Evaluation of Novel Drug Targets for Schizophrenia Treatment Using a Model of Cortical and Basal Ganglia Circuitry

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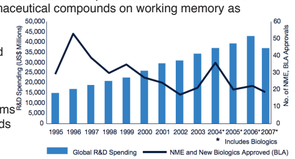
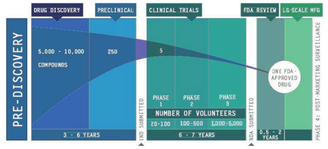
1 Introduction: Biomarkers and Drug Development

The purpose of this project is to develop, refine and validate a computational neuronal model for working memory to calculate the effects of pharmaceutical compounds on working memory as a measure for cognitive function.

The long-term goal is to develop a well-calibrated support platform for clinical development of pharmacological therapies. The clinical development of new pharmacological therapies may be accelerated by predicting clinical symptoms to show the effects of pharmacological compounds before clinical trials of new investigational drugs.



Computational studies may improve the chances for clinical success of new compounds by supporting the design of proof-of-concept and dose-finding studies. They also can optimize a specific design and help interpret the results of clinical trials and evaluate the comparative differences between known drugs.



90% of CNS drugs fail in clinical trials.

The high failure rate of drugs in clinical development is leading to an unsustainable business model for the pharmaceutical industry. One reason for this failure rate is the translational disconnect between the outcomes in preclinical animal models and the clinical equivalent.

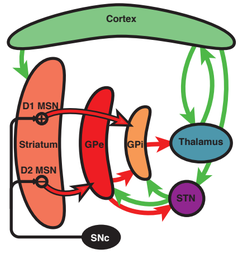
2 Disorders involving the basal ganglia

Parkinson's Disease:

Symptoms of Parkinson's disease are characterized by movement disorders such as tremors, rigidity, and slowness of movement. The cause is a loss of dopamine generating neurons in the substancia nigra that project to the striatum. Symptomatic treatments include replacing the lost dopamine systemically. However, many patients are resistent to L-dopa therapy, so other forms of treatment would be benificial.

Schizophrenia:

The principal target of antipsychotic (neuroleptic) medications is to block D2 receptors in the striatum. Therefore, positive symptoms of schizophrenia are assumed to involve neural processing in the ventral striatum that is coupled to the prefrontal cortex. Potential side effects of antipsychotic drugs are extrapyramidal symptoms (EPS) that resemble Parkinson's motor deficits. A computational platform that simulates Parkinson's like neural activity will help to assess the EPS liability of novel compounds.



Huntington's Disease:

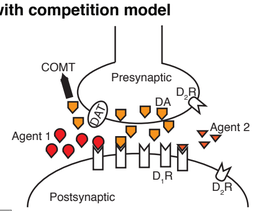
Degeneration of D2 medium spiny neurons in the striatum appear to be a principal pathology of Huntington's disease. By simulating the neural acitivity we may seek symptomatic therapies.

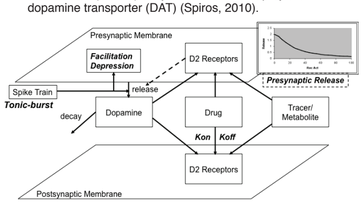
Our **goal** is to implement pathologies associated with these diseases in numerical models of neuronal circuitry to seek ***symptomic pharmaceutical treatments***.

3 Receptor activation calculated with competition model

To link pharmaceutical properties of drugs to brain function in our biophysical circuit models, we have developed a receptor competition model to calculate how receptor activation changes in the presence of pharmacological agents.

A dopaminergic synapse is shown where dopamine interacts with the presynaptic D2 receptor in a negative feedback cycle and with postsynaptic D1 and/or D2 receptors. Dopamine is degraded by the Catechol-O-methyl Transferase (COMT) enzyme and is taken up by the dopamine transporter (DAT) (Spiros, 2010).





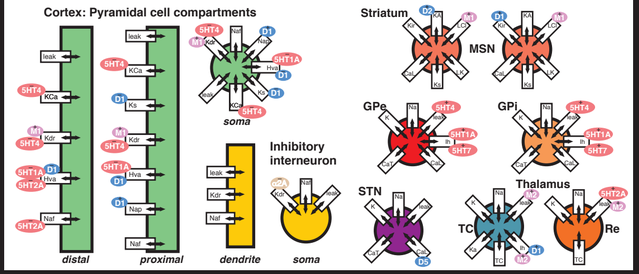
$$\frac{d}{dt}[D_n] = k_{on} \cdot [dop] \cdot [D_f] - k_{on} \cdot K_d \cdot [D_n]$$
$$\frac{d}{dt}[D_d] = k_{on} \cdot [drug] \cdot [D_f] - k_{on} \cdot K_d \cdot [D_d]$$
$$\frac{d}{dt}[D_m] = k_{on} \cdot [metabolite] \cdot [D_f] - k_{on} \cdot K_d \cdot [D_m]$$
$$\frac{d}{dt}[D_t] = k_{on} \cdot [tracer] \cdot [D_f] - k_{on} \cdot K_d \cdot [D_t]$$
$$D_f = D_o - D_n - D_d - D_m - D_t$$

We have used similar models to calculate the activation of other postsynaptic dopamine receptors and specific serotonergic, noradrenergic, glutamatergic, GABAergic and muscarinic synapses.

Compartemental model of neurons to represent functional activity

We have constructed a compartmental model that simulates cortical and basal ganglia spiking activity using the neuronal simulation package NEURON (Hines, 1997). Eight types of neurons are included in the model: Pyramidal cells and inhibitory interneurons (Durstewitz, et al, 1999), striatial medium spiny (MSN) neurons (Gruber, et al, 2003), GPe, GPi, subthalamic nucleus (STN) neurons (Rubin & Terman, 2004), thalmocortical (TC) neruons and reticular nucleus (RE) neurons (Bazhenov, et al, 98).

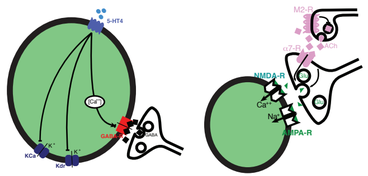
Each cell type is modeled with membrane conductances to simulate their functional role in the circuit, as well as the receptor activations due to the pharmacology that change the spiking activity. Each compartment of each model neuron obeys the membrane current balance equation of the Hodgkin-Huxley formalism.

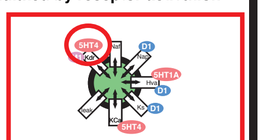


5 Membrane currents of compartments are modulated by receptor activation

The receptor effects are the key to including pharmacology in the models and to calibrate the models with human clinical data. The effects of neural modulators are introduced by coupling the activation of receptors to changes in membrane and synaptic currents.

Although signaling pathways from G-protein coupled receptors can be highly complex, these effects modulate, rather than drive the overall activity of the network. Therefore, we approximate the modulation of receptors by pharmacological agents as a perturbation of the state of the system. We therefore use a first-order (linear) approximation of the changes caused by pharmacology to alter the effects of receptor activation.





Serotonin 5-HT4 receptors couple to the membrane potential of the pyramidal cell soma via a delayed rectifier current (Kdr). The membrane potential, V_s, is computed by numerically integrating the equations in each compartment. The first order rate constants in the Hodgkin-Huxley formalism are dependent on the membrane potential through functions for each channel type.

$$C\frac{dV_s}{dt} = I_{Kdr} + I_{Na} + \cdots$$
$$I_{Kdr} = -g_{Kdr} \cdot n^4 (V_s - E_K)$$
$$\frac{dn}{dt} = \alpha_n(V_s)(1-n) - \beta_n(V_s)n$$
$$g_{Kdr} = \bar{g}_{Kdr} \cdot (1 - 0.5 \cdot P^K_{5HT4} \cdot act5HT4)$$

6 Synaptic currents are modulated by receptors

The synaptic connections are based on the kinetics of AMPA, NMDA, GABA, and mGluR currents (Destexhe, 1994).

Excitatory synapses include both AMPA and NMDA currents. Parameters include: maximal inward depolarizing conductance, rise time constant, and decay time constant.

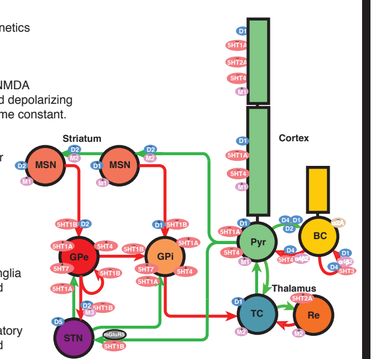
$$g_{glu}(t) = \bar{g}(e^{-t/\tau_{decay}} - e^{-t/\tau_{rise}})$$

Inhibitory synapses represent $GABA_A$ receptor currents using a similar scheme as excitatory synapses.

Pyramidal cells receive inhibitory inputs from inhibitory interneutons at the soma and are recurrently coupled (Durstewitz, et al 1999)

All other neurons couple thought he basal ganglia loop through the striatum, globus pallidus, and thalamus.

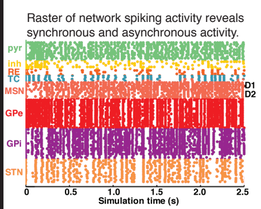
Each model neuron receives fluctuating excitatory and inhibitory currents to simulate background synaptic activity.

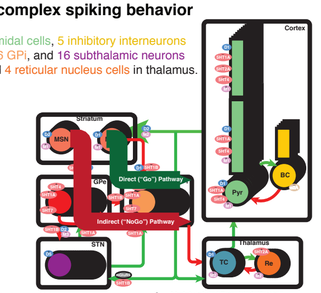


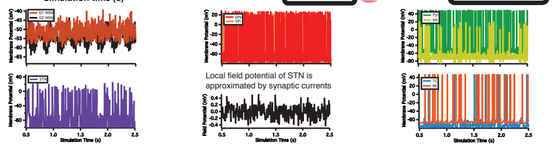
7 Network generates complex spiking behavior

The model simulates the spiking activity of 10 pyramidal cells, 5 inhibitory interneurons in the cortex; 10 medium spiny neurons, 16 GPe, 16 GPi, and 16 subthalamic neurons in the basal ganglia; and 4 thalamocortical cells and 4 reticular nucleus cells in thalamus.

Raster of network spiking activity reveals synchronous and asynchronous activity.







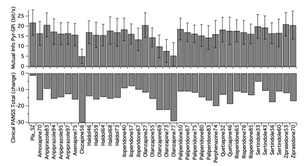
Local field potential of STN is approximated by synaptic currents

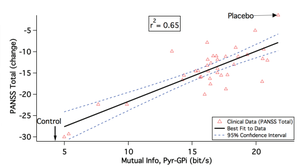
8 Implementation of pathology associated with schizophrenia

Schizophrenia pathology has been implemented by

1. Decreased the NMDA function (lower the maximum conductance) (Javitt, 1991).
2. Reduction in cortical free dopamine level and DA receptor stimulation (Laruelle, 2003), and increase in striatal dopamine levels.
3. Increased in the background noise (Winterer, 2004).
4. Reduced GABA maximum conductance and longer time constant (Lewis, 2007).

The magnitudes of these pathologies are calibrated to match the change in readouts that are associated with the diseased state in clinical studies.

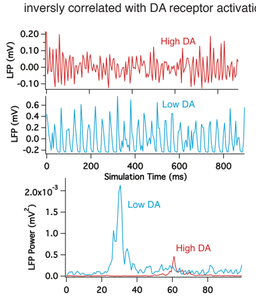




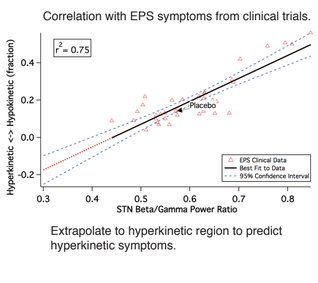
The parameters for each receptor (D1, 5-HT1A, etc) have been searched to maximize the correlation with total PANSS score under stable treatment by antipsychotic drugs.

9 Calibration of extrapyramidal motor symptoms

Recordings during deep brain stimulation surgery suggests that high beta frequency band power is associated with hypokinetic symptoms and high gamma band power (with low beta) is associated with hyperkinetic symptoms. We found that the ratio of beta to gamma frequency band power in the subthalamic nucleus is inversly correlated with DA receptor activation.



Correlation with EPS symptoms from clinical trials.

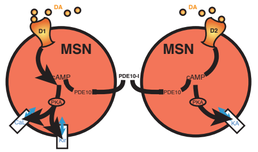


Extrapolate to hyperkinetic region to predict hyperkinetic symptoms.

The parameters for each receptor (D1, 5-HT1A, etc) have been searched to maximize the correlation with clinical fraction of patients who developed EPS under stable treatment by antipsychotic drugs.

10 PDE10 as a Novel Target for Schizophrenia

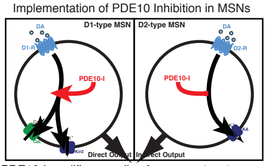
PDE10 is an enzyme that degrades cAMP and is primarily found in the medium spiny neurons of the striatum. Because of this restricted location, and because PDE10 controls the dopamine pathways, considerable research & development has focused on developing PDE10 as a target for schizophrenia treatment.



- PDE10 inhibition acts as a D1 agonist and D2 antagonist.
- D2 antagonism suggests good antipsychotic efficacy.
- But, D1 agonism may lead to hyperkinetic motor symptoms.

Low DA concentration, => D2 antagonism dominates,
High DA concentration (SZ), => D1 agonism dominates.
(Sotty, et al, 2009)

Implementation of PDE10 Inhibition in MSNs



We represent intracellular kinetics as a single parameter:

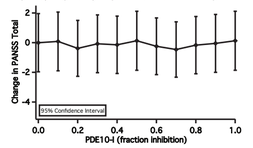
1. The baseline coupling parameters are calibrated using clinical data
2. The modification by PDE10 inhibitors is estimated by applying preclinical data.

This approach approximates the steady state of PDE10-I inhibition kinetics.

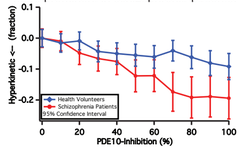
PDE10-I modifies coupling from receptors to currents

11 Estimation of PDE10-I Efficacy and Motor Side Effects

PDE10-I does not have strong antipsychotic efficacy due the unaffected D2 site on the presynaptic synapse from cortical inputs.

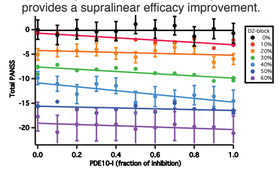


Because D1 agonism dominates when DA concentration is high, motor side effects are more prominent in schizophrenia patients.

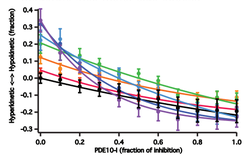


Combination therapy simulation suggests a dose sparing strategy.

Combining PDE10-I with a D2 antagonist provides a supralinear efficacy improvement.



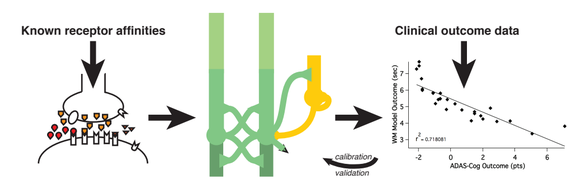
PDE10-I and D2 antagonists together can moderate their motor side effects.



12 Conclusions and Future Directions

Given the high rate of failures in the pharmaceutical industry, any advance in predicting the efficacy and dose parameters of new compounds can save valuable resources.

A computational model can combine known pharmacology with physiology and clinical data...



...to predict the results of complicated interactions to yield an estimate of a new compound's efficacy.

In addition to translational applications in drug development, the model may reveal mechanisms for clinical treatment changes such as memantine in late stages of the disease.

We have previously demonstrated this methodology with models of EEG and working memory to predict the effects of pharmaceutical therapies for schizophrenia and Alzheimer's disease.