Using Biophysical Computational Neural Models to Investigate Neuropsychiatric Disorders

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From computational neuroscience → computational psychiatry . . .

Psychiatry has fundamental problems in defining and diagnosing mental disorders/illness, partly due to obvious difficulties in measuring origins of symptoms (brain is largely inaccessible).

In order to better understand, diagnose, and treat mental disorders, clinicians/scientists should leverage insights gained from the integrative methodologies used in computational and experimental neuroscience.

However, computational neuroscience is a complex field, taking years of training. . .

To allow computational neuroscience and psychiatry to make the largest impact, new computational/algorithmic tools are needed that integrate multiscale brain dynamics and behavior, and allow scientists to rapidly test their hypotheses on the neural origins of mental disorders.
Outline: modeling tools (solutions) & modeling case studies

1. Build open-source modeling tools (Human Neocortical Neurosolver: HNN) to help researchers understand circuit level origins of human brain dynamics (EEG/MEG)
2. Use auditory thalamocortical models to link functionally relevant brain rhythms in non-human primate to human electrophysiological data
3. Use hippocampal network models to study schizophrenia
4. Use multi-scale models of primary motor cortex to study neocortical hyperexcitability and its pharmacological treatments
5. Use models of sensory/motor cortex to understand learning/behavior → beyond deep learning?
1. Problem in human neuroscience

**Question:** How do we link human macroscopic, noninvasively measured MEG/EEG signals to their underlying cell/circuit-level generators?

**Data:** Source localized human MEG/EEG current dipole signals

**Model:** Biophysical circuit models of the thalamocortical system that generate current dipole signals directly comparable to experimental data

**Result:** New open-source modeling tool allowing clinicians/researchers to import their data and use the model to simulate commonly observed patterns (event-related potentials, low frequency rhythms), enabling hypothesis testing of circuit-level generators of the observed patterns

Neymotin et al., eLife 2020
New open-source modeling tool: Human Neocortical Neurosolver (HNN)

- Use biophysical thalamocortical models to test hypotheses on cell/circuit-level origins of human neural dynamics in health & disease
- Imports Human MEG/EEG data for model comparison/fitting

[Image of HNN website]

- [https://hnn.brown.edu](https://hnn.brown.edu) includes background, tutorials, documentation, publications (eLife)
- HNN workshops/presentations at Computational Psychiatry ([http://computationalpsychiatry.org/cp18/](http://computationalpsychiatry.org/cp18/)), Cutting EEG, and SFN meetings, ...
The HNN model simulates the primary currents contributing to MEG/EEG
HNN’s laminar neocortical microcircuit model

Layered cortical network of pyramidal neurons and interneurons

Individual neurons are compartmental models using parallel conductance equations with standard Hodgkin-Huxley ion channels

Pyramidal neurons generate current dipole signal directly comparable to source-localized signals obtained from MEG/EEG experiments
Activating HNN’s microcircuit model

Proximal drive represents synaptic inputs from thalamic core

Distal drive represents synaptic inputs from thalamic matrix and corticocortical feedback

Each type of drive pushes pyramidal neuron dendrite current flow in opposing directions
HNN’s graphical user interface
Low-frequency alpha/beta rhythms widely observed in human MEG/EEG signals, altered in disease

Source-localized MEG signals from somatosensory cortex have transient alpha/beta events inversely correlated with attention/detection of tactile stimuli; alpha/beta events detectable in auditory/visual cortex, with similar function (i.e. inhibition of unattended modality: Lakatos et al., Nature Neurosci 2016)

Low frequency oscillations (delta, theta, alpha, low gamma) are altered in schizophrenia (Lisman JAMA Psychiatry 2016; Lakatos et al., J Neurosci 2013; Kopell et al.)
Using HNN to model alpha/beta rhythms

Stochastic 10 Hz rhythmic inputs to proximal/distal dendrites in phase (antiphase) produce beta (alpha) rhythms/events

Model beta mechanism validated with invasive laminar electrode array recordings (Sherman et al., PNAS 2016)

Use the software to investigate origins of rhythms, how circuit alterations lead to reduced/enhanced ability to respond to stimuli in health and in disease

Next: use invasive laminar electrode array (LFP/CSD/MUA) data from nonhuman primates to optimize/validate models and investigate auditory/speech processing
2. Integrating electrophysiology in nonhuman primates (NHP) during auditory stimulus/speech processing with computer modeling

**Question:** How does thalamocortical circuitry generate and potentially use oscillations to support auditory & speech processing? Why does the circuitry fail to properly entrain to stimuli in neuropsychiatric disorders?

**Data:** Multi-area/multilaminar ephys data (thalamus, A1, V1) at multiple scales (single-unit, multi-unit, LFP, CSD, ECoG) from Lakatos lab @ NKI; human iEEG data from S. Bickel (Northwell)

**Model:** Detailed biophysical thalamocortical system circuits

**Result:** Model generates LFP/CSD comparable to experiment, allowing prediction on circuit generators, mechanisms, and neuromodulation targets
At rest: complex temporal pattern of oscillations

Using the data (Lakatos lab) to optimize the model
Integrating NHP electrophysiology during auditory processing with modeling

1. Determine mechanisms supporting flexible oscillations needed to track rhythmic auditory stimuli (speech). **Model** determines strengths of connectivity between cortex and thalamus, suggests ways to increase oscillation flexibility.

2. Determine thalamocortical mechanisms of oscillatory phase reset for aligning brain rhythms to stimuli, could be used to parse auditory objects. **Model** predicts in vivo neuromodulation strategies to improve this process.

3. Determine mechanisms supporting auditory object formation, hypothesized to occur through periodic inhibition. **Model** tests how different interneuron populations contribute to this process, providing additional in vivo neuromodulation strategies.

Different A1 L2/3 ensembles show phase synchronization for vowels (< 8 KHz; low-frequency tuned) or consonants (> 10 KHz; high-frequency tuned), which tend to occur out-of-phase.
Model: neuronal populations

Neurons: multi-compartment, conductance-based.

Excitatory neurons: intratelencephalic (IT), pyramidal tract (PT), spiny stellate (ITS), corticothalamic (CT) and MGB thalamocortical (TC).

Inhibitory neurons: somatostatin (SOM), parvalbumin (PV), neurogliaform (NGF), vasoactive intestinal peptide (VIP), and thalamic reticular nucleus (RT).

Geometry: Simplified morphologies. Dendritic lengths sized to match the macaque cortex dimensions.

Model built with NetPyNE platform (https://netpyne.org  Dura-Bernal et al., eLife 2019)
Model Development Challenge: pyramidal neurons have unknown spatial distribution of ion channels

- Full spatial channel distribution is unknown, but experimental literature indicates certain spatial constraints (e.g. HCN density increases distally)

**Requirement:** develop detailed models with full dendrite reconstruction (~700 compartments) and simplified models (6 representative compartments) in order to produce accurate circuit dynamics

**Goal:** optimize model channel densities (Na, K, Ca, HCN) in order to reproduce observed in vitro activity from current clamp recordings

**Solution:** Use sequential optimization: 1. subthreshold fits; 2. firing property fits

Neymotin et al., J Neurophysiology 2016
Model neuron optimization

Cell types in each layer fitted to macaque or rodent electrophysiology data via multi-objective evolutionary optimization algorithm or via hand-tuning.

Passive parameters (e.g. leak channel, HCN channel conductance, capacitance) were tuned to fit RMP and other features of subthreshold traces, including steady state voltage and sag.

Active parameters (e.g. fast Na, K, Ca, BK channel density) were then tuned to fit features like firing rate curves, action potential shape, and adaptation.

Neymotin et al., J Neurophysiology 2016
Model: data-driven circuit connectivity

Experimental circuit mapping data constrains model connectivity

E → E/I from mouse V1,S1,A1,M1 (Levy & Reyes 2012; Yoshi et al 2015; Billeh et al 2019; Lefort et al 2009; Allen Brain Institute)

I → E/I from mouse V1,S1,A1,M1 (Sohn et al 2016; Naka et al 2016; Tremblay et al 2016; Pi et al 2013; Pi et al 2013)
Model includes biophysically-detailed LFP → comparison with *in vivo* data

The A1 model simulates laminar local field potentials, and will be used to determine the origin of different oscillation patterns observed in the data.
Providing auditory stimuli to the model

Pathway: sound wave → cochlea → inferior colliculus (IC) → MGB → A1

Full pathway allows comparison of NHP and model data to determine circuit mechanisms supporting sound/speech processing.
Biophysical thalamocortical system model to predict origin of different oscillations

Model: thalamic core/matrix interconnected bidirectionally with neocortex → creates oscillations

Neocortical neurons (pyramidal neurons, stellate cells, PV/SOM/VIP/NGF interneurons) arranged in 6 cortical layers; thalamic neurons arranged in thalamic nuclei (reticular, relay)

Model simulates laminar LFP, CSD, MUA comparable to experimental data

Short/long inhibition produces the different oscillation frequencies observed; we will use the model to test origin of NHP data and provide neuromodulation predictions to enhance auditory processing

Next: using biophysical neural circuit models to investigate origins and treatments for neuropsychiatric disease
3. Hippocampal network model to study neuropsychiatric disorders

**Background:** A mutation in the HCN1 gene (5p21) is near one of 108 loci implicated in schizophrenia (Schizophrenia Working Group, Nature 2014). Another mutation is in the GRIN2A gene (glutamate ionotropic NMDAR subunit 2A on 16p13), a subunit that forms part of the ionotropic NMDA-type glutamatergic receptor (NMDAR). The psychomimetic ketamine (NMDAR antagonist) is used to model the disorder.

**Question:** NMDAR & HCN channel changes are implicated in schizophrenia. How do these alterations impact hippocampal dynamics & information processing? Can we use biophysical circuit models to predict effects of gene/circuit alterations contributing to the disorder, & match experimental observations?

**Data:** Hippocampal oscillations in mouse in vivo show less theta, more gamma after ketamine; human gamma/other oscillatory alterations in schizophrenia

**Model:** Hippocampal CA3 circuit; ketamine simulated by setting NMDA receptor conductance to zero (blockade); NMDA, HCN mutations via conductance change

**Result:** Model generates realistic oscillations, predicts ketamine’s site of action, disease mechanisms, and novel target for therapy.
In vivo: altered hippocampal oscillations after applying psychomimetic ketamine

Lazarewicz et al., J Cognitive Neurosci 2010
**Model:** Circuit-level biophysical model of hippocampal CA3 containing interconnected pyramidal neurons, OLM interneurons, basket interneurons, medial septum (MS) inputs
CA3 model generates theta/gamma

Neymotin et al., J Neurosci 2011
CA3: looking for ketamine’s site of action

NMDA OFF=0, NMDA ON=1

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Neymotin et al., J Neurosci 2011
Simulated ketamine: reduced theta, increased gamma

Adapted from J Neurosci 31(32):11733, Fig 7
Simulated ketamine: reduced theta, increased gamma

Neymotin et al., J Neurosci 2011
Simulated ketamine: OLM NMDA receptor conductance regulates theta/gamma

OLM cell NMDA receptor conductance changes can account for lower theta & higher gamma amplitudes seen in schizophrenia (e.g. in ketamine models)

Neymotin et al., Hippocampal Microcircuits, Springer 2018
Simulation predicts that higher HCN density in basket cells could also produce higher gamma power observed in schizophrenia models.

Model HCN mutations by changing HCN conductance.

Basket interneurons contribute to gamma rhythms through periodic inhibition of pyramidal neurons and other basket cells.

Providing extra depolarization to the basket cells through higher HCN density, causes heightened basket activity and more prominent gamma activation.

Basket HCN density does not impact theta rhythms.

Neymotin et al., Hippocampal Microcircuits, Springer 2018
Treatment: restoring oscillations via current injection to OLM cells

Neymotin et al., J Neurosci 2011
Aberrant oscillations → altered function?

Use transfer entropy to link dynamics/oscillations and function by measuring information transferred through the simulated hippocampal network.

Neymotin et al., J Comp Neurosci 2011; Neymotin et al., J Neurosci 2011; Neymotin et al., Hippocampal Microcircuits, Springer 2018; Sherif et al., NJP Schizophrenia (under review)
Ketamine: increased gamma reduces network responsiveness to outside “world”

Oscillatory power is linked with the level of information processing in the network: overly high gamma power produces more stereotyped firing patterns and suggests mechanism for hallucinations (loss of responsiveness to external information (outside world) and over-reliance on internal information)

Neymotin et al., J Comp Neurosci 2011; Neymotin et al., J Neurosci 2011; Neymotin et al., Hippocampal Microcircuits, Springer 2018
More generally: intermediate excitability and synchrony/gamma support optimal information throughput

Synchrony/gamma displays inverted-U relationship with information transfer

Overly weak synchrony/gamma associated with sparse firing and low information throughput (L1)

Overly high synchrony/gamma associated with stereotyped firing and low information throughput (L2)

Intermediate synchrony/gamma supports optimal throughput (H1,H2)

Sherif et al., NJP Schizophrenia (under review)
Excitability and synchrony impact response to driving input and information flow

Low excitability: driving input insufficient to reach threshold and trigger firing, reducing information flow from driving input.

Moderate excitability: pyramidal neurons close to firing threshold → driving input is enough to push cells into firing,

High excitability: pyramidal neurons pushed back-and-forth between synchronized firing with little driving input influence relative to internal drive, and synchronized inhibition with little input influence due to distance from threshold.

Sherif et al., NJP Schizophrenia (under review)
4. Multiscale simulations for pharmacological treatments of neocortical hyperexcitability

**Question:** Can we use multiscale models to assist development of novel multitarget therapies for complex neurological/psychiatric disorders?

**Data:** Mouse primary motor cortex (M1) circuit-mapping data; current clamp recordings for L5 pyramidal neurons

**Model:** Multiscale model of M1

**Result:** Combining model with machine learning approach was successful in predicting pharmacological targets to treat hyperexcitability disorders

Neymotin et al., Frontiers in Pharmacology 2016
Family of motor cortex models shows three types of dynamics

Model ion channel densities randomly perturbed, creating a family of models showing three clusters of distinct dynamics → 1. normal (low synchrony), 2. seizure/latch-up (high intermittent synchrony), 3. dystonia (high sustained synchrony)

Neymotin et al., Frontiers in Pharmacology 2016
Dystonia & seizure have strong oscillations. In seizure, many cells are in depolarization blockade.
“Average” treatments won’t work (failure of averaging; blue physiological, red pathological)

Average parameters from each class do not produce simulations representative of the class.

The multiple, distinct manifestations of pathology, demonstrate utility of personalized medicine.
Machine learning approach predicts that targeting combinations of several receptors is a more effective treatment option than a single target.

The most important determinants of hyper-excitability were Na, K, and Ca channel densities.

Neymotin et al., Frontiers in Pharmacology 2016
5. Sensorimotor learning in detailed circuit models

- **Questions:** Can we model the circuit mechanisms, dynamics, and learning that support sensory integration relevant for purposeful behavior? How well do realistic biophysical circuit models with biologically plausible learning rules perform against commonly used deep reinforcement learning algorithms? Can we use the more detailed circuit models to better understand in vivo learning mechanisms?

- **Data:** Electrophysiology, fMRI recorded during sensorimotor learning and decision-making experiments

- **Model:** Spiking neuronal networks of sensory, visual, and motor cortex trained using spike-timing dependent reinforcement learning

- **Result:** Models utilize sensory information to learn appropriate behavioral responses
Scaling up to behavior: sensorimotor learning

Neymotin et al., Neural Comput 2013
Trained network reaches target

Neymotin et al., Neural Comput 2013
Learning enhances information transfer

After learning, relevant sensory information is utilized more effectively.
Learning produces attractors

A

B

C

D
Motor cortex/spinal cord model trained to control more realistic arm model & robot arm

6-layered neocortical architecture: each layer can perform distinct computations (gathering information in input layers, routing/selecting information to send in output layers)

Dura-Bernal et al., Front Neurorobotics 2015
Training biophysical circuit models to play games

Video game frames converted to topographic inputs that drive non-homogenous Poisson process

Visual hierarchy feeds to motor population command layers which learn to process dynamic sensory information to produce behaviors maximizing reward

Only using learning rules that are considered *biologically-plausible*
Testing influence of architecture: visual hierarchy, recurrent connectivity, and top-down influence
Conclusions

● Our software/models enable researchers to predict mechanistic origins and functions of neural oscillations and activity patterns through integrating modeling with behavioral experiments while performing invasive intracranial laminar electrode array recordings in nonhuman primates and noninvasive MEG/EEG recordings in humans.

● Oscillatory power was linked with the level of information processing in networks: overly high gamma power produced more stereotyped firing patterns and may suggest a loss of responsiveness to external information (outsideworld), and potentially explains aspects of hallucinations in schizophrenia.

● We used our models standalone, and in combination with machine learning approaches, to derive novel pharmacological and electrostimulation therapies for neuropsychiatric disorders, such as schizophrenia.

● Ongoing work: training detailed circuit models of thalamocortical system to perform behaviors through streaming of dynamic signals (speech/video) and biologically-plausible learning rules.
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