Delay Differential Analysis of Human Schizophrenia MMN Data

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Delay Differential Analysis of MMN Data

- Mismatch Negativity
- The Data Set
- Review of Delay Differential Analysis
- Methods
- Preliminary Results
- Future Work

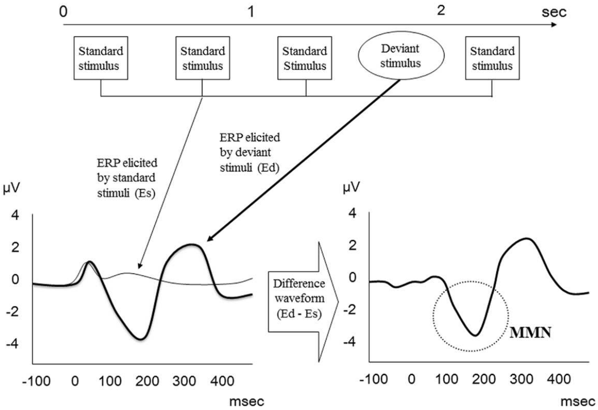
Schizophrenia: the need for biomarkers

- Schizophrenia is one of the most disabling and costly disease worldwide (top 10)
- The current standard of care suffers from a lack of objective and quantitative biomarkers
- Diagnoses are obtained through patient questionnaires and behavioral observation
- Mismatch negativity (MMN) is an EEG biomarker that shows promise in classifying schizophrenia

Mismatch Negativity

- The ERP response to deviant stimuli in a series of standard stimuli (ssdssdssssdsss)
- Auditory MMN
  - Use stimuli that differ in duration or pitch
  - Observe subject's change detection response
    - Subject does not have to be attentive
  - Two decades of research shows that schizophrenia patients consistently have reduced amplitude ERP to deviant tones
    - Correlations between amplitude reduction and symptom severity
- Other benefits of MMN
  - Well-tolerated
  - Non-invasive

Mismatch Negativity



Nagai, Tatsuya, Mariko Tada, Kenji Kirihara, Tsuyoshi Araki, Seiichiro Jinde, and Kiyoto Kasai. "Mismatch Negativity as a "Translatable" Brain Marker Toward Early Intervention for Psychosis: A Review." Frontiers in Psychiatry 4 (2013).

The Data Set

- 1630 human subjects from 5 sites
  - 753 controls
  - 877 schizophrenia patients (no other Axis 1 psych diagnoses)
- EEG MMN data
  - Auditory "oddball duration" paradigm
    - 50 ms standard tone and 100 ms deviant tones
    - 450 ms between tones
  - 2 channel recordings

Delay Differential Analysis–Review

What is delay differential analysis (DDA)?

Tool for non-linear dynamical classification of time series

What is the basic process?

1. Roughly fit a delay differential equation (DDE) to a time series
2. Use coefficients and root-mean-square error as distinguishing features for classification
3. Try different DDEs to come up with best classification

Why DDA?

- DDA is reliable even for short time series
- computations are fast
- DDA is noise insensitive
- no pre-processing of data
- small feature space compared to traditional techniques
- 3-4 features: no overfitting

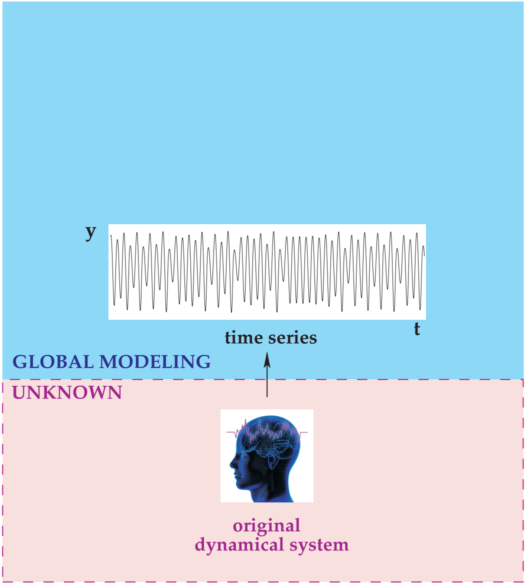
Dynamical System Analysis

Dynamical System Analysis

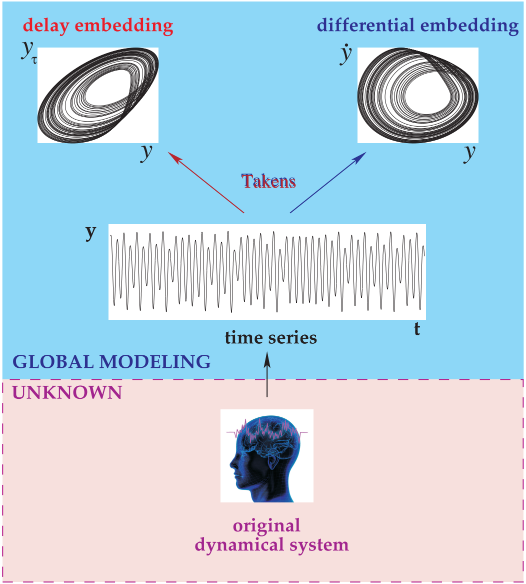
UNKNOWN

original
dynamical system

Dynamical System Analysis



Dynamical System Analysis



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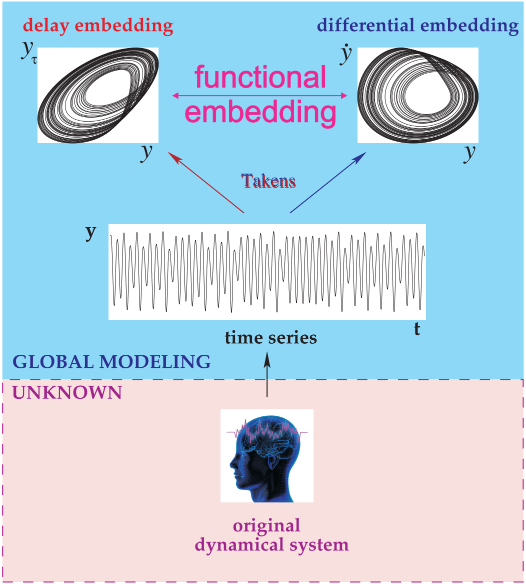
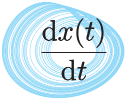
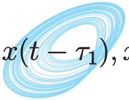


Delay differential analysis is done in the time domain,

not in the spectral domain!





$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = f(a, x(t-\tau_1), x(t-\tau_2), \dots)$$

Delay Differential Analysis (DDA)

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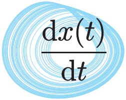
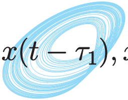




$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = f(a, x(t-\tau_1), x(t-\tau_2), \ldots)$$

linear terms: dominant time scales (frequencies)

non-linear terms: frequency/phase couplings, feedback

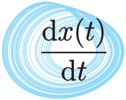
DDE has

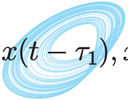
- n delays: $\tau_1, \tau_2, \ldots \tau_n$
- l terms with coefficients $a_1, a_2, \ldots, a_l$
- degree m of nonlinearity

$\Rightarrow$ coefficients a_k and model error ρ as features to identify

dynamical differences in data

General Model





$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = f(a, x(t-\tau_1), x(t-\tau_2), \ldots)$$

$$\begin{aligned}
\dot{x} \quad = \quad & a_1 x_{\tau_1} + a_2 x_{\tau_2} + a_3 x_{\tau_1}^2 + a_4 x_{\tau_1} x_{\tau_2} \\
& + a_5 x_{\tau_2}^2 + a_6 x_{\tau_1}^3 + a_7 x_{\tau_1}^2 x_{\tau_2} + a_8 x_{\tau_1} x_{\tau_2}^2 \\
& + a_9 x_{\tau_2}^3 + a_{10} x_{\tau_1}^4 + a_{11} x_{\tau_1}^3 x_{\tau_2} \\
& + a_{12} x_{\tau_1}^2 x_{\tau_2}^2 + a_{13} x_{\tau_1} x_{\tau_2}^3 + a_{14} x_{\tau_2}^4
\end{aligned}$$

$$x_{\tau_j} = x(t - \tau_j)$$

Structure (Model) Selection

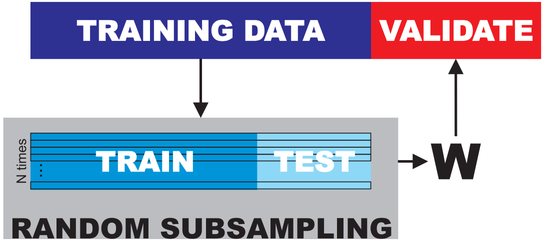
Select **one** fixed model with a fixed set of delays
(e.g. $\dot{x} = a_1 x_{\tau_1} + a_2 x_{\tau_2}^2$)

supervised or unsupervised

classification: best separation between classes of data

lowest error DDE model from data — dynamical deviation from that stage

Repeated Random Subsampling



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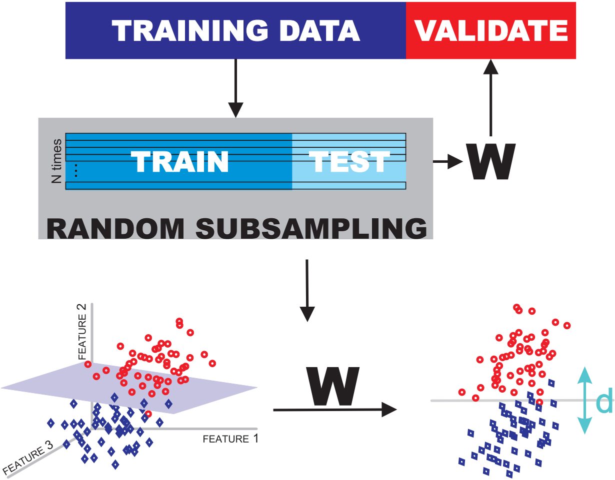
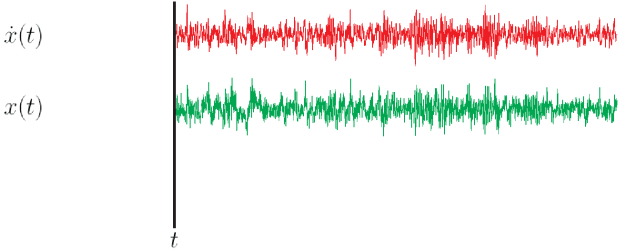


Delay Differential Equation

$$\dot{x}(t) = a_1\, x(t-\tau_2) + a_2\, x(t-\tau_1)^2$$



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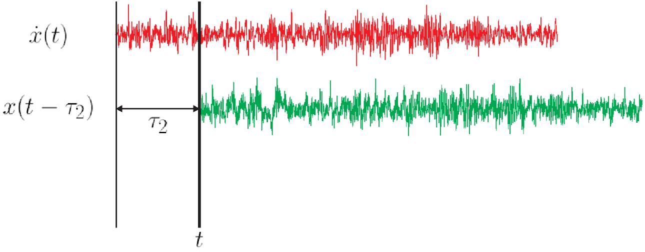

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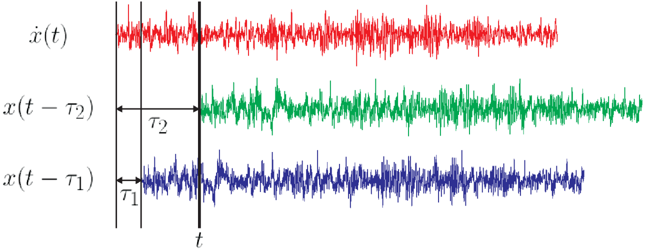

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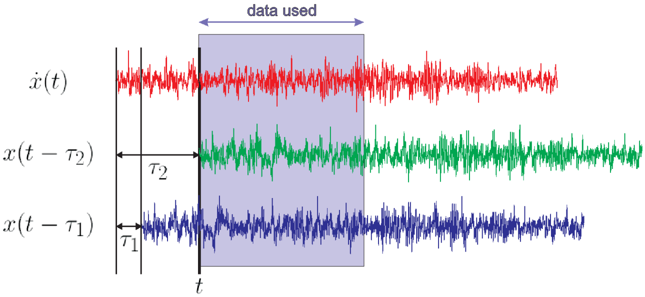

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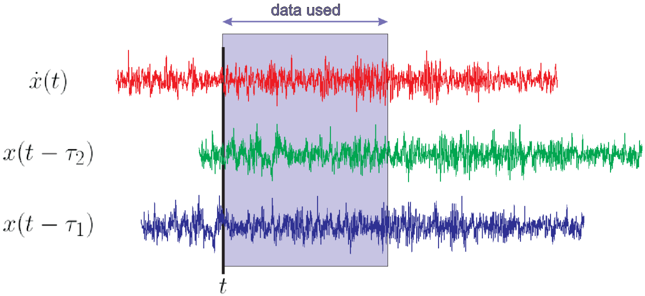

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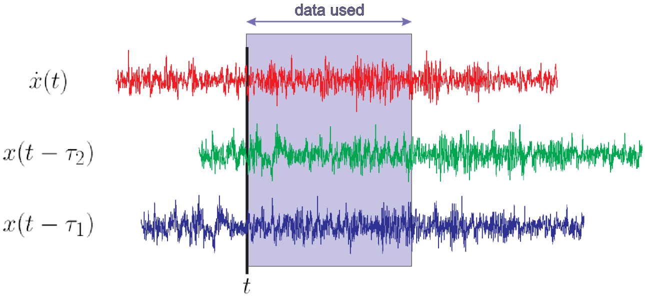

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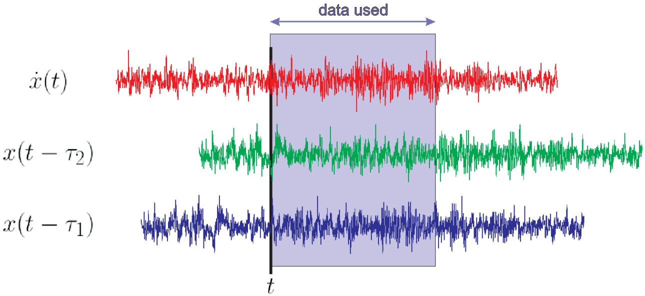

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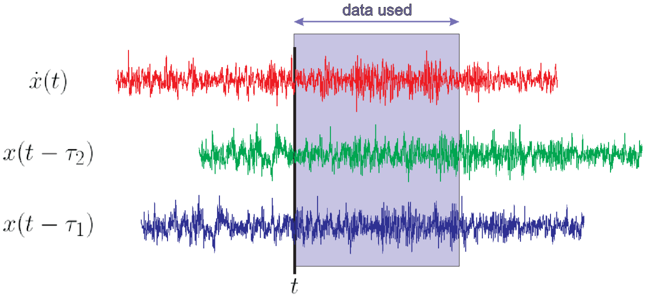


Cross-Validation Processes for Windowing across Trials

Three Kinds:

1. Single-Matrix Time Independent (SMTI) cross-validation
2. Multi-Matrix Time Dependent (MMTD) cross-validation
3. Single-Matrix Time Dependent (SMTD) cross-validation

Each kind of cross-validation is characterized by the **length of the CV feature space** and the **effective number of trials**.

Single-Matrix Time Independent CV

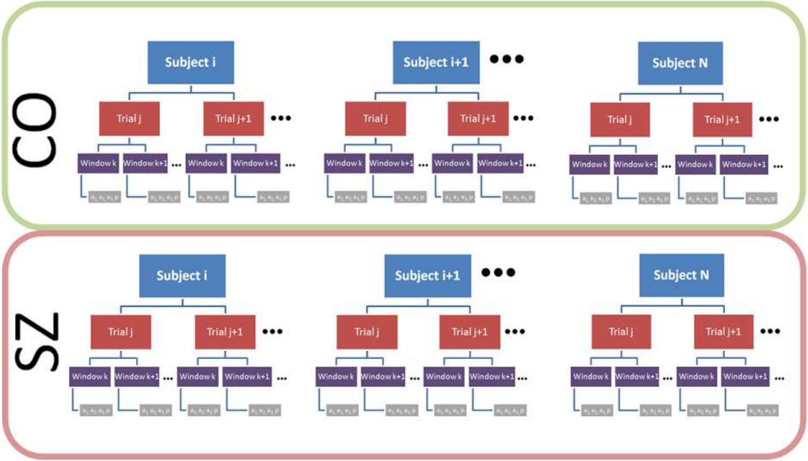
Idea: Treat each window as a separate trial.

$$\text{effective number of trials} = \text{NTrials} \times \text{WN}$$
$$\text{length of CV feature space} = \text{NTerms} + 1$$

Best suited for:

picking out time-invariant differences in dynamics between classes.

Cross-Validation Feature Space



Multi-Matrix Time Dependent CV

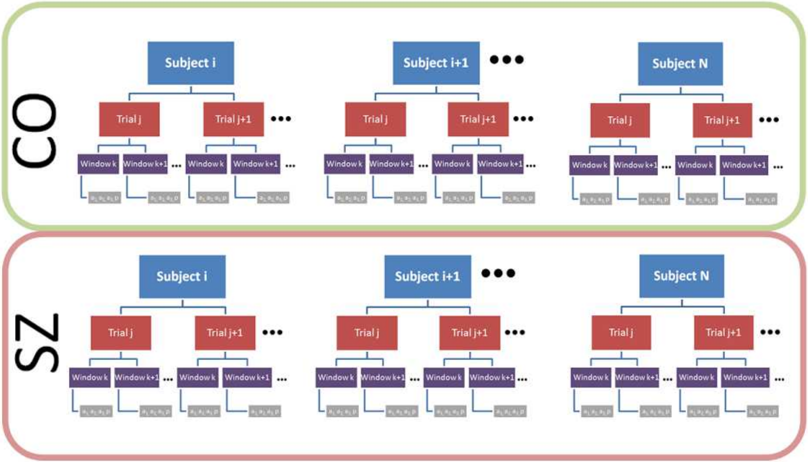
Idea: A separate feature matrix is formed for each window number. Cross-validation is performed on each feature matrix individually.

$$\text{effective number of trials} = \text{NTrials}$$
$$\text{length of CV feature space} = \text{NTerms} + 1$$

Best suited for:

identifying regions of particularly pronounced dynamical difference between conditions.

Cross-Validation Feature Space



Single-Matrix Time Dependent CV

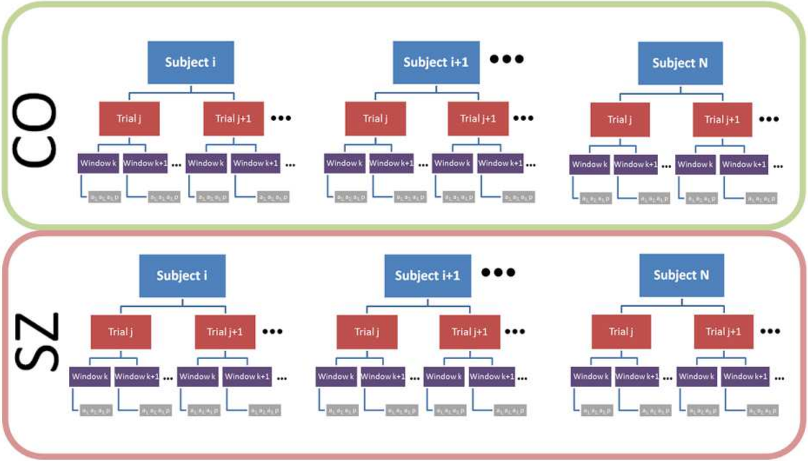
Idea: Concatenate features from each window to create extended cross-validation feature space

$$\text{effective number of trials} = \text{NTrials}$$
$$\text{length of CV feature space} = (\text{NTerms} + 1) \times \text{WN}$$

Best suited for:

classifying between conditions with time-dependent but differing dynamics

Cross-Validation Feature Space



Results–PRELIMINARY

CV Type	Model	Tau 1	Tau 2	A' Ind. Trials
SMTD	4	26	19	0.6890
SMTI	4	26	19	0.6745
MMTD 1	2	19	26	0.6770
MMTD 2	4	26	19	0.6824
MMTD 3	4	25	18	0.6693

- Only **10** randomly chosen subjects for each class
- Segments following deviant tones

Continuing Work

- Classification between conditions of time segments following standard tones, deviant tones
- Classification between segments following standard tones and segments following deviant tones within subjects
- Explore windowing options
- Use longer data segments containing multiple tones
- How best can DDA be implemented specifically for MMN?
- Expand analysis to whole data set

Acknowledgements

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