Neuronal Communication Networks: Modeling & Simulation for Memory & Plasticity

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Acknowledgement to my team

Future perspective

- **Silicon technology era**
  - is coming to an end (2030-2040)

- **Molecular technology era**
  - is starting and will be dominating our lives for next 80 years (2010 – onwards)
Nanomachine?

- **Definition:**
  - A device consists of nano-scale components, able to perform a simple specific task at nano-level
    - communicating, computing, data storing, sensing and/or actuation

- **Features:**
  - Self-contained
  - Self-assembly
  - Self-replication
  - Locomotion
  - Able to communicate in a cooperative manner for more complex tasks

- **Applications:**
  - Health status monitoring, diagnostics, targeted treatments, etc.

- **Two categories of nanomachines**
  - Biological nanomachines (molecular machines)
  - Nanomaterial-based nanomachines
Design principles

- Ultra low power design
- Extremely small footprint
- Highly specific, accurate, and stable sensors
- Better energy scavenging with hibernation
- Flexible structure – bendable
- Bio-compatible

Nanomaterial Based Design

Bio-inspired Design
Biology: radically different

- Cells are nanoscale-precise biological machines
- They communicate and interact/cooperate

Eukaryotic Cell

Prokaryotic Cell

Eukaryotic Cell Tissue

Bacteria Population

Courtesy Prof. Ian Akyildiz
Cells as biological nanomachines

Nucleus and Ribosomes = Biological Memory And Processor
Mitochondria = Biological Battery
Chemical receptors = Biological Sensors/Molecular
Gap Junctions = Molecular Transmitters

Courtesy Prof. Ian Akyildiz
One gram of DNA can store 700 terabytes of data. That’s 14,000 50-gigabyte Blu-ray discs! Can last for some 50 years.

Grand Challenge

- EU - Human Brain Flagship Project, 2012-2022
- USA - Brain Research through Advancing Innovative Neurotechnologies (BRAIN), 2013-2023

$1bn
Next generation of systems neuroengineering

- Neural recordings and stimulation: much smaller, denser, longer-lasting
- Optogenetic/EM stimulation: arbitrary spatio-temporal, cell-type specific lighting
- Optical imaging: improved calcium and voltage indicators, combined with primate’s behavior and emotion
- Wireless bi-directional communication: much smaller, lower power, fully implantable, lasting for 10 years
- Anatomical information: need to know neurons and connections of neurons resynchronization/stimulation
- New modeling: more than just a “big data”/machine learning problem
  - Need new theoretical computational, data analytical approaches
    - E.g., dynamical systems, dimensionality reduction, network models
  - Need a new decode algorithms embracing motor, control, and learning theory
    - E.g., combining decoder design, decoder adaption, and neuron adaptation

- Notes from IEEE EMBC, BRAIN Workshop, Aug. 2014 -
Brain Machine Interface

<table>
<thead>
<tr>
<th>Application</th>
<th>Data rate</th>
<th>Power Consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG (12 leads)</td>
<td>288 kbps</td>
<td>Low</td>
</tr>
<tr>
<td>ECG (6 leads)</td>
<td>71 kbps</td>
<td>Low</td>
</tr>
<tr>
<td>Glucose monitoring</td>
<td>1600 bps</td>
<td>Very Low</td>
</tr>
<tr>
<td>SpO2</td>
<td>32 bps</td>
<td>Low</td>
</tr>
<tr>
<td>WCE</td>
<td>&gt;2 Mbps</td>
<td>Low</td>
</tr>
<tr>
<td>WCE with VGA (640 × 480 p, 24 bits, 30 fps)</td>
<td>210.9 Mbps</td>
<td>Low</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>10 bps</td>
<td>High</td>
</tr>
<tr>
<td>Audio</td>
<td>1.4 Mbps</td>
<td>High</td>
</tr>
<tr>
<td>EMG</td>
<td>320 kbps</td>
<td>Low</td>
</tr>
<tr>
<td>EEG</td>
<td>43.2 kbps</td>
<td>Low</td>
</tr>
<tr>
<td>Neural monitoring (512 sensors)</td>
<td>430 Mbps</td>
<td>Low</td>
</tr>
</tbody>
</table>

RF interface:
MICS band: 403-405 MHz, 431 MHz
ISM: 3.1 – 4.8 GHz (IR-UWB)

Brain in the loop

Is RF communication a viable technique for brain communication networks?
Brain/Neuron

- Hippocampus: Plays important role in consolidation of information from short-term to long-term memory. Often the first region attacked by Alzheimer's.
- Around $10 \times 10^9$ neurons make out the cerebral cortex with a possibility of $100 \times 10^{12}$ connections.
- The network is sparse, i.e. a connectivity factor of $10^{-6}$ out of total number of possibilities.
Communication system

Nobel Prize 2013

James Rothman: a set of genes for vesicle traffic

Randy Schekman: protein machinery to fuse vesicles with their targets to enable communications

Thomas Südhof: signals instruct vesicles to release their cargo with precision and timing

Disturbances in this system will result to conditions such as neurological diseases, diabetes, and immunological disorders
Typical circuit model – static

- Stochastic nature
- Dynamics
Equivalent Stochastic Model

Neuron-to-Neuron Communication Model

[Diagram showing the process of signal transmission from one neuron to another, including steps such as action potential stimulation, propagation, and reception, along with components like soma, axon hillock, ion channels, neurotransmitters, and noise sources.]
Communication Network Model
**Neuron**: soma, dendritic tree, axon.

**Astrocytes**: surroundings of the neuronal environment are supposed to play an active role in the neuronal communication.

**Tripartite synapse**: pre-synaptic neuron, post-synaptic neuron, astrocyte. Communication by means of glutamate neurotransmitter and AMPA/NMDA receptors.

Indirect Stimulation via astrocytic calcium wave

- Propagation of $[Ca^{2+}]$/inositol,4,5-triphosphate (IP$_3$) through gap junctions (calcium wave)
- Astrocytic glutamate neuroTTX release in the tripartite synapse
- Slow inward current (SIC) and miniature PSC in neurons
- AMPA/NMDA receptors on the post-synaptic side may be affected by the increased glutamate concentration (plasticity, LTP/LTD)

Optogenetic stimulation recalls fear memory

Targeting hippocampal neurons with sparse electric signals delivered by an optical cable
EM/rodents experimental results

- Motivation: experiments performed by Arendash's team (ADRC-Univ. of South Florida) where transgenic mice were exposed to CDMA mobile phone radiations.

- **Experiment:**
  - CDMA system: 918 MHz, pulse transmission, TX antenna in the middle of a 4x4x4 m³ cage (whole body exposure), control/transgenic Alzheimer’s disease (AD) mice

- **Results:**
  - After 8 months of controlled exposure, AD mice experienced a beta-amyloid reduction (believed to be one of the main responsible for AD). Improved cognitive behavior.
  - No temperature increase (thermal effects are neglected)

Hypotheses

1. Reduced synthesis of the neurotransmitter acetylcholine.
2. Beta amyloid deposits, forming plaques, which disrupt neural cell structure.
3. Non-plaque type oligomers, bind to surface of neural receptors, causing disruption of synapse.
4. N-APP binds to the death receptor DR6, forming self-destructive pathway.
5. Coating of the axon – myelin breakdown.
Stimulate neurons

- Invasive: injecting electric current inside the neuron using electrodes
- Non-invasive: EM exposure on the skull to excite a large region of neurons
- Nanomachine-to-neuron interface

- Can the biological system act like demodulator of a radio signal?
  - carrier frequency, modulation frequency, signal shape/spectrum, power levels, non linear dynamics due to plasma effects, etc.

- Is it possible to have non-thermal effect only?
  - Compensation due to blood brain barrier, ELF effects on dielectric constants modifications in neuronal cell, etc.

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Communication scenario: the neuronal cell can be considered part of a transmission system where the information is represented with *Action Potential* (AP) patterns propagating in the neuronal network.

In order to simplify the analysis, it is possible to consider local radiation in a single volume of tissue (*Voxel – volumetric pixel*).
EM simulations on HUGO model

HUGO – a digital human model, where each tissue has been labelled with dielectric constants

White matter – nerve fibers; gray matter - tissues

Induced current

$E=10\text{V/m}$

$E=100\text{V/m}$

Each presynaptic signal in the postsynaptic membrane, called postsynaptic potential (PSP):

Positive variation: depolarized membrane, Excitatory PSP (EPSP)

Negative variation: hyperpolarized membrane, Inhibitory PSP (IPSP).

Sum of EPSPs and IPSPs above threshold a postsynaptic spike is generated.

Synaptic Nanomachine shall give activation of postsynaptic ion channels in the target cells, evoking multiple PSPs to drive the output potential!
**Synaptic Nanomachine**

**Gap junctions:** two cellular membranes in direct contact are separated by 3 nm and for each side, clusters of connexine (Cx36) proteins combine to form a channel with diameter 1-2 nm, the connexone, allowing bidirectional flows of ions between cells.

- Synthetic connexines assembled in-situ by SnMs could allow the opening of additional ion channels enhancing the neuronal activity.

- This method is motivated by neuroscientific studies reporting the important role of **gap junctions** in oscillatory behaviors and synchronization phenomena between neurons.

Mesiti and Balasingham. Nanomachine-to-Neuron Communication Interfaces for Neuronal Stimulation at Nanoscale. In the IEEE Journal on Selected Areas in Communications (JSAC) - Special Issue on Emerging Technologies in Communications. 2013;31(12):695--705

Neuron size: 4-100 μm (1 μm = 10^{-6} m)
Equivalent Neuron-Nanomachine Interface

Each individual post synaptic potential contribution \( \omega_{ij} \epsilon_{ij}(t-t_j) \) to one SnM, activated in \( t = t_j \). Obtain the Equivalent Neuron-Nanomachine scheme (EqNN). Describes the input/output function between nanomachine inputs and output signal of the specific target neuron:

Mesiti and Balasingham. Nanomachine-to-Neuron Communication Interfaces for Neuronal Stimulation at Nanoscale. In the IEEE Journal on Selected Areas in Communications (JSAC) - Special Issue on Emerging Technologies in Communications. 2013;31(12):695--705
Scenario 1: Stimulation of Excitatory Neurons

- Neuronal (population) response
- 100 Excitatory (E) neurons
- 25 Inhibitory (I) neurons
- 10 SnMs stimulating 30 (E)-neurons with activation rate $R_a=20$ Hz

In some neurons, both (E) and (I), are synchronized with the stimulus impulse (red inputs) regulated by the nanomachines connected to the target neurons.

Mesiti and Balasingham. Nanomachine-to-Neuron Communication Interfaces for Neuronal Stimulation at Nanoscale. In the IEEE Journal on Selected Areas in Communications (JSAC) - Special Issue on Emerging Technologies in Communications. 2013;31(12):695--705
End-to-end Stochastic Model

Planned physical experiments

Wideband Vivaldi antenna (300 – 4400 MHz)

USRP2 – GNU radio platform
<table>
<thead>
<tr>
<th>Layer</th>
<th>Entity</th>
<th>Description and Research Areas</th>
<th>Research Fields</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRANSMISSION</strong></td>
<td>RF source</td>
<td>Signal characteristics (Transmission power, Modulation, Frequency)</td>
<td>• Communications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Electromagnetism</td>
</tr>
<tr>
<td><strong>FILTERING</strong></td>
<td>Skull/Body Barrier</td>
<td>Resistivity and capacitance of the skull and body mass</td>
<td>• Electromagnetism</td>
</tr>
<tr>
<td><strong>PROCESSING</strong></td>
<td>RF Induced Currents</td>
<td>Identification of current and voltage induced by residual EM fields after skull filtering</td>
<td>• Electromagnetism</td>
</tr>
<tr>
<td></td>
<td>Neuron</td>
<td>Membrane potential interactions with RF currents</td>
<td>• Chemical processes</td>
</tr>
<tr>
<td></td>
<td>Action Potential Firing</td>
<td>Combined RF-spiking neuron modeling. Spike trains characterization with RF signal parameters</td>
<td>• Information Theory</td>
</tr>
<tr>
<td></td>
<td>AP Transmission</td>
<td>Electrochemical transmission along axons and dendrites. Information capacity of communication paths</td>
<td>• Neuron modeling</td>
</tr>
<tr>
<td><strong>NETWORKING</strong></td>
<td>Neuronal Network</td>
<td>Small-world network, neuronal connectivity, synchronization</td>
<td>• Statistical Mechanics</td>
</tr>
<tr>
<td></td>
<td>Network Paths</td>
<td>Reconstruction of pruned paths after brain disease. Enhance the neuronal activity between missing path. Disruption of β-amyloid plaques in Alzheimer's.</td>
<td>• Graph Theory</td>
</tr>
<tr>
<td><strong>EFFECTS</strong></td>
<td>Structural alterations</td>
<td>Improved neuronal activity. Connections between neurons, Small-world network characteristics (PL, Clustering)</td>
<td>• Neuroscience</td>
</tr>
<tr>
<td></td>
<td>Cognitive and Behaviour</td>
<td>Functional alterations related to neuronal network structure. Expected improvement in cognitive tasks, usually impaired in neurodegenerative diseases, Expected improvement in short term memory, Visual, spatial and numeric memory alterations.</td>
<td>• Psychology</td>
</tr>
</tbody>
</table>
New research topics, conf’s. & j’s.

i. Nano-Electromagnetic (EM) communications
ii. Graphene based nano-antennas
iii. EM channels in terahertz
iv. Plasmonic/quantum communications
v. Molecular communications
vi. Information theory for nano communications
vii. Protocols and architectures
viii. Nano computing
ix. Nano/molecular electronics
x. Internet of nano things
xi. Middleware design for nanonetworks
xii. Security for nano communication networks

ACM NANOCOM 2014 Call For Papers

The 1st International Summer School on Nanocommunications

May 21 – 25, 2013
Tampere, Finland

IEEE Transactions on NanoBioscience
Cross and multidisciplinary collaboration needed to solve difficult problems that will have huge societal impact. Innovation opportunity to valorize the technologies.

“I think the biggest innovations of the 21st century will be at the intersection of biology and technology. A new era is beginning.” Steve Jobs