An Introduction to Pathodynamics from the View of Liver Homeostasis Using the Ornstein-Uhlenbeck Process

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Outline

1. Sources of Error in Lab Measurements
2. Additional Problems with Reference Regions
3. Stochastic Processes
4. Description of Pathodynamics
5. Examples and Results
6. Future Directions

1. Sources of Error in Lab Measurements

Sources of Error

- Variations due to the patient
  - Controllable biological variables
    - Posture
    - Hospitalization and immobilization
    - Exercise
    - Athletic training
    - Circadian variation
    - Recent meal (effects up to 12 hr)
    - Smoking
    - Alcohol

Sources of Error

- Variations due to the patient
  - Long-term biological influences
    - Age
    - Gender
    - Race
    - Environment (eg, altitude, heat exposure)
    - Menstrual cycle
    - Diet (eg, vegetarianism, malnutrition)

Sources of Error

- Variations and errors due to specimen handling
  - Tourniquet duration (> 3 min)
  - Puncture trauma
  - Labeling (eg, ID, sample time)
  - Site of blood draw
    - Finger stick
    - Arterial
    - Intravenous line

Sources of Error

- Variations and errors due to specimen handling (cont'd)
  - Contamination
  - Interferences and altered states
    - Hemolysis and leakage from cells
    - Anticoagulants and preservatives
    - Icteric (bilirubin) serum
    - Lactescent (lipid) serum
    - Drugs or metabolites

Sources of Error

- Variations and errors due to specimen handling (cont'd)
  - Freezing
  - Long-distance transportation (airplane)
    - Pressure changes
    - Vibration
    - Temperature changes
  - Evaporation
    - Increases concentrations of all constituents

Sources of Error

- Analytical variation
  - Bias
    - Operational (inherent in the procedure or instrumentation)
    - Misadjustment
    - Wear
    - Miscalibration
  - Variability
    - Increases with concentration in many cases
    - Dilutional

Sources of Error

- Analytical variation (cont'd)
  - Variability
    - Technician
    - Instrument
    - Environment (eg, temperature, humidity)
    - Reagents
  - Mistakes

2. Additional Problems with Reference Regions

Problems with Reference Ranges

- Not sampled from representative population (not randomly sampled)
- Calculated incorrectly
- Sample size too small
- May have no statistical meaning
- Not meant to be externally valid

Ref: Trost (2006)

UMVU Elliptical Reference Region Estimator

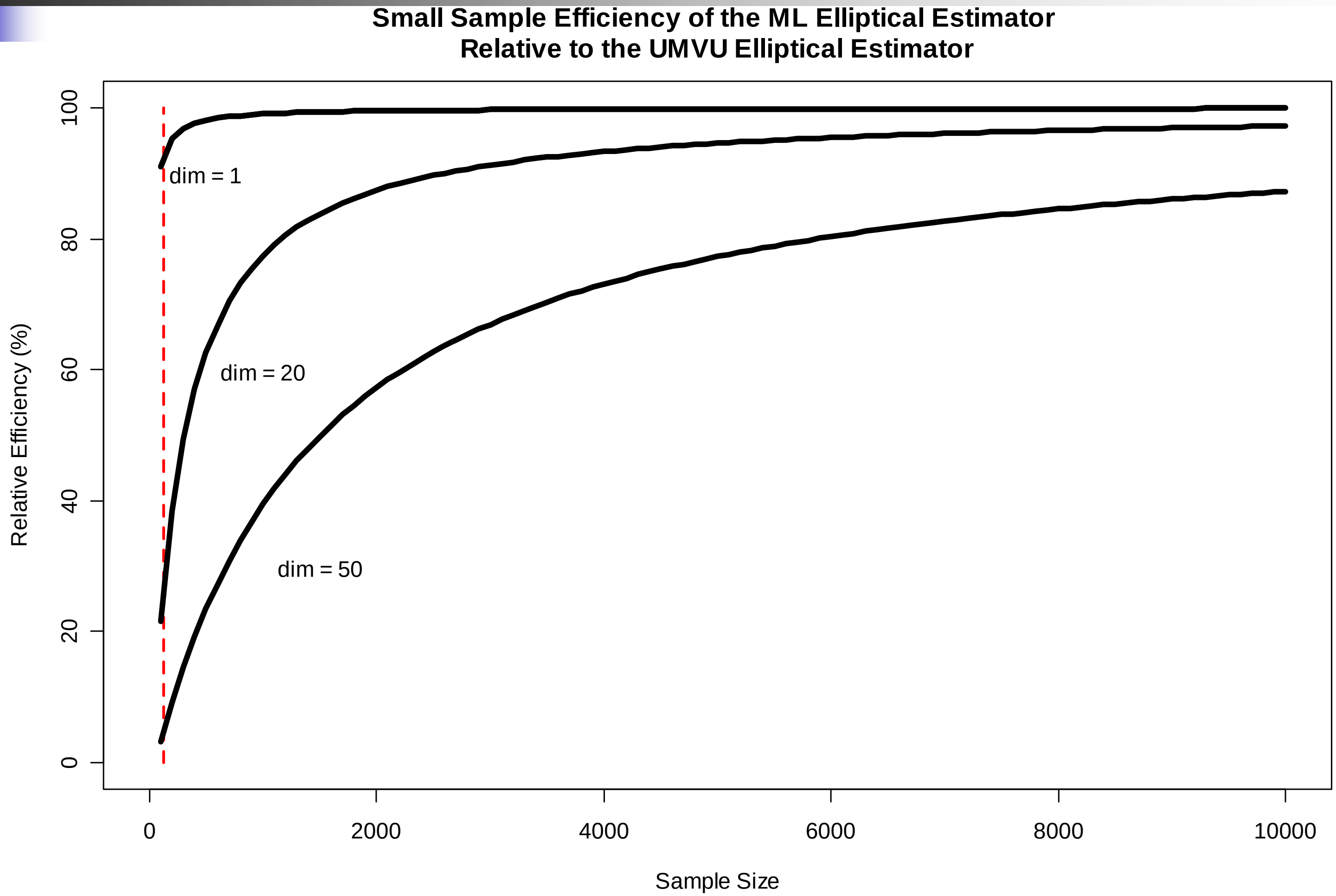
$$(\mathbf{Z}_\alpha - \mathbf{M})' \mathbf{\Sigma}^{-1} (\mathbf{Z}_\alpha - \mathbf{M}) = \chi_p^2(\alpha)$$

$$\breve{\varepsilon}(\mathbf{Z}_\alpha) = \frac{n-p-2}{n} (\mathbf{Z}_\alpha - \overline{\mathbf{X}})' \mathbf{S}^{-1} (\mathbf{Z}_\alpha - \overline{\mathbf{X}}) - \frac{p}{n}$$

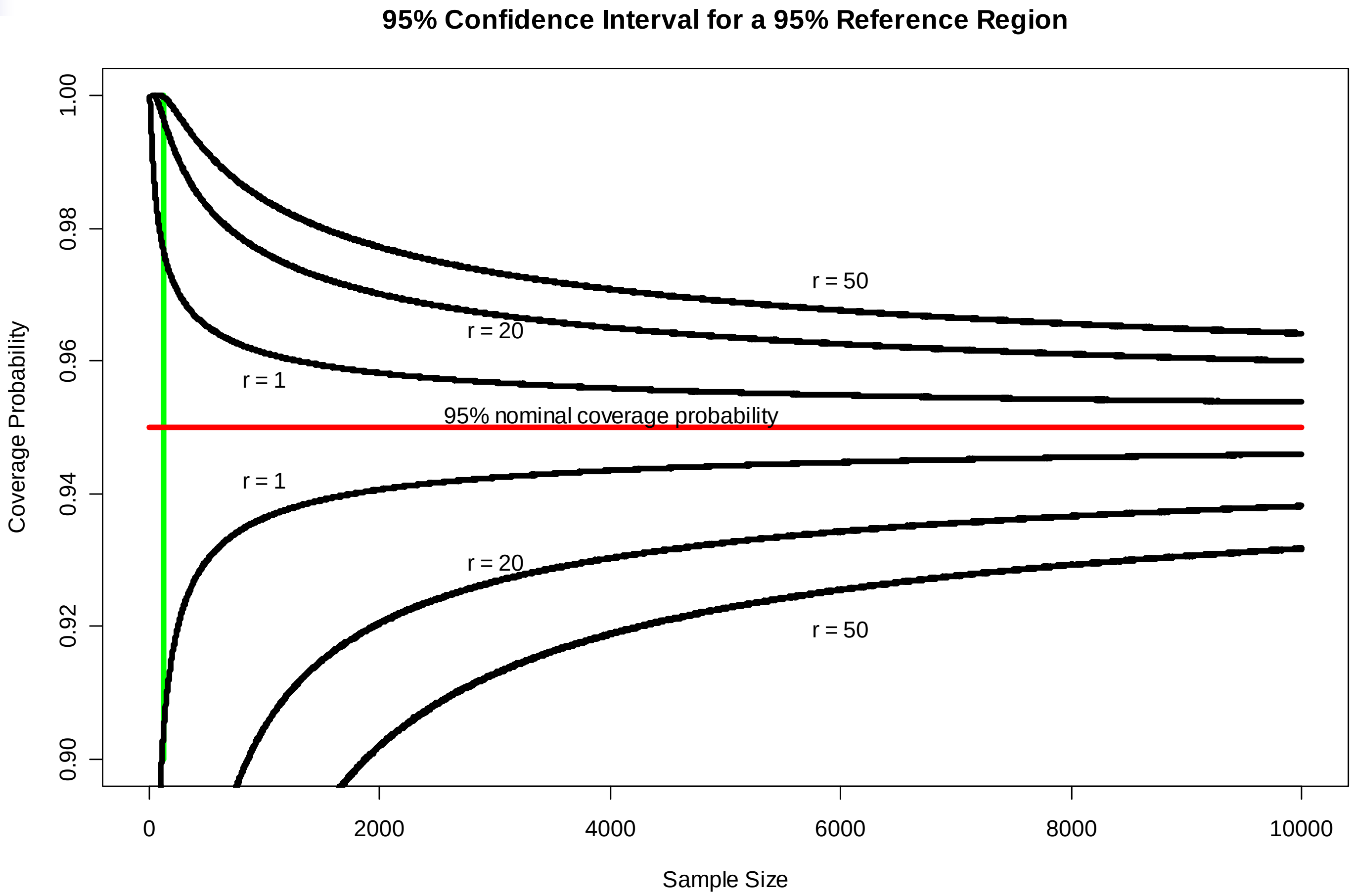
$$E[\breve{\varepsilon}(\mathbf{Z}_\alpha)] = \chi_p^2(\alpha)$$

$$V[\breve{\varepsilon}(\mathbf{Z}_\alpha)] = \frac{2}{n-p-4} \left(\frac{(n-2)p}{n^2} + \frac{2(n-2)}{n} \chi_p^2(\alpha) + \left(\chi_p^2(\alpha)\right)^2 \right)$$

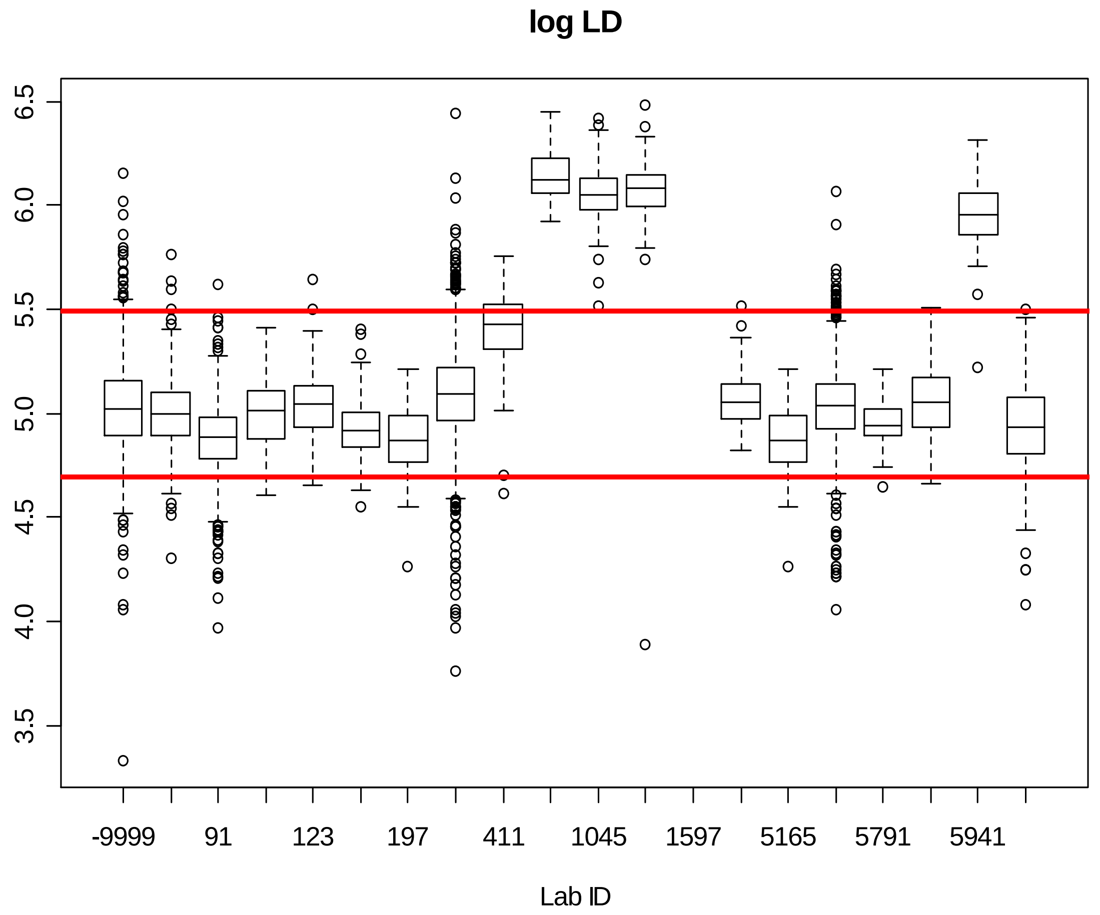
MLE Efficiency



UMVU Coverage Probability by Sample Size



Interlaboratory Variability



3. Stochastic Processes

Types of Stochastic Processes

- Discrete state, discrete time
  - Markov chain
- Discrete state, continuous time
  - Markov process
- Continuous state, discrete time
  - Time series
- Continuous state, continuous time
  - Brownian motion process

Definition

- Random vector

$$\mathbf{X}_p(\omega) : \omega \rightarrow \Re^p$$

- Stochastic process

$$\mathbf{X}_p(t,\omega) : (t,\omega) \rightarrow T \times \Re^p$$

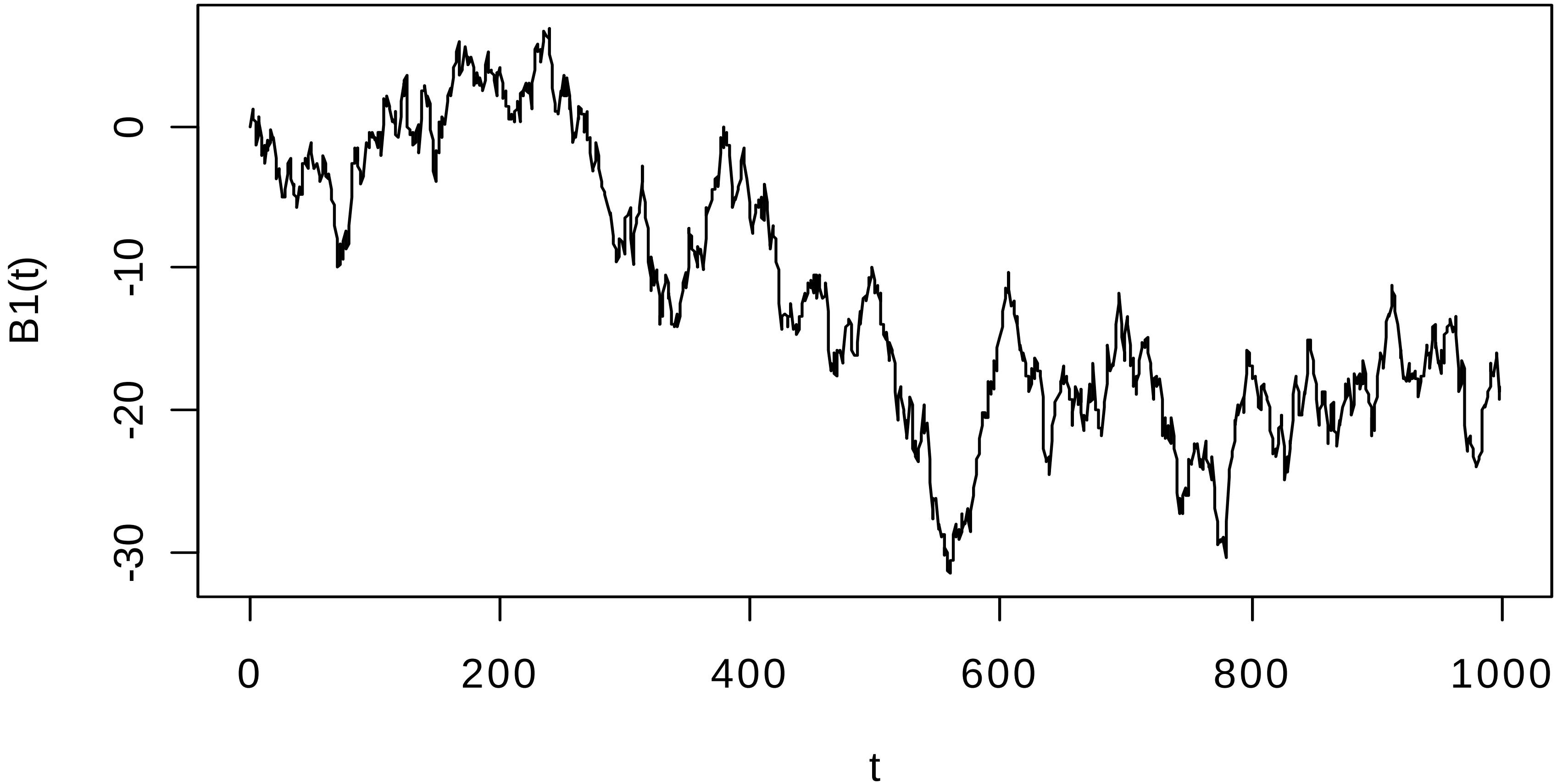
Standard Brownian Motion

- A stochastic process ($\mathbf{B}_t$) with the characteristics:
  - A p-dimensional Gaussian process with mean **0** and variance $t\mathbf{I}_p$
  - Independent increments
  - Continuous in t almost always

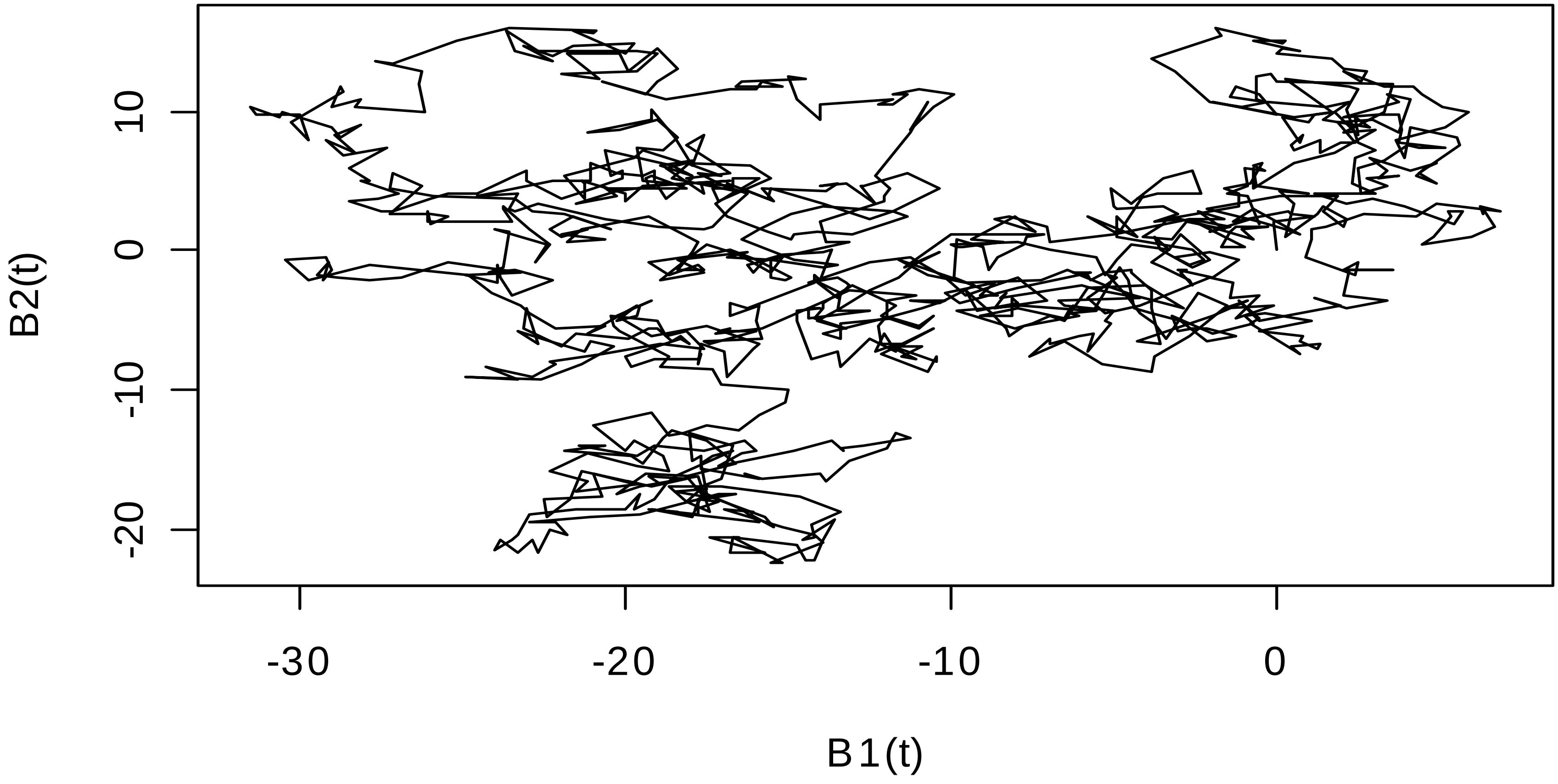
Standard Brownian Motion

- Additional properties
  - Stationary
  - Markovian
  - Martingale
  - $Cov[B_s, B_t] = t - s$, for $s \leq t$
  - Scaling: $B_{ct}/c^{1/2}$ is SBM
  - Time-inversion: $tB_{1/t}$ is SBM
  - Not differentiable

1-D Brownian Motion



2-D Brownian Motion



4. Description of Pathodynamics

Clinical Definition of Pathodynamics

- Person -- a Brownian particle in p-dimensional clinical measurement space acted on by internal and external forces
- Pathodynamics – forces and motions that characterize a diseased biological system

Analogy to the First Law of Thermodynamics

$$\Delta energy = \Delta work + \Delta heat$$

$$dU = dW + dQ$$

$$\Delta health = \Delta biowork + \Delta bioheat$$

A Mathematical Definition

$$\Delta health = \Delta biowork + \Delta bioheat$$

$$\frac{dX}{dt} = f(X) + \text{"noise"}$$

$$dX = dW(X) + dQ(X)$$

$$dX_t = \alpha(X_t, t)dt + \theta(X_t, t)dB_t$$

Homeostasis: Ornstein-Uhlenbeck Process

$$dx_t = -\alpha(x_t - \mu)dt + \theta dB_t$$

$$= \text{homeostatic force} \times \text{displacement}$$

$$+ \text{scaled Brownian motion}$$

$$\Delta health = \Delta biowork + \Delta bioheat$$

Homeostasis: Ornstein-Uhlenbeck Process

$$x_t = \mu - e^{-\alpha t}\left(\mu - x_0\right)$$

$$+ \theta e^{-\alpha t} \int_0^t e^{\alpha s} \theta dB_s$$

Ito integral

Homeostasis

x_t is Gaussian stochastic process with

$$E\left[x_t\right] = \mu - e^{-\alpha t}\left(\mu - x_0\right) \underset{t \to \infty}{\longrightarrow} \boxed{\mu}$$

$$V\left[x_t\right] = \theta^2 e^{-2\alpha t}\left(\int_0^t e^{2\alpha s} ds\right)$$

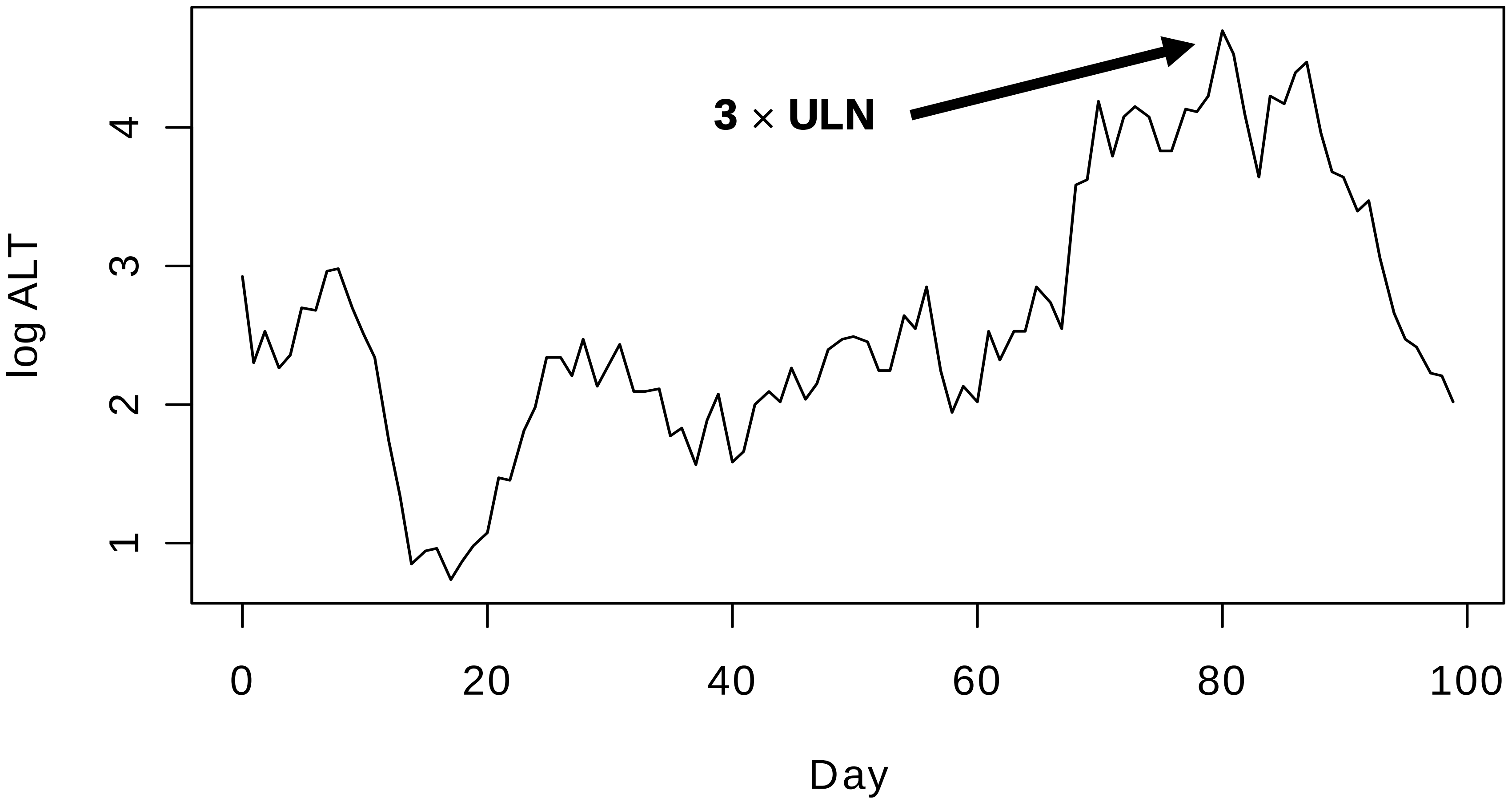
$$= \frac{\theta^2}{2\alpha}\left(1 - e^{-2\alpha t}\right) \underset{t \to \infty}{\longrightarrow} \boxed{\frac{\theta^2}{2\alpha} = \sigma^2}$$

Autocorrelation Structure

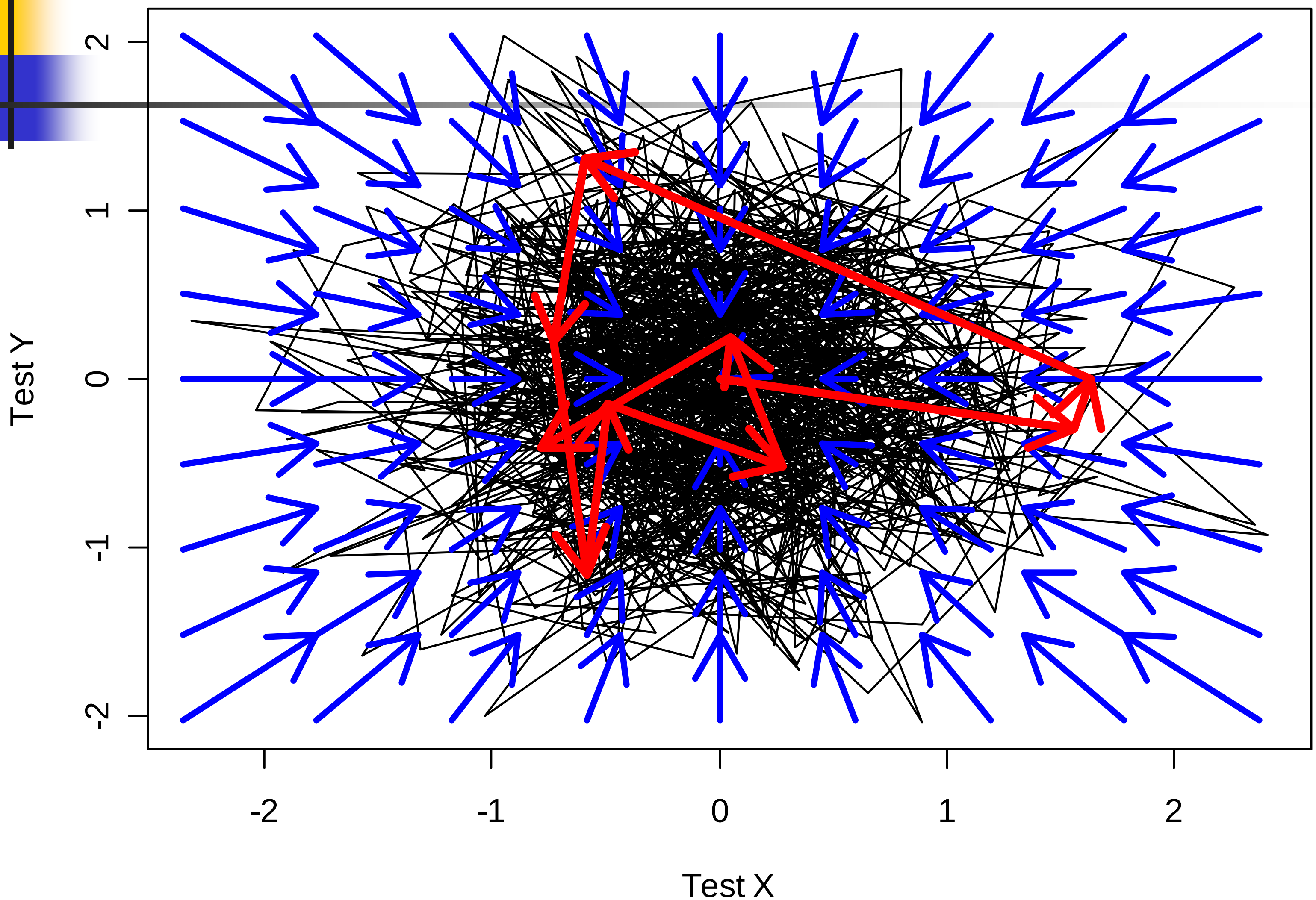
$$Corr\left[x_s, x_t\right] = e^{-\alpha(t-s)}, t \geq s$$

5. Examples and Results

Random Sample Path of OU Process under Homeostasis



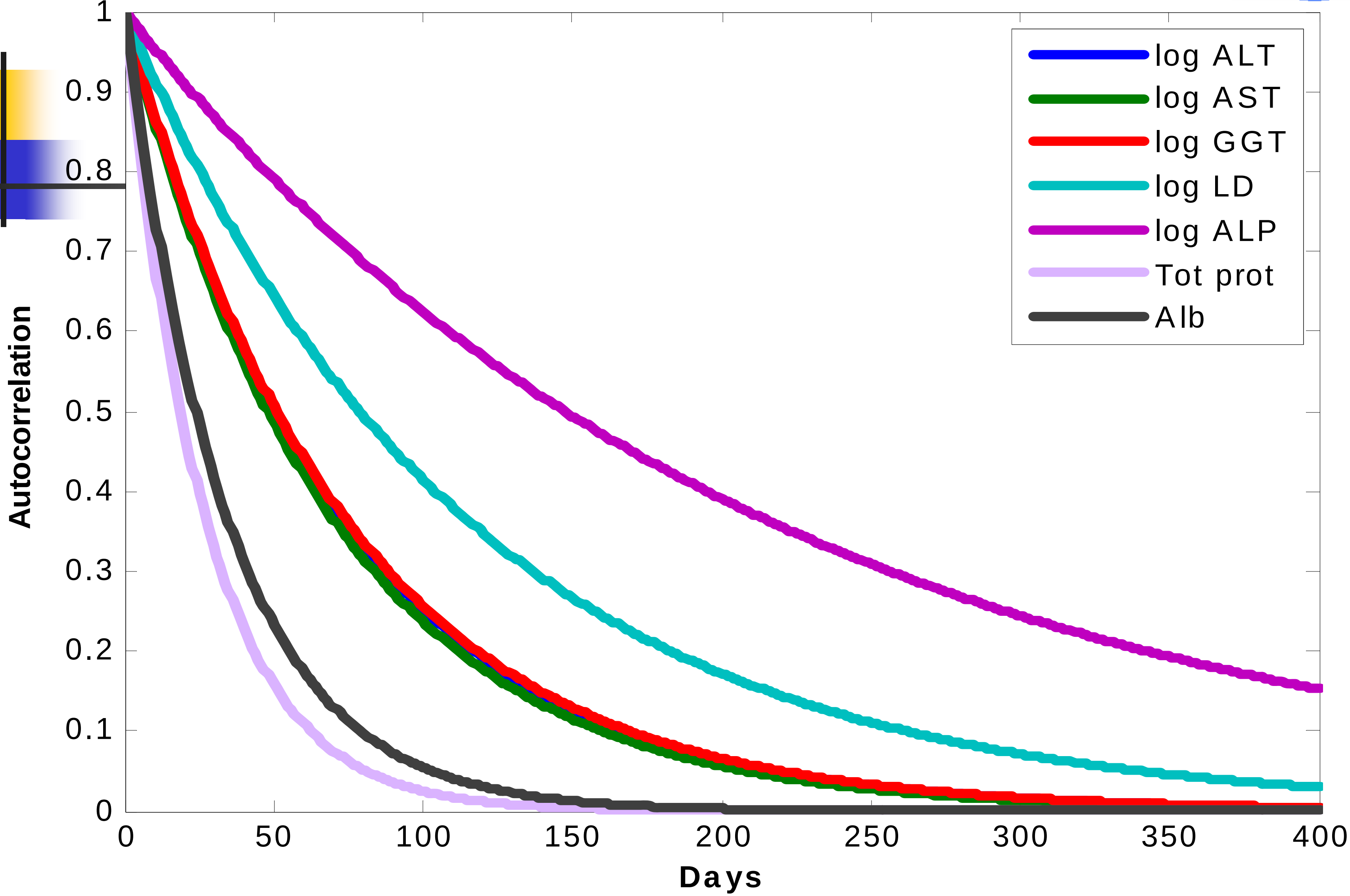
Brownian Motion with Restoring Force: Homeostasis



Preliminary Univariate Results

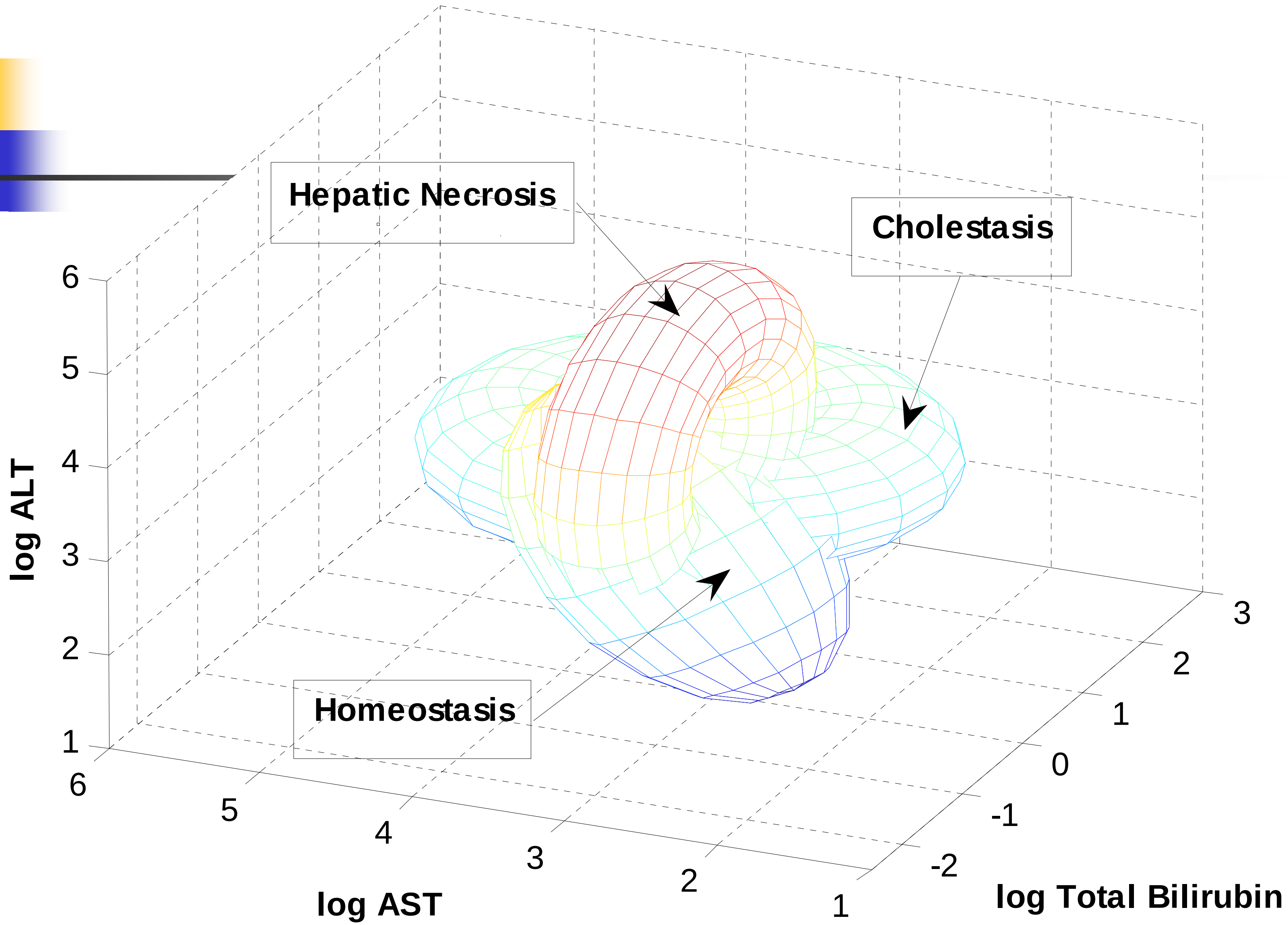
Measure	μ	α	θ	$\sigma^2(\infty)$	$\sigma^2(7)$
log ALT	2.98	0.0138	0.0871	0.2421	0.0483
log AST	3.06	0.0144	0.0666	0.1541	0.0281
log GGT	2.84	0.0136	0.0763	0.2147	0.0371
log LD	5.00	0.0088	0.0485	0.1338	0.0155
log ALP	4.31	0.0047	0.0285	0.0856	0.0055
Tot prot	7.23	0.0369	0.1321	0.2365	0.0954
Albumin	4.41	0.0291	0.0752	0.0971	0.0325

Univariate Autocorrelations of Liver Tests



6. Future Directions

Pathodynamic Trajectories



Clinical Pathology
(System Identification/Classification)

- Diagnostic Regions/Patterns in Clinical Space
  - Probability density level sets
  - Force fields
  - Velocity fields
- Diagnostic Regions/Patterns in Parameter Space
  - “Temperature” space
  - “Friction” space
  - Phase space

Clinical Therapy
(Control Theory)

- What is controllable?
- What are the best modes of control?
- How do we infuse clinical medicine with the concept of stochastic dynamic systems and control?
- Who is going to do the research needed to advance the science and mathematics?

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Questions?

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