Computational Pharmacology: Simulating Circuits of the Brain for Drug Development

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Computational Neuropharmacology: Simulating Circuits of the Brain for Drug Development

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Mathematical Models of Microcircuits

Validate Models with Clinical Data

Ingredients:
- Neural Dynamics
- Receptor Activation

Goals:
- Clinical Outcome Prediction
- Drug Discovery

Techniques and intuition from computational neuroscience
Computational Neuropharmacology

**Schizophrenia: Symptoms & Pathologies**

**Computational Models of Mental Illness:**
Neurons, synapses and modulators

**Example:** Working Memory Model

**Pharmaceutical Industry:** Progress & Projections

**Other Projects...**
Symptoms of Schizophrenia

— A spectrum of psychotic disorders characterized by distortions of reality, withdrawal from social contact, and disturbances of thought and language.

**Positive Symptoms**: Delusions, hallucinations, thought disorders, movement disorders

**Negative Symptoms**: Blunted affect, difficulty initiating speech, lack of pleasure in life, decreased activity

**Cognitive Symptoms**: Working memory, attention, executive function, problem solving
1% of the population worldwide has schizophrenia.

Schizophrenia is the 8th leading cause of disability worldwide among 15-44 year-olds.

Sham et al (1994)

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Schizophrenia: Pathologies

**AUDITORY SYSTEM**
Enables humans to hear and understand speech. In schizophrenia, overactivity of the speech area (called Wernicke’s area) can create auditory hallucinations—the illusion that internally generated thoughts are real voices coming from the outside.

**BASAL GANGLIA**
Involved in movement and emotions and in integrating sensory information. Abnormal functioning in schizophrenia is thought to contribute to paranoia and hallucinations.

Excessive blockade of dopamine receptors in the basal ganglia by traditional antipsychotic medicines leads to motor side effects.

**FRONTAL LOBE**
Critical to problem solving, insight and other high-level reasoning. Perturbations in schizophrenia lead to difficulty in planning actions and organizing thoughts.

**OCCIPITAL LOBE**
Processes information about the visual world. People with schizophrenia rarely have full-blown visual hallucinations, but disturbances in this area contribute to such difficulties as interpreting complex images, recognizing motion, and reading emotions on others’ faces.

**LIMBIC SYSTEM**
Involved in emotion. Disturbances are thought to contribute to the agitation frequently seen in schizophrenia. Blunted affect.

**HIPPOCAMPUS**
Mediates learning and memory formation, intertwined functions that are impaired in schizophrenia.

(Javitt, 2004)
Schizophrenia: Causes

Gottesman, 2003
**Challenge**: Construct a tractable model without making it too simple for an accurate simulation of mental disease.
Do Mental Illnesses Have Predictable Dynamics?

Dynamics of Bipolar Disease

Elegant model & useful for treatment strategies, but difficult for developing new treatments.

(Huber, Braun, Krieg 1999)
Neuron doctrine: the nervous system is made up of discrete individual cells.
Computational Models of the Brain

Neurons are complicated capacitors

\[ C \frac{dV}{dt} = I \]
Computational Models of the Brain

Voltage gated channels regulate polarization of neurons

\[
\frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)n
\]
Computational Models of the Brain

Hodgkin-Huxley Equation quantify membrane potential of neurons

\[
C \frac{dV}{dt} = I - g_{Na}m^3h(V - V_{Na}) - g_K n^4(V - V_K) - g_L(V - V_L)
\]

\[
\frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(V)m
\]

\[
\frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(V)h
\]

\[
\frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)n
\]
Computational Models of the Brain

Synapses connect neurons.
Computational Models of the Brain

Presynaptic spike $\Rightarrow$ transmitter release $\Rightarrow$ postsynaptic potential change

\[ I_{syn} = g_{syn}(t)(V - E_{syn}) \]

\[ g_{syn}(t) \models \text{Presynaptic release probability, Postsynaptic receptor conductance} \]
Computational Models of the Brain

Receptor types: Ionotropics and Metabotropics

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Computational Models of the Brain

Second messenger pathways

Second messenger model:
Linear relation between receptor activation and effect based on experimental values of %-change.

Pathologies

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Pathologies of Schizophrenia

Some genes can be related to pathologies and suggest mechanisms of disease.

(Meyer-Lindenberg, 2006)
PET scan of a schizophrenic brain. While patients performed a working memory task, the less the prefrontal cortex (red) activated, the more dopamine increased in the striatum (green).

Drugs that treat schizophrenia are “dirty”
Drugs for Schizophrenia have Complicated Binding Kinetics

Receptor selectivity of various drugs for schizophrenia.

(Kapur, 2003)
Computational Models of the Brain

Receptor Activation Model: Differential equations simulating binding dynamics in a synaptic cleft

1. Estimate physiological presynaptic spike pattern.

2. Calculate diffusion from Stokes-Einstein equation and removal.

3. Calculate competitive binding on presynaptic receptors affecting release.

4. Calculate competitive binding on postsynaptic receptors.

5. Calculate fraction of receptor activation.
Computational Models of the Brain

Connectivity determines function of the neural circuit

Implementation of normal and diseased state

Hippocampus

Signal Processing of the Direct & Indirect Pathways

Prefrontal Cortex

Model Output

Bits/sec information content
**Working Memory Model**

Network dynamics -- Noisy potential well model

\[
\frac{dR_e}{dt} = -R_e - W_{ei} F_i(R_i) + W_{ee} F_e(R_e)
\]

\[
\frac{dR_i}{dt} = -R_i + W_{ie} F_e(R_e) + W_{ii} F_i(R_i)
\]

\[
F_e(R) = 1 + \tanh(R - 2)
\]

\[
F_i(R) = 1 + \tanh(R - 3)
\]
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Working Memory Model
Connectivity & Neural Compartments

Pyramidal cell
Inhibitory Interneuron
B
B
B
Soma
B
B
B
Basal
Distal
Proximal
Output

20 Pyramidal cells (10 stimulated)
10 Inhibitory interneurons

B = background stimulus

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Working Memory Model

Network dynamics -- Noisy potential well model

(Durstewitz, 2006)
Working Memory Model

Stochastic working memory bursts

- pyr rate (Hz/cell) = 21, inhib rate (Hz/cell) = 56.625
- pyr rate (Hz/cell) = 25, inhib rate (Hz/cell) = 65.6833
- pyr rate (Hz/cell) = 17, inhib rate (Hz/cell) = 51.5167
- pyr rate (Hz/cell) = 17, inhib rate (Hz/cell) = 56.4
**Working Memory Model**

Schizophrenia pathology

**D1-R activation**: The prefrontal cortex is in a hypo-dopaminergic state (Davis, 1991), therefore the D1-R activation is reduced

**NMDA-R function**: There is a dysfunction in the NMDA-R associated with schizophrenia, therefore the NMDA-R maximum conductance is reduced.

**GABA-R conductance**: A dysfunction of GABA transporters in schizophrenia (Lewis, 2005) leads to an up-regulation of GABA-R receptors so that the GABA-R conductances is increased.

**Background noise**: Patients with schizophrenia display a loss of signal to noise ration in brain function (Winterer, 2000), therefore the background noise is increased.
Working Memory Model

Add receptors for drug actions.

Pyramidal cell

Inhibitory Interneuron

dendrite

soma

B = background stimulus

distal

proximal

soma

basal

Output

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Working Memory Model

Process of tuning the working memory model

**Step A:** Calculate receptor activation from competition model for all receptors in the micro-circuit model in the presence of each drug dose.

**Step B:** Modify membrane currents due to drug action.

**Step C:** Run network model.

**Step D:** Recursively modify receptor effects to find best fit with clinical data.
Working memory span results for various drug treatment for schizophrenia and genetic variants of COMT.

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Working Memory Model

Correlation between ISB Working Memory model and clinical dataset

9 clinical interventions, 5 antipsychotics + COMT genotype (Weickert 2003, Bertolino 2004)
Developing Drugs

1. Build model that shows strong correlations between existing drugs and their clinical outcome.
2. Consider wide range of receptor occupancies to determine which has best clinical outcome.
3. Throw out cases that have bad side effects.
4. Determine likely Ki’s to develop best drug.
5. Check with competition model that Ki’s lead to desired occupancies.

R₁, R₂, R₃

Drug Ki’s

Receptor Occupancies

Model

Clinical Outcome

Competition Model

EPS

Side Effect

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Pharmaceutical Industry

Number of discoveries have decreased as costs increase.

![Graph showing the relationship between R&D spending and NME approvals over time.](image)
Pharmaceutical Industry

When do drugs fail in development?

Clinical Trials

Phase I: First in humans. Small group (20-100) of normals. Assess the safety, tolerability, pharmacokinetics.

Phase II: Larger groups of patients and controls. Assess dose and efficacy.

Phase III: Large randomized controlled trials. Assess effectiveness relative to "gold standard" treatment.

(Kola, 2004)
Limitations of Animal Models

- Differences in drug metabolism
- Placebo response
- Different neurotransmitter wiring
- Incomplete pathology in transgenic mice
- Different drug affinities
- Absence of functional genotypes

Geerts, CNS Drugs 23,915
Computational Pharmacology in the Drug Pipeline

Select multiple-receptor compounds.

Predict dose requirements in human subjects.

Screen for possible side effects.

Pre-screen compounds before clinical trials. (pharmacokinetics)

Experimental design for large trials.

Comparisons of marketed drugs.

Screening by FDA. (Entelos)
Other projects...

- Midbrain (striatum) model to develop new polypharmacy drugs for schizophrenia validated with the PANSS (Positive and Negative Syndrome Scale).

Greater than three-fold improvement over the “gold standard” single-receptor prediction.
The model output is a signal that is Fourier analyzed to extract the power in important brain wave frequency bands. Changes in model output predicts changes in human EEG caused by drug therapy.
Pharmaco-EEG module simulates brain waves generated by a network of neurons in the human cortex.

Each of the 120 model neurons in the network contains the biophysical details of membrane currents, synaptic connections and drug actions. Oscillations emerge from the network activity to simulate changes in brain waves caused by drug effects.
Other projects...

• Extra-pyramidal symptom model is re-purposed as a Parkinson’s disease symptom model to screen orphaned drugs for new therapy (M.J. Fox Foundation).

• Develop treatments for cognitive impairment in Alzheimer’s disease.

• Virtual clinical trials for drug effectiveness on genetic variants.
In Silico Biosciences, Inc.

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Schizophrenia

— A spectrum of psychotic disorders characterized by distortions of reality and disturbances of thought and language and withdrawal from social contact.

Dementia praecox (“premature dementia”) refers to a chronic, deteriorating disruption in cognitive or mental functioning such as in attention, memory, and goal-directed behavior. - Emil Kraepelin (1896).

“Schizophrenia” was coined by Eugen Bleuler (1908) to mean a “splitting of the mind” to describe the separation of function between personality, thinking, memory, and perception.

“Schizophrenia is a disease of language and logic.” - David Lewis (2009)
Development of pharmaceutical therapy for Schizophrenia

1947: Synthesized promethazine with sedative and antihistaminic effects.

1948: Pierre Huguenard used promethazine to induce relaxation and indifference in surgical patients.

Henri Laborit, believed the compound caused 'artificial hibernation', or "chemical lobotomy"

1952: Jean Delay and Pierre Deniker, First clinical trial on 38 psychotic patients with chlorpromazine. Improvements in thinking and emotional behaviour.

By 1954, chlorpromazine (Thorazine) was being used in the United States to treat schizophrenia.

1959: Paul Janssen, “finding a treatment for amphetamine intoxication would provide a cure for paranoid schizophrenia”. Haloperidol reversed amphetamine intoxication in mice.