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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 <u>or parts of it</u> (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 <u>positive (therapeutic) effects</u> 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 <u>controlled</u> 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.

- 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

1) N-APP: N-terminal fragment of amyloid precursor protein

2) DR6: Death Cell Receptor 6

[Ar2010] – G.W. Arendash et al. *"Electromagnetic Field Treatment Protects Against and Reverse Cognitive Impairment in Alzheimer's Disease Mice"* - Journal of Alzheimer's Disease Vol. 19 - 2010

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 m^3 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

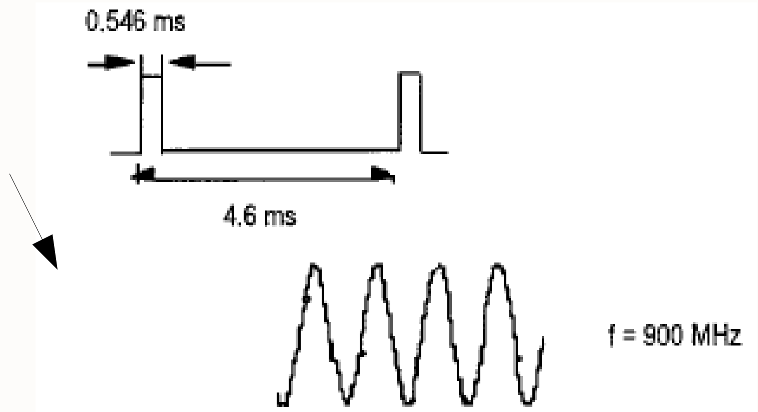
RF signals: GSM/CDMA

- 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]

- 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)

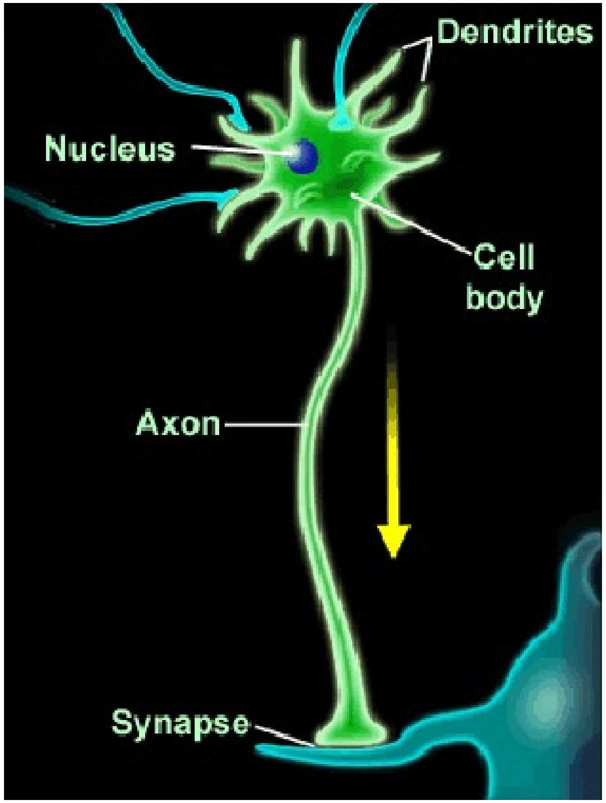
- Low-frequency components could be generated:
  - 1500 Hz component for power control in FDD (fast power control tends to compensate for the channel variations due to movement)
  - 100 Hz component for TDD (similarly to GSM)

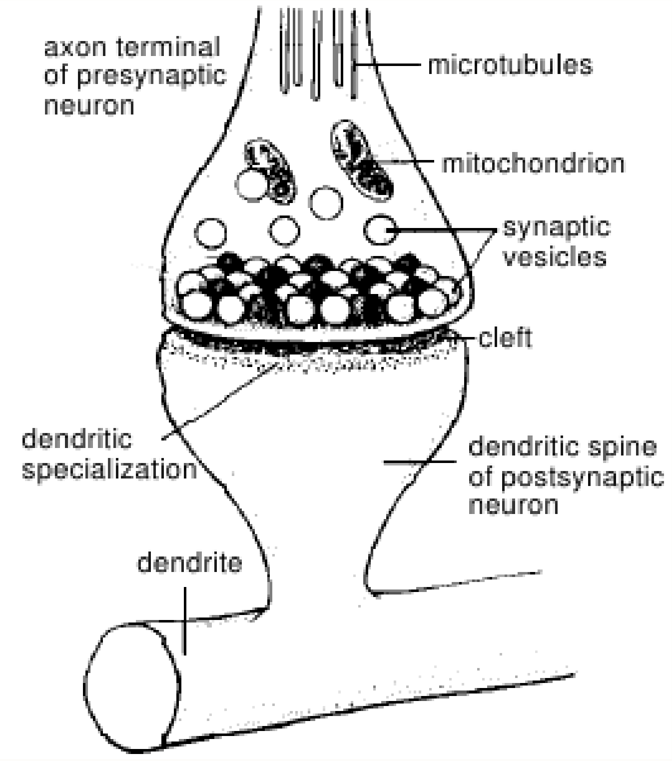
2G/3G operate with microwaves signals and low-frequency components

  - 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.

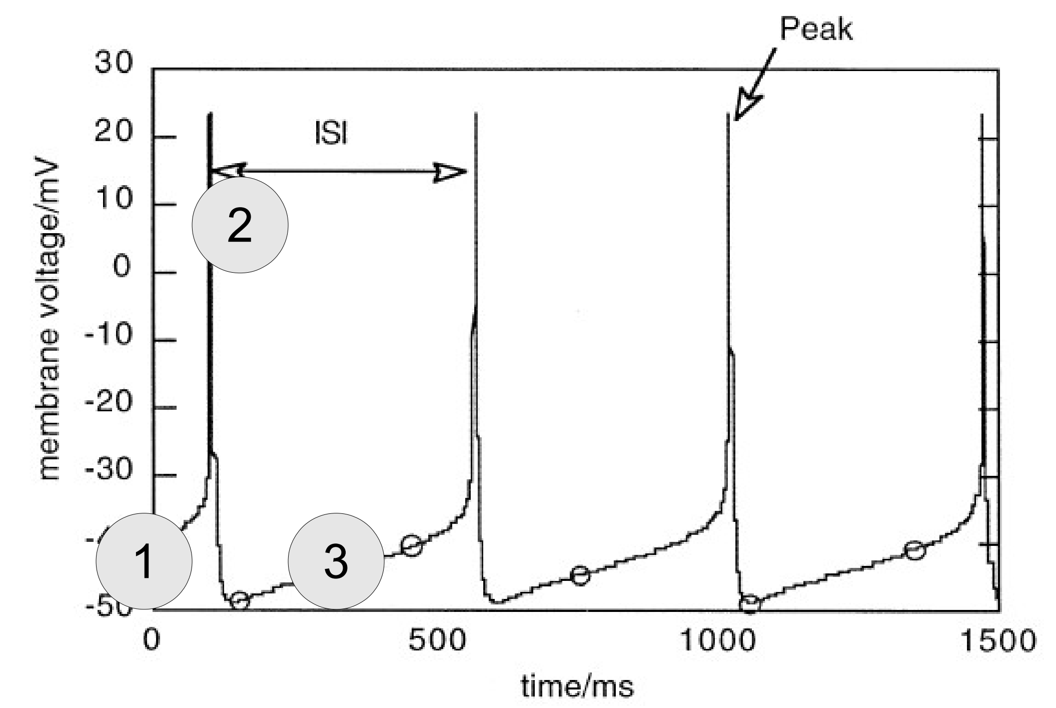
- Neuron structure and synapse:





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.



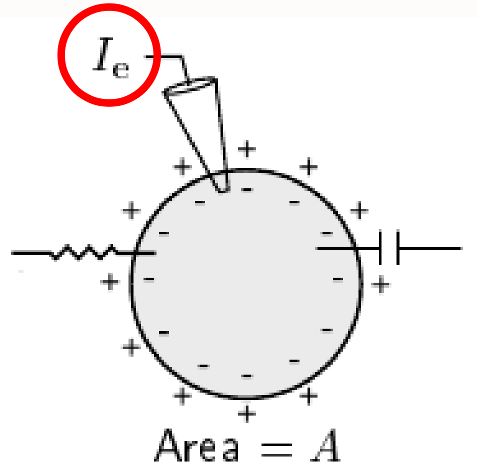
(1) Membrane potential V increases from the equilibrium potential (-65 mV)

(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 $\mathbf{K^+}$ and $\mathbf{Na^+}$ ions

Capacity $\boldsymbol{C_m}$ and resistance $\boldsymbol{R_m}$ characterize the membrane

The input current ***Ie*** 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

[Da2001] – Dayan, Abbot - "*Theoretical Neuroscience*" - The MIT Press - 1st Edition 2001

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

$$\begin{aligned} i_m &= i_{\mathrm{K}} + i_{\mathrm{Na}} + i_L \\ &= n^4 \, g_{\mathrm{K}} \, (V - E_{\mathrm{K}}) + m^3 \, h \, g_{\mathrm{Na}} \, (V - E_{\mathrm{Na}}) + \\ & \quad + g_L \, (V - E_L) \end{aligned}$$

(Membrane total current)

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

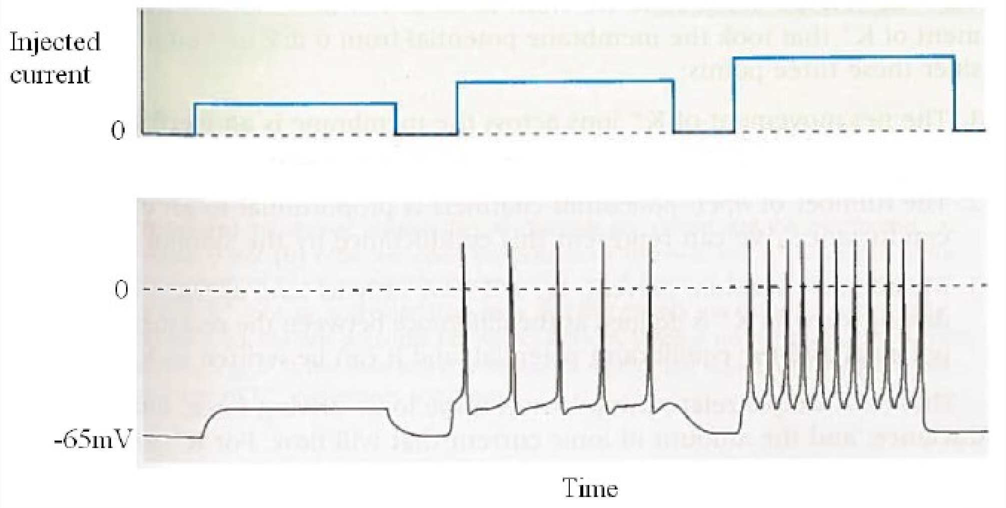
(Membrane potential dynamic)

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.

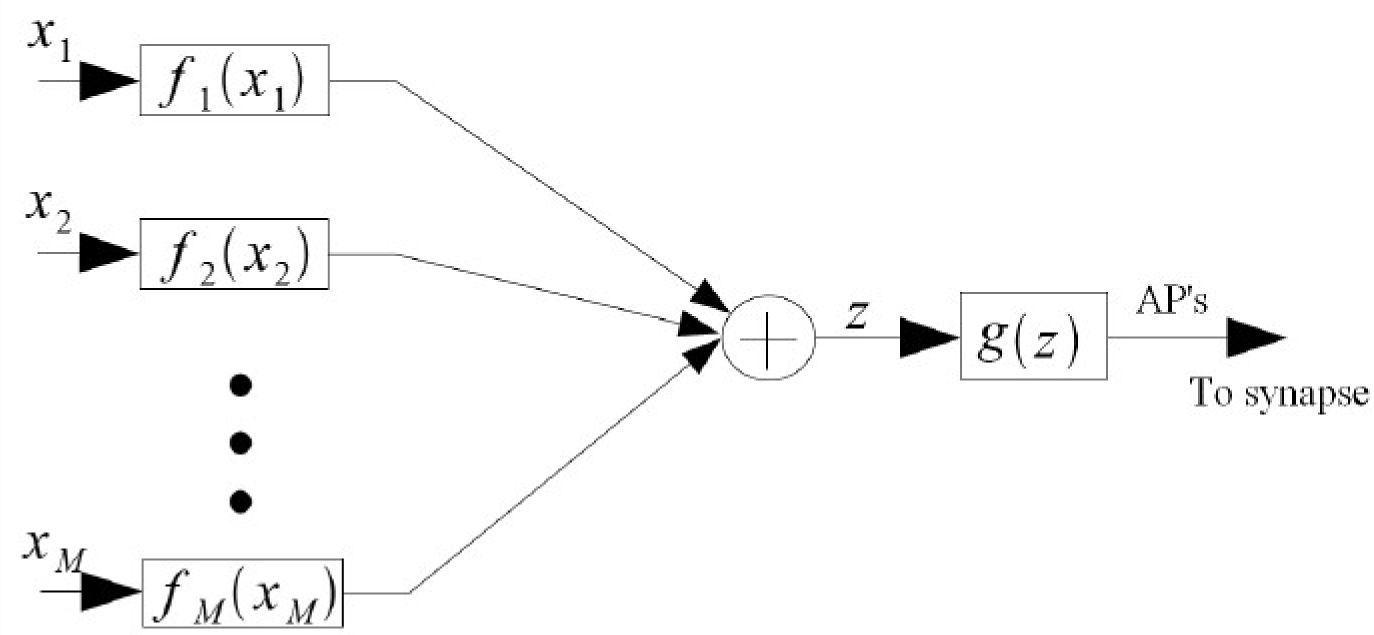


Inter spike interval (ISI) depends on the input current

The ***firing rate*** is the number of spikes in the unit of time: 1/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

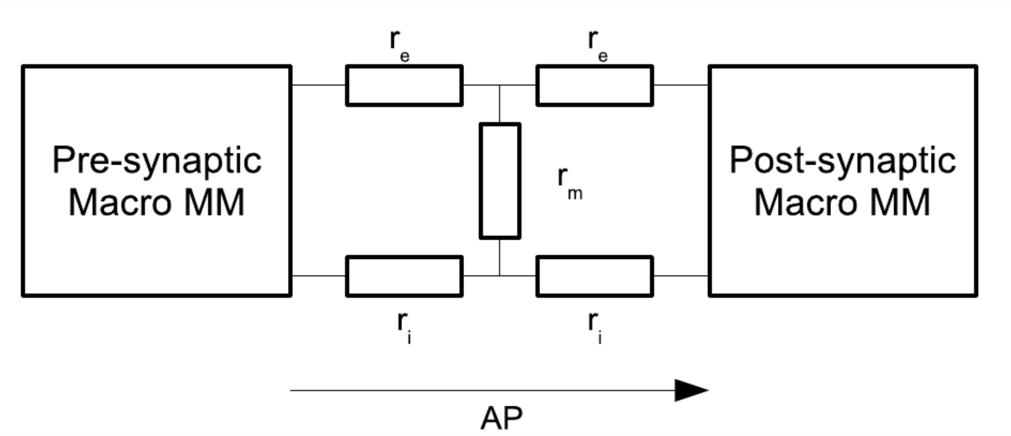
Neurons modeling and RF stimuli: research



- x_i: synaptic output or AP's from neuron i.
- $f_i(x_i)$: synaptical 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

Integrated neurons and EM field 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)



APs propagate along an equivalent circuital model of the axon

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

The EM field is considered as an additive perturbation of the membrane potential

[Ap2000] – Apollonio et al. - “*Integrated Model for the Analysis of Biological Effects of EM Fields Used for Mobile Communications*” - IEEE Trans. on Microwave Theory and Techniques – Vol.48, No.11, November 2000

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]:

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

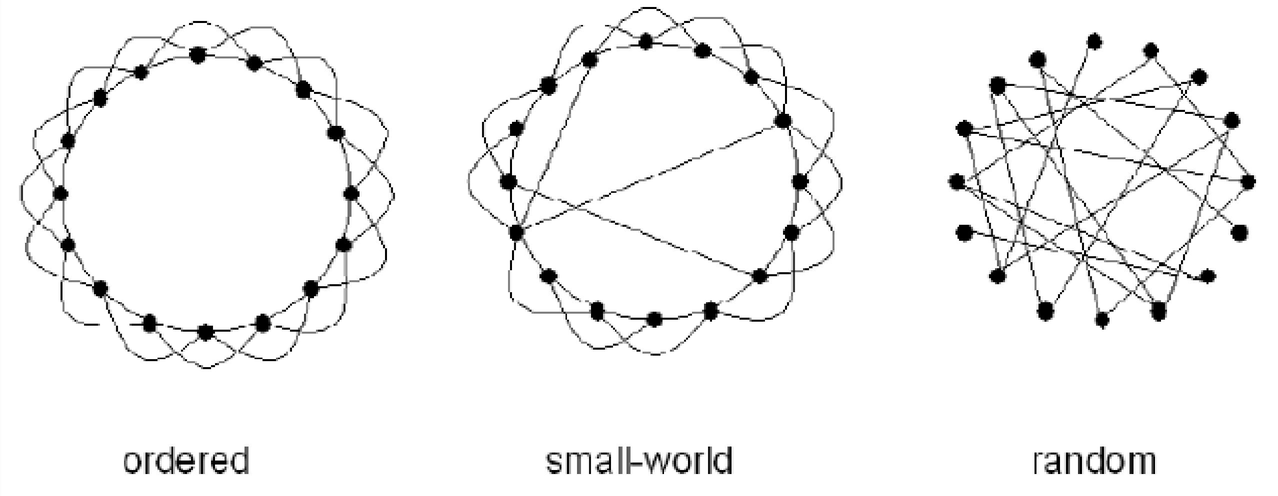
r: refractory period
δt: temporal slot

[Ce2010] – Cessac et al. - "*Overview of facts and issues about neural coding by spikes*" - Journal of Physiology – Paris 104, 2010

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

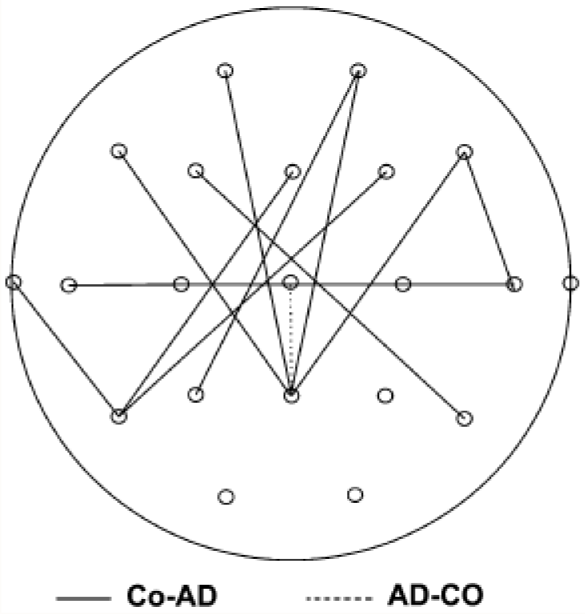
- *fMRI analysis with threshold demonstrated the Small-World* Network properties of synchronizing neural activity between different brain regions



- 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



[Stam2007] – Stam et al. - “Small-World Networks and Functional Connectivity in Alzheimer's Disease” - Cerebral Cortex – No. 17, January 2007

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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