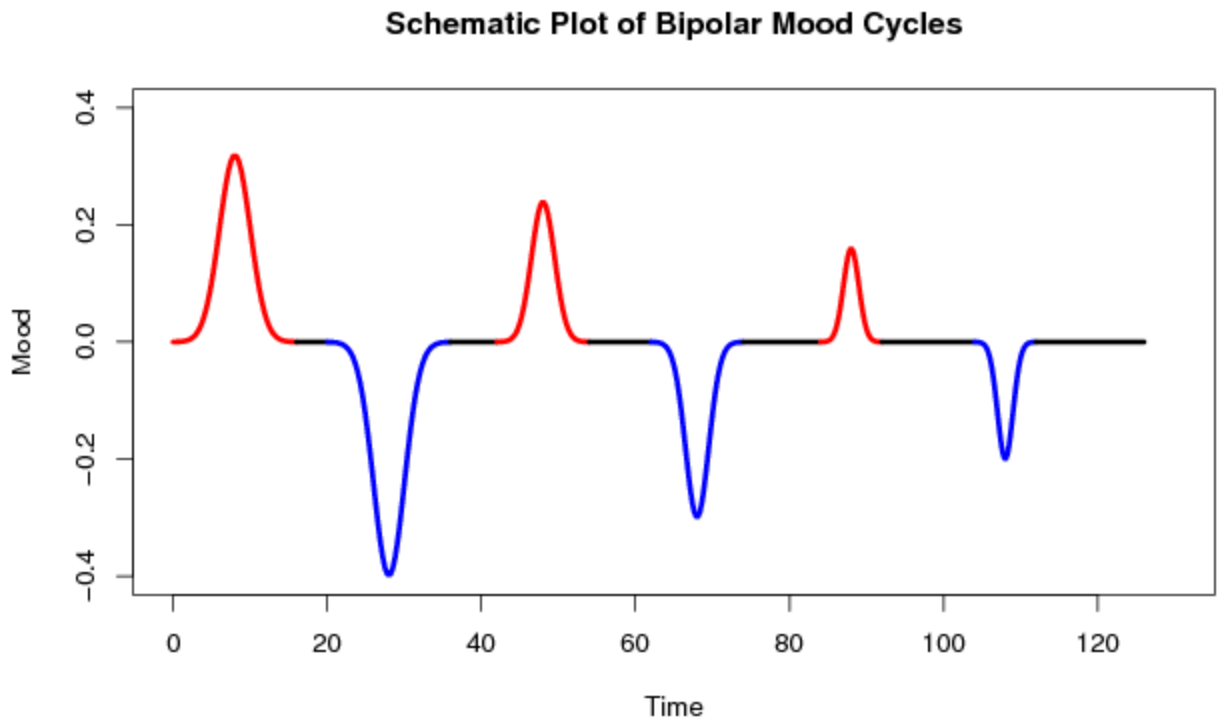
  where s(t) is a spline basis vector and η_i is the vector of spline coefficients.

- Treat the coefficients as having a fixed component (e.g. based on group membership) and a random effect. $\eta_i = \mu_{z_i} + \gamma_i, \quad \gamma \sim N(0, \Gamma)$

- This allows you to borrow strength across curves, deal with sparsity, handle covariance structure appropriately, etc.

BP Study: Non-standard Functional Data

- In our application cyclicity rather than mean change is the key characteristic and feature alignment is likely impossible
- We need to transform to our raw data to a different scale.



Challenges for BP Data

- Sparsity and irregularity of gold-standard data. Probably not seeing true peaks or precise timing of cycles.
- High degree of individual variation in pattern of mood episodes. Subjects may need to be referenced to self rather than absolute standard.
- While described as “cyclical” the pattern of mood episodes can be very irregular.
- The relationship between gold standard and self report measures is not well validated.

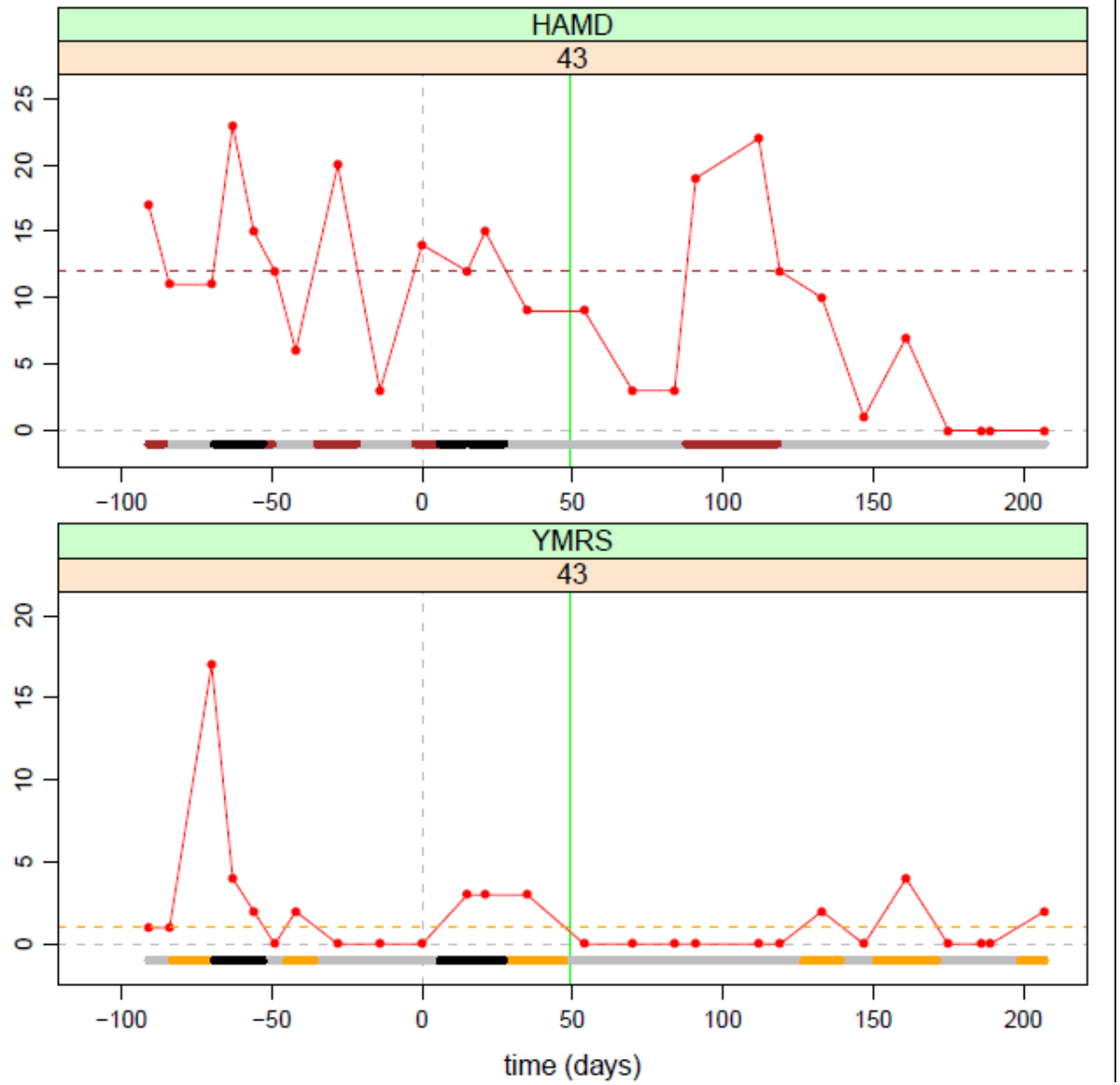
A State-Based Approach

- Use HAMD and YMRS measurements to assign subjects to states at each time point (euthymic, depressed, manic, mixed)
- Look at transitions from one state to another over time.
- Fits with clinicians' view of disorder as episodic
- Avoids trying to directly model or align the irregular shapes of the trajectories
- If movement across states is Markov, long run % of time in each state can be computed by treatment arm and switching patterns assessed

Preprocessing

- Clinician designations of mood states unavailable
- Instead we used an approach akin to a combination of the regularization and filtering methods common to classical FDA:
  - Interpolate the observed HAMD and YMRS points
  - Determine whether subject is high or low on each measure at a given time and assign state
  - Splits can be based on clinical thresholds or subject's pre-treatment distribution (e.g. median or cluster)

Patient Data With Mood States



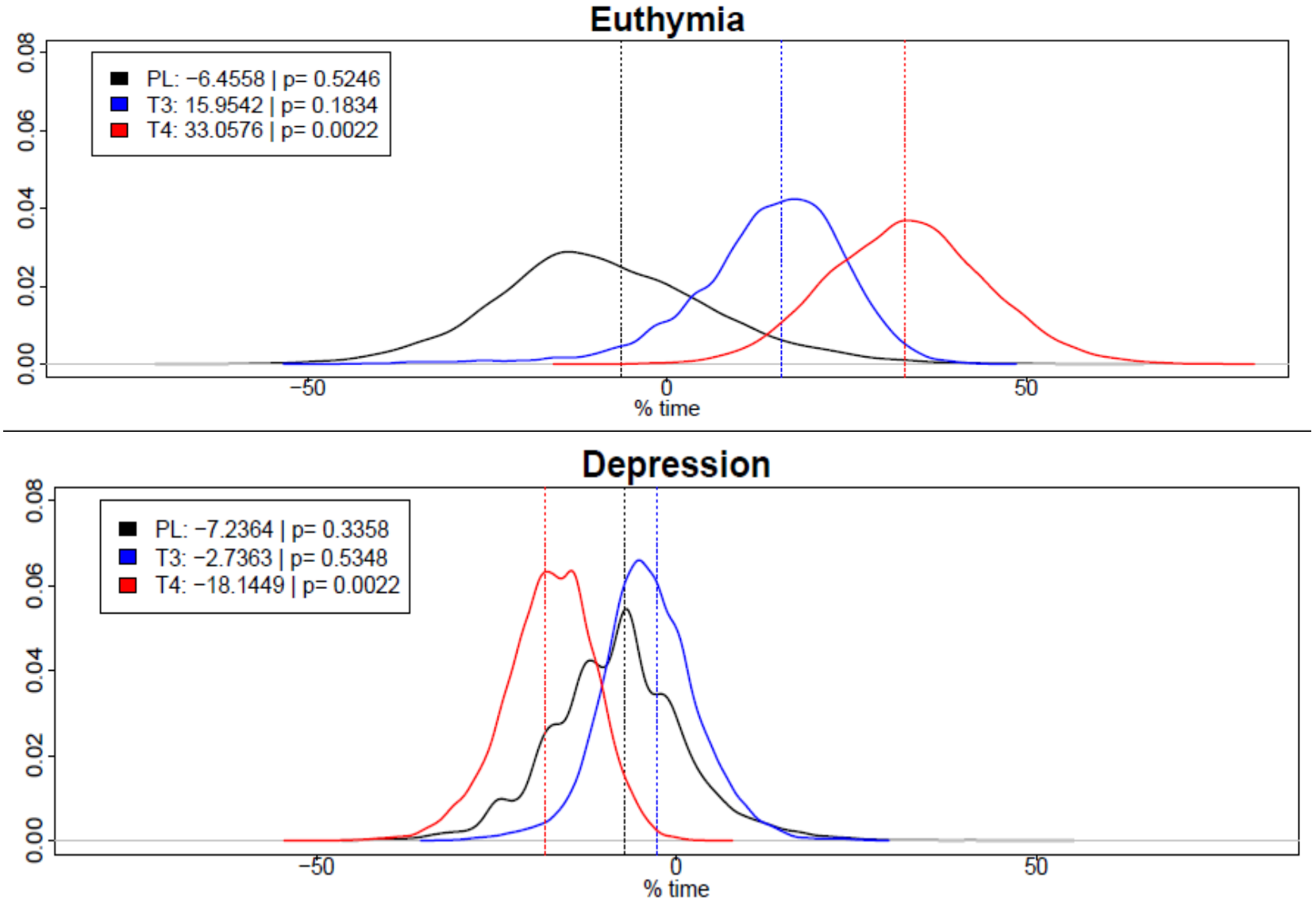
Transition Patterns and Long Run Mood Distribution

- Discretize state functions at weekly intervals (like regularization)
- Create transition matrices (probability of movement from one state to another) for each treatment group before and after initiation
- Calculate long run percentage of time group members are expected to spend in the four states before and after treatment
- Borrows strength for each group across curves.
- Subjects with more follow-up get higher weight

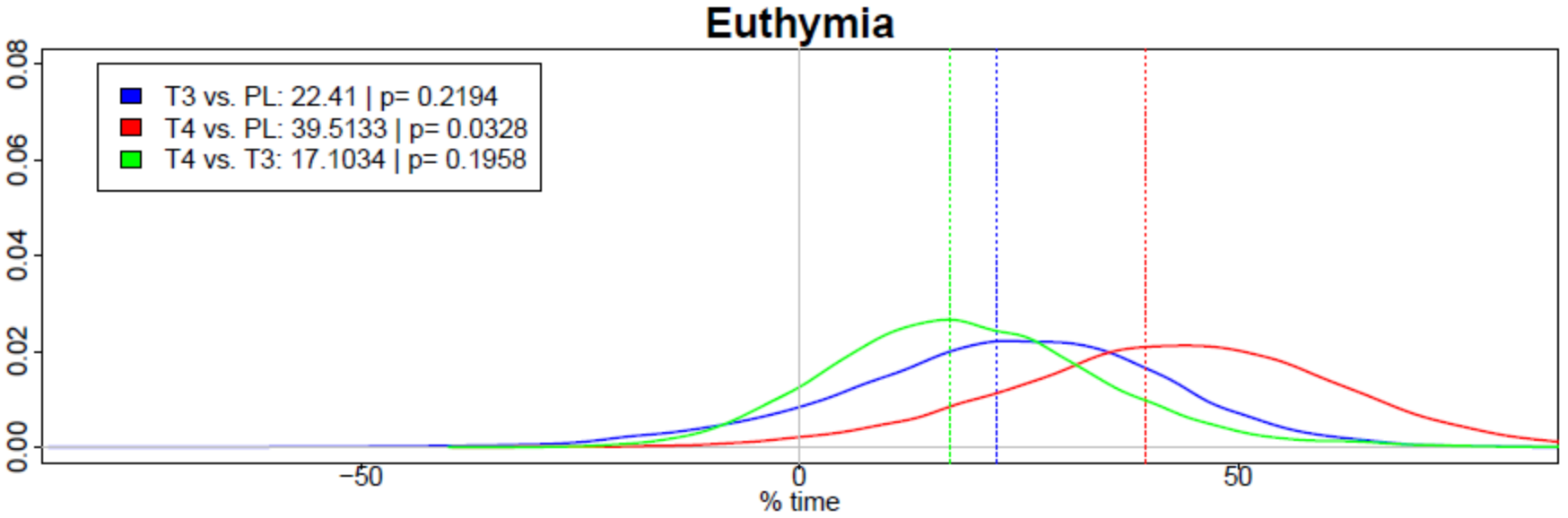
Medication Effects

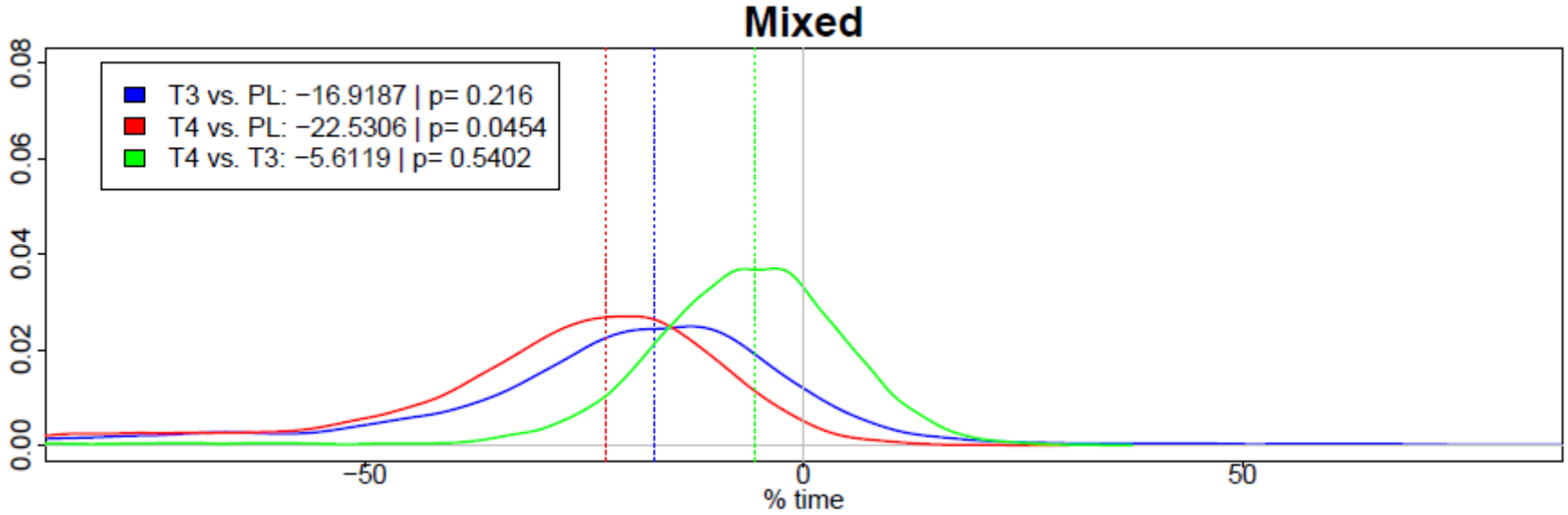
- We want to test for
  - Within treatment group improvements in mood state distributions (more time in E, less in D, M, D+M)
  - Between group differences in mood state changes
- Booststrap approach:
  - Resample subjects and recalculate transition matrices and long run distributions
  - Compute distribution of pre-post differences in % time in each state within group and similarly for pairwise group differences in change scores

Within Group Effects



Between Group Effects





Summary of Treatment Results

- In the T4 group there are significant increases in time spent in euthymia and decreases in time spent in depression and mixed state relative to baseline.
- No within group changes for T3 or placebo
- Improvement in time spent in euthymia and mixed states is significantly greater for T4 compared to placebo.
- High variability in placebo group affects power

Issues With State-Based Approach

- Does not take advantage of information about severity
- Does not fully tease apart components of periodicity (length, frequency, switching pattern of episodes)
- Does not take advantage of daily self-report data

A Model Based Approach

- Intuitively we imagine that sequences of episodes (depressed, manic, mixed) are generated according to some process, e.g. correlated Poissons.
- Rates for those processes are functions of time, and treatment group and possibly subject specific factors.
- Each episode has a severity (peak amplitude) and length which are also functions of time and group.
- There is also probably a baseline noise process.
- Two possible formulations:
  - Rate, severity and length are constant before and after treatment.
  - Rate, severity and length vary continuously as a function of time after treatment.

A Functional Data Problem

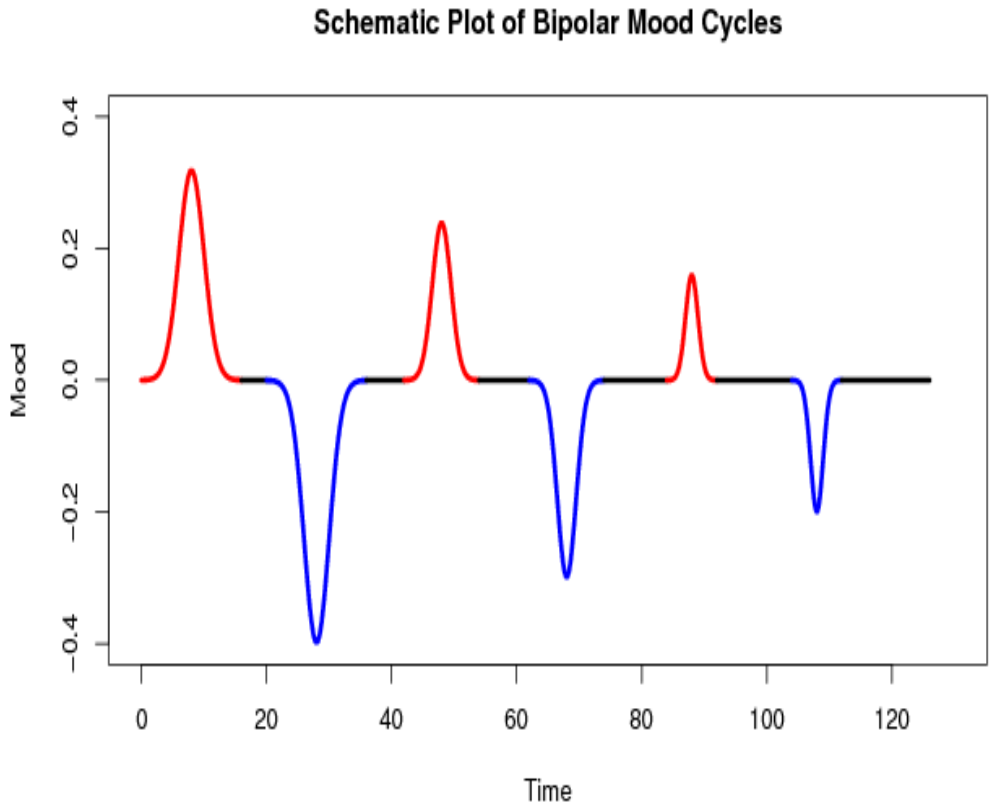
- If we had the actual episode rates, severities and lengths at given points in time we could use classical FDA techniques to model those functions
- Our observed data are raw HAMD, YMRS and patient self report scores. How can we transform these get to the desired functional scale?

The Transformation Scheme

- Current approach: Model episodes as having a particular functional form (e.g. bell-shaped bumps, triangles).
- Use existing data to estimate location, height and length of episodes for each subject.
- This gives us points on three functions: amplitude, episode length, time between episodes. Values are treated as being observed at the center of each episode or non-episode.
- The episode rate at the observed time points can be estimated based on the above three functions

Expected Trajectories Post-Tx

- Rate decreases over time
- Amplitude decreases over time
- Episode length decreases over time
- Between episode spaces get longer over time



Fitting Procedures?

- Fit the observed points for each subject. We want curves that
  - Have a low mean squared error
  - Have a "reasonable" number of episodes
  - Have "reasonable" distributions for amplitude and severity.
- This suggests something with an MCMC flavor, looking through the space of possible fits with priors on the above parameters.
- Tradeoff between fitting the raw data points as opposed to the model parameters of interest.

Fitting procedures?

- An alternative is to view the curve fitting and transformation as a joint process, finding the group rate, severity and duration processes that fit best according to a likelihood model.
- Overall more appealing, but also more complicated.

Work In Progress

- Based on our model we have a simulator that creates HAMD and YMRS trajectories which are very comparable to our observed data.
- We are currently working on methods for both fitting procedures. Complicating features:
  - Choice of order of iteration
  - Label switching/birth, death and overlap of episodes
  - Individual variations in what counts as an episode
  - Noise processes.
- Given a fixed number of episodes it turns out we can do a good job of estimating the other features, even in the presence of noise.

Other Research Avenues

- Use chrono-record data to estimate subjects' cycle rate and use that to make stronger model-based assumptions about the form of the trajectory for HAMD, YMRS.
- Incorporate information about variability in thyroid hormone levels
- Joint estimation and correlation of trajectories

Conclusions

- Studies of bipolar disorder provide a rich source of interesting data sets and problems in the domain of functional data analysis.
- The irregular cyclical nature of the data means that the raw trajectories require some form of transformation in conjunction with FDA methods
- Episodic illness are common in psychiatry and other fields, as is the practice of characterizing diseases using health states. Thus potential exists for broad application of new techniques.

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