Towards multi-layered multi-area models of cortical networks

December 6-11th 2015, workshop
“Connecting Network Architecture and Network Computation”
Banff International Research Station (BIRS), Alberta, Canada

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www.csn.fz-juelich.de
www.nest-initiative.org
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
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**

(Thomson et al. 2002)

<table>
<thead>
<tr>
<th>Type of connection</th>
<th>Connectivity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>L5 pyramid to L5 pyramid</td>
<td>1:11 (15:163)</td>
</tr>
<tr>
<td>L2/3 pyramid to L2/3 pyramid</td>
<td>1:4 (65:247)</td>
</tr>
<tr>
<td></td>
<td>1:10 (8:81)</td>
</tr>
<tr>
<td>L4 excitatory to L4 excitatory</td>
<td>1:5.7 (4:23)</td>
</tr>
<tr>
<td>L3 pyramid to L5 pyramid</td>
<td>1:1.8 (16:29)</td>
</tr>
<tr>
<td>(Postsynaptic apical dendrite)</td>
<td></td>
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<tr>
<td></td>
<td>1:1 (2:2)</td>
</tr>
<tr>
<td>L5 pyramid to L3 pyramid</td>
<td>1:29</td>
</tr>
<tr>
<td>L4 excitatory to L3 pyramid</td>
<td>1:3.6 (7:25)</td>
</tr>
<tr>
<td>(Presynaptic spiny stellate) (n = 4)</td>
<td>1:10 (7:70)</td>
</tr>
<tr>
<td>L5 pyramid to L5 interneuron</td>
<td>1:10.4 (7.73)</td>
</tr>
<tr>
<td>L5 interneuron to L5 pyramid</td>
<td>1.8 (5.73)</td>
</tr>
</tbody>
</table>

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Target specificity

- correction for bias in anatomical method
Convergence and divergence

- dominated by within-layer connections
- \( e \rightarrow e \) divergence reflects "standard" loop
- \( e \rightarrow i \) divergence reflects target-specific feedback
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

available at: www.opensourcebrain.org
Transfer function of LIF with synaptic filtering

central building block of theory describing fluctuations and oscillations in spiking networks

- complicated two-dimensional Fokker-Planck equation
- reduction to one dimension with effective boundary conditions
- result: analytical expression correct for biologically relevant frequencies

Anatomical origins of oscillations

- spike rates accurately predicted by mean-field theory
Anatomical origins of oscillations

Identifying anatomical origins of coexisting oscillations in the cortical microcircuit

Hannah Bos, Markus Diesmann, Moritz Helias
(Submitted on 2 Oct 2015)

Oscillations are omnipresent in neural population signals, like multi-unit recordings, EEG/MEG, and the local field potential. They have been linked to the population firing rate of neurons, with individual neurons firing in a close-to-irregular fashion at low rates. Using mean-field theory we predict the spectra generated in a layered microcircuit model of V1, composed of leaky-integrate-and-fire neurons and based on connectivity compiled from anatomical and electrophysiological studies. The model exhibits low- and high-gamma oscillations visible in all populations. Since locally generated frequencies are imposed onto other populations, the origin of the oscillations cannot be deduced from the spectra. We develop a universally applicable systematic approach that identifies the anatomical circuits underlying the generation of oscillations in a given network. Based on a mean-field reduction, we derive a sensitivity measure resulting in a frequency-dependent connectivity map that reveals connections crucial for the peak amplitude and frequency of the observed oscillations and identifies the minimal circuit generating a given frequency. The low-gamma peak turns out to be generated in a sub-circuit located in layer 2/3 and 4, while the high-gamma peak emerges from the inter-neurons in layer 4. Connections within and onto layer 5 are found to regulate slow rate fluctuations. We further demonstrate how small perturbations of the crucial connections have significant impact on the population spectra, while the impairment of other connections leaves the dynamics on the population level unaltered. The study uncovers the contact point for mechanisms regulating the spectra of the cortical microcircuit.

- advanced mean-field analysis
- explanation of power spectrum
- sensitivity measure exposes subcircuits generating oscillations at various frequencies
Frequency resolved sensitivity measure

- $\gamma$ oscillation generated in a sub-circuit within layer 2/3 and 4

- high-$\gamma$ generated in population 4I

- slow rate fluctuations originate from layer 5
Response to transient inputs

A

B

5 Hz

L2/3e

L4e

L5e

L6e

evoked response

Sakata and Harris (2009) Neuron
Response to transient inputs

- T = -0.4
- T = +0.4

T = -0.4

T = +0.4
Hypothesis on cortical flow of activity

- handshaking between layers

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)?
Simulation Technology: the NEST Initiative

collaborative effort and community building

Major goals:

- systematically publish new simulation technology
- produce public releases under GPL

- origins in 1994, collaboration of several labs (since 2001)
- registered society (since 2012)
- teaching in international advanced courses:
  - Okinawa Computational Neuroscience Course OCNC, Japan
  - Advanced Course in Computational Neuroscience ACCN, Europe
  - Latin American School on Computational Neuroscience LASCON, South America

www.nest-initiative.org

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e.g.: Morrison et al. (2005) Neural Computation
Zaytsev, Morrison (2013) Frontiers in Neuroinformatics
Supercomputers ready for use as discovery machines for neuroscience

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

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2 RIKEN Brain Science Institute, Wako, Japan
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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

Spiking network simulation code for petascale computers

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

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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 – 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)?
Mechanisms at finite size differ from limit

inhomogeneous connectivity \( \begin{pmatrix} J_{EE} & J_{EI} \\ J_{IE} & J_{II} \end{pmatrix} \)  

homogeneous connectivity \( \begin{pmatrix} J_E & J_I \\ J_E & J_I \end{pmatrix} \)  

\[ c_{\text{int}}^{\text{ext}} + c_{\text{int}} \]

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>network size</td>
<td>( 10^4 ) - ( 10^8 )</td>
<td>( 10^4 ) - ( 10^{10} )</td>
</tr>
<tr>
<td>covariance ( c )</td>
<td>( 10^{-4} ) - ( 10^{-12} )</td>
<td>( 10^{-8} ) - ( 10^{-12} )</td>
</tr>
<tr>
<td>full theory</td>
<td>[ c_{\text{int}}^{\text{ext}} ]</td>
<td>[ c_{\text{int}}^{\text{ext}} ]</td>
</tr>
<tr>
<td>convergence of ( c_{\text{ext}} )</td>
<td>[ c_{\text{int}}^{\text{ext}} ]</td>
<td>[ c_{\text{int}}^{\text{ext}} ]</td>
</tr>
</tbody>
</table>

inhomogeneous connectivity \( J_{EE} \) \( J_{EI} \) \( J_{IE} \) \( J_{II} \)  

biologically relevant range of model

convergence of \( c_{\text{ext}} \)  

\[ c_{\text{int}}^{\text{ext}} \]

Renart et al. 2010 Science

no convergence \( c_{\text{ext}}^{\text{int}} \) approx 0


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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

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
Effective connectivity and correlations

\[
S_i(\mu, \sigma) \times \begin{pmatrix} J_{ij}K_{ij} \end{pmatrix} = W_{ij}
\]

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 $d = 0$, 

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

$W$ uniquely determines temporal structure

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

→ each $W_{kl}$ determines unique $\omega$-dependence unless some delays are equal

- narrower set of exceptions when transfer functions are identical
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

I. Intra-areal synapses
II. Intra-areal synapses replaced by random input
III. Cortico-cortical synapses
IV. External input represented by random input
V. Thalamic 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 $3.2 \cdot 10^6$ neurons and $3 \cdot 10^{10}$ synapses

architectural types provided by C. Hilgetag (private communication)
Availability of cortico-cortical connectivity

labeling:
y-axis: odd areas
x-axis: even areas

Markov et al. (2012)
Cereb Cortex
Laminar patterns

Sending side

- Feedforward
- Feedback

From Markov et al. (2014), J. of Comparative Neurology

Receiving side

- Synapse layer: CoCoMac database
- Receiving synapse type: Computed from Binzegger et al. (2004)

Fraction of cortico-cortical synapses in each layer

<table>
<thead>
<tr>
<th>Cell body location</th>
<th>23E</th>
<th>23I</th>
<th>4E</th>
<th>4I</th>
<th>5E</th>
<th>5I</th>
<th>6E</th>
<th>6I</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2/3</td>
<td>0.57</td>
<td>0.18</td>
<td>0.25</td>
<td>0.003</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>L4</td>
<td>0.16</td>
<td>0.84</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>L5</td>
<td>0.73</td>
<td>0.16</td>
<td>0.03</td>
<td>0.09</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L6</td>
<td>0.76</td>
<td>0.10</td>
<td>0.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synapse location</td>
<td></td>
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</tbody>
</table>

From Binzegger et al. (2004), J Neurosci
Stabilization of multi-area network

Fundamental activity constraints lead to specific interpretations of the connectome

Jannis Schuecker, Maximilian Schmidt, Sacha van Albada, Markus Diesmann, Moritz Hellas
(Submitted on 19 Sep 2015)

The integration of incoming experimental data into coherent models of the brain is an increasing challenge of modern neuroscience. Such models provide a bridge between structure and activity, and identify the mechanisms giving rise to experimental observations. Nevertheless, structurally realistic network models of spiking neurons are necessarily under-constrained even if experimental data on brain connectivity are incorporated to the best of our knowledge. Guided by physiological observations, any model must therefore explore the parameter ranges within the uncertainty of the data. Based on simulation results alone, however, the mechanisms underlying stable and physiologically realistic activity often remain obscure. We here employ a mean-field reduction of the dynamics, which allows us to include activity constraints into the process of model construction. We shape the phase space of a multi-scale network model of primate visual cortex by systematically refining its connectivity.

Fundamental constraints on the activity, i.e., prohibiting quiescence and requiring global stability, prove sufficient to obtain realistic layer- and area-specific activity. Only minimal adaptations of the structure are required, showing that the network operates close to an instability. The procedure identifies components of the network critical to its collective dynamics and creates hypotheses for structural data and future experiments.

- advanced mean-field analysis
- constraints: prohibiting quiescence and requiring global stability
- refinement of connectivity within uncertainty margins
- identifies components critical for collective dynamics

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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

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Multi-area model: Dynamical results

- Maximilian Schmidt
- Sacha van Albada
- Rembrandt Bakker

- **Goal of the study:**
  - achieve a realistic ground state with low firing rates and heterogeneous laminar patterns
  - study interactions and slow oscillations between areas

Experimental data provided by Kelly Shen and Gleb Bezgin

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Summary

- full-scale model of microcircuit explains prominent features
- is building block of further studies (www.opensourcebrain.org)
- mean-field theory explains oscillations and stability
- necessity of brain scale models
  - increase self consistency
  - compute meso- and macroscopic measures of activity
- necessity of full scale models
  - irreducibility: already 2nd order statistics affected
  - verify mean-field results
- feasibility:
  - supercomputers and software available (www.nest-initiative.org)
  - stabilization within uncertainty margins of constraints possible