A biophysical computational model to guide drug development using human electroencephlograph

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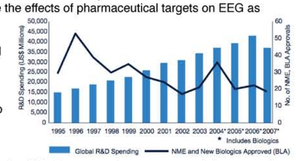
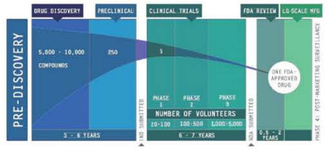
1 Introduction: Biomarkers and Drug Development

The purpose of this project is to develop, refine and validate a computational neuronal model for electroencephalograph (EEG) signal to calculate the effects of pharmaceutical targets on EEG as a noninvasive biomarker for brain dysfunction.

The long-term goal is to develop a well-validated support platform for the clinical development of pharmacological therapies. The clinical development of new pharmacological therapies may be accelerated by predicting EEG signals to show the effects of pharmacological target engagement for an investigational drug.



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 non-invasive biomarkers such as pharmaco-EEG.



90% of CNS drugs fail in clinical trials.

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

2 EEG provides biomarkers for schizophrenia

The source of EEG signals is the population activity of cortical neurons, generated by oscillations in neuronal microcircuits detected by electrodes placed on the scalp. The expression of schizophrenia as a pathology of these microcircuits is becoming better understood, and can be implemented in computational models (Silberberg, 2007, Orban, 2006) of neuronal activity in the cortex.

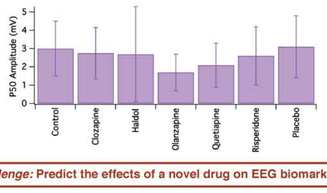
Clinical data that we use to validate our model include the following measures:

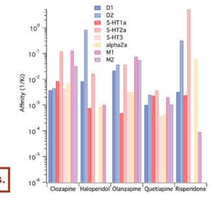
1. Theta band power (Winterer 2000,Venables 2009) is greater in patients with schizophrenia.

2. Alpha band power decreases in patients with schizophrenia (Molina, 2004).

3. Theta/gamma power ratio has been associated with cognitive deficits (Moretti, 2009).

4. P50 amplitude is smaller in SZ and modulated by by antipsychotic drugs (Turetsky 2009, Adler 2004):



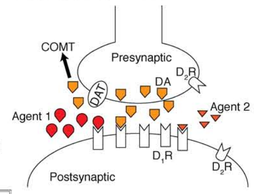


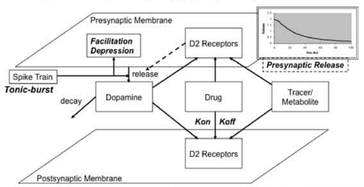
Challenge: **Predict the effects of a novel drug on EEG biomarkers.**

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).





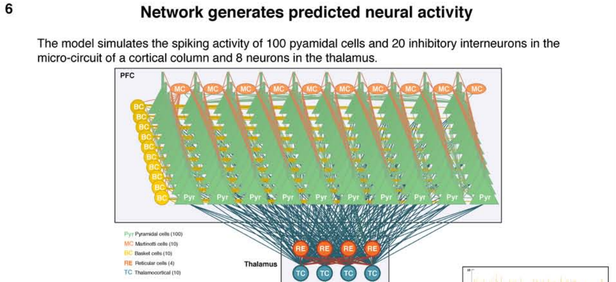
$$\frac{d}{dt}[D_n] = k_{on} \cdot [dop] \cdot [D_f] - k_{on} \cdot K_d \cdot [D_n]$$
$$\frac{d}{dt}[D_d] = k_{on} \cdot [drug] \cdot [D_f] - k_{on} \cdot K_d \cdot [D_d]$$
$$\frac{d}{dt}[D_m] = k_{on} \cdot [metabolite] \cdot [D_f] - k_{on} \cdot K_d \cdot [D_m]$$
$$\frac{d}{dt}[D_t] = k_{on} \cdot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

We have used similar models to calculate the activation of postsynaptic D1, D3 and D4 receptors and specific serotonergic, noradrenergic, glutamatergic, GABAergic and muscarinic synapses.

4 Membrane currents of compartments are modulated by receptor activation

We have constructed a compartmental model that simulates the EEG signal generated in cortex using the neuronal simulation package NEURON (Hines, 1997). Five types of neurons are included in the model: In the cortex we include 100 pyramidal cells (Pinsky & Rinzel 1994), 10 basket cells and 10 Martinotti cells, and in the thalamus we include 4 thalamocortical cells and 4 reticular cells

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.



As an example, the serotonin receptor 5-HT4 couples 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 sum is over all types of ion conductances in each model compartment. The voltage-sensitive membrane conductances are calculated using activation and inactivation variables. The first order rate constants in the Hodgkin-Huxley formulation are dependent on the membrane potential, V, through empirical functions for each channel type.

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

5 Synaptic currents are modulated by receptors

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

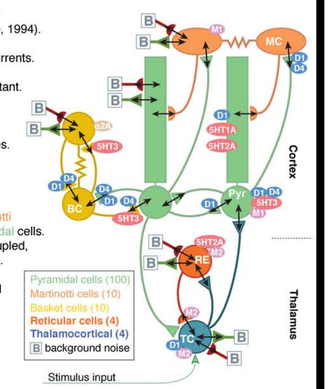
Excitatory synapses include both AMPA and NMDA currents. Parameters include maximal inward depolarizing conductance, rise time constant, and decay time constant.

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

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

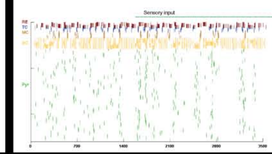
Pyramidal cells receive inhibitory inputs from all basket cells at the soma and from all Martinotti cells on the dendrite. The basket cells are connected with each other and to the Martinotti cells. The Martinotti cells receive excitatory inputs from a subset of pyramidal cells. Thalamocortical and reticular cells are reciprocally coupled, and the thalamocortical cells project to pyramidal cells.

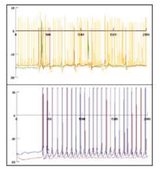
Each model neuron receives fluctuating excitatory and inhibitory currents to simulate background synaptic activity (Destexhe, 2001).



6 Network generates predicted neural activity

The model simulates the spiking activity of 100 pyamidal cells and 20 inhibitory interneurons in the micro-circuit of a cortical column and 8 neurons in the thalamus.

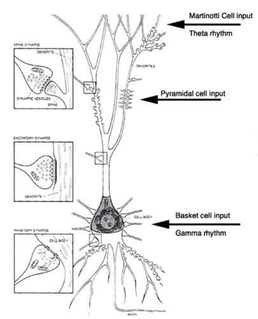




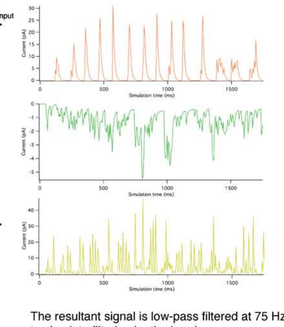
The spike raster (left) and membrane potentials of representative cells (right) show the interlocking rhythms of thalamocortical (alpha), basket (gamma) and Martinotti (theta) cells are imposed on slow firing pyramidal cells.

7 EEG is calculated from synaptic currents

We estimate the predicted EEG signal by using a forward model of EEG generation where the EEG is a weighted sum of the synaptic currents into the pyramidal cells. The weighting normalizes the layer-dependent effects of synaptic currents on scalp recordings and is calibrated using human EEG recordings.



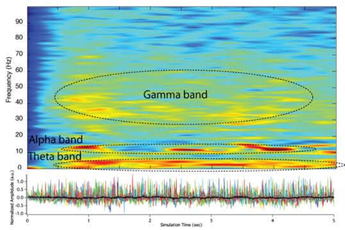
(Nunez, 1981)

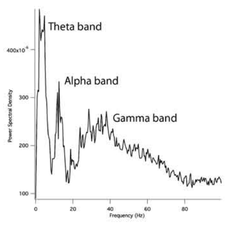


The resultant signal is low-pass filtered at 75 Hz to simulate filtering by the head.

8 Initial callibration for frequency of oscillations

The network paramaters such as average synaptic currents are initially tuned to generate the oscillatory dynamics of cortical circuits. Theta is the frequency band with the highest power in EEG and arises from interactions between pyramidal and Martinotti cells. Gamma band oscillations arise from synchronized fast-spiking inhibitory interneurons represented in our model by basket cells. Alpha band oscillations arise from activity in the thalamus and propagates to the cortex via thalamocortical cells.

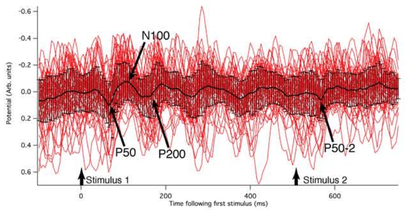




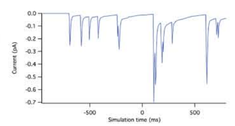
The computational model is a hybrid translational product that combines neurophysiological data from animal models and specific human pathology and genotype data with an explicit neurophysiology of relevant drug targets. We validate the model by assessing the correlation between the effects of known drugs on model network oscillations and their effects on EEG in clinical trials.

9 Evoked response potentials are used to further calibrate the model

Evoked responses are simulated by excitatory synaptic inputs to cortical neurons from a burst of spikes in thalamocortical neurons transmitted via AMPA and NMDA currents to represent sensory inputs.



Suppression of the second P50 response is caused by both cortical dynamics and a reduction of the second thalamocortical input current due to GABAB receptors in the thalamic circuit.



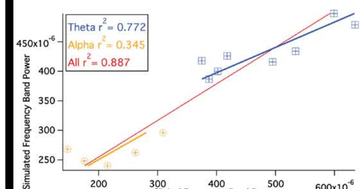
10 Schizophrenia pathology implemented in the cortical model

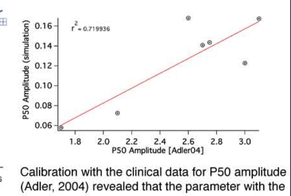
Schizophrenia pathology has been incorporated by

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

The magnitude of these pathologies are calibrated to match the change in EEG measure that is associated with the diseased state in clinical studies.

The parameters for each receptor (D1, 5-HT1A, etc) were varied to maximize the correlation with clinical measurements of theta and alpha band power and P50 amplitude.





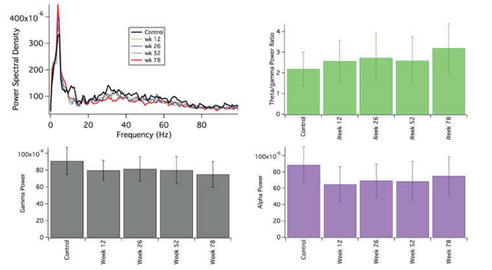
Calibration with the clinical data for P50 amplitude (Adler, 2004) revealed that the parameter with the strongest effect is the muscarinic receptors in the thalamus.

11 Implementation of pathology associated with Alzheimer's disease

The hallmark of Alzheimer's disease in the EEG signal is a "slowing" of the signal such that the high frequency power is decreased and the low frequency power is increased.

There are two mechanisms that we have implemented to represent Alzheimer's disease:

1. Deletion of pyramidal cells and excitatory synapses that increases over time.
2. Cholinergic deficit that affects the muscarinic receptors.

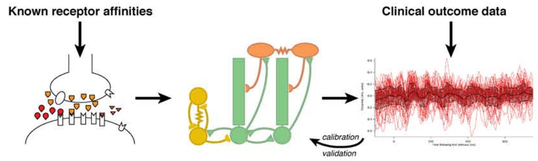


Power spectral density for simulation of longitudinal changes due to pathology of Alzheimer's disease demonstrates "slowing" of EEG as gamma is reduced and theta is increased over time.

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 compounds efficacy.

In addition to translational applications in drug development, the model may reveal mechanisms for clinical measures such as the thalamic M1 receptor source of the P50 responses observed in Adler, et al (2004).

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