Nonlinear cortical responses in EEG evoked by continuous wrist manipulations

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Human motor control

Contents
• SYS ID of human motor control
• Cortical responses to sensory stimuli
• Nonlinear neural connectivity

The Central Nervous System
• Closed loop system
• Many feedback loops
  – Movement control
  – Thermoregulation
  – Pain modulation
  – Cardiovascular system
  – etc.
Human Motor Control

- How do we control our limbs?
- In face of¹:
  - Redundancy
  - Noise
  - Delays
  - Uncertainty
  - Nonstationarity
  - Nonlinearity

Motivation: movement disorders

- Contribute to improvement of ‘Quality of Life’ of people with movement disorders:
  - Stroke
  - Parkinson’s disease
  - Healthy aging
- Urgent need for objective measures & personalized therapy:
  - Better understanding of pathophysiology of movement disorders
  - Better diagnosis of movement disorders
  - Optimal therapy for individual patient

Approach

- Investigate Human motor control with engineering background
  - Central nervous system forms a closed-loop feedback system
  - ‘Reverse engineering’ of the human (‘optimal’ humanoid)

System identification

- Neuromuscular system involves feedback:
  - perturbation required to untangle a functioning feedback loop
- Intact closed loop system:
  - Unambiguous and natural task
  - External perturbation => force controlled manipulators
  - Closed loop system identification
What about the brain?

- SYS ID of human motor control
- Cortical responses to sensory stimuli
- Nonlinear neural connectivity

Longitudinal clinical study (ongoing)
- "Active" & "Passive" robot task
- Weeks post stroke
- Imaging & MRIs
- Over 200 EEG recordings
- Screening & Baseline
- Clinometrics

Past Expertise

4D EEG
Recording brain activity

**EEG: Electroencephalography**

- Electrodes measure electrical potential at scalp
  - Noisy data
  - Volume conduction
  - Requires many parallel oriented neurons to fire synchronously
- Preparation
  - Applying conductive gel (>30 minutes)
  - Determining electrode locations in 3D (>20 minutes)
- Data analysis
  - Manually remove all trials which contain artefacts
    - Eye blinks
    - Movements
  - Separate signals

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Functional impairment after stroke

**Brain damage → reduced motor function**

**Cortical control**
- Direct generation of movement
- Sensory integration
- Reflex modulation

**Functional impairments**
- Spasticity
- Hemiplegic paralysis
- Synergy between joints

**Optimal recovery**
- Timely prognosis
- Personalized treatment
- Exploit cortical plasticity

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Functional outcome after stroke

![Graph showing probability of recovery over weeks after stroke]

Recovery prediction could be done within **four weeks after stroke** based on Flugel-Mayer assessment of motor function.

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4D-EEG project goal

**To develop a new methodology for assessing the dynamics of cortical activity during motor control**

**System identification**
- High-density electroencephalogram (EEG)

**Multisite stimulation**
- Enhanced cortical response (SNR)
- Improved source localization
- Signal propagation in the brain
Cortical response to sensory stimuli

- Electroencephalography
  - Poor SNR
  - Many repetitions

- Transient stimuli
  - Event related potential (ERP)

- Continuous stimuli
  - Steady state response (SSR)
  - Mechanically evoked SSR (MSSR)

EEG experiments and analysis

Conventional approach

- Event-related potential
  - Present stimulus (electrical)
  - Repeat experiment (in this case ~1000x)

Objective

- Characterize the MSSR at the cortex (i.e. EEG) and therewith establish the type of system identification tools which can be applied
  - Is the response linear?
    - If nonlinear: even or odd nonlinearity?
  - Is the response time-invariant?

Method: detecting nonlinearities

Pintelon & Schoukens, 2012
Method: detecting time-variance

- Output signal LTI system
- Output signal LTV system

Lataire et al., 2008

Literature on MSSR

- MSSR has been mostly recorded using a single sine stimulus
  - Vibrotactile system
  - Proprioceptive system
- Out of all 37 found MSSR publications
  - 26 do not report on the presence of higher harmonics
  - 11 do report on the presence of higher harmonics
    - 1 reports sub-harmonics
- Non-stationarity of EEG often reported

Experiment

- Instruction: relax
  - Auditory disturbances
  - Visual disturbances
  - 1 day EEG
- Two experiments
  - 1 subject
  - 3 summed trials
  - 3 subjects
- 128 channel EEG
- Experiment 1: single sinusoid
  - Disturbing: 50 Hz
  - 3 trials of 50s

Cortical response

Contralateral sensorimotor cortex

 Ipsilateral sensorimotor cortex
Conclusion experiment 1

- Response is dominated by 2nd harmonic
  - Highly nonlinear response
- Neighbouring frequencies of harmonics are not above noise level
  - No slow time-variant behaviour
- Repeatable response over trials
- Subharmonic frequencies are not above noise level
  - Response is periodic with the input

Experiment 2: three sinusoids

- Investigate intermodulation (e.g. $f_1 + f_2$)
  - Can reveal order of NL
- 3 subjects
- Period of 1 s
  - Excited frequencies: 3, 7 and 11 Hz
    - Only odd frequencies, allowing distinction between even and odd nonlinear distortions
- 20 trials of 48s
- Results
  - No time-variant behaviour
  - No subharmonics
Results for all subjects

<table>
<thead>
<tr>
<th>Power [%]</th>
<th>Excited</th>
<th>2nd order</th>
<th>3rd order</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject 1</td>
<td>7</td>
<td>76</td>
<td>10</td>
<td>7</td>
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<tr>
<td>Subject 2</td>
<td>16</td>
<td>56</td>
<td>20</td>
<td>8</td>
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<tr>
<td>Subject 3</td>
<td>10</td>
<td>68</td>
<td>14</td>
<td>8</td>
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</table>

Conclusions on MSSR

- The observed cortical response:
  - Is time-invariant
  - Is highly nonlinear
    - Linear measures (e.g., linear coherence) will not suffice
      - Mainly even nonlinearity
    - No subharmonics
- The MSSR allows for application of a broad range of nonlinear system identification tools

Cortical response to sensory stimuli

Quantifying Nonlinear Contributions to Cortical Responses Evoked by Continuous Wrist Manipulation

Martijn P. Vlieuc, Student Member, IEEE; Teodoros Sidi-Saccharis, Member, IEEE; Atletar N. Vrcelj, Frans C. T. van der Helm, and Alfred C. Schouten

Experiment 3

- 11 subjects, 2 tasks
  - Passive task ('do nothing'), angular perturbations
  - Active task ('keep position'), torque perturbation
### Experiment 3

- Perturbations:
  - random phase multisine with 10 frequencies
  - 1 s period with 1, 3, 5, 6, 9, 11, 13, 15, 19, 23 Hz
- M=7 realizations, each P=210 periods

### Recording and analysis

- Recorded signals
  - Torque, angle, EMG (flexor&extensor), EEG (128 ch.)
- Calculate power in
  - Excited frequencies, even & odd harmonics

\[
\hat{E}_{X,total} = \sum_{j=1}^{1} \left( \frac{1}{M} \sum_{m=1}^{M} \left( \frac{1}{P} \sum_{p=1}^{P} \hat{X}^{2m+1}(f) \right) \right)^{1/2}
\]

\[
\hat{E}_{X,even} = \hat{E}_{X,total} - \hat{E}_{X,odd}
\]

\[
\hat{X}^{2m+1}(f) = \frac{1}{P} \sum_{p=1}^{P} \left| \chi^{2m+1}(f) \right|^{2}
\]

### Nonlinearities

<table>
<thead>
<tr>
<th>NSR [dB]</th>
<th>NSRmedian [%]</th>
<th>Tm [%]</th>
<th>Tm_odd [%]</th>
<th>Tm_even [%]</th>
<th>Tm_median [%]</th>
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</thead>
<tbody>
<tr>
<td>Passive task</td>
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<td></td>
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<td>0.00</td>
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<td>0.00</td>
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<tr>
<td>Active task</td>
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<td>0.00</td>
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</tbody>
</table>
Conclusions

- Mechanics
  - 99% in excited freqs
  - ~linear, muscle visco-elasticity?

- EMG
  - 25% power in harmonics
  - Nonlinearity of muscle spindle

- EEG
  - ≤80% power in harmonics
    - => highly nonlinear!
  - Nonlinearity of muscle spindle

Modelling the cortical response

Modeling the Nonlinear Cortical Response in EEG Evoked by Wrist Joint Manipulation

Martin P. Visser, Georgios Boutsourakis, Member, IEEE, John Latour, Member, IEEE, Maarten Schouwenaars, Member, IEEE, Alfred C. Schouwenaars, Fellow, IEEE, and Frank C. T. van der Helm

Contents

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Objective

to explore how the brain interacts with neuromuscular system using a new methodology based on nonlinear analysis and multi-sine perturbations

- Multi-sine mechanical perturbation
- Nonlinear analysis in frequency domain
Nonlinearity in frequency domain

Linear vs. Nonlinear System:

Frequency relations between input and output:
- Harmonics
- Intermodulation between two frequencies
- Intermodulation among multiple frequencies

\[ f_z = a_1 f_1 + a_2 f_2 + \ldots + a_n f_n \]

Multi-spectral phase coherence

Linear cases:

\[ \Delta \phi_{xy} = \phi_x(f) - \phi_y(f) \]

Nonlinear cases:

\[ \Psi_{xy}(f_i; a_j) = \frac{1}{K} \sum_{k=1}^{K} \exp \left( \sum_{j=1}^{n} a_j \phi_i(f) - \phi_j(f) \right) \]

- Nonlinear input-output relation
- Directional connectivity
- Time delay in a nonlinear system

Experiment (11 subjects)

- Constant flexion torque (right wrist, 1 Nm)
- A wrist manipulator applied a position perturbation (7, 13, 29 Hz)
- Recording:
  - 128 channel EEG
  - Bipolar EMG (m.flexor/extensor carpi radialis)
  - Mechanical data (torque, position)

Nonlinear phase coherences

Nonlinear phase coherence between different signals up to 3rd order, as so to study the nonlinear interaction in different pathways.
- Perturbation: EMG, reflexes (spinal and transcranial)
- Perturbation: EEG, afferent pathway (transcranial)
- EEG+EMG, efferent pathway (transcranial)
Afferent pathway from sensor to brain

\[ 41 \text{ ms} \]

Perturbation → brain


Perturbation to EMG

• Nonlinear interaction:
  Perturbation → EMG > Perturbation → EEG

• Time delay (mean ± std.):
  Perturbation → EMG 33 ± 6 ms < Perturbation → EEG 43 ± 8 ms


Brief discussion

• Perturbation to EEG
• Perturbation to EMG

Dominant role of the spinal loop in the nonlinear muscle activity in response to mechanical perturbation.

Brief discussions

• sensory signal arrives at the primary somatosensory cortex,
• the transcortical reflex loop only weakly contributes to the nonlinear connectivity in the stretch reflex.
Conclusion

- A useful tool to characterize nonlinear interactions between the periphery and central nervous systems during motor tasks.
- New insights on neuronal connectivity in the stretch reflex, in terms of nonlinear phase coupling.
- A normative reference for future clinical studies related to motor disorders and rehabilitation.
- Potential applications to other complex neural systems such as the visual/auditory system.

Summarizing

- Human motor control
  - Closed-loop system
- Cortical response to sensory stimuli
  - Highly nonlinear (~80%)
- Multi-spectral phase coherence
  - Nonlinear connectivity & directionality

4D-EEG project team

Delft University of Technology
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  - Miquel Sans, MSc
  - Lucas Haring, MSc
  - Dirk Hoevenaar, MSc

Wish list

- Time-variability
  - Movement
  - Adaptation
- Detect non-linearity
  - Kind of non-linearity
  - Location in the loop
- Statistics
  - Variance over repetitions/subjects
  - Difference between conditions
  - ...