Applications of Complex Systems Biology to the Study of Neural Systems

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Overview

- Neural Systems and Development
  - Activity Dependent Development and Neural Plasticity
  - Complexity as a measure of maturation and neurodevelopment
  - Summary of Results

Plasticity and Activity Dependent Development

- Neural Plasticity is a dynamic process by which the brain develops
- This process is affected by:
  - Nature (e.g. genetic programming)
  - Nurture (e.g. environmental stimulus)
  - Niche (e.g. development)
- Environmental perturbations (e.g. premature birth) can upset this natural process, potentially leading to long-term developmental deficit.

The Developmental Niche

- New brain research suggests the first five years of life are most critical for brain development.
- Synapses, which connect neurons, are created at great speed during the first three years of life.
- The part of the brain responsible for seeing, hearing, speech production and receptive language is most active during the first few years of life.
  - At birth about 25 percent of the brain's connections are formed.
  - By age 3, 90 percent of the brain is hardwired.
- Translational Research Question:
  - What are the effects of genetic and environmental stresses on brain connectivity and long term neural development ?

Complex Systems Biology: An integrative approach to link genotypes and phenotypes with the environment and behaviors through measurements to improve understanding

Measurements:

- EEG Patterns
- Heart Rate
- Blood Pressure
- Temperature …

Genes • • • • • ▶ ***Phenotype*** ◀ • • • **Environment**

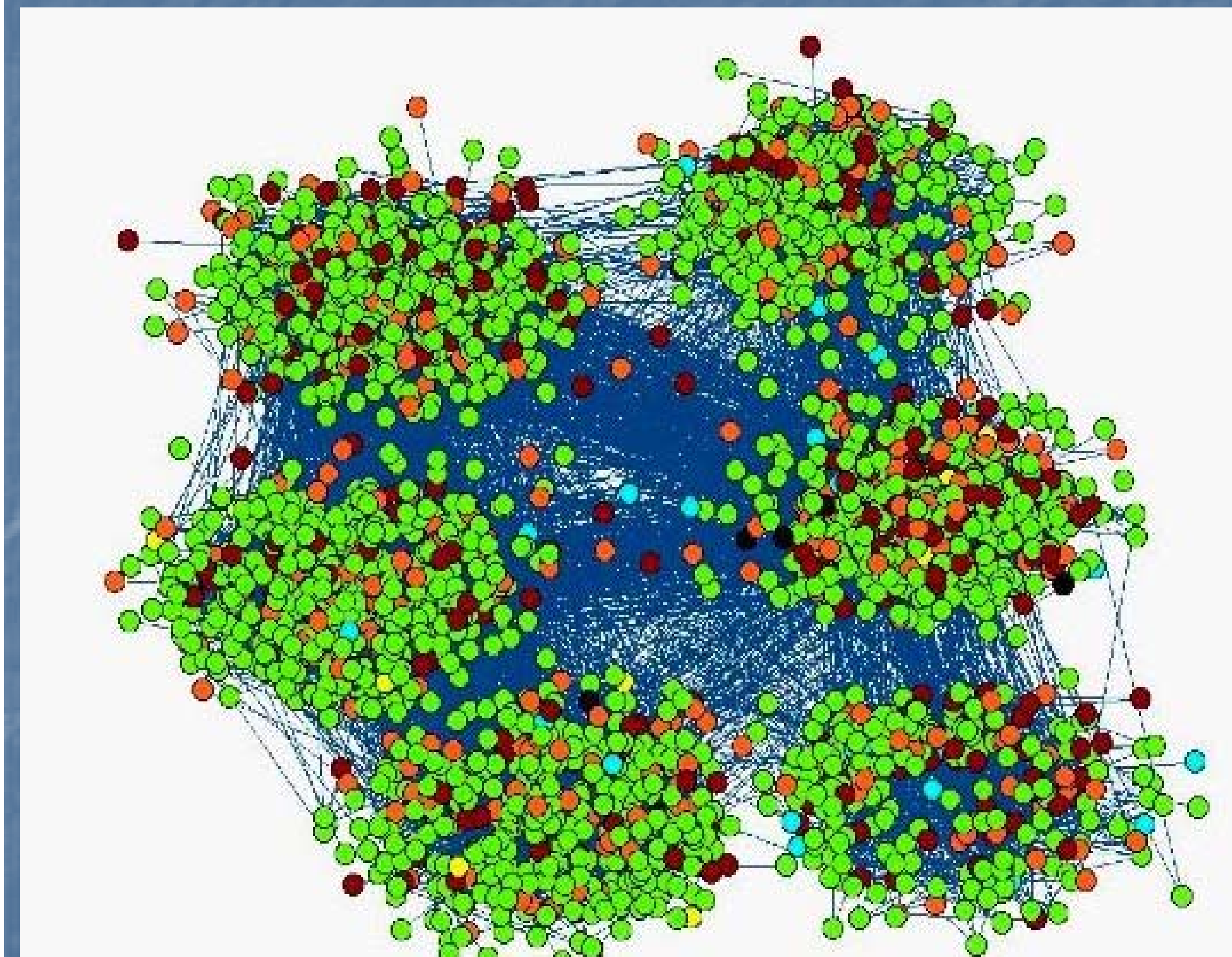
Bioinformatics and Computational Genomics

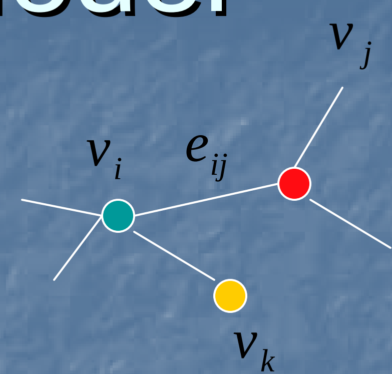
External Stimuli: Positive and Negative Influences

Understanding:

- Biology
- Health
- Development
- Disease

Complex Network Model





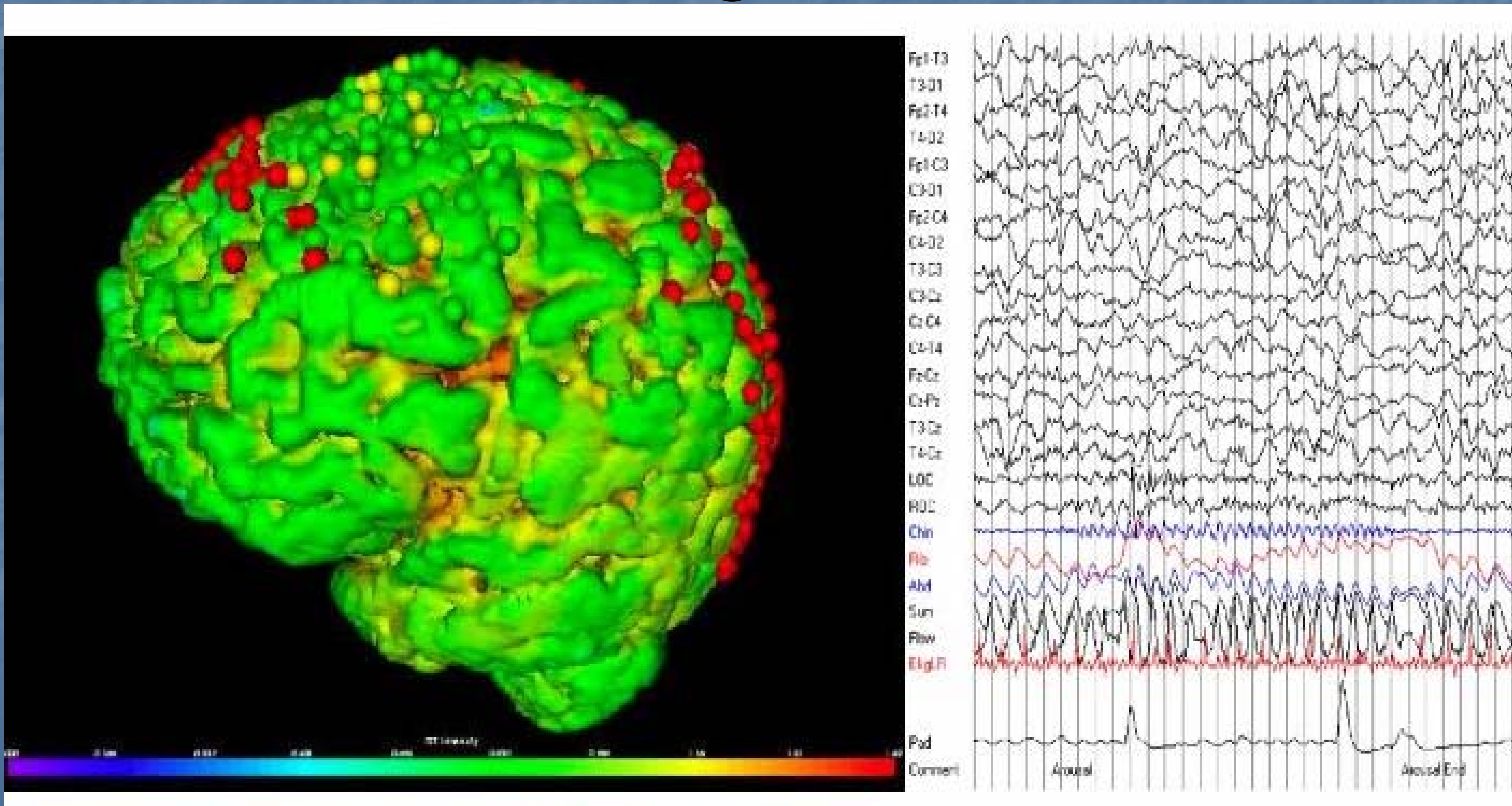
$N_i = \{v_j\}$ such that $e_{ij} \in E$

Where E = the set of Edges

The degree (k_i)

of node $v_i = |N_i|$

A Measure of Brain Connectivity and Complexity using EEG



The Brain as a Dynamical System

- A dynamical system consists of 2 parts
  - state
  - dynamics
- The state is defined as the information necessary at any given time instant to completely describe the future evolution of the system.
- The dynamics define how the state evolves over time.
- For stable systems, the trajectory of the system approaches a subset of the state space called an *attractor* as time approaches infinity.

Complexity and Dimension

- Geometric properties of the attractor can be used to characterize the system
  - Periodic
  - Quasi-periodic
  - Chaotic
- One method commonly used to quantify dynamical system properties is the *correlation integral* (C_r).
- C_r measures the probability that points on the attractor have pair-wise distances $\leq r$.
- There are two steps to calculating C_r:
  - Step 1: Attractor is reconstructed (embedding);
  - Step 2: C_r is calculated from the reconstructed state vectors.

Attractors and Dimension

- Attractor
  - set of states towards which the system state trajectories are drawn over time – characterizes the long term behavior of the system
- Dimension
  - related to the amount of information required to specify a point on the attractor
- More complex system behavior - more information is required to describe this behavior and the dimension is one way to measure this complexity
- Not all attractors have integer dimension
  - Strange Attractors or Fractals

Correlation Dimension

- At small distances *r*, the correlation integral behaves as a power of ν, i.e., $C_r \propto r^{\nu}$.
- The exponent ν is defined as the correlation dimension (D_2).
- The correlation dimension characterizes the active degrees of freedom or complexity of the system.
- The higher the correlation dimension, the more complex the system.

Experimental Measurement of the Attractor

- Measurement of the system attractor

  $$y(t)=F(x(t)) : R^k \rightarrow R^m$$

  - k is the dimension of attractor
  - m is the embedding dimension

- Embedding the attractor
  - One-to-one mapping that preserves differential information
  - Also preserves fractal invariants (dimensions, Lyapunov exponents)
  - Guaranteed for m > 2k (Whitney)

Attractor Reconstruction from a Time Series

- Time Delay Embedding from a one-dimensional time series measurement s(t):

  $$y(t)=H(x(t))=(s(t), s(t-\tau),\ldots, s(t-(m-1)\tau))$$

  - Embedding guaranteed for $m > 2k$ (Takens)
- Other Methods of Reconstruction
  - Derivative Coordinates – Decreases SNR
  - Coordinates from Singular Systems Analysis – Increases Ill-conditioning

Correlation Dimension

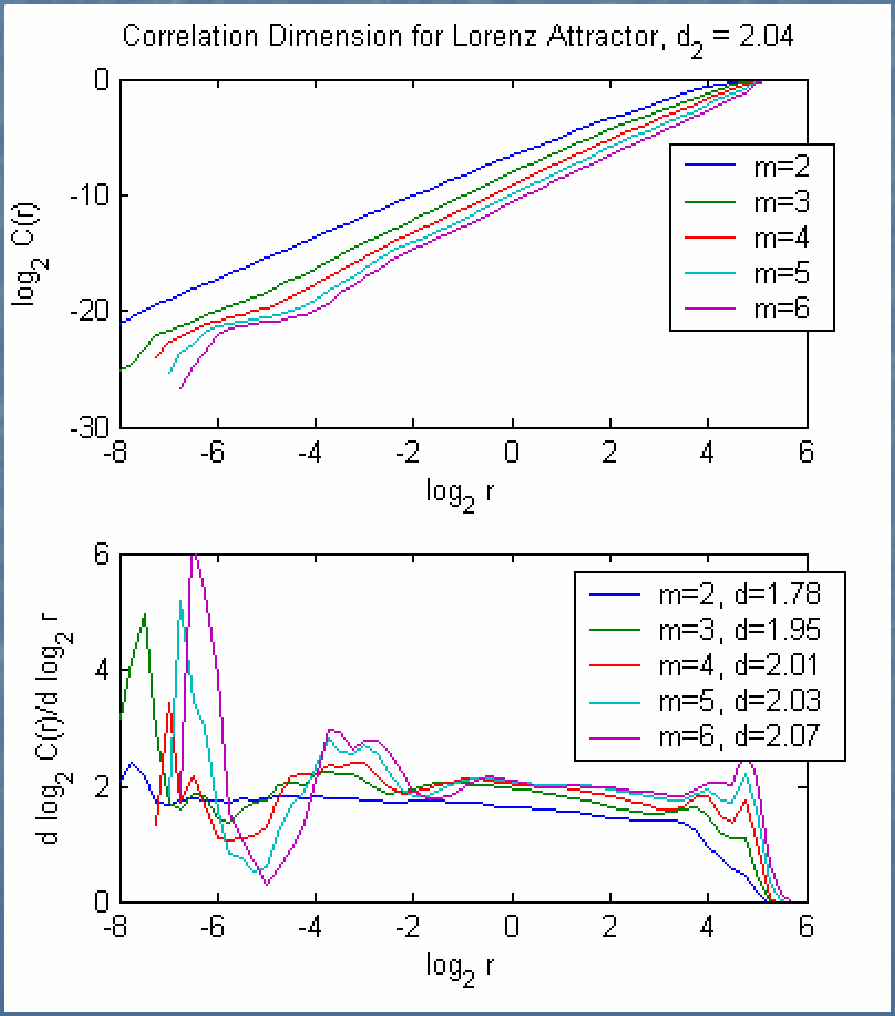
Correlation Integral:

C(r) = $\lim_{N\to\infty} \frac{1}{N^2} \sum_{i=1,j=1}^{N} \Theta(r - |x_i - x_j|)$

- Counts number of pairs of points with inter-point distance less than r

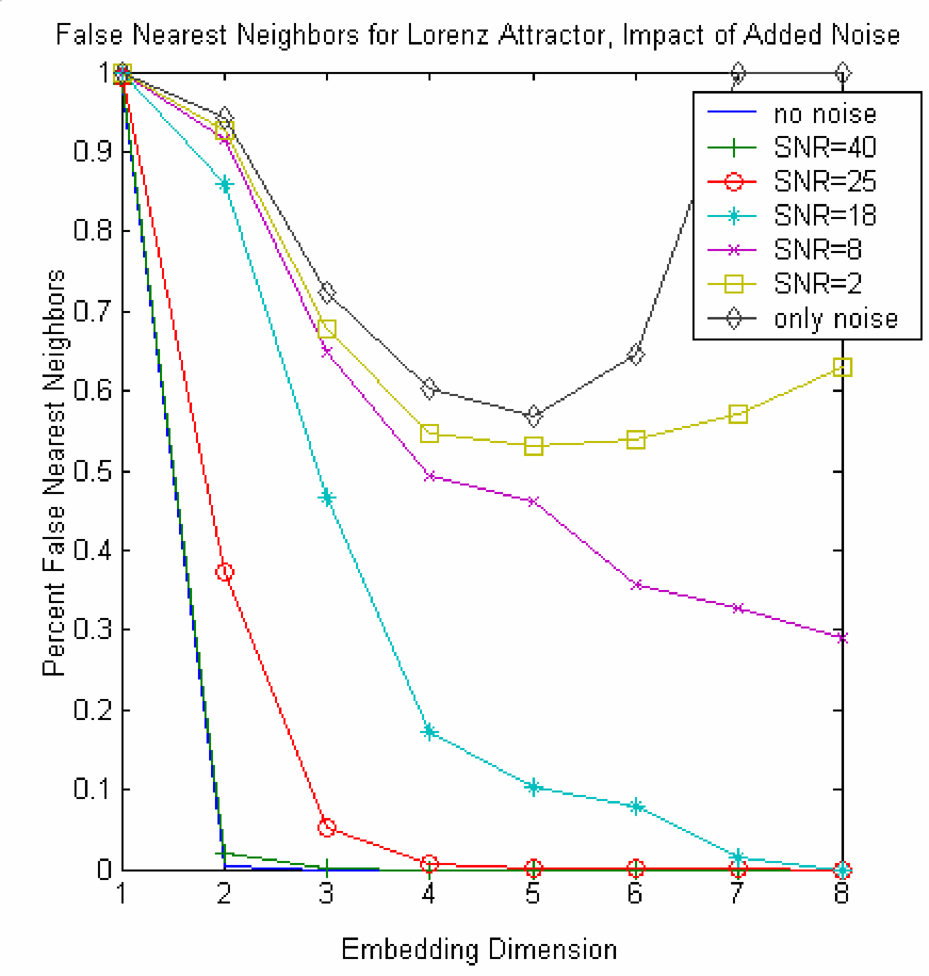
- For small r, C(r) ≈ r^{D_2}

∴ D_2 = slope of $\frac{\log C(r)}{\log r}$ in linear region



Selection of the Embedding Dimension

- Goal: Find minimum embedding dimension required to unfold dynamics of the attractor
- False Nearest Neighbors
  - Measures percentage of neighboring points that are close together due to projection of attractor onto subspaces with too small an embedding dimension
  - Okay for selection of minimum embedding dimension
  - Reveals noise level of time series



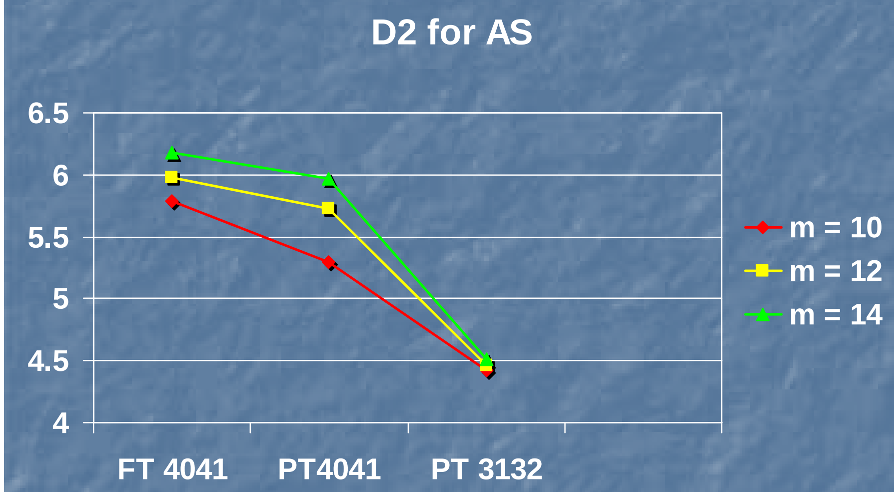
Experimental Study

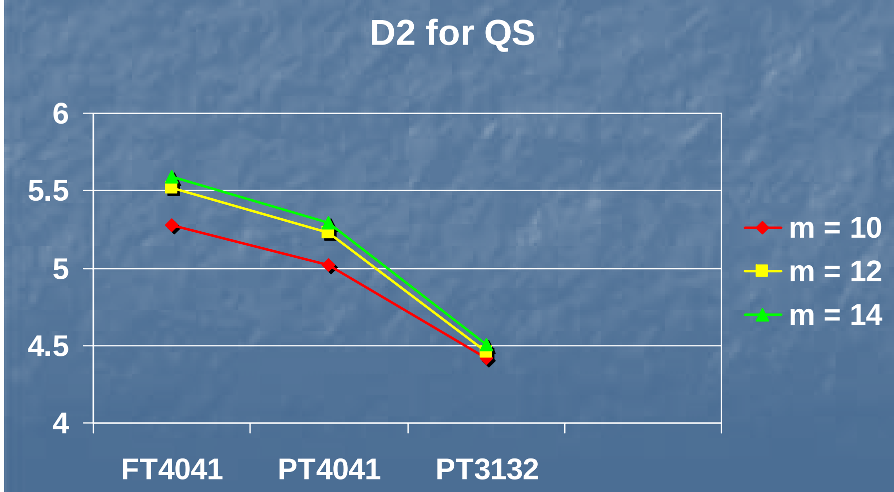
- EEG data sets: Healthy Neonates born at 31-32 thru full term.
- Data acquisition:
  - Bipolar digital EEG recordings at 12 bits and 64 Hz
- 6 data sets of 3 groups analyzed: full term (FT) (at age 40-41 weeks), preterm (PT) (at age 40-41 weeks) and preterm (PT) (at age 31-32 weeks)

Experimental Analysis

- Time series (EEG) data is segmented into 2-minute epochs
- The epochs for full-term neonates (CA=40-41 weeks) and preterm babies (CA=40-41 weeks) are separated according to their sleep stages, i.e., active sleep (AS) and quiet sleep (QS).
- The epochs for preterm neonates (CA=31-32 weeks) are not grouped by sleep state.
- C_r is computed from the EEG time series using embedding dimensions m=10,12 and 14 while the time delay is varied from 1 to 10 samples.
- The local slopes for the most linear region of the log C_r versus log r provide estimates of D_2.

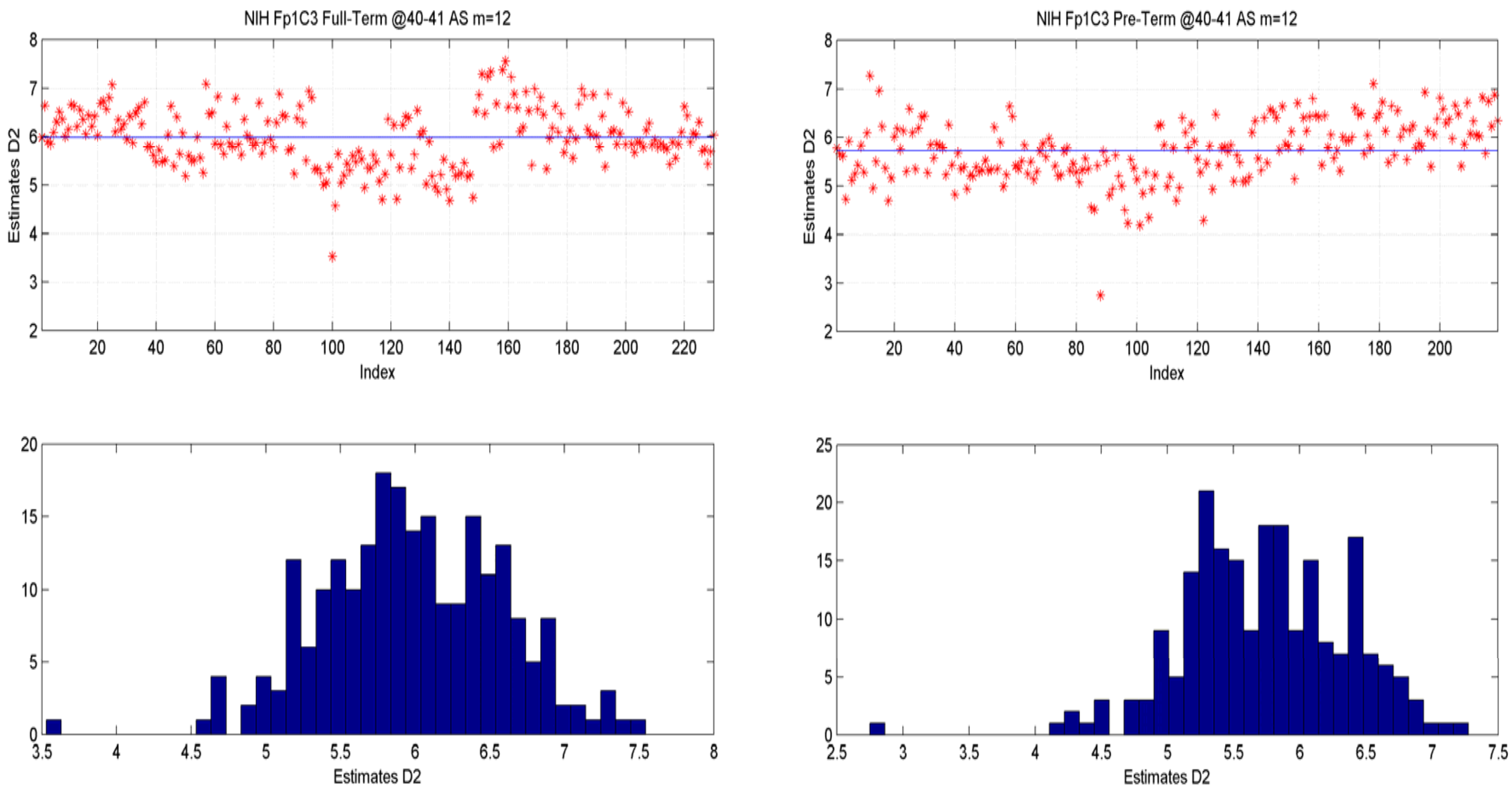
Results for Channel Fp1-C3



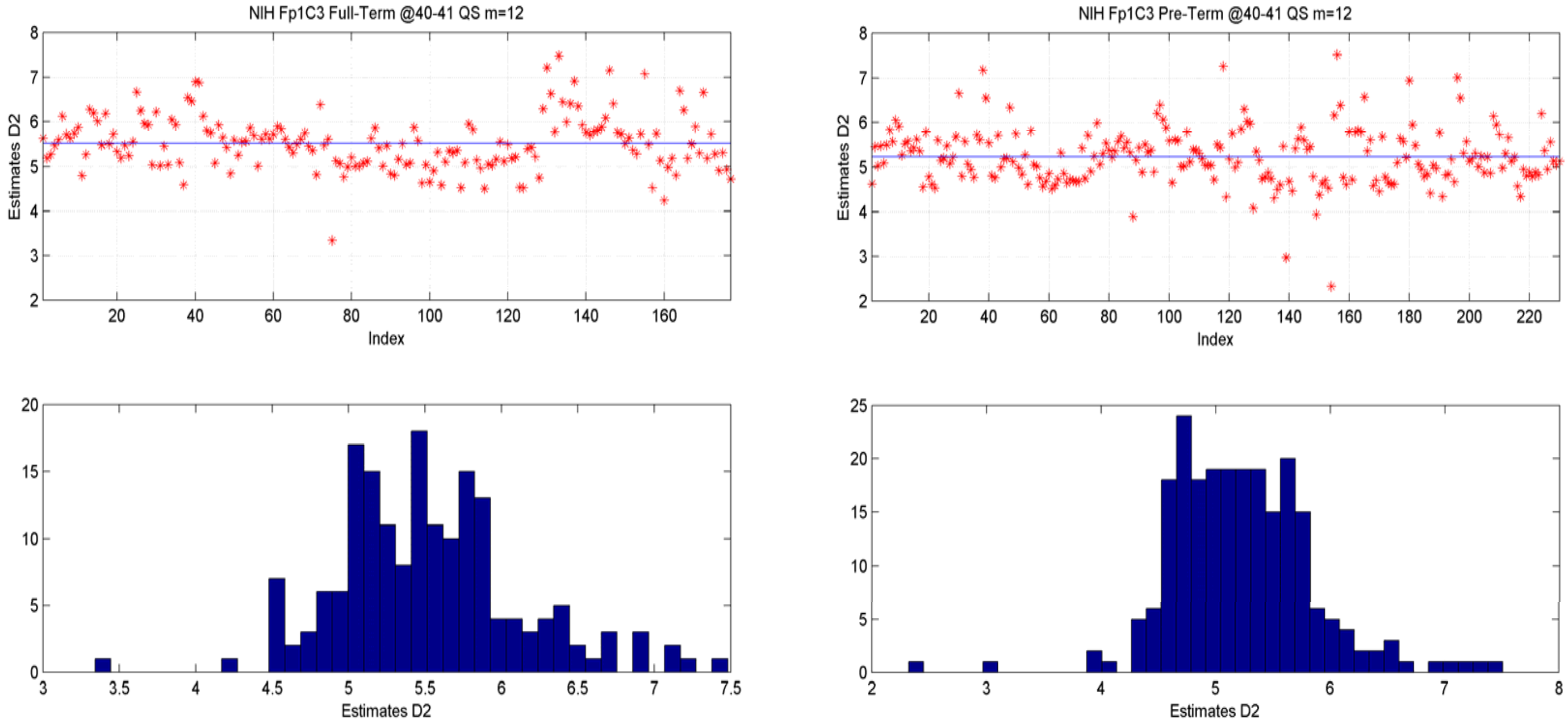


m	FT 4041 (AS)	FT 4041 (QS)	PT 4041 (AS)	PT 4041 (QS)	PT 3132
10	5.79 +/- 0.54	5.28 +/- 0.59	5.30 +/- 0.57	5.02 +/- 0.59	4.42 +/- 0.71
12	5.98 +/- 0.61	5.52 +/- 0.61	5.73 +/- 0.63	5.23 +/- 0.64	4.46 +/- 0.73
14	6.18 +/- 0.61	5.59 +/- 0.62	5.9662 +/- 0.62	5.29 +/- 0.62	4.51 +/- 0.71

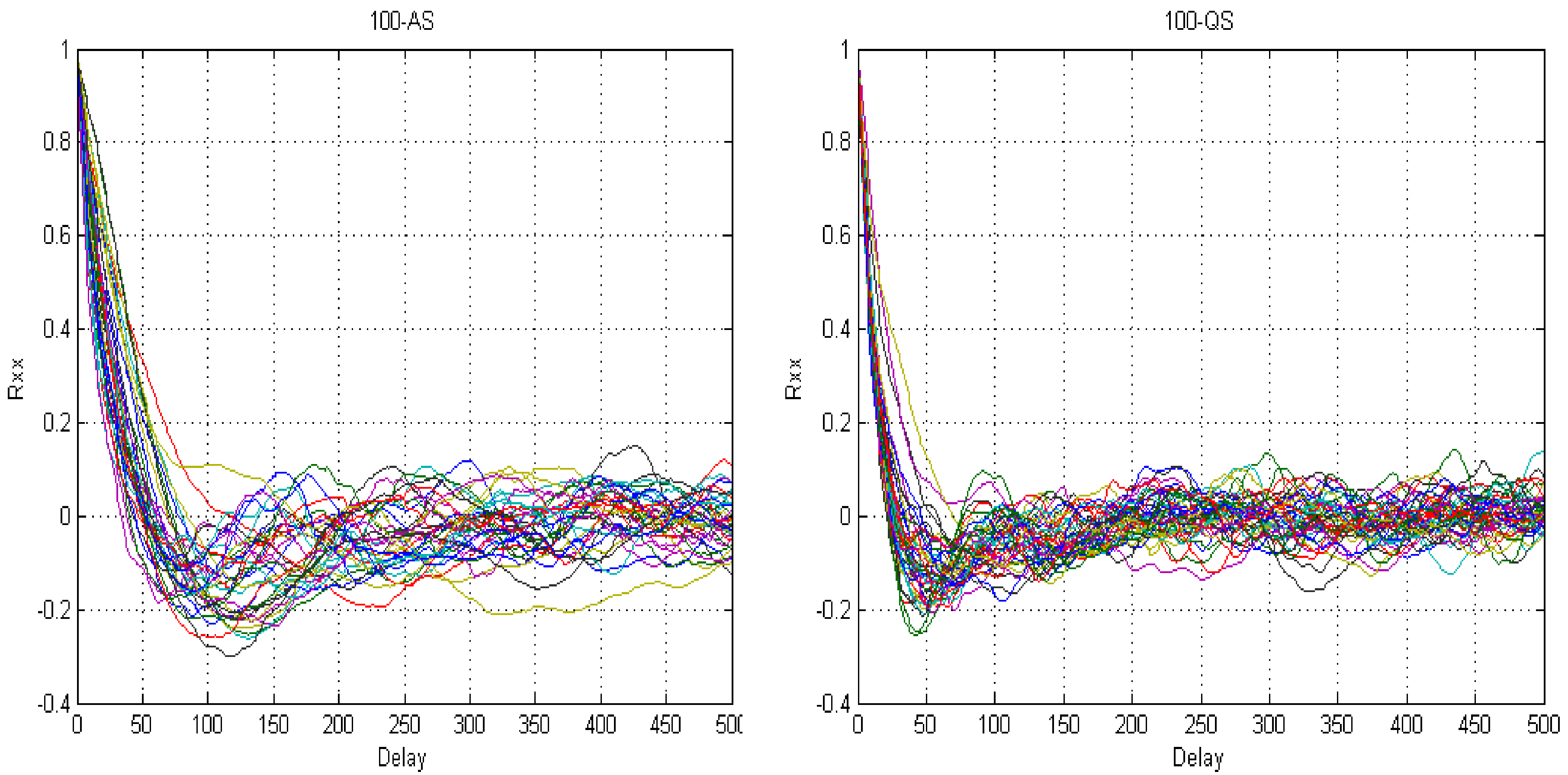
Results for Fp1-C3 (AS)



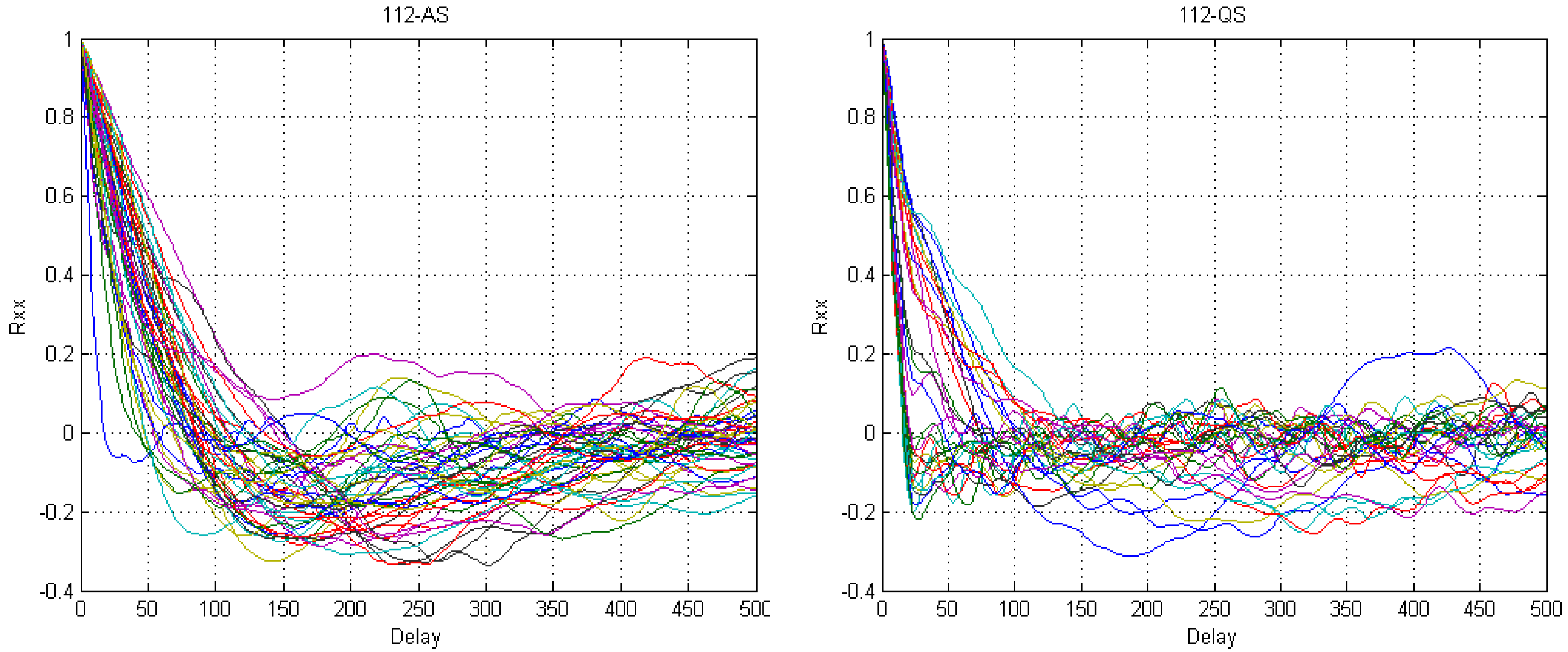
Results for Fp1-C3 (QS)



FT4041 R_{xx} (AS & QS)



PT4041 R_{xx} (AS & QS)



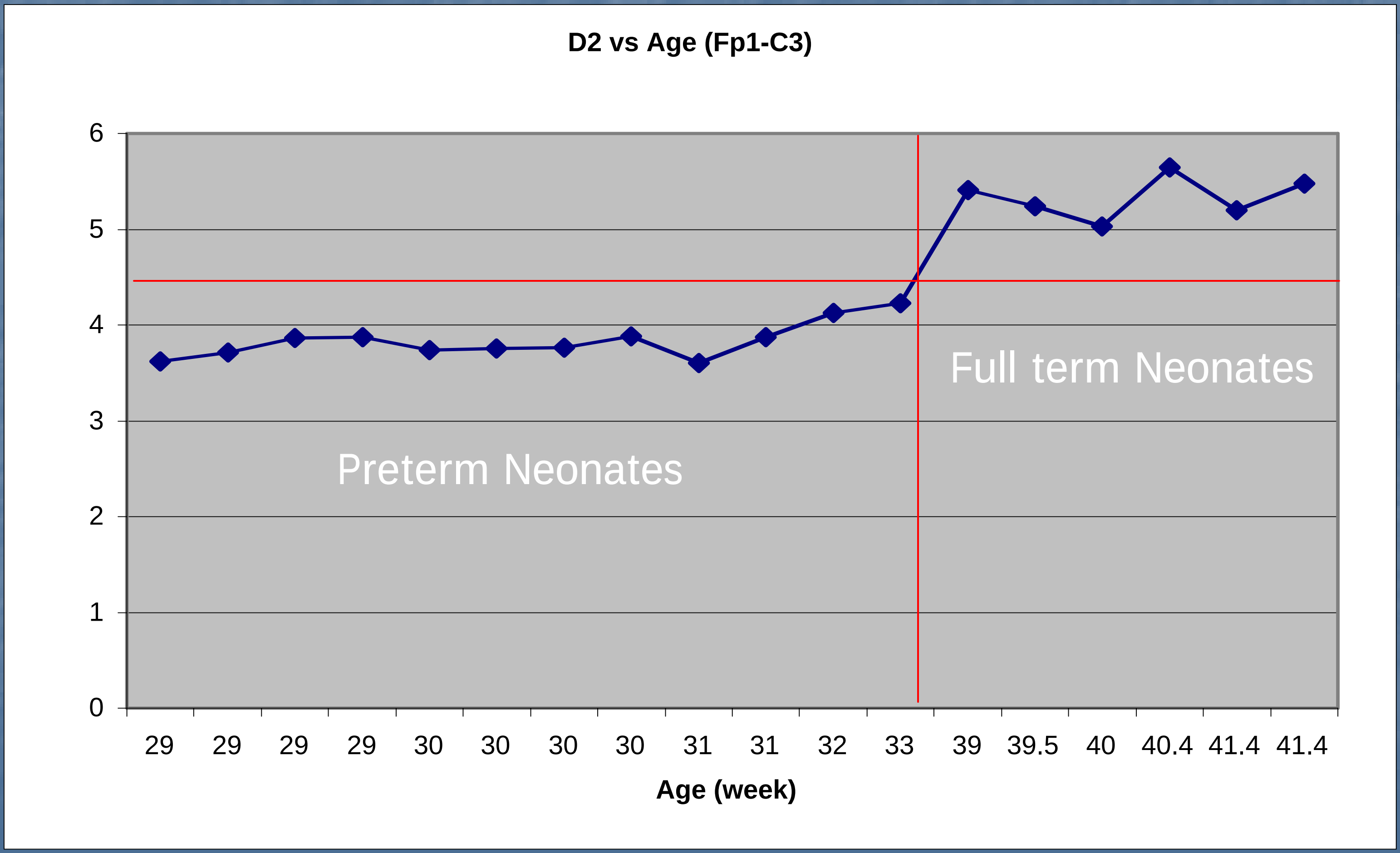
Statistical Analysis

T-test for the Null Hypothesis (H_0) that the mean D_2 for FT4041, PT4041, PT3132 and Surrogate data are from the same distribution: 1=reject and 0=can not reject

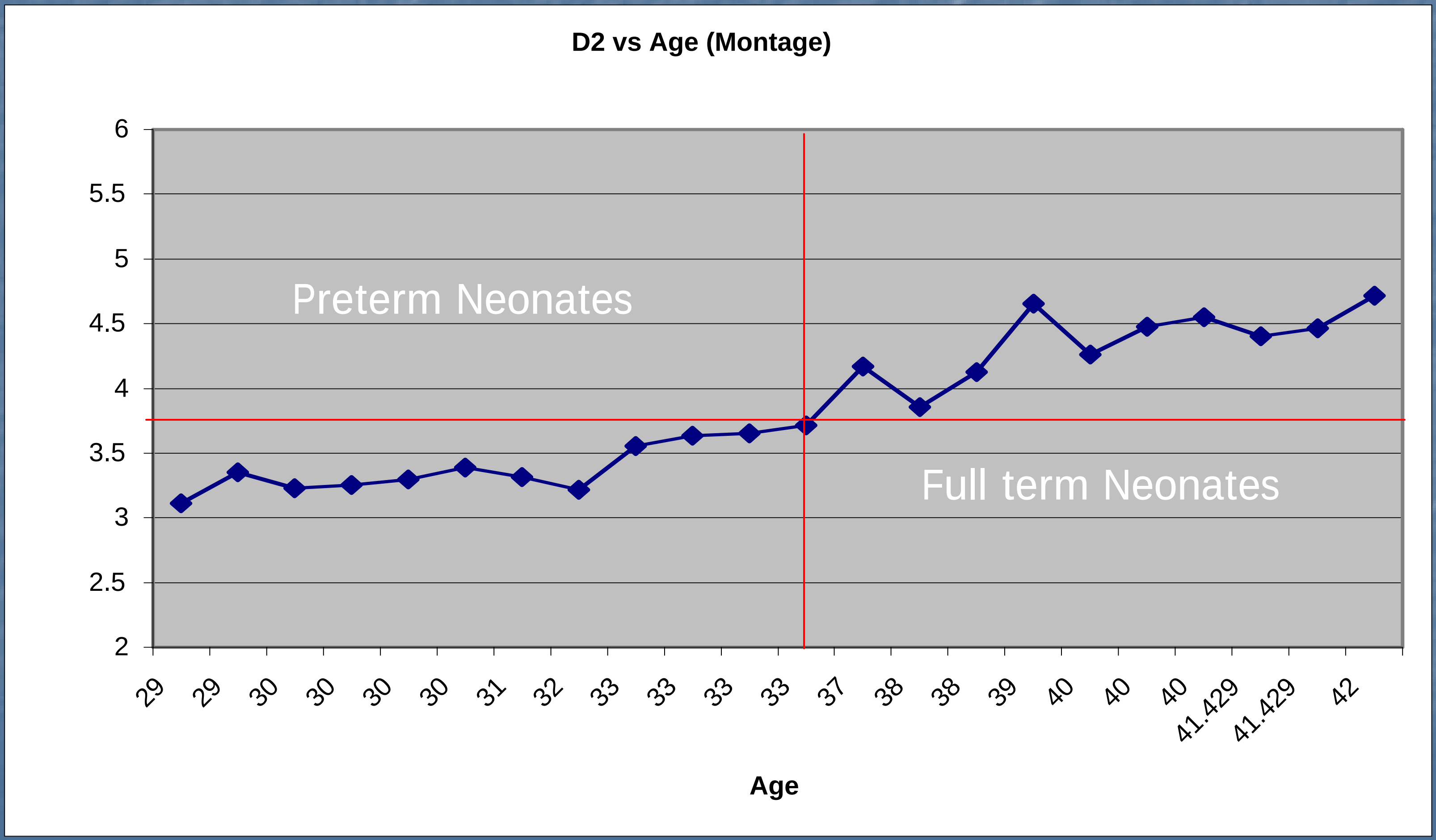
	FT4041AS	FT4041QS	PT4041AS	PT4041QS	PT3132
FT4041AS	0	1, p<5 e-006	1, p<2 e-04	1, p<1 e-10	1, p<2 e-070
FT4041QS	1, p<5 e-006	0	1, p<1 e-10	1, p<4 e-005	1, p<7 e-066
PT4041AS	1, p<2 e-04	1, p<1 e-10	0	1, p<1 e-007	1, p<1 e-064
PT4041QS	1, p<1 e-10	1, p<4 e-005	1, p<1 e-007	0	1, p<6 e-067
PT3132	1, p<2 e-070	1, p<7 e-066	1, p<1 e-064	1, p<6 e-067	0
Surrogate	0	1, p<4 e-04	0	1, p<1 e-008	1, p<5 e-086

Conclusions: (1) There is a statistically significant difference between FT and PT at same CA (40-41 weeks) (2) PT is less complex than FT, (3) EEG in AS in FT and PT at 40-41 weeks is statistically similar to the surrogate, (4) Complexity of the EEG for FT and PT at 40-41weeks in QS and PT at 31-32 weeks is dominated by nonlinearity.

D_2 Complexity and Neural Development



D_2 Complexity and Neural Development



Conclusions

- Plasticity is an activity dependent dynamic process in developing organisms
- Neurodevelopment in neonates can be assessed using a computational phenotype that quantifies “complexity” in the EEG during sleep
- Complexity increases along the developmental trajectory during the neonatal period

Acknowledgements

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Thank You