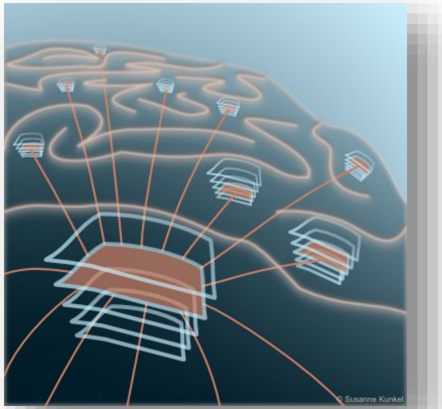


Necessity and feasibility of brain-scale simulation at cellular and synaptic resolution

April 24-29 2016
Workshop on High-Performance Computing,
Stochastic Modeling and Databases in Neuroscience
NeuroMat
São Paulo, Brazil

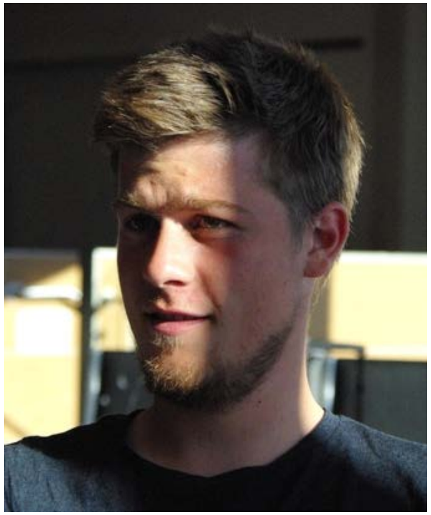
Markus Diesmann
Institute of Neuroscience and Medicine (INM-6)
Institute for Advanced Simulation (IAS-6)
Jülich Research Centre

www.csn.fz-juelich.de

Team

modeling

reproducibility



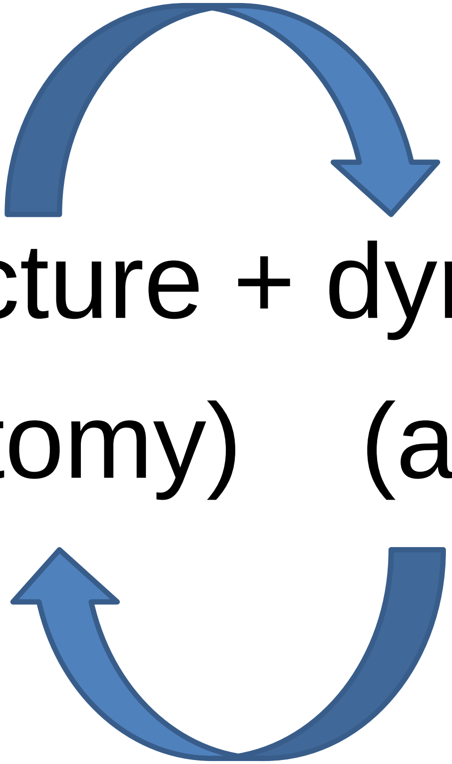
Maximilian Schmidt

Sacha J van Albada

Sonja Gruen

others mentioned on the way

Model components in neuroscience



emerging network activity

model = structure + dynamics

(anatomy) (activity)

plasticity

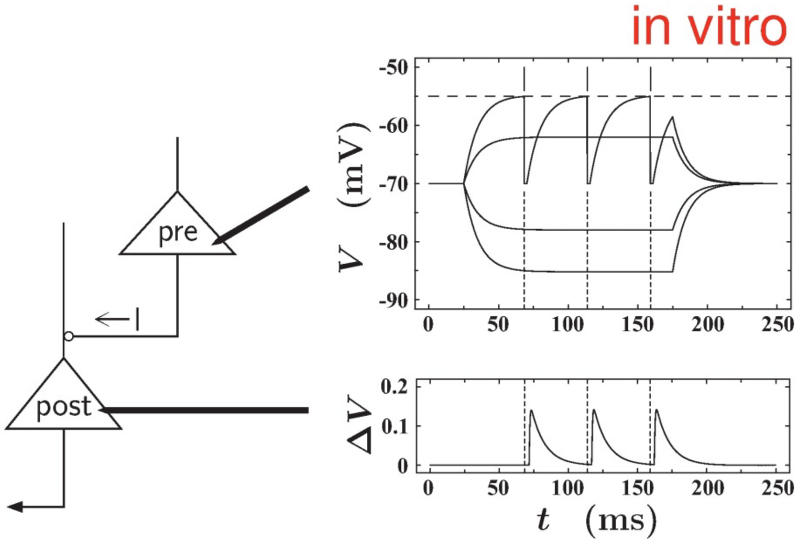
Top-down and bottom-up

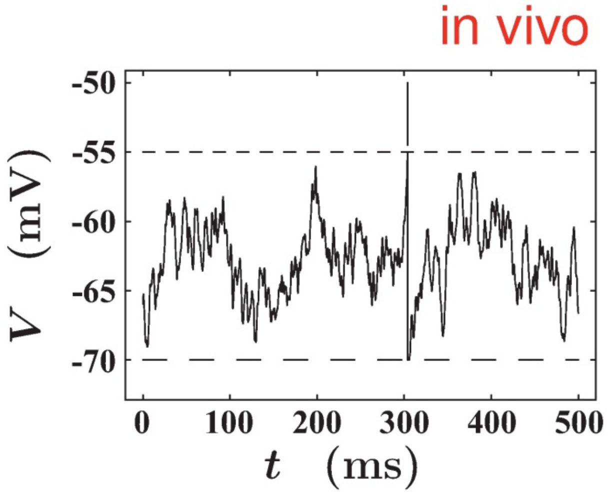
the computer analogy:

system	computer	brain	
top	multiplication	maze navigation	system-level behavior
	⇓	⇓	
	logical algorithm	TD-learning	system-level theory
	⇕	⇕ ?	
	electrical circuit	neuronal network	
	⇑	⇑	
	transistor	I&F neuron model	
	⇑	⇑	
bottom	electrons	spikes	(bio)physics

comparison between levels: compatibility and consistency

Interactions between neurons





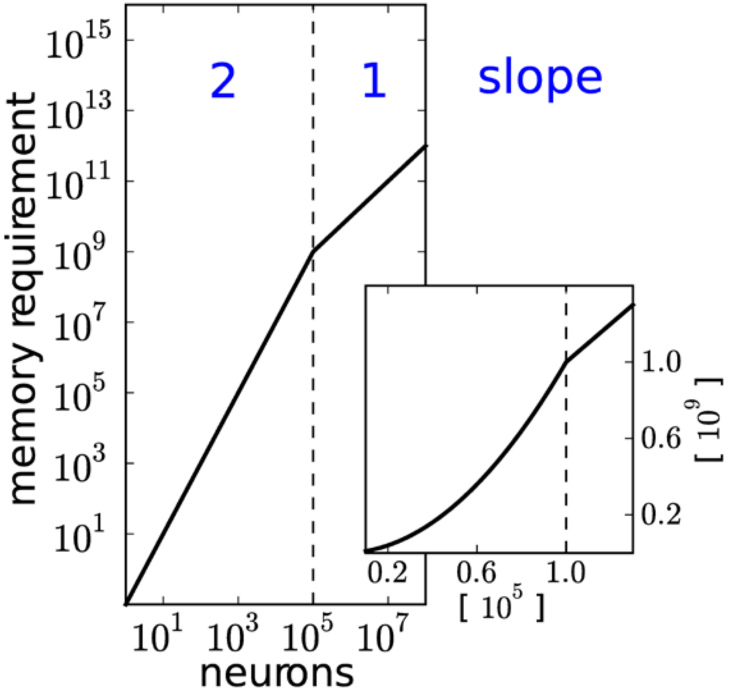
- current injection into pre-synaptic neuron causes excursions of membrane potential
- supra-threshold value causes spike transmitted to post-synaptic neuron
- post-synaptic neuron responds with small excursion of potential after delay
- inhibitory neurons (20%) cause negative excursion

- each neuron receives input from 10,000 other neurons
- causing large fluctuations of membrane potential
- emission rate of 1 to 10 spikes per second

Realistic local cortical networks

- connectivity $c = 0.1$
- synapses per neuron = 10^4

⇒ minimal network size = 10^5



- network $N = 10^5$
    - considered elementary unit
    - corresponding to $1\ \mathrm{mm}^3$

- total number of synapses = $(cN) \cdot N$

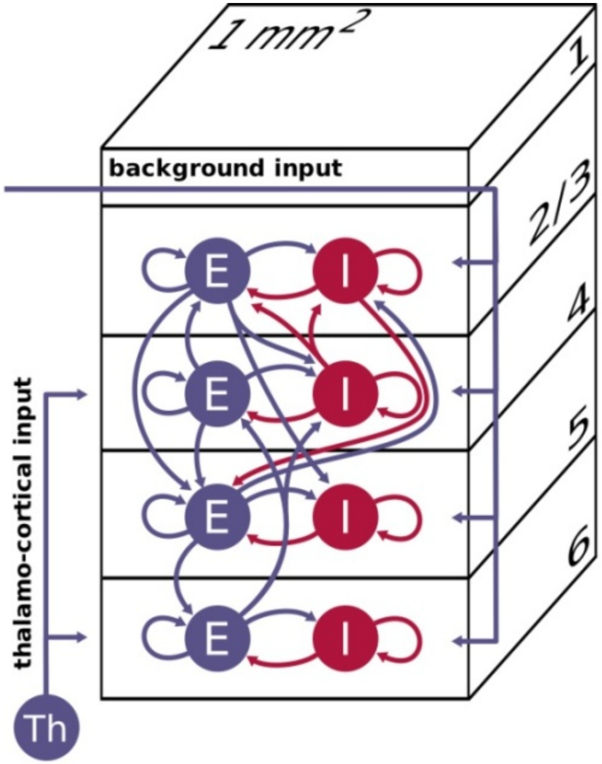
⇒ possible

Morrison A, Mehring C, Geisel T, Aertsen A, Diesmann M (2005) Neural Comput 17(8):1776-1801

Morrison A, Straube S, Plesser HE, Diesmann M (2007) Neural Comput 19(1):47-79

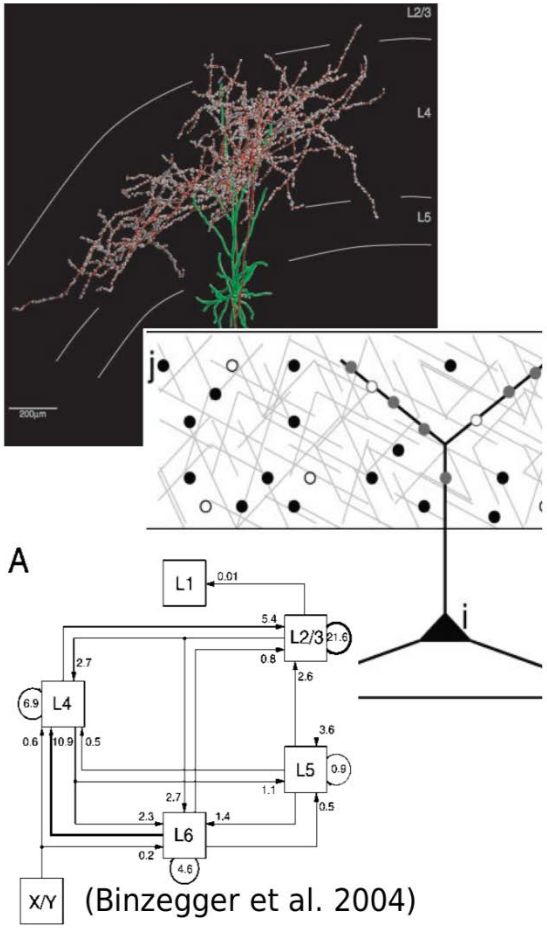
Minimal layered cortical network model

- 1 mm^3
- 1 billion synapses, 100,000 neurons
- 2 populations of neurons per layer:
  - E: Excitatory
  - I: Inhibitory
- E and I identical neuronal dynamics
- laterally homogeneous connectivity
- layer- and type-specific C_{ij}^{xy}



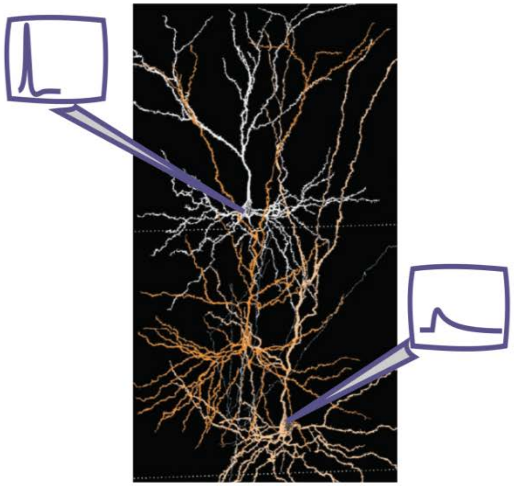
Anatomical data sets

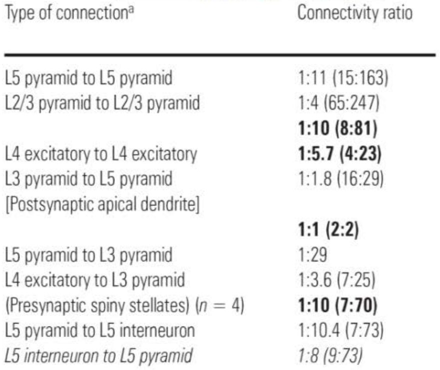
in vivo anatomy



(Binzegger et al. 2004)

in vitro physiology





Type of connection[a]	Connectivity ratio
L5 pyramid to L5 pyramid	1:11 (15:163)
L2/3 pyramid to L2/3 pyramid	1:4 (65:247)
	1:10 (8:81)
L4 excitatory to L4 excitatory	**1:5.7 (4:23)**
L3 pyramid to L5 pyramid	1:1.8 (16:29)
[Postsynaptic apical dendrite]	
	1:1 (2:2)
L5 pyramid to L3 pyramid	1:29
L4 excitatory to L3 pyramid	1:3.6 (7:25)
(Presynaptic spiny stellates) ($n = 4$)	**1:10 (7:70)**
L5 pyramid to L5 interneuron	1:10.4 (7:73)
L5 interneuron to L5 pyramid	*1:8 (9:73)*

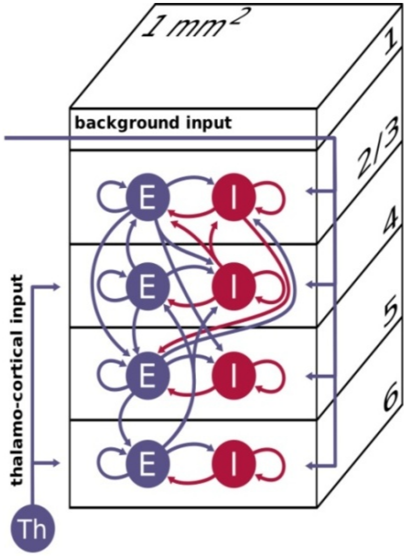
(Thomson et al. 2002)

Local cortical microcircuit

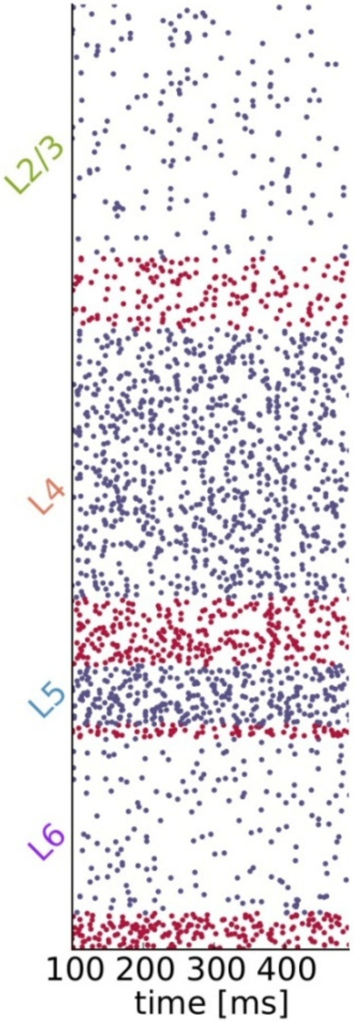
taking into account layer and neuron-type specific connectivity is sufficient to reproduce experimentally observed:

- asynchronous-irregular spiking of neurons
- higher spike rate of inhibitory neurons
- correct distribution of spike rates across layers
- integrates knowledge of more than 50 experimental papers

Potjans TC & Diesmann M (2014) The cell-type specific connectivity of the local cortical network explains prominent features of neuronal activity. *Cerebral Cortex* 24 (3): 785-806

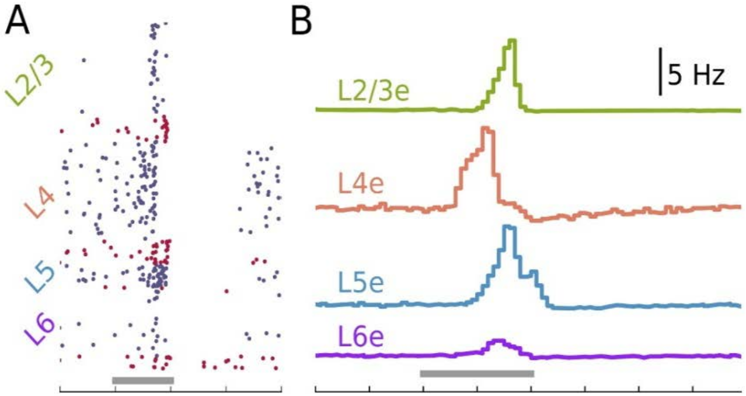


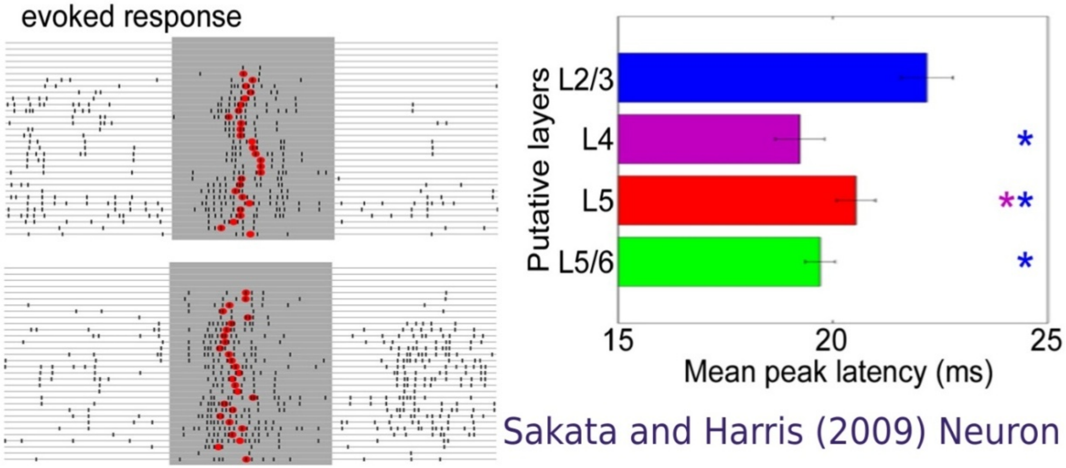
10^5 neurons
10^9 synapses



available at: www.opensourcebrain.org

Response to transient inputs





Sakata and Harris (2009) Neuron

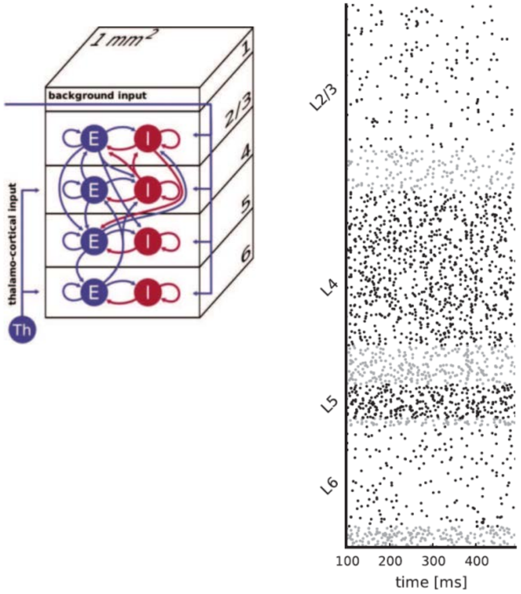
Building block for mesoscopic studies

- collaboration with Gaute Einevoll (UMB, Norway)

nest::
simulated()

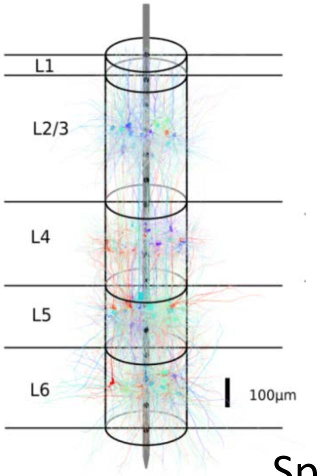
LFPy

NEURON
for empirically-based simulations of
neurons and networks of neurons



+

´Morphology



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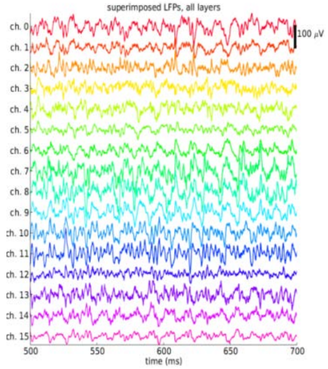
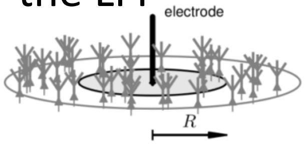
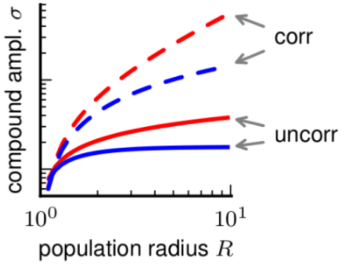
Laminar LFP profile



Spatial reach of the LFP

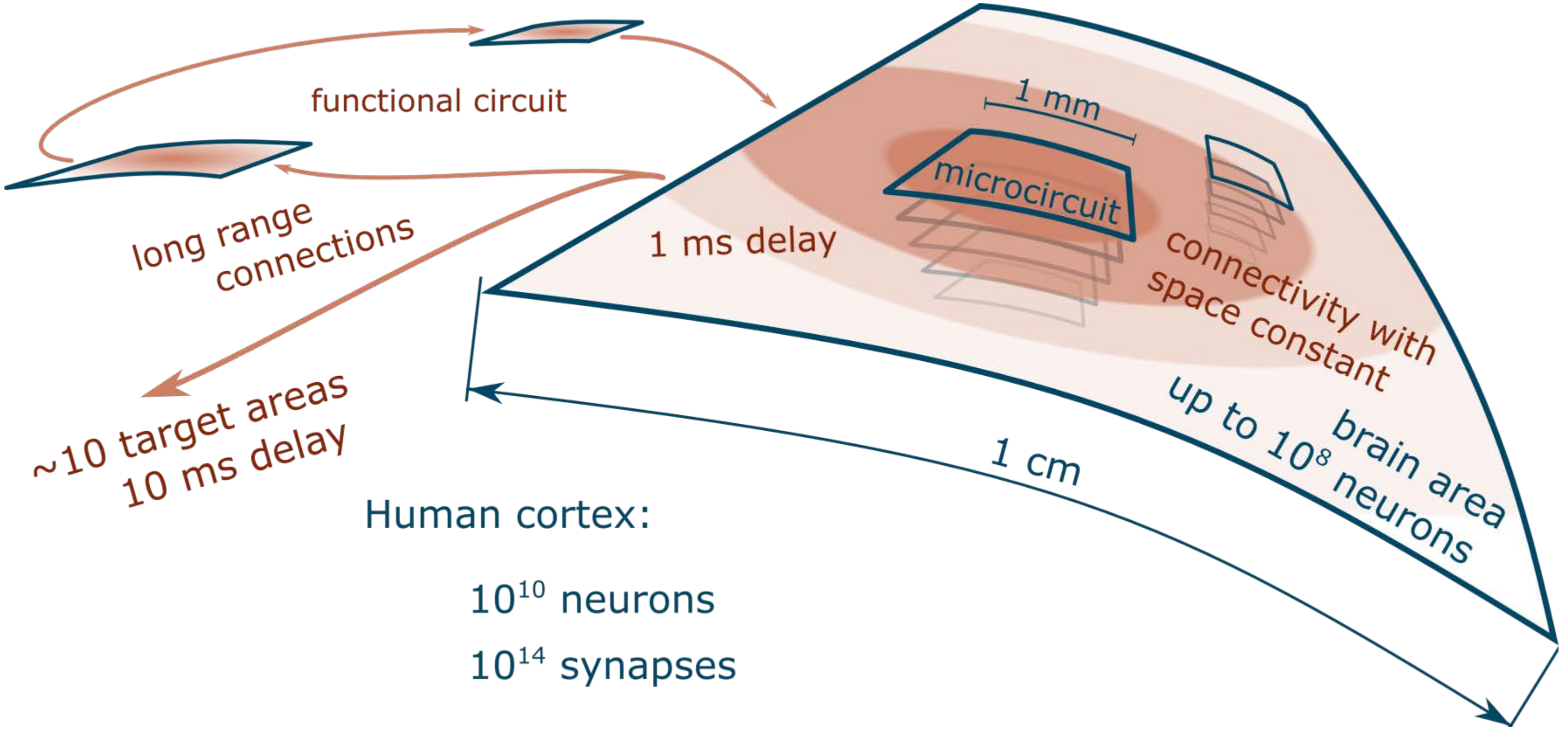




Linden H, Tetzlaff T, Potjans TC, Pettersen KH, Grün S, Diesmann M, Einevoll GT (2011) Modeling the spatial reach of the LFP. *Neuron* 72(5):859-872

Critique of local network model

a network of networks with at least three levels of organization:



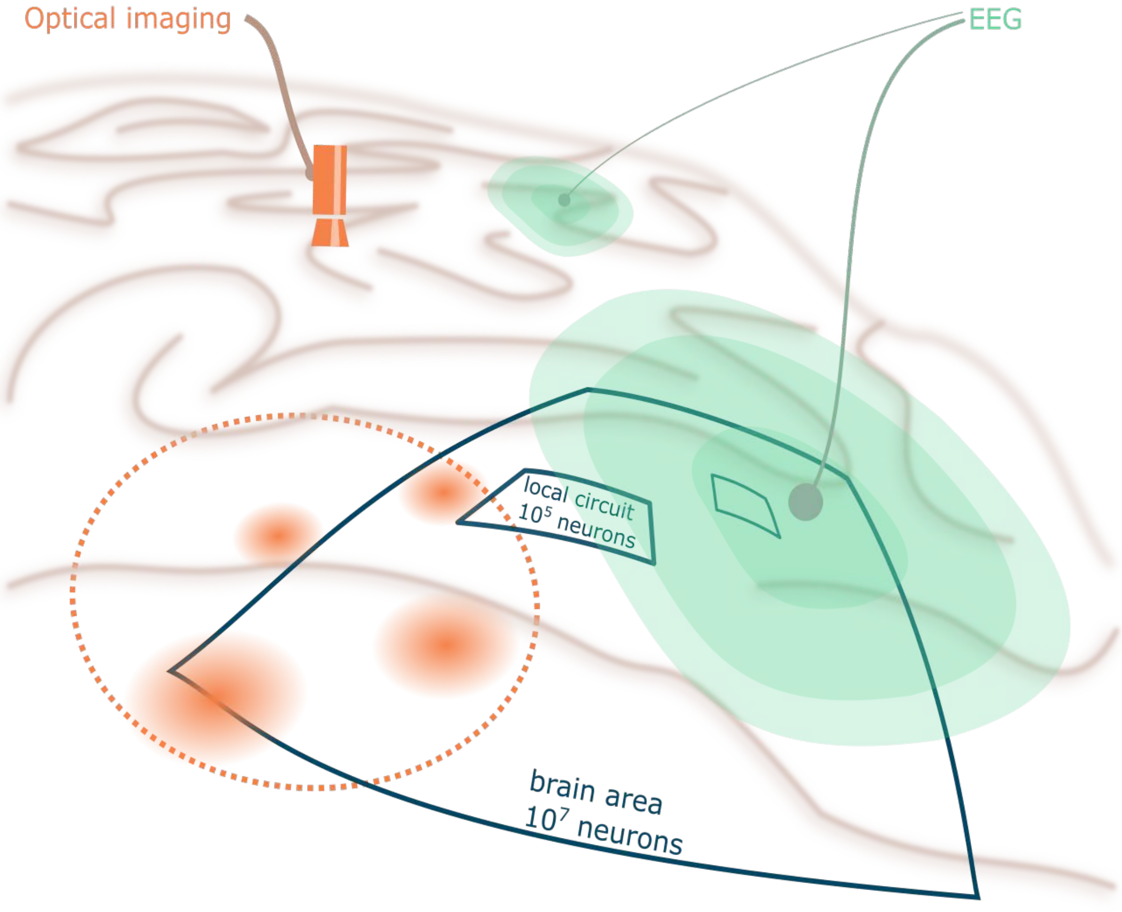
- neurons in local microcircuit models are missing 50% of synapses
- e.g., power spectrum shows discrepancies, slow oscillations missing
- solution by taking brain-scale anatomy into account

Meso- and macro-scale measures

brain-scale networks basis for:
- further measures by forward modeling
- comparison with mean-field models

mesoscopic measures
- local field potential (LFP)
- voltage sensitive dyes (VSD)

and macroscopic measures
- EEG, MEG
- fMRI resting state networks



Feasibility and necessity

- Can we do simulations at the brain scale?
- Do we need to simulate full scale (at cellular resolution)?

frontiers in NEUROINFORMATICS

ORIGINAL RESEARCH ARTICLE
published: 02 November 2012
doi: 10.3389/fninf.2012.00026

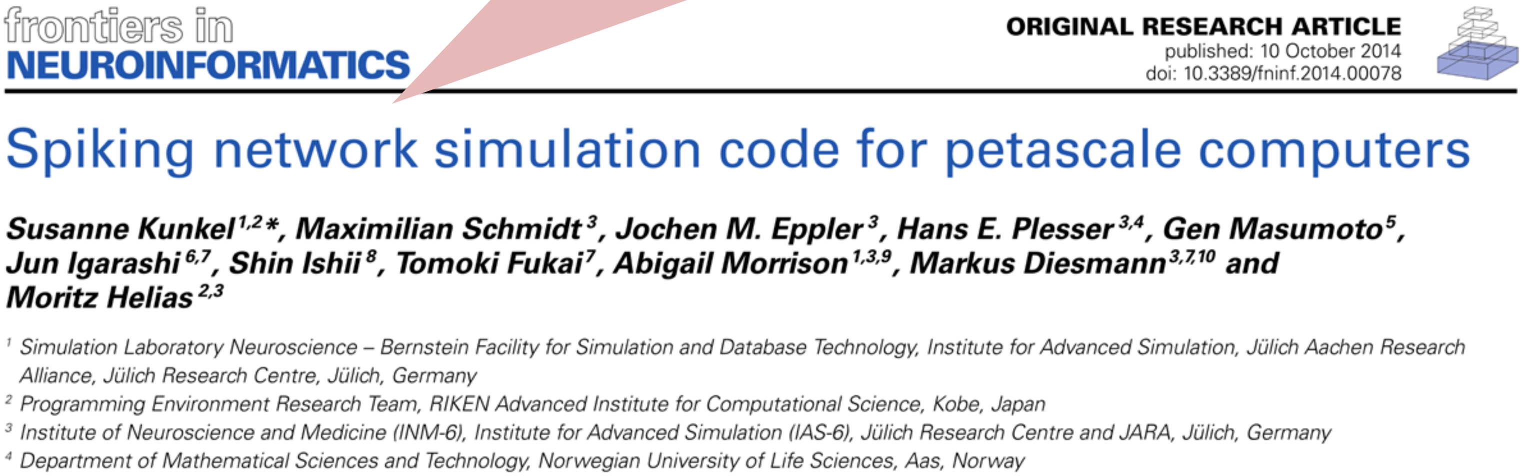
Supercomputers ready for use as discovery machines for neuroscience

Moritz Helias[1,2]*, Susanne Kunkel[1,3,4], Gen Masumoto[5], Jun Igarashi[6], Jochen Martin Eppler[1], Shin Ishii[7], Tomoki Fukai[6], Abigail Morrison[1,3,4,8] and Markus Diesmann[1,2,4,9]

[1] *Institute of Neuroscience and Medicine (INM-6), Computational and Systems Neuroscience, Jülich Research Centre, Jülich, Germ*
[2] *RIKEN Brain Science Institute, Wako, Japan*
[3] *Simulation Laboratory Neuroscience – Bernstein Facility for Simulation and Database Technology, Institute for Advanced Simulation, Jülich Aa Alliance, Jülich Research Centre, Jülich, Germany*
[4] *Bernstein Center Freiburg, Albert-Ludwig University of Freiburg, Freiburg, Germany*

makes supercomputers accessible for neuroscience

provides the evidence that neuroscience can exploit petascale systems



frontiers in NEUROINFORMATICS

ORIGINAL RESEARCH ARTICLE
published: 10 October 2014
doi: 10.3389/fninf.2014.00078

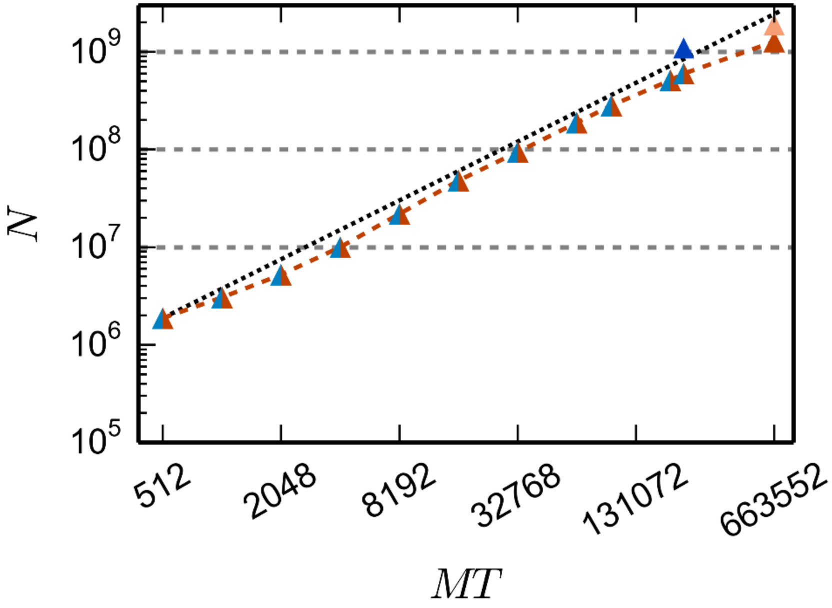
Spiking network simulation code for petascale computers

Susanne Kunkel[1,2]*, Maximilian Schmidt[3], Jochen M. Eppler[3], Hans E. Plesser[3,4], Gen Masumoto[5], Jun Igarashi[6,7], Shin Ishii[8], Tomoki Fukai[7], Abigail Morrison[1,3,9], Markus Diesmann[3,7,10] and Moritz Helias[2,3]

[1] *Simulation Laboratory Neuroscience – Bernstein Facility for Simulation and Database Technology, Institute for Advanced Simulation, Jülich Aachen Research Alliance, Jülich Research Centre, Jülich, Germany*
[2] *Programming Environment Research Team, RIKEN Advanced Institute for Computational Science, Kobe, Japan*
[3] *Institute of Neuroscience and Medicine (INM-6), Institute for Advanced Simulation (IAS-6), Jülich Research Centre and JARA, Jülich, Germany*
[4] *Department of Mathematical Sciences and Technology, Norwegian University of Life Sciences, Aas, Norway*

NEST – Maximum network size

- using 663,552 cores of K
- using 229,376 cores of JUQUEEN
- worst case: random network
- exc-exc STDP

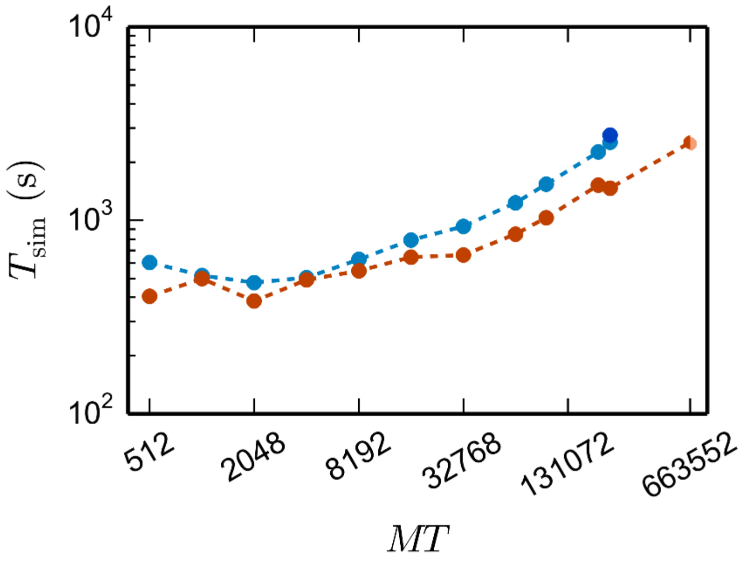


- largest general network simulation performed to date:
- 1.86x10^9 neurons, 6000 synapses per neuron
- 1.08x10^9 neurons, 6000 synapses per neuron

NEST simulation software

NEST – Scaling of run time

- runtime for 1 second biological time:
- between 6 and 42 min on K computer
- between 8 and 41 min on JUQUEEN
- wiring: between 3 and 15 min

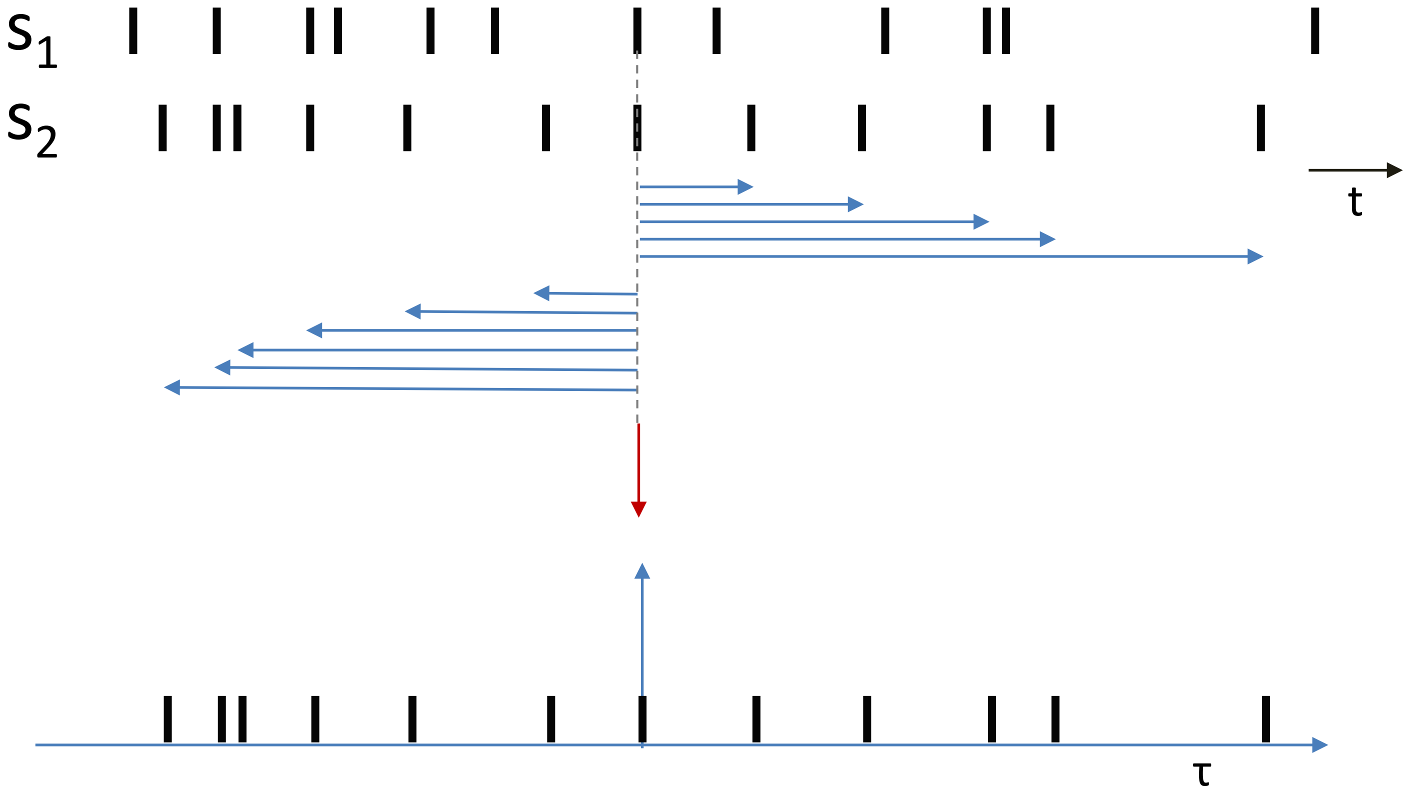


- still not fast enough for studies of plasticity
- need to increase multi-threading

Feasibility and necessity

- Can we do simulations at the brain scale? ✓
- Do we need to simulate full scale (at cellular resolution)?

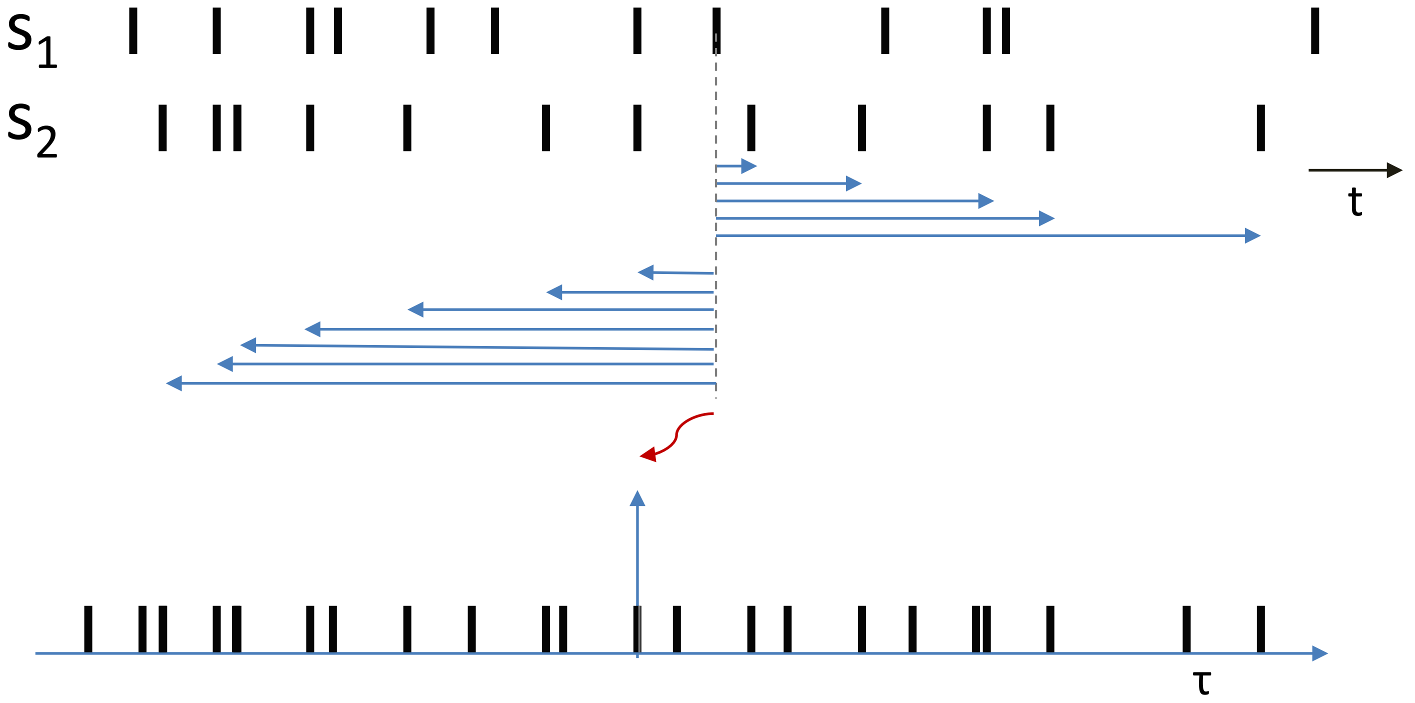
Measure of neural interaction: Cross-Correlation



The cross-correlation represents the probability of finding any spike in train s_2 as a function of time before or after a spike in train s_1 : $\rho(\tau) = \int s_1(t)s_2(t-\tau)dt$

Perkel et al, 1967

Cross-Correlation



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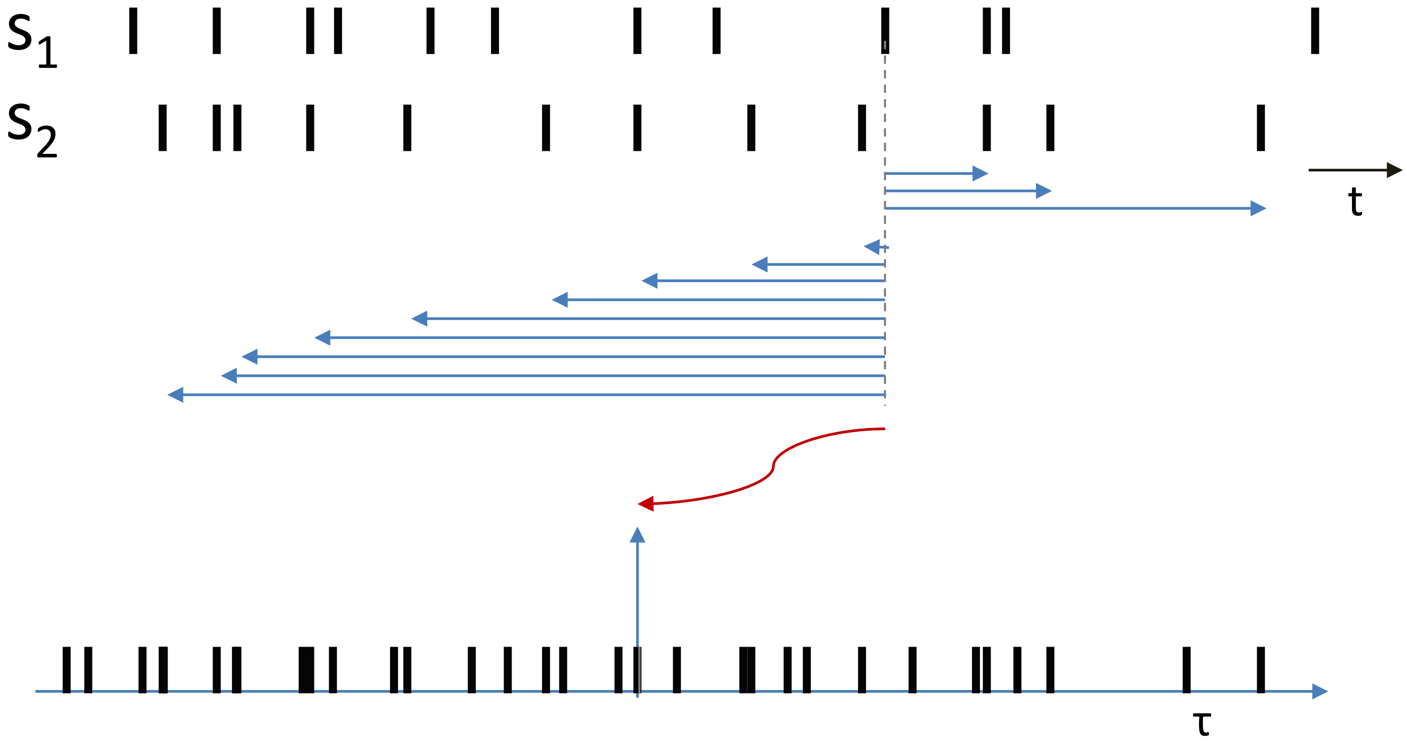
Perkel et al, 1967

Cross-Correlation



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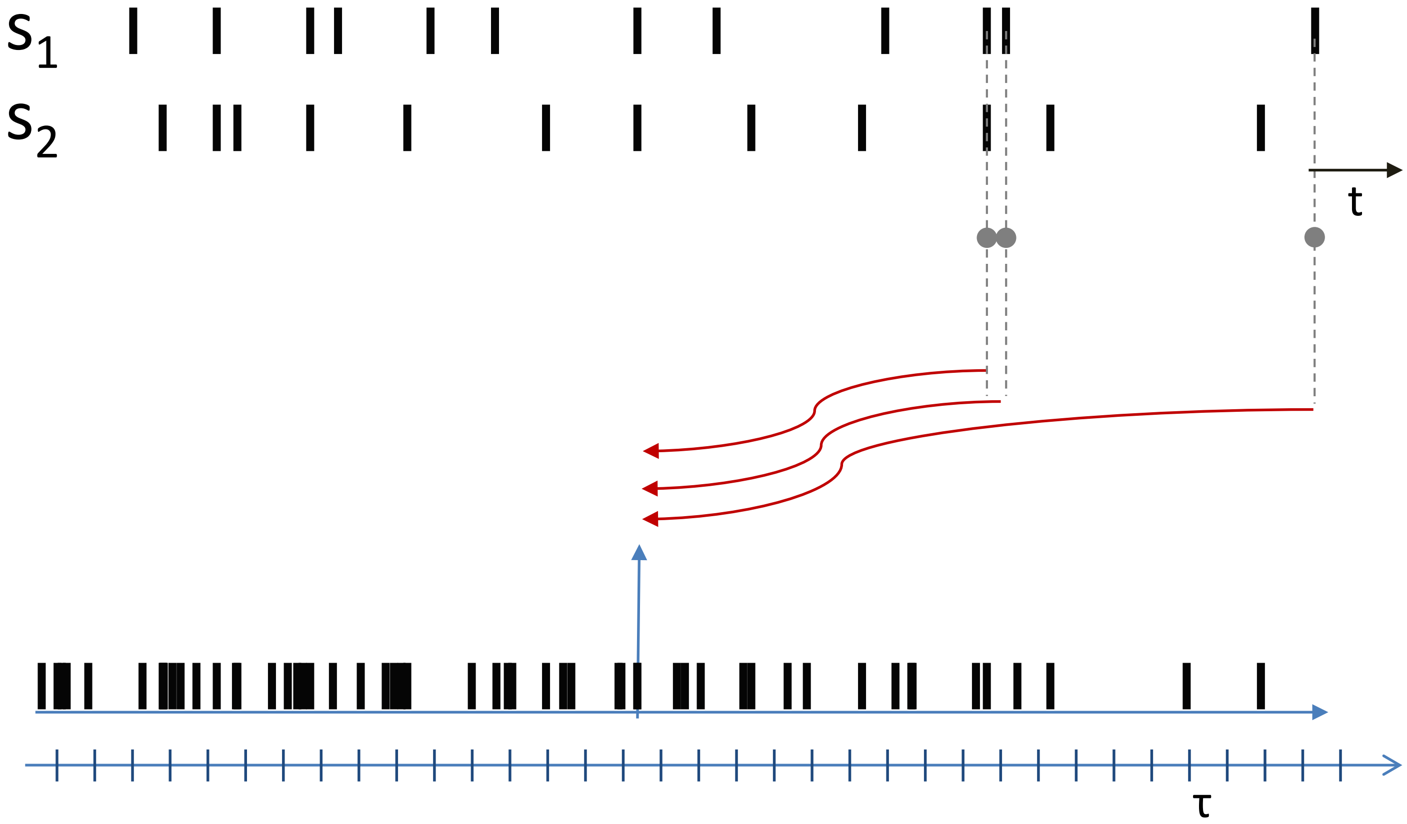
Perkel et al, 1967

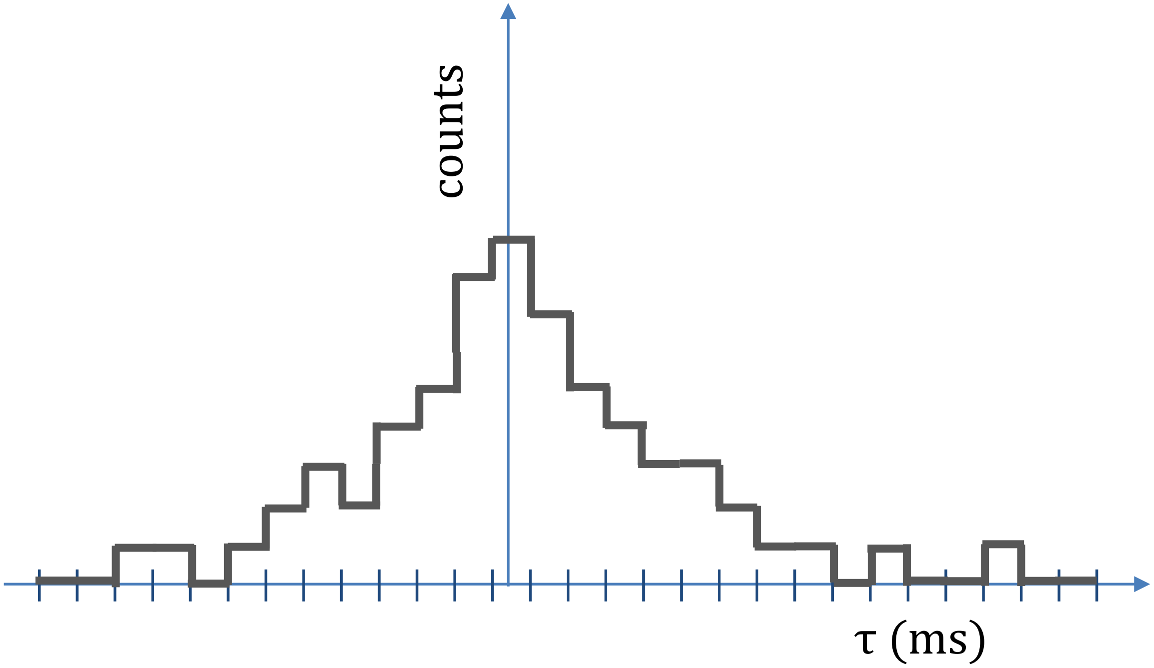
Cross-Correlation Histogram: Binning

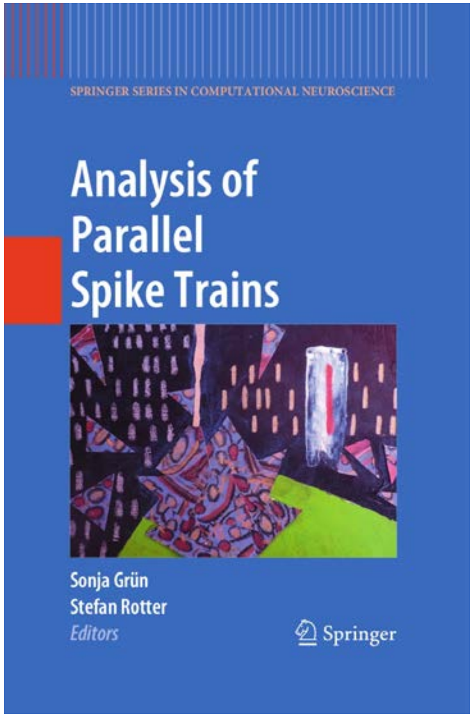


The cross-correlation histogram results by binning of the cross-correlation function

Perkel et al, 1967

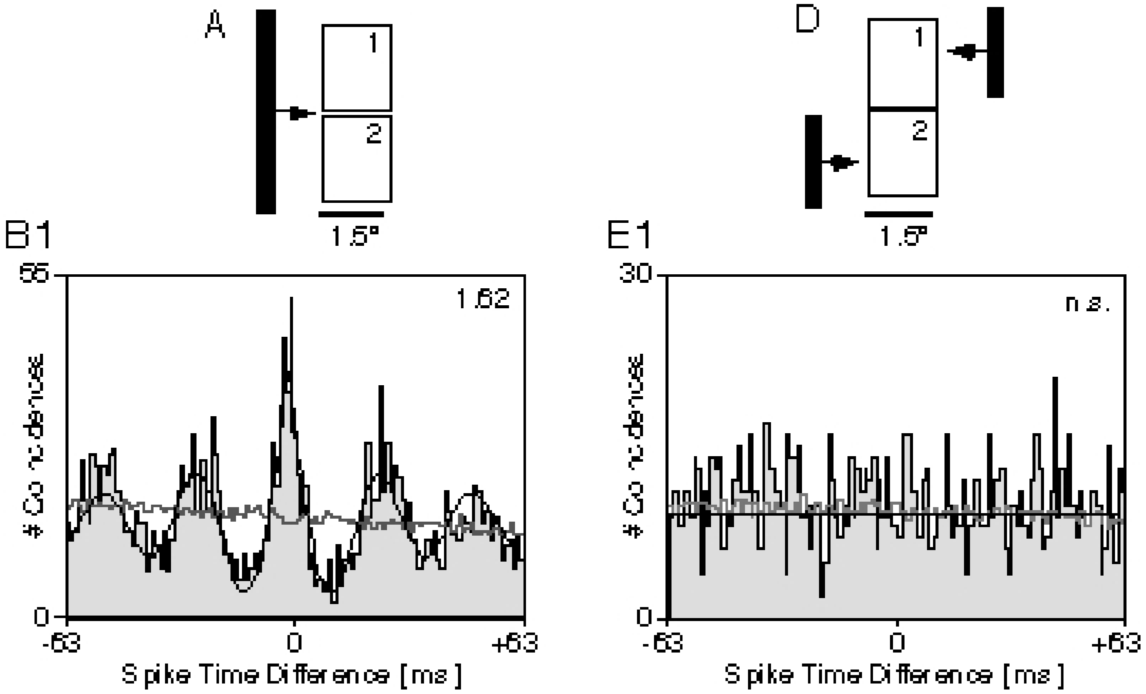
Cross-Correlation Histogram (CCH)





- number of coincidences for each time delay τ
- often task of neuroscientist: significance of correlation

Perception Related Correlation

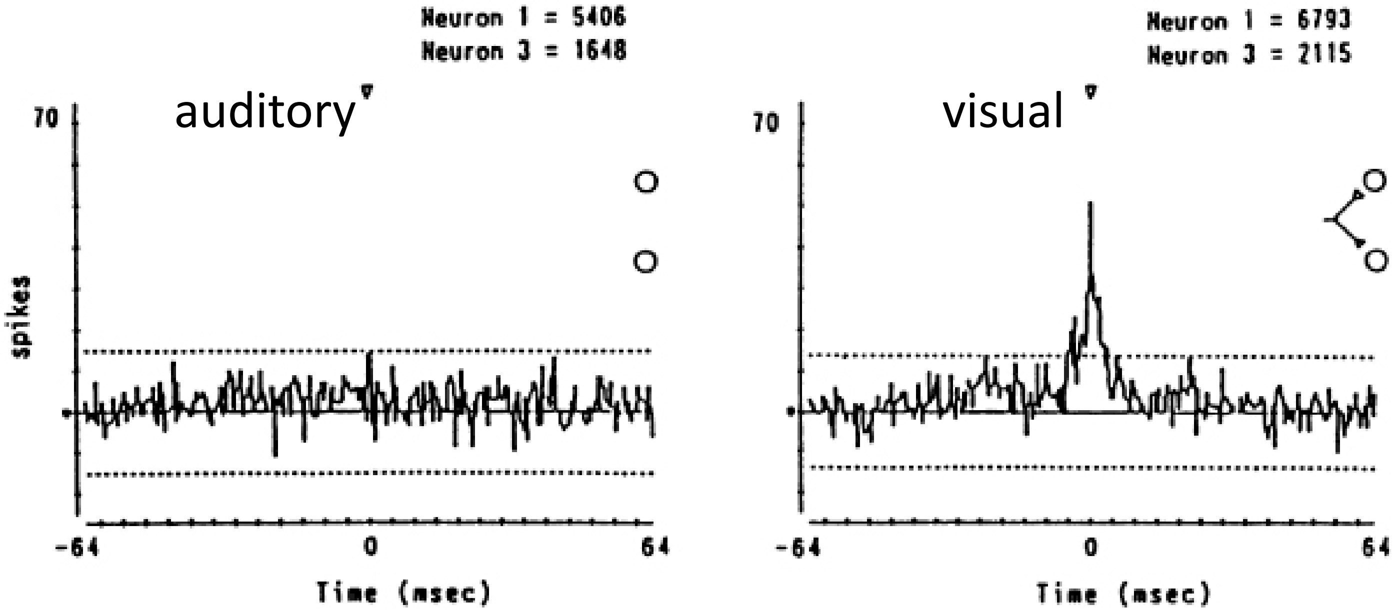


Freiwald et al (1995) NeuroReport 6: 2348--2352

- Simultaneous recording of two single units (stereotrodes) from different colums of visual cortex (A17) of cat
- Long bar condition induces synchronized spike responses
- Dual bar condition: absence of synchronization

→ interpretation: Gestalt perception requires binding (by synchrony)

Functional Correlation

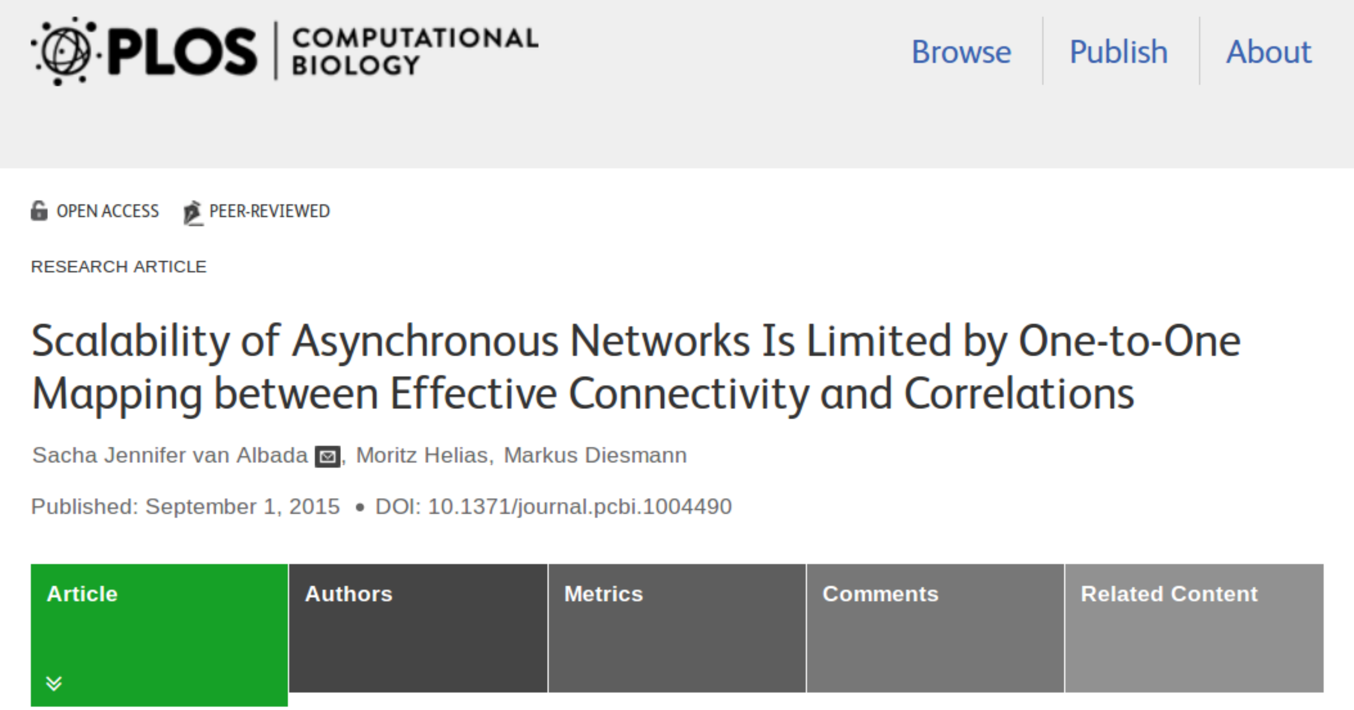


Sakurai, Y. (1999) Neuroscience & Biobehavioral Reviews 23: 785-796

- two simultaneously recorded neurons in CA1 of a rat performing an auditory or visual discrimination task
- task related correlation only for visual task (although spike rates in same range in both tasks)

→ interpretation: these two neurons belong to a cell assembly processing visual information

Networks generally not reducible



RESEARCH ARTICLE

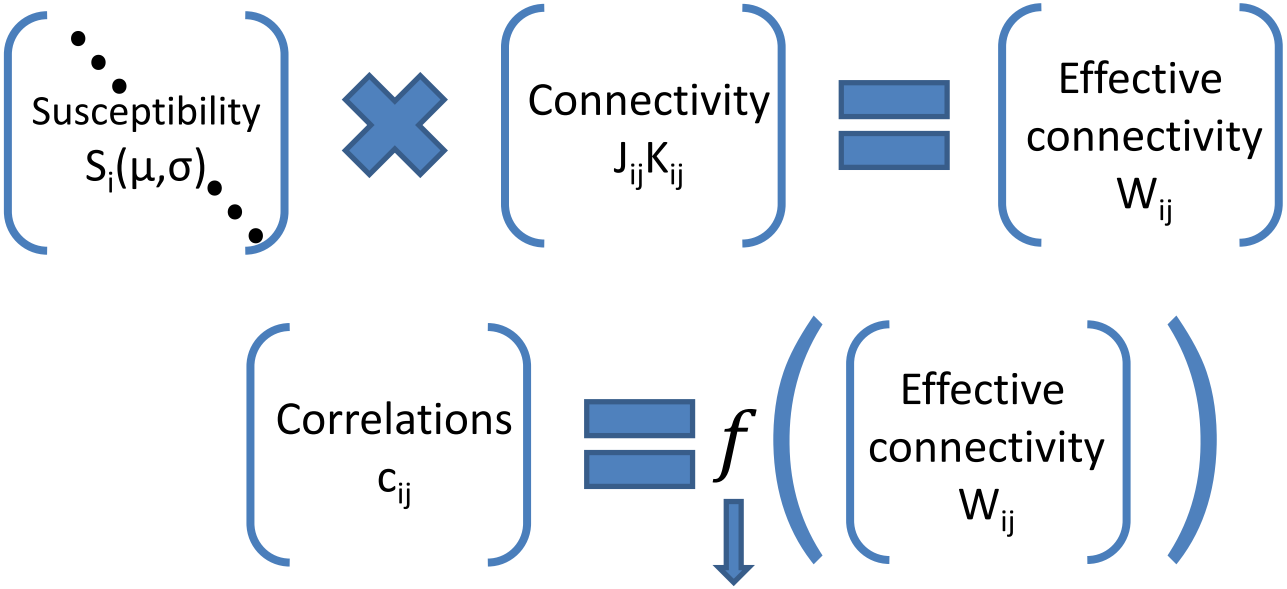
Scalability of Asynchronous Networks Is Limited by One-to-One Mapping between Effective Connectivity and Correlations

Sacha Jennifer van Albada, Moritz Helias, Markus Diesmann

Published: September 1, 2015 • DOI: 10.1371/journal.pcbi.1004490

- downscaling works well for first order statistics like spike rate
- severe constraints already for second order like spike correlation
- spike correlation drives mesoscopic measures like LFP and EEG

Effective connectivity and correlations



Susceptibility $S_i(\mu,\sigma)$ × Connectivity $J_{ij}K_{ij}$ = Effective connectivity W_{ij}

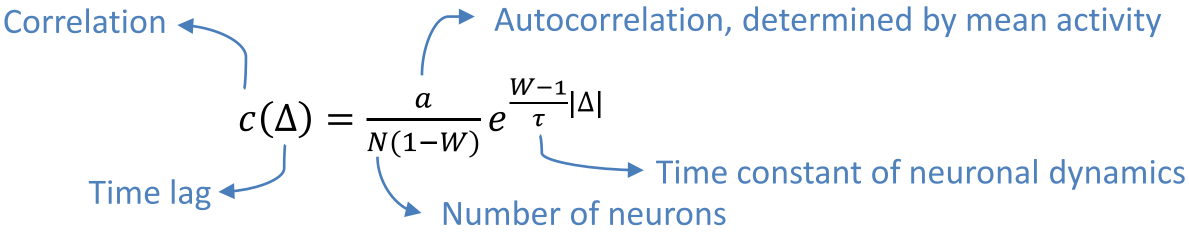
Correlations c_{ij} = f (Effective connectivity W_{ij})

One-to-one under:

- fixed single-neuron parameters and delays
- stationarity
- diffusion approximation
- absence of degeneracies

Uniqueness of effective connectivity

- for single-population binary network with $d = 0$,



Correlation

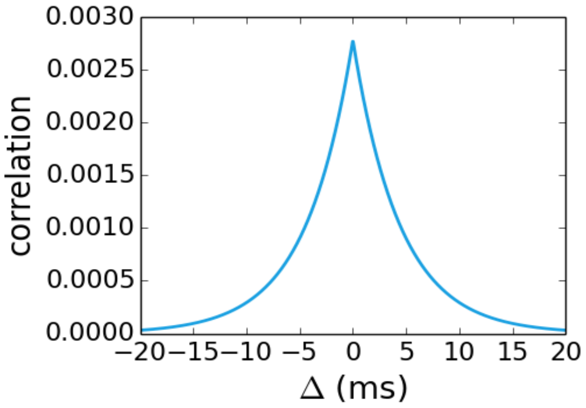
Autocorrelation, determined by mean activity

$$c(\Delta) = \frac{a}{N(1-W)} e^{\frac{W-1}{\tau}|\Delta|}$$

Time constant of neuronal dynamics

Time lag

Number of neurons



→ W uniquely determines temporal structure

- more generally, $C_{ij}(\omega) = \sum \tilde{f}\left(W_{kl}\frac{e^{\pm i\omega d_{kl}}}{1\mp i\omega\tau_k}\right)$

→ each W_{kl} determines unique ω-dependence unless some delays are equal

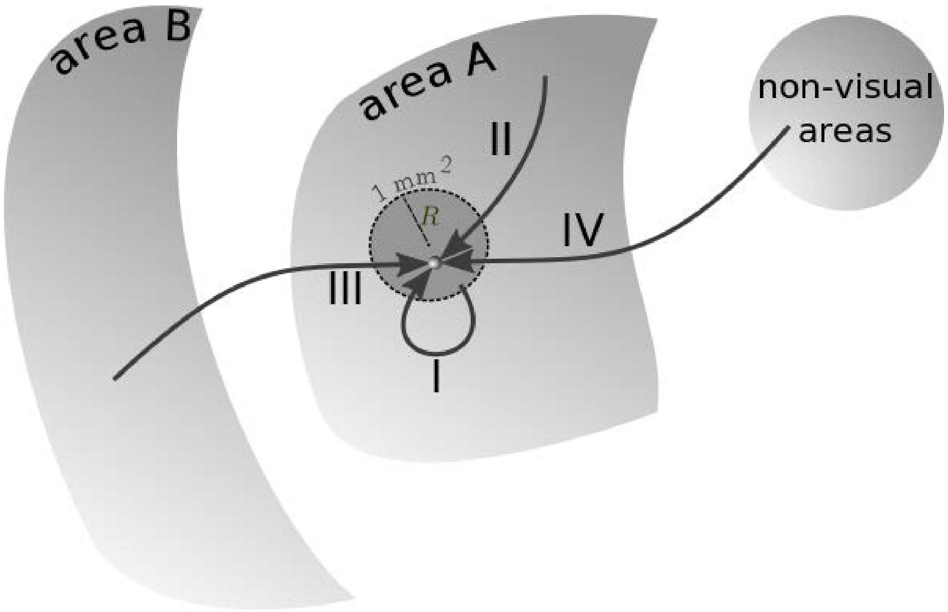
- narrower set of exceptions when transfer functions are identical

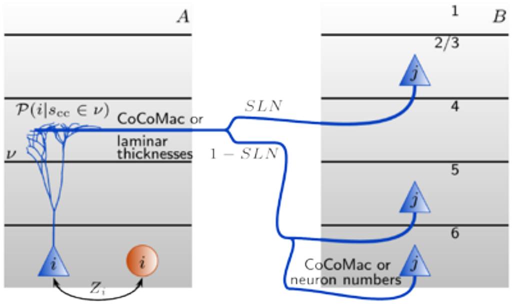
$$\left(\begin{array}{c}\text{Effective}\\ \text{connectivity}\\ \text{W}_{\text{ij}}\end{array}\right) = f^{-1}\left(\left(\begin{array}{c}\text{Correlations}\\ \text{C}_{\text{ij}}\end{array}\right)\right)$$

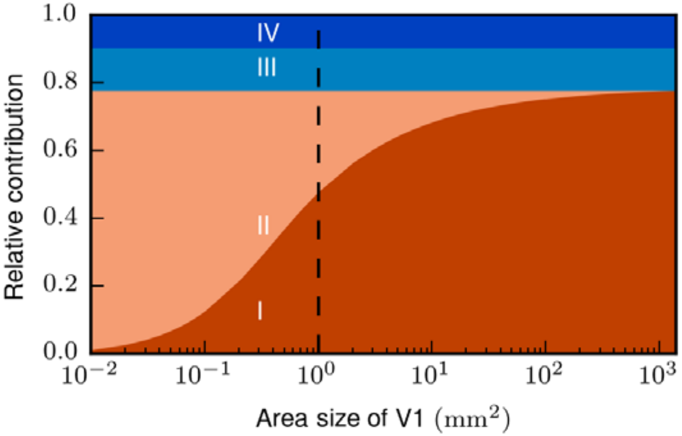
Feasibility and necessity

- Can we do simulations at the brain scale? ✓
- Do we need to simulate full scale (at cellular resolution)? ✓

Toward a self-consistent model





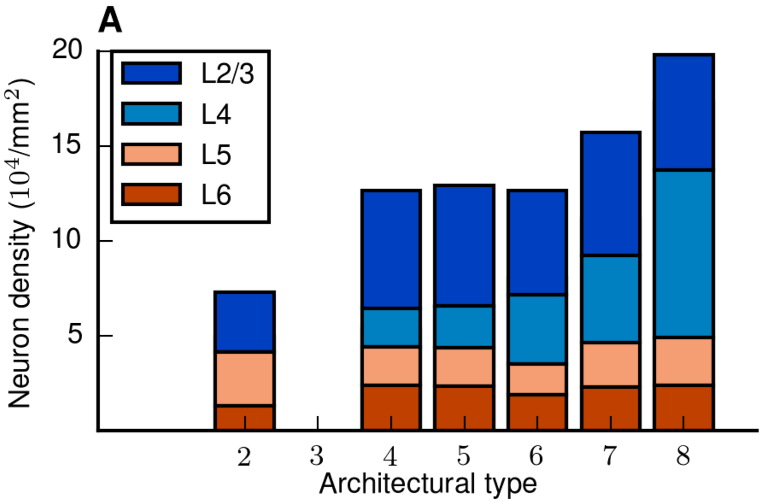


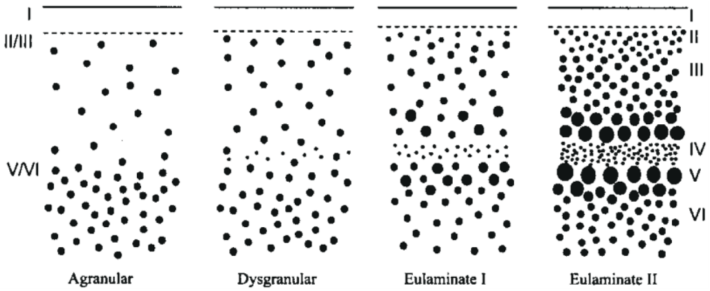
1. **Intra-areal synapses**
2. **Intra-areal synapses replaced by random input**
3. **Cortico-cortical synapses**
4. **External input represented by random input**

- Sacha van Albada
- Maximilian Schmidt
- Rembrandt Bakker

Multi-area model of macaque visual cortex

- rich anatomical data sets available (e.g CoCoMac)
- close to human
- 32 areas structured in layers comprising $8{\cdot}10^8$ neurons
- downscaled model with $4.1{\cdot}10^6$ neurons and $3.9{\cdot}10^{10}$ synapses

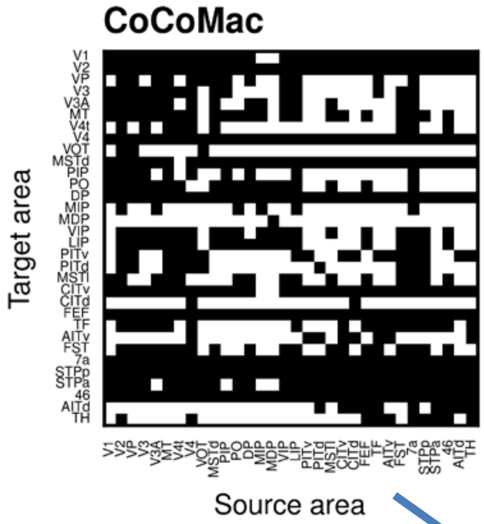


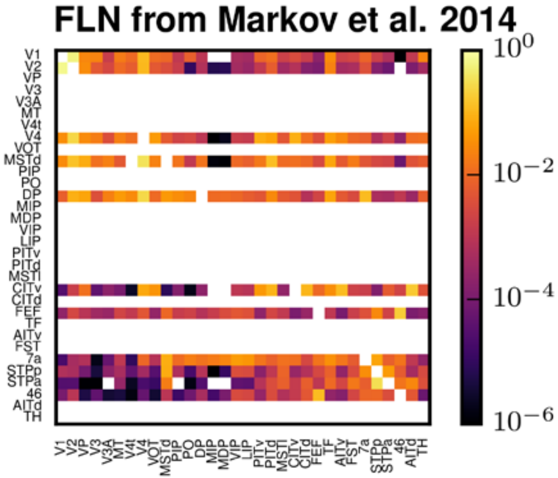


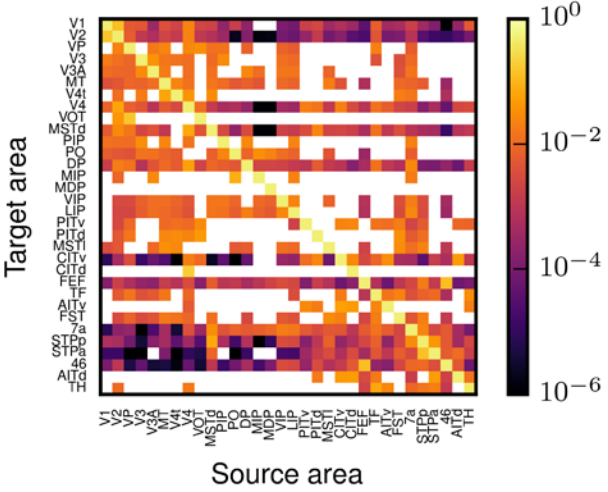
From Dombrowski et al. (2001), Cereb Cortex

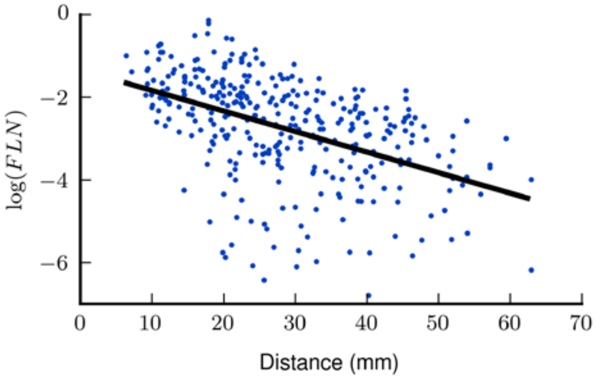
architectural types from Hilgetag et al. (2015)
with data by Helen Barbas

Construction of cortico-cortical connectivity


CoCoMac


FLN from Markov et al. 2014

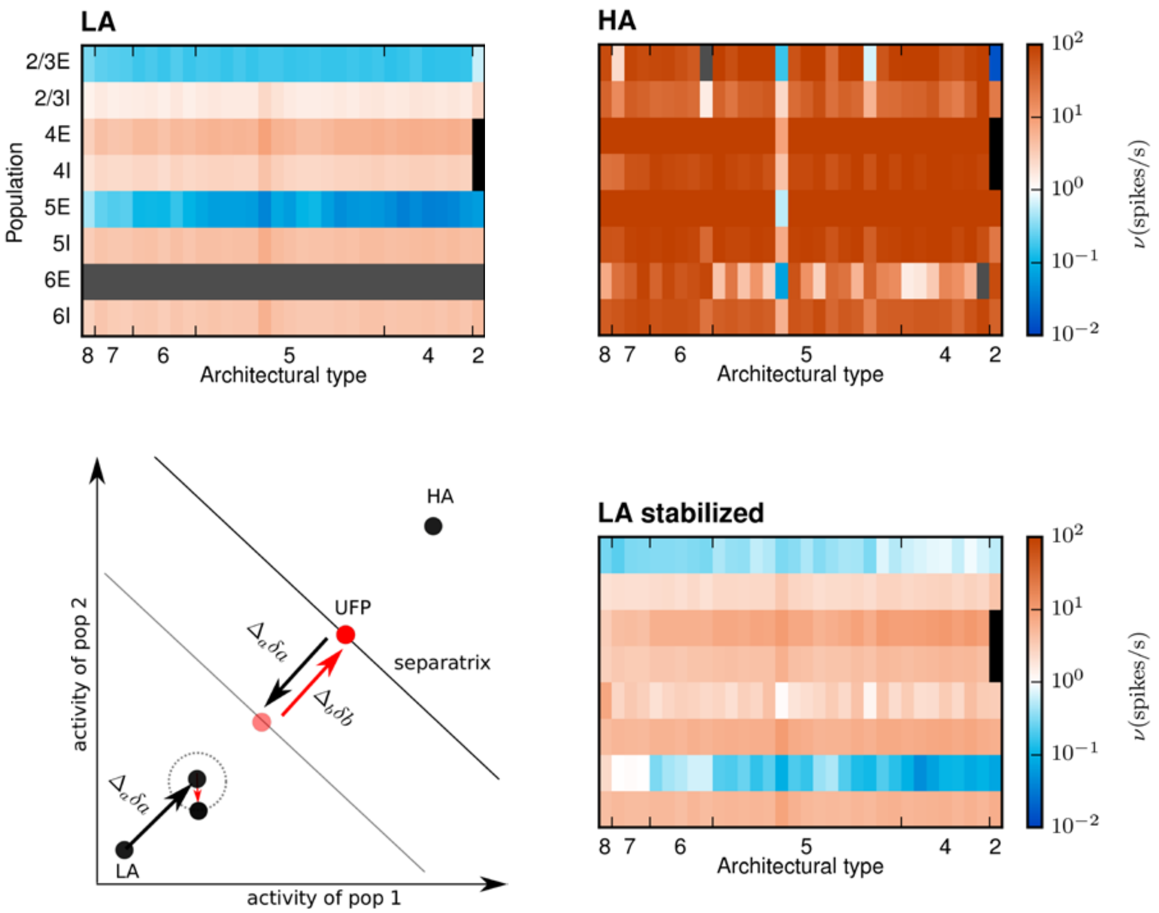




Ercsey-Ravasz et al. (2013), Neuron

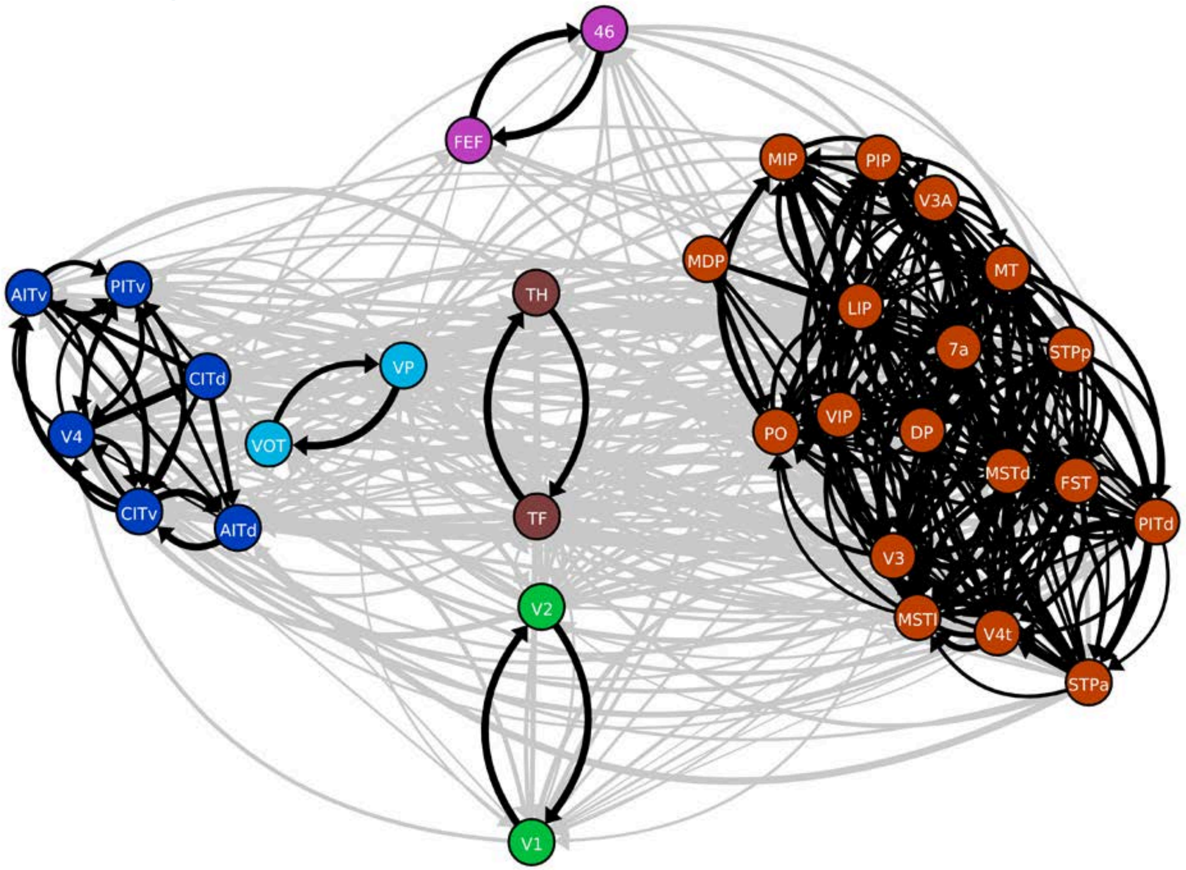
Stabilization of multi-area network

- partly quiescent low activity (LA)
- unrealistic high activity (HA)
- goal: Increase excitation while preserving global stability
- method: control location of separatrix by modifying model connectivity
- inclusion of dynamical constraints into model definition
- feedback link to structural experiments



Schuecker J, Schmidt M, van Albada SJ, Diesmann M, Helias M (2016) arXiv:1509.03162

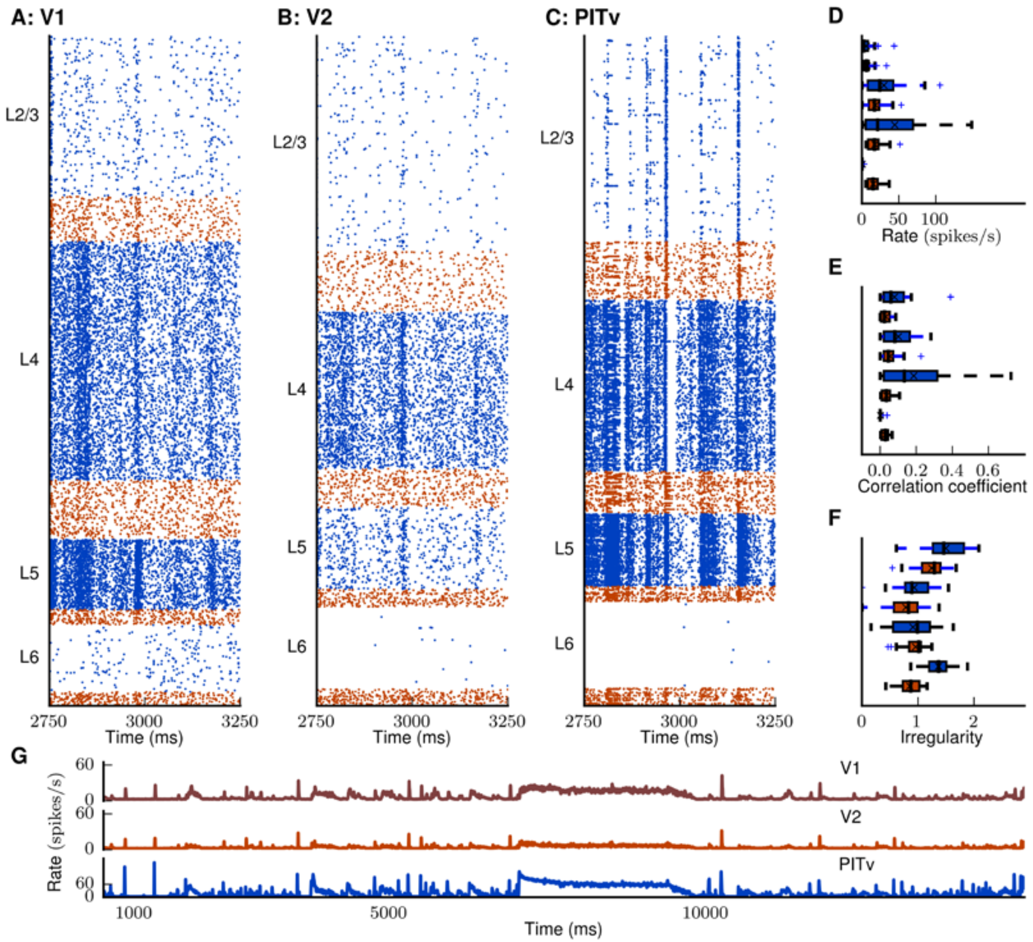
Structural connectivity reveals functionally relevant community structure

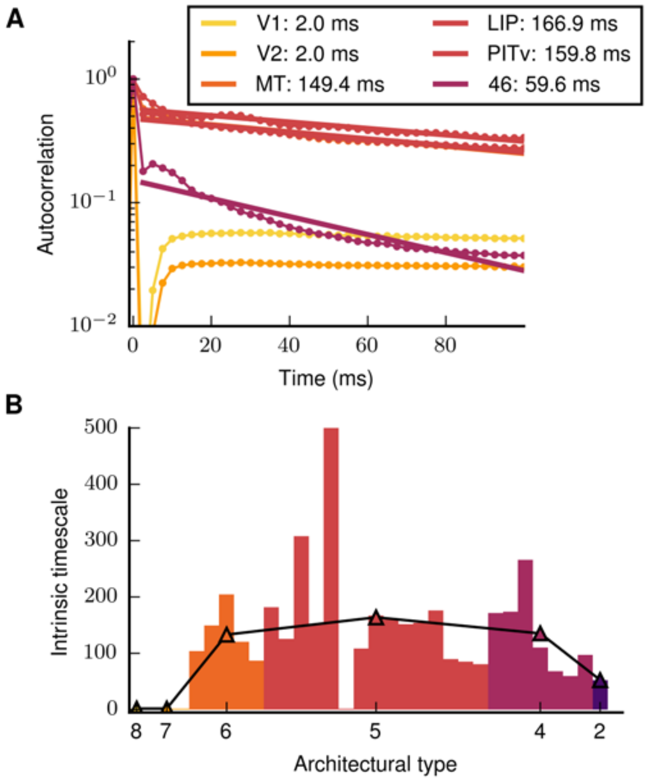


clustering by map equation method (Rosvall et al. 2010)

Multi-area model: Dynamical results

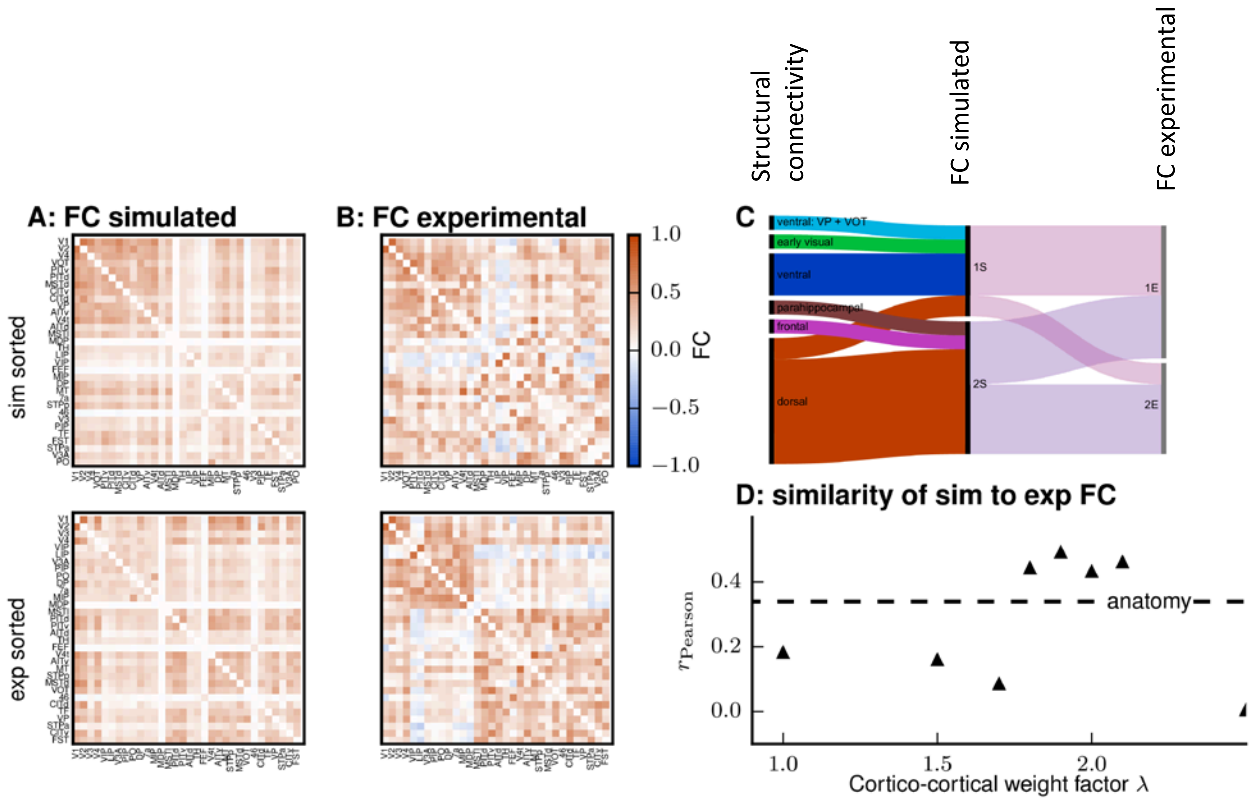
- stable resting state with heterogeneous laminar rate patterns and irregular firing
- cortico-cortical interactions trigger increased time scales in higher visual areas

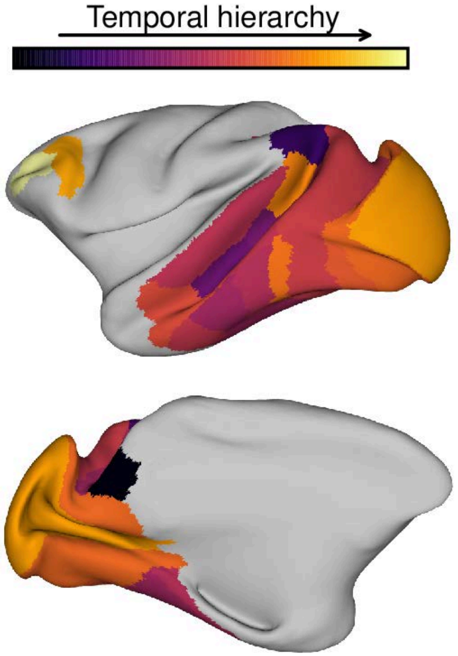




Multi-area model: Dynamical results

- activity propagates in feedback direction
- inter-area interactions mimic experimental resting-state fMRI





FC sorted according to Louvain clustering (Blondel et al. 2008)

Schmidt M, Bakker R, Shen K, Bezgin G, Hilgetag CC, Diesmann M, van Albada SJ (2016) arXiv:1511.09364

Key Challenge

- **Reproducibility** is the ability of an entire experiment or study to be duplicated, either by the same researcher or by someone else working independently. Reproducing an experiment is called **replicating** it. Reproducibility is one of the main principles of the **scientific method**.

[From Wikipedia]

- here we are talking about the reproducibility of modeling and analysis, not experiments

Simplest example

- PhD student left the lab, now the reviews came back, and another person wants to reproduce a figure of the manuscript
  – as experience shows in most cases this does not work

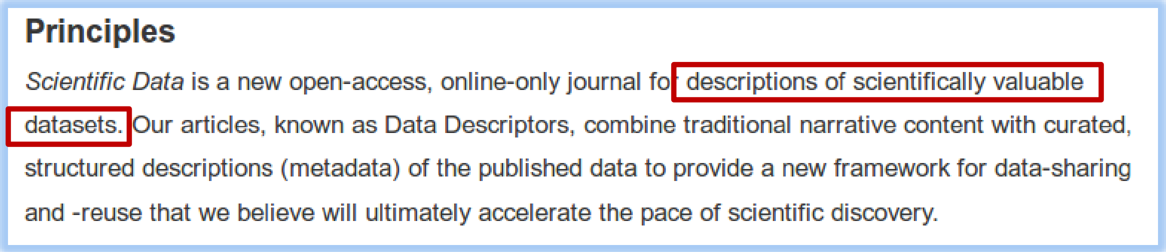
Consequences of current situation

- slow down of scientific progress
- complexity barrier: without new technologies more advanced modeling and analysis impossible → violation of “discovering truth by building on previous discoveries”
- reduced efficiency of use of research funds

Isaac Newton: “If I have seen further, it is by standing on the shoulders of giants” [from: Wikipedia]

New journals emerge

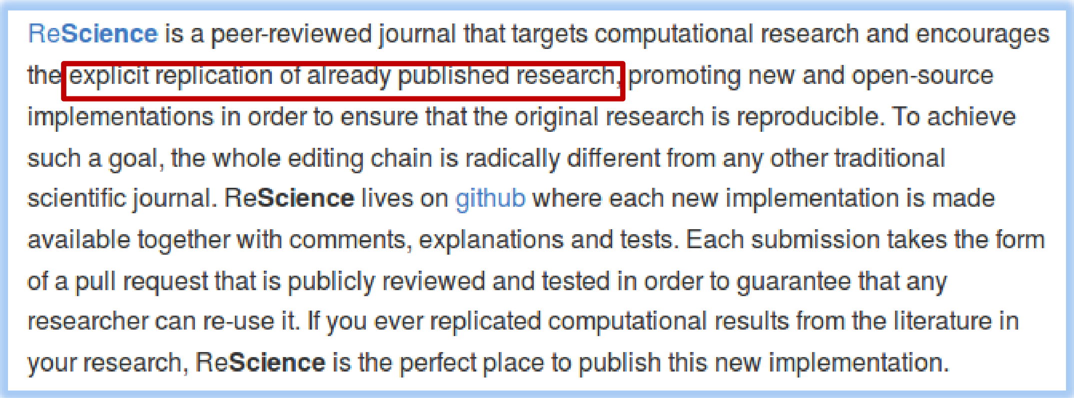
- Scientific Data: www.nature.com/sdata/



Principles

Scientific Data is a new open-access, online-only journal for descriptions of scientifically valuable datasets. Our articles, known as Data Descriptors, combine traditional narrative content with curated, structured descriptions (metadata) of the published data to provide a new framework for data-sharing and -reuse that we believe will ultimately accelerate the pace of scientific discovery.

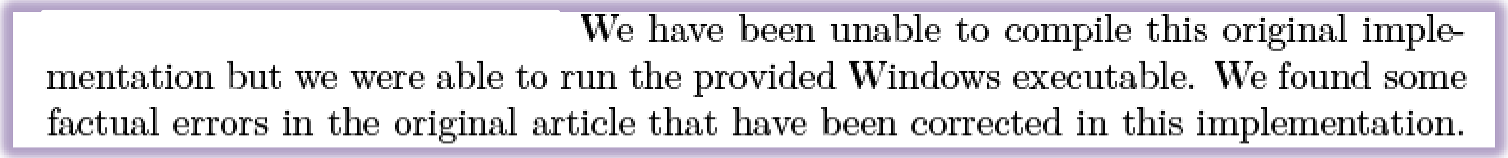
- ReScience: github.com/ReScience/ReScience/wiki



Re**Science** is a peer-reviewed journal that targets computational research and encourages the explicit replication of already published research, promoting new and open-source implementations in order to ensure that the original research is reproducible. To achieve such a goal, the whole editing chain is radically different from any other traditional scientific journal. Re**Science** lives on github where each new implementation is made available together with comments, explanations and tests. Each submission takes the form of a pull request that is publicly reviewed and tested in order to guarantee that any researcher can re-use it. If you ever replicated computational results from the literature in your research, Re**Science** is the perfect place to publish this new implementation.

Levels of reproducibility

- in the weakest sense: running the same program leads to the same result
- actually wanted: reproducibility in the stronger sense, i.e. conceptual insight, control, understanding



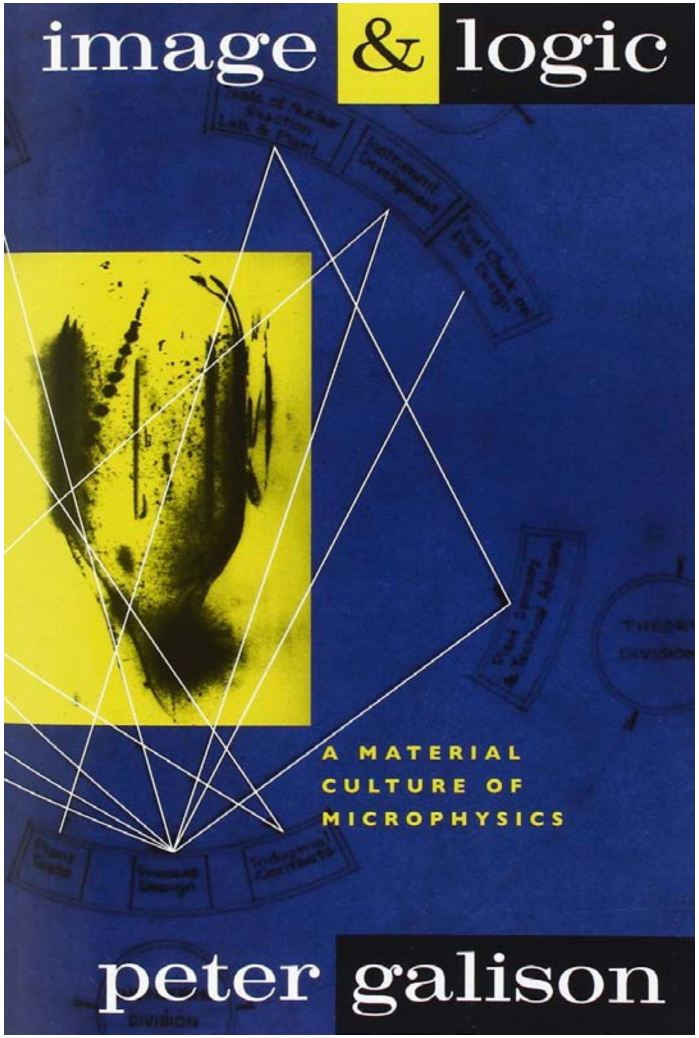
We have been unable to compile this original implementation but we were able to run the provided Windows executable. We found some factual errors in the original article that have been corrected in this implementation.

From: [Re] Interaction between cognitive and motor cortico-basal ganglia loops during decision making: a computational study, M. Topalidou and N.P. Rougier, ReScience, volume 1, issue 1, 2015.

Collaboration: conditions and consequences

- have experience from other branches of science
- example of high energy physics (982 pages)
- accounts of the sociological and organizational problems are elucidating
- a cultural transformation was induced

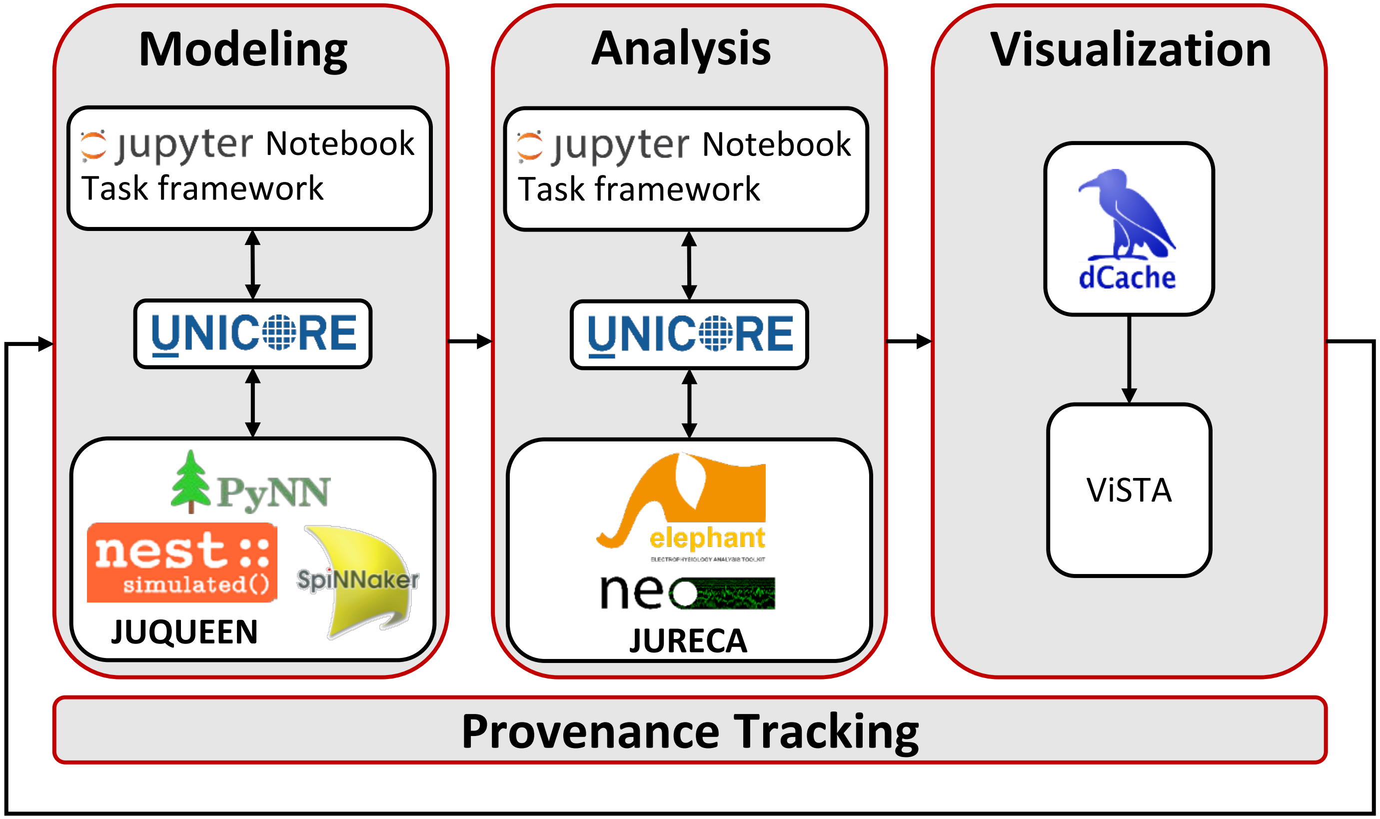
- even better example may be meteorology



Infrastructure for collaborative work

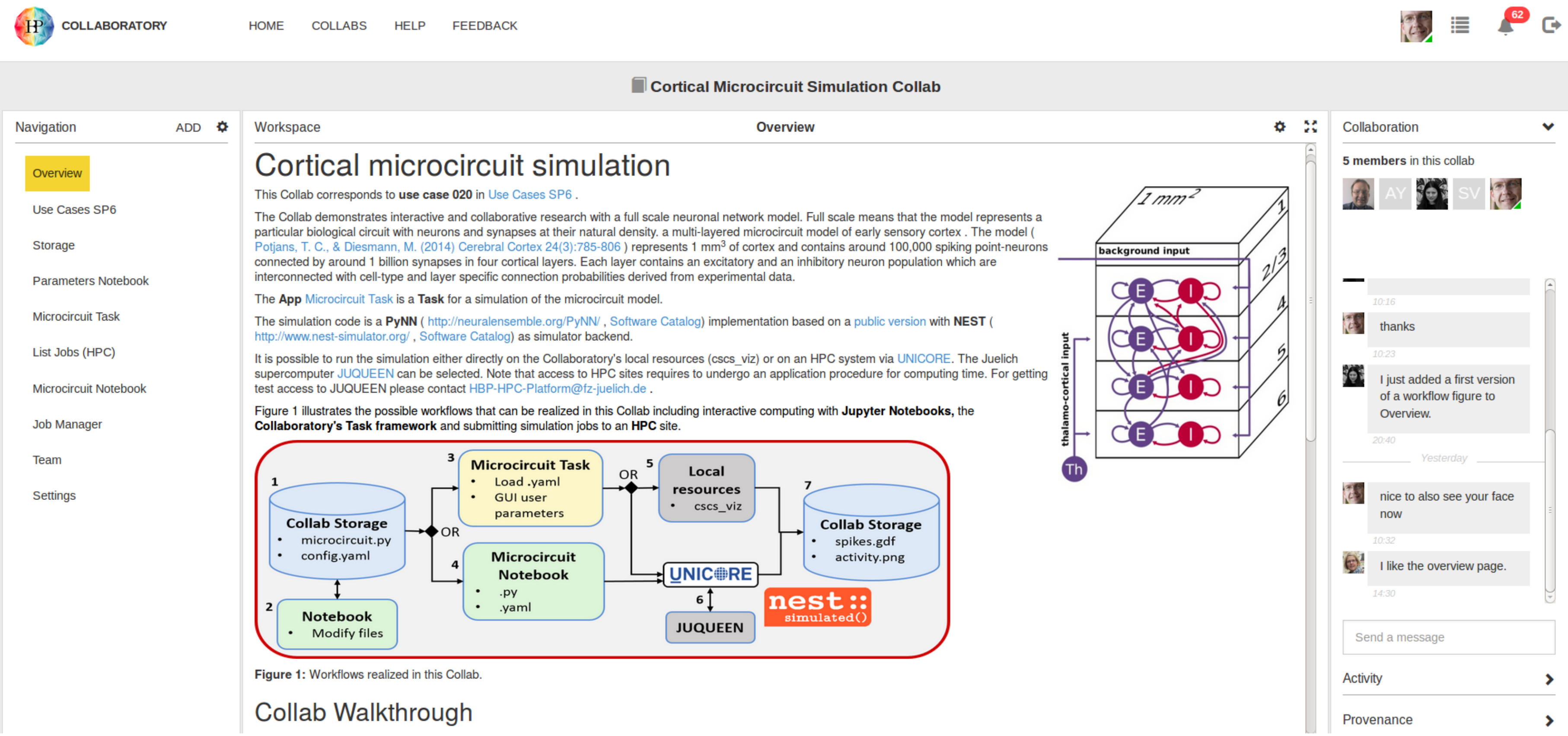
- long-term support of tools
- infrastructure for collaboration of scientists
- infrastructure for data integration and model re-use
- infrastructure for provenance tracking and review
- HBP platform open since We March 30th 2016
  check https://collab.humanbrainproject.eu

A Collaboratory



- mapping of the complete integrative loop of research

Collaboratory, example



Cortical microcircuit simulation

This Collab corresponds to **use case 020** in Use Cases SP6 .

The Collab demonstrates interactive and collaborative research with a full scale neuronal network model. Full scale means that the model represents a particular biological circuit with neurons and synapses at their natural density. a multi-layered microcircuit model of early sensory cortex . The model (Potjans, T. C., & Diesmann, M. (2014) Cerebral Cortex 24(3):785-806) represents 1 mm^3 of cortex and contains around 100,000 spiking point-neurons connected by around 1 billion synapses in four cortical layers. Each layer contains an excitatory and an inhibitory neuron population which are interconnected with cell-type and layer specific connection probabilities derived from experimental data.

The **App** Microcircuit Task is a **Task** for a simulation of the microcircuit model.

The simulation code is a **PyNN** (http://neuralensemble.org/PyNN/ , Software Catalog) implementation based on a public version with **NEST** (http://www.nest-simulator.org/ , Software Catalog) as simulator backend.

It is possible to run the simulation either directly on the Collaboratory's local resources (cscs_viz) or on an HPC system via UNICORE. The Juelich supercomputer JUQUEEN can be selected. Note that access to HPC sites requires to undergo an application procedure for computing time. For getting test access to JUQUEEN please contact HBP-HPC-Platform@fz-juelich.de .

Figure 1 illustrates the possible workflows that can be realized in this Collab including interactive computing with **Jupyter Notebooks,** the **Collaboratory's Task framework** and submitting simulation jobs to an **HPC** site.

Figure 1: Workflows realized in this Collab.

Collab Walkthrough

5 members in this collab

AY
SV

10:16

thanks

10:23

I just added a first version of a workflow figure to Overview.

20:40

Yesterday

nice to also see your face now

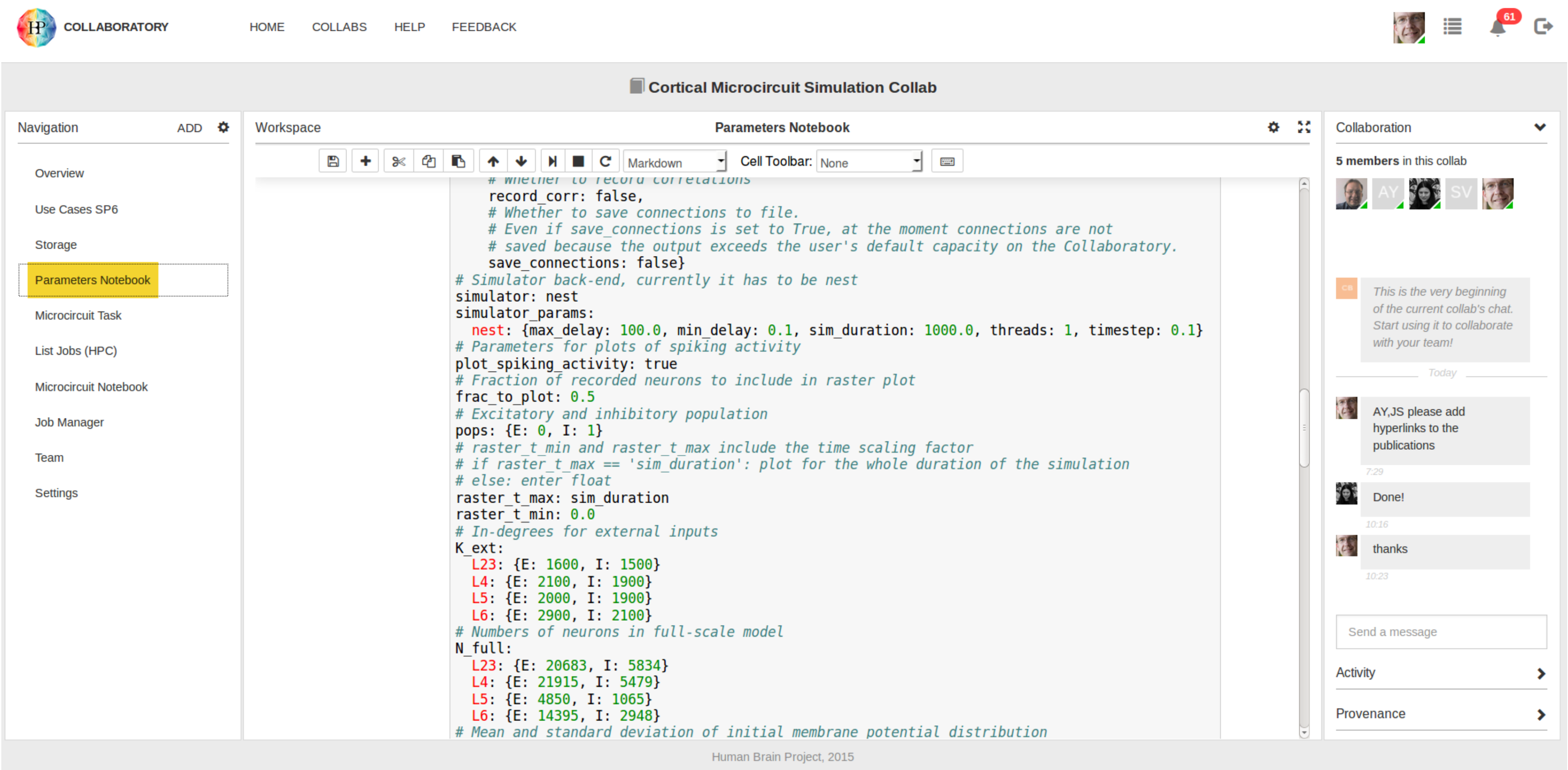
10:32

I like the overview page.

14:30

- example “collab”
- mapping of complex workflows

Collaboratory, example



```
    # whether to record correlations
    record_corr: false,
    # Whether to save connections to file.
    # Even if save_connections is set to True, at the moment connections are not
    # saved because the output exceeds the user's default capacity on the Collaboratory.
    save_connections: false}
# Simulator back-end, currently it has to be nest
simulator: nest
simulator_params:
  nest: {max_delay: 100.0, min_delay: 0.1, sim_duration: 1000.0, threads: 1, timestep: 0.1}
# Parameters for plots of spiking activity
plot_spiking_activity: true
# Fraction of recorded neurons to include in raster plot
frac_to_plot: 0.5
# Excitatory and inhibitory population
pops: {E: 0, I: 1}
# raster_t_min and raster_t_max include the time scaling factor
# if raster_t_max == 'sim_duration': plot for the whole duration of the simulation
# else: enter float
raster_t_max: sim_duration
raster_t_min: 0.0
# In-degrees for external inputs
K_ext:
  L23: {E: 1600, I: 1500}
  L4: {E: 2100, I: 1900}
  L5: {E: 2000, I: 1900}
  L6: {E: 2900, I: 2100}
# Numbers of neurons in full-scale model
N_full:
  L23: {E: 20683, I: 5834}
  L4: {E: 21915, I: 5479}
  L5: {E: 4850, I: 1065}
  L6: {E: 14395, I: 2948}
# Mean and standard deviation of initial membrane potential distribution
```

5 members in this collab

This is the very beginning of the current collab's chat. Start using it to collaborate with your team!

Today

AY,JS please add hyperlinks to the publications

7:29

Done!

10:16

thanks

10:23

- research on integration with style of work of computational neuroscientist (python notebook)

Summary

- full-scale model explains prominent features of network activity
- is building block of further studies (www.opensourcebrain.org)
- need for brain-scale models
    - increase self consistency
    - compute meso- and macroscopic measures of activity
- need for full-scale models
    - irreducibility
    - verify mean-field results
- machines ready for use by neuroscience (www.nest-initiative.org)
- full-scale model of macaque visual cortex
- functional connectivity shows correspondence with fMRI
- problem of reproducibility, research and funds required to overcome

References

Potjans TC, Diesmann M Cerebral Cortex (2014) 24(3):785-806

Kunkel S, Schmidt M, Eppler JM, Plesser HE, Masumoto G, Igarashi J, Ishii S, Fukai T, Morrison A, Diesmann M, Helias M (2014) Front Neuroinform 8:78

van Albada SJ, Helias M, Diesmann M PLoS Comput Biol (2015) 11(9):e1004490

Schuecker J, Schmidt M, van Albada SJ, Diesmann M, Helias M (2016) arXiv:1509.03162

Schmidt M, Bakker R, Shen K, Bezgin G, Hilgetag CC, Diesmann M, van Albada SJ (2016) arXiv:1511.09364