Open Issues in High-Fidelity Simulation of the Connectome

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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 ($\sim$ cm^3), low resolution (0.3 μm)
- Electorn microscopy: Low volume ($\sim 50^3$ 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 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 mm $\times$ 0.5 mm $\times$ 0.5 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.
  - Cofidence-based editing
  - Human computing, Crowd-sourcing
  - Coupled with simulationn

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 parellization.
- 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

- Function:How = Principle:Why – we need explanation, not just description.
- Emphasis on function alone can lead to phenomenological (i.e., descriptive) models, not explanatory models.
- Too much emphasis on predicion 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

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