Open Issues in High-Fidelity Simulation of the Connectome

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Yoonsuck Choe\textsuperscript{1} and Jaerock Kwon\textsuperscript{2}

\textsuperscript{1}Texas A&M University
\textsuperscript{2}Kettering University
Overview

• Issues to be resolved to successfully simulate the connectome.

• Issues remaining to be resolved once we have high-fidelity simulation of the connectome.
Part I: Issues to be Resolved
No One Imaging Modality Is Sufficient

- Light microscopy: High volume (∼ cm$^3$), low resolution (0.3 μm)
- Electron microscopy: Low volume (∼ 50$^3$ μm$^3$), high resolution (∼ 10 nm).
- Both are high-throughput and produces massive volumes of data.
Imaging Is Only the Beginning

Reconstruction and simulation efforts can far exceed imaging effort.

- Data acquisition: 8 years developing the instrument, 2 weeks of imaging (mouse, $1 \text{ cm}^3$, 2TB [note: human brain is about 1,500 times that])

- Tracing and validation: still on-going algorithm development and validation. $128^3$ voxel cube takes minutes to trace: Tracing 2TB of data will take $\sim 10$ years (single CPU, 5 minutes per cube), i.e., 260 times the imaging time.

- Model/simulation: Blue brain project runs two orders of magnitude slower than realtime with about 10,000 processors, to simulate $2 \text{ mm} \times 0.5 \text{ mm} \times 0.5 \text{ mm}$ (single column, about 10,000 neurons). $\sim 7,500$ such simulations needed for full mouse brain.

The above does not even include validation.
Validation Is Tough

- Manual validation defeats the purpose of automated reconstruction.

- Alternative validation approaches:
  - Physical phantoms
  - Digital phantoms: noise modeling, etc.
  - Confidence-based editing
  - Human computing, Crowd-sourcing
  - Coupled with simulation
Determining Connectivity and Beyond

- For LM, need to estimate connectivity.
- For EM, need to identify synapses.
- Other important considerations:
  - Sign of the link (excitatory or inhibitory)
  - Weight of the link (synaptic efficacy)
  - Delay of the link
  - Plasticity of the link
Simulation: From Structure to Function

- Many important quantities unknown, besides the connectivity (previous slide).
- Role of a single link: Does altering a single link lead to massive changes in network behavior?
- Numerical instability in simulation.
- Communication overhead hampering parallelization.
- Analysis of simulation results (next topic).
Part II: Issues Remaining to be Resolved
What’s That Question Again?

- Suppose we have an accurate simulation of the brain (any brain).
- What issues still remain in understanding the brain function?
Is the Brain Enough to Understand the Brain?

• Brain is part of the body and a lot of function is performed by the peripheral nervous system.

• To fully understand brain function, it must be understood in the context of the entire body.

• Imaging whole organisms may be necessary for a true understanding of brain function.
The Phenomenological Trap

- Emphasis on function alone can lead to phenomenological (i.e., descriptive) models, not explanatory models.
- Too much emphasis on prediction can have similar consequences.
Risk of Doubling our Task

- Without a proper theoretical framework for analysis, the resulting simulation can be as complex and hard to understand as the real brain.

- Such blind simulation doubles our task.

- However, it can still be useful, in certain ways.
Conceptual Breakthrough Needed

- Posing the right questions.
- Developmental perspective.
- Evolutionary perspective.
- Relationship between time and brain function.
References