BMES Workshop on Parameter Estimation Methods in Physiological Modeling
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Statistical Considerations and Techniques for Understanding Physiological Models, Data, and Treatment

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Outline

- Modeling discussion
- What statistics actually does
- Exploratory data analysis
- Parametric fitting
- Nonparametric fitting
- Stochastic modeling

Grandfatherly Advice in One Slide

- If your model is an attempt to understand a “slow” phenomenon, relative to the data rate and “unmodeled” variations in data, then nonlinear least squares comparison is perfectly reasonable.
- If you are modeling fast phenomena with fluctuations that are inherent in the process, then a stochastic dynamic model may be required.
- Statistical theory for nonlinear least squares, which is closely related to standard linear model theory, can be applied and works reasonably well.
- Do not forget to do some basic pre and post data analysis
  - Covariance and empirical model fitting can help detect dynamics
  - Analysis of the residuals from the fit provides an important post-mortem tool
  - Cross validation can also be helpful

Modeling the planets

- God’s creation must follow the perfect path: circles
- Circles don’t fit the data: epicycles
- Kepler: ellipses are simpler than lots of epicycles
- Newton: law of gravitation “explains” ellipses
- Einstein: relativity “explains” gravity
- Quantum mechanics: does God play dice in perfect circles? now what?

Modeling atmospheric turbulence

- Navier-Stokes equations of fluid flow
  - Conservation of momentum, energy, mass
  - Complicated partial differential equations
  - Exhibit complex output behavior

$$\frac{\partial u}{\partial t} + (u \bullet \nabla) u = \mu \Delta u - \nabla p$$

$$\nabla \bullet u = 0$$

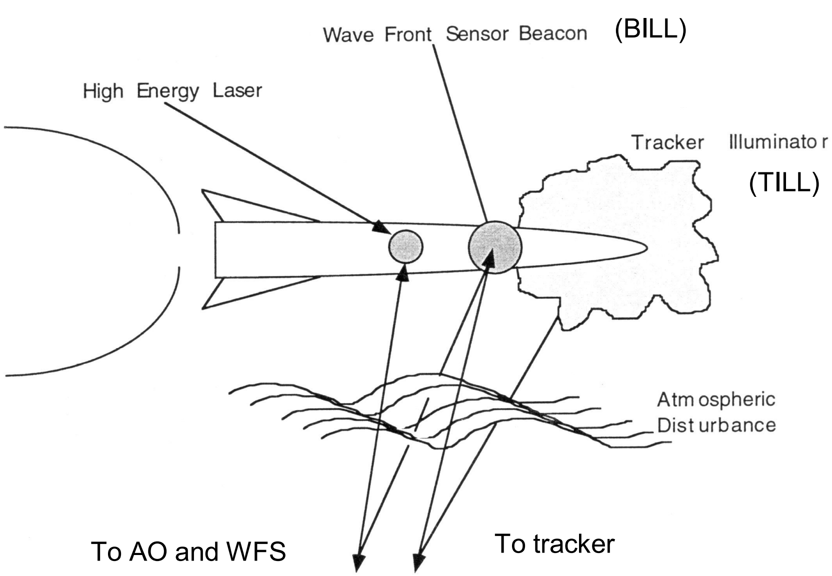
- Kolmogorov's 2/3 law
  - Scaling analysis of flow equations
  - Mean plus fluctuations in the flow
  - Covariance of the fluctuations

$$u = u_0 + \eta$$

$$E\left|\eta(x+h) - \eta(x)\right|^2 = C\left|h\right|^{2/3}$$

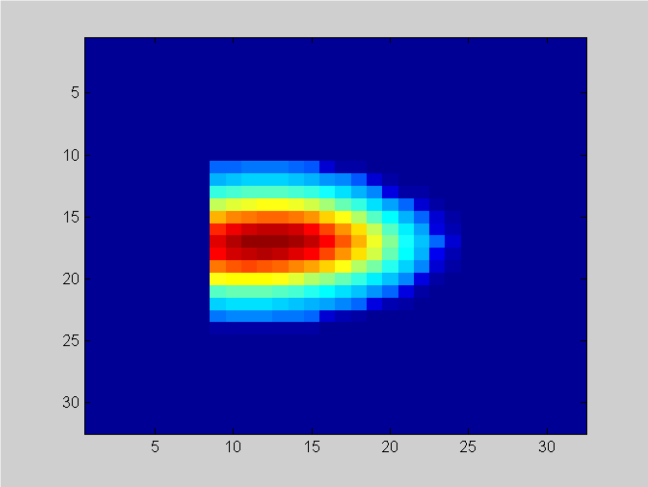
- Is the model the differential equation or the covariance?

Problem: Tracking a missile

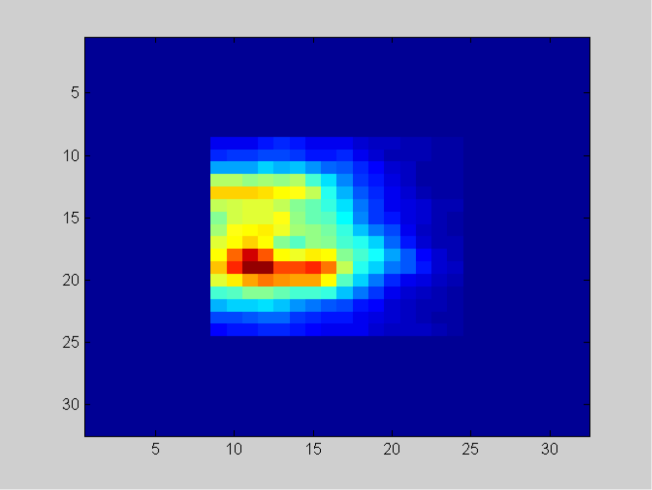


- Aircraft sends out laser beacon signal
- Atmosphere distorts the light
- Signal reflects from missile, propagates back to aircraft
- Return path also distorts laser signal
- First signal used to steer
- Second signal used to correct high order aberrations
- Third beam is the weapon

Tracking via images



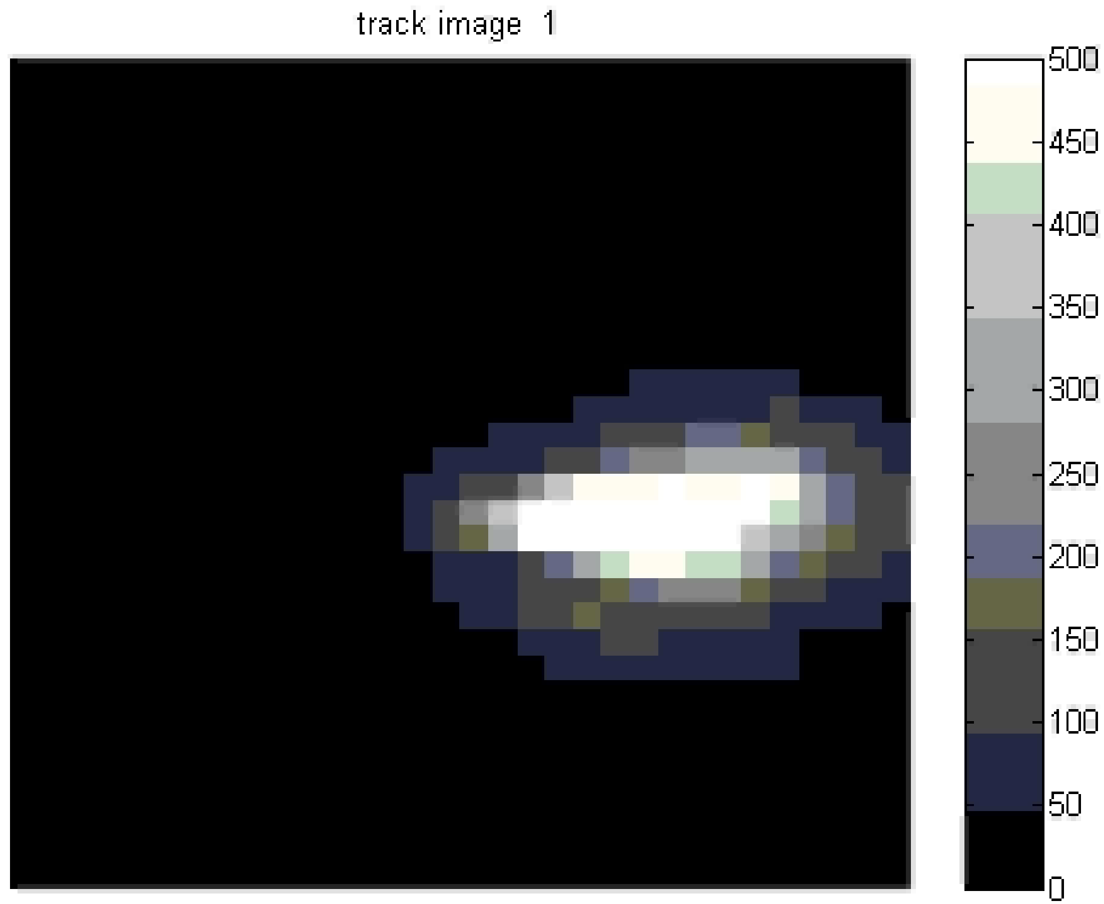
reference image



actual data

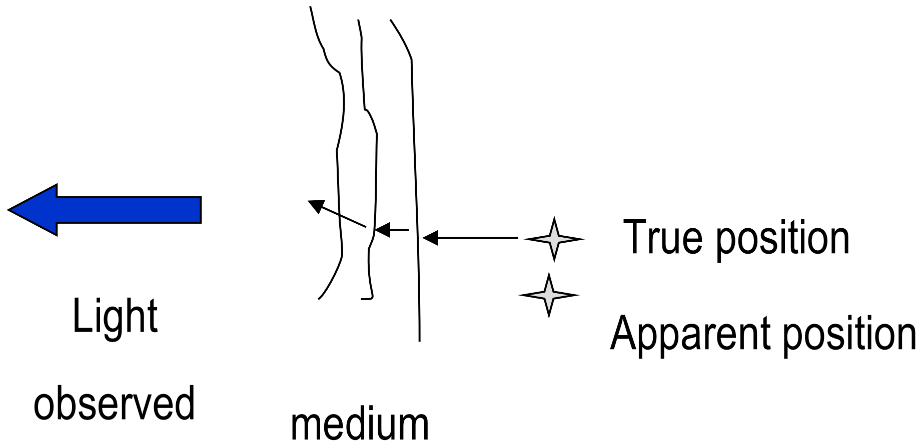
- Images must be compared quantitatively
- Goal: keep the tip in the center of the image plane
- Difference in desired and observed tip position determines line-of-sight adjustment

Tracking via images



The funny part...

- The goal is ***not*** to remove the noise: it's to estimate it.



Firing bullets:

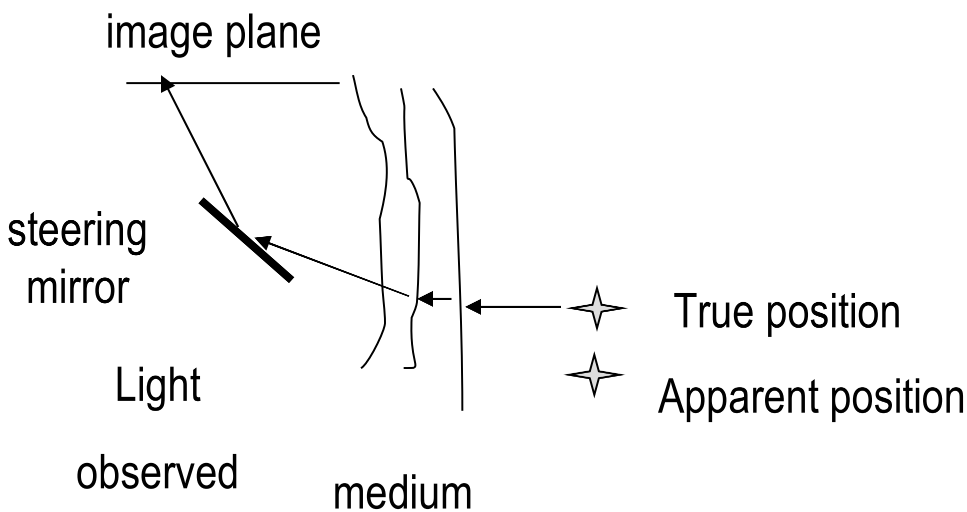
shoot at true position

Firing light:

shoot at apparent position

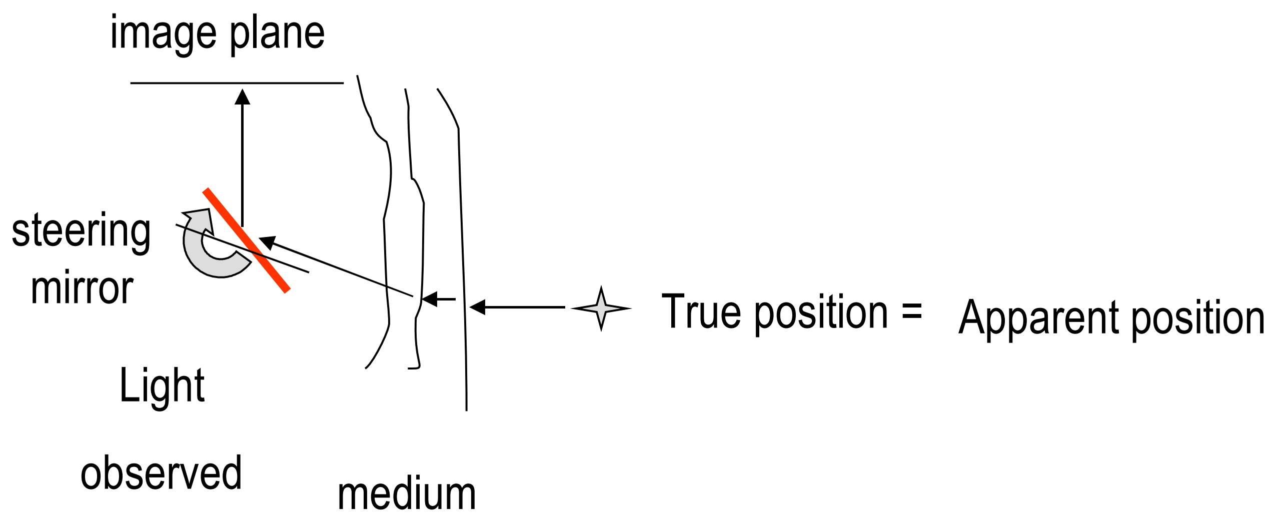
More on the funny part...

- The goal is ***not*** to remove the noise: it's to estimate it.

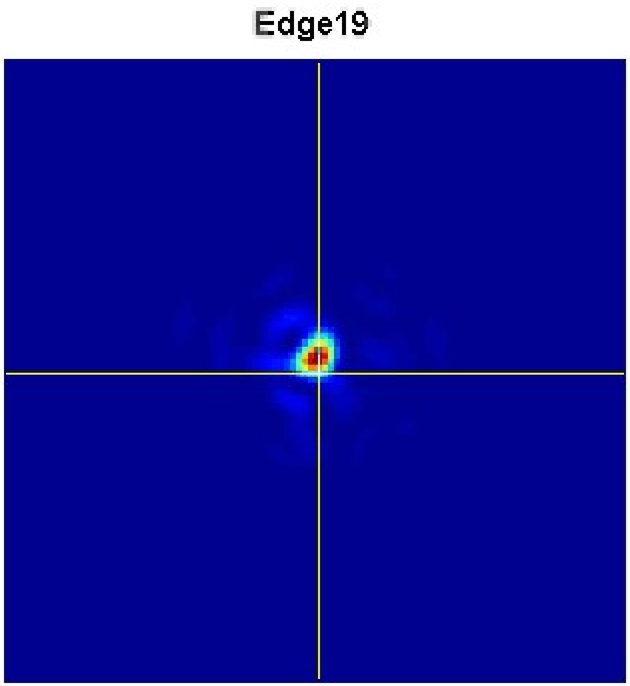


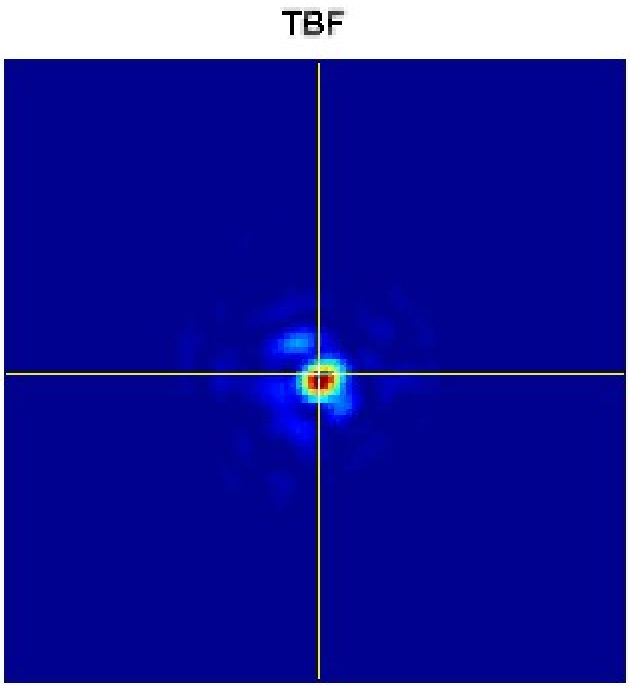
Fixing the funny part...

- The goal is ***not*** to remove the noise: it's to estimate it.



Controllers Based on Two Models





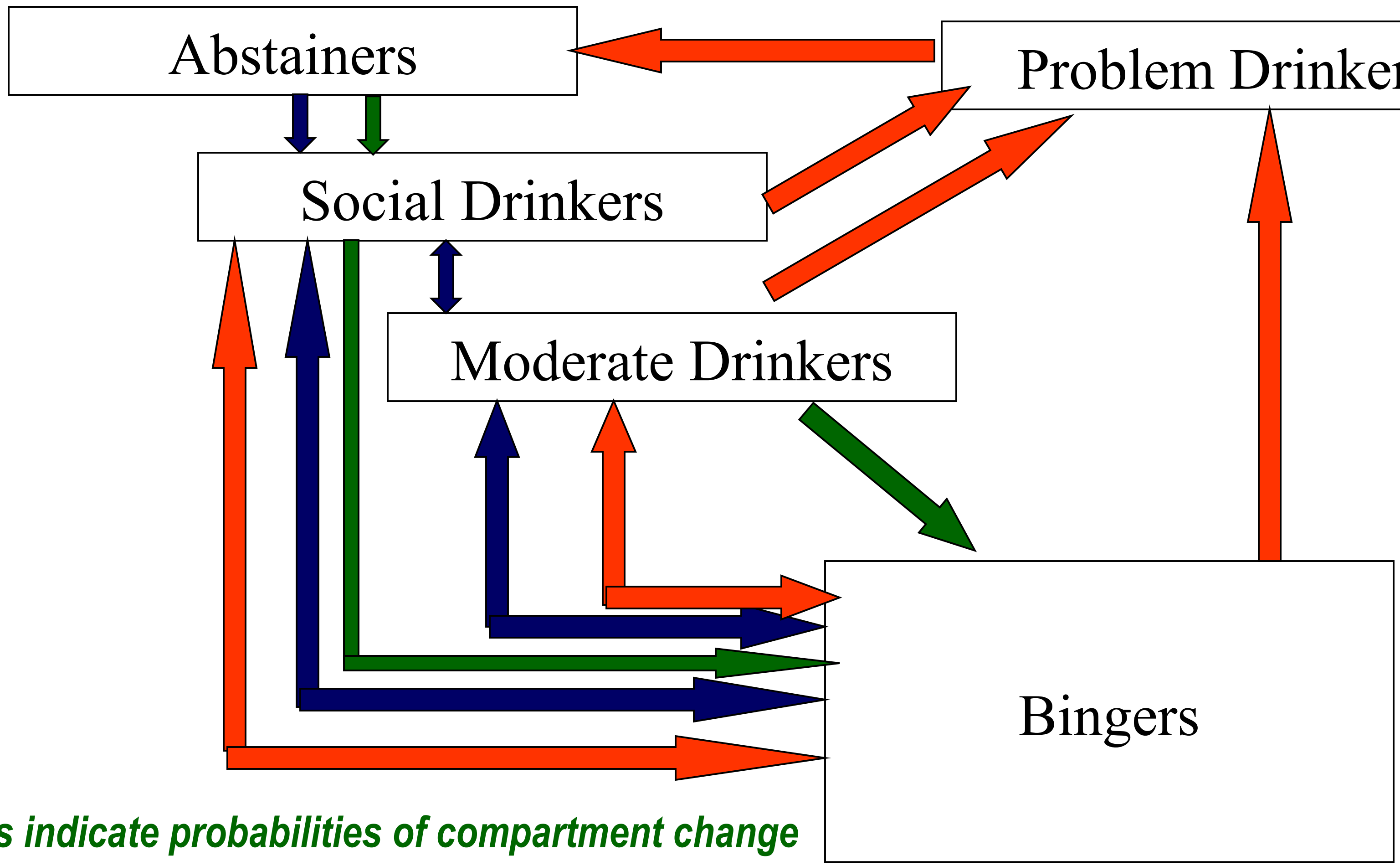
Modeling College Drinking

- Individual interventions have (at best) limited help
- Alcohol is a factor in
  - 40% of academic problems
  - 28% of dropouts
- 42% of students binge
- Binging correlates significantly with rape
- 1400 deaths per year related to alcohol
- Can administrators and politicians develop policy mechanisms to help?
  - Curfew, zoning, marketing restrictions, enforcement, …?

Modeling of populations

- Compartments
  - Lump together “like” individuals
  - Interactions in terms of compartments, not individuals
  - External influences in terms of compartments, not individuals
  - Gives a sense of “average” behavior
- Individuals (Agents)
  - Everyone is (potentially) unique
  - Interactions and external influences work on individuals
  - Aggregate information can be determined by averaging
  - Price of flexibility, variability is complexity

Compartments connected



Arrows indicate probabilities of compartment change

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ODEs

$$\frac{dN_1}{dt}=-d_1N_1-n_{12}\frac{\sum_{i=2}^{5}N_i}{\sum_{i=1}^{5}N_i}N_1-s_{12}N_1N_2+r_{41}N_4+r_{21}N_2$$

$$\frac{dN_2}{dt}=-d_2N_2+n_{12}\frac{\sum_{i=2}^{5}N_i}{\sum_{i=1}^{5}N_i}N_1-n_{25}\frac{N_5}{\sum_{i=1}^{5}N_i}N_2+s_{12}N_1N_2+(s_{52}-s_{25})N_2N_5$$
$$+(s_{32}-s_{23})N_2N_3+r_{52}N_5-r_{25}N_2-r_{24}N_2-r_{21}N_2$$

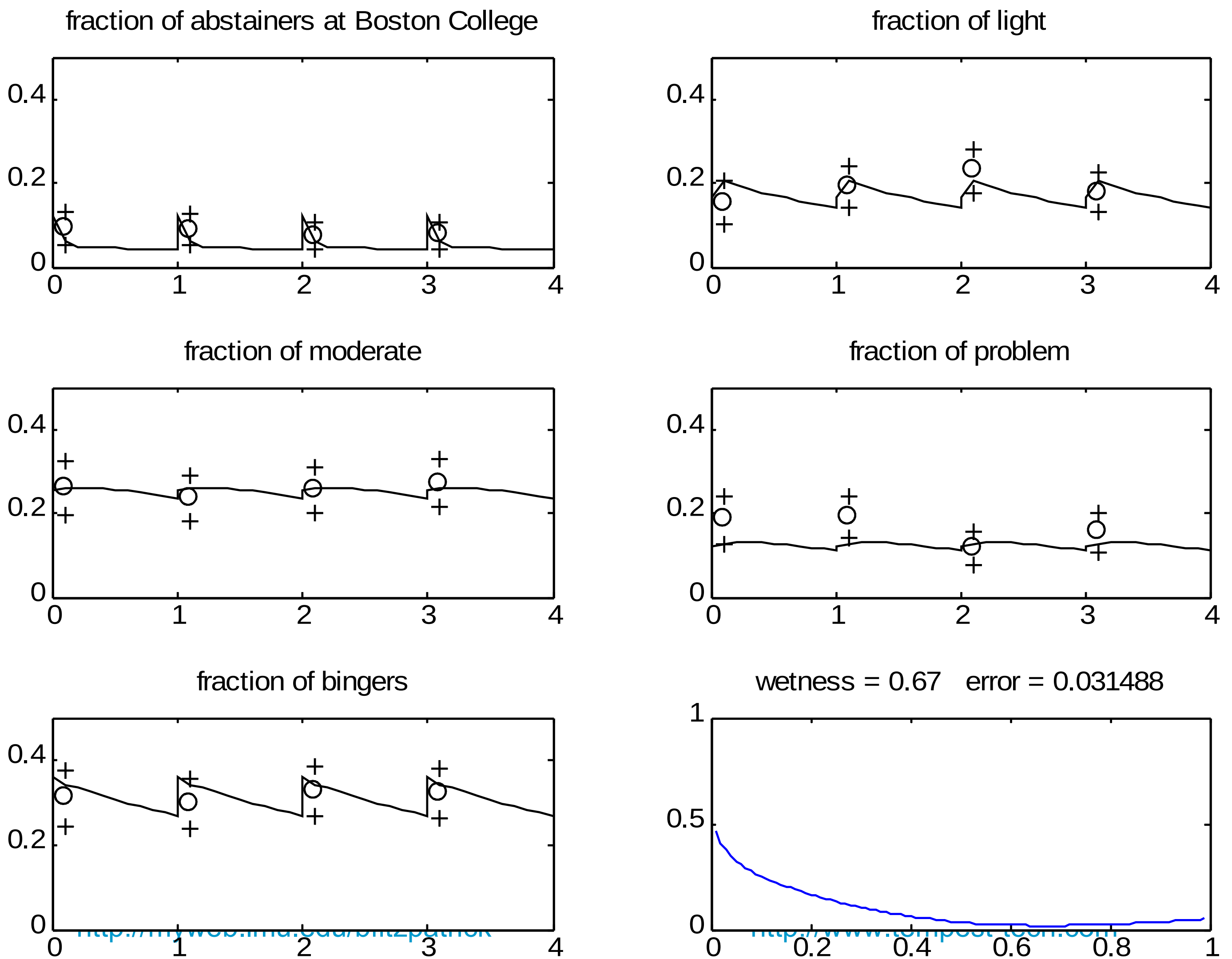
$$\frac{dN_3}{dt}=-d_3N_3-n_{35}\frac{N_5}{\sum_{i=1}^{5}N_i}N_3-(s_{32}-s_{23})N_2N_3+(s_{53}-s_{35})N_3N_5-(r_{34}+r_{35})N_3+r_{53}N_5$$

$$\frac{dN_4}{dt}=-d_4N_4+r_{34}N_3+r_{54}N_5-r_{41}N_4+r_{24}N_2$$

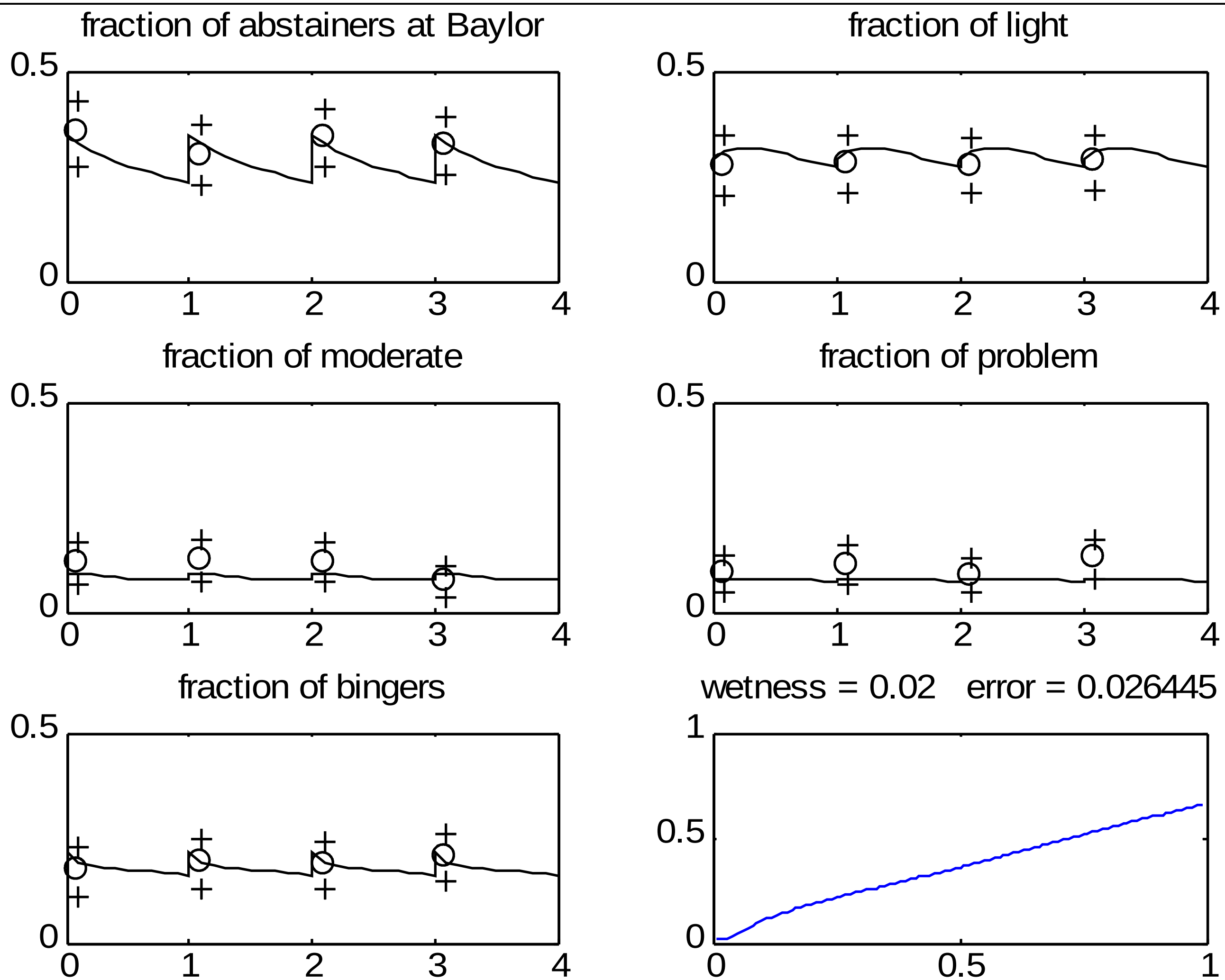
$$\frac{dN_5}{dt}=-d_5N_5+n_{25}\frac{N_5}{\sum_{i=1}^{5}N_i}N_2+n_{35}\frac{N_5}{\sum_{i=1}^{5}N_i}N_3-(s_{52}-s_{25})N_2N_5+(s_{53}-s_{35})N_3N_5-r_{52}N_5$$
$$+r_{25}N_2-r_{54}N_5-r_{53}N_5+r_{35}N_3$$

$$\Delta N_j(t_k)=N(t_k^+)-N(t_k^-)=c_j\sum_{i=1}^{5}[N_i(t_{k-1}^+)-N_i(t_k^-)],\quad j=1,2,3,4,5,\quad t_k=1,2,3,\cdots$$

Data and Model for Boston College



Data and Model for Baylor



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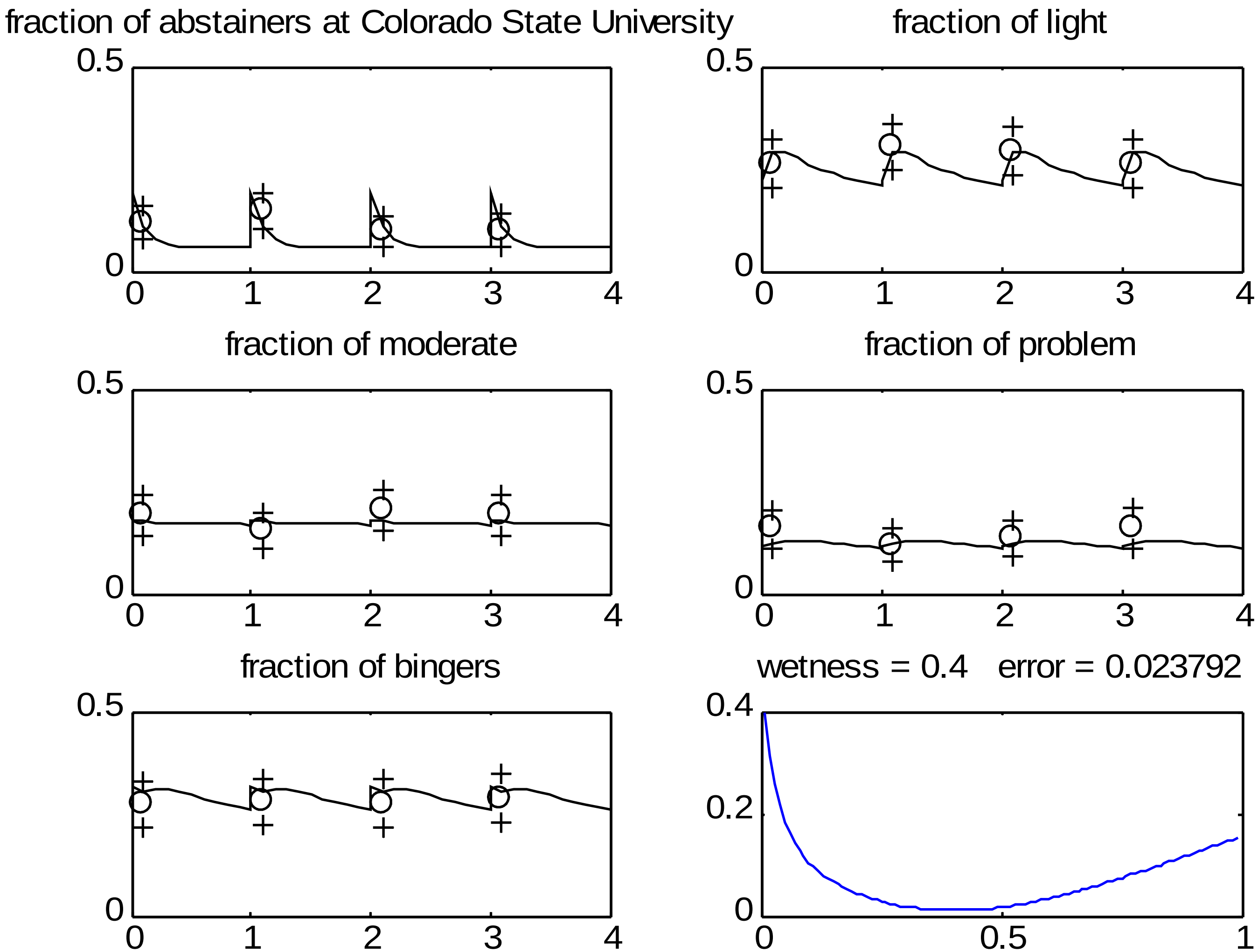
Data and Model for Colorado State



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Modeling: what it is

- Modeling: an attempt to understand something by creating a likeness
  - Architectural scale model in cardboard of a skyscraper
  - Map of Palo Alto
  - Mathematical equations describing gravity
- A model is a simplified representation of reality
- Models can be mental, verbal, graphical, physical, or mathematical
- Models can contain various levels of detail and provide various levels of accuracy
- Models may contain hypotheses about phenomena
- Models can only be demonstrated to be false
  - Validity is the absence of evidence to reject

Modeling basics: why and how

- The goal governs the approach
  - Qualitative understanding
  - Quantitative understanding
  - Quantitative prediction
  - Design/decision making

- The phenomena govern the approach
  - Repeatability (at what level of accuracy)
  - Individual differences
  - Environmental effects
  - Dynamics
  - External/exogenous influences
  - Scales (in time, space, size)

Occam's razor: keep it simple!

Model requirements

- Simple enough to be “study-able”
- Complex enough to capture phenomena of interest
- Parameters estimable and relate-able to problem domain
- Predictions to be quantitatively accurate
- Policy decision impacts to be quantitatively well predicted
- ***A model is at best as good as the assumptions on which it is based***

Possible Approaches

- Empirical statistical approach
  - Collect data
  - Fit a statistical model
    - Linear model, heirarchical linear model, multivariate/covariance, etc
  - Test hypotheses
  - Often motivated by below but tuned for individual situation
- Theoretical mathematical approach
  - Quantify behaviors
  - Develop equations
  - Solve/simulate
  - Test hypotheses
  - Can be simple or complex, depending on goals

Modeling and Uncertainty

- Individual patient uncertainty
  - Parametric? Bayesian approaches are ideal
- Patient activity uncertainty
  - Exogenous? Plant noise and stochastic differential equations
- Measurement sensor noise
  - The noise for which many standard statistical methods have been designed

Inductive and Deductive Science

- Collect data
- Get idea
- Submit proposal
- Manipulate idea to fit data
- Repeat until funding dries up

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- Submit proposal
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- Manipulate data to fit idea
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Statistics: the science of data

- Statistics is the science of
  - Collecting,
  - Organizing,
  - Analyzing, and
  - Interpreting data

- Branches of statistics
  - Descriptive
  - Inferential

Questions statistics attempts to answer

- What patterns exist in my data?
- How good are my parameter values?
- Do these samples have the same structure?
- What data should I collect?

Descriptive statistics

- Basic parametrics
  - Means, variances
  - Covariances
- Basic nonparametrics
  - Histograms
  - Emprical CDFs
- Parametric nonparametrics
  - Autocovariance functions
  - PSDs
  - Nonparametric regression

Inferential Statistics

- Three basic problems
  - Parameter estimation
  - Interval estimation (confidence intervals)
  - Hypothesis testing

- Requirements
  - Parameter and noise to data model
  - Data probability distribution function

- Except in the simplest settings, a lot of computation is required

Caution: what statistics does not do

- No definitive decisions!
  - Assumptions are often unverifiable
  - Decisions may not be robust to “decision parameters”
- Two populations: X & Y
- Test that they have the same mean

$$H_0 : \mu_X = \mu_Y$$
$$H_A : \mu_X \neq \mu_Y$$

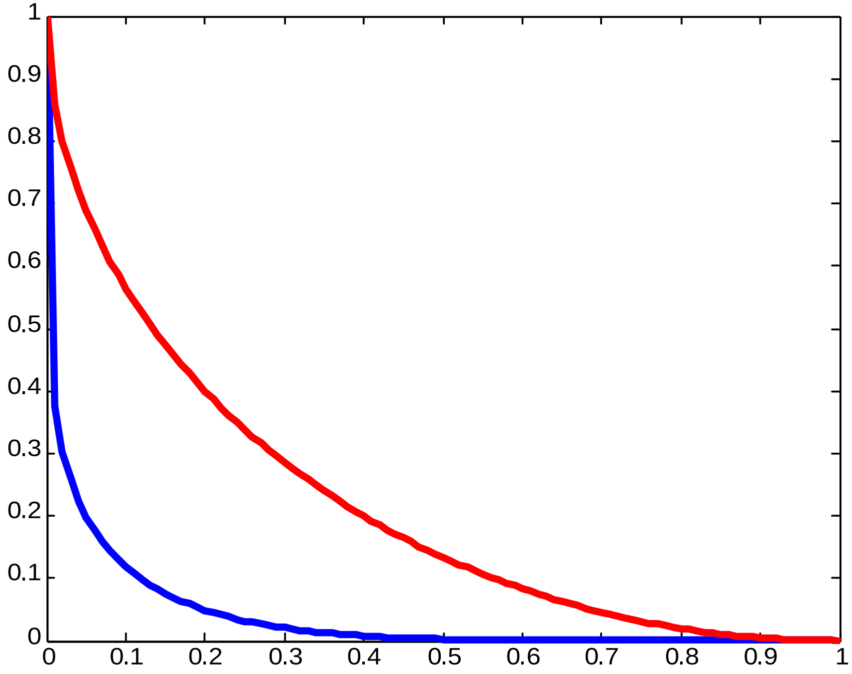
$$\frac{\bar{X} - \bar{Y}}{S_p} \sim T$$

- Stat = 2.3, is it significant? Yes at the 0.05 level, but no at the 0.01 level.
- Phrasing: We either reject H_0 or we fail to reject H_0

More on (Moron?) Hypothesis Testing

- Two types of errors
  - Reject H0 when it is true α
  - Fail to reject H0 when it is false β
  - Typically the probabilities of these erors are
    - Coupled
    - Move in competing directions when test criteria changes

- ROC (receiver operating characteristic) compares the two erros



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Techniques of Inferential Statistics

- Frequentist or classical statistics
  - Maximum likelihood
  - Least squares
  - Likelihood ratio tests
  - Asymptotics justify application
- Bayesian statistics
  - Maximum a posteriori
  - Posterior mean
  - Posterior hypothesis probability
  - Computationally intensive

Things We Want from Estimators

- Unbiasedness
  - Is the theoretical mean value of the estimator equal to the parameter it's estimating?
- Consistency
  - Does the estimator converge to the parameter's true value as the number of observations increases?
- Minimal variance
  - Does this estimator have less variability than other possible estimators?
- Asymptotic normality
  - Is the probability distribution of the estimator converging to a normal distribution as the number of observations increases?

Bayesian statistical methods

- Use probability distributions to model uncertainty
  - Unknown parameters to be estimated
  - Measurements and observations
- Compute conditional probabilities for inference

$$\theta = \text{unknown parameter}$$
$$\pi(\theta) = \text{prior probability density}$$
$$y = \text{measurement vector}$$
$$p(y|\theta) = \text{measurement density (conditional)}$$
$$\pi(\theta|y) = \text{posterior}$$

- Requires a lot of thought/investigation to obtain p.

Bayesian inference

- Bayes' theorem:

$$\pi(\theta|y) = \frac{p(y|\theta)\pi(\theta)}{\int_{\Theta} p(y|\theta')\pi(\theta')d\theta'}$$

- The posterior is used for estimation and other inference

$$\theta_{MAP} = \arg\max \pi(\theta|y)$$

$$\theta_{PM} = \int_{\Theta} \theta\pi(\theta|y)d\theta$$

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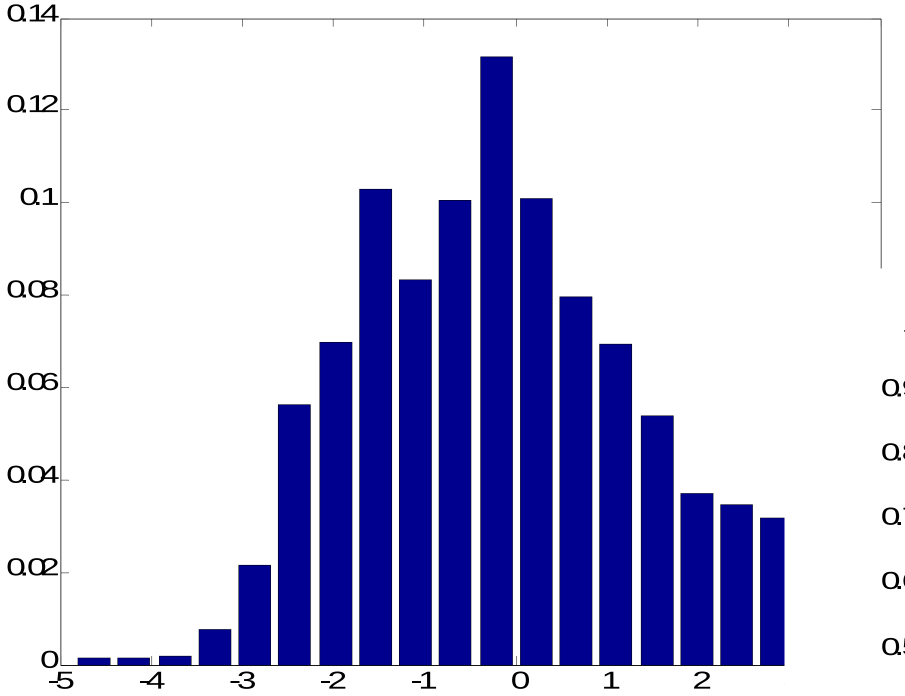
Looking for patterns and structure

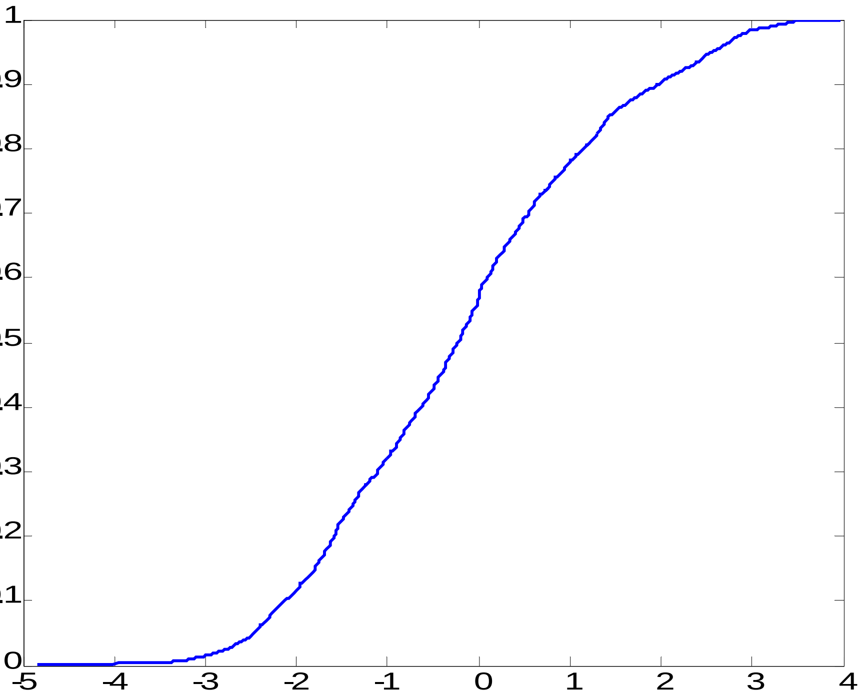
- Standard practice: means and variances
- Frequency analysis: basic variability
  - Histogram
  - CDF
- Correlation analysis: related variables
  - Dot-plots
  - Correlation coefficients and r^2
- Temporal analysis
  - Time domain
  - Frequency domain

Basics



histogram

cumulative



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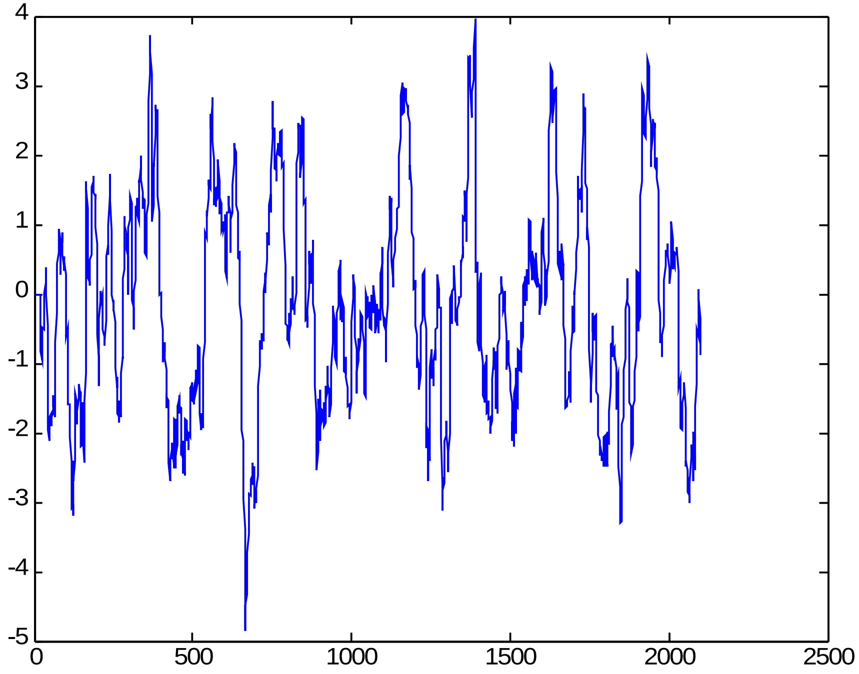
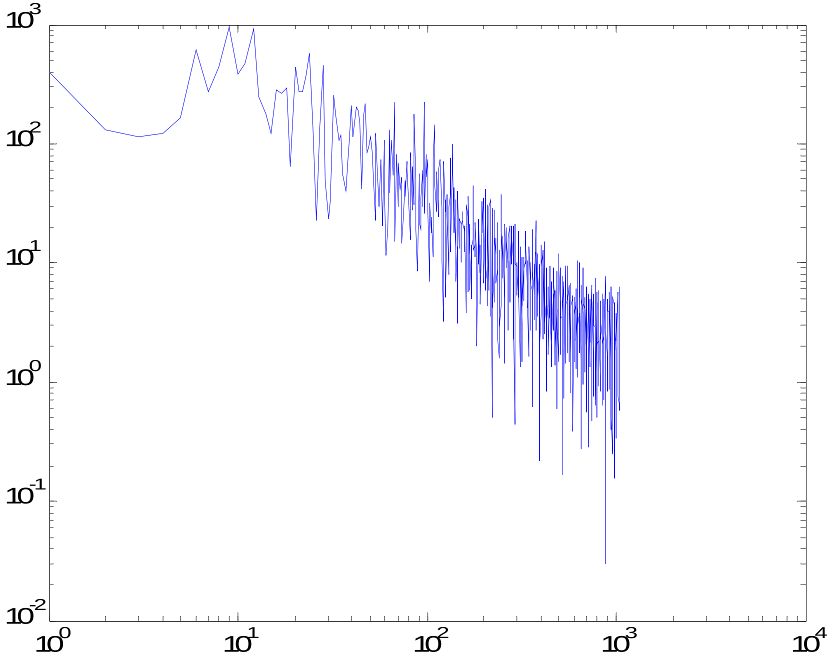
Time Series Analysis

- Traditional tools
  - Autocovariance
  - Variogram
  - Power spectrum (PSD)
  - Autoregression (AR)
  - AR moving average (ARMA)
  - FARIMA (fractional..integrated…)
- More “modern” tools
  - Nonlinear models
  - Wavelet analysis
  - Local covariance
  - Change point

Time and Frequency





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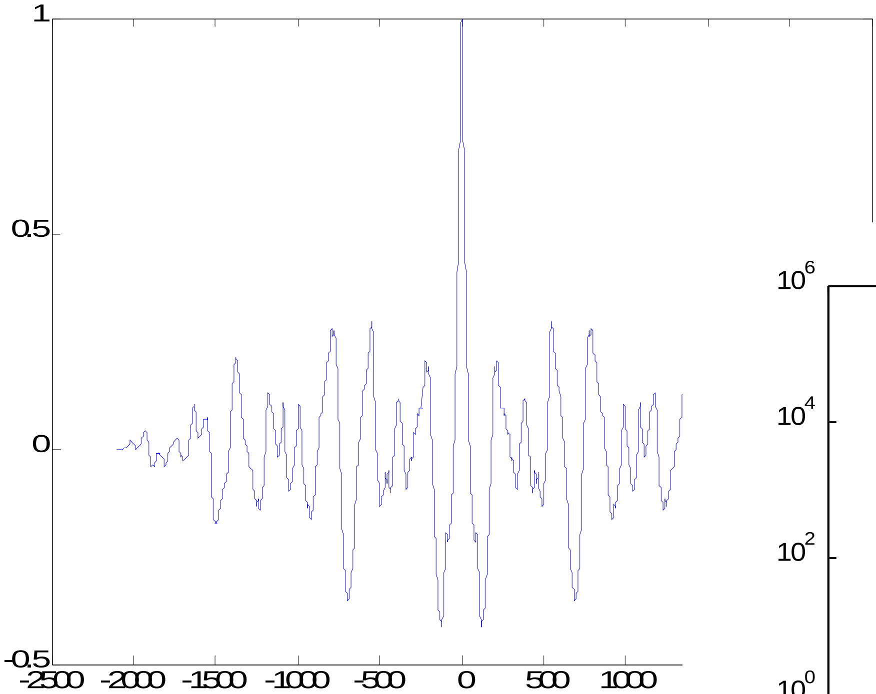
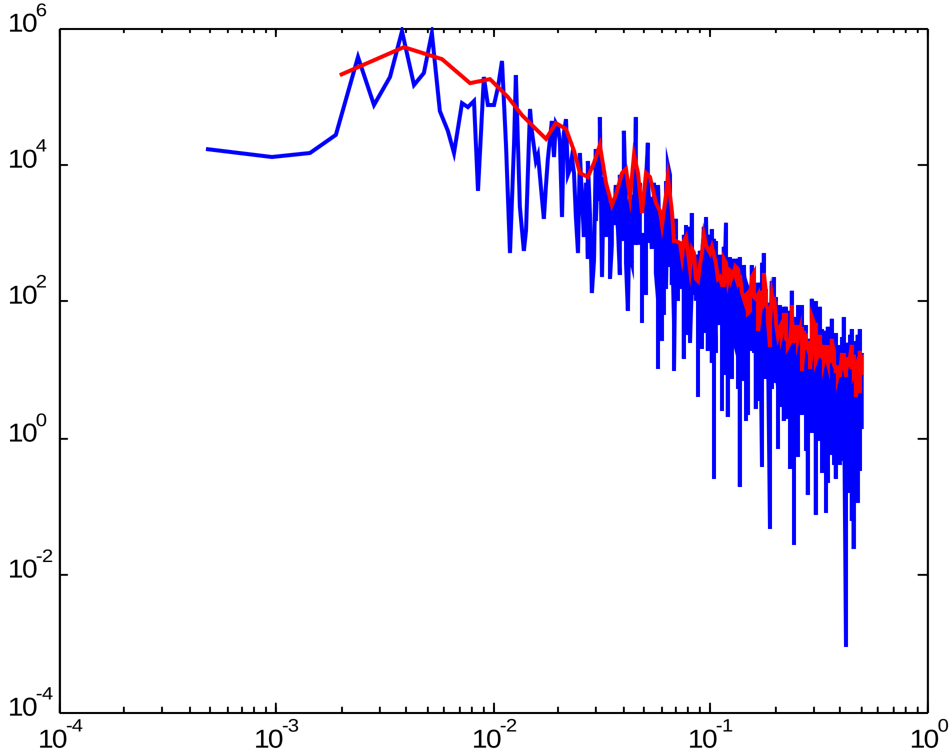
Second Moments



Standard PSD is NOT consistent



Autocovariance is consistent

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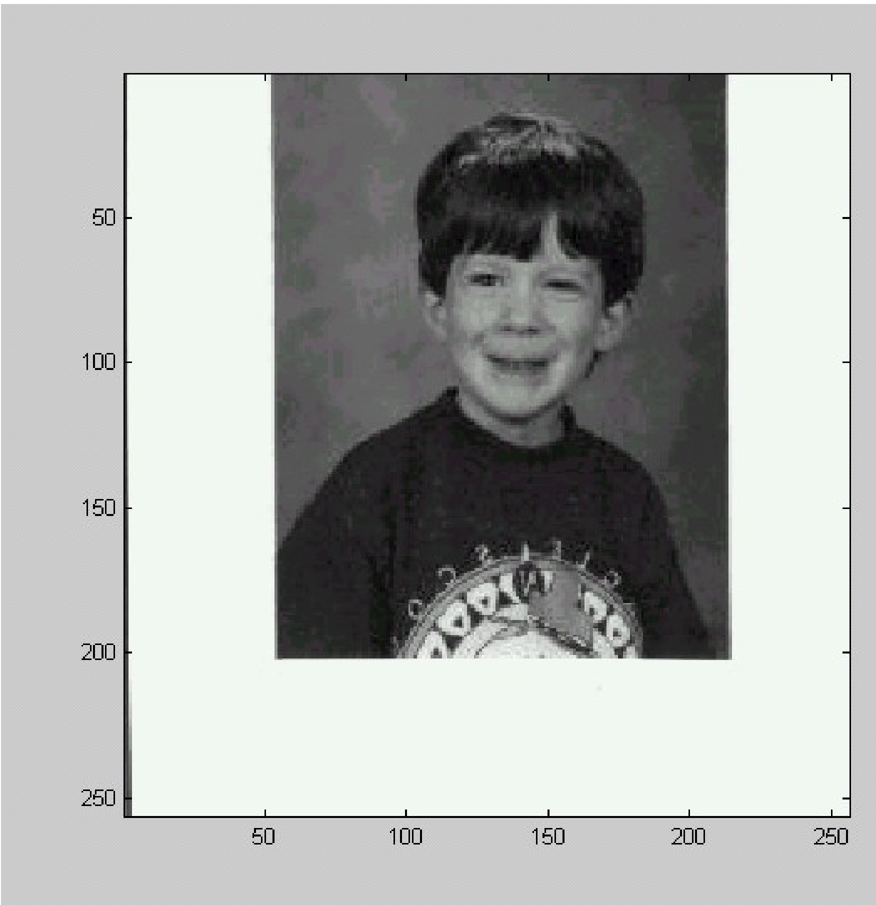
Two photographs: don’t forget the phase



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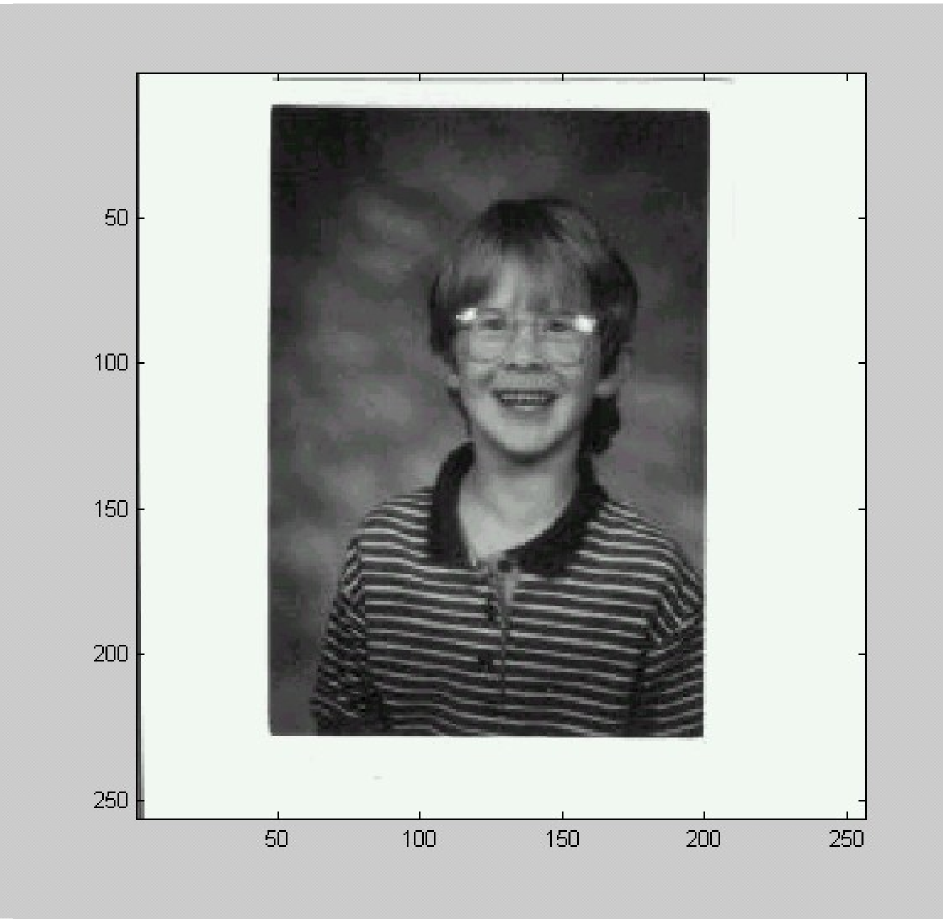

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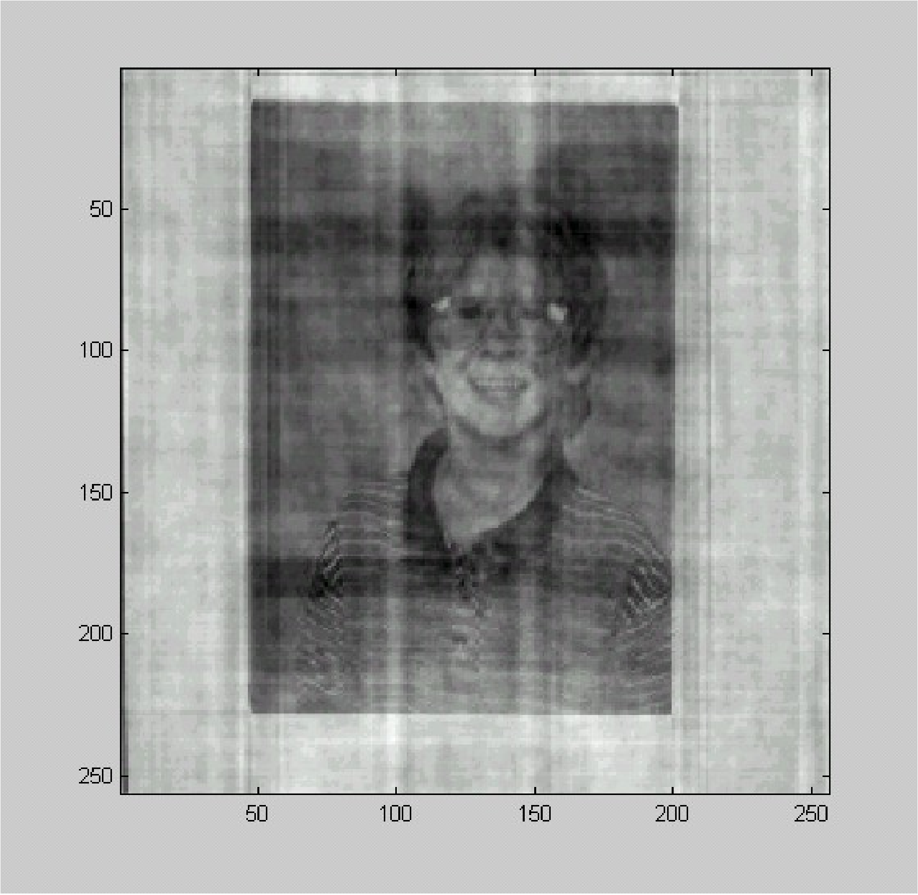
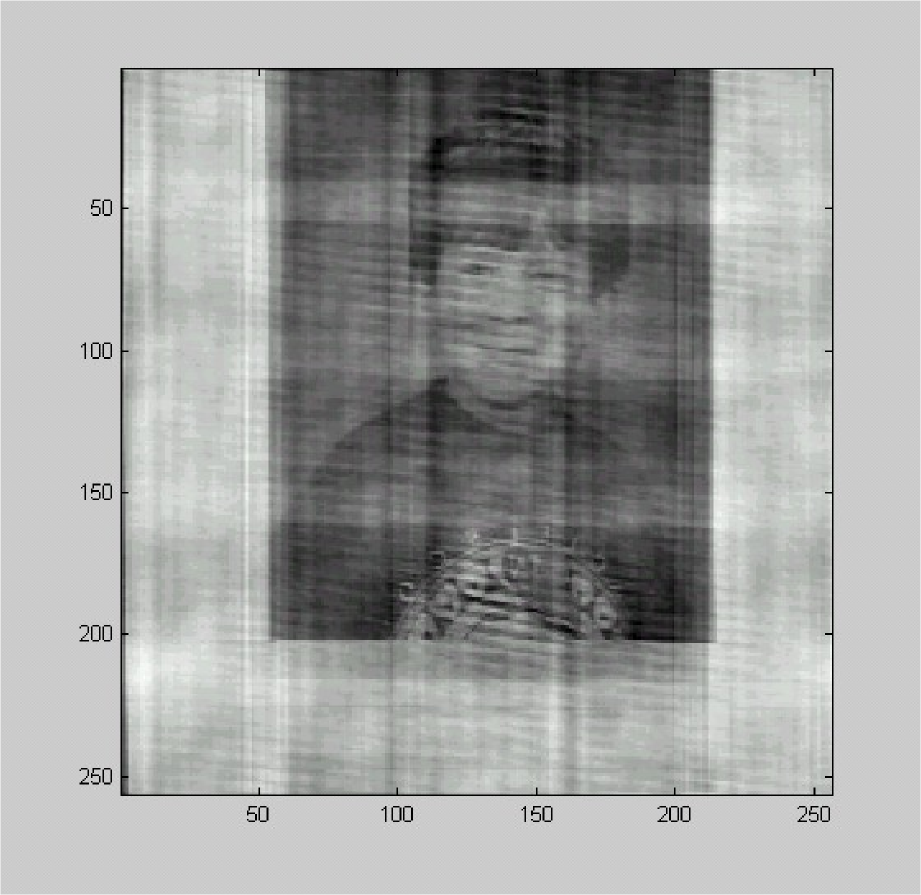
Fourier transform, swap phases, inverse F.T.





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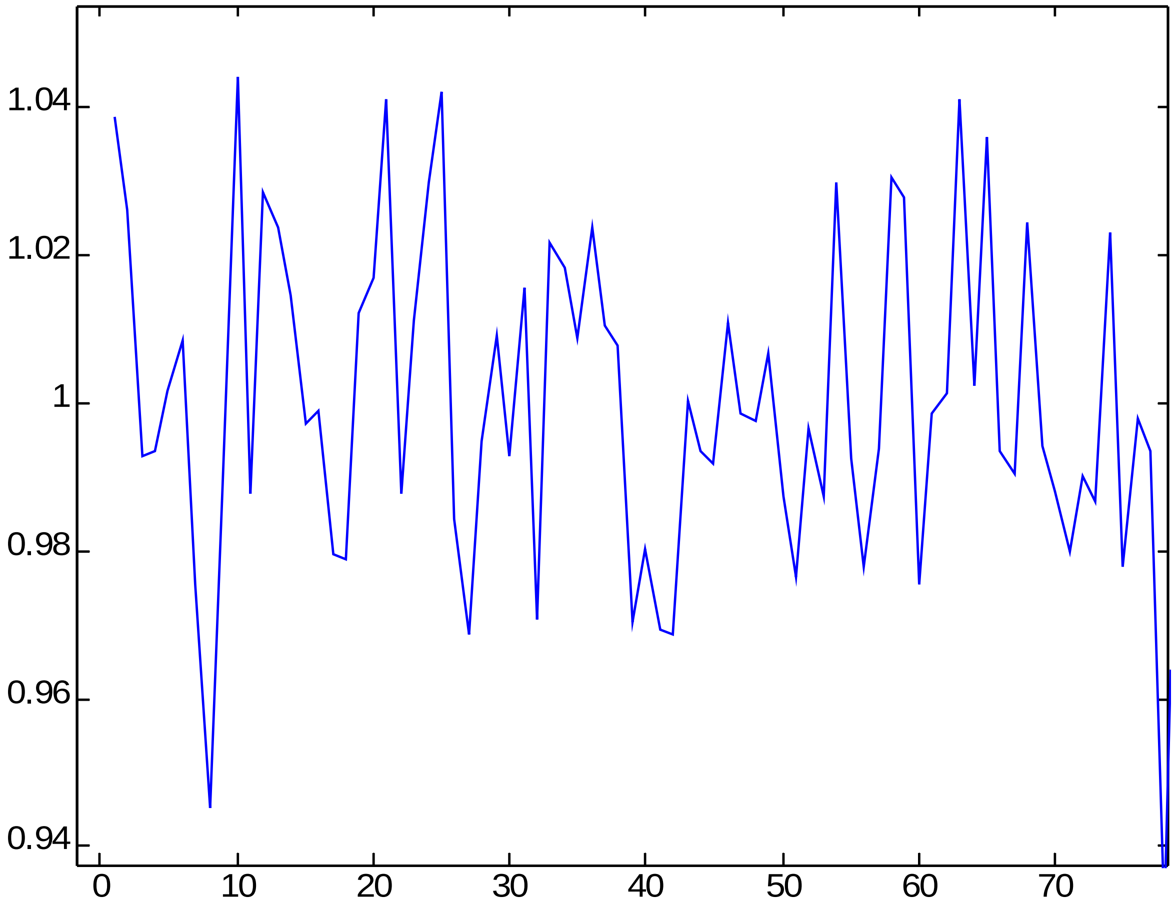
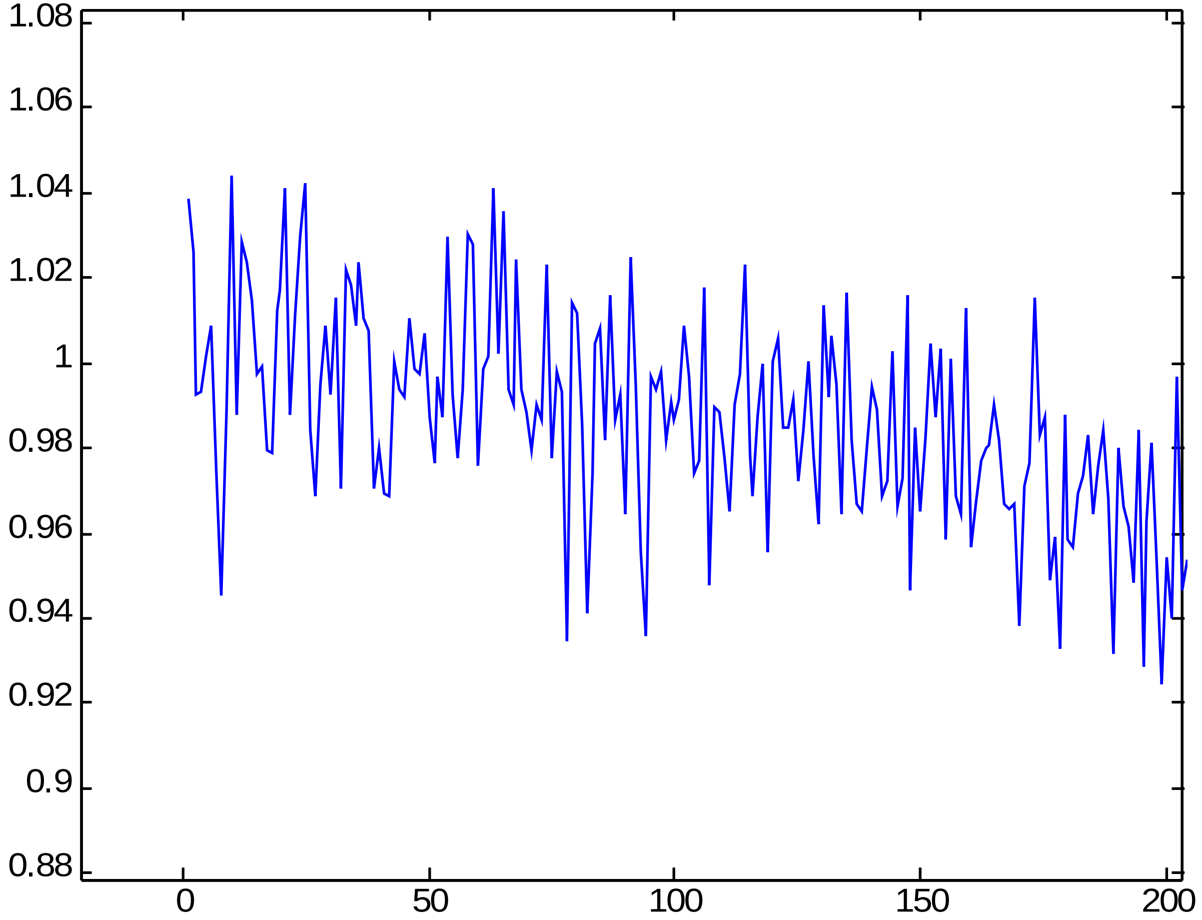
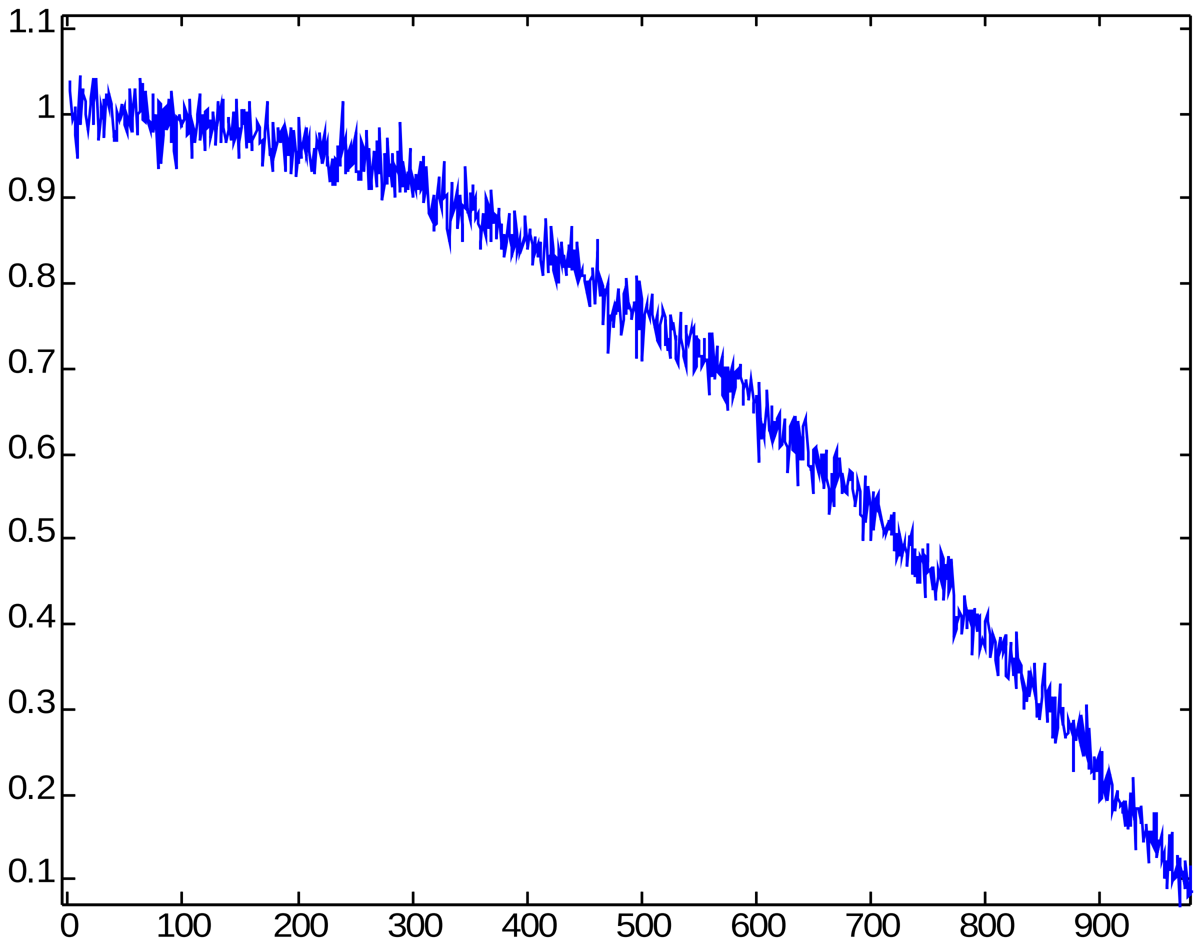
Stationarity



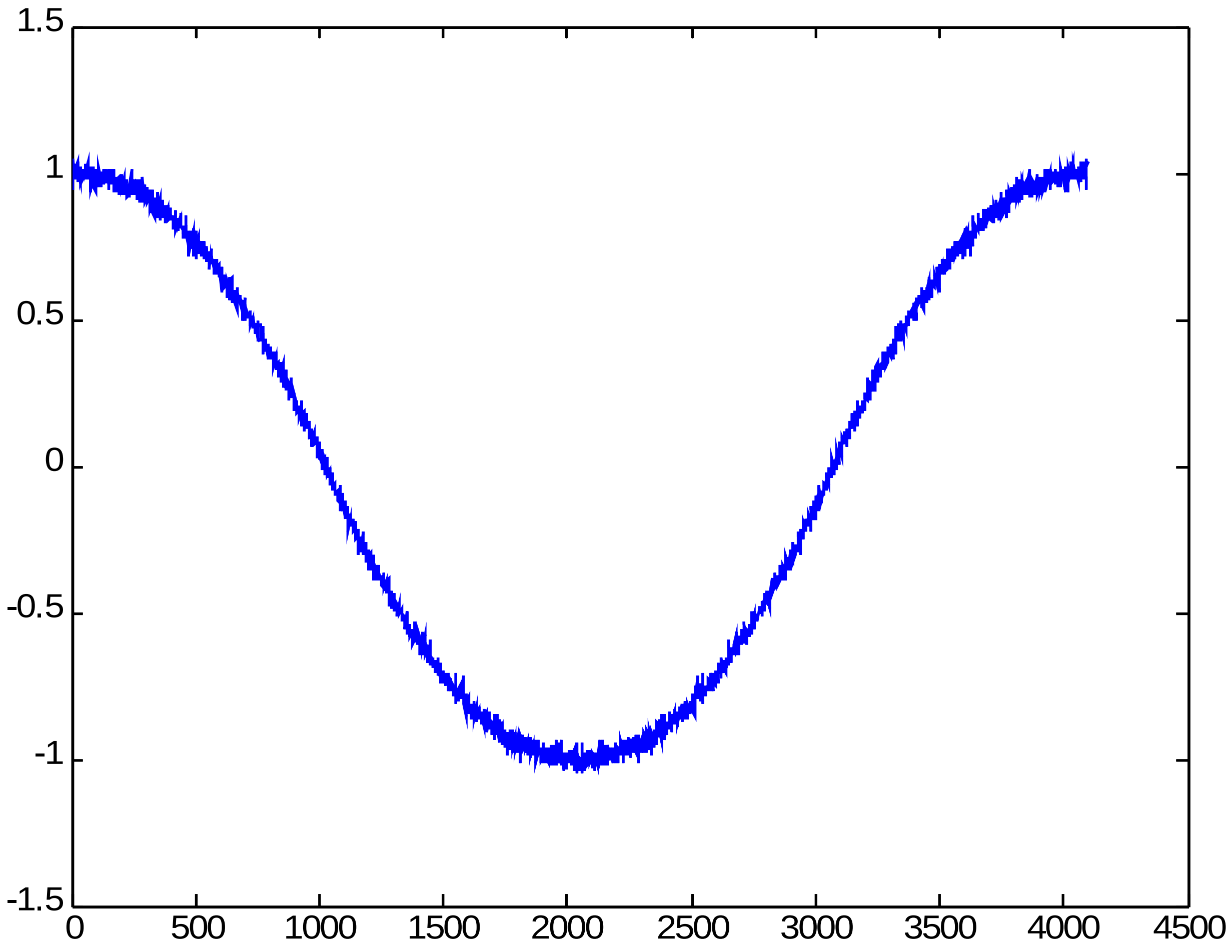
Stationarity



Stationarity

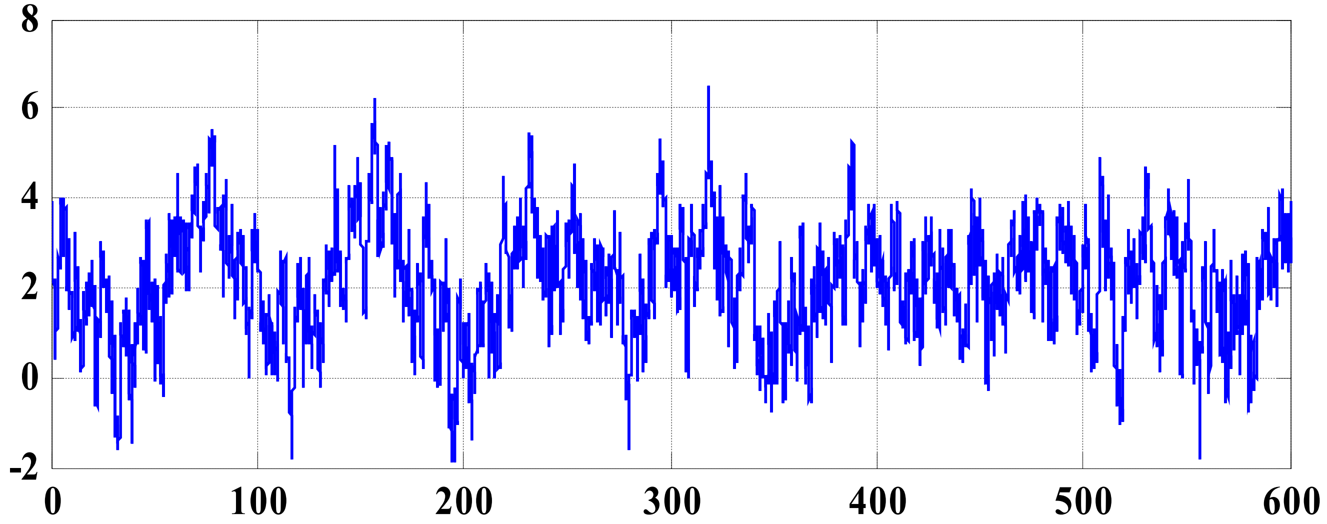


Stationarity

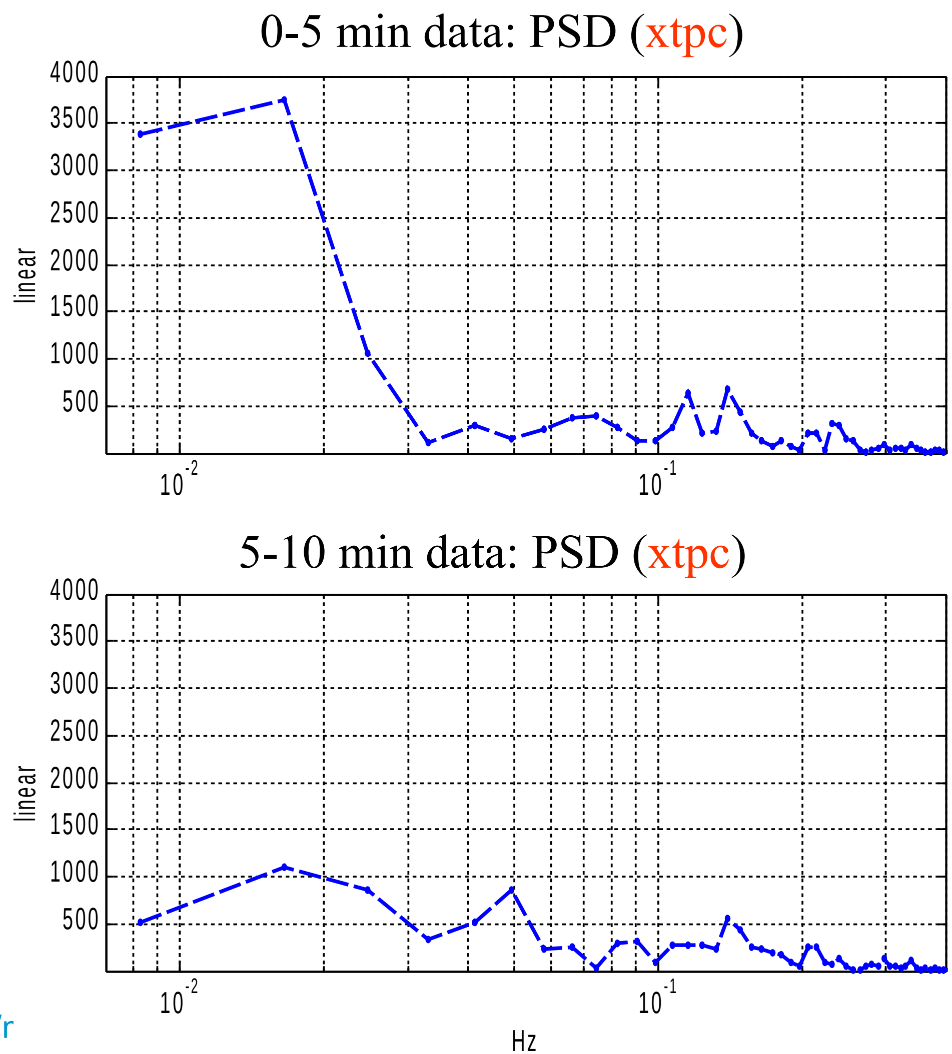


Modeling Atmospheric Turbulence

- 10 minutes of data
- Is it stationary?



PSD's 0-5 minute and 5-10 minute segments.



Nonparametric parametrics?

- Parameter is the covariance
- Estimate the covariance function from data

- Assume stationarity: autocovariance

- Smooth changes: local autocovariance
- Abrupt changes: change-point methods
- Dunno: try wavelets

Nonstationarity: stationary increments

- Brownian motion or random walk: not stationary, but the "derivative" is
- Variogram (or structure function) is a helpful quantity

$$\Gamma(s) = E\left|X(t+s) - X(t)\right|^2$$

- Fractional Brownian motions (long memory processes, 1/f noise, etc) have the form

$$\Gamma(s) = E\left|X(t+s) - X(t)\right|^2 = C\left|s\right|^{2H}$$

  - H is the Hurst parameter: H=1/2 is Brownian motion

Estimating the Variogram

- Standard estimator

$$\hat{\Gamma}(h) = \frac{1}{N_h} \sum_{i=1}^{N_h} \left| X(t_i) - X(t_i + h) \right|^2$$

- This estimator can be fit to functional forms
  - Log-linear regression can estimate the Hurst parameter

- A similar technique, DFA or Detrended Fluctuation Analysis, is used in certain cardiovascular problems

Local Covariance Approach

- Use a sliding window to construct multiple stationarily-modeled covariance functions
- These covariances are examined in terms of the local Karhunen-Loeve expansions (approximately cosine bases)
- In each window, the expansion is compared to the covariance by how well its Hilbert-Schmidt norm compares: how well it captures the total variance in the basis vector directions
- Best window is the one that provides the maximal total variance

Change-Point Approach

- Time series modeled as conditional $g_\theta(y_t \mid y_{t-1}, \cdots, y_1, y_0)$

- Parameter changes/is constant

$$H_0 : \theta = \theta_0$$

$$H_A : \text{there is an } r \text{ with } 1 \le r \le n \text{ such that}$$

$$\theta = \theta_1, 1 \le t \le r$$

$$\theta = \theta_2, r+1 \le t \le n$$

Wavelet Approaches

- Decompose by scale (as in Fourier) and time-locality

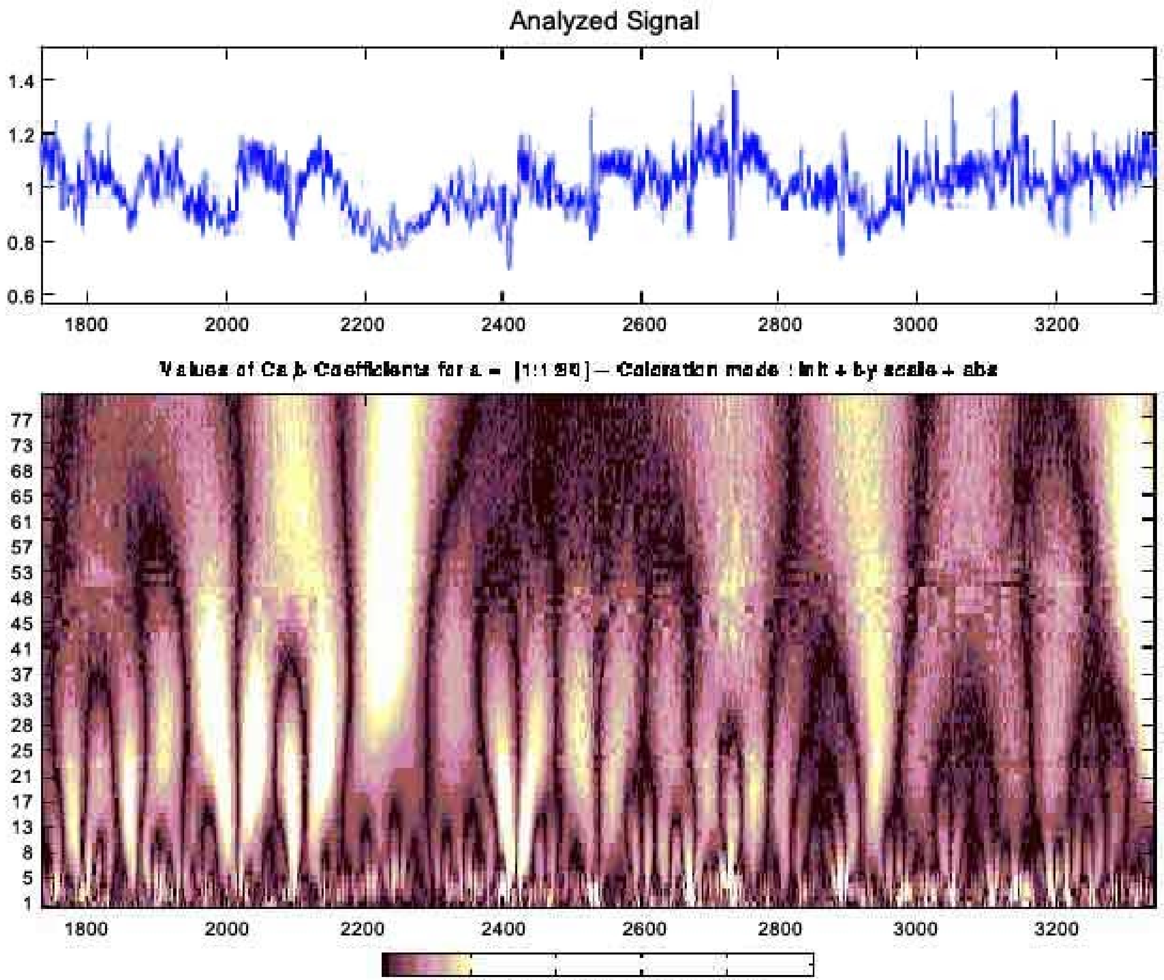
$$W_f(s,a) = |s|^{-\frac{1}{2}} \int_{-\infty}^{\infty} f(x)\psi^*\left(\frac{x-a}{s}\right)dx$$

- Reconstruction has a similar form

$$f = C_\psi^{-1} \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \frac{\langle f, \psi^{s,a} \rangle}{s^2} \psi^{s,a} \, ds\, da$$

- Choice of the wavelet function is important

Wavelet decomposition (from physionet)



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Inferential Wavelets

- Statistical theory for the decomposition exists (in some form)
  - Dependence on the underlying mother wavelet
  - Dependence on the underlying data structure (eg power law)
- Tools for segmentation of signals exist
  - Compare scale estimate to theoretical scale stats
- Parameter estimation tools exist
  - The power in the power law

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Model-Based Statistics

- Data = Model plus Noise
  - Is plus really “+”?
- How does noise enter the data?
- What is the probabilistic structure of the noise?
- What parameters are unknown?

Simplest Parametric Model

- Data: $Y_k \approx y(t_k)$
- Model: $f(t_k, u_k, \theta)$
  - u is an exogenous or control input variable
  - θ is the unknown parameter
- Statistical observation model: $Y_k = g(t_k) + \varepsilon_k$
  - ε_k are independent identically distributed random variables
- Fitting criteria

$$J_n(\theta) = \sum_{k=1}^{n} \left| Y_k - f(t_k, u_k, \theta) \right|^2$$

What is known

- Consistency

$$\hat{\theta}_n = \arg\min J_n \to \theta^*$$

$$\theta^* = !\arg\min \int_{TxU} \left| f(t,u,\theta) - g(t) \right|^2 d\mu(t,u)$$

$$\frac{1}{n} J_n(\hat{\theta}_n) \to \sigma^2 + \int_{TxU} \left| f(t,u,\theta^*) - g(t) \right|^2 d\mu(t,u)$$

- Asymptotic Normality

$$\sqrt{n}\left(\hat{\theta}_n - \theta^*\right) \to N(0,V)$$

$$V = \sigma^2 \left(\int_{TxU} \frac{\partial f}{\partial \theta}(t,u,\theta) \frac{\partial f^T}{\partial \theta}(t,u,\theta) d\mu(t,u) \right)^{-1}$$

Model selection through hypothesis testing

$$H_0 : \theta \in \Theta_0 = \{\theta \in \Theta : H\theta = h\}$$

$$H_A : \theta \notin \Theta_0$$

$$\tilde{\theta}_n = \arg\min\{J_n(\theta) : \theta \in \Theta_0\}$$

$$\frac{J_n(\tilde{\theta}_n) - J_n(\hat{\theta}_n)}{J_n(\hat{\theta}_n)} \to \chi^2(p-q)$$

$p =$ dimension of Θ

$q =$ dimension of Θ_0

Problems with This Approach

- Is the data really model plus noise?
- Is the parameter really identifiable?
  - Common assumption is $g(t) = f(t, u, \theta^*)$
- Is the noise really iid random noise?
- Do we have enough data for the asymptotics?
- Test becomes less powerful as dimensions increase

- ***This hypothesis test is not validation!***
  - ***Compares a simpler model to a more complicated one!***

Analysis of Residuals

- Are the residuals (Gaussian) white noise?
  - Are there unmodeled trends remaining?
    - If so, we need to revisit the model
  - Are the residuals correlated?
    - If so, we may want to estimate the covariance and re-estimate with weighted least squares.
  - Are the residuals non-Gaussian?
    - If so, we may want to apply maximum likelihood
- Do the residuals indicate outliers?
  - If so, we need to consider robust estimation techniques, such as MAD

Adjusting the Fitting Approach

- Weighted Least Squares

$$J_n(\theta) = \sum_{k=1}^{n} \frac{\left| Y_k - f(t_k, u_k, \theta) \right|^2}{\sigma_k^2}$$

- Minimum Variance

$$J_n(\theta) = \left(Y - f(\theta) \right)^T V^{-1} \left(Y - f(\theta) \right)$$

- Maximum Likelihood

$$J_n(\theta) = p\left(Y - f(\theta) \right), \quad p \text{ is the pdf of the residual vector}$$

- Minimum Median Absolute Deviation

$$J_n(\theta) = \text{Median}\left(Y - f(\theta) \right)$$

Outline

- Modeling discussion
- What statistics actually does
- Exploratory data analysis
- Parametric fitting
- Nonparametric fitting
- Stochastic modeling

Bayesian Nonparametric Regression

- Data: $Y_k \approx y(t_k)$
- Model: $f(t_k, u_k, \theta)$
  - u is an exogenous or control input variable
  - θ is the unknown parameter
- Statistical observation model: $Y_k = g(t_k) + \varepsilon_k$
  - ε_k are independent identically distributed random variables
- Prior probability measure on the space of continuous functions

Bayesian Nonparametric Regression

- Prior variance $E_\pi\left(g^2\right) = \tau^2 \int_T \left|\nabla g\right|^2 d\mu$
- Maximum a posteriori

$$J_n^\pi(g) = \sum_{k=1}^{n} \left|Y_k - g(t_k)\right|^2 + \tau^2 \int_T \left|\nabla g\right|^2 d\mu$$

- Model testing? Compute the posterior probability…

Model Test of Fit

- Compute the posterior probability

$$\int_S d\pi(g|y)$$

$$S = \{ f(\bullet, u_{(\bullet)}, \theta) : \theta \in \Theta \}$$

$$S = \{ |g - f(\bullet, u_{(\bullet)}, \theta)| < \delta, \theta \in \Theta \}$$

- Computing with Monte Carlo simulation
  - Sample from the prior
  - Average

- ***Could be viewed as validation***
  - ***But within the assumed framework of the measurement model***

Hierarchical Bayesian Approach

- Start with a simple model

$$Y_k = f(t_k, u_k, \theta) + \varepsilon_k$$

- Determine the residuals

$$\hat{\varepsilon}_k = Y_k - f\left(t_k, u_k, \hat{\theta}_n\right)$$

- Estimate the distribution of the residuals (emprical CDF, covariance)
- Use this estimate as the conditional
- Back to Bayes

Outline

- Modeling discussion
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Stochastics in Multiple Points in the Model

$$\dot{x}(t) = h(t, x(t), \theta, \eta(t))$$

$\eta(t) =$ plant noise

$$y(t) = L(x(t), \varepsilon(t))$$

$\varepsilon(t) =$ measurement noise

$$\dot{x}(t) = h(t, x(t), \theta) + \sigma(t, x(t), \theta)\dot{\eta}(t)$$

$$y(t) = L(x(t), \theta) + \tau(x(t), \theta)\varepsilon(t)$$

$=$ about the most complicated thing we can do

Nonlinear filtering: particle filters

- Discrete time approximation
- Bayes rule determines the posterior at each step
- Posterior probabilities can be difficult to compute

$$x_{t+1} = x_t + \Delta t h(t, x_t, \theta) + \Delta t \sigma(t, x_t, \theta) \dot{\eta}(t)$$
$$y_t = L(x_t, \theta) + \tau(x_t, \theta) \varepsilon(t)$$

- Generate a large number of sample paths
- Follow them over time
- Approximate the posterior by Monte Carlo

Starting the conversation

- How much of the signal needs to be modeled?
- How do we iterate?
  - Approximate model fit
  - Look at the residual for unmodeled dynamics
  - Estimate statistics of the residual
  - Return to the model fit
- Multiple patients/multiple observations of single patient

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