Radio Frequency (RF) Technology for Applications in Neuronal Degenerative Diseases

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Introduction and motivations/1

- Existing wireless communication devices are a continuous source of low-power radio frequency (RF) signals in the microwave (MW) and extremely/super-low (ELF-SLF) frequency domains.

- Cellular and cordless phones, WLAN transceivers and Ultra-Wide Band (UWB) are experiencing an enormous increase in the everyday life for communication and sensoring.

- High power electromagnetic devices in the MW domain are of common use in radar systems and medical diagnoses and therapy.

**Matter of fact:** Typical users and clinical operators expose the whole body or parts of it (hands, arms, brain) to continuous RF radiations without knowledge on the possible negative biological effects.

**Question:** Only negative effects? What about positive effects?
Introduction and motivations/2

• Microwave RF exposure can induce two main categories of biological effects:
  - **Thermal**: possible cellular alterations induced by acute MW radiation heating with temperature increase [*well investigated*]
  - **Non-thermal**: negligible temperature increase and possible long-term effects [*discordant experimental results*]

• In recent experiments on transgenic mice, evidences of possible positive (therapeutic) effects on neuronal diseases have been noticed

• The interaction mechanisms between RF and living cells are still unknown (non homogeneous experiments, long term observations, high complexity of living systems)

• **Final aim**: understand how (and “if”) a **controlled** microwave exposure can be employed to enhance the neuronal activity, particularly when brain connections are damaged by neuronal diseases (i.e., Alzheimer)
RF exposure: non-thermal biological effects

- Non-thermal effects are characterized by negligible temperature increase in the living tissue and possible long-term effects after chronic exposure.

- Some examples:
  - **Biological demodulation**: the brain activity appears to be particularly sensitive to low-frequency (30-300 Hz) modulated signals. Possible "frequency resonance" effects.
  - **Brain electroencephalography (EEG) alterations** in alpha (8-13 Hz) and beta (13-30 Hz) rhythms after ELF-modulated MW exposure
  - **Blood-barrier permeability** is altered after pulse-modulated microwave exposure
  - **Circularly polarized MW** may influence, in different ways, the DNA repair mechanism in *E. coli* cells
  - **Increased cognitive processes** (speed and memory) after short duration MW exposure (30 min, GSM/CDMA). Strongly subject-dependent results.
RF therapy for Alzheimer's disease

- Finding novel methods to employ RF exposure in therapeutical application was highly motivated by recent experiments performed by Arendash's team [Ar2010] (Univ. of South Florida) where transgenic mice were exposed to CDMA mobile phone radiations.

- Short overview of possible Alzheimer causes:
  - Reduced synthesis of *acetylcholine* neurotransmitters
  - Deposit of *beta-amyloid plaques* on the neuronal cell
  - Synapses disruption caused by *oligomers binding*
  - *N-APP*\(^1\) *binding* to death receptor DR6\(^2\) forming self-destructive paths
  - *Axon coating*
  - *Tau protein* fuses and clumps causing death of neurons

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1) N-APP: N-terminal fragment of amyloid precursor protein
2) DR6: Death Cell Receptor 6

RF therapy for Alzheimer's disease

The initial hypothesis of Arendash et al. was to show that cellphone exposure is harmful for the brain and the nervous system.

**Experiment:**
- RF source: CDMA system operating at 918 MHz, Specific Absorption Rate (SAR) of 0.25 W/Kg
- TX antenna in the middle of a 4x4x4 m³ cage
- Control mice, transgenic Alzheimer Disease (AD) mice

**Results:**
- AD mice improved their cognitive behaviour
- After 8 month controlled exposure, both AD and control mice experienced a beta-amyloid reduction (believed to be one of the main responsible for AD)
- No temperature increase (thermal effects are neglected)
RF therapy for Alzheimer's disease

• Behavioural results are, however, subject to the selected population, possible non-homogeneous exposure conditions

• Experiments revealed a possible positive interaction between pulse modulated RF signal of typical CDMA mobile phone and biological effects on AD impaired mice

• Results are twofold:
  – mobile phones improve certain cognitive task and memory
  – GMS/CDMA based technology could provide novel therapeutical tools

However the hidden mechanisms remain undisclosed and unknown
RF signals: GSM/CDMA

- GSM and CDMA/UMTS based signals can be considered ubiquitous in human life and many concerns arose about their interaction with living organisms

**GSM technical characteristics:**

- Operating frequency: 900 – 1800 MHz (GMSK modulation)
- TDMA access (Time division multiple access): each device transmits during time slots of 0.577 ms within a 8-slot window (4.615 ms, duty cycle 1:8)

- Low-frequency components generated at 217 Hz (1 / 4.615 ms)

[Apollonio, D'Inzeo et al.2000]
RF signals: GSM/CDMA

• Similarly, 3G W-CDMA/UMTS devices employ Time Division Duplex and Frequency Division Duplex access (FDD, TDD) techniques

**W-CDMA (Wideband Code Division Multiple Access)**

- 1920 MHz - 1980 Mhz (uplink FDD)
- 2110 MHz - 2170 Mhz (downlink FDD)

• Low-frequency components could be generated:
  - 1500 Hz component for power control in FDD (fast power control tends to compensate for the channel variations due to movement)
  - 100 Hz component for TDD (similarly to GSM)

2G/3G operate with microwaves signals and low-frequency components

- Thermal and non-thermal biological effects are expected
Wireless communication transmission can be characterized by suitable parametric mathematical models. In order to unveil the interactions with external RF stimuli, a theoretical model of the neuronal cell is needed as well.

Neuron structure and synapse:
Neurons modeling

• Neuronal messages are transmitted by means of the **Action Potential (AP)** firing mechanism originated in the soma by a sudden change in the electric characteristics of the neuronal cell membrane.

  (1) Membrane potential $V$ increases from the equilibrium potential (-65 mV)

  (2) The potential reaches a threshold, the AP is fired along the axon

  (3) Potential reset

• **Inter Spike Interval (ISI)** depends on the Aps coming from other neurons and on external stimuli (several AP generation mechanisms are still unknown)
The spiking neuronal cell can be represented with a *passive* equivalent electronic circuit [Da2001]:

Basically, the cell membrane potential $V$ is regulated by the concentration of $K^+$ and $Na^+$ ions.

Capacity $C_m$ and resistance $R_m$ characterize the membrane.

The input current $I_e$ interacts with the potential, altering the equilibrium.

The (passive)-Integrate-and-Fire model is based on this representation and provide a simple model to evaluate the potential dynamics:

$$\tau_m \frac{dV}{dt} = E_L - V + \frac{I_e}{A}$$

$\tau_m = C_m R_m$ is the time constant characterizing the dynamic of the current on the membrane surface.

$E_L$ is the equilibrium potential.

Neurons modeling

- More detailed model have been proposed in the past. One of the most popular is the *Hodgking-Huxley* model (1952), where a combination of ionic currents are taken into account in the total membrane current

\[
    i_m = i_K + i_{Na} + i_L = n^4 g_K (V - E_K) + m^3 h g_{Na} (V - E_{Na}) + g_L (V - E_L)
\]  

(Membrane total current)

\[
    \frac{C_m}{A} \frac{dV}{dt} = -i_m + \frac{I_e}{A}
\]  

(Membrane potential dynamic)

\(g_j\) are the conductances for a given ion (K\(^+\), Na\(^+\), L = leakage)

\(E_j\) are the equilibrium potentials \(n,m,h\) are parameters (gating variables regulated by differential equations)
Neurons modeling and RF stimuli: observations

• Existing neuron model should include somehow a further current component induced by the external electromagnetic stimuli, e.g., $i_{RF}$

• Any change in the input and membrane current could induce a deviation from the normal behavior of the membrane potential.

Inter spike interval (ISI) depends on the input current

The **firing rate** is the number of spikes in the unit of time: $1/\text{ISI}$

• The modulation of the firing rate is one of the possible biological method to encode information. Any alteration could compromise the correct neuronal behaviour
Neurons modeling and RF stimuli: research

- $x_i$: synaptic output or AP’s from neuron $i$.
- $f_i(x_i)$: synapical propagation
- $g(z)$: Pulse frequency modulation (firing mechanism) with threshold
- Research: Find correct model and determine the effect of electromagnetic fields on ion gates and neurotransmitters → include this in the model
In the recent past, Apollonio et al. [Ap2000] proposed an integrated model to evaluate the effects of EM fields used for mobile communications under a reductionist approach (the system is divided in structural and functional levels).

Each Macro Markov Model exemplifies a single neuron response to EM field by using the Hodgkin-Huxley model. Ca⁺, K⁺ and Na⁺ ionic channels are modeled with a 2 (3 for Ca⁺) stages Markov chain representing the open/close channel events.

APs propagate along an equivalent circuital model of the axon. The EM field is considered as an additive perturbation of the membrane potential.

Neuronal information coding

• Inter spike interarrivals can be described by a stochastic process, e.g., a renewal Poisson process.

• In a similar way to classical communication channels, it is possible to represent the spike train with a binary sequence $B_s(t)$ ($1 =$ spike, $0 =$ no-spike) whose entropy in a given temporal window $T_s$ is:

$$H(B_s) = -\frac{1}{T_s} \sum_{B_s} P\{B_s(t)\} \log_2 P\{B_s(t)\}$$

*Example:* Entropy of H1 spiking neurons in the fly visual system = 157 bit/s

• [Ce2010] evaluated the maximal amount of information for N spiking neurons observed in $[0, T]$:

$$N \frac{T}{r} \log_2 \left( \frac{T}{\delta t} \right) \text{bits}$$

$r$: refractory period

$\delta t$: temporal slot

Neuronal networks

- Neuronal cell in the brain are connected one another, forming a neural network. Recent studies observed that small independent clusters of neurons are linked and synchronized with other clusters.

- *fMRI analysis with threshold demonstrated the Small-World Network* properties of synchronizing neural activity between different brain regions.

- Clustering coefficient and Path-Length characterize the network:
  - $C$: likelihood that neighbours of a vertex are connected
  - $L$: average of the shortest distance between pairs of vertices
Small-world networks in Alzheimer's disease

- Stam et al. [Stam2007] investigated the abnormal functional brain organization in AD patients.
- The brain network graph was retrieved applying a threshold to the *synchronization likelihood* matrix determined from filtered EEG.
- C coefficient and PL computed for different threshold.
- **Result**: AD patients showed no significant changes in C whereas PL was longer than control patients.
- Loss of complexity and less optimal organization of the brain.

The main idea

- Understanding the mechanisms behind the interactions between RF signals and neuronal cell and biological effects
- Design of suitable RF therapy instruments
- Controlled RF exposure of patients affected by neuronal diseases (AD)
- A positive reaction in the neurons spiking mechanism could force the Action Potential emission, enabling the construction of new neuronal paths which will replace the missing paths
- Controlled RF exposure could also disrupt the beta-amyloid plaques responsible of AD disease, restoring the existing (and not working) synaptic connections
Proposed research framework

The proposed framework can be arranged as follows:

1) Introduce an improved mathematical *parametric* model for single neurons under (modulated) realistic RF signal exposure

2) Analyze the theoretical mechanisms for different signal characteristics: frequency, transmitting power, modulation type

3) Incorporate the single neuron model into the brain network

4) Investigate the interactions between input RF signal and network alterations (e.g., clustering, path-length, mutual information)

5) Experimental set up to verify the proposed theoretical assumption and results with real scenarios (experiments on transgenic mice and possible human volunteers)
Conclusions

- Experimental evidences on positive biological effects induced by RF exposure (anatomy, biology/medicine, network theory, information theory and signal processing)
- An integrated and layered mathematical model of the neuronal processes and the small-world brain network for the investigation of hidden mechanisms under several scenarios
- Modeling anatomical networks (adjacency matrix-axons) and functional connectivity (covariance matrix-deviation from independence)
- Our main aim is to provide a small contribution to understand if particular signal characteristics can induce positive alteration in the brain behavior
- This would pave the way to future investigation in the development of novel non-invasive treatment of neuronal diseases as Alzheimer's, based on controlled RF exposure of the damaged area of the brain
Thank you.

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