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

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NeuroMat
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Team

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modeling  reproducibility

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:

<table>
<thead>
<tr>
<th>System</th>
<th>Computer</th>
<th>Brain</th>
<th>System-level behavior</th>
<th>System-level theory</th>
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<tr>
<td>Top</td>
<td>multiplication ↓ logical algorithm ↑ electrical circuit ↑ transistor ↑ electrons</td>
<td>maze navigation ↓ TD-learning ↑ neuronal network ↑ I&amp;F neuron model ↑ spikes</td>
<td>(bio)physics</td>
<td></td>
</tr>
</tbody>
</table>

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 = $10^4$
  $\Rightarrow$ minimal network size = $10^5$

- Network $N = 10^5$
  - Considered elementary unit
  - Corresponding to $1 \text{ mm}^3$

- Total number of synapses = $(cN) \cdot N$
  $\Rightarrow$ possible

Minimal layered cortical network model

- 1 mm³
- 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

in vitro physiology

Type of connection | Connectivity ratio
---|---
L5 pyramid to L5 pyramid | 1:11 (15:163)
L2/3 pyramid to L2/3 pyramid | 1:4 (65:247)
L4 excitatory to L4 excitatory | 1:10 (8:81)
L3 pyramid to L5 pyramid | 1:5.7 (4:233)
(Postsynaptic apical dendrite) | 1:1.8 (16:29)
L5 pyramid to L3 pyramid | 1:1 (2:2)
L4 excitatory to L3 pyramid | 1:3.6 (7:25)
(Presynaptic spiny stellate) (n = 4) | 1:10 (7:70)
L5 pyramid to L5 interneuron | 1:10.4 (7:73)
L5 interneuron to L5 pyramid | 1:8 (5:73)

(Binzegger et al. 2004) (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


available at: [www.opensourcebrain.org](http://www.opensourcebrain.org)
Response to transient inputs

A

L2/3
L4
L5
L6

B

L2/3e
L4e
L5e
L6e

5 Hz

evoked response

Sakata and Harris (2009) Neuron
Building block for mesoscopic studies

- collaboration with Gaute Einevoll (UMB, Norway)


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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.

Human cortex:

- $10^{10}$ neurons
- $10^{14}$ synapses
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)?
Supercomputers ready for use as discovery machines for neuroscience

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provides the evidence that neuroscience can exploit petascale systems

Spiking network simulation code for petascale computers

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makes supercomputers accessible for neuroscience
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:
  - $1.86 \times 10^9$ neurons, 6000 synapses per neuron
  - $1.08 \times 10^9$ neurons, 6000 synapses per neuron
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)?
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
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Perkel et al, 1967
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$$\rho(\tau) = \int s_1(t)s_2(t - \tau)dt$$

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 $\tau$
- often task of neuroscientist: significance of correlation
Perception Related Correlation


- Simultaneous recording of two single units (stereotrodes) from different columns 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

- 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

- 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

\[
\begin{align*}
\text{Susceptibility } S_i(\mu, \sigma) \times \text{Connectivity } J_{ij} K_{ij} &= \text{Effective connectivity } W_{ij} \\
\text{Correlations } c_{ij} &= f(\text{Effective connectivity } W_{ij}) \\
\end{align*}
\]

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 \( d = 0 \),

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

\( \Rightarrow W \) uniquely determines temporal structure

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

\( \Rightarrow \) each \( W_{kl} \) determines unique \( \omega \)-dependence unless some delays are equal

- narrower set of exceptions when transfer functions are identical

\[
\begin{pmatrix}
\text{Effective connectivity} \\
W_{ij}
\end{pmatrix}
\quad = \quad \begin{pmatrix}
\text{Correlations} \\
C_{ij}
\end{pmatrix}
\quad = \quad f^{-1}
\]
Feasibility and necessity

- Can we do simulations at the brain scale? ✓
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Toward a self-consistent model

I. Intra-areal synapses
II. Intra-areal synapses replaced by random input
III. Cortico-cortical synapses
IV. External input represented by random input

- Sacha van Albada
- Maximilian Schmidt
- Rembrandt Bakker

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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

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

From Dombrowski et al. (2001), Cereb Cortex
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

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)

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/](http://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** 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. ReScience lives on [github](https://github.com) 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, ReScience 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

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](https://collab.humanbrainproject.eu)
A Collaboratory

- mapping of the complete integrative loop of research
Collaboratory, example

- example “collab”
- mapping of complex workflows

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

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Summary

- full-scale model explains prominent features of network activity
- is building block of further studies ([www.opensourcebrain.org](http://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](http://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


