Neuro-Forschung bei Siemens: Einige Beispiele

Gruppe: “Bioanologue Technologies and Solutions” (BTS)
Team:

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Focus Areas

Bio-analogue Technologies & Solutions

Learning Communication Networks

Knowledge Discovery & Decision Support

Advanced Control, Prognosis & Diagnosis

Learning Methods for Business Processes
Bioanalogous Technologies and Solutions

**Computational Neuroscience**
- Neurodynamical top-down Cognition Models
- Neurostatistical Modeling

**Neuronal Bioinformatics**
- Pathway Inference of Genetic Networks
- Inference of Genetic Predispositions

**Human Brain**
- Diagnosis
- Therapy Planning

**Neural Model**
- Drug Screening
- Drug Discovery

**Metabolism**
- Diagnosis

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Complexity of the Brain

• Structured, nonlinear, recurrent, dynamical system
• Parallel and distributed signal processing with $10^{11}$ neurons, $10^{15}$ synapses (!)
• Cortical „Hardware“ seems roughly uniform despite different tasks
Anatomy of the Primary Visual Cortex

Slices through macaque V1

Nissl stain (Hubel and Wiesel, 1977)  CO-stain (Blasdel and Lund, 1983)
Important Cell Types in the Visual Cortex

- pyramidal cell (McGuire et al., 1990)
- basket cell (Lund and Yoshioka, 1991)
- chandelier cell

Excitatory neurons: 5%
Inhibitory neurons: 5%
Funktionsweise des Neurons

Signal: Aktionspotential, „Spike“

Signalfluss:
Dendrit --> Soma --> Axon--> Synapse---> Dendrit ...

(a) Spike kommt an;
    Synapse injiziert Strom I
    Membranspannung steigt (PSP)

(b) Viele PSPs summieren sich
    Bei Schwellenspannung: Spike

(c) Spike läuft Axon entlang
    verzweigt sich mit dem Axon

(d) Spike kommt an.....

Biologisches Lernen (Hypothese):

Synaptischer Strom I ändert sich in Abhängigkeit
von der Zeit und der Hirnaktivität („LTP, LTD“.....)

Einführung: Lernen in Statistik und Biologie
Technik: funktionelle Kernspintomographie

- „functional Magnetic Resonance Imaging“ (fMRI)
- Magnetmomente der Atome werden in einem starken Magnetfeld angeregt (Magnetresonanz)
- Sie relaxieren in den Grundzustand zurück
- Die Relaxation wird durch Gradientenfelder ortsabhängig gemacht (=> Imaging)
- Die Relaxation ist abhängig von der molekularen Umgebung
  -- Wasserstoffkonzentration: strukturelle MRI
  -- Paramagnetische Substanzen (Hbr): funktionelle MRI
Distributed Processing: What- and Where Systems of the Visual Cortex

(Haxby et al., 1994)
Workflow of Neurocognitive Modeling

**Microscopic**
- Neurophysiology

**Mesoscopic**
- Funktional Imaging (fMRI, MEG, EEG)

**Macroscopic**
- Neuropsychology

**Data Generation**
- Data Integration
- Data Modelling
- Exploitation

**Data**
- Statistical Modelling
- Neurodynamical Modelling
- Modelling

**Exploitation**
- Clinical
- Industrial
- Academic

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Modeling Human Cognition

- Long Term Memory
- Cognitive Control
- Emotion

- Conflict Evaluation
  - Motor Planning
  - Conflict Signalling
  - Error Signalling

- Biased Competition Networks
  - Design for Technical / Industrial Applications

- Working Memory
  - Attentional Filtering
  - Object/Spatial Memory
  - Rule Memory

- Attention
  - Object-Based Attention
  - Spatial Attention

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Biased Competition Networks: Principle

- Sensory input layer
- Attention layer
- Working memory layer
- Neuron pools: object specific, object specific, non-selective, inhibitory
- Attention filtering
- Bias
- Competition
- Long-term memory
- Working memory layer: space WM, object WM
- Decision layer
- Rule memory layer
Neurodynamical Spiking Neuron and Mean-Field Models

Brain: $10^{11}$ Neurons

Networks of Spiking Neurons

Integrate and Fire Model:
$$\tau_n \frac{d}{dt} V_n(t) = -g_m(V_n(t) - V_L) - I_{syn}(t)$$

Linked Pools in a Mean-Field model

Mean-Field Model:
$$\tau \frac{d}{dt} I_B = -I_B + aF(A) + I_{ext} + ...$$

Neuron Pools

Pool Activity:
$$A(t) = \lim_{\Delta t \to 0} \frac{n_{spikes}(t, t + \Delta t)}{M \Delta t}$$
Neurodynamical Models: Integrate and Fire Neurons

Spiking Neuron -> Integrate-and-Fire Model:

\[ \tau_m \frac{d}{dt} V_i(t) = -g_m(V_i(t) - V_L) - I_{syn}(t) \]

Synaptic currents:

\[ I_{syn}(t) = I_{AMPA,ext}(t) + I_{AMPA,rec}(t) + I_{NMDA,rec}(t) + I_{GABA,rec}(t) \]

Synaptic dynamics:

\[ I_{AMPA,ext}(t) = g_{AMPA,ext}(V_i(t) - V_E) \sum_j w_{ij}s_{AMPA,ext}^j(t) \]

\[ \frac{d}{dt}s_{AMPA}^j(t) = -\frac{s_{AMPA}^j(t)}{\tau_{AMPA}} + \sum_k \delta(t - t_{k}^j) \]

\[ \ldots \]
Neurodynamical Models: Mean-Field (Brunel and Wang 2001)

\[
\tau_m \frac{d}{dt} V_i(t) = -(V_i(t) - V_L) - g_{syn}(V_i(t) - V_{syn}) \sum_j s^{syn}_j(t)
\]

\[
\sum_j s^{syn}_j(t) \rightarrow N\tau_{syn} v + \Delta S(t)
\]

\[
\tau \frac{d}{dt} V_i(t) = -(V_i(t) - V_L) - \mu(v) + \sigma(v) \sqrt{\tau} \eta(t)
\]

\[
v(t_0) = 1/\langle T \rangle \quad v = F(\mu(v), \sigma(v))
\]

Mean-Field (Poisson Spike-Train)

Ornstein-Uhlenbeck

First-Passage-Time

\[
F(\mu, \sigma) = (\tau_{refr} + \tau_m) \int_{\beta(\mu, \sigma)}^\alpha(\mu, \sigma) \sqrt{\pi} e^{x^2} (1 + \text{erf}(x))^{-1} dx
\]

Pool-Activity

\[
v(t) = \lim_{\Delta t \to 0} \frac{n_{spikes}(t, t + \Delta t)}{N\Delta t}
\]
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Given: Particular Features (Target Object)
Function: Scanning (Attentional Window Scans the Entire Scene)

Visual Search

Given: Particular Spatial Location (Target Position)
Function: Binding (Attentional Window Bind Features for Identification)

Object Recognition

Visual Attention: Motivation
What- and Where Systems of the Visual Cortex

(Haxby et al., 1994)
Biased Competition: Neurodynamical Model of Visual Attention

- **LGN**: "Where"
- **V1-V4**: "What"
- **PP**: "Where" (Spatial Location)
- **IT**: (Object Recognition)
- **IT Pool**: (Object Specific)
- **PP Pool**: (Location Specific)

**Network Diagram**:
- **LGN** to **V1-V4** (Feature Extraction)
- **V1-V4** to **IT** (Object Recognition)
- **IT** to **PP** (Spatial Location)
- **PP** to **IT** (Object Specific)
- **IT** to **LGN** (Location Specific)

**Inhibitory Pools**:
- **V1-V4**: Inhibitory Pool
- **IT**: Inhibitory Pool
- **PP**: Inhibitory Pool
- **LGN**: Inhibitory Pool

**Gabor Jets**

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Biased Competition: Results for Visual Search
Biased Competition: Results for Object Recognition

Spatial Location

Activity

IT
Target
Distractor

V1
Time

PP

Tower (Winner)

Octave 1
Octave 2
Octave 3

Top-Down Biased Location
Visual Neglect: Neurodynamical Modeling

Symptoms

Fixation Pattern of Neglect Patient

„Neglect“ Unknown Objects

saccades

Before Learning

IT

V1-V4

„Neglect“-Lesion (Increased Noise)

After Learning

IT

V1-V4

„Neglect“ Known Objects

Model Prediction: Object Teaching Improves Performance

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Visual Neglect: Prediction for Rehabilitation Strategy

Fixation Pattern for Simulated Neglect

(a) neglect

(b) top-down effect on neglect
Visual Neglect: Rehabilitation Success

Fixation Profiles of female Neglect Patient (Univ. Birmingham)
Modeling Human Cognition: Attentional Filtering

Cognitive Control

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- Emotion

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Attentional Filtering in Focused Attention Task

**Task:**
Saccade to first appearance of target (fish) in sequence of objects (fish, bear, hamburger) and cued side only!

**Measurements:**
Monkey Prefrontal Cortex

(Everling et al., Nat. Neurosci. 5:671 (2002))
Biased Cooperation-Competition (BCC) Model for Attentional Filtering

The four possible input-combinations for the bilateral task

**Target-bias:** from rule-memory, specifies identity of target

**Attentional bias:** from spatial working memory, specifies cued side
Conclusion:
- Competition and Cooperation together produce attentional filtering
- Attentional facilitation is mediated by cooperation
- Attentional suppression is mediated by competition
Modeling Human Cognition: Motor Planning under Conflict

- Long Term Memory
- Emotion
- Cognitive Control
- Conflict Evaluation
  - Motor Planning
  - Conflict Signalling
  - Error Signalling
- Biased Competition Networks
  - Design for Technical/Industrial Applications
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Saccade Planning under Conflict: Experiment and Model

Saccade countermanding task

Climbing activity in FEF determines saccade execution

Successful conflict handling (countermanding) is reflected by FEF neurons

(Hanes et al., J. Neurophysiol. 79:817 (1998))
Saccade Planning under Conflict: Preliminary Results

- A stop signal can interrupt the motor plan, depending on the timing
- Handling conflict can be understood as an emergent dynamic process

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- Inference of Genetic Predispositions

Metabolism
- Drug Discovery

Diagnosis
- Therapy Planning

Drug Screening

Human Brain

Neural Model
Genome and Proteome: A Regulatory Network

**Genome**
- About 30,000 Genes
- Cover 2-3% of DNA
- Same for most cells

**Proteome**
- Set of expressed proteins
- Subset of about $10^6$ proteins
- Differs between cells in a characteristic way

**Genetic Predisposition**

**Gene-Expression**

**DNA-Microarrays**

**Regulation**

**Networks**

**Genome and Proteome**: A Regulatory Network
Microarray Technology

Snapshot of gene expression in a cell monitoring thousands of genes simultaneously.

Basics
- Each spot contains DNA-fragments from a specific gene.
- cDNA can base-pair with DNA.

Protocol
- Extract mRNA from the cell.
- Use mRNA to produce cDNA.
- Label cDNA (red or green).
- Combine the red and green colored cDNA.
- Put mixed cDNA on DNA-chip.
- Some of the cDNA bounds to spots.
- Wash off unbounded cDNA.
- Scan the chip with a red and a green laser to detect bound cDNA.

\[ \log_2 \frac{Cy5}{Cy3} \]
Disease Markers from Gene-Expression

Aims:

- Data driven categorization of global gene-expression patterns
- On-the-fly prediction of disease characteristics
Example: ALL- Subtype Biomarkers from Gene-Expression

- Expression profile is a highly sensitive marker for disease
- Expression profile is a highly sensitive marker for disease subtype

ALL = Acute Lymphoblastic Leukaemia

Data:
St. Jude Hospital, Memphis

gene-expression profiles from 327 patients
Life Science Support by Genetic Network Simulation: Example

Genome
- About 30,000 Genes
- Cover 2-3% of DNA
- Same for most cells

Regulation

Expression

Proteome
- Set of expressed proteins
- Subset of about $10^6$ proteins
- Differs between cells in a characteristic way

Wrong action

Disease

Genetic Networks

Proteins

DNA

transcription

mRNA

translation

Expression

Wrong action

Disease
Gene Regulation and Genetic Networks

PTM = post-translational modification
RR = regulatory region
GeneSim™: Genetic Network Simulator

Aims:

• Understanding emergent systems-level properties of living cells
• Estimation and analysis of genetic regulatory networks
• Identification of drug targets
• Systematic control over genetic programs (tissue regeneration...)

Drug Targets
Disease Mechanisms
Genetic Programs
Life Models
Modelling regulatory mechanisms

A Bayes net can be used as to model of regulatory network of genes.

Each node represents a gene.

Edges describe causal relationships between two genes, e.g. regulatory mechanisms.

The type of regulation is encoded in the Conditional probability table.

Gene D influences gene E

Gene D acts as an activator on gene E

To get such a model we have to learn a Bayes net from microarray data.
GeneSim™: Network Learning and Exploration

Gene expression data set

Learning

(GENESIM)

Exploration

Genetic Network Learner
Genetic Network Explorer

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GeneSim™: Interventional Studies

- "no intervention"
- "activate gene 33355_at"
- "activate gene 38679_g"
- measured ALL data

(GENESIM)

Genetic Network Learner

Genetic Network Explorer

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Through chromosomal translocation PBX1 becomes an oncogene probably causing childhood ALL. It activates other genes that are either normally not expressed or expressed at low levels.

“gene 33355_at“ is the proto-oncogene PBX 1
### Monogenetic

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<th>Gene</th>
<th>Function</th>
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<td>37350_at</td>
<td>PSMD10</td>
<td>proteosome subunit, protein degradation</td>
</tr>
<tr>
<td>0.531</td>
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<td>HNRHP2</td>
<td>RNA-binding</td>
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<tr>
<td>0.432</td>
<td>38518_at</td>
<td>SCML2</td>
<td>embryogenesis, transcription factor</td>
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<td>38317_at</td>
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<td>0.378</td>
<td>36139_at</td>
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<td>energy generation</td>
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### Bi-genetic

<table>
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<th>Score</th>
<th>Gene 1</th>
<th>Gene 2</th>
<th>Function</th>
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<td>TGFB1</td>
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</tbody>
</table>
GeneSim™: Structure Analysis

Real ALL Data

Network Structure

Learning

Exploration

(GENESIM)

Genetic Network Learner

Genetic Network Explorer

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