# Systems Biology in Action

INT3007 – Systems Biology

21 November 2022

# Outline

- Systems Biology **labs** @ UM
  - Maastricht Centre for Systems Biology
  - Maastricht Brain Imaging Centre
- Systems Biology **research** @ UM
  - Irene Hemel, PhD student (MaCSBio)
  - Tonio Weidler, PhD student (Cognitive Neuroscience)
- Systems Biology **education** @ UM
  - Student's perspective
  - Your future in Systems Biology

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# Maastricht Centre for Systems Biology (MaCSBio)


## Mike Gerards

*Assistant professor*


macsbio
MAASTRICHT CENTRE FOR SYSTEMS BIOLOGY

# MaCSBio

- One of the newer FSE institutes (established in 2015)

- Scientific director
  - Prof. Dr. Ilja Arts

- Team
  - 4 professors
  - 1 associate professor
  - 4 assistant professors
  - 2 postdocs
  - 6 PhD students
  - 1 research assistant

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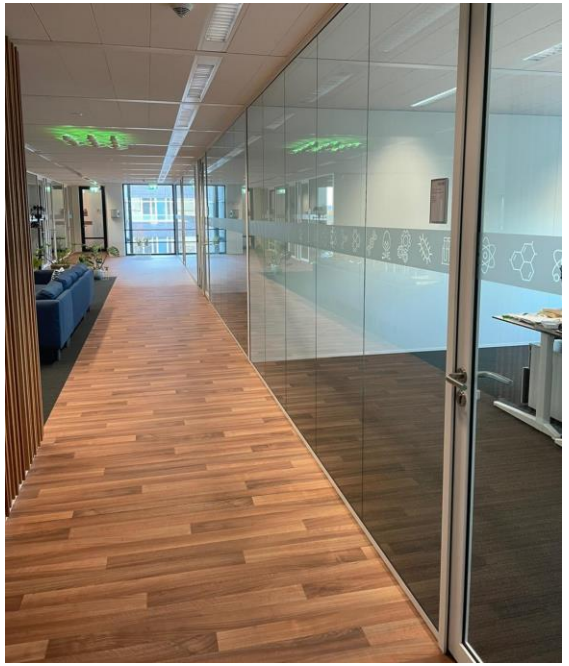
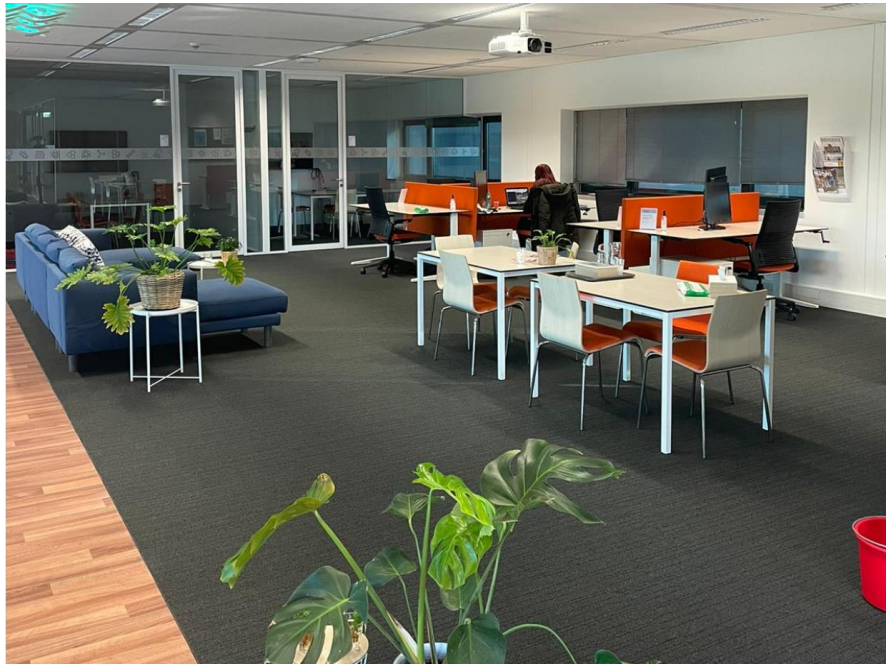
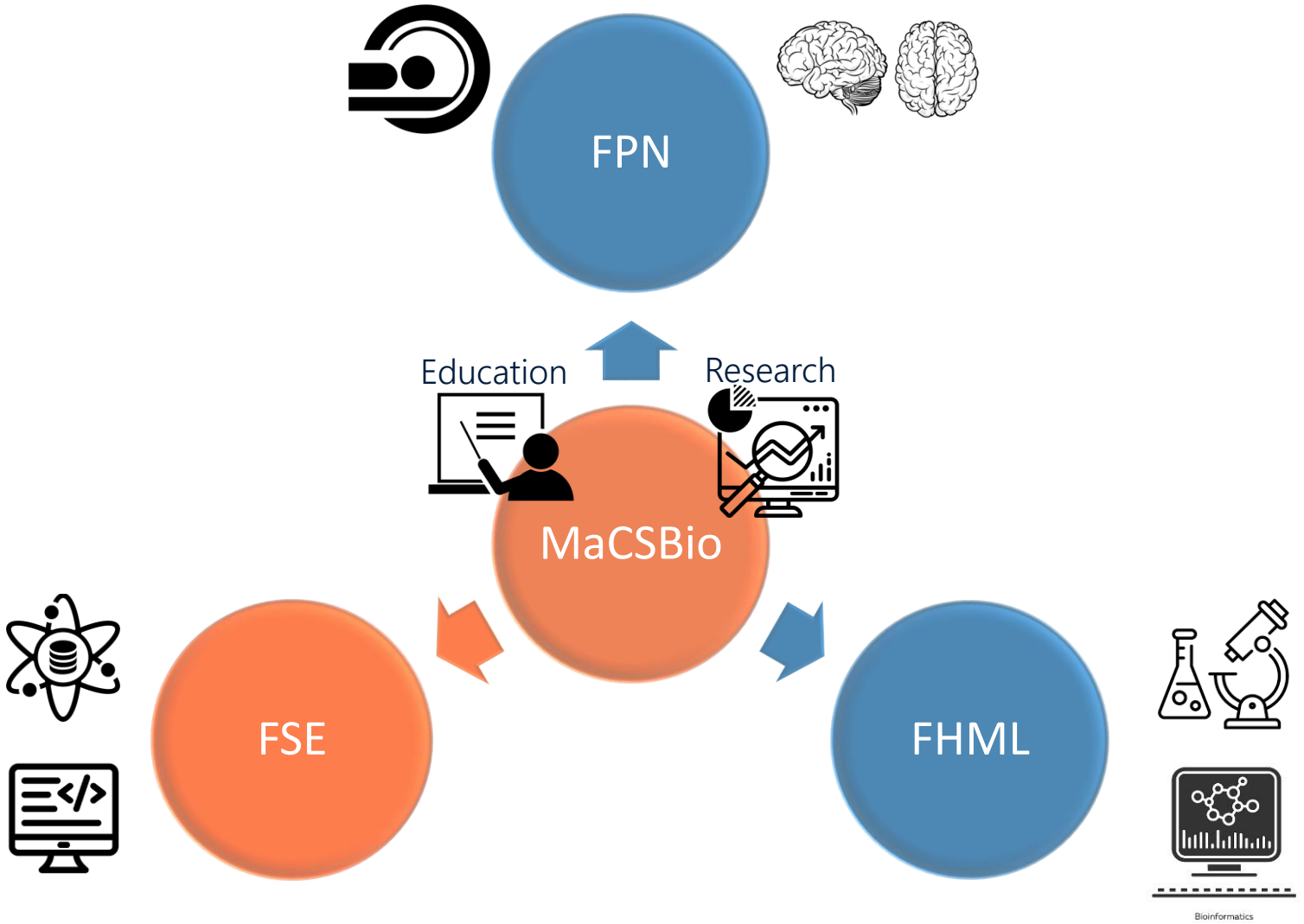




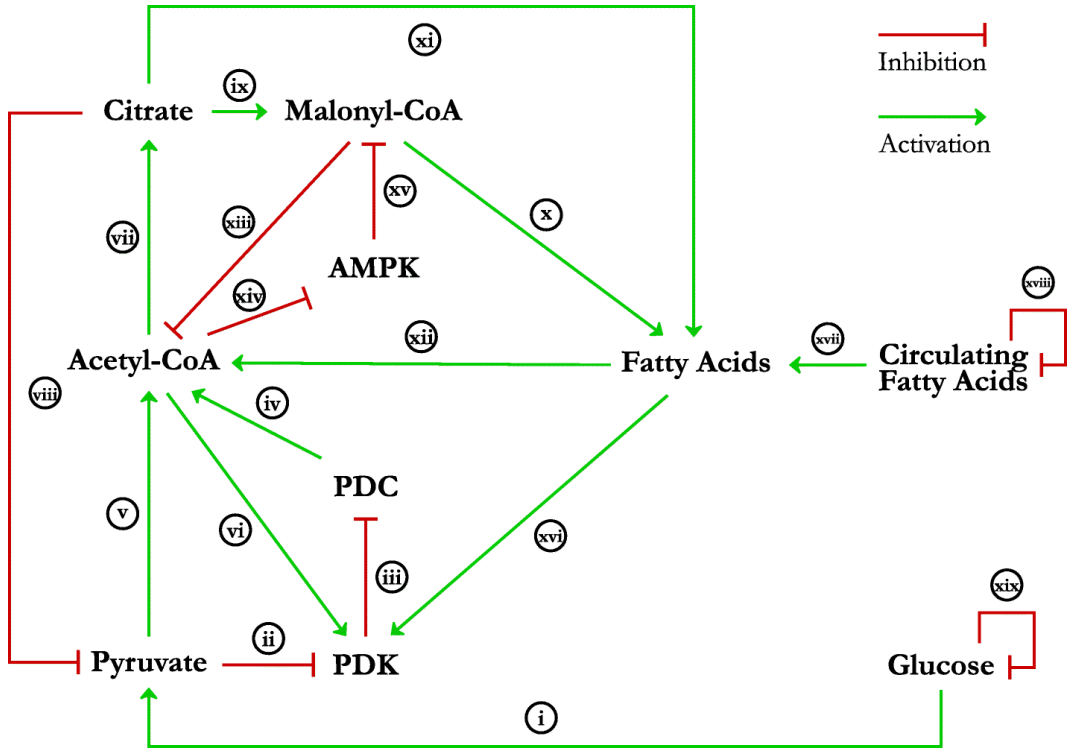
# Interdisciplinary research




https://www.maastrichtuniversity.nl/research/maastricht-centre-systems-biology

# Research lines

- *Systems BioMedicine*
  - Diabetes, cardiology, cell senescence, immunometabolism

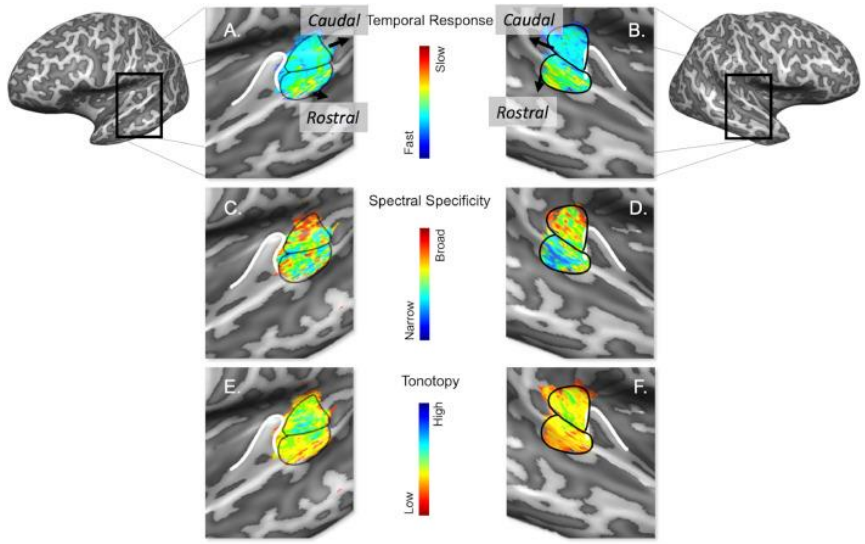



https://doi.org/10.1186/s12263-019-0647-5

# Research lines

- *Systems BioMedicine*
  - Diabetes, cardiology, cell senescence, immunometabolism

- *Computational Neuroscience*
  - Computational neuroscience, neural networks, learning, brain metabolism, mitochondria



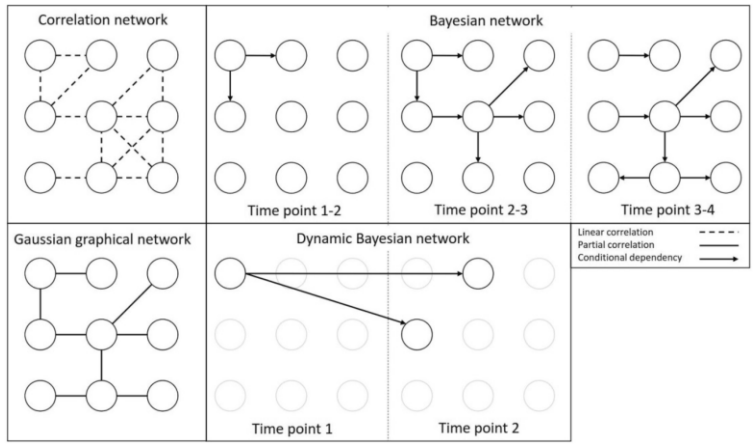

https://doi.org/10.1016/j.neuroimage.2021.118575

# Research lines

- *Systems BioMedicine*
  - Diabetes, cardiology, cell senescence, immunometabolism

- *Computational Neuroscience*
  - Computational neuroscience, neural networks, learning, brain metabolism, mitochondria

- *Systems Toxicology*

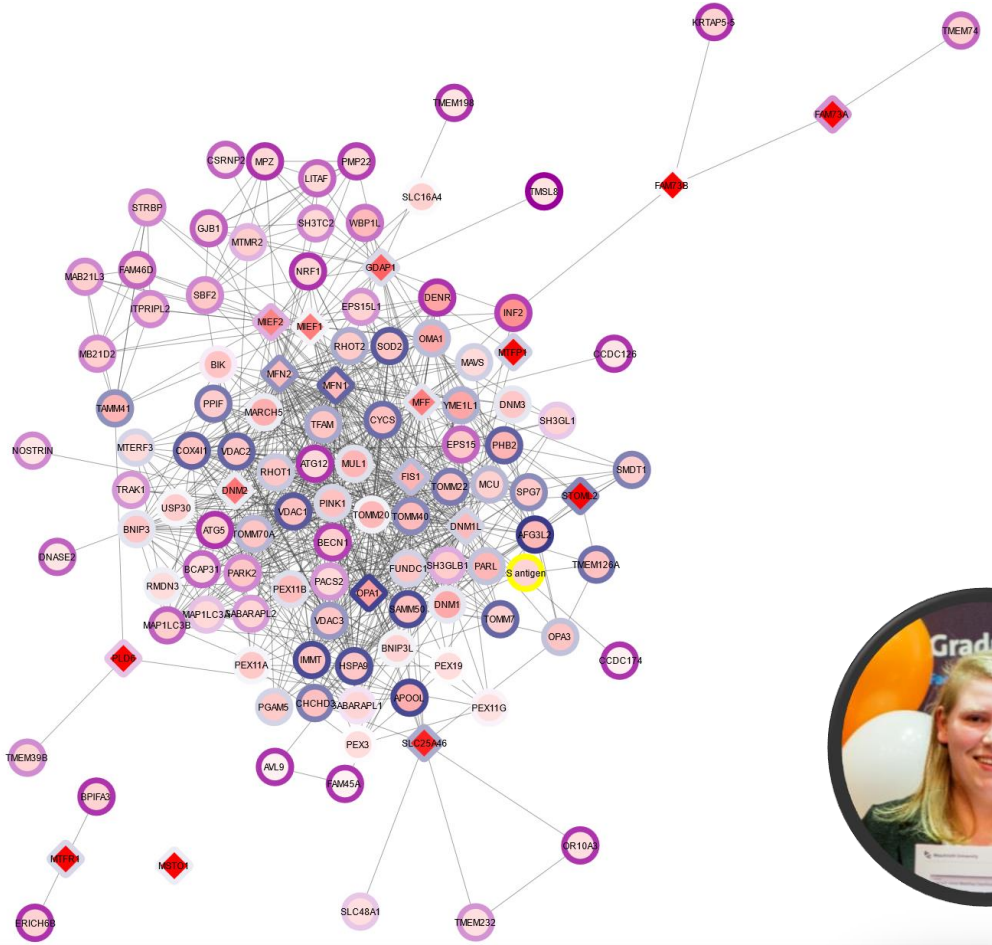



https://doi.org/10.1007/s00204-019-02585-5

# Systems Biology to study Mitochondrial Biology

- Protein-protein interaction network
  - Build network of known proteins
  - Extended with 100 proteins

- Selected candidates
  - Proteins with unknown function
  - Pathway enrichment analysis

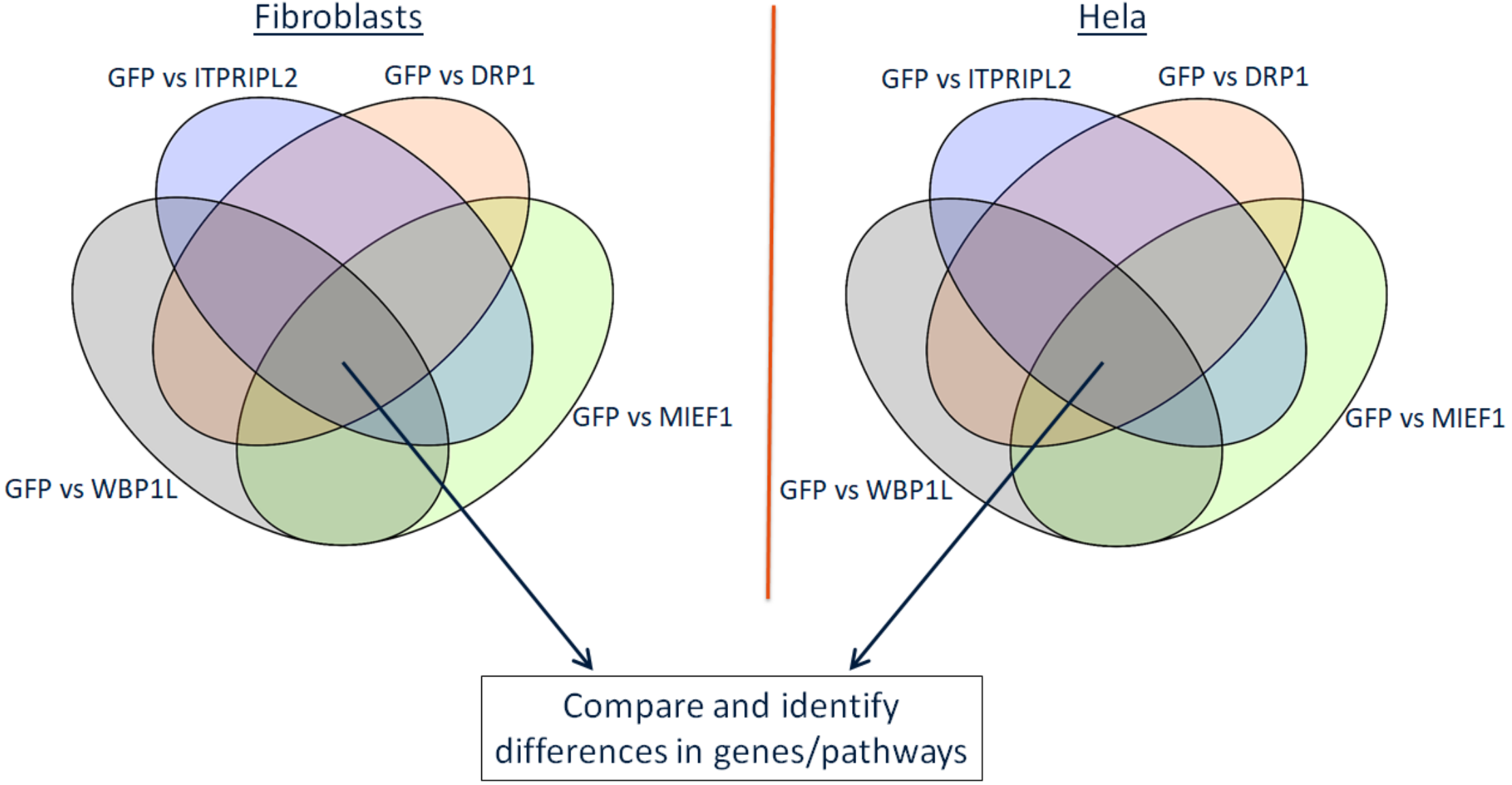




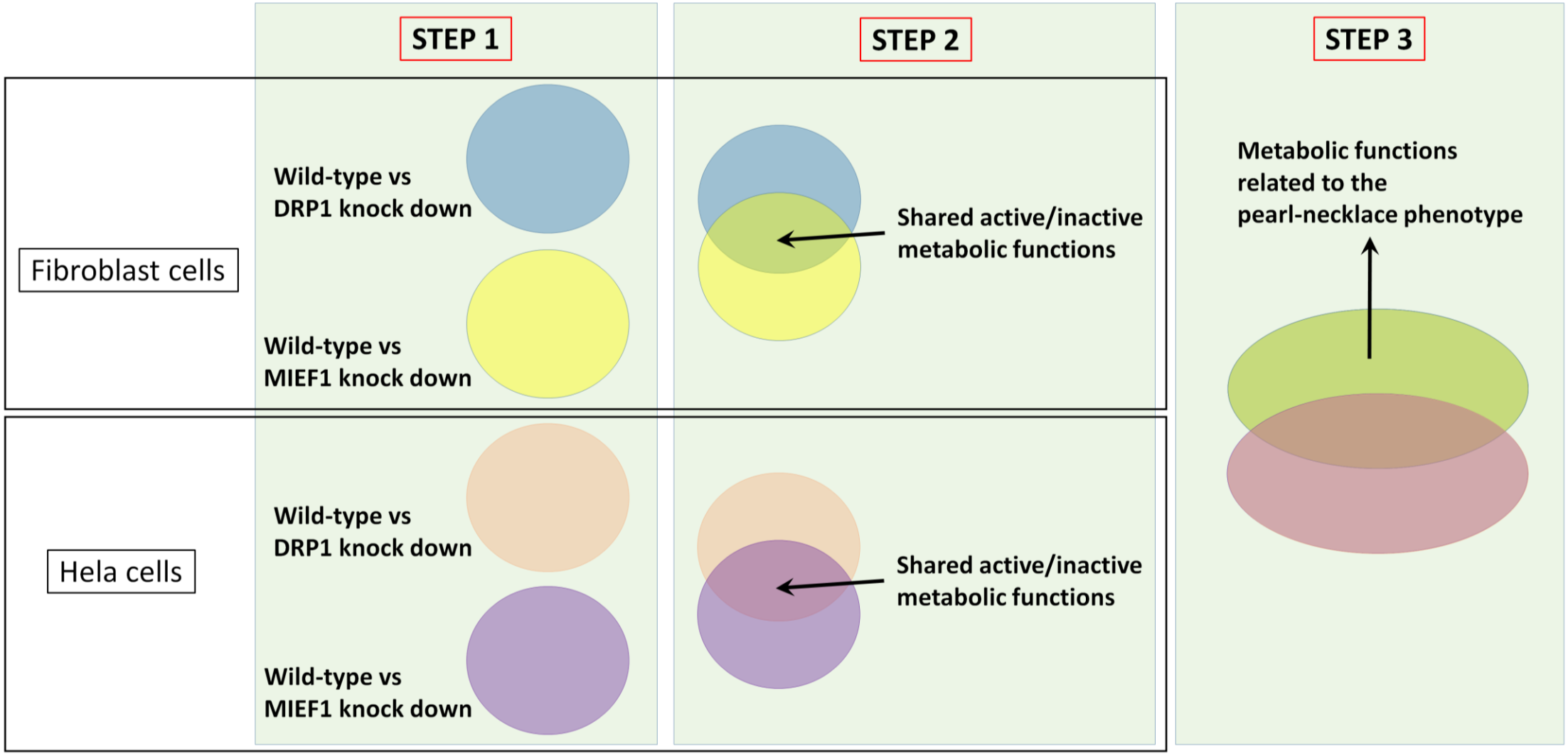
*Szklarcyk D, et al. (2017) Nucleic acids research*

*Kutmon M, et al. (2013) PloS one*

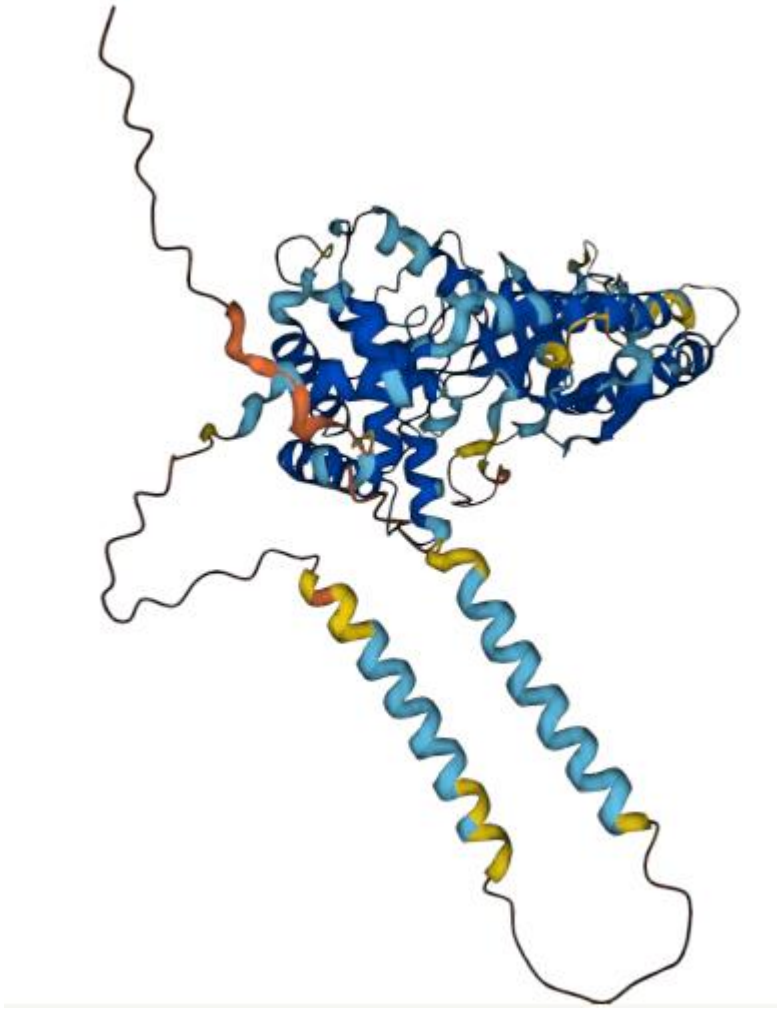
# RNAseq: DGE and pathway enrichment analysis

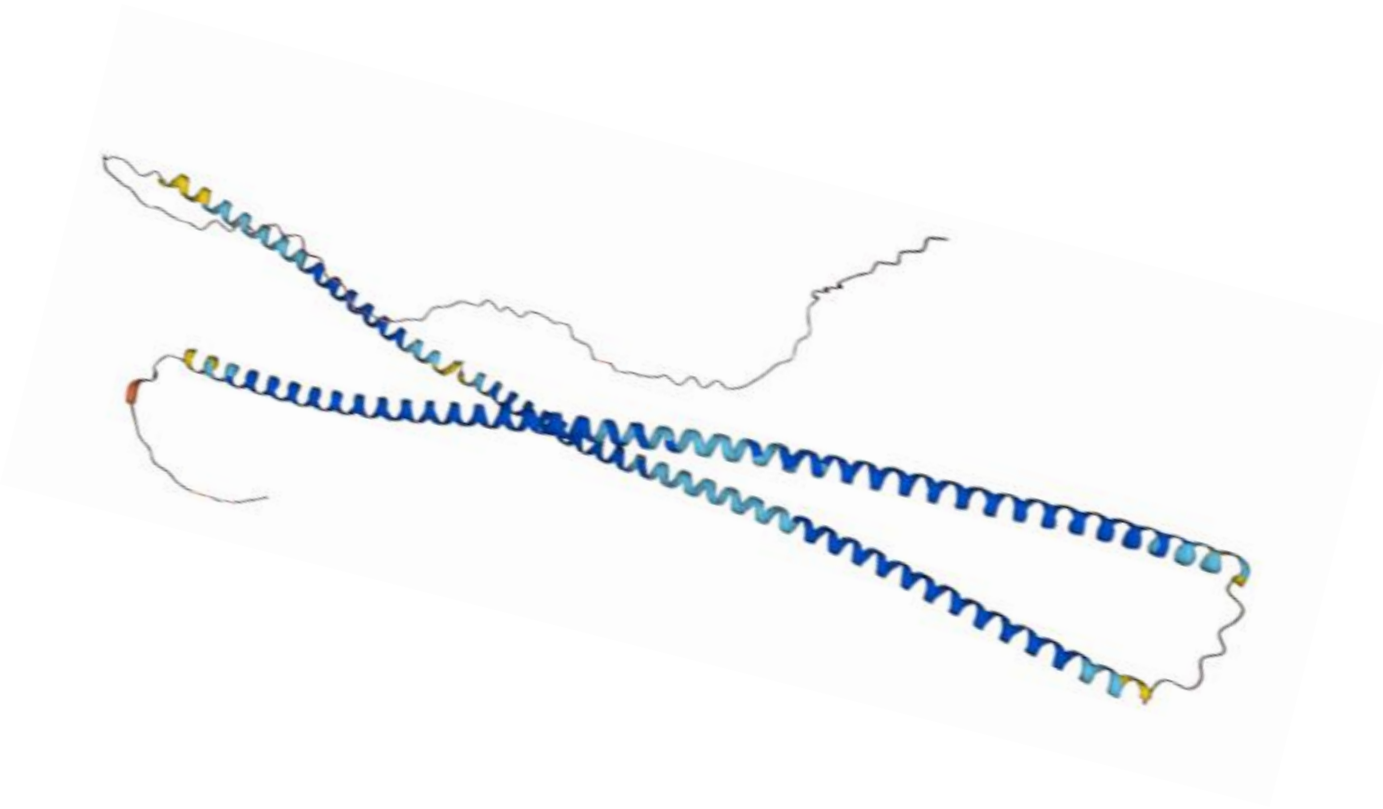


# RNAseq: Metabolic function analysis

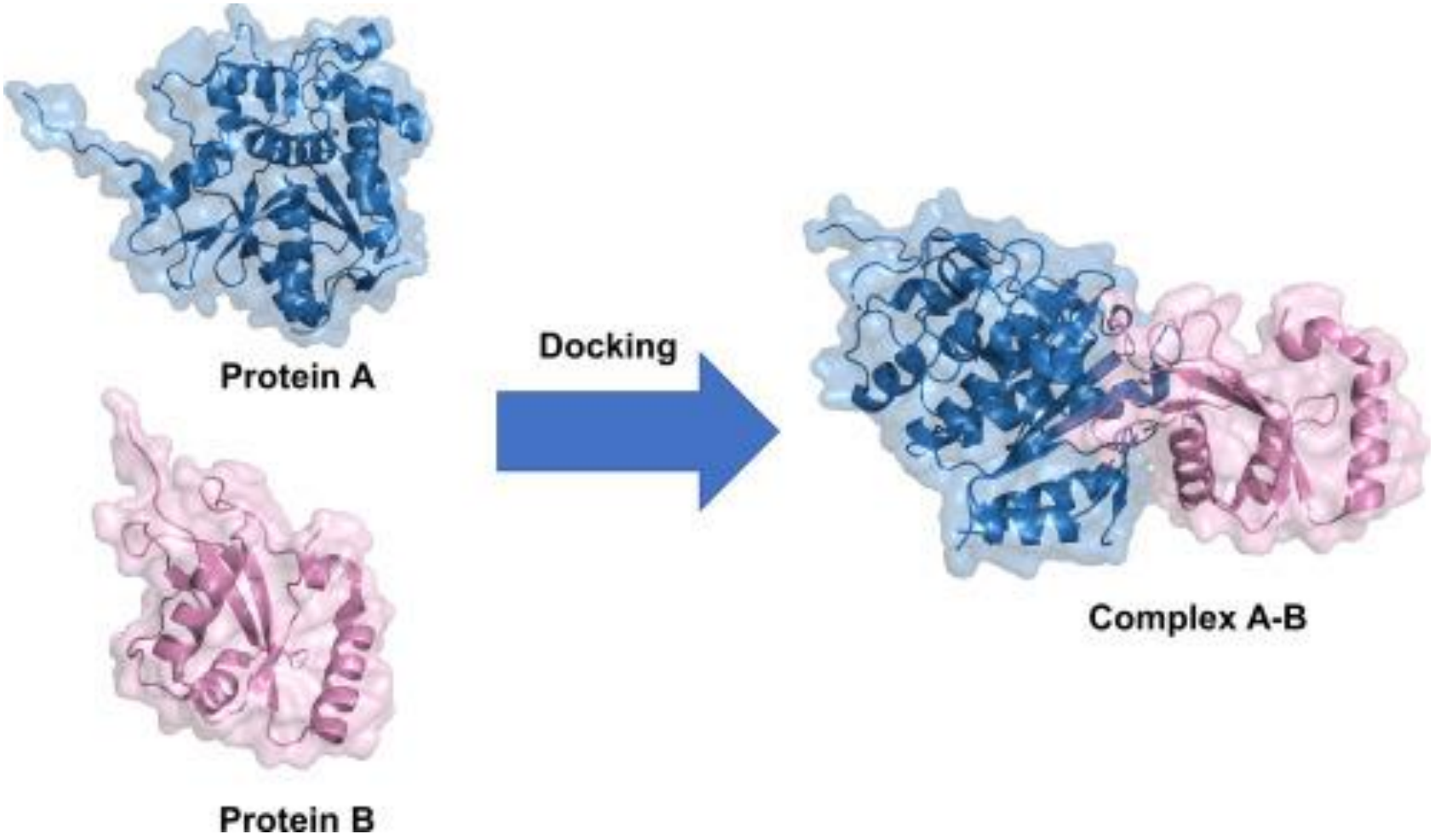


# Structural Biology: protein structure



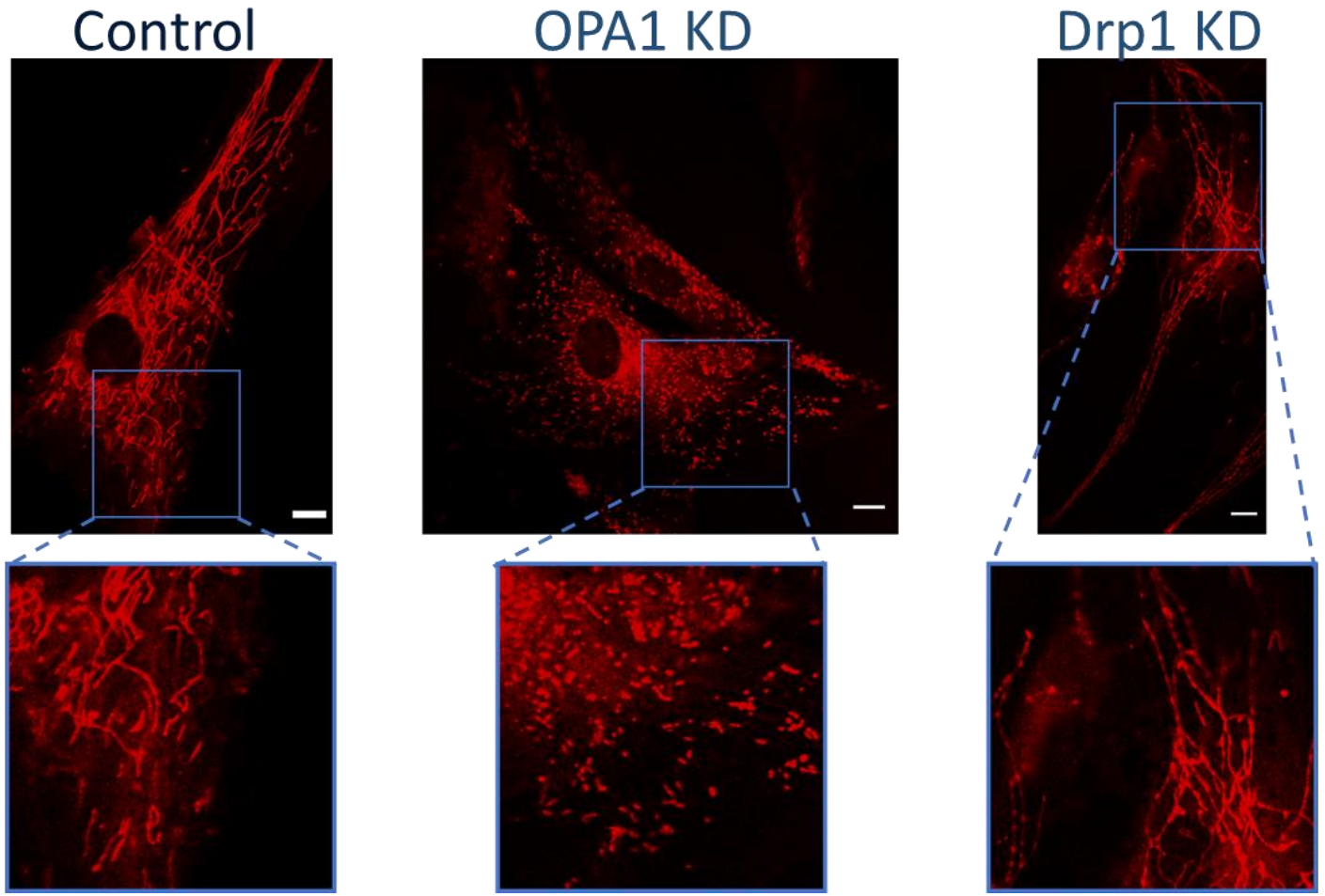


# Structural Biology : protein structure and interactions



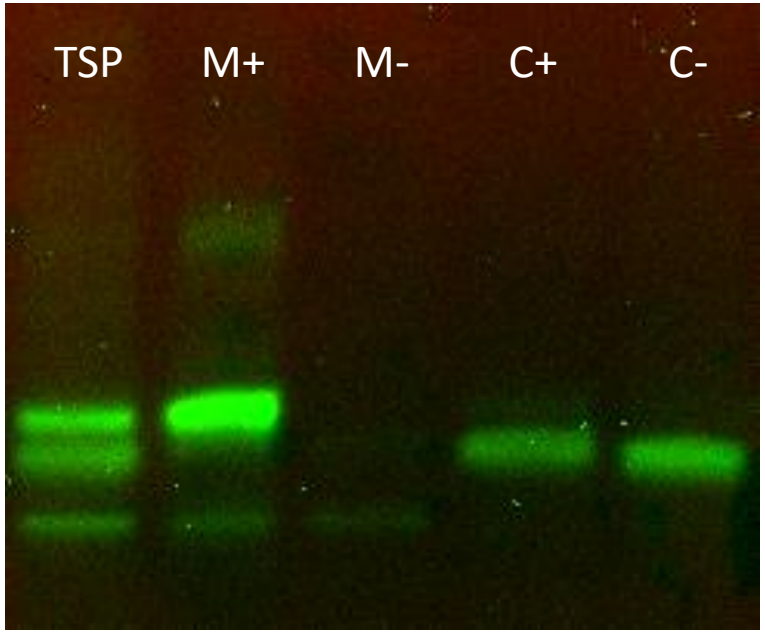
# Functional validation in the lab

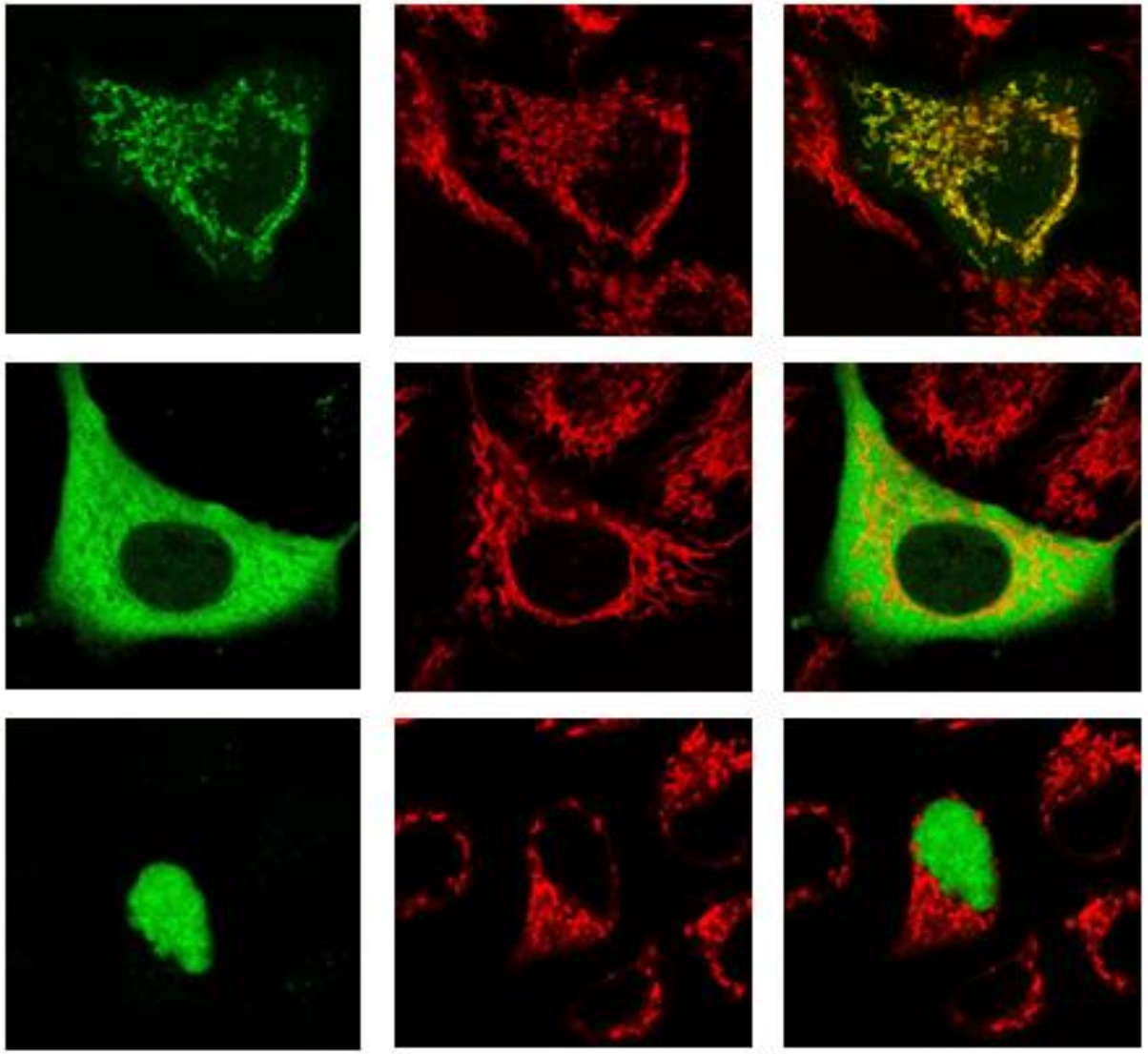
- Knock down (KD) studies



# Functional validation in the lab

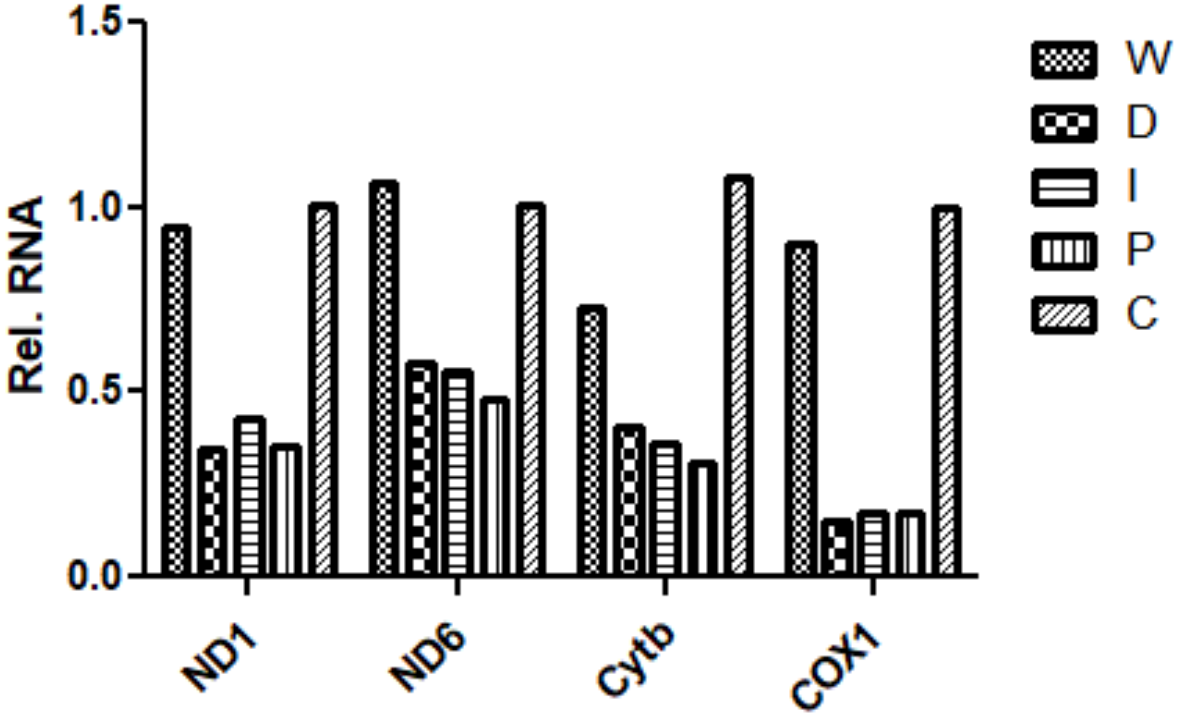
- Knock down (KD) studies
- Cellular localisation
  - Microscopy
  - Westernblot analysis



# Functional validation in the lab

- Knock down (KD) studies
- Cellular localisation
  - Microscopy
  - Westernblot analysis
- Gene expression analysis
- Protein-protein interaction
- .....



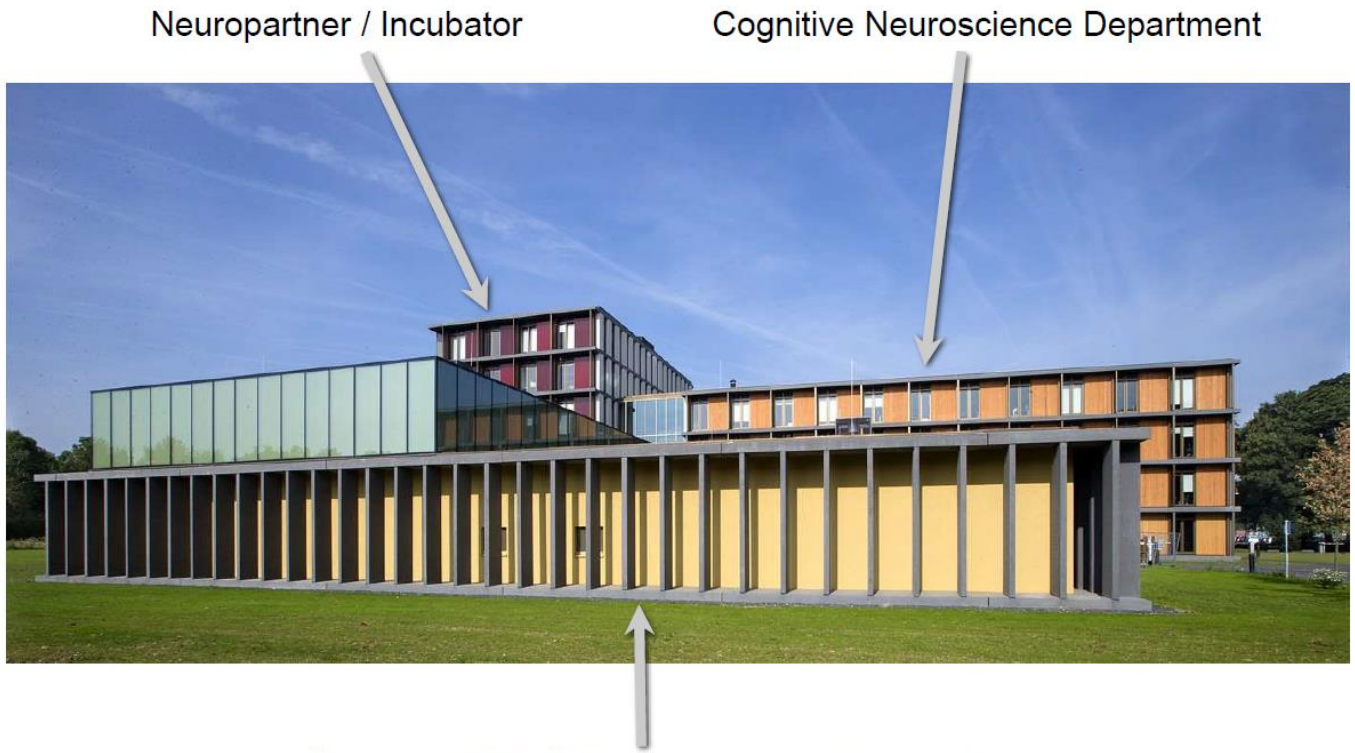
# Maastricht Brain Imaging Centre


## Judith Peters

*Associate professor*

# Human Neuroscience Research at UM

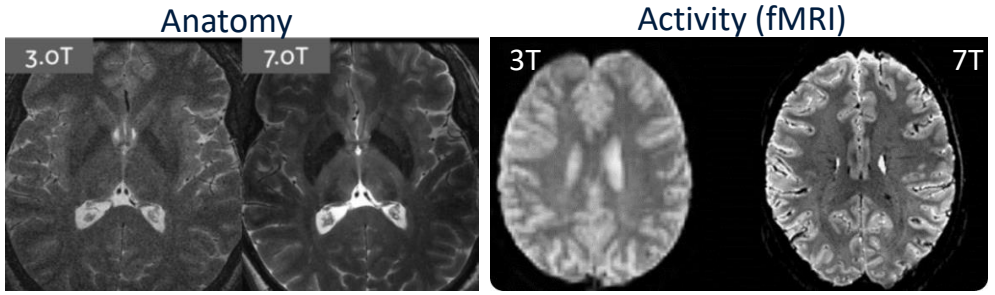
The **Maastricht Brain Imaging Centre**
Oxfordlaan 55 / Universiteitssingel 40
(Faculty of Psychology and Neuroscience)
www.maastrichtuniversity.nl/research/maastricht-brain-imaging-centre



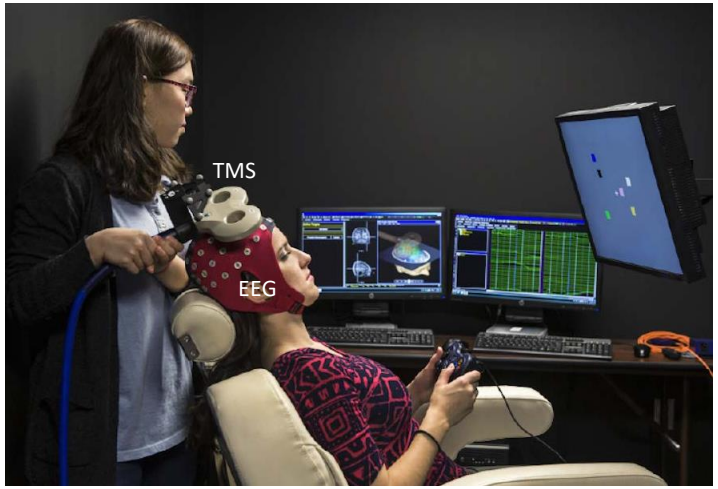

- Research line 1 — Auditory Perception and Cognition
- Research line 2 — Brain and Emotion
- Research line 3 — Computational architecture of visual processing streams
- Research line 4 — Brain and Language
- Research line 5 — Developmental Cognitive Neuroscience
- Research line 6 — Brain Stimulation and Cognition
- Research line 7 — MR Methods for Neuroscience
- Research line 8 — Perception, Attention and Learning
- Research line 9 — Methods
- Research line 10 — Multiscale Imaging of Brain Connectivity

# Neuroimaging labs at the Maastricht Brain Imaging Centre

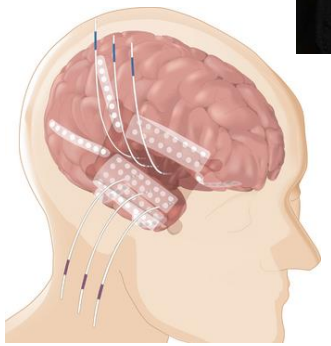
- (functional) Magnetic resonance imaging (MRI/fMRI)
  - ✓ 0 Tesla MR scanner (dummy)
  - ✓ 3 Tesla (3T) MR scanner
  - ✓ **7 Tesla** (7T) MR scanner
  - ✓ **9.4 Tesla** (9.4T) MR scanner




- Non-invasive Brain Stimulation (NIBS)



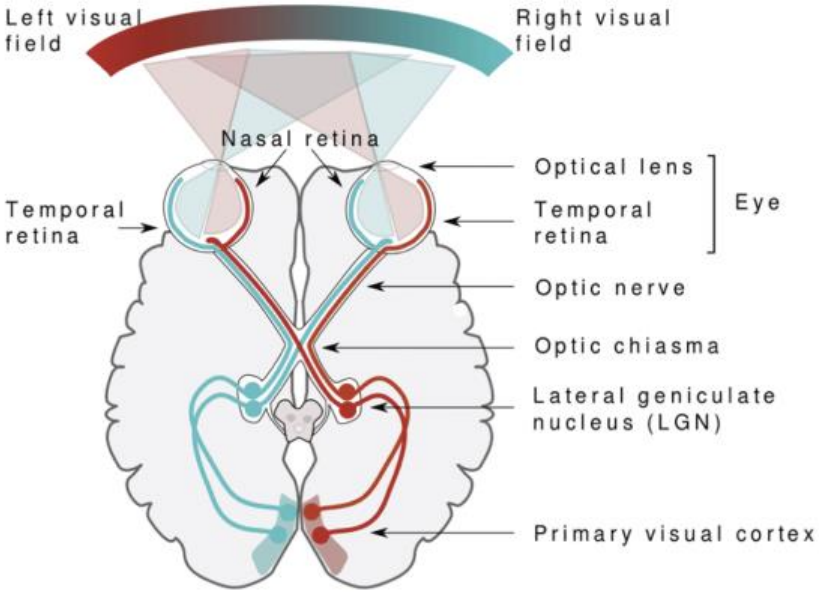

- Electroencephalography (EEG)
- Intracranial recordings (with MUMC+)

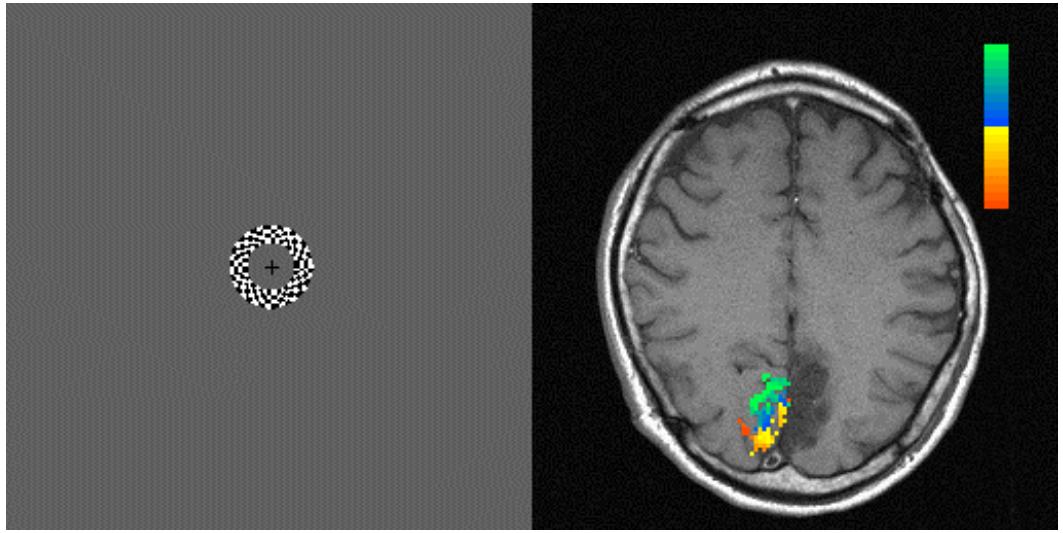


*For details on these Neuroimaging methods, see lecture week 6*

# Demo of a real-time 7 Tesla fMRI experiment

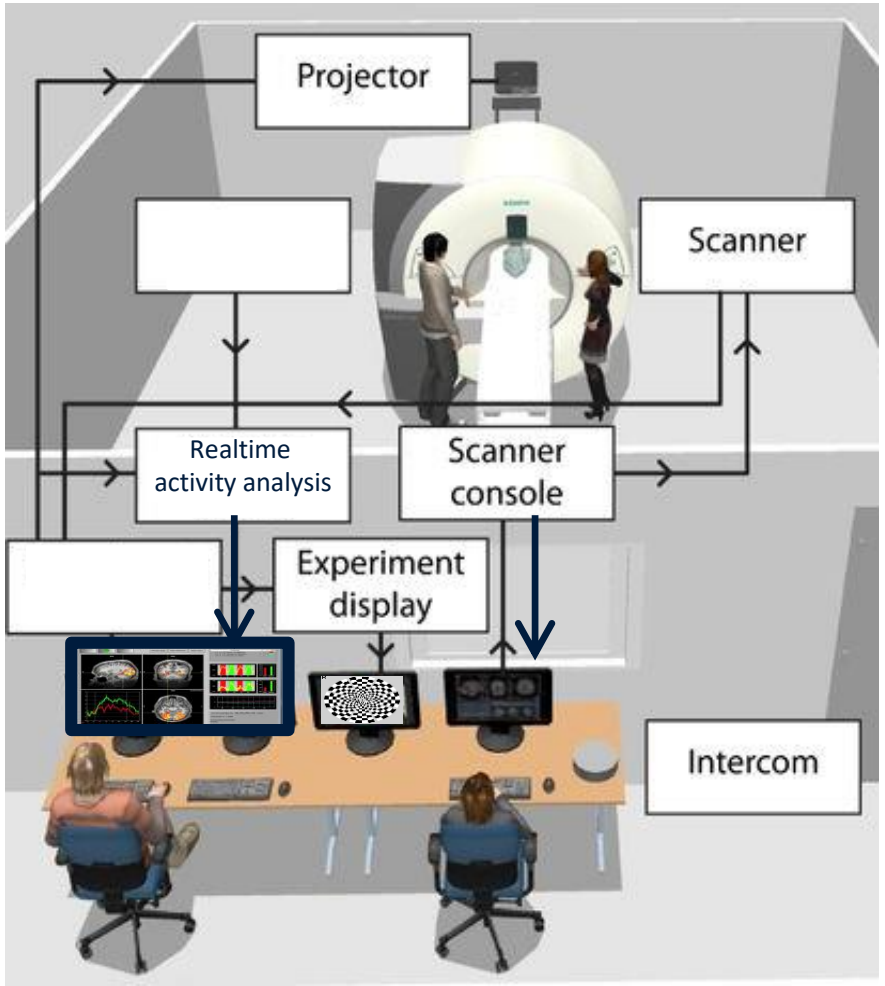
- Mapping of the visual field



# Demo of a real-time 7 Tesla fMRI experiment

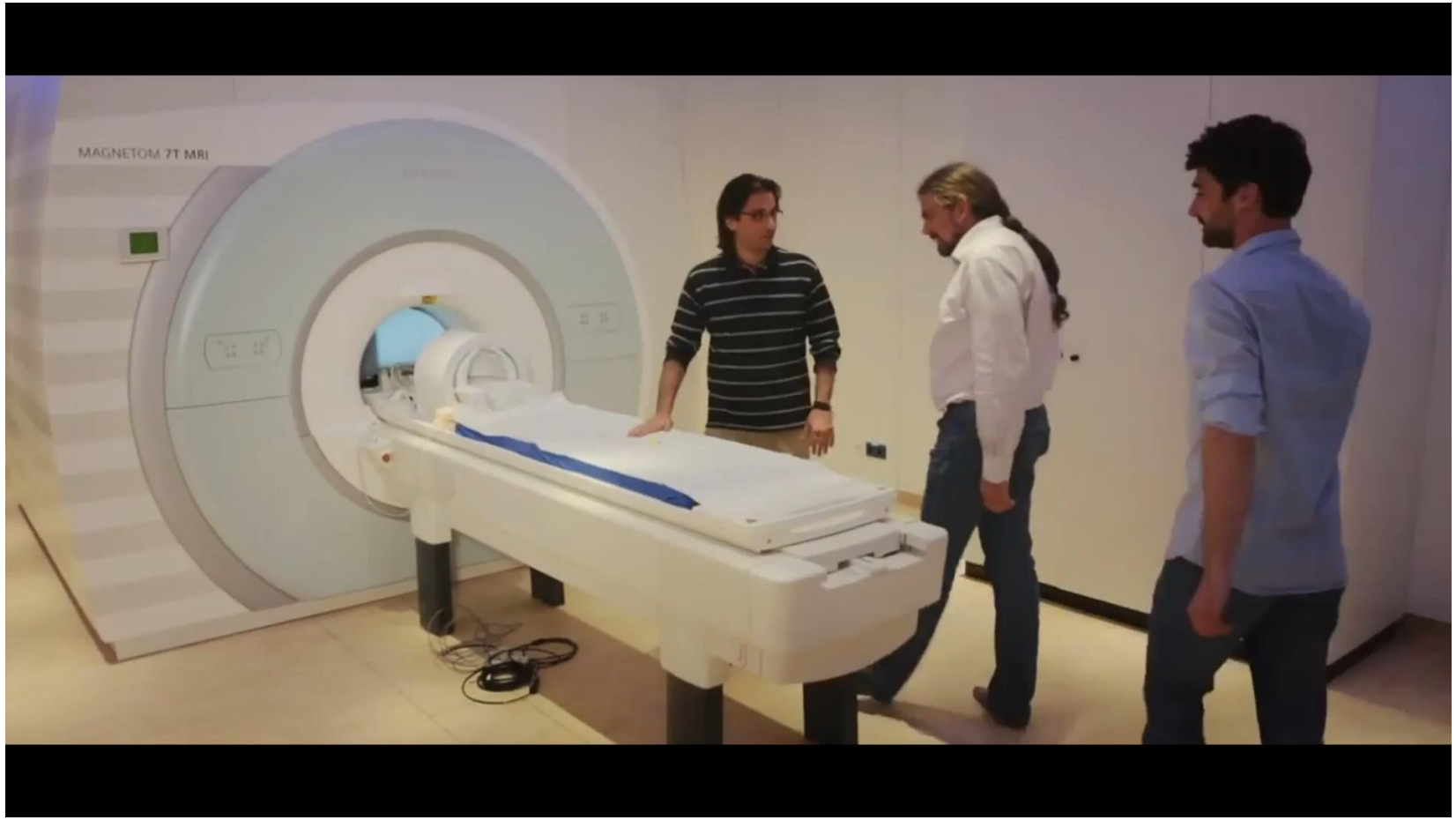
- Setup




Cf. 7T to earth's magnetic field (at equator):
$0.305 \times 10^{-4}$ Tesla

# Demo of a real-time 7 Tesla fMRI experiment

- Measuring activity in the visual perception brain areas



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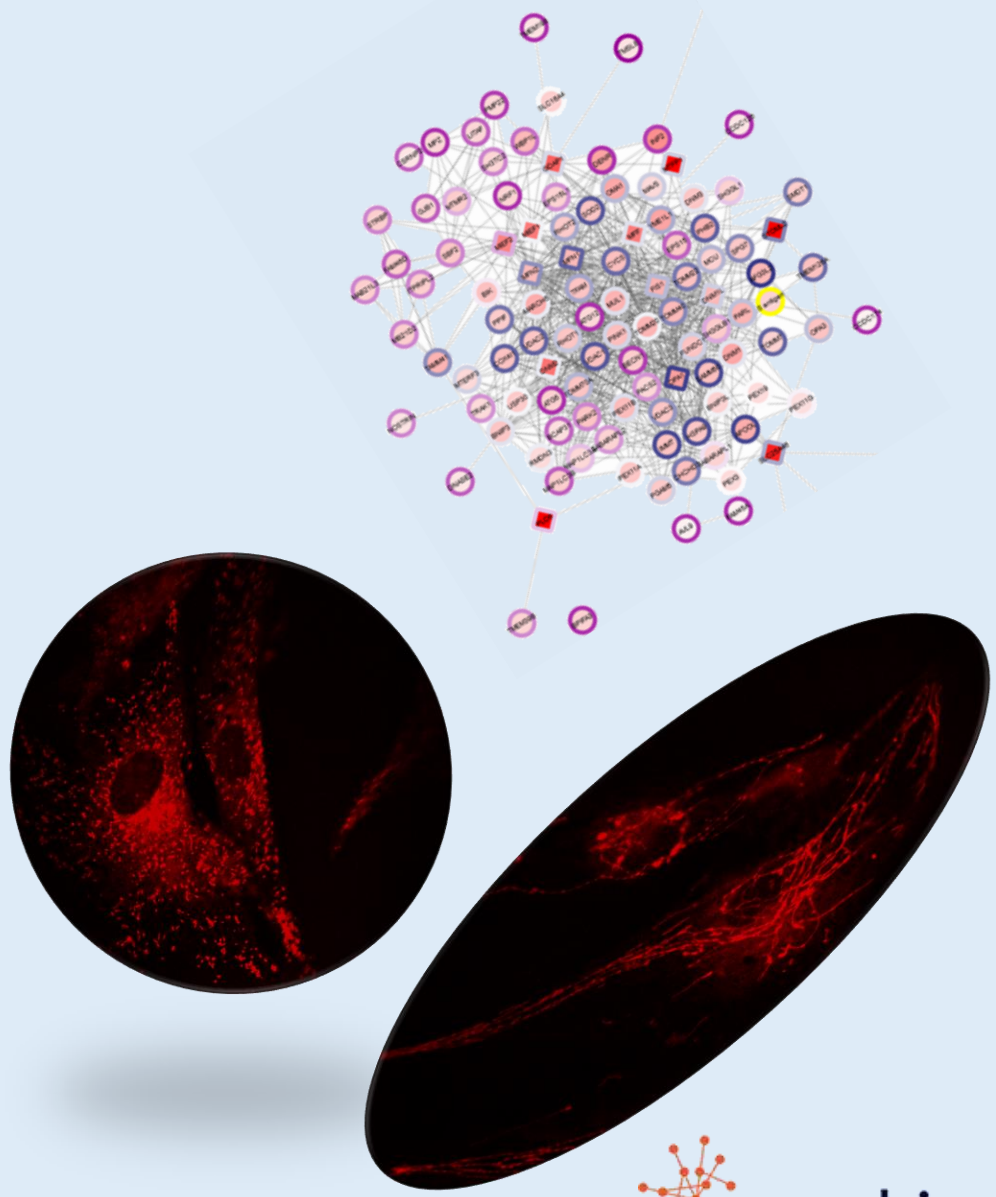
# Systems biology cycle



## Irene Hemel

*PhD student*

# Understanding mitochondrial dynamics



Irene Hemel

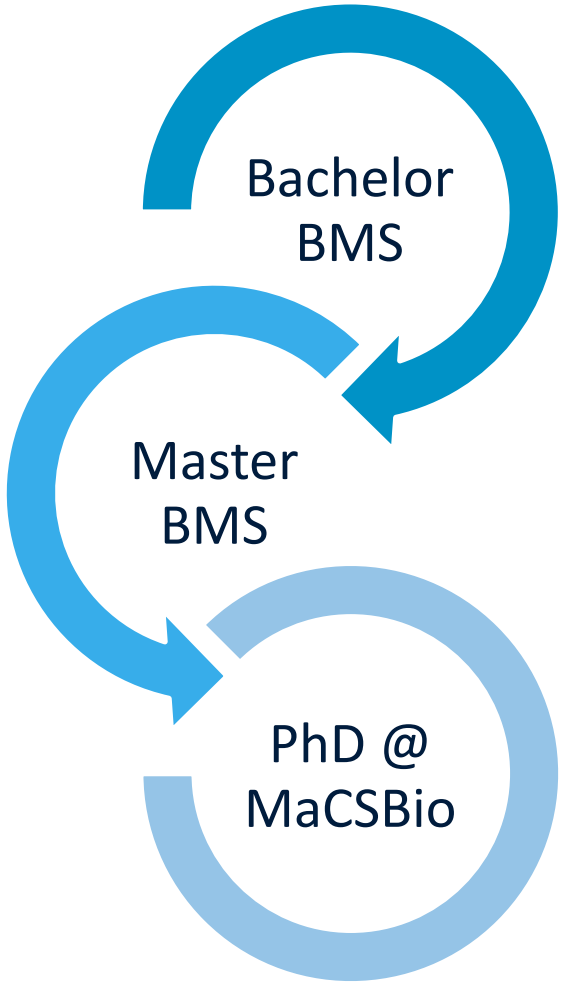
INT3007 – Systems Biology

21 November 2022

Maastricht University

macsbio
MAASTRICHT CENTRE FOR SYSTEMS BIOLOGY

# My background




Systems biology course

↓

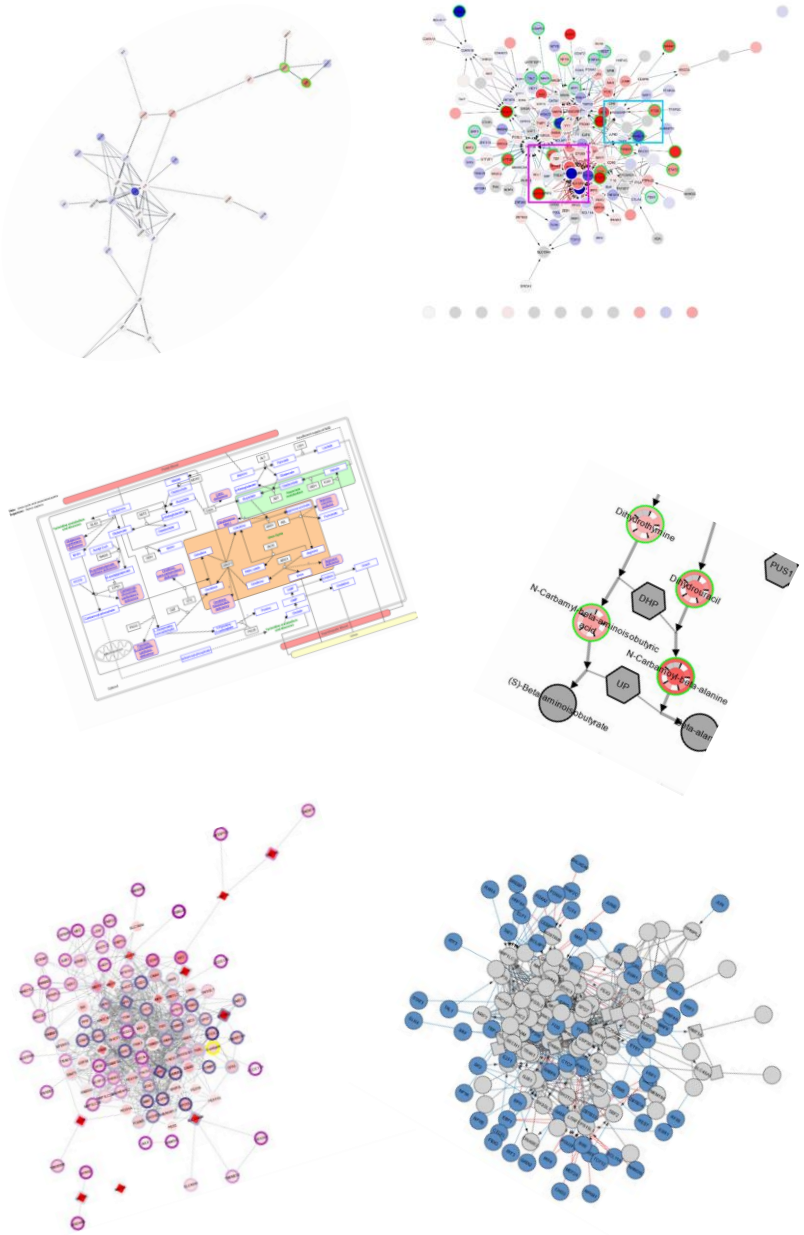
Internships at BiGCaT

- Epigenetics in SLE
- Automated visualization of biomarkers

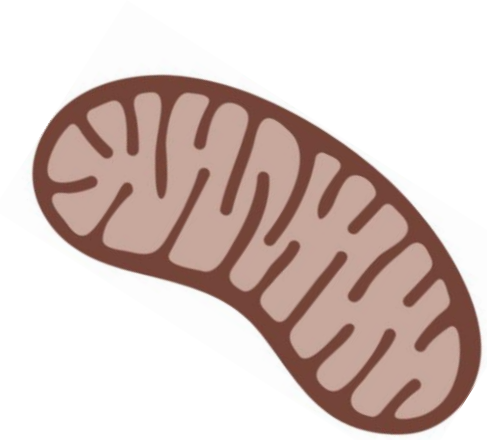
↓

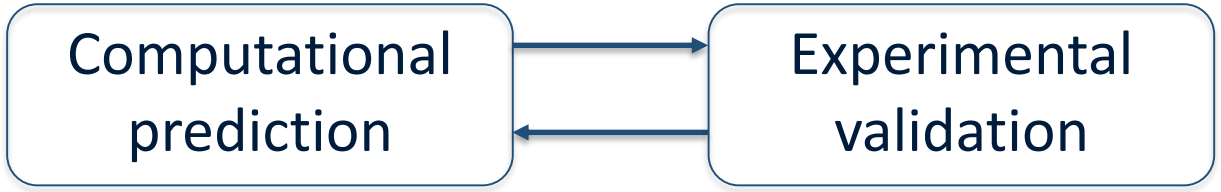
Internship at MaCSBio

- Protein identification in mitochondrial dynamics



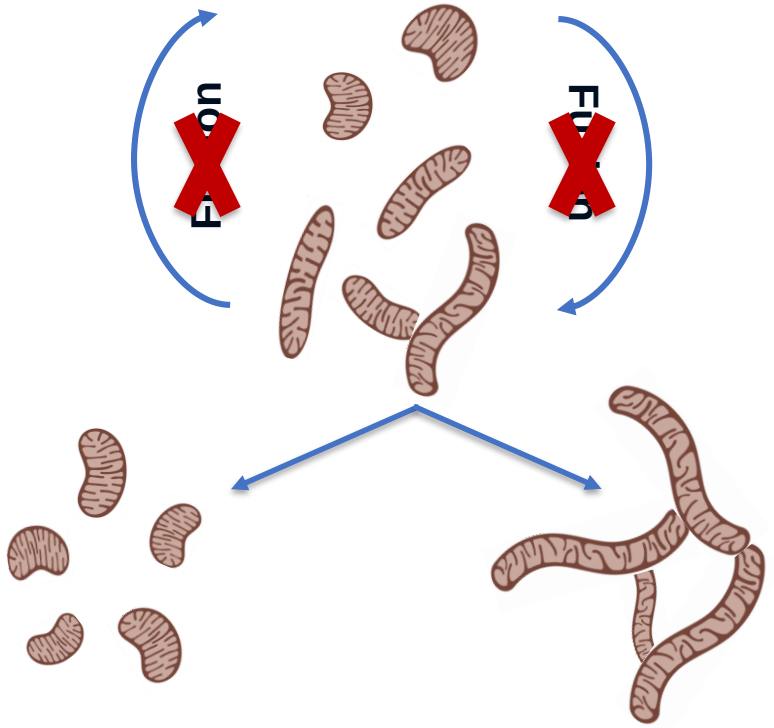
# Protein identification in mitochondrial dynamics





# Mitochondrial dynamics

- Mitochondria adapt morphology to cellular needs
  - Through fission and fusion
- Defects linked to neurological disorders
  - Charcot-Marie-Tooth disease
  - Alzheimer's disease
- Not all involved proteins known



# Computational approach

Query list based on literature

↓

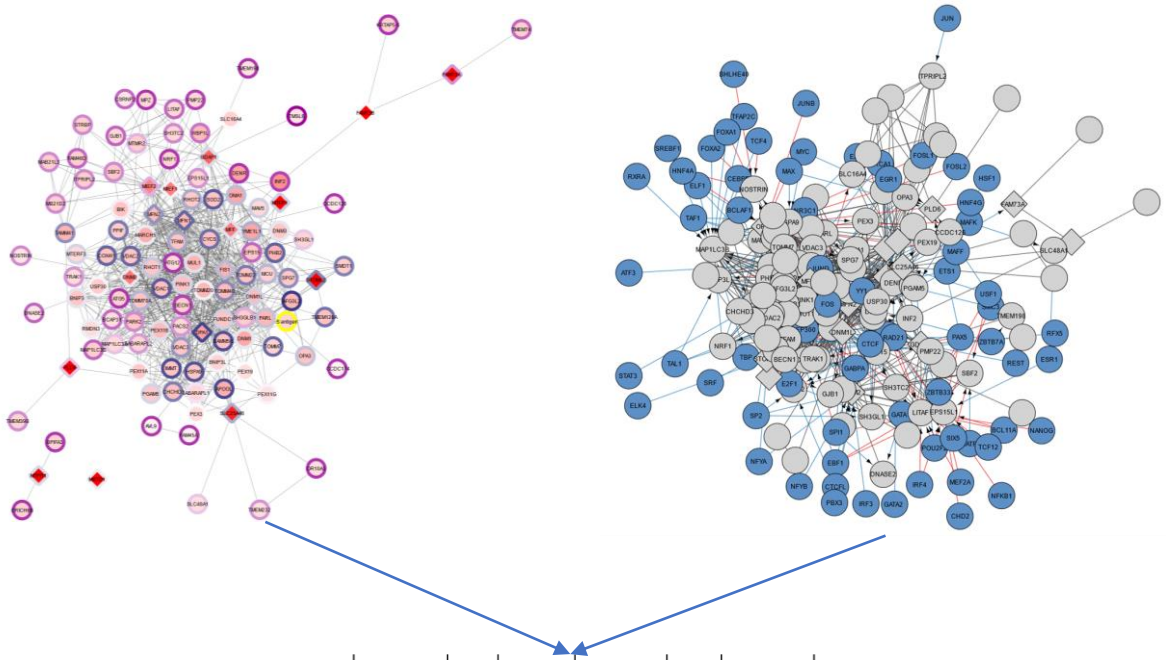
Create a protein-protein interaction and transcription factor network

↓

Combined analysis from networks

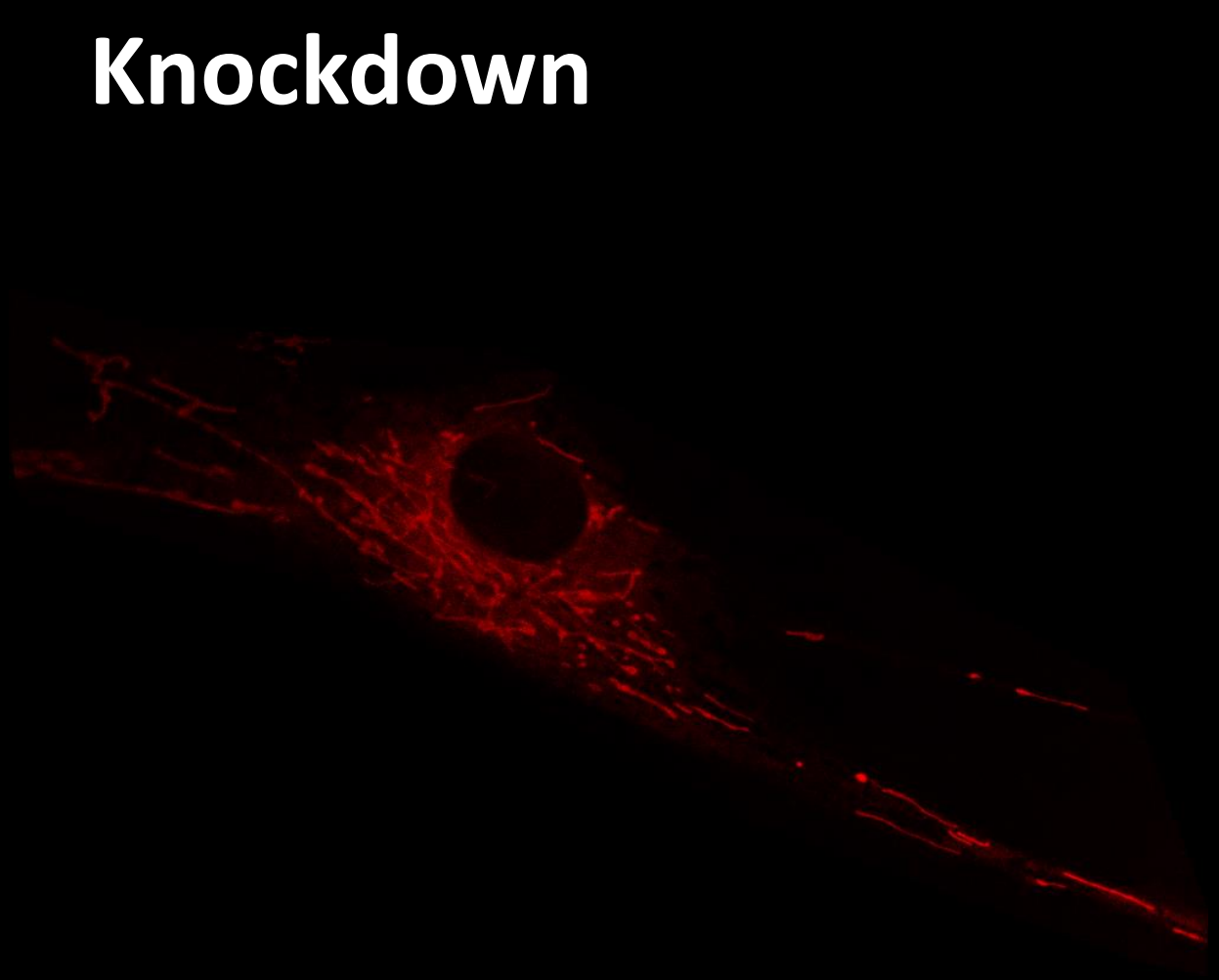
↓

Selected candidates
→ Without function



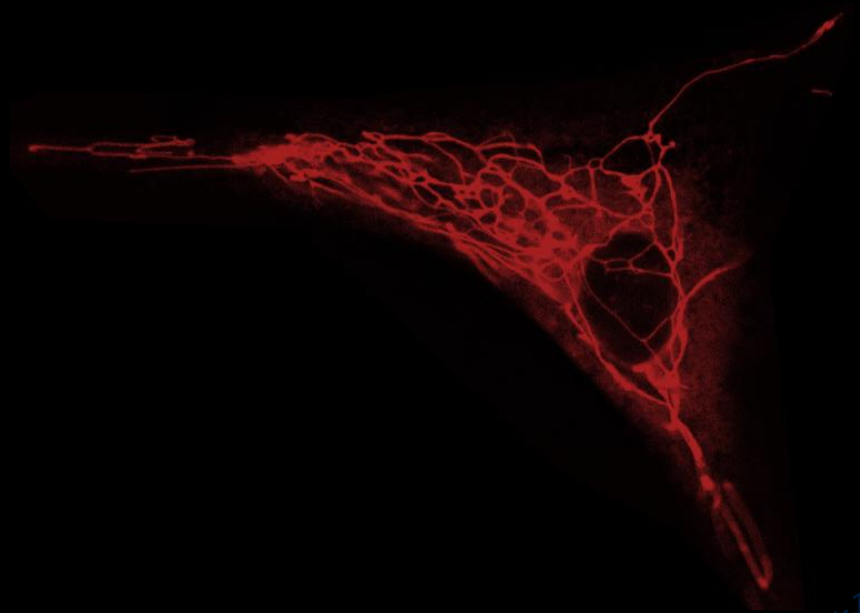
| Protein | Heat propagation | Heat rank | MitoCarta Score | Input connections | Degree | Transcription factors | Total score |
|---|---|---|---|---|---|---|---|
| TOMM40 | 0.131182 | 15 | 20.24 | 6 | 27 | 4 | 5.5 |
| PINK1 | 0.120645 | 20 | 6.99 | 7 | 45 | 2 | 4.5 |
| TOMM20 | 0.140519 | 12 | 2.21 | 9 | 39 | 1 | 4 |
| MAP1LC3B | 0.094725 | 50 | -8.28 | 4 | 20 | 5 | 4 |
| INF2 | 0.216132 | 1 | -10.01 | 6 | 6 | 1 | 3.5 |
| DENR | 0.175506 | 2 | -10.7 | 8 | 13 | 1 | 3.5 |
| DNM1 | 0.166562 | 5 | 4.05 | 9 | 22 | 0 | 3.5 |
| PHB2 | 0.144878 | 9 | 26.92 | 4 | 17 | 2 | 3.5 |
| MUL1 | 0.14382 | 10 | 5.2 | 7 | 20 | 1 | 3.5 |
| PARL | 0.141301 | 11 | 10.25 | 6 | 21 | 0 | 3.5 |
| CYCS | 0.120711 | 19 | 24.94 | 6 | 29 | 0 | 3.5 |
| VDAC1 | 0.118752 | 22 | 28.18 | 6 | 40 | 0 | 3.5 |
| TOMM22 | 0.118075 | 23 | 22.57 | 5 | 20 | 1 | 3.5 |
| COX4I1 | 0.115569 | 25 | 26.47 | 5 | 28 | 0 | 3.5 |
| HSPA9 | 0.107546 | 37 | 29.55 | 4 | 29 | 2 | 3.5 |
| EPS15 | 0.10552 | 41 | -8.07 | 3 | 8 | 3 | 3.5 |
| YME1L1 | 0.171633 | 3 | 13.73 | 8 | 18 | 0 | 3 |
| OMA1 | 0.167029 | 4 | 11.22 | 8 | 17 | 0 | 3 |
| MARCH5 | 0.15741 | 7 | 3.27 | 8 | 19 | 0 | 3 |
| AFG3L2 | 0.137422 | 13 | 33.61 | 5 | 19 | 0 | 3 |

# Knockdown



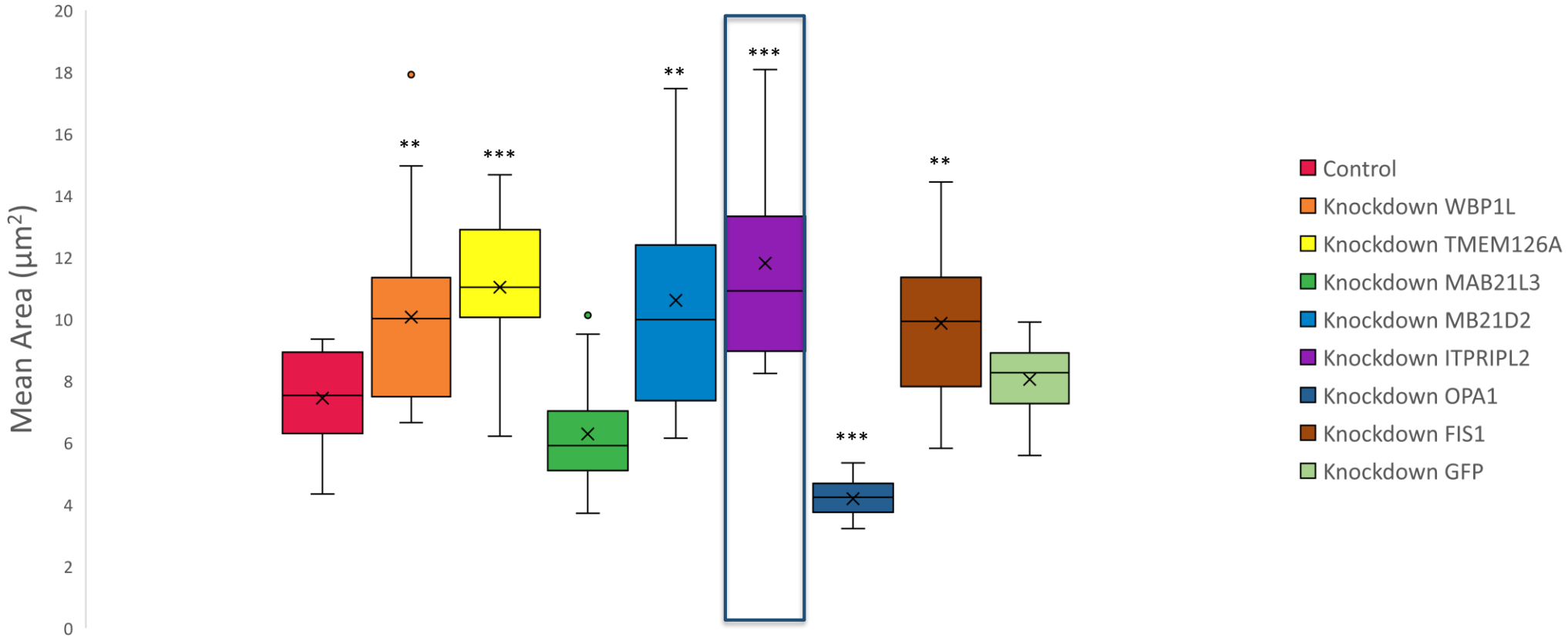
Control

TMEM126A



ITPRIPL2

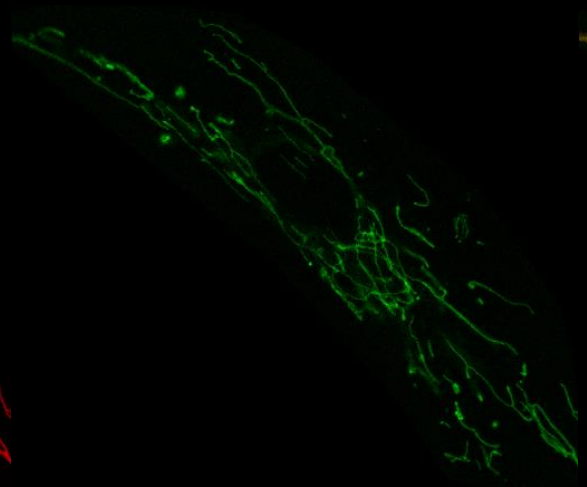
# Morphology changes



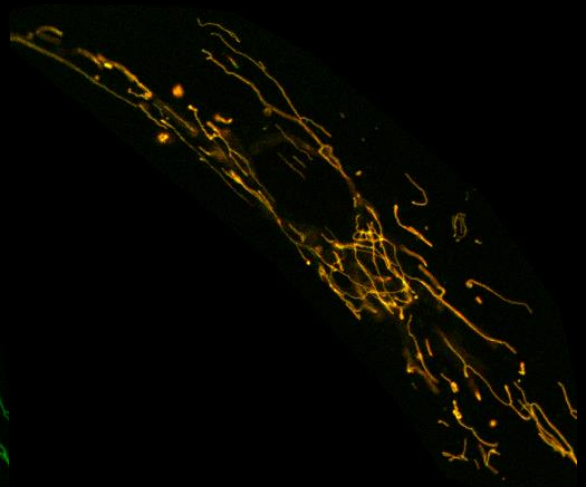
# Localisation

Overexpression tagged protein → overlap with organelle staining

Protein of interest



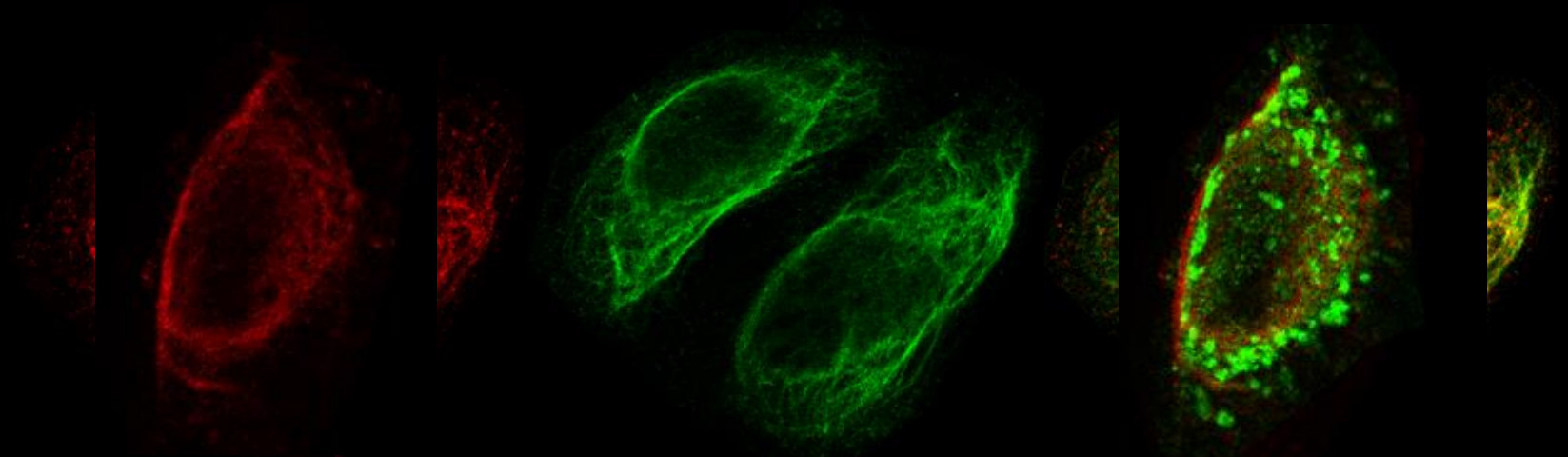
Organelle



Combined

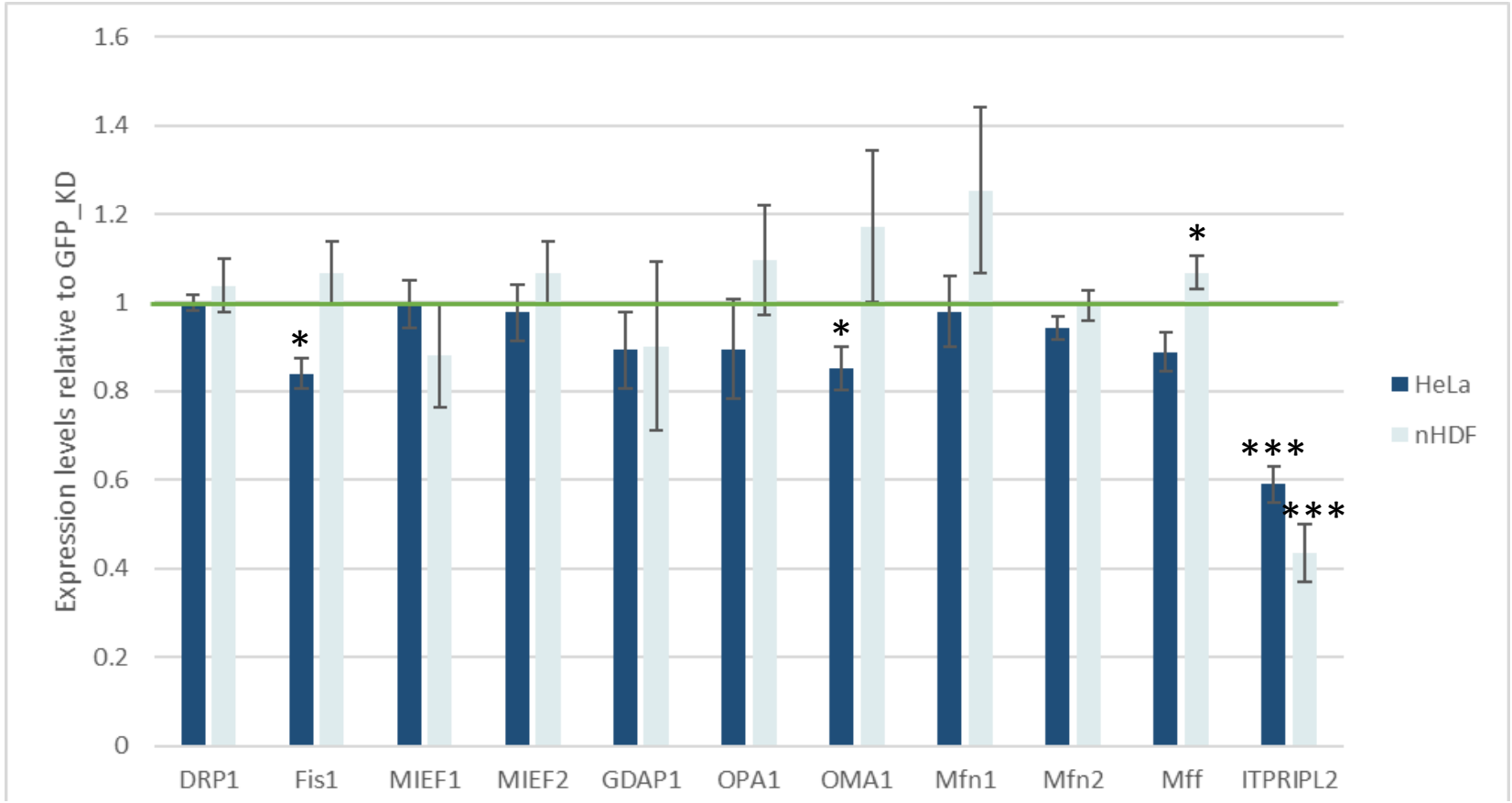
# ITPRIPL2

- Not mitochondrial
- Cytoskeleton component?
  - Intermediate filaments



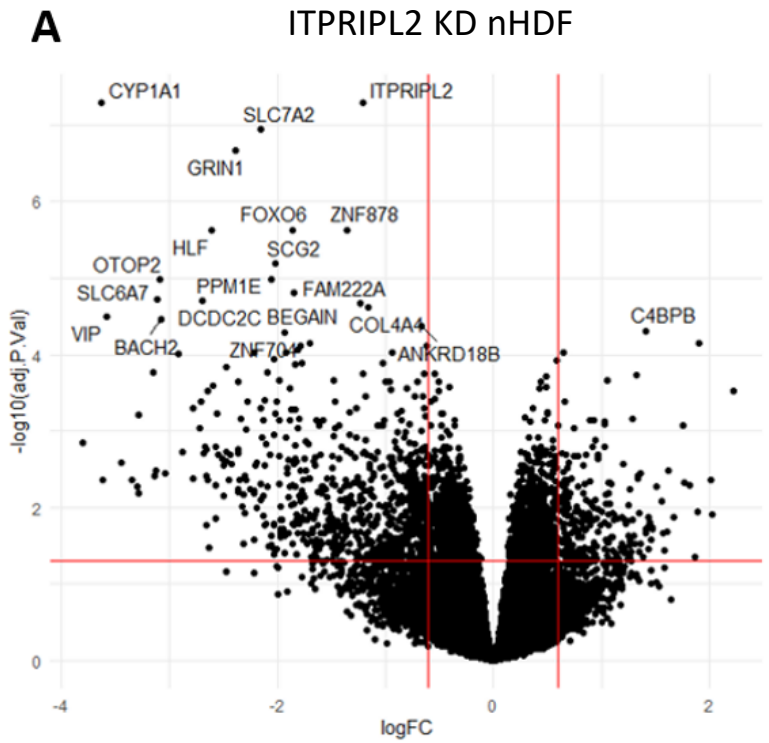
# Fission/fusion genes

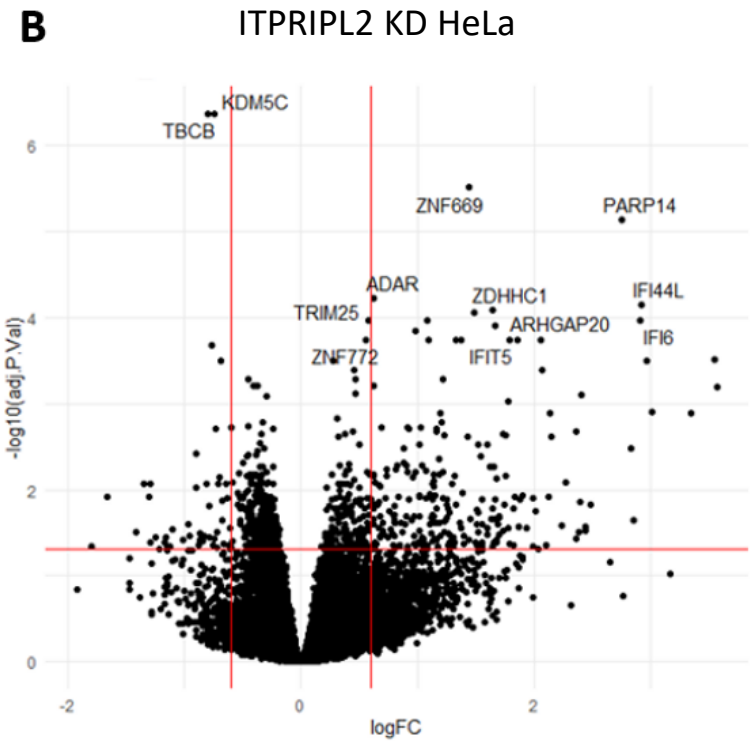
- Minor changes in mRNA levels upon ITPRIPL2 knockdown

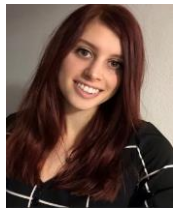


# RNAseq

- RNAseq data for GFP and ITPRIPL2 knockdown
  - From both nHDF and HeLa cells

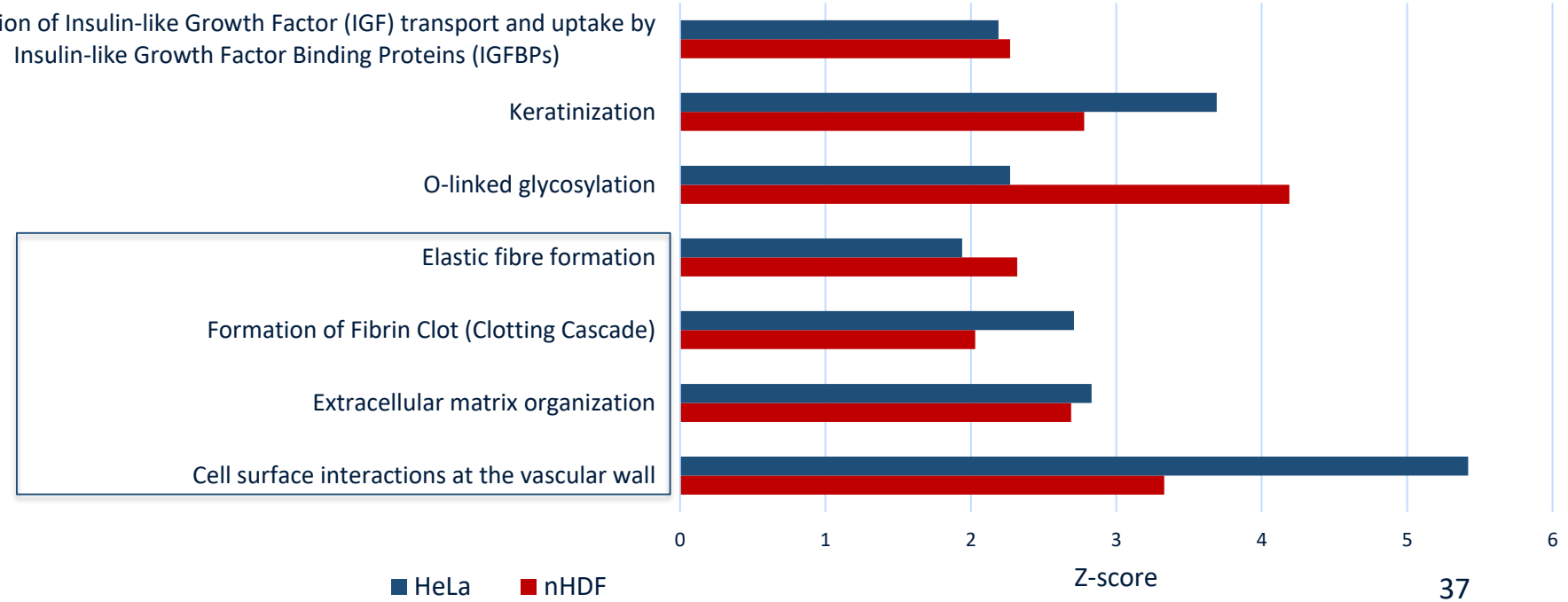


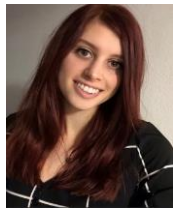



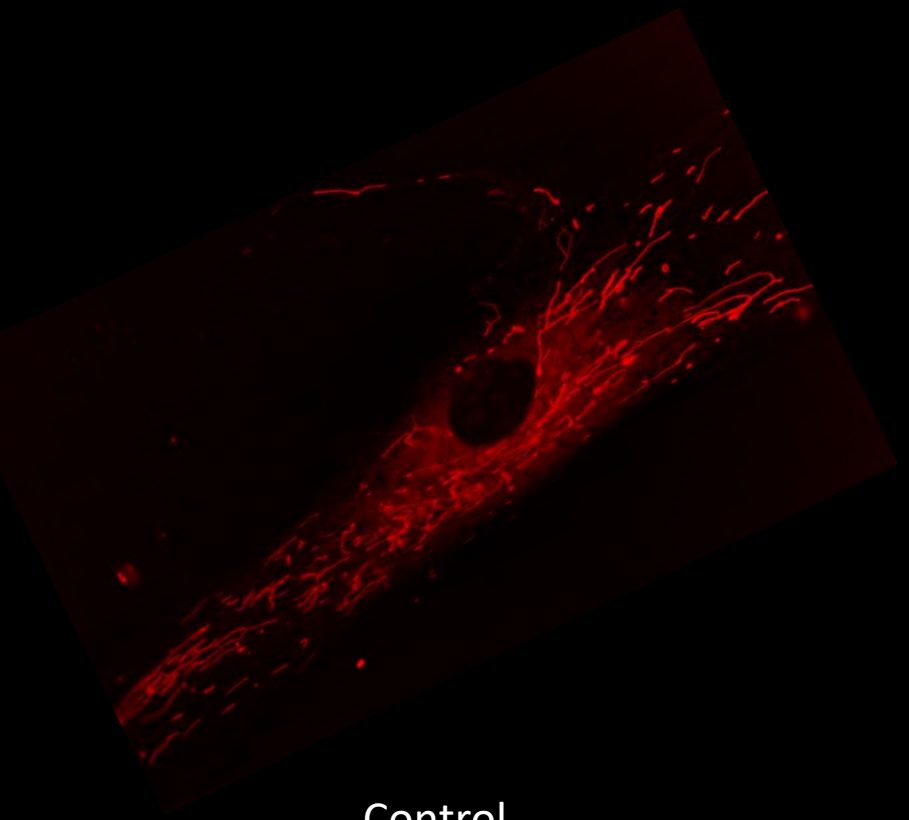
# RNAseq

- Pathway enrichment analysis
  - Pathways enriched in both cell types
  - Immune and cell cycle related pathways
  - 7 pathways linked to vimentin
    - Wound healing

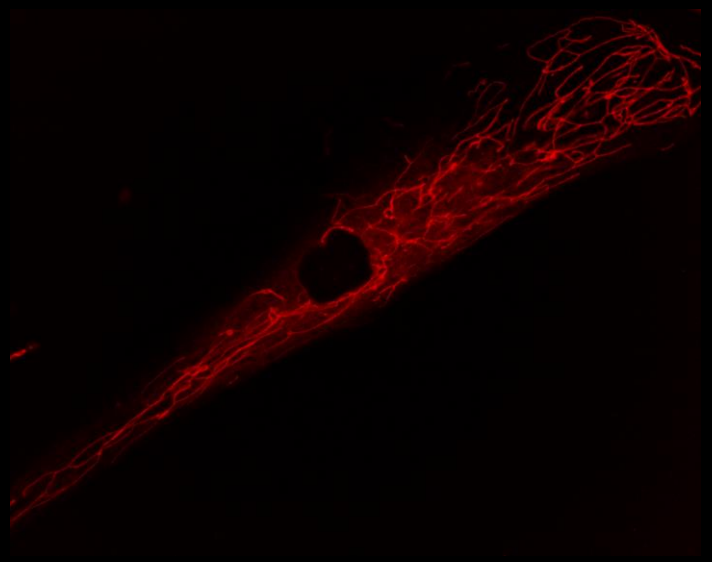


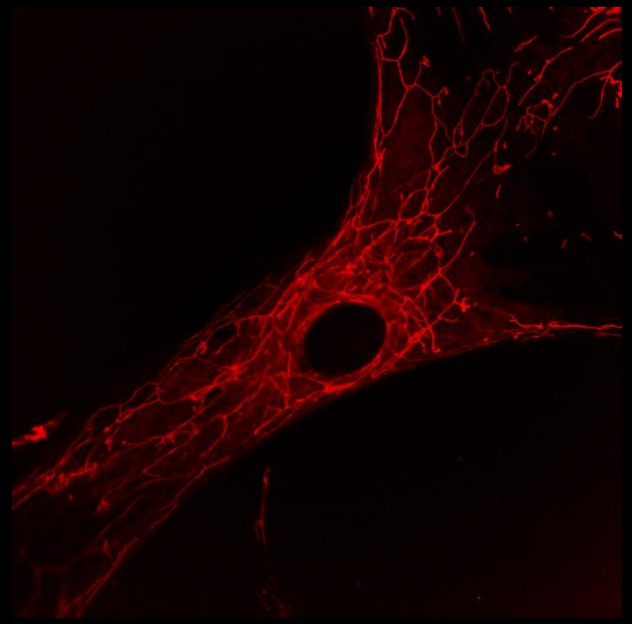
# Intermediate filaments and mitochondrial dynamics



Control



ITPRIPL2
knockdown



Vimentin
knockdown

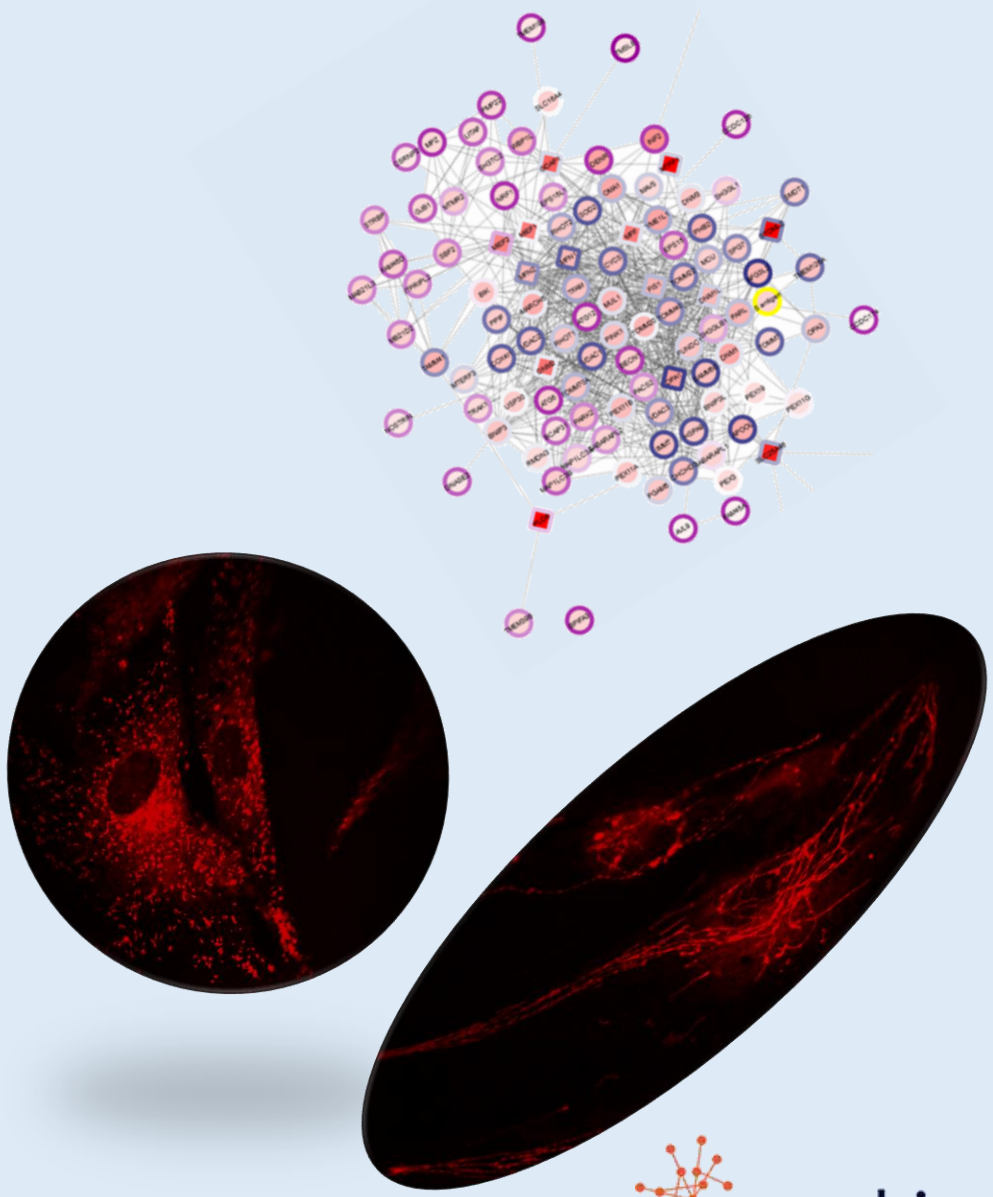
# Conclusions

- PPi network analysis can identify mitochondrial dynamics related proteins

- ITPRIPL2 is associated with intermediate filaments
  - Prove direct interaction → Pull-down
  - Structural modelling
  - Evolutionary conservation

- Intermediate filaments play a crucial role in fission
  - How do ITPRIPL2 and IF in general influence fission?
  - Analyse RNAseq data in more detail

# Questions?



Maastricht University

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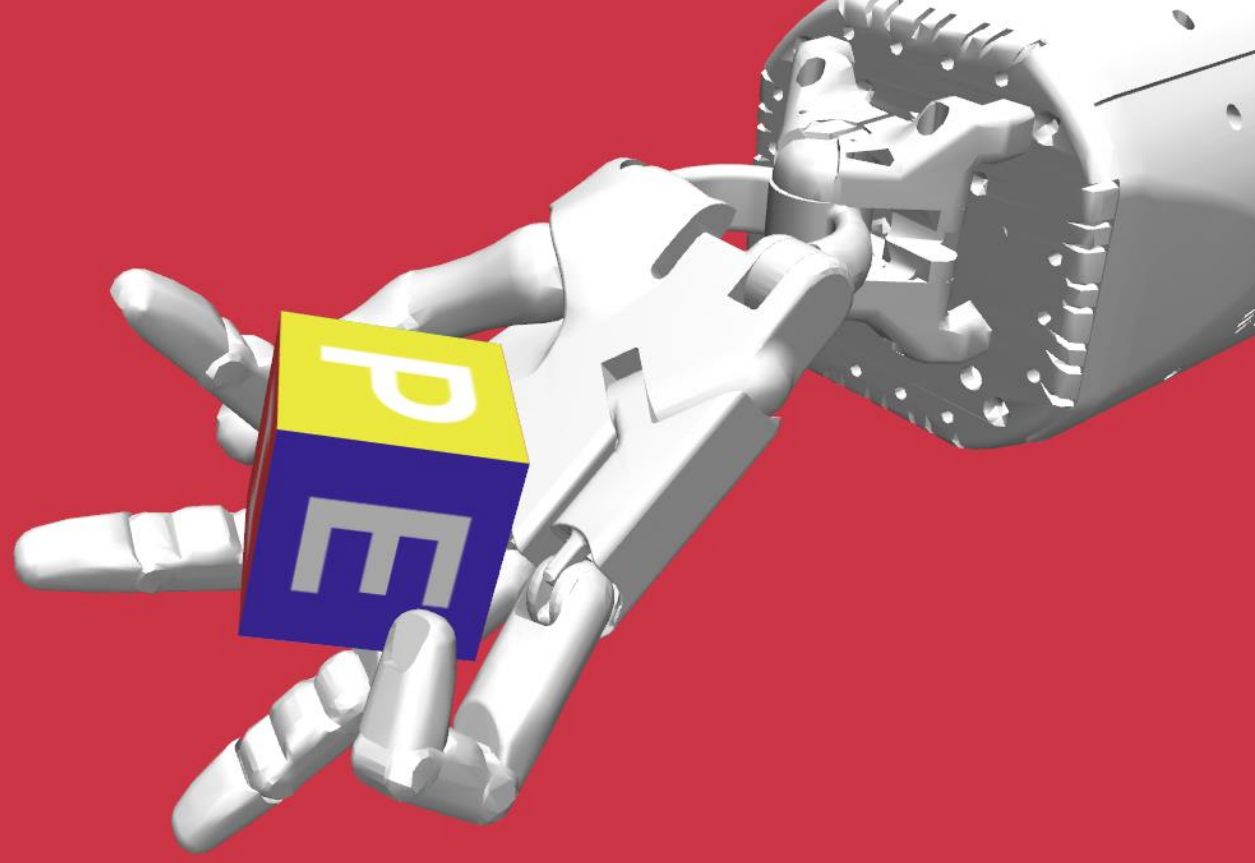
MAASTRICHT CENTRE FOR SYSTEMS BIOLOGY

# Cognitive Neuroscience


## Tonio Weidler

*PhD student*




CCN Maastricht

# HUMAN DEXTERITY

## GOAL DRIVEN MODELS OF THE SENSORIMOTOR SYSTEM

Tonio Weidler

November 2022

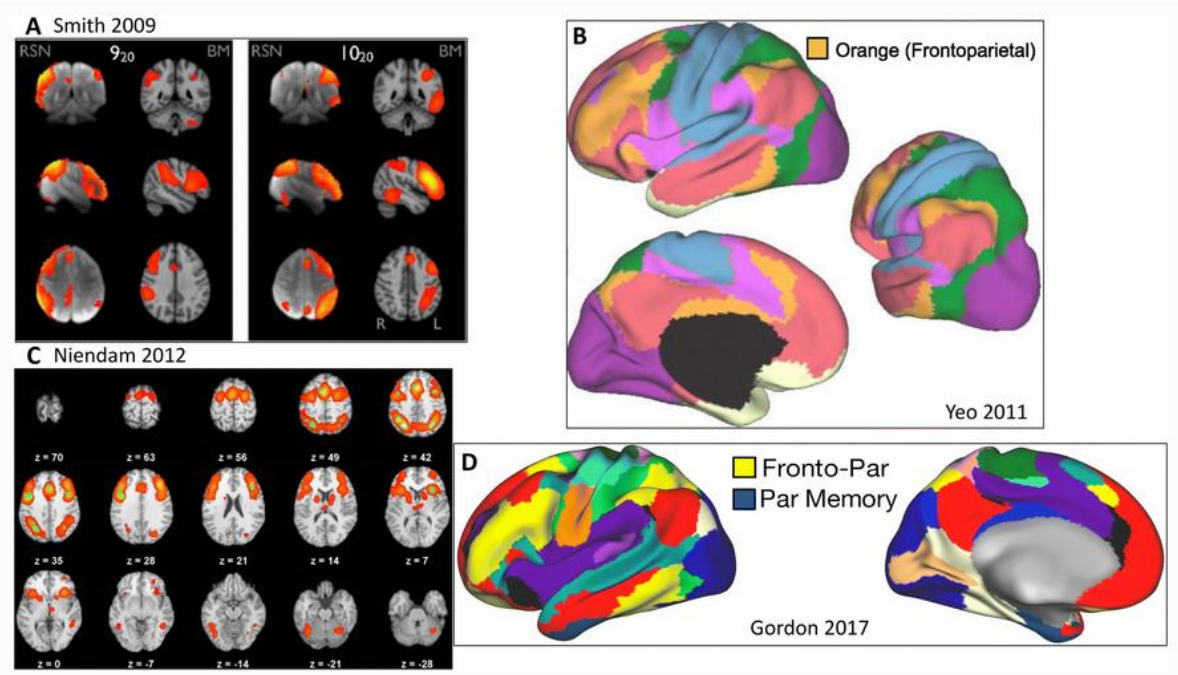
EBRAINS

Human Brain Project

STUDYING THE NEUROCOMPUTATIONS UNDERLYING

# HUMAN DEXTERITY

A **large-scale brain network** enables unmatched dexterity

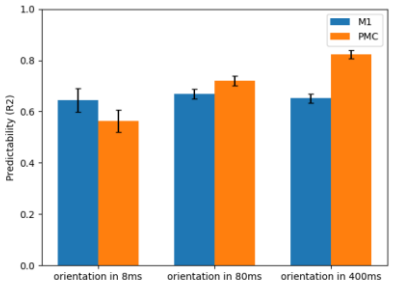



Left Image: Uddin, L. Q., Yeo, B. T. T., & Spreng, R. N. (2019). Towards a Universal Taxonomy of Macro-scale Functional Human Brain Networks

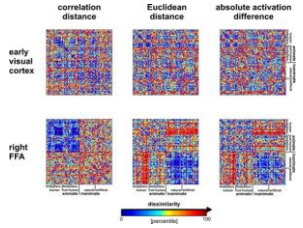
# TAKING A GOAL-DRIVEN APPROACH

## BUILDING THE FRONTOPARIETAL NETWORK TO GENERATE HYPOTHESES

1. **Model** biologically inspired ANN architecture
2. **Train** on human task under humanoid constraints
3. **Analyze** neurocomputations
4. **Compare** to human data

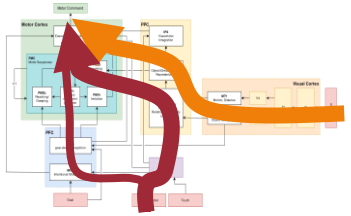



Analysis

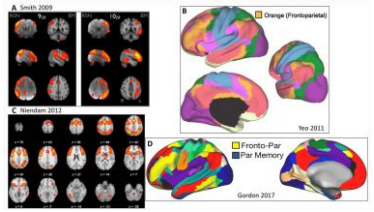



[3]

Validation



Hypothesis Generation



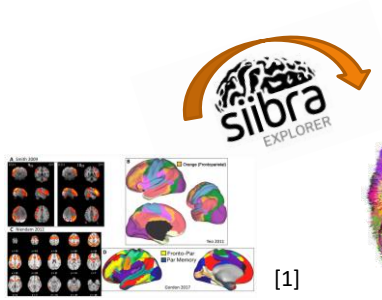

[2]

Hypothesis Testing


[1] Yamins, D., DiCarlo, J. Using goal-driven deep learning models to understand sensory cortex. *Nat Neurosci* **19**, 356–365 (2016).
[2] Uddin, L. Q., Yeo, B. T. T., & Spreng, R. N. (2019). Towards a Universal Taxonomy of Macro-scale Functional Human Brain Networks
[3] Kriegeskorte, Nikolaus, Marieke Mur, and Peter Bandettini. “Representational Similarity Analysis - Connecting the Branches of Systems Neuroscience.” *Frontiers in Systems Neuroscience* 2 (2008).

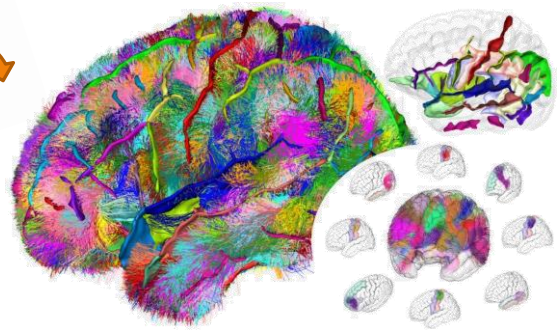
INSPIRING THE MODEL

# PLAUSIBILITY CONSTRAINTS




[1]

Functional Neuroimaging Literature

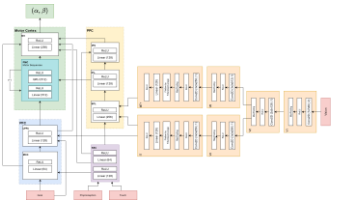


EBRAINS Multilevel Human Brain Atlas

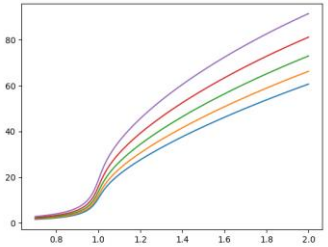
Cell density

Cell types

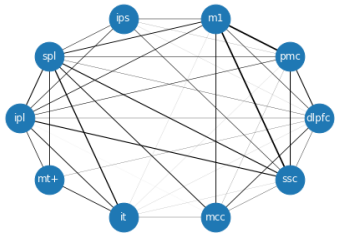
Cytoarchitectonics

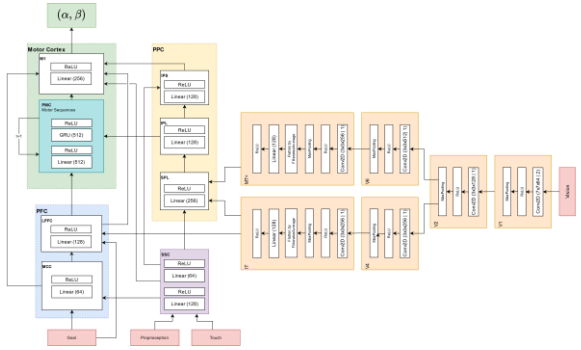


Relative Layer Sizes



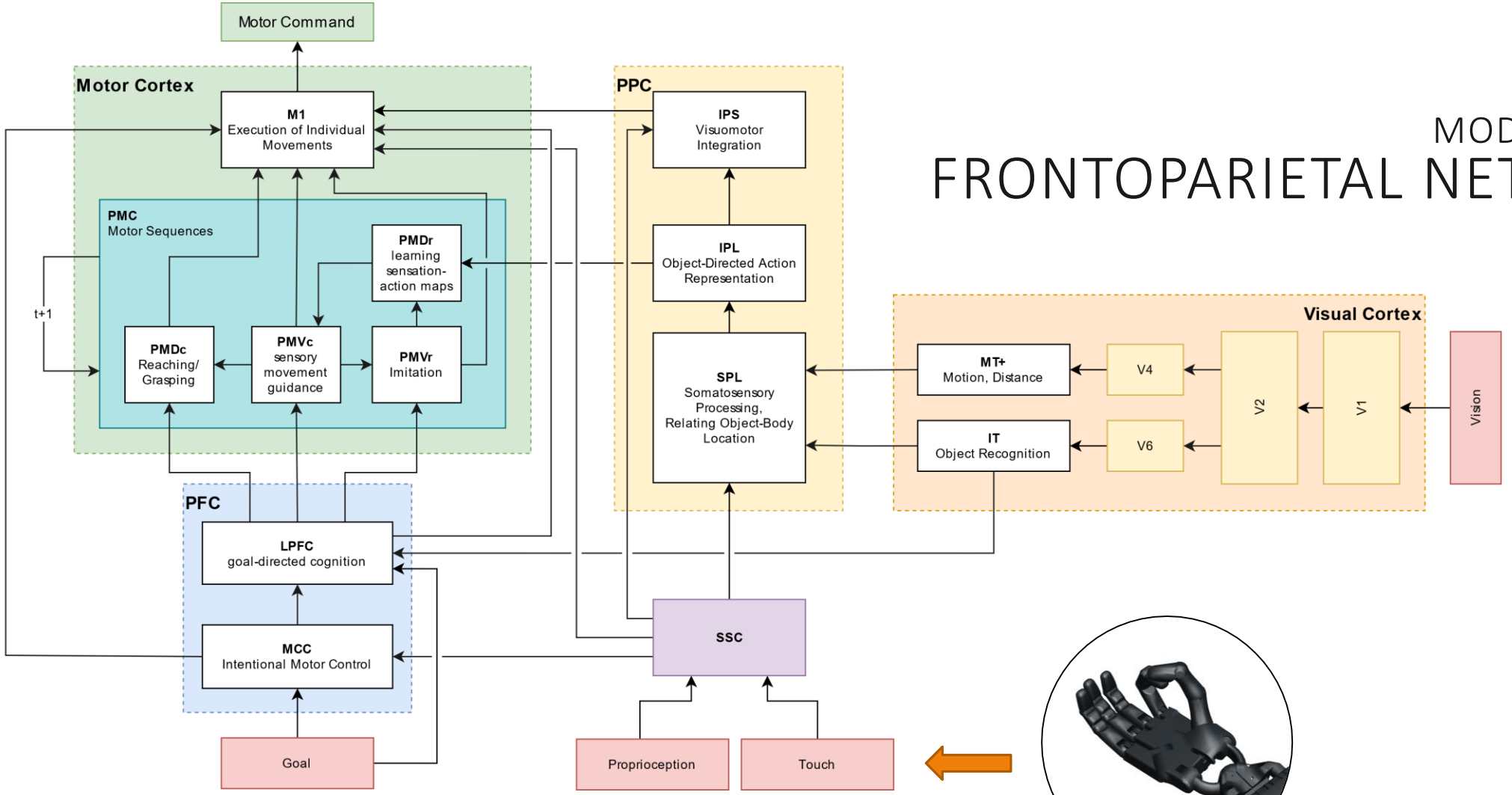

Unit-specific activation functions

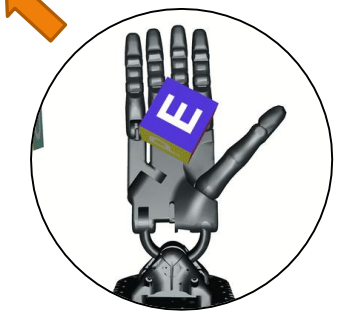


[1] Uddin, L. Q., Yeo, B. T. T., & Spreng, R. N. (2019). Towards a Universal Taxonomy of Macro-scale Functional Human Brain Networks

# MODEL OF THE FRONTOPARIETAL NETWORK



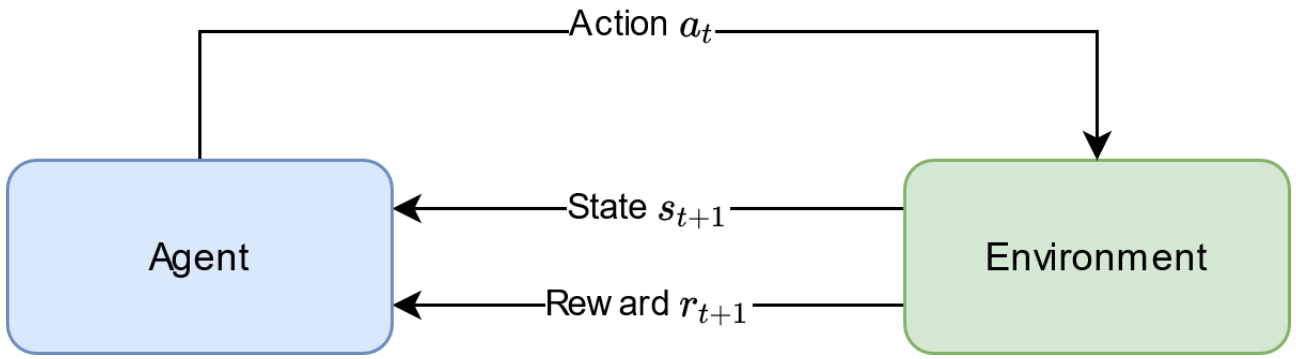
100x100px RGB Images



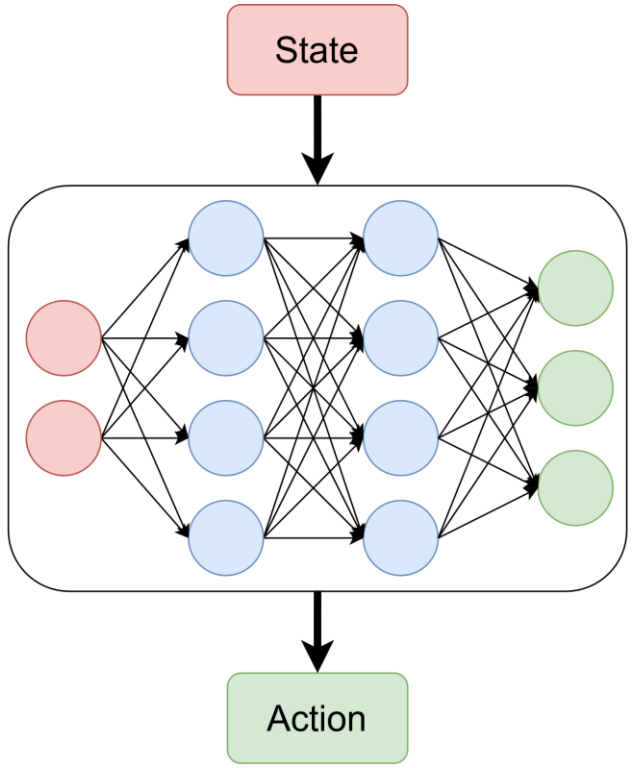
92 Touch Sensors

Joint Angles & Velocities

# (DEEP) REINFORCEMENT LEARNING




1. Agent **acts** in an environment
2. Environment **feedbacks** its new state and a reward
3. Agent can **update** its behavior based on reward
4. Agent can base **next action** on state



LEARNING TO PERFORM

# OBJECT MANIPULATION

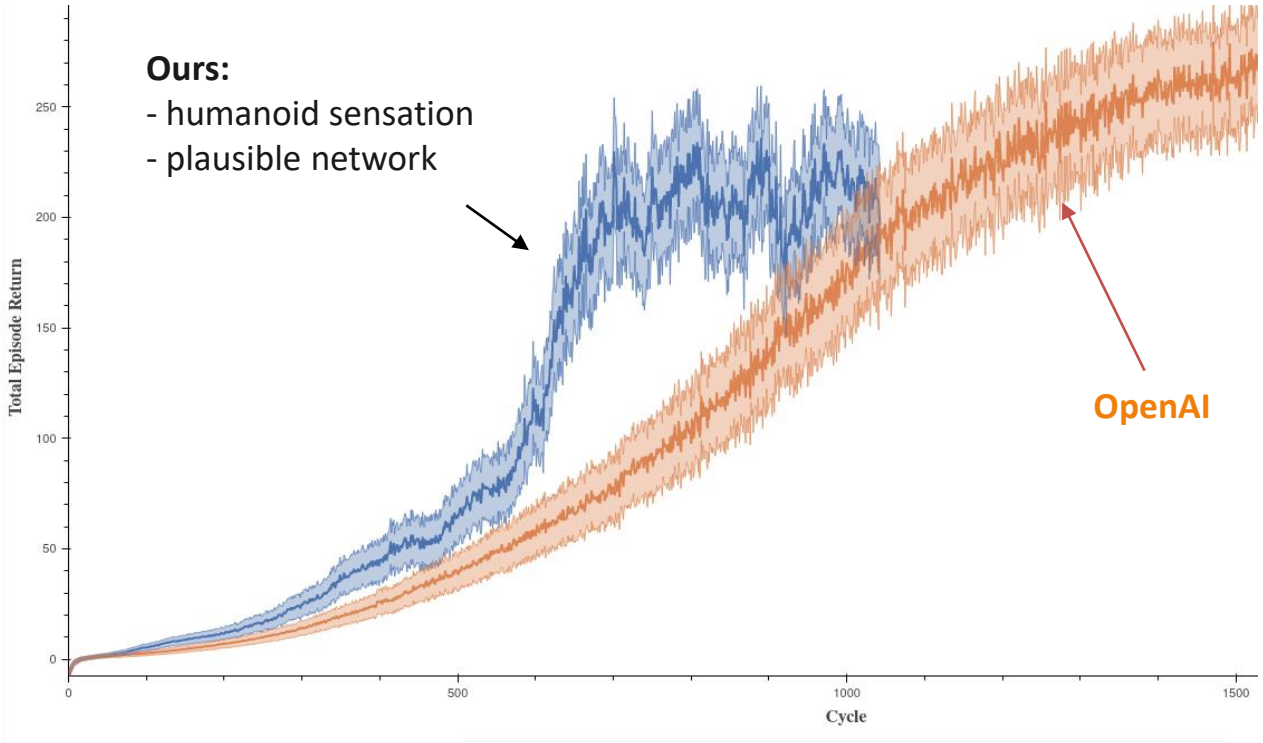
**Objective**

- rotate cube into target orientation
- no dropping

Reward

- **punish** dropping
+ **reward** progress and achieving goals

# IN-HAND OBJECT MANIPULATION




Training

- ~48h wall time
- ~2 years of simulated experience

Distribution

- 384 CPUs
- 32 GPUs

TWEAKING BEHAVIOR THROUGH PLAUSIBLE REWARDS

# SMOOTHING WITH FORCE PENALTY

**Motivation**: Human motion tries to minimize applied muscle force (e.g., Pedotti et al., 1977)

**without force punishments**

$$r = r - \sum_{a \in A} (F_a)^2$$

where $A$ is the set of actuators

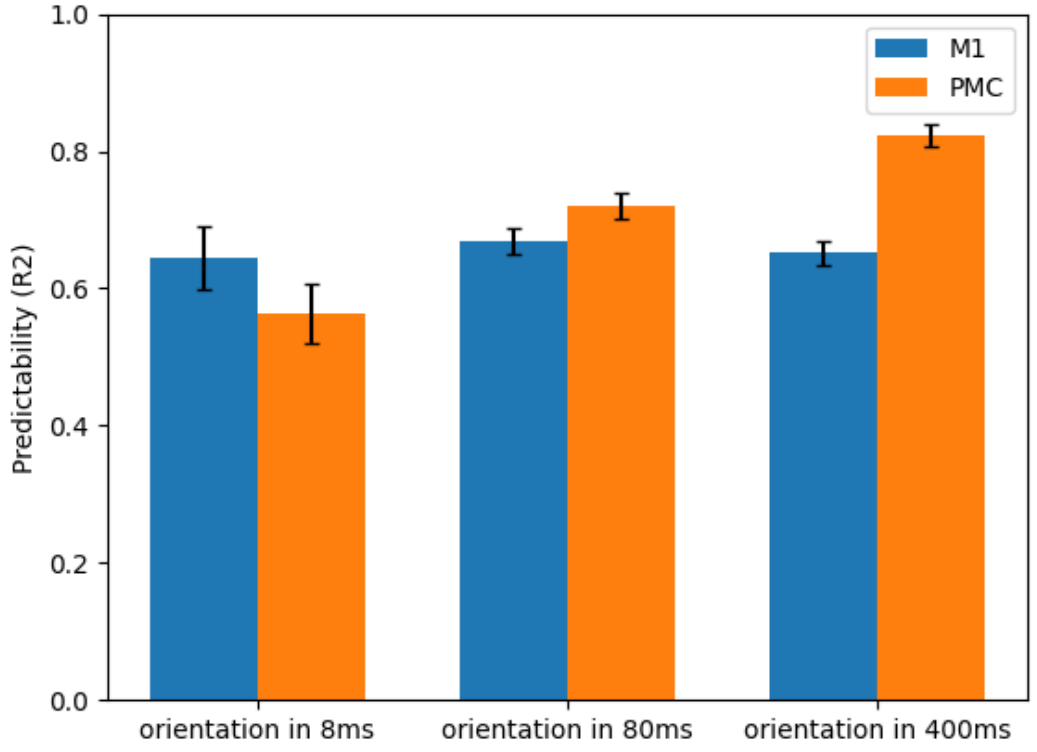
**with force punishments**

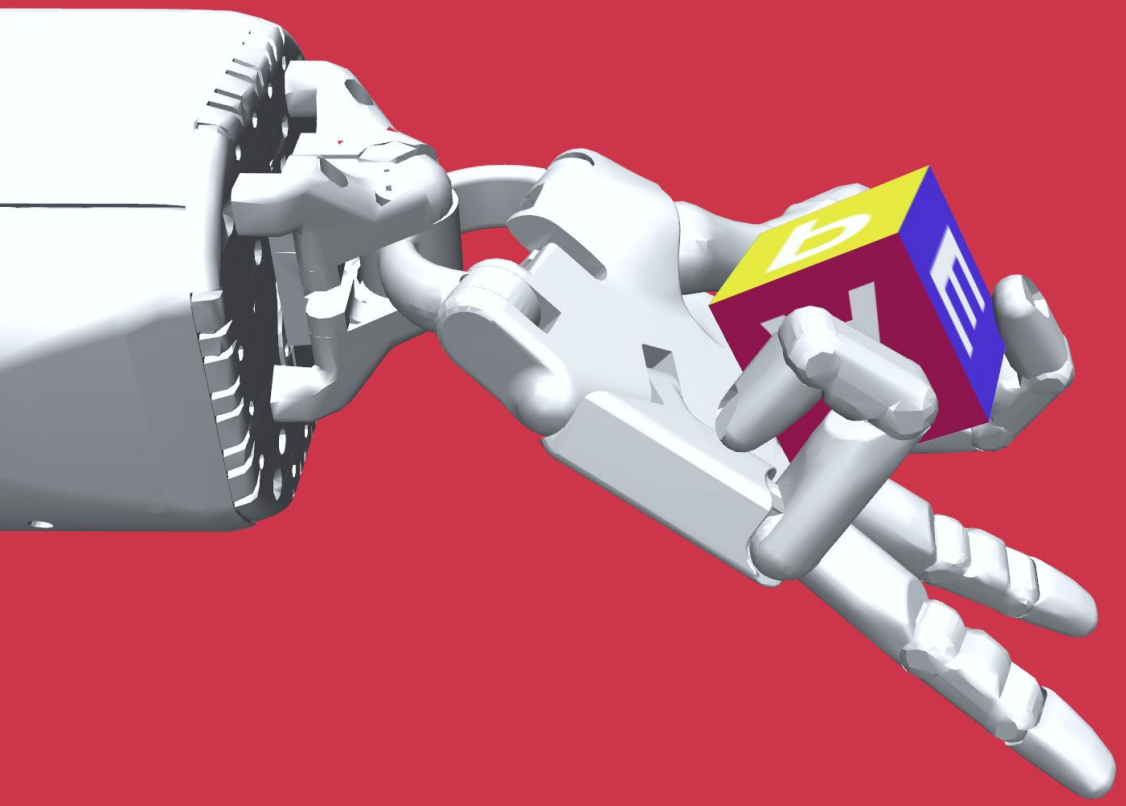
ANALYSIS PREVIEW

# IN-SILICO DECODING

Decoding model representations

1. Run independent episodes
2. Ridge regression to predict information from activations
3. Regression performance indicates role of representations





# Questions?

For more on our lab:
ccnmaastricht.com

Want to know more/get in contact?
t.weidler@maastrichtuniversity.nl

HUMAN DEXTERITY

HOW THE BRAIN COORDINATES HAND MOVEMENTS

EBRAINS

Human Brain Project

# Outline

- Systems Biology **labs** @ UM
  - Maastricht Centre for Systems Biology
  - Maastricht Brain Imaging Centre
- Systems Biology **research** @ UM
  - Irene Hemel, PhD student (MaCSBio)
  - Tonio Weidler, PhD student (Cognitive Neuroscience)
- Systems Biology **education** @ UM
  - Student's perspective
  - Your future in Systems Biology

# Maastricht Brain Imaging Centre


## Hannah Schultheiß

*MSB student*
*former MSP student*


Maastricht Science Programme

macsbio
MAASTRICHT CENTRE FOR SYSTEMS BIOLOGY

Maastricht University

# Who am I?

- MSP 2018-2021
  - Focus on neuroscience, chemistry, programming
  - Systems biology projects

- BTR in the field of computational neuroscience / systems neuroscience

- MSc Systems Biology 2021-2023

# BTR

## Modelling Homeostatic Plasticity in the Auditory Cortex to Investigate the Mechanisms underlying Tinnitus

Supervisor: Michelle Moerel

# BTR

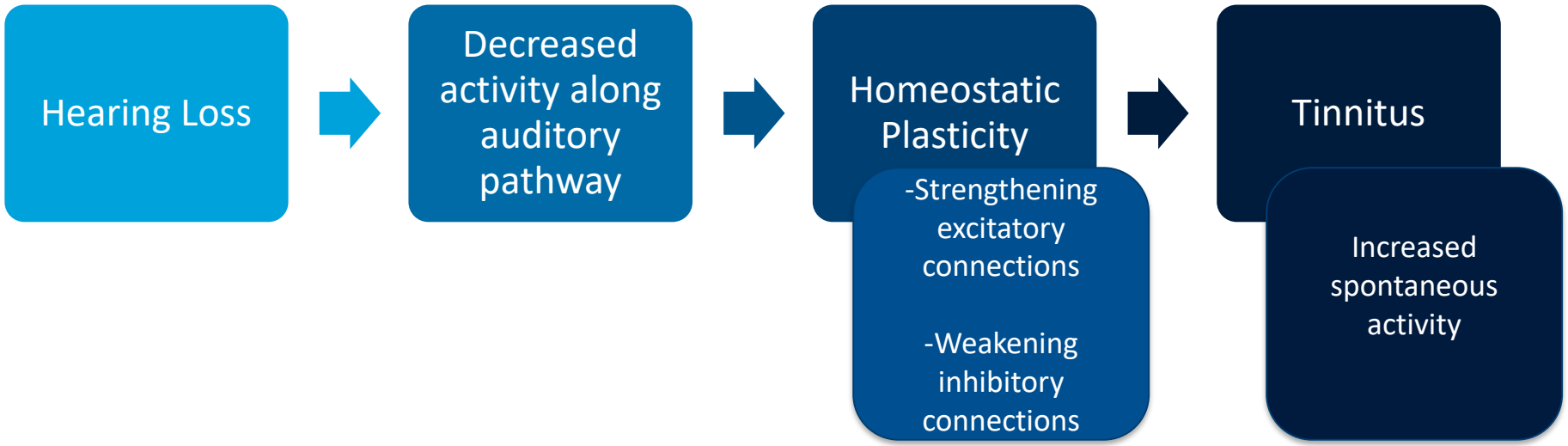
- Tinnitus:
  - Cortical changes underlying tinnitus are not well understood

- Homeostatic Plasticity (HSP)

# BTR

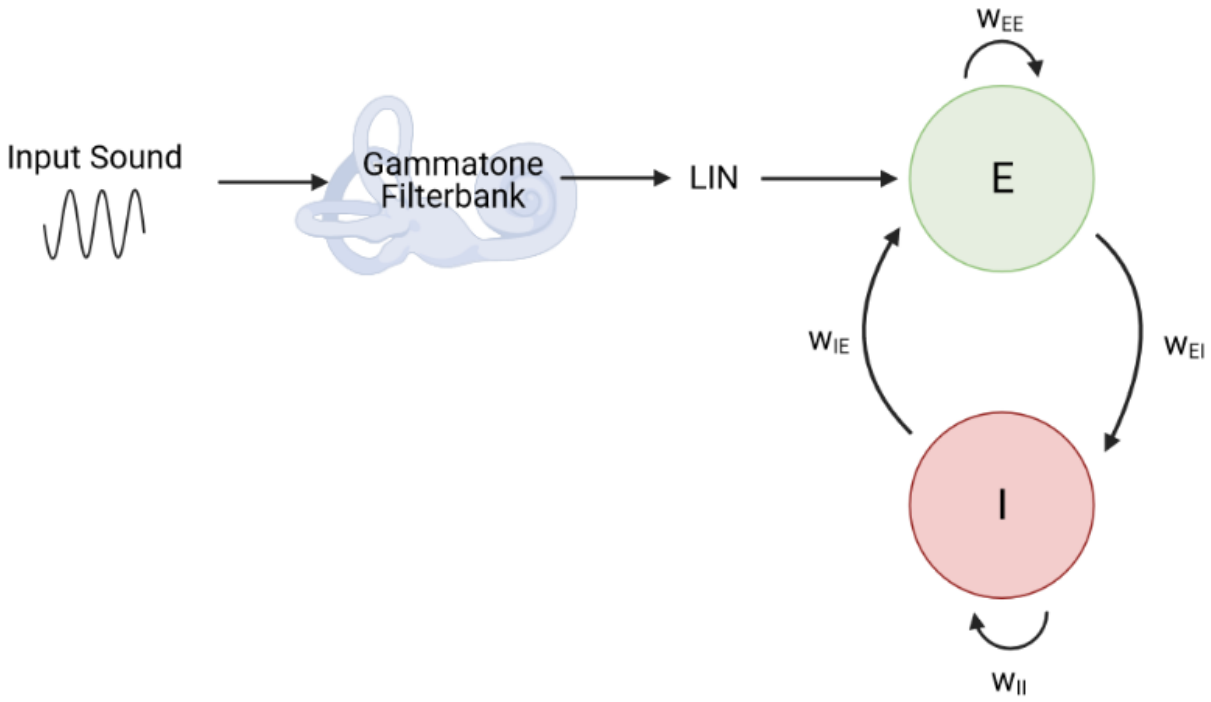
- Tinnitus:
  - Cortical changes underlying tinnitus are not well understood

- Homeostatic Plasticity (HSP)



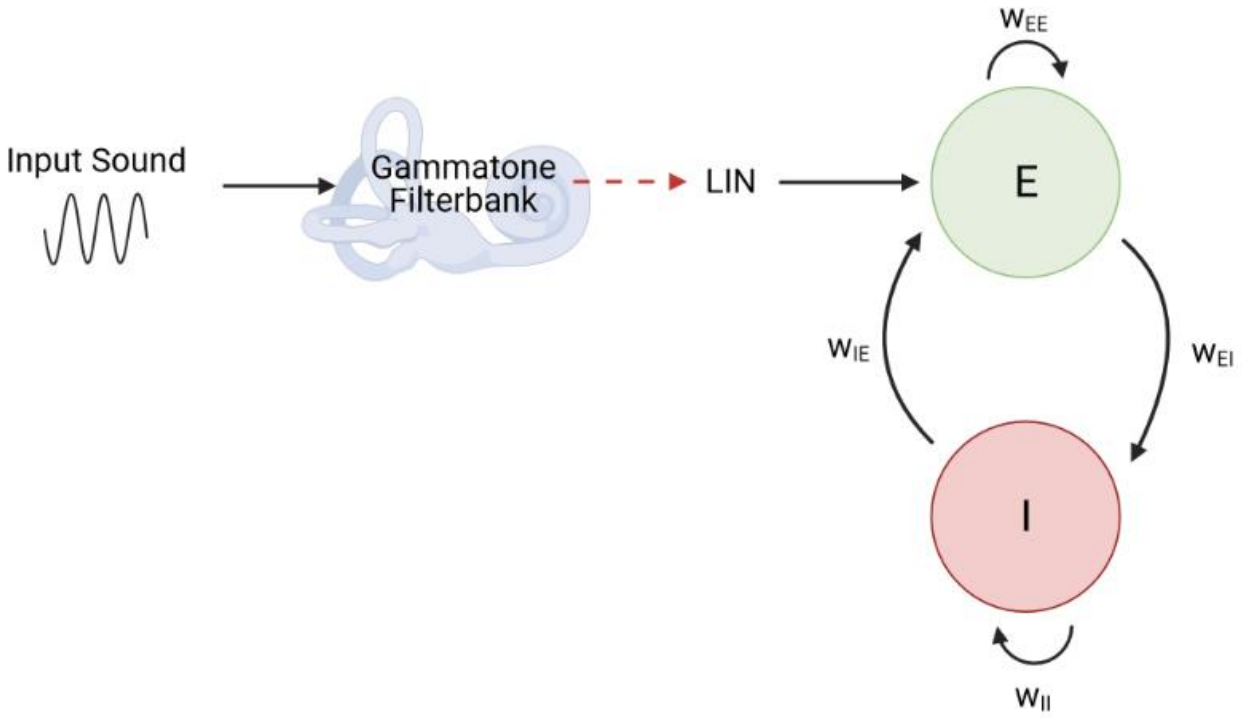
# BTR

## Healthy



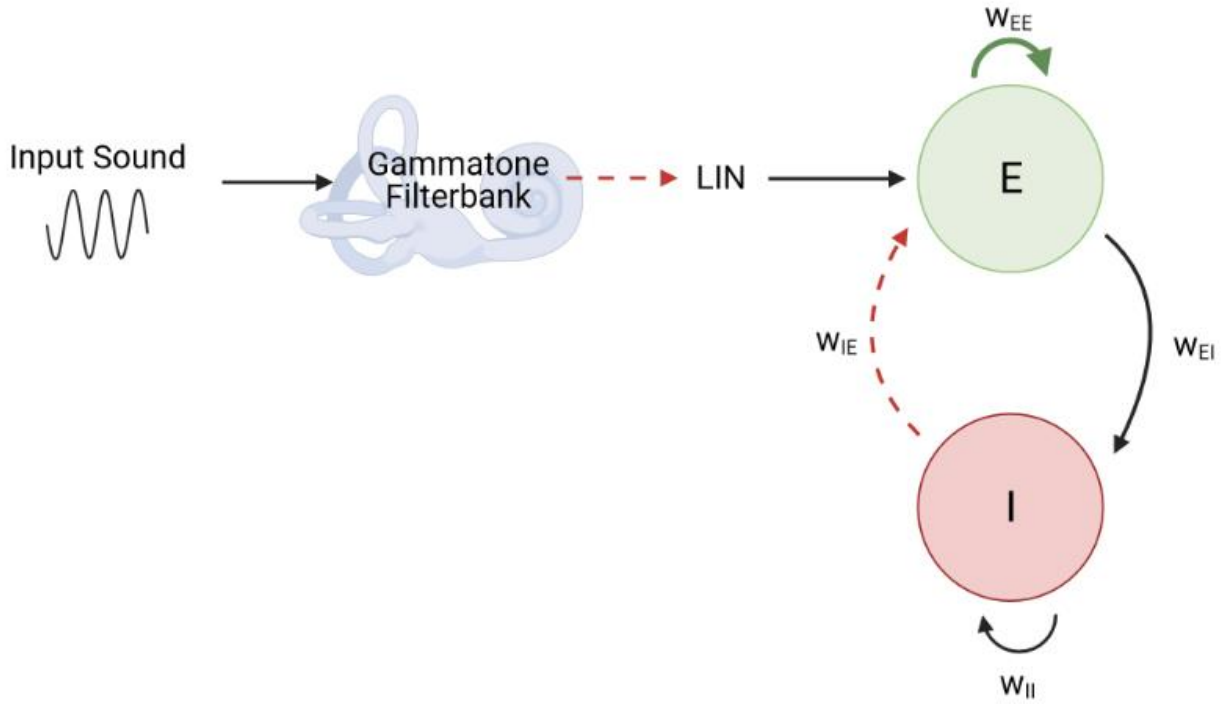
# BTR

## Hearing Loss



# BTR

## HSP



# BTR Conclusions

- Implementation of HSP led to changes that could represent tinnitus

- Cortical signatures of tinnitus are also associated with comorbidity disorders
  → could not prove the presence of tinnitus in the model

# Today: MSc Systems Biology

- Multidisciplinary approach
  → fits well with MSPs ideology

- Students come from very different scientific fields

- Close contact to researchers

# Project Periods

- Period 3:
  - Understanding sex-related differences in cardiac energy metabolism through genome-scale metabolic models in patients with dilated cardiomyopathy

- Period 6:
  - The Role of Axonal Action Potential Backpropagation in Neuronal Communication

# Master Thesis Internship

- SISSA in Trieste, Italy

- Supervisor: Michele Giugliano
- Part of the IN-FET project
- Topic: Differences in excitability across different types of cortical neurons

# Any Questions?

Email:
h.schultheiss@student.maastrichtuniversity.nl

# Your future in Systems Biology

Michiel Adriaens

*Assistant professor*


**Master**

→ Faculty of Science and Engineering

## Systems Biology

Do you want to better understand the underlying mechanisms of life? Would you like to contribute to integrating the scientific fields of biology and mathematics in order to open new perspectives for a deeper insight into biology, development of diseases and possibly the development of new therapies? Then Systems Biology is the right programme for you!

Systems Biology will become mainstream in biological sciences this century. It can be used to systematically gather knowledge at all levels, from molecules to entire systems and its integration into quantitative (computer) models. These models make accurate simulation of biological processes possible.

This programme will give you the knowledge and practical skills necessary to unravel the complexity of these systems and use it for academic, industrial and societal progress. After you've graduated, your ability to unify life sciences and mathematics will make you a great candidate for a career in medical research, drug development and biotechnology. Read more

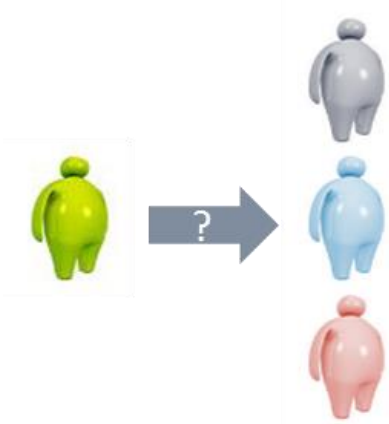
# Why Systems Biology?

*Citizen science*

*Replace animal testing*

*Basic research*

*Diagnostics*




*Personalized medicine*


# Scientific challenges of the future…

- … are multidisciplinary and international
- … need teams spanning scientific disciplines to develop solutions
- … require a new generation of scientists

# So we need you!

# How to be trained in systems biology:

# Master Programme!

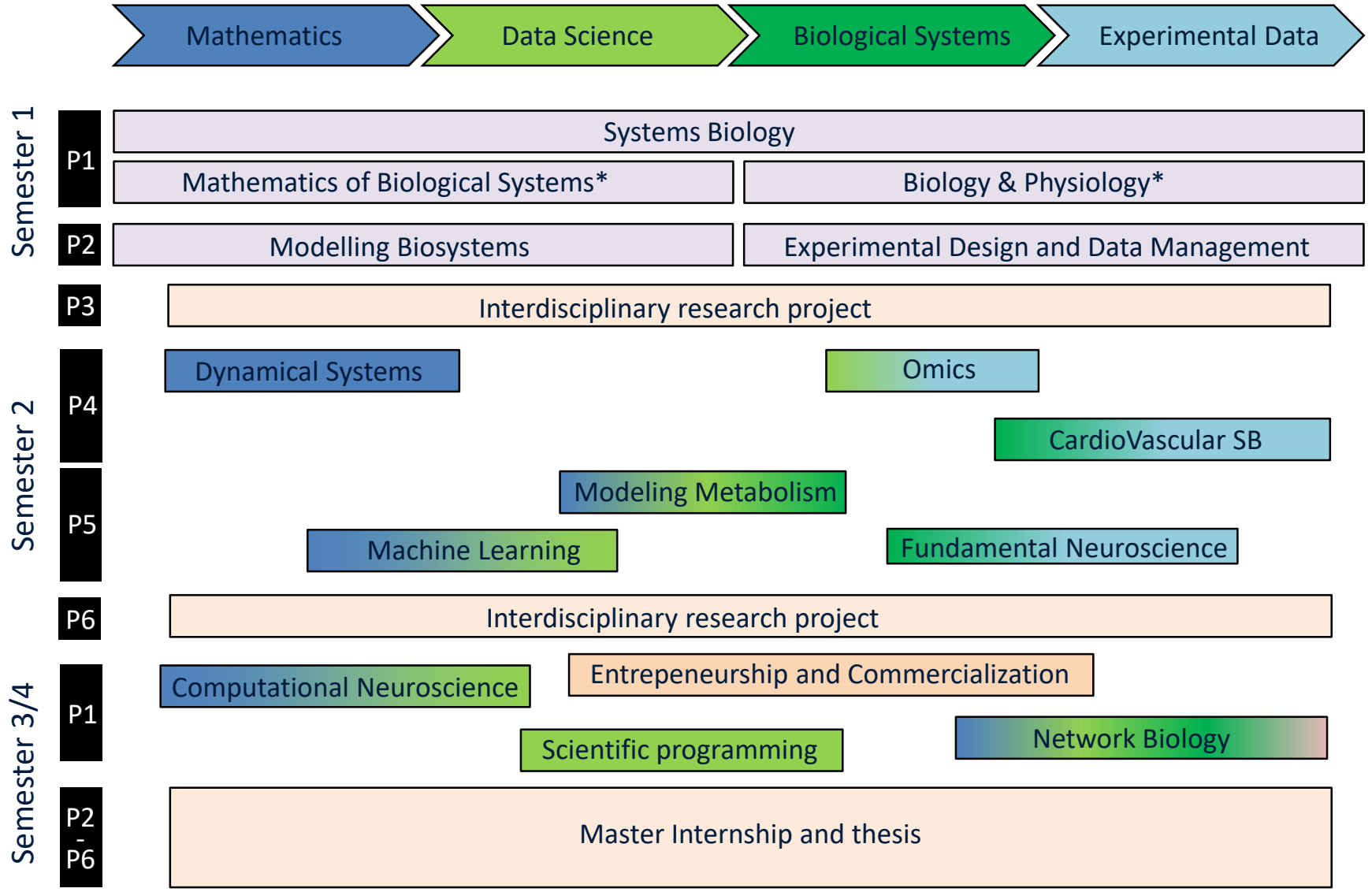
# Need for students…

- who have a broad interest in combining biology, computer science, and mathematics
- who do not want to be limited to a fixed, highly specialized programme
- who want to learn how to think, work and communicate across disciplines

# Master Systems Biology

- 2 year, full-time master
  - At Faculty of Science and Engineering

- Number of students:
  - 2015: 3 students
  - …
  - 2020: 16 students
  - 2021: 21 students
  - 2022: 22 students




**Followed course depends on previous education*

# Teaching by active researchers!

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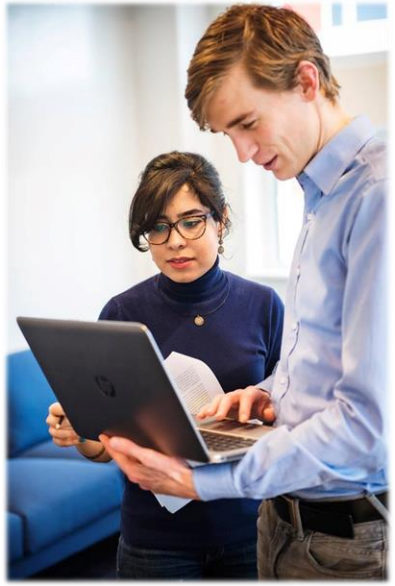
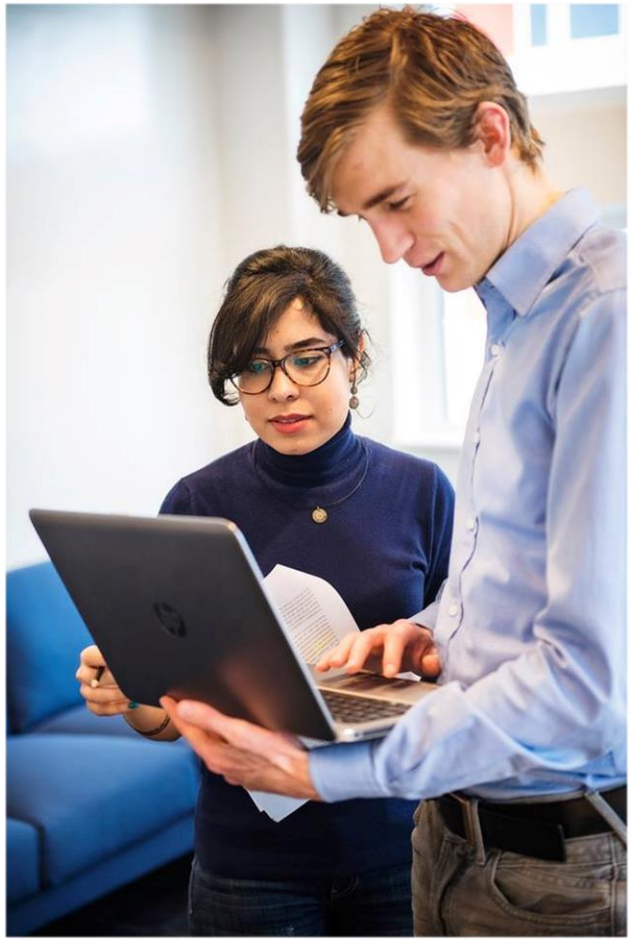


/macsbio
@MaCSBio
https://www.maastrichtuniversity.nl/macsbio

# Academic advisors: so you don’t get lost!



- **Every student** has an academic advisor throughout the 2 year SB Master
- Academic advisor gives **guidance and advice** regarding your **personal curriculum**
- Academic advisors are **active researchers** in the field of Systems Biology

# But what about programming? Math? Biology?

- Motivation to study across disciplines is most important!

- Proficiency in the English language

- Ideally 15 ECTS in mathematics/statistics at bachelor level

  → Can be waived based on individual background: contact us!

# Contact for Master Programme

- Fse-master@maastrichtuniversity.nl

- Website with more information:
  - www.maastrichtuniversity.nl/education/master/systems-biology

28 Nov
14:30

## Systems Biology | Online Experience Day

**Are you curious to find out what it is like to study at the master's programme Systems Biology at Maastricht University? Join our Online Experience Day and find out!**

During the Online Experience Day, you will have the opportunity to find out what studying Systems Biology is like. You will follow a short programme presentation giving you a better understanding of the curriculum. This is followed by a question and answer session where you meet the programme director, an academic staff member and a current student. Next to this, you will learn more about one of the research projects to illustrate our education method and research projects.

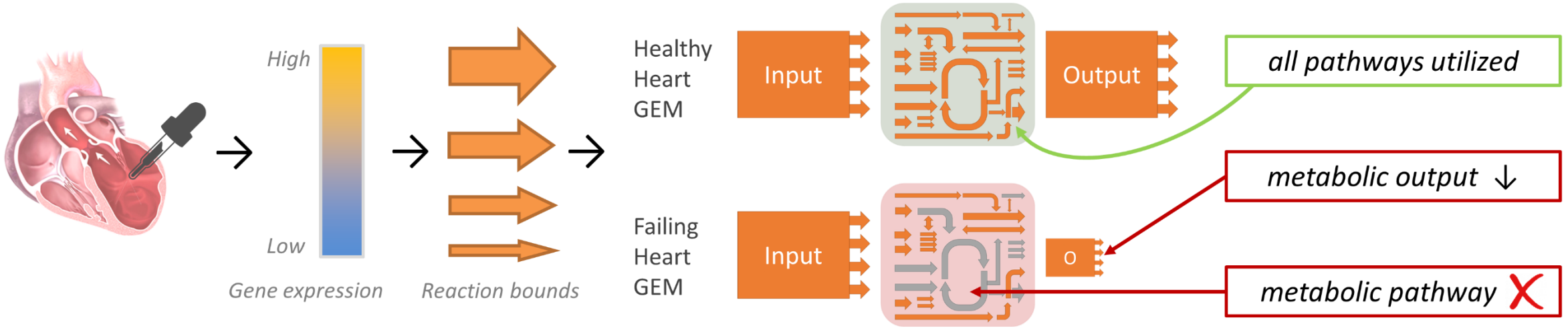
Our Online Experience Day gives you a unique chance to find out if this master's programme is the right match for you!

https://www.maastrichtuniversity.nl/events/systems-biology-online-experience-day-3

# How to be trained in systems biology:

# Internships (BTRs) and MSP Projects!

# Example: metabolism of the heart




Biopsy → Omics → Modeling → Diagnosis!

# Your role as a student during internship

- Using existing tools with new data
  - Learn how to use tools and interpret the results
  - Stronger focus on biology
- Expand existing tools with new functionality
  - Learn how to make something new and compare results with the old
  - Stronger focus on programming
- Or a mixture of both!

# Career opportunities

| | |
|---|---|
| **Researcher**<br>PhD research | Universities, hospitals, applied science organizations, pharmaceutical and biotech companies |
| **Policy maker** | Government organizations, centres for population health, environment, genetics, prevention |
| **Entrepreneur** | Specialized Systems Biology company (“life sciences incubator”) |

michiel.adriaens@maastrichtuniversity.nl

# Outline

- Systems Biology **labs** @ UM
  - Maastricht Centre for Systems Biology
  - Maastricht Brain Imaging Centre
- Systems Biology **research** @ UM
  - Irene Hemel, PhD student (MaCSBio)
  - Tonio Weidler, PhD student (Cognitive Neuroscience)
- Systems Biology **education** @ UM
  - Student's perspective
  - Your future in Systems Biology

We hope you enjoyed
this interim lecture on
Systems Biology in Action at UM

Martina Summer-Kutmon, PhD
email: martina.kutmon@maastrichtuniversity.nl