Processing Signals from EEG Electrodes and Protein Molecules: Convergence of DSP, Machine Learning, and Digital Design

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Communications everywhere
Data Rate

DATA RATE TRENDS

ISSCC TechTrends 2011
Medical

@hospital

sensing

Advice

Processing
Medical Advice

@home +
New Applications of DSP

- Information/Data analysis for multi-sensor applications
- Sophisticated features from DSP, Machine Learning, Pattern Recognition, and Information Fusion
- Applications in Biomedical Applications
- Build on Wireless Infrastructure or create new wireless sensors
Outline

• Seizure Prediction
• Biomolecular Signal Processing
Seizure Prediction/Detection Group

Yun-Sang Park

Michael Brown

Lan Luo

Prof. Tay Netoff
Biomolecular Signal Processing Group

Hua Jiang

Sasha Kharam

Prof. Marc Riedel
Seizure Prediction Device: A Pacemaker for the Brain

- Seizure prediction using spectral power features and SVM-classification (Freiburg database)
- Implantable seizure predictor – low-cost/power (2-4 electrodes)
- Seizure detection on large scale data – preliminary results (100+ electrodes)
Goal: Seizure Alert Device

- Provides warnings
- Allows for rescue therapy
- Must work in **real-time** on an **implantable** device
- Low power consumption (battery life > 1 year)
  → few linear features (4-5) and a simple classifier
Seizure Prediction based on EEG

- Prediction: classification of preictal (prior to a seizure) from interictal (between seizures)
- Detection: classification of ictal from non-ictal
Seizure Prediction Using SVMs

- Mainly consists of **feature extraction** and **SVM-classification**
- Features: **spectral power in 9 bands** from 20-sec-long window
  - δ(0.5-4Hz), θ(4-7Hz), α(8-13Hz), β(13-30Hz), γ(30-50Hz, 50-75Hz, 75-100Hz, 100~Hz), and **Total**
  - **Bipolar** (space-differential) and/or **time-differential** preprocessing
- SVM-classification with RBF kernel
  - **Cost-sensitive SVMs** for highly unbalanced datasets
- Freiburg EEG database
  - [https://epilepsy.uni-freiburg.de/freiburg-seizure-prediction-project/eeg-database](https://epilepsy.uni-freiburg.de/freiburg-seizure-prediction-project/eeg-database)
  - 18 of 21 patients selected who have ≥ 3 seizure recordings

Keshab K. Parhi
(A) Raw

(B) Bipolar

(C) Time-diff

(D) Bipolar & Time-diff
Kalman filter for post-processing

• Reduce # of FPs while maintaining the sensitivity
• The change rate of two continuous windows should undergo smooth transition $\rightarrow$ 2\textsuperscript{nd} order Kalman filter

• True state $f_k$ does not change a lot: $\dot{f}_{k+1} = \dot{f}_k + N(0, \sigma_w^2)$
• Noisy estimate of the state $s_k$: $s_k = f_k + N(0, \sigma_v^2)$

$F_{k+1} = \begin{bmatrix} 1 & \Delta T \\ 0 & 1 \end{bmatrix} F_k + w_k$
$s_{k+1} = \begin{bmatrix} 1 & 0 \end{bmatrix} F_{k+1} + v_{k+1}$

where $F_k = [f_k \quad \dot{f}_k]'$, $w_k \sim N(0, Q)$, $Q = \begin{bmatrix} \frac{\Delta T^4}{4} & \frac{\Delta T^3}{2} \\ \frac{\Delta T^3}{2} & \Delta T^2 \end{bmatrix} \sigma_w^2$, $v_k \sim N(0, \sigma_v^2)$
Kalman filter for post-processing

- Reduce # of FPs while maintaining the sensitivity
- The change rate of two continuous windows should undergo smooth transition $\rightarrow$ 2\textsuperscript{nd} order Kalman filter
## Results

<table>
<thead>
<tr>
<th>PSD</th>
<th>Sens (%)</th>
<th>FP/hr</th>
<th>FP%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw</td>
<td>93.8</td>
<td>0.29</td>
<td>13.7</td>
</tr>
<tr>
<td><strong>Bipolar</strong></td>
<td>97.5</td>
<td>0.27</td>
<td>13.0</td>
</tr>
<tr>
<td>Time-diff</td>
<td>92.5</td>
<td>0.20</td>
<td>9.49</td>
</tr>
<tr>
<td><strong>Bipolar/time-diff</strong></td>
<td>93.8</td>
<td>0.23</td>
<td>10.7</td>
</tr>
</tbody>
</table>

# patients = 18, # seizures = 80
Total interictal hours = 437

- Bipolar improves sensitivity; time-diff improves FP rate
- Accepted in *Epilepsia* in May 2011
  
## Results’ Comparison with Others in Same Freiburg Database

<table>
<thead>
<tr>
<th>Group</th>
<th># Pat</th>
<th># Sz</th>
<th>Interictal hours</th>
<th>Prediction horizon (min)</th>
<th>Sens (%)</th>
<th>FP/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winterhalder, et al., 2003</td>
<td>21</td>
<td>88</td>
<td>509</td>
<td>30</td>
<td>42</td>
<td>0.15</td>
</tr>
<tr>
<td>Aschenbrenner, et al., 2003</td>
<td>21</td>
<td>88</td>
<td>509</td>
<td>50</td>
<td>34</td>
<td>0.10</td>
</tr>
<tr>
<td>Maiwald, et al., 2004</td>
<td>21</td>
<td>88</td>
<td>509</td>
<td>32</td>
<td>30</td>
<td>0.15</td>
</tr>
<tr>
<td>Schelter, et al., 2006</td>
<td>4</td>
<td>20</td>
<td>96</td>
<td>40</td>
<td>70</td>
<td>0.15</td>
</tr>
<tr>
<td>Park, et al., 2011</td>
<td>18</td>
<td>80</td>
<td>437</td>
<td>30</td>
<td>97.5 (B)</td>
<td>0.27 (B)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>92.5 (T)</td>
<td>0.20 (T)</td>
</tr>
</tbody>
</table>
Towards an Implantable Seizure Predictor!

- Features limited to 4-5
- Target power consumption: 50 microwatt
- Reduce computational complexity: Feature consolidation, Feature Selection by maximizing divergence, Implement Circuits operating with least power for 256 Samples/Sec to achieve batter life of at least a year
### Results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sensitivity Predicted/Available : %</th>
<th>Advance Prediction Time Shortest/Longest : Avg.</th>
<th>Overall FP per hour / %FP</th>
<th>Without Seizure FP per hour / FP%</th>
<th>Near Seizure FP per hour / FP%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4/4 : 100%</td>
<td>7 min. / 127 min. : 64 min.</td>
<td>0.095 / 6%</td>
<td>0.078 / 2.2%</td>
<td>0.3 / 24.75%</td>
</tr>
<tr>
<td>3</td>
<td>5/5 : 100%</td>
<td>27 min. / 83 min. : 65 min.</td>
<td>0.25 / 7.8%</td>
<td>0.256 / 8%</td>
<td>0.11 / 4.6%</td>
</tr>
<tr>
<td>4</td>
<td>5/5 : 100%</td>
<td>18 min. / 101 min. : 68 min.</td>
<td>0.04 / 3.44%</td>
<td>0.026 / 2%</td>
<td>0.17 / 16%</td>
</tr>
<tr>
<td>5</td>
<td>4/5 : 80%</td>
<td>14 min. / 95 min. : 52 min.</td>
<td>0.276 / 20.4%</td>
<td>0.282 / 21%</td>
<td>0.2 / 8.4%</td>
</tr>
<tr>
<td>6</td>
<td>3/3 : 100%</td>
<td>7 min. / 64 min. : 39 min.</td>
<td>0.34 / 44%</td>
<td>0.31 / 44.3%</td>
<td>0.59 / 37.3%</td>
</tr>
<tr>
<td>7</td>
<td>3/3 : 100%</td>
<td>12 min. / 97 min. : 41 min.</td>
<td>0.053 / 2.4%</td>
<td>0.02 / 0.67%</td>
<td>0.29 / 26%</td>
</tr>
<tr>
<td>9</td>
<td>5/5 : 100%</td>
<td>55 min. / 137 min. : 87 min.</td>
<td>0.242 / 6.6%</td>
<td>0.264 / 6.1%</td>
<td>0.08 / 9.4%</td>
</tr>
<tr>
<td>10</td>
<td>5/5 : 100%</td>
<td>14 min. / 67 min. : 43 min.</td>
<td>0.508 / 23.4%</td>
<td>0.479 / 23%</td>
<td>0.78 / 29%</td>
</tr>
<tr>
<td>11</td>
<td>2/4 : 50%</td>
<td>63 min. / 140 min. : 102 min.</td>
<td>0.502 / 21.5%</td>
<td>0.485 / 0.76%</td>
<td>1.63 / 19.5%</td>
</tr>
<tr>
<td>12</td>
<td>4/4 : 100%</td>
<td>5 min. / 55 min. : 19 min.</td>
<td>0.08 / 4.25%</td>
<td>0.065 / 0.1%</td>
<td>0.53 / 16.75%</td>
</tr>
<tr>
<td>14</td>
<td>4/4 : 100%</td>
<td>36 min. / 81 min. : 64 min.</td>
<td>0.8 / 43.5%</td>
<td>0.848 / 46.1%</td>
<td>0.21 / 4.75%</td>
</tr>
<tr>
<td>15</td>
<td>4/4 : 100%</td>
<td>32 min. / 134 min. : 80 min.</td>
<td>0.61 / 35.7%</td>
<td>0.645 / 38%</td>
<td>0.16 / 8.75%</td>
</tr>
<tr>
<td>16</td>
<td>2/5 : 40%</td>
<td>12 min. / 84 min. : 59 min.</td>
<td>0.606 / 19.6%</td>
<td>0.662 / 21.8%</td>
<td>0.06 / 0.94%</td>
</tr>
<tr>
<td>17</td>
<td>4/5 : 80%</td>
<td>48 min. / 103 min. : 76 min.</td>
<td>0.347 / 23.7%</td>
<td>0.322 / 17.3%</td>
<td>0.64 / 18.7%</td>
</tr>
<tr>
<td>18</td>
<td>2/5 : 40%</td>
<td>7 min. / 8 min. : 8 min.</td>
<td>0.273 / 10.5%</td>
<td>0.205 / 7%</td>
<td>1.07 / 36.4%</td>
</tr>
<tr>
<td>19</td>
<td>3/4 : 75%</td>
<td>24 min. / 45 min. : 38 min.</td>
<td>0.68 / 39%</td>
<td>0.68 / 40.4%</td>
<td>0.59 / 22.6%</td>
</tr>
<tr>
<td>20</td>
<td>3/5 : 60%</td>
<td>10 min. / 18 min. : 13 min.</td>
<td>0.685 / 42.5%</td>
<td>0.717 / 42.4%</td>
<td>0.4 / 43%</td>
</tr>
<tr>
<td>21</td>
<td>3/5 : 60%</td>
<td>23 min. / 40 min. : 30 min.</td>
<td>0.577 / 26.9%</td>
<td>0.523 / 25.4%</td>
<td>1.1 / 43.2%</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>65/80 : 82.5%</strong></td>
<td><strong>53 min.</strong></td>
<td><strong>0.386 / 21.1%</strong></td>
<td><strong>0.385 / 19.2%</strong></td>
<td><strong>0.495 / 24%</strong></td>
</tr>
</tbody>
</table>

(M Brown, T. Netoff, K. Parhi, submitted to IEEE EMBC 11)
Remarks

• Established seizure predictor based on SVM-classification and Kalman filter: 97.5% sensitivity and 0.27 FP rate with bipolar spectral power features
• Towards implantable device: 82.5% sensitivity and 0.39 FP rate with 8 selected power features and linear classifier
• Build seizure detector with least number of electrodes, features and fusion of simple classifiers (ongoing)
• Extend our approaches into Mayo database
Other Projects

- Screen Fundus Images for Diabetic Retinopathy
- Design Deep Brain Stimulation Therapy for Parkinsons and Dystonia
- Language Understanding in Schizophrenia Patients
- Lung Sound Analysis
Chemical Reactions

- Modeled by mass action kinetics
- Reaction speed determined by rate constant and concentration of reactants

\[ C + O_2 \xrightarrow{k} CO_2 \]

\[ -\frac{d[C]}{dt} = -\frac{d[O_2]}{dt} = \frac{d[CO_2]}{dt} = k[C][O_2] \]
Chemical Reactions: Assumptions

- Chemical A generated from a large and replenishable source

  \[ \phi \rightarrow A \]

- Chemical A transferred to some chemical type no longer part of the system

  \[ A \rightarrow \phi \]
Previous Works: Analog Multiplier

• An analog implementation of multiplier (Hayat et al, HFSP Journal, Oct 08)

\[ A + B \xrightarrow{k_1} A + B + C \]

\[ C \xrightarrow{k_2} \phi \]

\[ \frac{d[C]}{dt} = k_1[A][B] = k_2[C] = 0 \]

\[ [C] = \frac{k_1}{k_2} [A][B] \]

• Dependent on chemical equilibrium
• Reaction rates \((k_1, k_2)\) affect precision
Previous Works: Biochemical Signal Processing

“The band-pass behavior is of most interest to us because it is this behavior that allows the usage of the same medium (e.g. calcium) for selective signal transmission to different systems. That is, if two pathways act as band-pass filters at different frequencies with respect to the same signaling molecule, then the molecule may be used to signal to each of the two pathways at those respective frequencies, independently.”

“A class of bimolecular reaction mechanisms can behave as a band-pass filter, but the behavior is very sensitive to the kinetic parameters.”

(Samoilov, Arkin, Ross, J. Phys. Chem. A, Oct 02)
DSP with Reactions

Input molecular type

Reactions

Output molecular type

10, 2, 12, 8, 4, 8, 10, 2, ...

5, 6, 7, 10, 6, 6, 9, 6, ...

How do we find such reactions?
Moving Average Filter: Chemical

But how do we implement DSP functions with reactions?
Computational Modules

Constant Multiplier

\[2X \rightarrow X_1\]
\[2X_1 \rightarrow X_2\]
\[2X_2 \rightarrow Y\]

\[[Y] = \frac{1}{8}[X]\]
Computational Modules

Adder
Fanout

\[ X \rightarrow A + B \]

\[ [X] = [A] = [B] \]
Molecular quantities are preserved over “computational cycles”. Contents in different delay elements are transferred synchronously.
RGB Scheme

We use a three compartment configuration for delay elements: we categorize the types into three groups: red, green and blue.

Every delay element $D_i$ is assigned $R_i$, $G_i$, and $B_i$. 
Absence Indicators

But how do we know that a group of molecules is **absent**?

\[
\begin{align*}
\emptyset & \xrightarrow{\text{slow}} r \\
R + r & \xrightarrow{\text{fast}} R
\end{align*}
\]
RGB Scheme

Delay Element

\[
\begin{align*}
R & \xrightarrow{\text{slow}} G \\
r & \xrightarrow{\text{slow}} B \\
g & \xrightarrow{\text{slow}} R \\
\emptyset & \xrightarrow{\text{slow}} r \\
\emptyset & \xrightarrow{\text{slow}} g \\
\emptyset & \xrightarrow{\text{slow}} b \\
R + r & \xrightarrow{\text{fast}} R \\
G + g & \xrightarrow{\text{fast}} G \\
B + b & \xrightarrow{\text{fast}} B \\
\end{align*}
\]

Oscillating!
Moving Average Filter

Signal transfer

\[
\begin{align*}
2R & \xrightarrow{\text{slow}} I_R \\
I_R & \xrightarrow{\text{fast}} 2R \\
I_R + X & \xrightarrow{\text{fast}} A + C + 2R \\
2C & \xrightarrow{\text{slow}} I_G \\
I_G & \xrightarrow{\text{fast}} 2G \\
I_G + R & \xrightarrow{\text{fast}} 3G \\
2B & \xrightarrow{\text{slow}} I_B \\
I_B & \xrightarrow{\text{fast}} 2B \\
I_B + G & \xrightarrow{\text{fast}} 3B \\
2Y & \xrightarrow{\text{slow}} I_Y \\
I_Y & \xrightarrow{\text{fast}} 2Y \\
I_Y + B & \xrightarrow{\text{fast}} 3Y, \\
b + R & \xrightarrow{\text{slow}} G \\
r + G & \xrightarrow{\text{slow}} B \\
g + B & \xrightarrow{\text{slow}} Y.
\end{align*}
\]

Computation

\[
\begin{align*}
g + X & \xrightarrow{\text{slow}} A + C \\
2C & \xrightarrow{\text{fast}} R \\
2A & \xrightarrow{\text{fast}} Y
\end{align*}
\]

Absence indicator

\[
\begin{align*}
\varnothing & \xrightarrow{\text{slow}} r \\
R + r & \xrightarrow{\text{fast}} R \\
Y + r & \xrightarrow{\text{fast}} Y \\
\varnothing & \xrightarrow{\text{slow}} g \\
G + g & \xrightarrow{\text{fast}} G \\
\varnothing & \xrightarrow{\text{slow}} b \\
B + b & \xrightarrow{\text{fast}} B \\
X + b & \xrightarrow{\text{fast}} X
\end{align*}
\]
Moving Average Filter

New cycle!
Simulation Results: Moving Average

- Output obtained by solving system kinetics equations
DNA Strand Displacement

\[ X_1 \rightarrow X_2 + X_3 \]

D. Soloveichik et al: “DNA as a Universal Substrate for Chemical Kinetics.” PNAS, Mar 2010
DNA Strand Displacement

$X_1 + X_2 \rightarrow X_3$

D. Soloveichik et al: “DNA as a Universal Substrate for Chemical Kinetics.” PNAS, Mar 2010
Moving Average Filter: DNA Level Reactions
Synchronous Sequential Components

- Synchronous sequential computation with chemical reactions: exact and rate independent designs
- Examples: Counter and FFT
- Technology-independent design (abstract chemical reactions)
- Technology-mapping (DNA strand displacement)
Implementing Clock

\begin{align*}
\emptyset & \xrightarrow{\text{slow}} r & R + r & \xrightarrow{\text{fast}} R \\
\emptyset & \xrightarrow{\text{slow}} g & G + g & \xrightarrow{\text{fast}} G \\
\emptyset & \xrightarrow{\text{slow}} b & B + b & \xrightarrow{\text{fast}} B \\
\emptyset & \xrightarrow{\text{slow}} v & Y + y & \xrightarrow{\text{fast}} V.
\end{align*}

\begin{align*}
R + v & \xrightarrow{\text{slow}} G \\
G + r & \xrightarrow{\text{slow}} B & R + I_G & \xrightarrow{\text{fast}} 3G \\
B + g & \xrightarrow{\text{slow}} V & 2B & \xrightarrow{\text{fast}} I_B \\
V + b & \xrightarrow{\text{slow}} R & G + I_B & \xrightarrow{\text{fast}} 3B \\
& & 2V & \xrightarrow{\text{fast}} I_V \\
& & B + I_Y & \xrightarrow{\text{fast}} 3V \\
& & 2R & \xrightarrow{\text{fast}} I_R \\
& & V + I_R & \xrightarrow{\text{fast}} 3R.
\end{align*}
Examples

Counter

4-point FFT
Digital Logic with Molecular Reactions

• Digital logic with chemical reactions: exact and rate independent designs
• Examples: Gates, flip-flops, counter and LFSR
• Technology-independent design (abstract chemical reactions)
• Technology-mapping (DNA strand displacement)
Representing A Bit: Old Methods

Presence means “1”

Absence means “0”

But leakage always happen
Representing A Bit: This Work

“0”

“1”
Representing A Bit: This Work

\[ X_0 + X_1 \rightarrow S_X \]
\[ S_X + X_0 \rightarrow 3X_0 \]
\[ S_X + X_1 \rightarrow 3X_1. \]
Implementing Logic Gates: AND Gate

X=0, Y=0/1

\[ X_0 + Z_1 \rightarrow X_0 + Z_0 \]

Y=0, X=0/1

\[ Y_0 + Z_1 \rightarrow Y_0 + Z_0. \]

X=1, Y=1

\[ X_1 + Y_1 \rightarrow X_1 + Y_1 + Z'_1 \]
\[ Z'_1 \rightarrow \emptyset \]
\[ Z'_1 + Z_0 \rightarrow Z_1. \]
Implementing Logic Gates: AND Gate
Implementing Logic Gates: OR Gate

X=1, Y=?

\[ X_1 + Z_0 \quad \rightarrow \quad X_1 + Z_1 \]

Y=1, X=?

\[ Y_1 + Z_0 \quad \rightarrow \quad Y_1 + Z_1 \]

X=0, Y=0

\[ X_0 + Y_0 \quad \rightarrow \quad X_0 + Y_0 + Z'_0 \]
\[ Z'_0 \quad \rightarrow \quad \emptyset \]
\[ Z'_0 + Z_1 \quad \rightarrow \quad Z_0. \]
Implementing Logic Gates: OR Gate
Implementing Logic Gates: XOR Gate

\[
\begin{align*}
X_0 + Y_1 &\quad \rightarrow \quad X_0 + Y_1 + Z_1' \\
X_1 + Y_0 &\quad \rightarrow \quad X_1 + Y_0 + Z_1' \\
Z_1' &\quad \rightarrow \quad \emptyset \\
Z_1' + Z_0 &\quad \rightarrow \quad Z_1.
\end{align*}
\]

\[
\begin{align*}
X_0 + Y_0 &\quad \rightarrow \quad X_0 + Y_0 + Z_0' \\
X_1 + Y_1 &\quad \rightarrow \quad X_1 + Y_1 + Z_0' \\
Z_0' &\quad \rightarrow \quad \emptyset \\
Z_0' + Z_1 &\quad \rightarrow \quad Z_0.
\end{align*}
\]
Implementing Logic Gates: XOR Gate
Example: Three-Bit Counter
Example: Three-Bit Counter

![Graph showing concentration over time for a three-bit counter](image-url)
Example: Linear Feedback Shift Register
Example: Linear Feedback Shift Register
Applications: Drug Delivery

- Decision can be used to deliver a drug or not or to trigger other actions
Applications: Pathway Activation

- Different pathways are activated with signals of different frequencies
Applications: Protein Cross-Talk Equalization/Cancellation ?

Hybrid

Far Echo

Near Echo

ANEXT & Others

FEXT

NEXT

Cable Attenuation and ISI
Remarks

• Key Contributions
  • Implementation of a delay element in chemical reactions
  • Clock for biochemical systems
  • Signal processing at biochemical and biomolecular level
  • Implement filters and transforms with biochemical signal processing
  • Applications in drug delivery, gene therapy, and cancer treatment
References


Conclusions

- Signal Processing, Machine Learning and Classification are important tools for biomedical signal processing
- Monitoring, Diagnosis, Prevention and Therapy driven by DSP
- Signal processing for monitoring and processing proteins
- Digital Circuits for low-power implementations
- Digital Circuits and DSP are not yet outdated!