Population models
for complex non-linear phenomena in biology:
from mitochondrial dynamics to brain networks

Chiara Favaretto
Advisor: Prof. Angelo Cenedese

Padova - February, 22\textsuperscript{nd}, 2018
Motivation
Motivation

BRAIN = CPU
Motivation

BRAIN = CPU

ENERGY
Motivation

COMPLEXITY

BRAIN = CPU

ENERGY
Motivation

BRAIN = CPU

COMPLEXITY

OSCILLATIONS

ENERGY
What if something goes wrong?
Motivation

What if something goes wrong?

Alzheimer

Who are you?
Motivation

What if something goes wrong?

Alzheimer

Stroke

Who are you?

I can’t see??

Blur vision
Motivation

What if something goes wrong?

Alzheimer

Stroke

Parkinson’s Disease
Motivation

What if something goes wrong?

Alzheimer

Stroke

Parkinson’s Disease

... and many others ...
Motivation

State of the Art:

we still don't know how to treat them
we still don't know how to predict them
they are related to energy-impairment
they are related to wrong oscillatory patterns
State of the Art:

- we still don’t know how to treat them
Motivation

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Our Aim
Motivation

State of the Art:

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Our Aim

To make use of Systems Theory to analyze and characterize some aspects on the complex relationship

BRAIN ↔ ENERGY
Motivation

State of the Art:

- we still don’t know how to treat them
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- they are related to energy-impairment
- they are related to wrong oscillatory patterns

Our Aim

To make use of Systems Theory to analyze and characterize some aspects on the complex relationship between BRAIN and ENERGY oscillations.
Outline: how did we handle this goal?
Outline: how did we handle this goal?

MITOCHONDRIA
Outline: how did we handle this goal?
Outline: how did we handle this goal?

2013

Review

Mitochondrial dynamics in neurodegeneration

Kie Itoh¹, Ken Nakamura²,³, Miho Iijima¹, and Hiromi Sesaki¹
Outline: how did we handle this goal?

Disturbed mitochondrial dynamics and neurodegenerative disorders
Florence Burté, Valerio Carelli, Patrick F. Chinnery and Patrick Yu-Wai-Man

MITOCHONDRIA

MITO DYNAMICS

Review
Mitochondrial dynamics in neurodegeneration: from cell death to energetic states
Mireille Khacho and Ruth S. Slack
Outline: how did we handle this goal?

Mitochondrial dynamics in neuronal injury, development and plasticity
Kyle H. Flippo and Stefan Strack*
Outline: how did we handle this goal?

OSCILLATIONS
Outline: how did we handle this goal?
Outline: how did we handle this goal?

**OSCILLATIONS**

**FULL & CLUSTERS**

**SYNC**

---

**Association of specific frequency bands of functional MRI signal oscillations with motor symptoms and depression in Parkinson’s disease**

Xiaopeng Song¹, Xiao Hu², Shuqin Zhou¹, Yuanyuan Xu¹, Yi Zhang², Yonggui Yuan¹, Yijun Liu¹, Huaiqi Zhu¹, Weiguo Liu¹ & Jia-Hong Gao¹-³
Outline: how did we handle this goal?

Neuronal firing patterns outweigh circuitry oscillations in parkinsonian motor control

Ming-Kai Pan,1,2# Sheng-Han Kuo,4 Chun-Hwei Tai,2 Jyun-You Liou,1 Ju-Chun Pei,2 Chia-Yuan Chang,3 Yi-Mei Wang,3 Wen-Chuan Liu,2 Tien-Rel Wang,2 Wen-Sung Lai,6,7 and Chung-Chin Kuo1,2#

Association of specific frequency bands of functional MRI signal oscillations with motor symptoms and depression in Parkinson’s disease

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OSCILLATIONS
FULL & CLUSTERS
SYNC
Outline: how did we handle this goal?

Neuronal firing patterns outweigh circuitry oscillations in parkinsonian motor control

Alzheimer’s disease disrupts alpha and beta-band resting-state oscillatory network connectivity

Association of specific frequency bands of functional MRI signal oscillations with motor symptoms and depression in Parkinson’s disease
Outline: how did we handle this goal?
Outline: how did we handle this goal?

- BRAIN
- SIGNALS ANALYSIS & MODELS
- MITOCHONDRIA
- MITO DYNAMICS
- OSCILLATIONS
- FULL & CLUSTERS SYNC
Mitochondria & Mitochondrial Dynamics

- double membrane-bound organelles found in all eukaryotic organisms
- possess their own genome (mitochondrial DNA)
  - involved in several tasks
  - generate most of the cells supply of ATP (= energy)
MITOCHONDRIA & MITOCHONDRIAL DYNAMICS

- Constant changes in shape, size, number and location
- Affected by mitochondrial morphology
- Controlled mainly by the processes of fission and fusion

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Population models for complex non-linear phenomena in biology
Models of Mitochondrial Dynamics in the Literature

Models of Mitochondrial Dynamics in the Literature

Drawbacks of the proposed models

Models of Mitochondrial Dynamics in the Literature


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**Drawbacks of the proposed models**

- not analytically analyzable
- hard to understand by biologists
- need artificial constraints to avoid instability
Models of Mitochondrial Dynamics in the Literature

- G. Dalmasso et al. PLoS ONE, 2017

**Drawbacks of the proposed models**

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- absence of ATP turnover
Models of Mitochondrial Dynamics in the Literature

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Our Contribution
Models of Mitochondrial Dynamics in the Literature

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**Our Contribution**

New mathematical model:
- analytically analyzable
- easy to understand by biologists
- complete and self-controlled
Models of Mitochondrial Dynamics in the Literature

Drawbacks of the proposed models

- not analytically analyzable
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- need artificial constraints to avoid instability
- absence of ATP turnover

Our Contribution

New mathematical model:

- analytically analyzable
- easy to understand by biologists
- complete and self-controlled
- inclusion of ATP turnover
Mitochondrial Dynamics: the Model

Exercise \(\rightarrow\) \(\beta\)-Adrenergic stimulation/
Cold

Energy Deprivation

\(\uparrow\text{NAD}^+\) \(\uparrow\text{AMP/ATP}\)

SIRT1

AMPK

PGC-1\(\alpha\)

NRF-1, NRF-2, ERR, RXR, PPAR

Mfn1/2

Opa1

Mff, Fis1, Mid49, Mid50

Pink1

Parkin

Ubiquitin

Parkin

Drp1

OXPHOS defect

ROS

mtDNA mutation

membrane proteins damage

membrane lipids damage

Aging

inner membrane fusion

outer membrane fusion

Mitochondrial Dynamics: the Model

Exercise \(\rightarrow\) \(\beta\)-Adrenergic stimulation/
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Aging
Mitochondrial Dynamics: the Model

Exercise → β-Adrenergic stimulation/

Cold

Energy Deprivation

Ca2+ → cAMP → CREB

SIRT1 → AMPK → PGC-1α → NRF-1, NRF-2, ERR, RXR, PPAR

⇑ NAD+ ⇑ AMP/ATP → SIRT1

Mfn1/2 → outer membrane fusion

Opa1 → inner membrane fusion

Drp1

Mff, Fis1, Mid49, Mid50

Pink1 → Parkin → Ubiquitin

Aging → ROS

mtDNA mutation

membrane proteins damage

membrane lipids damage

OXPHOS defect

biogenesis
Mitochondrial Dynamics: the Model

Exercise → \( \beta \)-Adrenergic stimulation/
Cold
Energy Deprivation

Ca\(^{2+} \) → CaMK/CN → cAMP → CREB → PGC-1\( \alpha \) → NRF-1, NRF-2, ERR, RXR, PPAR

\( \uparrow \) NAD\(^{+} \) → SIRT1 → AMPK

Exercise, \( \beta \)-Adrenergic stimulation/
Cold → Ca\(^{2+} \) → CaMK/CN → cAMP → CREB → PGC-1\( \alpha \) → NRF-1, NRF-2, ERR, RXR, PPAR

NAD\(^{+} \) → SIRT1 → AMPK

damage

Aging → ROS → mtDNA mutation → membrane proteins damage

membrane lipids damage

Parkin → Ubiquitin

Mfn1/2 → outer membrane fusion

Opa1 → Inner membrane fusion

Drp1

Mff, Fis1, Mid49, Mid50

Pink1 → Parkin → Ubiquitin

damage
Mitochondrial Dynamics: the Model

Exercise → β-Adrenergic stimulation/
Cold
Energy Deprivation
Ca2+
cAMP
CREB
NAD+
AMP/ATP
SIRT1
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PGC-1α
NRF-1, NRF-2, ERR, RXR, PPAR

Parkin
Mfn1/2
Opa1
Mitochondrial Dynamics: the Model

mitophagy

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Mitochondrial Dynamics: the Model
Mitochondrial Dynamics: the Model

- Exercise
  - β-Adrenergic stimulation/
  - Cold
  - Energy Deprivation
  - Ca2+
  - cAMP
  - CaMK/CN
  - CREB
  - PGC-1α

- NRF-1, NRF-2, ERR, RXR, PPAR

- NAD+
- AMP/ATP
- SIRT1
- AMPK
- PGC-1α
- α

- Aging
  - ROS
  - mtDNA mutation

- OXPHOS defect
- membrane proteins damage
- membrane lipids damage

- Mfn1/2
- Opa1
- outer membrane fusion
- Inner membrane fusion

- Drp1

- Mff, Fis1, Mid49, Mid50

- Pink1
- Parkin
- Ubiquitin

- fission
Mitochondrial Dynamics: the Model

Exercise → β-Adrenergic stimulation/Cold

Energy Deprivation

Ca2+ → CaMK/CN → CREB

NAD+ → SIRT1 → AMPK

AMP/ATP → NRF-1, NRF-2, ERR, RXR, PPAR

PGC-1α → PGC-1α

ATP production

Mfn1/2 → Opa1

Mff, Fis1, Mid49, Mid50

Drp1

Pink1 → Parkin → Ubiquitin

Aging → ROS → mtDNA mutation

mtDNA mutation → OXPHOS defect

Energy Deprivation → Oxidative Phosphorylation (OXPHOS) defect

Defects in mitochondrial dynamics and function are associated with age-related diseases such as neurodegenerative disorders, diabetes, and cancer. This diagram illustrates the complex interplay between mitochondrial dynamics, energy balance, and cellular stress responses. Understanding these processes is crucial for the development of therapeutic strategies to counteract mitochondrial dysfunction.
Mitochondrial Dynamics: the Model

- Exercise
- \( \beta \)-Adrenergic stimulation/
- Cold
- Ca\(^{2+} \)
- CaMK/CN
- cAMP
- CREB
- NAD\(^+ \)
- AMP/ATP
- SIRT1
- AMPK
- PGC-1\(\alpha \)
- NRF-1, NRF-2, ERR, RXR, PPAR
- ATP consumption
- OXPHOS defect
- ROS
- mtDNA mutation
- membrane proteins damage
- membrane lipids damage
- Aging
- Parkin
- Mfn1/2
- Opa1
- Drp1
- Mff, Fis1, Mid49, Mid50
- Pink1
- Parkin
- Ubiquitin
- ATP consumption
Mitochondrial Dynamics: the Model

Exercise $\rightarrow$ $\beta$-Adrenergic stimulation/
Cold

Ca$^2+$
CaMK/
CN

creb

PGC-1α

NRF-1, NRF-2, ERR, RXR, PPAR

$\uparrow$NAD$^+$ $\uparrow$AMP/ATP

SIRT1 AMPK

PGC-1α

NRF-1, NRF-2, ERR, RXR, PPAR

Aging ROS
OXPHOS defect
mtDNA mutation
membrane proteins damage
membrane lipids damage

Feedback regulation

Mfn1/2
Opa1

Parkin
Mff, Fis1, Mid49, Mid50

Drp1

Pink1
Parkin
Ubiquitin
Mitochondrial Dynamics: the Model

\[ \dot{x}_h = (\alpha_0 + \alpha_1 K x_{ATP}) x_h + \psi_1 x_f - \delta x_h - \phi x_h x_d \]

\[ \dot{x}_d = \delta x_h + \psi_2 x_f - \phi x_h x_d - \mu x_d \]

\[ \dot{x}_f = \phi x_h x_d - (\psi_1 + \psi_2) x_f \]

\[ \dot{x}_{ATP} = \beta x_h + \epsilon x_d + \eta x_f - u \cdot x_{ATP} \]

- \( \alpha \): biogenesis
- \( \delta \): damage
- \( \mu \): mitophagy
- \( \phi \): fusion
- \( \psi_1, \psi_2 \): fission
- \( \beta, \eta, \epsilon \): atp production
- \( u \): energy stress
Mitochondrial Dynamics: the Model

Differential equations

\[
\begin{align*}
\dot{x}_h &= \left( \alpha_0 + \frac{\alpha_1}{K + x_{\text{ATP}}^n} \right) x_h + \psi_1 x_f - \delta x_h - \varphi x_h x_d \\
\dot{x}_d &= \delta x_h + \psi_2 x_f - \varphi x_h x_d - \mu x_d \\
\dot{x}_f &= \varphi x_h x_d - (\psi_1 + \psi_2) x_f \\
\dot{x}_{\text{ATP}} &= \beta x_h + \varepsilon x_d + \eta x_f - u \cdot x_{\text{ATP}}
\end{align*}
\]

- \( x_h \): healthy
- \( x_d \): damaged
- \( x_f \): fused
- \( u \): input
Mitochondrial Dynamics: the Model

Differential equations

\[ \dot{x}_h = \left( \alpha_0 + \frac{\alpha_1}{K + x_{ATP}^n} \right) x_h + \psi_1 x_f - \delta x_h - \varphi x_h x_d \]

\[ \dot{x}_d = \delta x_h + \psi_2 x_f - \varphi x_h x_d - \mu x_d \]

\[ \dot{x}_f = \varphi x_h x_d - (\psi_1 + \psi_2) x_f \]

\[ \dot{x}_{ATP} = \beta x_h + \varepsilon x_d + \eta x_f - u \cdot x_{ATP} \]

\( x_h \): healthy
\( x_d \): damaged
\( x_f \): fused
\( u \): input

Main issue:
nonlinearities \( \rightarrow \) complex stability analysis
Mitochondrial Dynamics: the Model

Differential equations

\[
\dot{x}_h = \left( \alpha_0 + \frac{\alpha_1}{K + x_{ATP}^n} \right) x_h + \psi_1 x_f - \delta x_h - \varphi x_h x_d
\]

biogenesis

\[
\dot{x}_d = \delta x_h + \psi_2 x_f - \varphi x_h x_d - \mu x_d
\]

damage

\[
\dot{x}_f = \varphi x_h x_d - (\psi_1 + \psi_2) x_f
\]

fusion

\[
\dot{x}_{ATP} = \beta x_h + \epsilon x_d + \eta x_f - u \cdot x_{ATP}
\]

atp production

atp use

Main advantages:
1. atp-dependence
2. opportunity to test several hypotheses

\( x_h \): healthy

\( x_d \): damaged

\( x_f \): fused

\( u \): input
ATP feedback advantage

$t = 50$ sec: energy stress increases

atp-feedback $\rightarrow$ system reactivity

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Equilibrium analysis

Equilibrium point

\[ \bar{x}_d = \frac{\psi_1 + \psi_2}{\psi_2 \varphi} \left( \frac{\alpha_1 - k \delta - \delta \bar{x}_{ATP}}{k + \bar{x}_{ATP}} \right) \]

\[ \bar{x}_f = \frac{\varphi}{\psi_1 + \psi_2} \cdot \bar{x}_h \bar{x}_d \]

\[ \bar{x}_h = \frac{(\psi_1 + \psi_2) \mu}{\delta (\psi_1 + \psi_2) - \psi_1 \varphi \bar{x}_d} \cdot \bar{x}_d \]

\[ \bar{x}_{ATP} = \text{solution of 3rd-deg poly} \]
Equilibrium analysis

\[ \bar{x}_d = \frac{\psi_1 + \psi_2}{\psi_2 \varphi} \left( \frac{\alpha_1 - k \delta - \delta \bar{x}_{\text{ATP}}}{k + \bar{x}_{\text{ATP}}} \right) \]

\[ \bar{x}_f = \frac{\varphi}{\psi_1 + \psi_2} \cdot \bar{x}_h \bar{x}_d \]

\[ \bar{x}_h = \frac{(\psi_1 + \psi_2) \mu}{\delta(\psi_1 + \psi_2) - \psi_1 \varphi \bar{x}_d} \cdot \bar{x}_d \]

\[ \bar{x}_{\text{ATP}} = \text{solution of 3rd-deg poly} \]

Nullclines analysis

- Damaged vs. healthy
- Fused vs. healthy
- Fused vs. damaged
Synchronization: the Kuramoto Model
Synchronization: the Kuramoto Model

**Oscillator:** generator of signals characterized by a periodic pattern $\rightarrow$ **PHASE**

![Diagram of Oscillations](image)
Oscillator: generator of signals characterized by a periodic pattern \( \rightarrow \) PHASE

**Kuramoto Model**

\[
\dot{\theta}_i = \omega_i + \sum_{j=1}^{n} a_{ij} \sin(\theta_j - \theta_i)
\]

\( \dot{\theta}_i \): natural frequency

\( \omega_i \): natural frequency
Oscillator: generator of signals characterized by a periodic pattern \( \rightarrow \text{PHASE} \)

Kuramoto Model

\[
\dot{\theta}_i = \omega_i + \sum_{j=1}^{n} a_{ij} \sin(\theta_j - \theta_i)
\]

\( G = (\mathcal{V}, \mathcal{E}) \): graph
\( \mathcal{V} = \{1, \ldots, n\} \): set of nodes
\( \mathcal{E} \subseteq \mathcal{V} \times \mathcal{V} \): set of edges
\( A = [a_{ij}] \): weighted adjacency matrix
Synchronization: the Kuramoto Model

**Oscillator**: generator of signals characterized by a periodic pattern $\rightarrow$ PHASE

**Kuramoto Model**

$$\dot{\theta}_i = \omega_i + \sum_{j=1}^{n} a_{ij} \sin(\theta_j - \theta_i)$$

- $\omega_i$: isolated dynamics
- $[a_{ij}]$: adjacency matrix
- $\sin(\theta_j - \theta_i)$: coupling function
Synchronization: the Kuramoto Model
Synchronization overview
Synchronization overview

Phase cohesiveness:

\[ |\theta_j(t) - \theta_i(t)| \leq \gamma \quad \forall i, j, t \]
Synchronization overview

Phase cohesiveness

\[ |\theta_j(t) - \theta_i(t)| \leq \gamma \quad \forall i, j, t \]
Synchronization overview

Phase cohesiveness

\[ |\theta_j(t) - \theta_i(t)| \leq \gamma \quad \forall i, j, t \]

Phase locking

\[ |\theta_j(t) - \theta_i(t)| \equiv \gamma \quad \forall i, j, t \]

Full network synchronization

\[ |\theta_j(t) - \theta_i(t)| \equiv 0 \quad \forall i, j, t \]
Synchronization overview

### Phase cohesiveness

\[ |\theta_j(t) - \theta_i(t)| \leq \gamma \quad \forall i, j, t \]

### Phase locking

\[ |\theta_j(t) - \theta_i(t)| \equiv \gamma \quad \forall i, j, t \]

### Phase synchronization

\[ |\theta_j(t) - \theta_i(t)| \equiv 0 \quad \forall i, j, t \]

\[ \theta_j - \theta_i = 0 \]
Synchronization overview

<table>
<thead>
<tr>
<th>Phase locking</th>
<th>Phase synchronization</th>
<th>Frequency synchronization</th>
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<tbody>
<tr>
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Synchronization overview

- Phase cohesiveness
- Phase locking
- Phase synchronization
- Frequency synchronization

Full network synchronization
Synchronization overview

Phase cohesiveness

Phase locking

Phase synchronization

Frequency synchronization

Full network synchronization

Clusters synchronization

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## Synchronization overview

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Clusters synchronization
Clusters synchronization

![Diagram of clusters synchronization](image)
Clusters synchronization

\[ \mathcal{P} = \{\mathcal{P}_1, \ldots, \mathcal{P}_4\}: \quad \bigcup_k \mathcal{P}_k = \mathcal{V} \quad \mathcal{P}_i \cap \mathcal{P}_j = \emptyset \]
Clusters synchronization

Phase & Frequency synchronizable $\mathcal{P}$
Clusters synchronization

\[ \exists \theta(0): \begin{cases} \theta_i(t) = \theta_j(t) \\ \dot{\theta}_i(t) = \dot{\theta}_j(t) \end{cases} \quad \forall i, j \in \mathcal{P}_k \text{ and } \forall k \]
Clusters synchronization: our contribution
Clusters synchronization: our contribution

<table>
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<tr>
<th>Analysis</th>
<th><strong>Necessary</strong> and <strong>sufficient</strong> conditions for clusters invariance</th>
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Clusters synchronization: our contribution

### Analysis

**Necessary** and **sufficient** conditions for clusters invariance

$t = 0$
| Analysis | Necessary and sufficient conditions for clusters invariance |

$t = 0$  

$t > 0$
Clusters synchronization: our contribution

**Analysis**

**Necessary and sufficient** conditions for clusters invariance

\[ \sum_{k \in \mathcal{P}_\ell} a_{ik} - a_{jk} = 0 \quad \forall i, j \in \mathcal{P}_z \quad \forall \ell \neq z \]

Generalized Equitable Partition (GEP)

\[ \mathcal{P}_1 = \{1, 2, 3\} \rightarrow \omega_1 \]
\[ \mathcal{P}_2 = \{4, 5, 6\} \rightarrow \omega_2 \]
Clustering synchronization: our contribution

**Analysis**

**Necessary and sufficient conditions** for clusters invariance

Generalized Equitable Partition (GEP)

\[ \mathcal{P}_1 = \{1, 2, 3\} \rightarrow \omega_1 \]

\[ \mathcal{P}_2 = \{4, 5, 6\} \rightarrow \omega_2 \]

\[ \sum_{k \in \mathcal{P}_2} a_{ik} - a_{jk} = 0 \quad \forall i, j \in \mathcal{P}_1 \]
Clustering synchronization: our contribution

**Analysis**

**Necessary and sufficient conditions** for clusters invariance

Generalized Equitable Partition (GEP)

\[ \mathcal{P}_1 = \{1, 2, 3\} \rightarrow \omega_1 \]
\[ \mathcal{P}_2 = \{4, 5, 6\} \rightarrow \omega_2 \]

\[ \sum_{k \in \mathcal{P}_1} a_{ik} - a_{jk} = 0 \quad \forall i, j \in \mathcal{P}_2 \]
Clusters synchronization: our contribution

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$t = 0$

$t > 0$
Clusters synchronization: our contribution

**Analysis**

*Necessary* and *sufficient* conditions for clusters invariance

**Control**

How to *modify* the adjacency matrix to impose clusters invariance with structural constraints

\[ t = 0 \]

\[ t > 0 \]
Clusters synchronization: control
Clusters synchronization: control

Task: Modify $A$ to make $\mathcal{P}$ invariant *without* modifying the dotted edges
Clusters synchronization: control

Task: Modify $A$ to make $P$ invariant without modifying the dotted edges

\[
\min_{\Delta} \| \Delta \|_F^2
\]

s.t. \((A + \Delta)\) respects GEP

$\Delta \in \mathcal{H}$ structural constraints
Task: Modify $A$ to make $P$ invariant \textbf{without} modifying the dotted edges

\[
\min_{\Delta} \| \Delta \|_F^2 \quad \text{Frobenius norm}
\]
\[
\text{s.t. } (A + \Delta) \text{ respects GEP}
\]
\[
\Delta \in \mathcal{H} \quad \text{structural constraints}
\]
Clusters synchronization: control

4. Population models for complex non-linear phenomena in biology
Clusters synchronization: control

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Population models for complex non-linear phenomena in biology
Brain

BRAIN

MITOCHONDRIA

MITO DYNAMICS

OSCILLATIONS

FULL & CLUSTERS SYNC
Brain

clusters of nodes
Brain

clusters of nodes

clusters of links
Brain clusters of links
Brain: a complex system

- SC
- EC
- FC
- DTI
- fMRI
- MEG

- TASK analysis
- clustered dynamics
- fMRI vs MEG
- REST vs TASK

• opposite behavior
• coherent behavior
Brain: a complex system

connectivity matrix

A1

? 

A2
Brain: a complex system

- Connectivity matrix
- Measured data

A1 → A2

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Brain: a complex system

Structural Connectivity

anatomical connections

A1

# fibers

A2

connectivity
matrix

SC

DTI

measured
data

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Effective Connectivity

- SC
- DTI
- fMRI
- MEG

source level
statistical measure

connectivity matrix
measured data

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Functional Connectivity

- SC
- EC
- FC
- DTI
- fMRI
- MEG

- recorded signal
- statistical measure
- measured data

connectivity matrix

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Brain: a complex system

- Connectivity matrix
- SC
- DTI
- fMRI
- MEG
- FC
- EC

Condition

Measured data

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Brain: a complex system

Task Activity
- any kind of activity
- only involved areas actived
- links: activity-dependent

Energy consumption

condition

Task

connectivity matrix

measured data

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Brain: a complex system

Resting State (RS)
- complete rest
- resting state network
- most energy

Energy consumption

Condition
- REST
- TASK

Connectivity matrix
- SC
- DTI
- fMRI
- MEG

Measured data

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Brain: a complex system

- A1
- A2
- Statistical measure
- Measured data
- Connectivity matrix
- SC
- EC
- FC
- DTI
- fMRI
- MEG
- TASK
- REST

Condition measured data connectivity matrix:
- SC
- EC
- FC
- DTI
- fMRI
- MEG
- TASK
- REST

Analysis of clustered dynamics:
- fMRI vs MEG
- REST vs TASK

- Opposite behavior
- Coherent behavior
Brain: a complex system

- clustered dynamics
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Brain: a complex system

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**Dorsal Attention Network (DAN)**

**Visual Network (VIS)**

- opposite behavior
- coherent behavior

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Brain: a complex system

- clusters dynamics
- fMRI vs MEG
- REST vs TASK

**analysis**

- Rest vs Task
- FMR vs MEG
- DAN vs VIS

**Clusters Dynamics**
- fMRI vs MEG
- REST vs TASK
- L-dFEF L-pIPS L-SPL R-dFEF R-pIPS R-SPL PreCu R-vTPJ L-MT L-V3AV7 L-V4V8 R-MT R-V3AV7 R-V4V8
### Brain: a complex system

- Clusters dynamics
- fMRI vs MEG
- REST vs TASK

#### Analysis
- Opposite behavior

<table>
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<tr>
<th></th>
<th>fMRI</th>
<th>delta</th>
<th>theta</th>
<th>alpha</th>
<th>beta</th>
<th>gamma1</th>
<th>gamma2</th>
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### fMRI delta theta alpha beta gamma1 gamma2

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<tr>
<th></th>
<th>L-dFEF</th>
<th>L-pIPS</th>
<th>L-SPL</th>
<th>R-dFEF</th>
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<th>R-SPL</th>
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- Opposite behavior
- Coherent behavior
Brain: a complex system

- clusters dynamics
- fMRI vs MEG
- REST vs TASK

- opposite behavior
- coherent behavior

**Analysis**

- clusters dynamics
- fMRI vs MEG
- REST vs TASK

**fMRI**

- delta
- theta
- alpha
- beta
- gamma1
- gamma2

**REST**

**TASK**

- DAN
- VIS

**TASK - REST**

- L-dFEF
- L-pIPS
- L-SPL
- R-dFEF
- R-pIPS
- R-SPL
- PreCu
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- L-MT
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Brain: a complex system

- analysis
  - clustered dynamics
  - fMRI vs MEG
  - REST vs TASK

- modeling
  - spiking models
  - Kuramoto Model
  - clusters dynamics

- condition
- measured data
- connectivity matrix

- REST
- TASK
- SC
- EC
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- FC
Brain: a complex system

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- REST
- TASK

connectivity matrix

- SC
- DTI
- EC
- FC
- fMRI
- MEG

measured data
Structural connectivity
Brain: a complex system

Structural connectivity

fMRI signals
Brain: a complex system

Structural connectivity

fMRI signals
Brain: a complex system

Structural connectivity

? 

fMRI signals
Brain: a complex system

Structural connectivity

phase model

fMRI signals
Brain: a complex system

Structural connectivity

- Rulkov Neuron Model
- Kuramoto Model
- Fitzhugh Nagumo Model

fMRI signals
Brain: a complex system

Structural connectivity

- Kuramoto Model

fMRI signals

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Structural connectivity

\[ \hat{\theta} \]

- Kuramoto Model

fMRI signals
Brain: a complex system

Structural connectivity

Kuramoto Model

\[ \hat{\theta} \]

\[ \theta \]

Phase transform

fMRI signals

\[ \theta \]

\[ \hat{\theta} \]
Brain: a complex system

Structural connectivity

- Kuramoto Model

- fMRI signals

- probability density function

- phase transform

- Structural connectivity

- SC, EC, FC, DTI, fMRI, MEG

- TASK, REST

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Brain: a complex system

Structural connectivity

\[ \hat{\theta} \]

probability density function

\[ \theta \]

phase transform

fMRI signals

- Kuramoto Model

\[ \theta_j - \theta_i \]

• real data

• model

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Population models for complex non-linear phenomena in biology
Conclusion & ongoing research
Conclusion & ongoing research

MITOCHONDRIA

MITO DYNAMICS
Conclusion & ongoing research

- population model
- mito dynamics + energy
- feedback regulation
- stability & sensitivity analyses
Conclusion & ongoing research

- population model
- mito dynamics + energy
- feedback regulation
- stability & sensitivity analyses

- non-linear feedback control
- damaged vs healthy model
- more classes
Conclusion & ongoing research

- full phase cohesiveness
- clusters phase cohesiveness
- phase locking
- sync invariance
Conclusion & ongoing research

- full phase cohesiveness
- clusters phase cohesiveness
- phase locking
- sync invariance

Open research

- clusters sync attractivity
- brain fitting

Results

- Oscillations
- Full & Clusters Sync

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Population models for complex non-linear phenomena in biology
Conclusion & ongoing research

- data analysis
- modeling
- rest vs task
- fMRI vs MEG
Conclusion & ongoing research

- data analysis
- modeling
- rest vs task
- fMRI vs MEG

- stroke modeling
- rest vs task
- fMRI vs EEG
- FC dynamics
Thanks to...

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Prof. Corbetta

Dr. Spadone

Prof. Cenedese

Prof. Franco

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Dr. Spadone

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Dr. Tiberi

Prof. Pasqualetti