

Local Neuronal Microcircuits

Egidio D'Angelo

Human Brain Project @ EU

Centro Fermi - Roma

Centro Fermi

Roma

*Dept. Brain & Behavioral Sciences
University of Pavia*

March 8, 2018

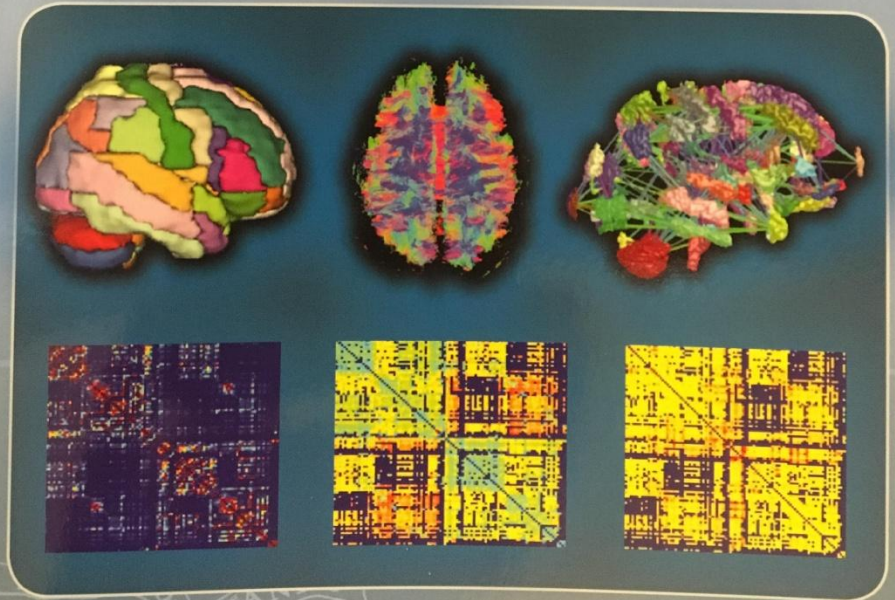
7 40 2017

1897-2017
120 anni e oltre
120 years and beyond

La Rivista
del Nuovo Cimento
della Società Italiana di Fisica

Modelling the brain: Elementary components
to explain ensemble functions

E. D'ANGELO AND C. GANDINI WHEELER-KINGSHOTT



The target of
“Centro Fermi”
project:

To explain fMRI
signals in terms
of neuronal
functions

How the problem can be conceptualized

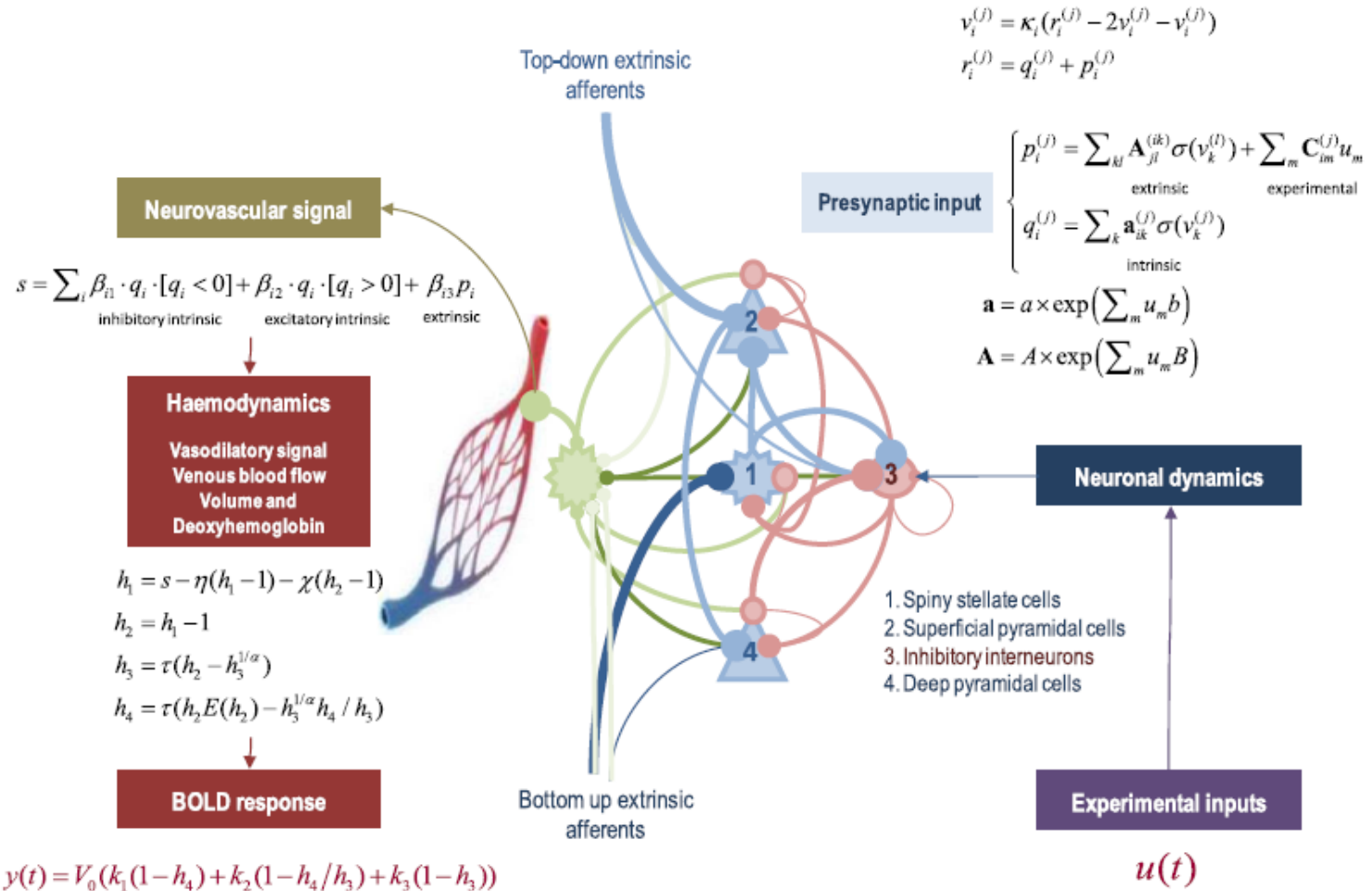


Dynamic causal modelling revisited

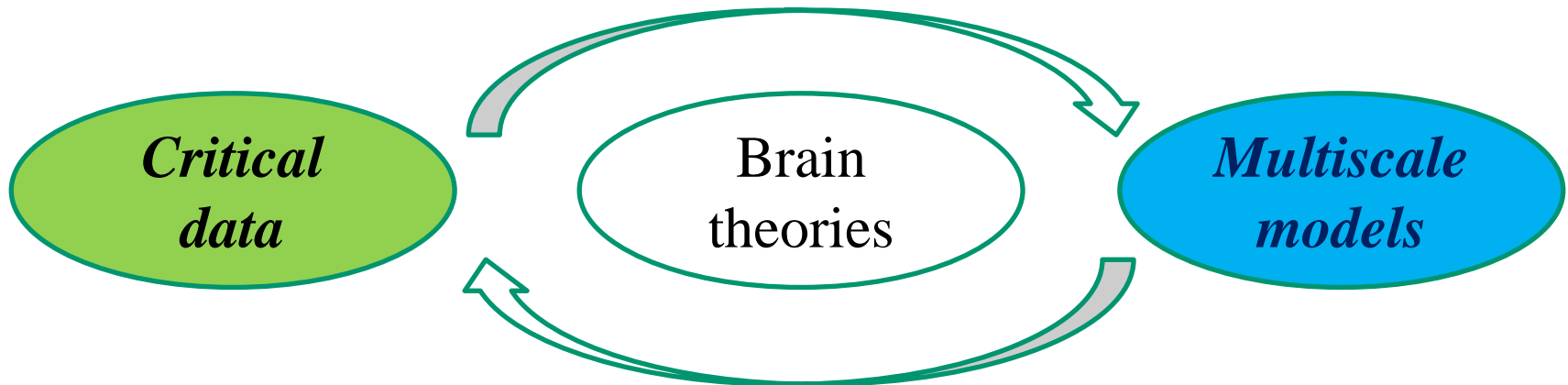
K.J. Friston et al.

K.J. Friston^{a,*}, Katrin H. Preller^{a,b}, Chris Mathys^{a,c}, Hayriye Caglan^{a,d}, Jakob Heinze^{a,e}, Adeel Razi^{a,f}, Peter Zeidman^a

NeuroImage xxx (xxxx) xxx–xxx



BACKGROUND

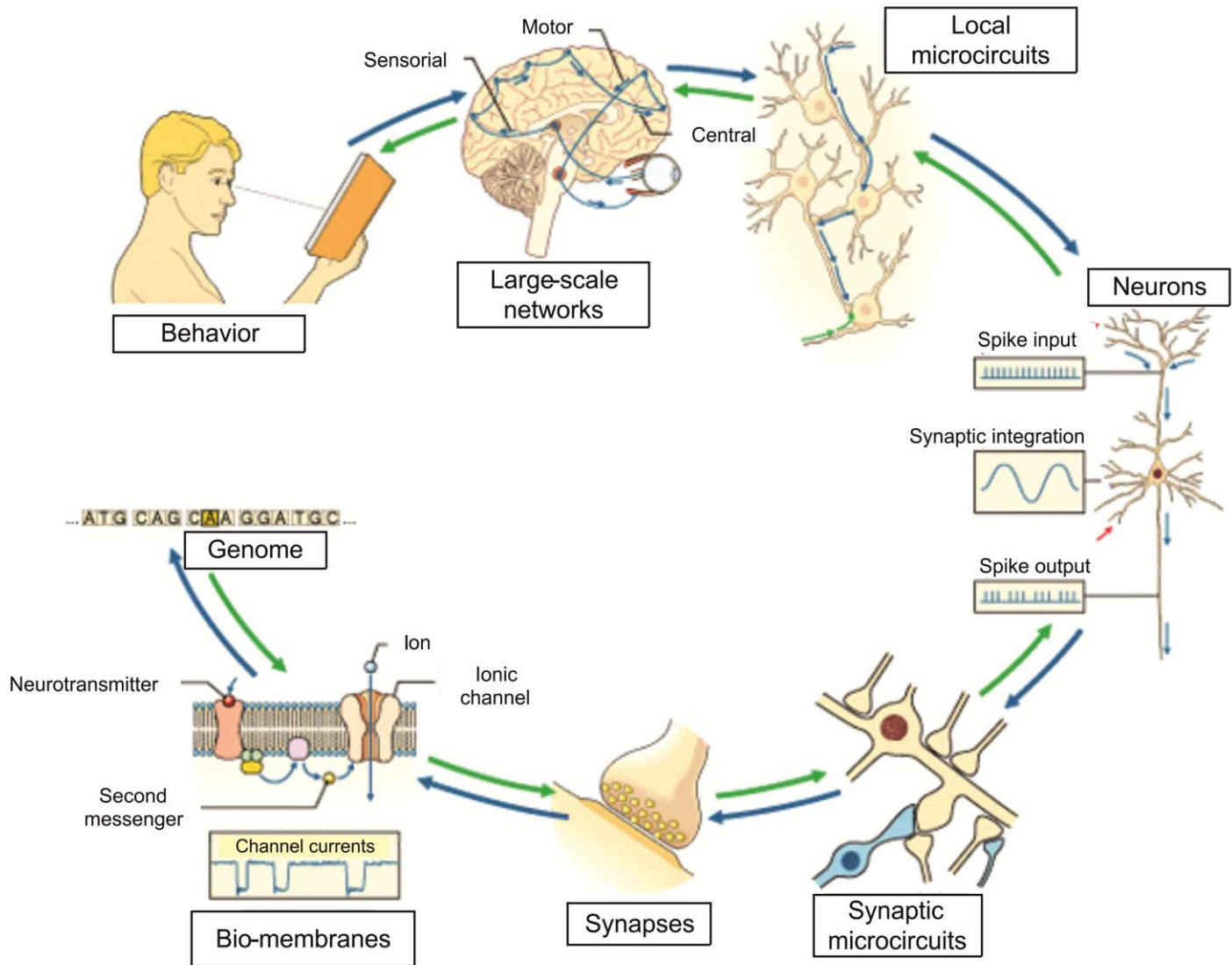


In collaboration with Human Brain Project

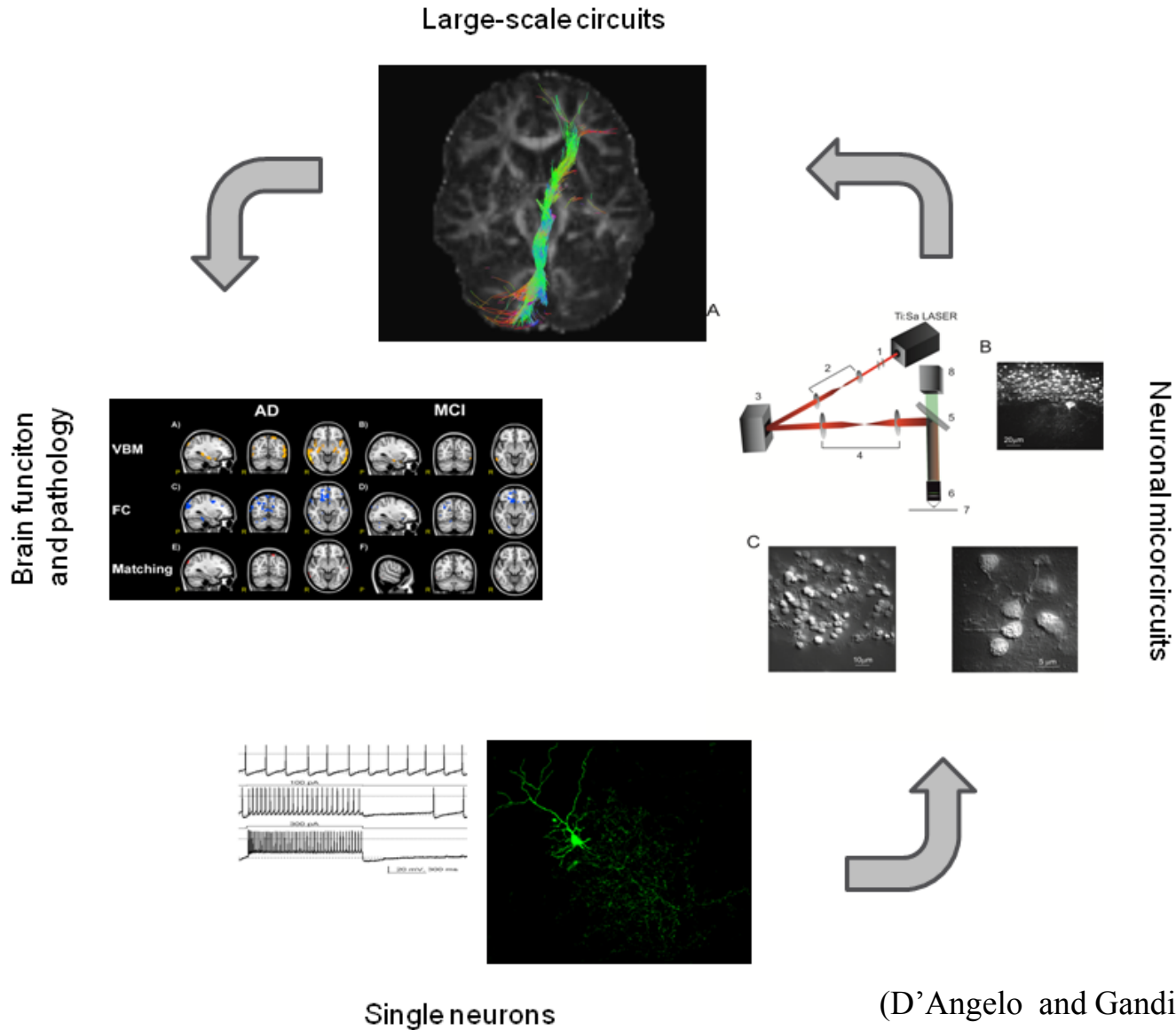


Human Brain Project

Multi-scale brain organization ...

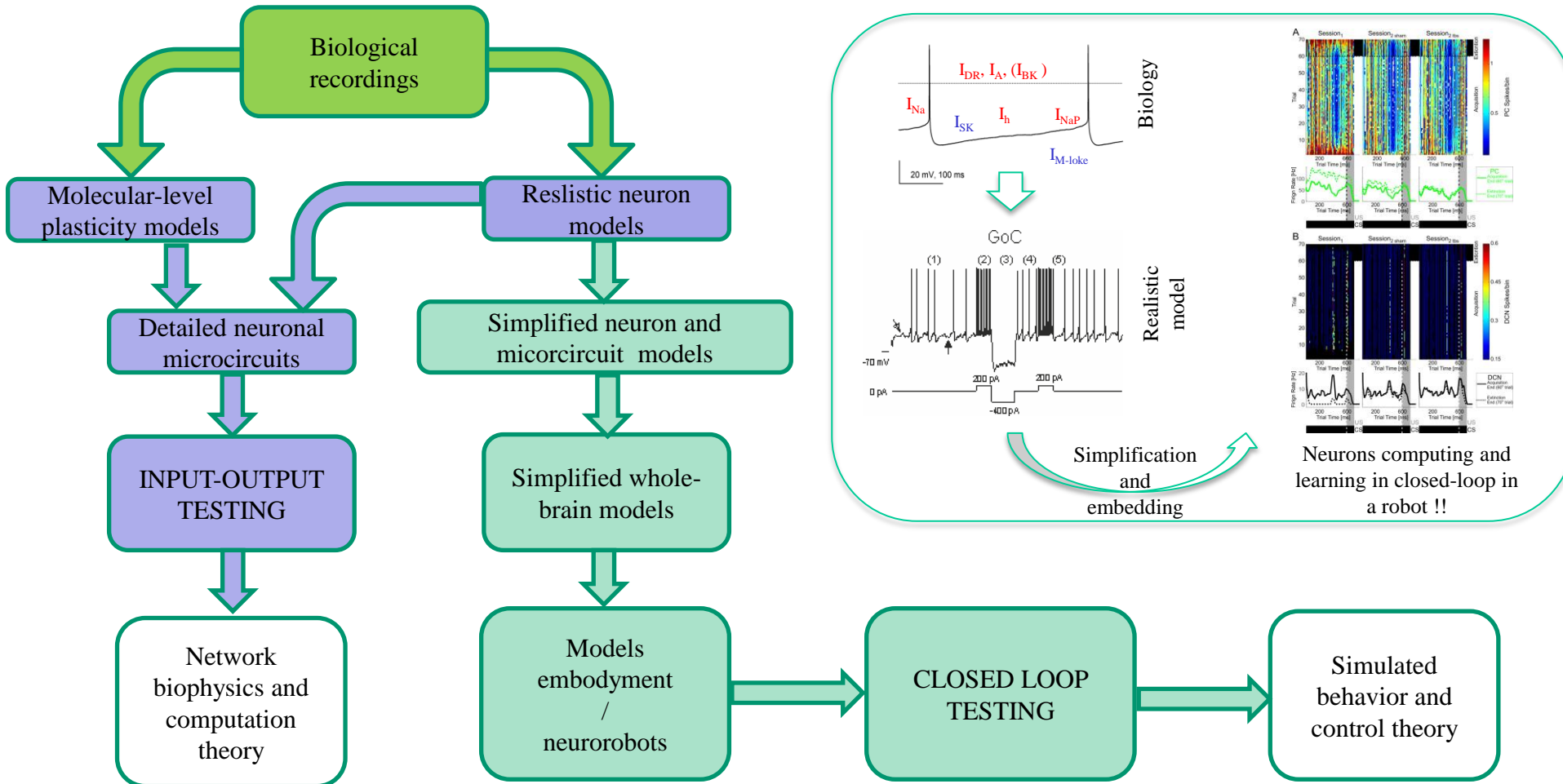


Multi-scale experimental analysis ...



(D'Angelo and Gandini, RNC, 2017)

Multi-scale brain modeling !!



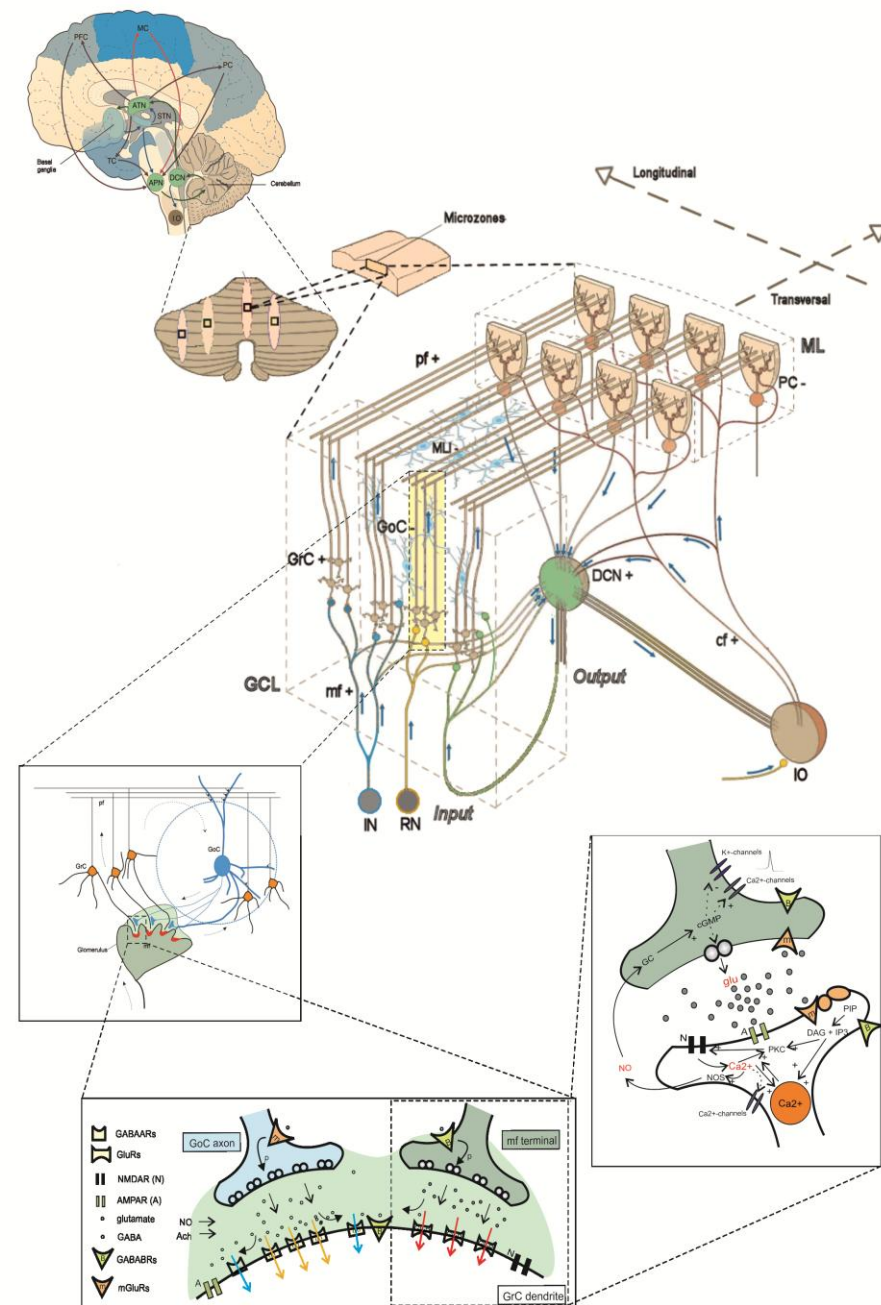
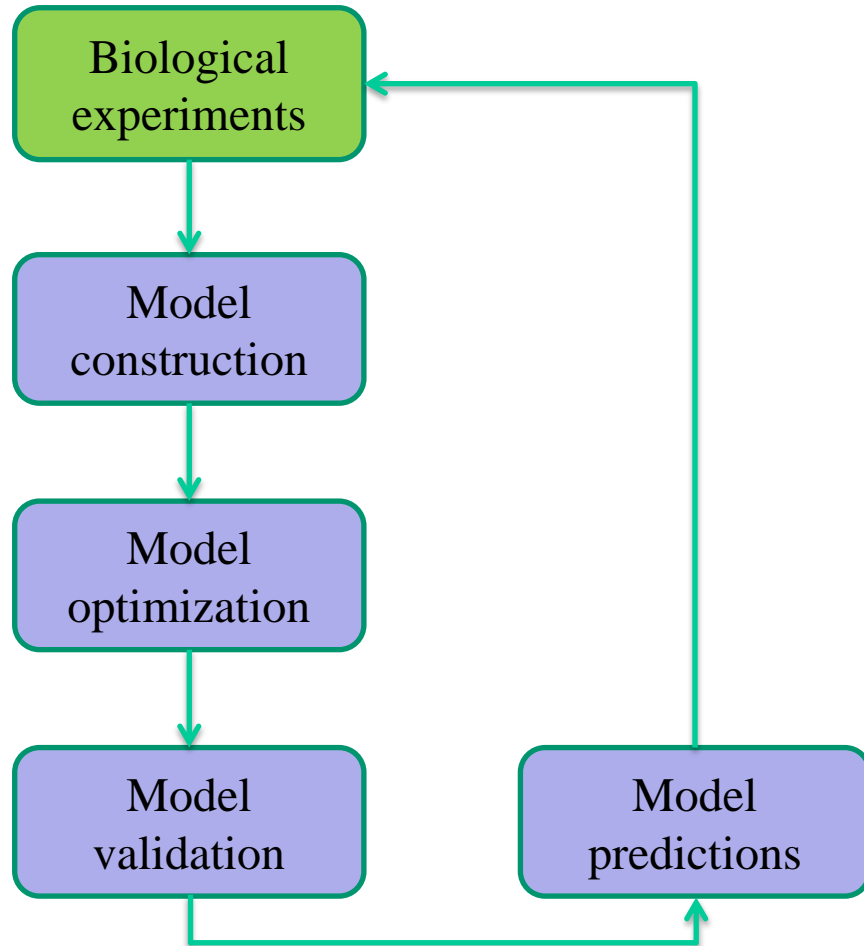
“Modeling the Brain” to “Understand the Brain”

The brain is a complex adaptive system (among the most complex of Universe) with multiscale organization. But we are missing the “project” as well as “critical data”.

- *What we have is information sufficient to start the reconstruction of brain functions in a model and the computational power required to simulate it.*
- *This approach will require combining top-down and bottom-up models (reverse engineering).*
- *By analysing spatio-temporal dynamics in the model, we will formulate hypothesis on brain function.*



Multi-scale modeling of the cerebellar network



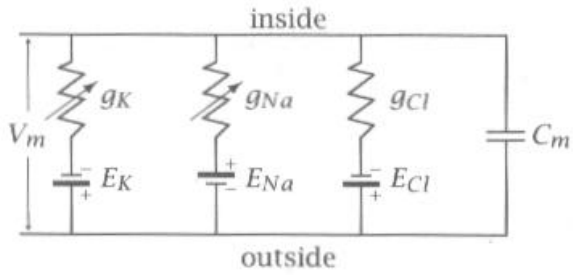
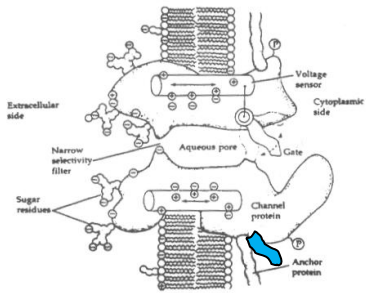
NEWS

Integrated experimental
research and
mathematical modeling

(1)

neurons and microcircuits

Mathematical methods for realistic modeling



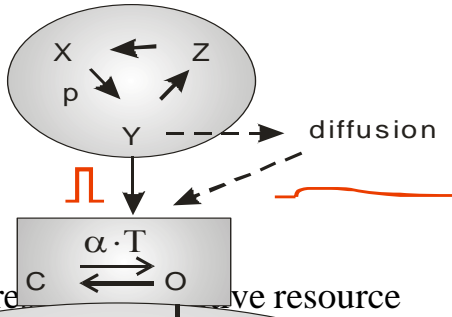
$$I = I_c + I_K + I_{Na} + I_{Cl}$$

$$I = C \frac{dV}{dt} + g_K(V - E_K) + g_{Na}(V - E_{Na}) + g_{Cl}(V - E_{Cl})$$

$$\left\{ \begin{aligned} \frac{dV}{dt} &= \frac{1}{\tau_m} \left(V - \frac{\sum_i g_i (V - E_i)}{g_{tot}} \right) \quad \text{dove } \tau_m = R_m / g_{tot} \\ \frac{dy_i}{dt} &= \alpha_i - (\alpha_i + \beta_i) y_i \end{aligned} \right.$$

$$g_i = g_i^{\max} y_{i-act}^n y_{i-inact}^m$$

$$\alpha_i, \beta_i = f(V, t)$$



active resource $\xleftrightarrow{\alpha \cdot T}$ O $\xleftrightarrow{\tau_{REC}}$ inactive resource

$$I = (g_{\max} \cdot O) \cdot (V - V_{rev})$$

Model of GRC intrinsic excitability



$$\frac{dx''}{dt} = \frac{z}{\tau_{REC}} - u \cdot x \cdot \delta(t - t_{SPIKE})$$

$$\frac{dy''}{dt} = -\frac{y}{\tau_1} + u \cdot x \cdot \delta(t - t_{SPIKE})$$

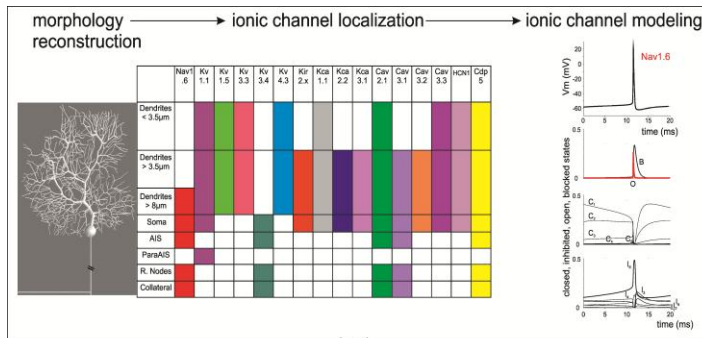
$$\frac{dz''}{dt} = \frac{y}{\tau_1} - \frac{z}{\tau_{REC}}$$

$$\frac{du''}{dt} = -\frac{u}{\tau_{FACIL}} + U \cdot (1 - u) \cdot \delta(t - t_{SPIKE})$$

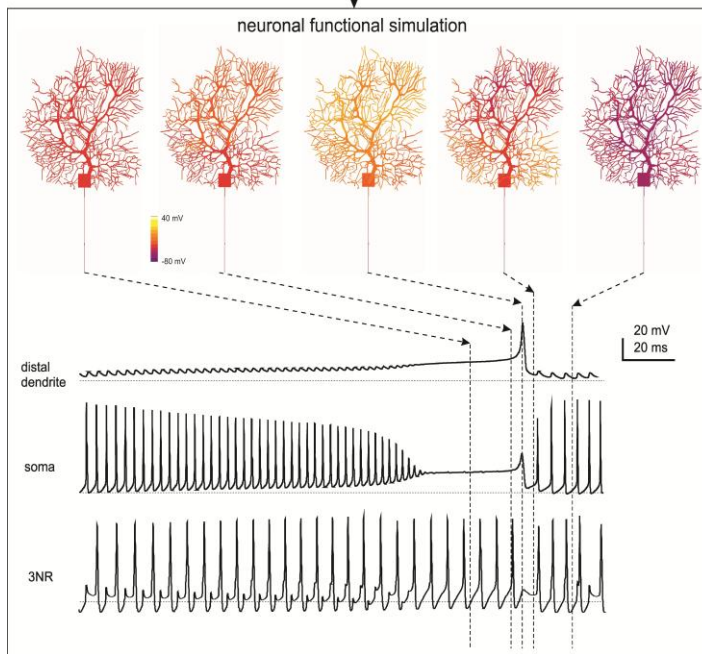
⇒ RECONSTRUCTION of PC model

RECONSTRUCTION

Morphology and channels from literature



maximum conductances calibration

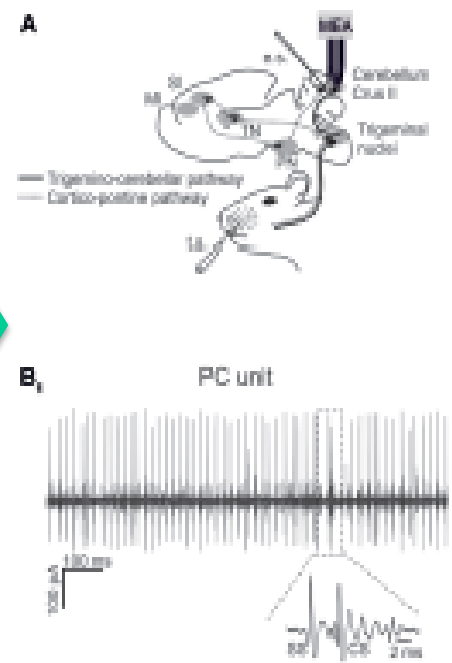


VALIDATION

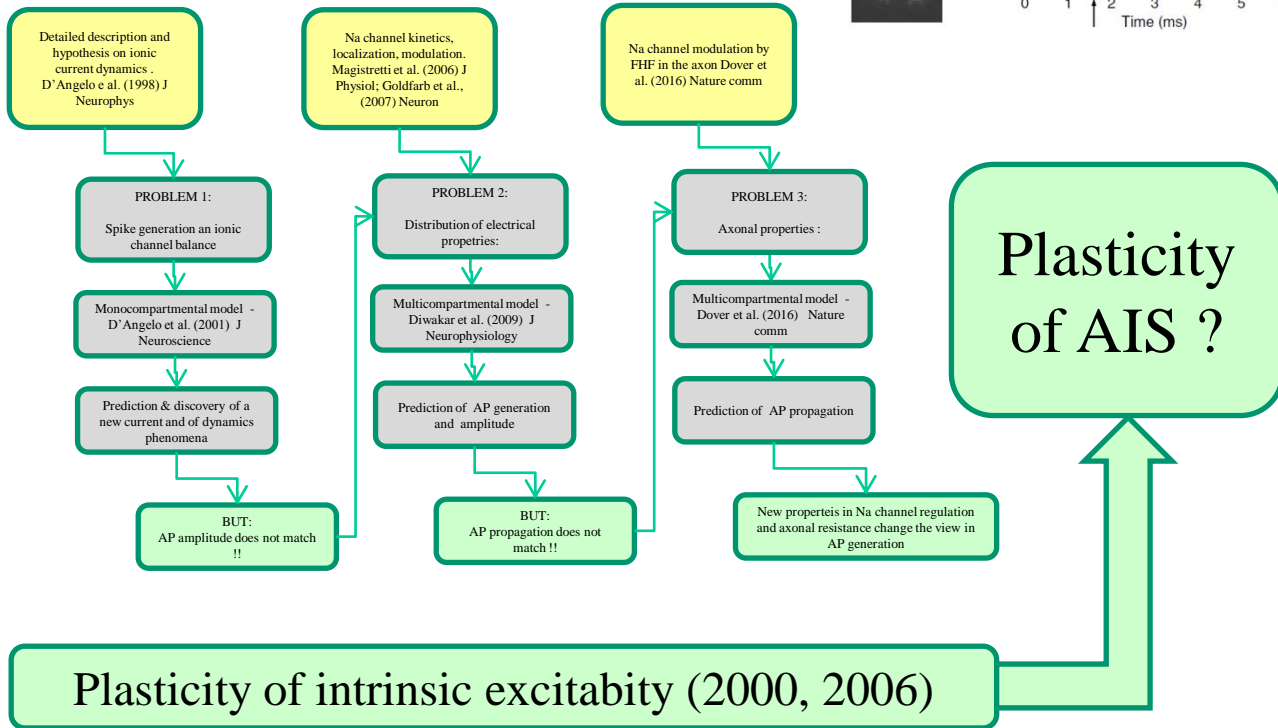
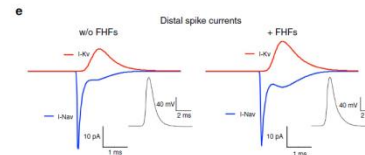
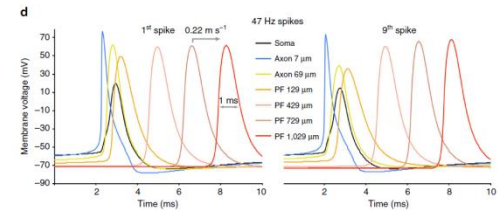
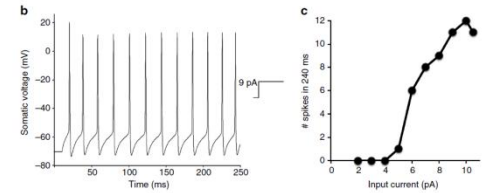
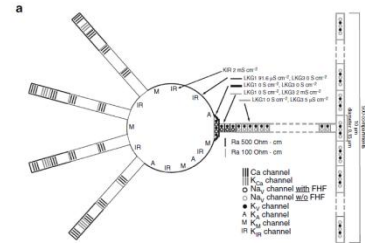
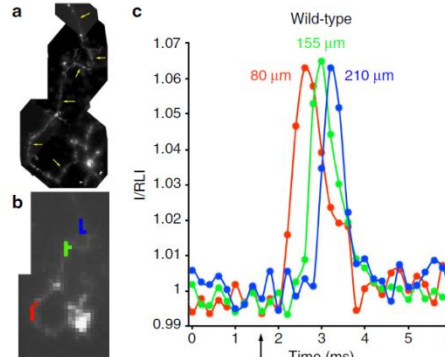
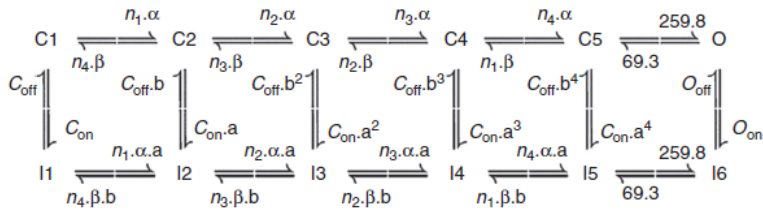
Validation against complex firing patterns



Advanced validation in vivo



Na channel modeling in Granule cell axons



Plasticity of AIS ?

Dover, ... D'Angelo, Goldfarb, Nature Comm. 2016

The general “membrane equation” and Hodgkin-Huxley model assume that there is *finite* membrane resistance, R_m , in the axon.

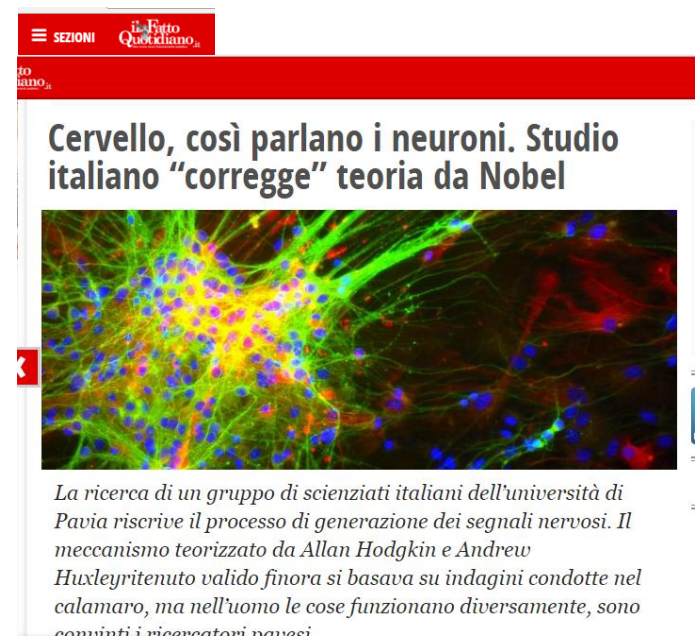
But here we have precisely determined that

$$R_m \rightarrow \infty$$

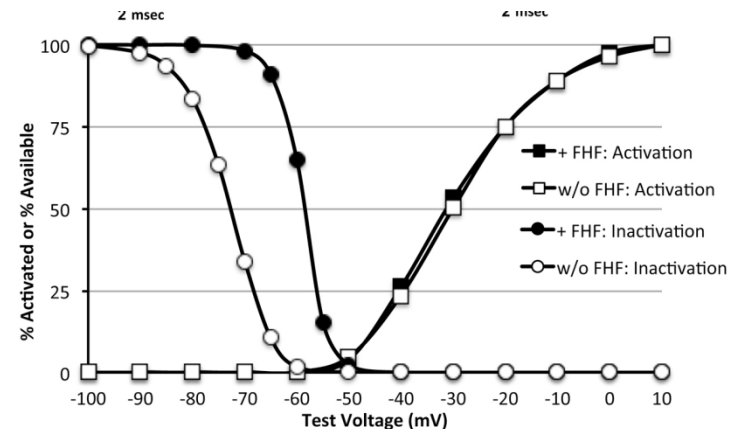
and therefore

$$\tau_m = R_m C_m \rightarrow \infty$$

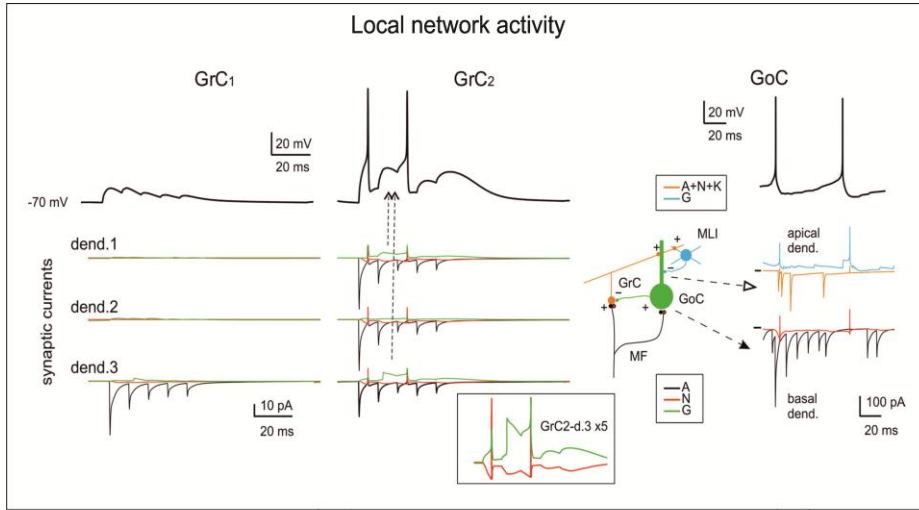
This imposes constraints on the ionic channel gating particles that cannot work in the classical HH manner. A correct functioning is achieved through the intervention of FHF, a modulatory protein that shifts the inactivation curves of the Na channel.



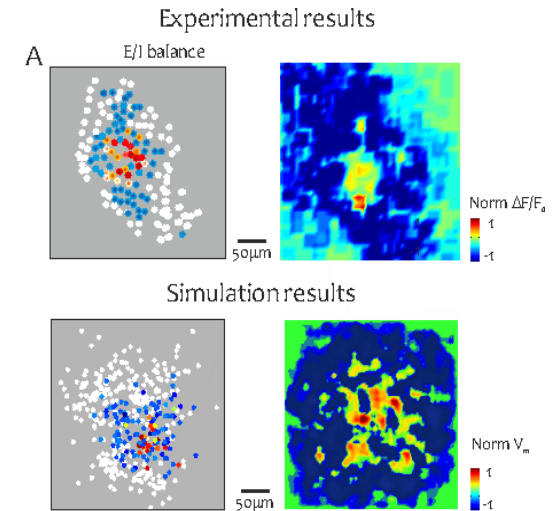
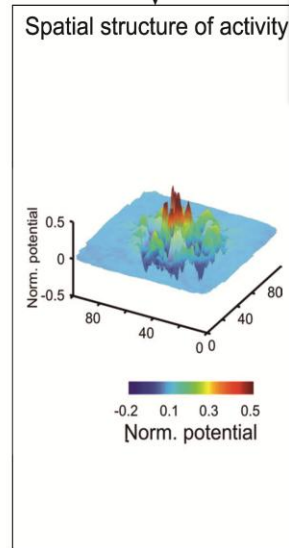
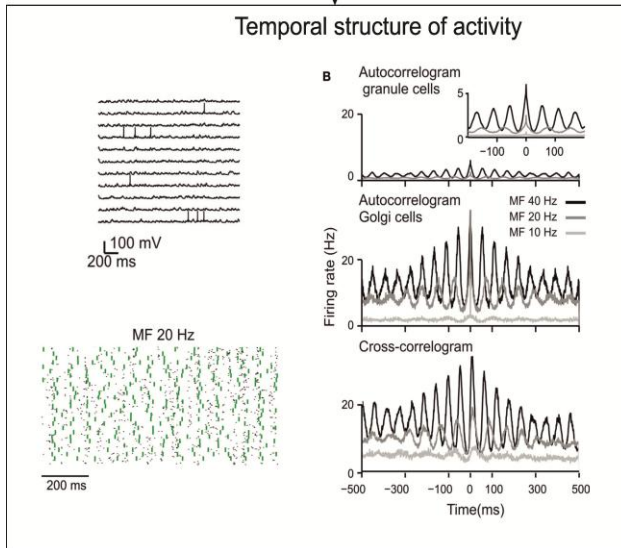
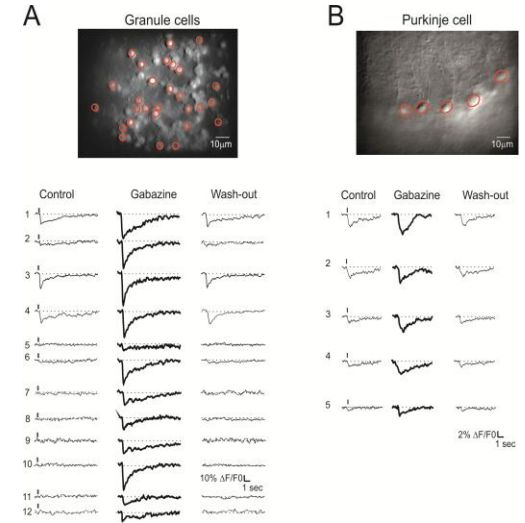
With such high resistance, tiny currents are needed to generate action potentials. 1 billion years evolution has selected a specialisation of Na channels for low energy consumption !!



⇒ PROPAGATION to MICROCIRCUIT



Validation
against
complex
output
space



NEWS

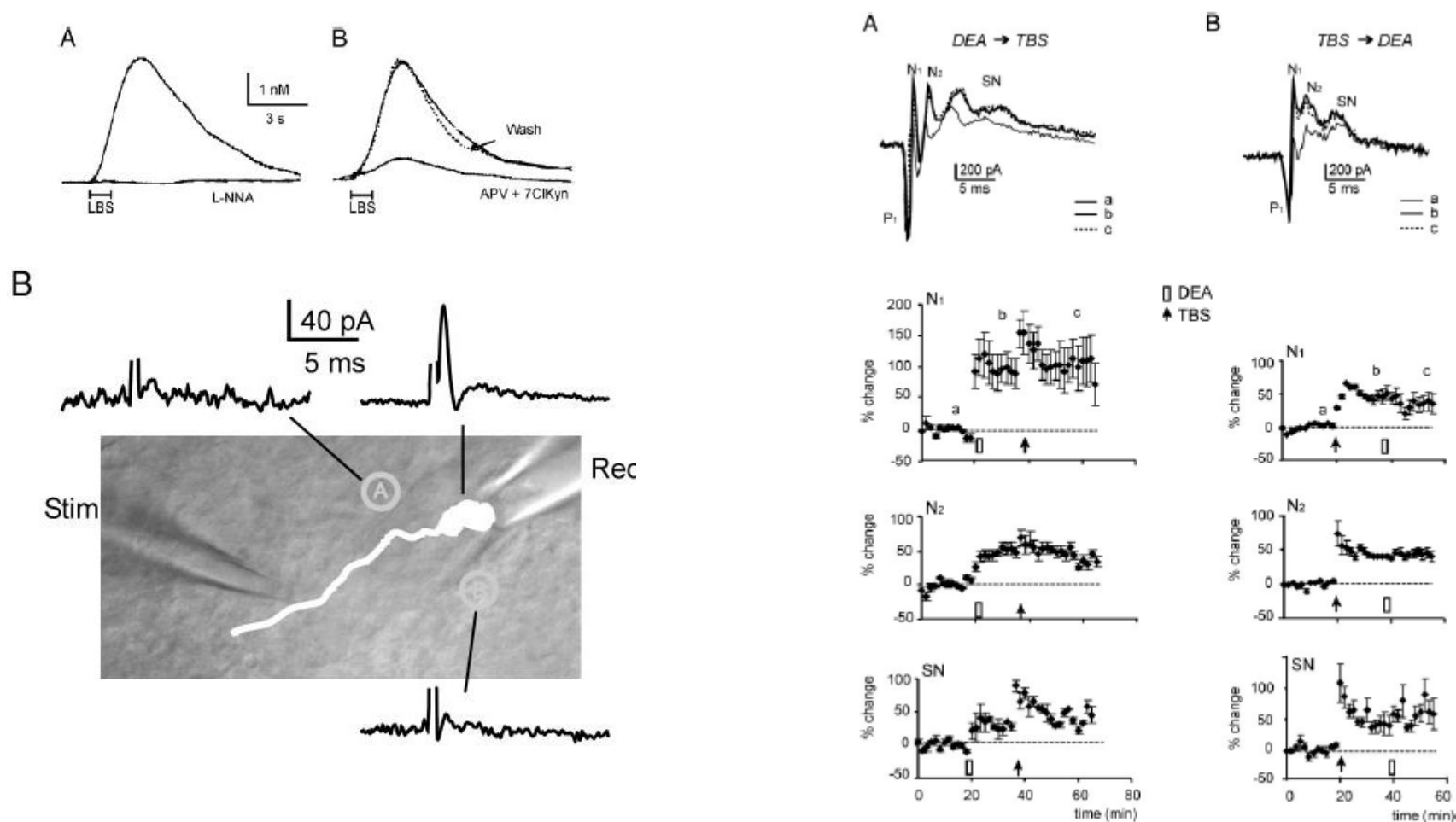
Integrated experimental
research and
mathematical modeling

(2)

Neurovascular coupling

NO Enhances Presynaptic Currents During Cerebellar Mossy Fiber— Granule Cell LTP

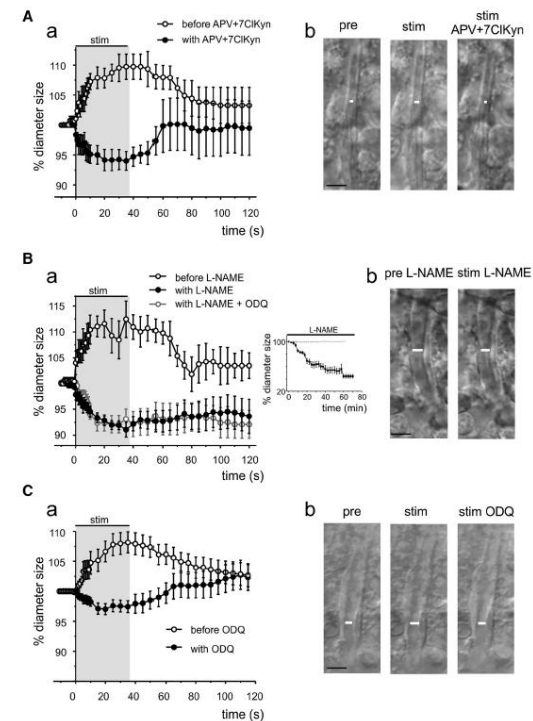
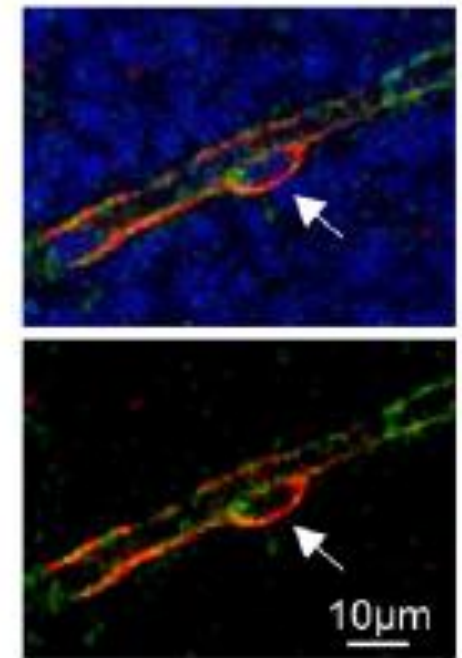
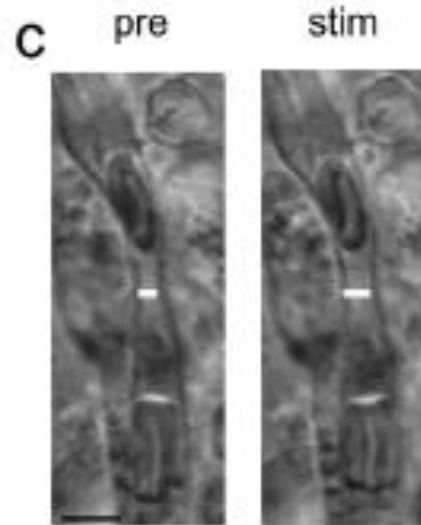
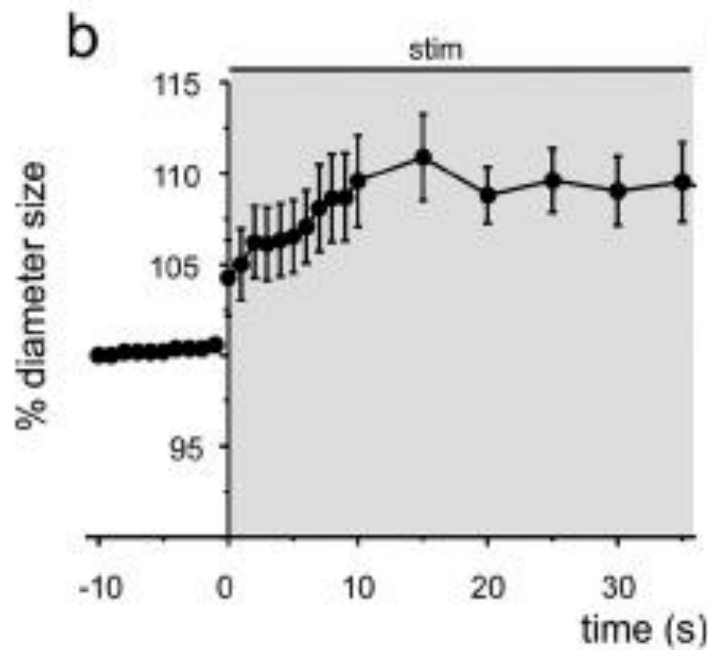
Arianna Maffei,^{1,*} Francesca Prestori,^{1,*} Katsuei Shibuki,³ Paola Rossi,¹ Vanni Taglietti,¹ and Egidio D'Angelo^{1,2}



Cellular/Molecular

Granular Layer Neurons Control Cerebellar Neurovascular Coupling Through an NMDA Receptor/NO-Dependent System

Lisa Mapelli,^{1,4*} Giuseppe Gagliano,^{1*} Teresa Soda,^{1,4} Umberto Laforenza,² Francesco Moccia,^{3†} and Egidio U. D'Angelo^{1,5†}

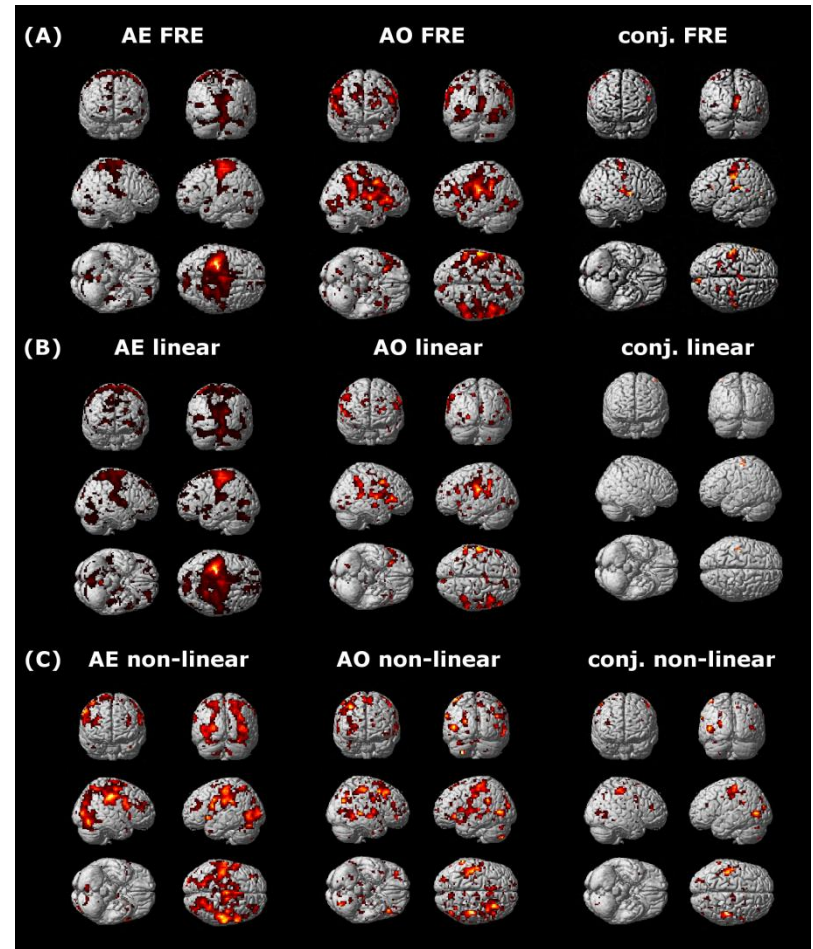
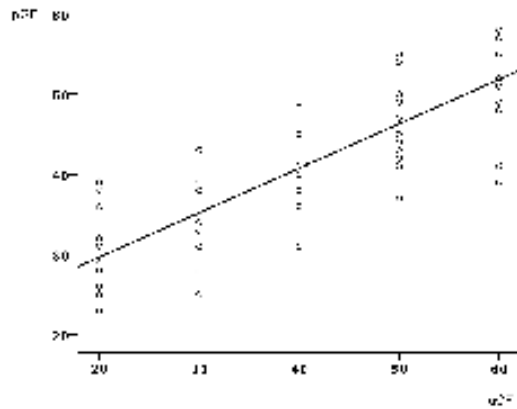
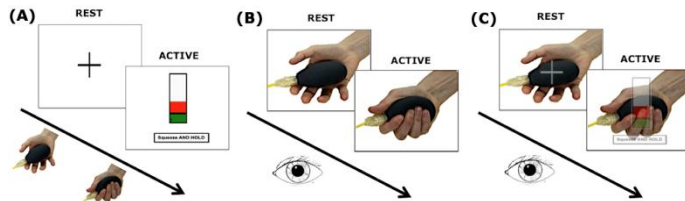


The final step:

Integration with brain models
and interpretation of fMRI
signals

OBSERVING CEREBELLUM IN ACTION

task-dependent fMRI (AEON “mirror” network)



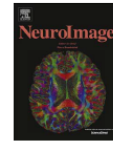
A priori models in Dynamic Causal Modeling



Contents lists available at ScienceDirect

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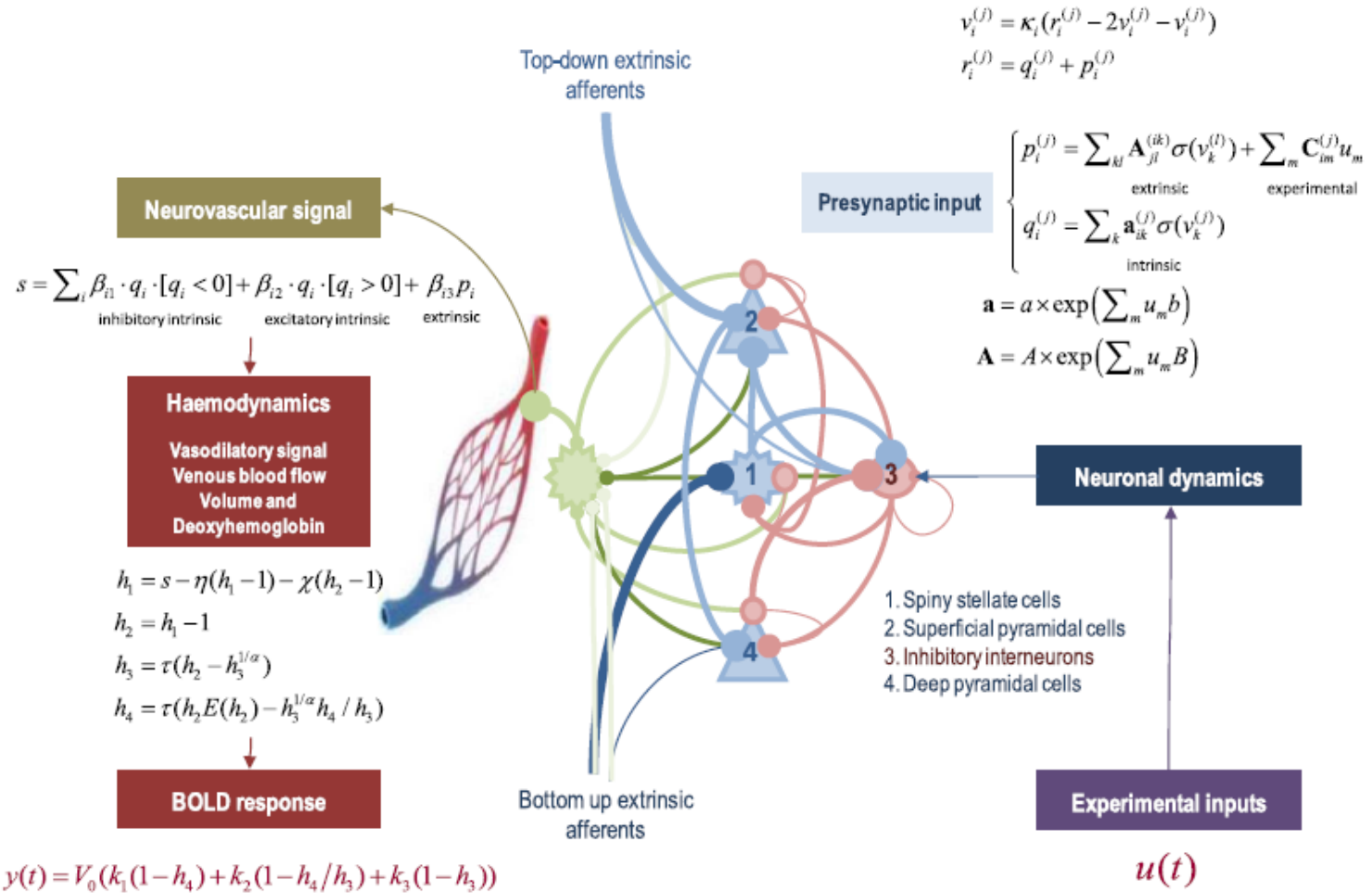


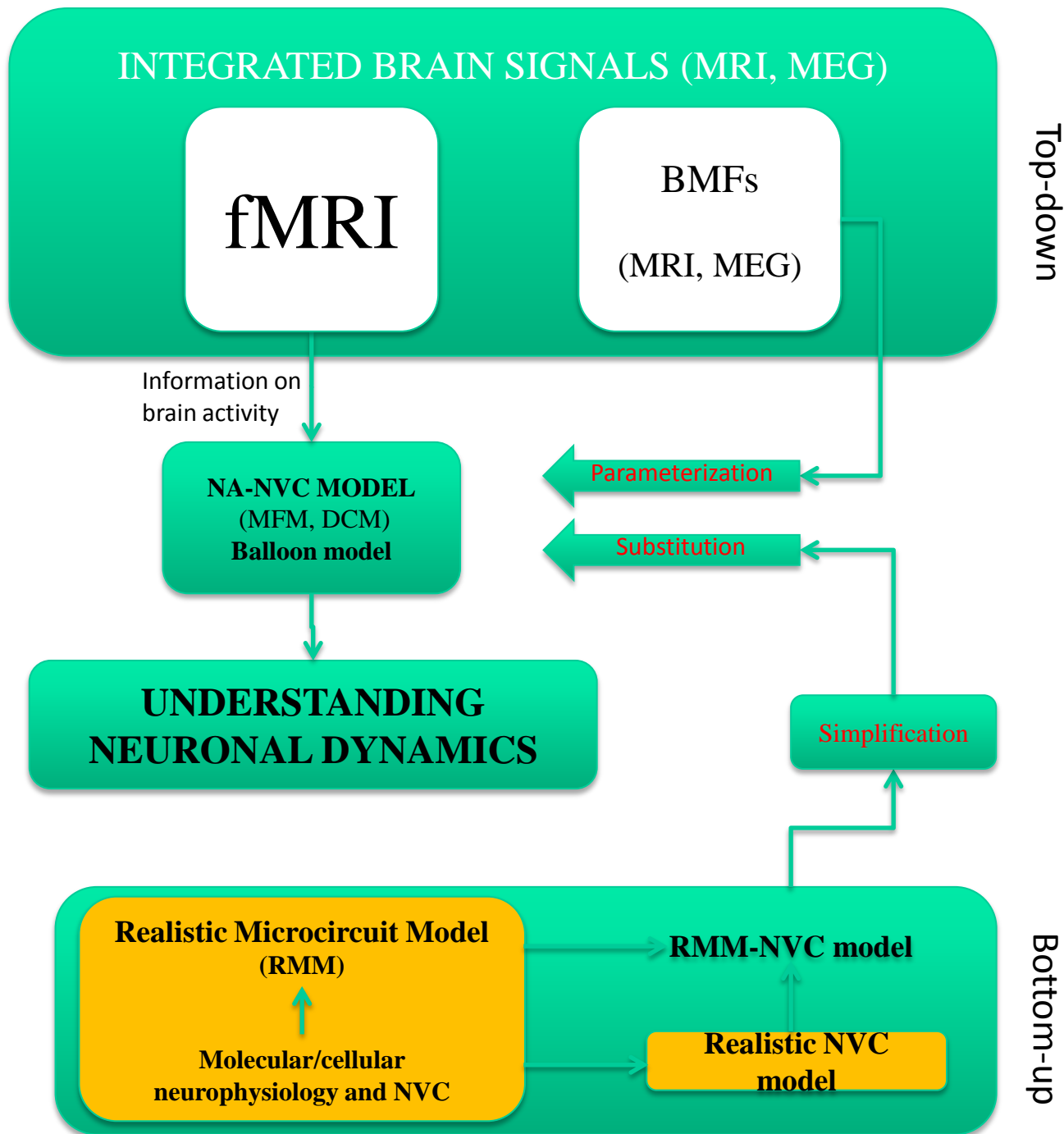
Dynamic causal modelling revisited

K.J. Friston et al.

K.J. Friston^{a,*}, Katrin H. Preller^{a,b}, Chris Mathys^{a,c}, Hayriye Caglan^{a,d}, Jakob Heinze^{a,e}, Adeel Razi^{a,f}, Peter Zeidman^a

NeuroImage xxx (xxxx) xxx–xxx





Cellular / Molecular
Biological recordings *in vitro*

construct

inspire

A priori model
(NM)

Realistic models
(RMM-NVC)

substitute

Balloon model

Fit / optimize

DCM

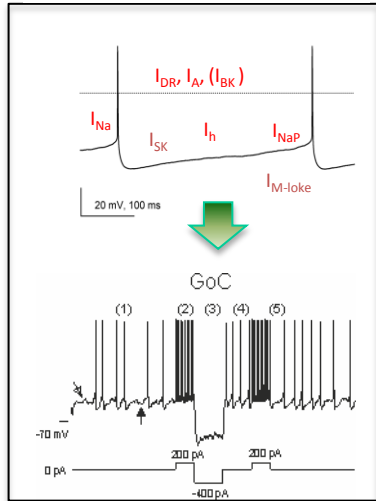
predict

Ensemble recordings *in vivo*
(fMRI)

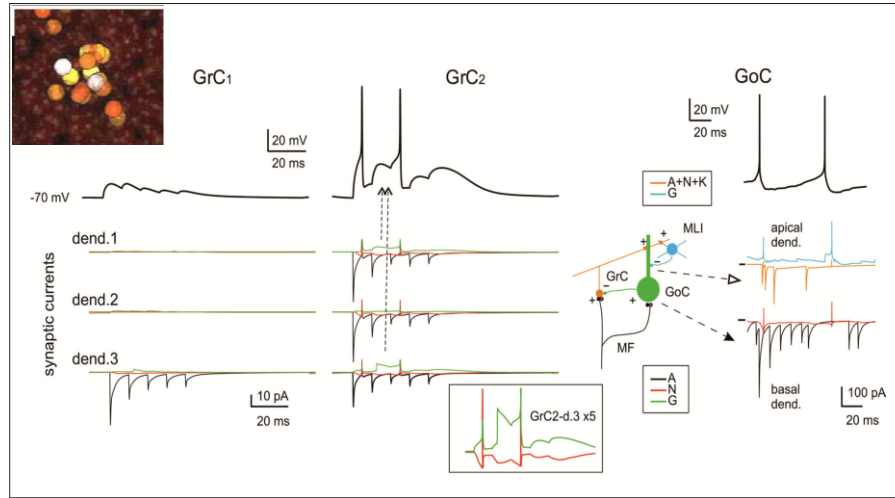
*Information about neuronal and synaptic
functions during fMRI*

predict

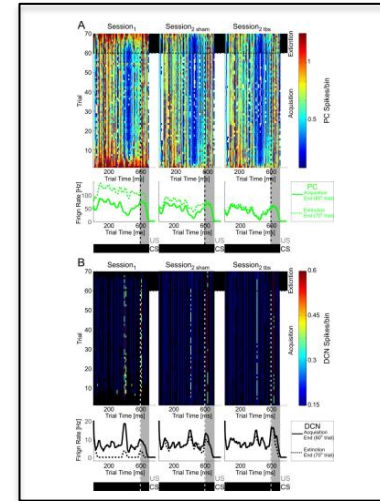
Realistic neuron model reconstruction



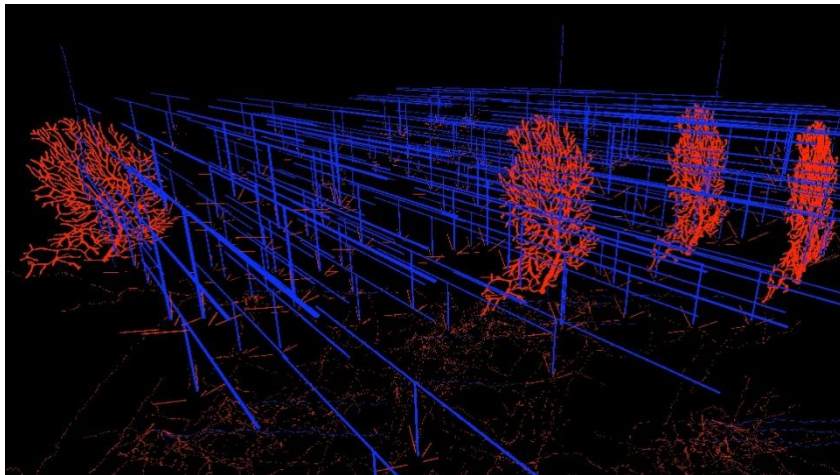
Realistic microcircuit model activity



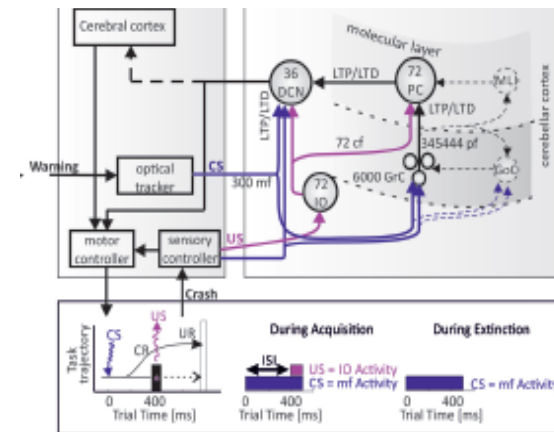
Simplified neuron model activity in closed-loop



Realistic microcircuit model reconstruction



Simplified SNN microcircuit model with plasticity in a controller emulating the brain



How we are doing it :

Collaborations

Projects

Courses

Community

Ettore Majorana Foundation for Scientific Culture

***School of Brain Cells and Circuits
“Camillo Golgi”***

***From cell physiology to integrated signals and
emerging brain functions***

***School Directors: Egidio D'Angelo & Claudia Gandini W-K
Course Directors: Egidio D'Angelo, Claudia Gandini W-K, Nikos Logothetis***

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TO PAY A PERMANENT TRIBUTE TO ARCHIMEDES AND GALILEO GALILEI, FOUNDERS OF MODERN SCIENCE
AND TO ENRICO FERMI, THE "ITALIAN NAVIGATOR", FATHER OF THE WEAK FORCES

Ettore Majorana

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Centro Studi e Ricerche Enrico Fermi



Human Brain Project



frontiers
in Cellular
Neuroscience





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CORRESPONDENCE • 07 MARCH 2018

Electric fish inspire inventors across the centuries

Egidio D'Angelo  & Paolo Mazzarello 

Inspired by the eel's electric organ, Thomas Schroeder and colleagues built a device that provides electricity in a variety of situations (*Nature* **552**, 214–218; 2017, and see go.nature.com/2hzh4jd). This example of technology derived from a biological concept has echoes of Alessandro Volta's invention of the battery more than two centuries earlier.

Volta (1745–1827) was professor of physics at the University of Pavia in Italy and a fellow of the Royal Society. On 20 March 1800, he sent a letter to Joseph Banks, president of the Royal Society, to communicate his new

[PDF version](#)

RELATED ARTICLES

An electric-eel-inspired soft power source from stacked hydrogels 



Volta e la torpedine su "Nature"

La rivista scientifica inglese pubblica un report di Mazzarello e D'Angelo

Cos'hanno in comune Alessandro Volta e un gruppo di ricercatori svizzero-americano? Secondo Egidio D'Angelo e Paolo Mazzarello - professori ordinari di fisiologia e storia della medicina all'Università di Pavia - li accomuna, a quanto pare senza saperlo (nel caso dei secondi) la stessa conclusione scientifica alla quale sono giunti a distanza di 220 anni l'uno dagli altri. Lo spiegano in una corrispondenza scientifica che sarà pubblicata domani sulla prestigiosa rivista inglese "Nature". La nota dal titolo *Electric fish*

inspire an age of invention prende spunto da un articolo recentemente pubblicato sulla stessa rivista da un gruppo di ricercatori svizzero-americano che ha sviluppato una tecnologia per la generazione di un potenziale elettrico biocompatibile dall'organo elettrico dell'anguilla *Electrophorus electricus*. Ispirati da questa straordinaria proprietà presente nel mondo animale, i ricercatori hanno costruito un "organo elettrico artificiale" dalle potenziali importanti applicazioni pratiche». Nel report non fanno cenno a Volta che, pure,

220 anni prima quando era professore all'Università di Pavia e socio della Royal Society di Londra, arrivò alla stessa deduzione creando la pila.

«E' una prova che la natura ha molto da insegnare. Ed è fonte di ispirazione invariata, capace di accendere la creatività umana, anche a distanza di secoli e in luoghi diversi - spiegano Mazzarello e D'Angelo - . Come i ricercatori svizzero-americani anche il fisico italiano rimase profondamente impressionato dalle proprietà dell'organo elettrico di un pesce particolare, la torpedine, e

ispirato dalle sue caratteristiche inventò lo strumento - la pila elettrica - che permise di domare e graduare, per la prima volta con una certa precisione, quella che all'epoca era una misteriosa forza della natura. La lettera di Alessandro Volta alla Royal Society di Londra del 20 marzo 1800, comunicando l'invenzione della batteria, sottolineava, quasi con le stesse parole recentemente usate, che il nuovo apparato doveva considerarsi una sorta di ricostruzione artificiale dell'organo elettrico della torpedine». *(m.g.p.)*

Ettore Majorana Foundation for Scientific Culture

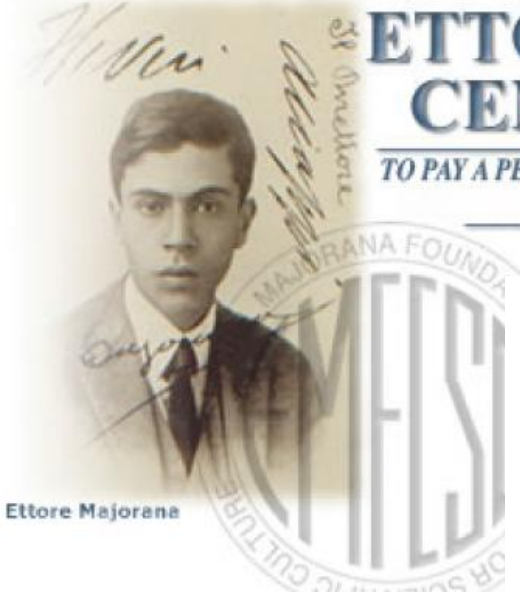
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Mitchell Goldfarb



Human Brain Project

Pubblicazioni 2016 (best in red)

- 1 E. D'Angelo, E. Galliano, C.I. De Zeeuw. The Editorial: The Olivo-Cerebellar System. *Front Neural Circuits*. 2016 Jan 12;9:66. doi: 10.3389/fncir.2015.00066. eCollection 2015.
- 2 K. B. Ramakrishnan, K. Voges, L. De Propriis, C.I. De Zeeuw, E. D'Angelo. Tactile Stimulation Evokes Long-Lasting Potentiation of Purkinje Cell Discharge In Vivo. *Front. Cell. Neurosci.*, 2016 Feb 18;10:36. doi: 10.3389/fncel.2016.00036. eCollection 2016.
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- 4 N. R. Luque, J. A. Garrido, F. Naveros, R. Carrillo, E. D'Angelo, E. Ros. Distributed Cerebellar Motor Learning: A Spike-Timing-Dependent Plasticity Model. *Front. Comput. Neurosci.*, 2016 Mar 2;10:17. doi: 10.3389/fncom.2016.00017. eCollection 2016.
- 5 C. Lega, T. Vecchi, E D'Angelo, Z Cattaneo. A TMS investigation on the role of the cerebellum in pitch and timbre discrimination. *Cerebellum Ataxias*. 2016 Mar 2;3:6. doi: 10.1186/s40673-016-0044-4. eCollection 2016.
- 6 JA Garrido, NR Luque, S Tolu, E D'Angelo. Oscillation-Driven Spike-Timing Dependent Plasticity Allows Multiple Overlapping Pattern Recognition in Inhibitory Interneuron Networks. *Int J Neural Syst*. 2016 Aug;26(5):1650020. doi: 10.1142/S0129065716500209. Epub 2016 Apr 15.
- 7 H. Parasuram, B. Nair, E. D'Angelo, M. Hines, G. Naldi, S. Diwakar. Computational Modeling of Single Neuron Extracellular Electric Potentials and Network Local Field Potentials using LFPsim. *Front. Comput. Neurosci.*, 28 June 2016 <http://dx.doi.org/10.3389/fncom.2016.00065>.
- 8 G. Florimbi, E. Torti, S. Masoli, E. D'Angelo, G. Danese, F. Leporati. The Human Brain Project: Parallel technologies for biologically accurate simulation of Granule cells. *Microprocessors and Microsystems (2016)*. <http://dx.doi.org/10.1016/j.micpro.2016.05.015>
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- 10 **A.A. Alahmadi, R.S. Samson, D. Gasston, M. Pardini, K.J. Friston, E. D'Angelo, A.T. Toosy, C.A.M. Wheeler-Kingshott. Complex motor task associated with non-linear BOLD responses in cerebro-cortical areas and cerebellum. *Brain Struct Funct*. 2016 Jun;221(5):2443-58. doi: 10.1007/s00429-015-1048-1. Epub 2015 Apr 29.**
- 11 D'Angelo E, Antonietti A, Casali S, Casellato C, Garrido JA, Luque NR, Mapelli L, Masoli S, Pedrocchi A, Prestori F, Rizza MF, Ros E. Modeling the Cerebellar Microcircuit: New Strategies for a Long-Standing Issue. *Front Cell Neurosci*. 2016 Jul 8;10:176. doi: 10.3389/fncel.2016.00176. eCollection 2016. Review. PubMed PMID: 27458345; PubMed Central PMCID: PMC4937064.
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- 13 **K. Dover, C. Marra, S. Solinas, M. Popovic, S. Subramaniam, D. Zecevic, E. D'Angelo, M. Goldfarb. FHF-independent conduction of action potentials along the leak-resistant cerebellar granule cell axon. *Nature Communications*. 26 September 2016 doi:10.1038/ncomms12895**
- 14 G.Z. De Vidovich, R. Muffatti, J. Monaco, N. Caramia, D. Broglio, E. Caverzasi, F. Barale, E. D'Angelo. Repetitive TMS on Left Cerebellum Affects Impulsivity in Borderline Personality Disorder: A Pilot Study. *Front Hum Neurosci*. 2016 Dec 5;10:582 [10.3389/fnhum.2016.00582](http://dx.doi.org/10.3389/fnhum.2016.00582)
- 15 F. Palesi, JD Tournier, F Calamante, N. Muhlert, G. Castellazzi, D. Chard D, E. D'Angelo, C.G.Wheeler-Kingshott. Reconstructing contralateral fiber tracts: methodological aspects of cerebello-thalamocortical pathway reconstruction. *Funct Neurol*. 2016 Oct/Dec;31(4):229-238.
- 16 A. Antonietti, C. Casellato, E. D'Angelo, A. Pedrocchi. Model-Driven Analysis of Eyeblink Classical Conditioning Reveals the Underlying Structure of Cerebellar Plasticity and Neuronal Activity. *IEEE Transactions on Neural Networks and Learning Systems*, in press.

Pubblicazioni 2017 (best in red)

1	Geminiani A, Casellato C, Antonietti A, D'Angelo E, Pedrocchi A. Multiple-Plasticity Spiking Neural Network Embedded in a Closed-Loop Control System to Model Cerebellar Pathologies. <i>Int J Neural Syst.</i> 2017 Jan 10:1750017. doi: 10.1142/S0129065717500174. PubMed PMID: 28264639.
2	Mapelli L, Gagliano G, Soda T, Laforenza U., Moccia F, D'Angelo E. Granular Layer Neurons Control Cerebellar Neurovascular Coupling Through an NMDA Receptor/NO-Dependent System. J Neurosci. 2017 Feb 1;37(5):1340-1351. doi:10.1523/JNEUROSCI.
3	Alahmadi AA, Pardini M, Samson RS, Friston KJ, Toosy AT, D'Angelo E, Gandini Wheeler-Kingshott CA. Cerebellar lobules and dentate nuclei mirror cortical force-related-BOLD responses: Beyond all (linear) expectations. <i>Hum Brain Mapp.</i> 2017 Feb 27. doi: 10.1002/hbm.23541
4	Sgritta M, Locatelli F, Soda T, Prestori F, D'Angelo E. Hebbian spike-timing dependent plasticity at the cerebellar input stage. J Neurosci. 2017 Feb 10. pii: 2079-16. doi: 10.1523/JNEUROSCI.2079-16.2016
5	Masoli S, Rizza MF, Sgritta M, Van Geit W, Schürmann F, D'Angelo E. Single Neuron Optimization as a Basis for Accurate Biophysical Modeling: The Case of Cerebellar Granule Cells. <i>Front. Cell. Neurosci.</i> , 15 March 2017 https://doi.org/10.3389/fncel.2017.00071
6	Colnaghi S, Colagiorgio P, Ramat S, D'Angelo E, Koch G, Versino M. (2017). After Effects of Cerebellar Continuous Theta Burst Stimulation on Reflexive Saccades and Smooth Pursuit in Humans. <i>Cerebellum.</i> 2017 Mar 16. doi:10.1007/s12311-017-0852-y. PubMed PMID: 28303385
7	Colnaghi S, Colagiorgio P, Versino M, Koch G, D'Angelo E, Ramat S. (2017). A role for NMDAR-dependent cerebellar plasticity in adaptive control of saccades in humans. <i>Brain Stimul.</i> 2017 Jul-Aug; 10(4):817-827. doi: 10.1016/j.brs.2017.05.001. Epub 2017 May 5. PubMed PMID: 28501325
8	Gandolfi D, Cerri S, Mapelli J, Polimeni M, Tritto S, Fuzzati-Armentero MT, Bigiani A, Blandini F, Mapelli L, D'Angelo E (2017). Activation of the CREB/c-Fos Pathway during Long-Term Synaptic Plasticity in the Cerebellum Granular Layer. <i>Front. Cell. Neurosci.</i> 28 June 2017; https://doi.org/10.3389/fncel.2017.00184
9	D'Angelo E., Gandini Wheeler-Kingshott C., <i>Modelling the brain: Elementary components to explain ensemble functions. Rivista del nuovo cimento, 14 July 2017, 40 (7)- pp 297-333, doi: 10.1393/ncr/i2017-10137-5.</i>
10	Masoli S, D'Angelo E. Synaptic Activation of a Detailed Purkinje Cell Model Predicts Voltage-Dependent Control of Burst-Pause Responses in Active Dendrites. <i>Front. Cell. Neurosci.</i> , 13 September 2017 https://doi.org/10.3389/fncel.2017.00278 . PubMed PMID: 28303385
11	Palesi F, De Rinaldis A, Castellazzi G, Calamante F, Muhlert N, Chard D, Tournier JD, Magenes G, D'Angelo E, Gandini Wheeler-Kingshott CAM. Contralateral cortico-ponto-cerebellar pathways reconstruction in humans in vivo: implications for reciprocal cerebro-cerebellar structural connectivity in motor and non-motor areas. Nature Scientific Reports , 2017 Oct 9;7(1):12841. doi: 10.1038/s41598-017-13079-8. PubMed PMID: 28993670; PubMed Central PMCID: PMC5634467.

RESEARCH MILESTONES

2016-2017:

- experimental analysis of neurovascular coupling (NVC) in the cerebellum – ACHIEVED, paper published
- experimental analysis of fMRI signals in complex tasks involving the cerebral and cerebellar cortical networks (CTX and CBL) – ACHIEVED, papers published, and in preparation
- elaboration of scaffold models and methodologies for brain modeling - ACHIEVED through HBP and CEREBNEST.

2018: exploit HBP infrastructure to model NVC in the cerebellum (in collaboration with AMRITA University, India)

2019: exploit HBP infrastructure to generate simplified CTX and CBL modules with NVC (in collaboration with POLIMI, CEREBNEST).

2020: use CTX and CBL modules to generate the final brain model and fit fMRI data through a “model inversion” procedure (in collaboration with UCL IoN/FIL and University of Marseille).

EDUCATION EVENTS (with support of Centro Fermi)

ERICE COURSES

2015 : Modeling the brain: from neurons to integrated systems - ACHIEVED

2016 : The cerebellum inside-out: cells, circuits and functions - ACHIEVED

2017: From cell physiology to integrated signals and emerging brain functions - ACHIEVED

2018: The sensory-motor system from cellular microcircuits to large-scale networks – CALL LAUNCHED

2019: TBD

2020: TBD

REQUIREMENTS

2018 – 1 postdoc

2019 – 1 postdoc

2020 – 1 postdoc