Seminario Effediesse 2019: Interazione fra neuroscienze e matematica: analisi della connettività cerebrale utilizzando i grafi.

Paolo Finotelli

Department of Mathematics
Politecnico di Milano

paolo.finotelli@polimi.it

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Overview

My research description

- My research interests lie in the field of connectomics in health and disease, with particular focus on the physical and topological changes of the functional connectivity.
- In particular, I am interested in understanding how the changes in topological and physical properties of the complex brain networks, could lead to model neurological diseases and, possibly, to forecast their onset.
- My approach involves network analysis tools (e.g. thresholding, clustering, modularity, networks comparison), mathematics and data recorded with M/EEG and fMRI.
- The aim is to detect individual differences in brain networks across healthy populations as well as in patients affected by brain injuries and diseases.

From Gray's Anatomy, Standring S., Chapter 2, 39^{th} edition, Elsevier Ltd. 2005

"The human nervous system is the most complex product of biological evolution. The constantly changing pattens of activity of its billions of interactive units represent the fundamental physics basis of every aspect of human behaviour and experience...However, our understanding of complex neural organization and function is quite rudimental, as is our ability to deal with its many pathologies. Multidisciplinary research into the nervous system is one of the most active areas of contemporary biology and medicine and rapid advances across a range of fronts bring with them the realistic prospect of better methods for prevention and treatment of many neurological diseases in the future."

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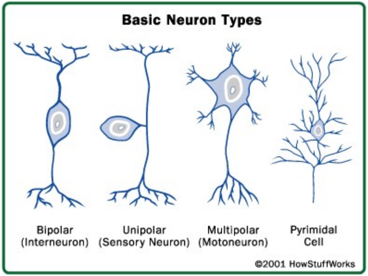
My vision about complexity in Neuroscience

There are two kinds of complexity depending on the working domain:

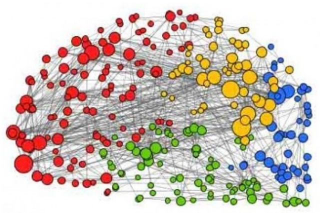
In Clinical Neuroscience

The neurons are complex cells since they are functionally and anatomically different.



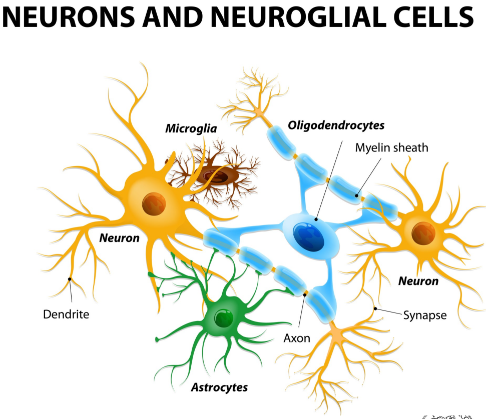
In Computational Neuroscience

According to Simon (The Sciences of the Artificial, 1981) complex systems as those that are "made up of a large number of parts that have many interactions", e.g. the brain!



The most important players in our brain

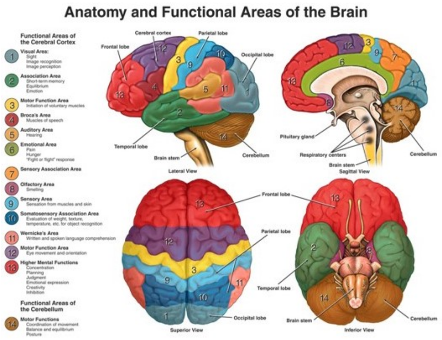
1. The human brain contains at least 90 billion neurons (nerve cells).
2. Each neuron interacts with about 10^3 other neurons at junctions called synapses.
3. Messages are sent to other neurons via axons as electrical spikes (nerve impulses). Each impulse is about 0.1 volt and lasts 1-2 msec (up to 480 kph!).
4. Glial cells help neurons wire together, nurture them, mop up dead cells, recycle used neurotransmitters, protect the brain from infection, etc.



The cerebral lobes

The cerebral cortex is divided into two connected hemispheres, which are subdivided into the occipital, the temporal, the parietal, and the frontal lobes.

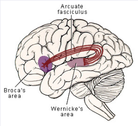
1. The occipital lobe is the brain region responsible for processing and interpreting visual information.
2. The temporal lobe is a major processing center for language and memory.
3. The parietal lobe houses the somatosensory cortex and plays an important role in touch and spatial navigation.
4. The frontal lobe is the seat of reasoning, decision-making, integration of sensory information, and the planning and execution of movement.



Structural and functional connectivity

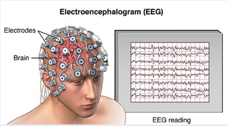
What is SC and how to measure it

SC refers to the anatomical connections between neural elements, such as axons and synapses between neurons at the microscale, as well as large-scale fiber bundles or fasciculi linking cortical areas and subcortical nuclei at meso- and macroscales.



What is FC and how to measure it

FC refers to a statistical dependence between physiological recordings that have been acquired from distinct neural elements.



Micro, meso, macro level of analysis

We can study the structural and functional connectivity at different spatial scales.

Example (A technique for brain mapping at macro-scale)

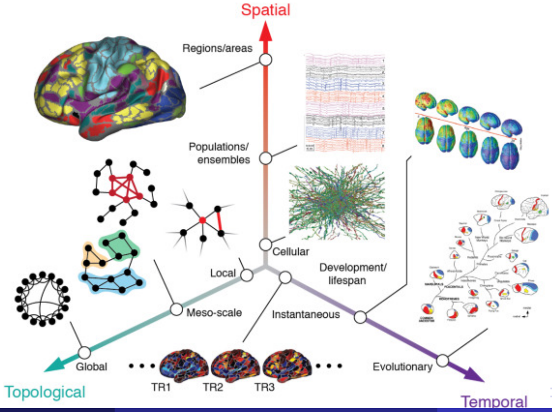
For example *MRI* maps whole brain anatomical and functional networks at **macroscopic scale** ($\sim 1 - 10mm^3$, order of $10^{-2}m$) in healthy volunteers and patients with neurological and psychiatric disorders.

Example (Techniques for brain mapping at meso- and micro-scale)

In the last 10 years, there have also been spectacular methodological developments in *tract tracing*, *optical microscopy*, *optogenetics*, *multielectrode recording*, *histological gene expression*, and many other neuroscience techniques that can now be used to map brain systems at **mesoscopic** ($\sim 10^{-4}$ m) and **microscopic scales** ($\sim 10^{-6}m$), under more controlled experimental conditions, and in a wider range of species.

Actually, the meaning of “scale” can vary depending on context. We focus on three possible definitions

Brain networks are organized across multiple spatiotemporal scales and also can be analyzed at topological (network) scales ranging from individual nodes to the network as a whole. Images of neuronal ensemble recordings, segmented axons, brain evolution, and gray-matter development.



Basic definition of matrix.

- A ***mxn* matrix** consists of *m·n* real numbers arranged in ***m* rows** and ***n* columns**.
- The entry in row *i* and column *j* of the matrix **W** is denoted by w_{ij}, *where* $i=1,\dots,m$ *and* $j=1,\dots,n$.
- **A *nxn* matrix is called a square matrix. It is a special case of the general one when *m*=*n*. Such a matrix has of $n \cdot n=n^2$ real numbers arranged in *n* rows and *n* columns.**

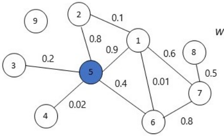
w_{11}	w_{12}	w_{13}	w_{14}	...	...	...	...	w_{1n}
w_{21}	w_{22}	w_{23}	w_{24}	...	...	...	...	w_{2n}
w_{31}	w_{32}	w_{33}	w_{34}	...	...	...	...	w_{3n}
...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...
w_{n1}	w_{n2}	w_{n3}	w_{n4}	...	...	...	...	w_{nn}

Graph: Mathematical definition

For our purposes, a graph is an ordered pair $G = (V, E)$ comprising a set V of vertices or nodes together with a set E of weighted edges or lines, which are 2-element subsets of V. **A graph can be represented as a matrix.**

In our example:

- ❑ We have a sym square matrix, whose order is *9x9* .
- ❑ The matrix consists of 81 real numbers arranged in 9 rows and 9 columns.
- ❑The entry in row $i=6$ and column $j=7$ of the matrix **W** is $w_{ij}=0.8$.
- ❑ The entries of the principal diagonal vanish since self-looping is forbidden.



$w_{67}=0.8$

This row shows the "interaction" of node 1 with nodes 1; 2; 3; 4; 5; 6; 7; 8; 9

0	0.1	0	0	0.9	0.01	0.6	0	0
0.1	0	0	0	0.8	0	0	0	0
0	0	0	0	0.2	0	0	0	0
0	0	0	0	0.02	0	0	0	0
0.9	0.8	0.2	0.02	0	0.4	0	0	0
0.01	0	0	0	0.4	0	0.8	0	0
0.6	0	0	0	0	0.8	0	0.5	0
0	0	0	0	0	0	0.5	0	0
0	0	0	0	0	0	0	0	0

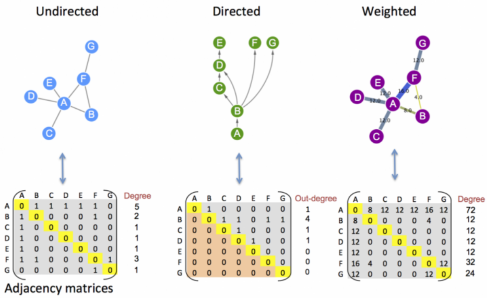
Question

How to compute the matrix $W = [w_{ij}]$ of the functional weights of a neural network?

Types of graphs

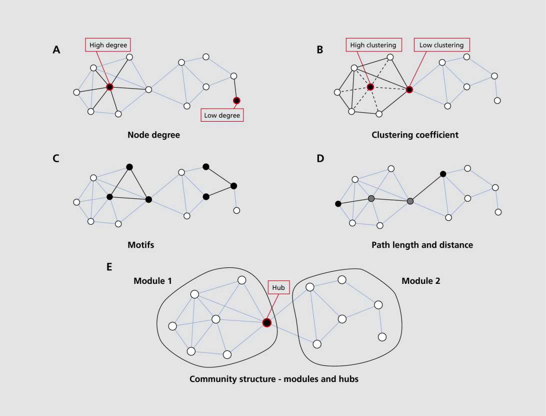
Some classical types of graphs:

- *Simple* (unweighted, undirected graph containing no graph loops or multiple edges) or *multi*.
- *Directed* (a network comprising directed connections or edges) or *undirected* (network comprising undirected connections (edges).
- *Weighted* (a triple $G = (E, V, w)$ where $w : E \to eVal$ is a function mapping edges or directed edges to their values, and eVal is the set (type) of possible values) or *unweighted*.

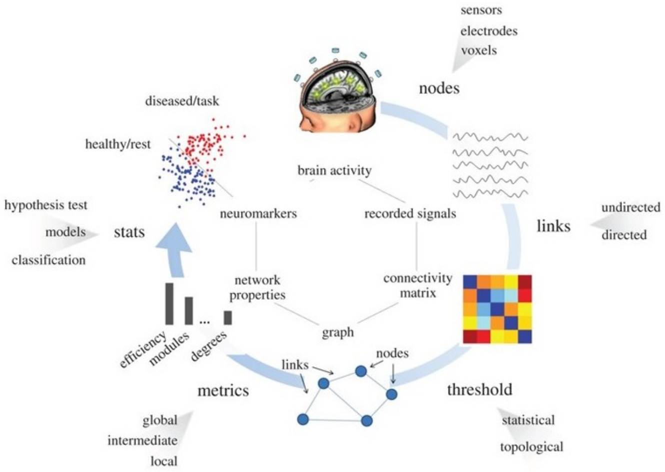


The importance of Graph Theory in Neuroscience

Graph theory is a flexible and powerful mathematical tool to understand systems of interacting elements, particularly suitable for investigating many aspects of brain organization (e.g. substructures of the brain network) in diverse kinds of data, when the structural and functional connections are described by a weighted matrix.

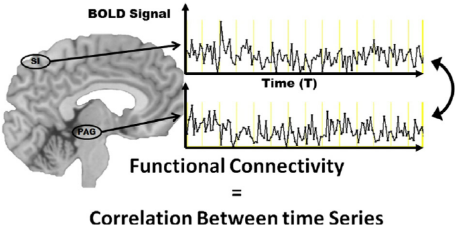


Pipeline for functional brain networks modelling and analysis



Problem

Generally, in literature $W = [w_{ij}] = [F_{ij}]$ where $F = [F_{ij}]$ is the matrix of the collected correlation data (e.g. M/EEG, fMRI, PET,...).



A few basic questions

- Is correlation enough?
- Does the structural connectivity matter?
- Does the network topology have any role?
- If yes, in which way?

The FD model applied to real data

The FD model (PF, PD AIB 2015) proposes a matrix W representing the intensity of the links between nodes, when also SC and network topology are taken into account.

FD model for real data

$$w_{ij}(t,\tau) = \frac{1}{w_{max}}\beta(i,j,\tau)e^{-[D_{ij}(t)-F^s_{ij}(t,\tau)]}$$

Being:

- t is the biological time; τ is the time of one single scan duration, $\tau \in I = [0,\bar{\tau}]$, where $\bar{\tau}$ is the global time of data acquisition.
- $\beta_{ij}(\tau) \backsim k(i)k(j)$ (first order approximation), where $k(i)$ and $k(j)$ are the degrees of node i and j respectively.
- $D_{ij}(t)$ the anatomical matrix. Since $\tau \ll t$, we can consider D constant over the whole data acquisition time ($\bar{\tau}$).
- $F^s_{ij}(t,\tau)$ is the thresholded $F_{ij}(t,\tau)$ (PF, Dulio, Varotto, Rotondi, Panzica. AIB 2016).

Applications of the FD model to real data

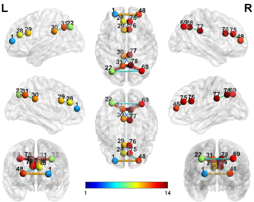
In the next slides, I will provide three examples:

1. A global study.
2. A local study.
3. An application to schizophrenia.

Ex #1: Identification of FC intensity changes and invariant properties in healthy people across the life span

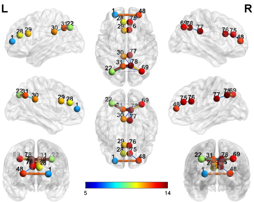
Material and aim

Subjects	133 males and females of different sex and age.
Data	rsfMRI.
Method	FD model.



Some results

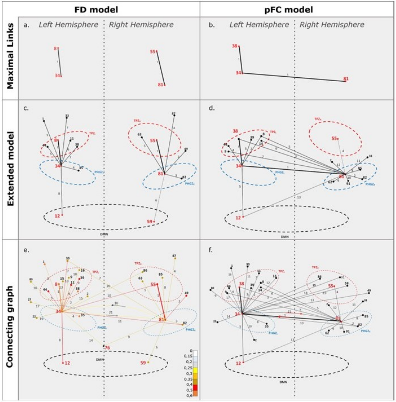
- Great overlapping in terms of W, between healthy males and females at RS.
- Two age groups (46-50 and 71-79) present statistically significant differences in W.



Ex #2: Analysis of PHGA by means of pFC and FD model

Material and aim

Subjects	133 males and females of different sex and age.
Data	rsfMRI.
Method	pFC and FD model.



Some results

- As expected, the majority of the significant links were highlighted by both methods.
- The FD model highlighted a greater number of links compared with pFC.

Ex #3: Analysis of the schizophrenics brain networks

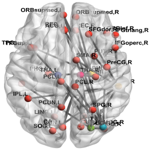
Material and aim

SZs	35 subjects.
HC	41 subjects.
Data	rsfMRI.
Method	pFC and FD model.

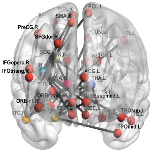
Some results

- FD model: Disrupted thalamocortical network in SZ, a key topic for schizophrenia.
- pFC model: Failure in extracting group differences after multiple comparison correction.

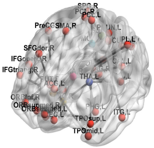
Impaired connections between HC and SZ group.



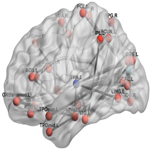
(Axial view)



(Coronal view)



(Custom view)



(Sagittal view)

An example of Translational Neuroscience

NFL Concussions and helmet to hemet collisions

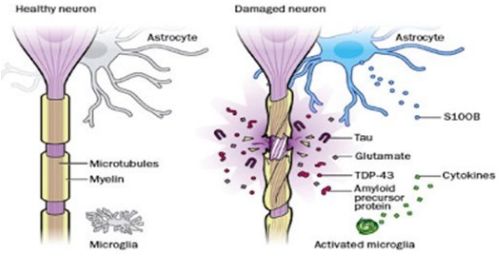
A case study: chronic traumatic encephalopathy (CTE)

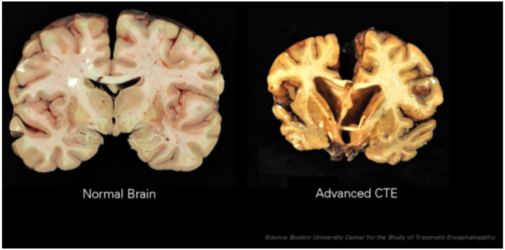
Michael Lewis Webster in short

1. Born on March 18, 1952. Died on September 24, 2002 by suicide.
2. An American football player (center).
3. He played in the NFL from 1974 to 1990.
4. He is a member of the Pro Football Hall of Fame.

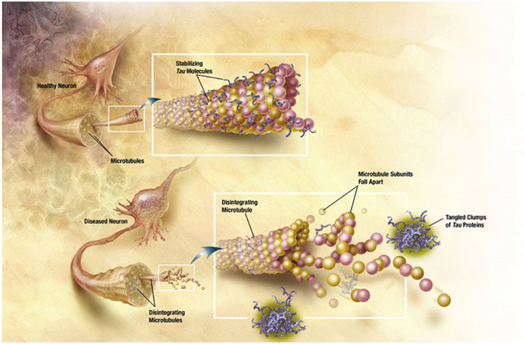
After retirement, Webster suffered from amnesia, dementia, depression, and acute bone and muscle pain. Maybe the multiple concussions during his career damaged his frontal lobe, which caused cognitive dysfunction.

A brain affected by CTE





Healthy neuron vs diseased neuron



The biggest question in CTE research today:

How can we diagnose CTE in a living person? PET scan? fMRI?

In conclusion, some highlights

- This seminar focused on pivotal recent studies regarding graph theory application on functional dynamic connectivity investigated by fMRI analysis at resting state.
- Network science and graph theory applications can help in understanding the brain and its diseases. Morover, our hope for the future is to understand how human cognitive functions are linked to neuronal network structure.
- Graph analysis applications represent an interesting probe to analyze the distinctive features of real life by focusing on functional connectivity networks.
- Graph theory might aid in monitoring the impact of eventual pharmacological and rehabilitative treatments.
- Application of graph theory to **patient** data might provide more insight into the pathophysiological processes underlying her/his brain disconnection.

In conclusion? This approach is a milestone in precision medicine, the medicine of the future.

Traditional medicine

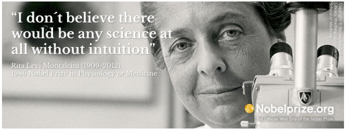
Traditional medicine follows a one-size-fits-all approach. Drugs and other therapies are designed to treat large groups of people with the same disease.

A critical point of traditional medicine

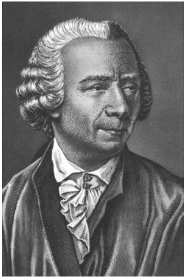
But not everyone responds to a treatment in the same way. Some drugs work very well for certain people, others do not. Finding the exact drug that works well can involve a lot of trial and error.

Precision medicine

Precision medicine takes things a step further. Doctors use information about you – your genes, lifestyle, and environment – along with the characteristics of your disease to select treatments that are most likely to work for you.



“I don´t believe there would be any science at all without intuition”
Rita Levi Montalcini (1909-2012),
1986 Nobel Prize in Physiology or Medicine
Nobelprize.org
The Official Web Site of the Nobel Prize



Thank you for your attention. Questions?