A biophysically realistic computer model of Alzheimer pathology to guide the development of symptomatic drugs

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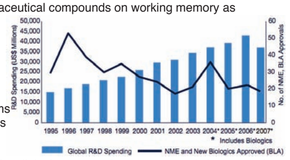
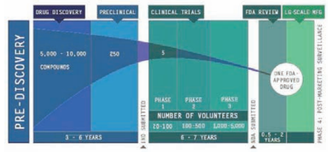
1 Introduction: Biomarkers and Drug Development

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.



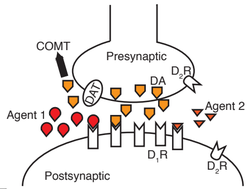
90% of CNS drugs fail in clinical trials.

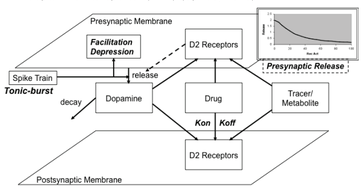
The high failure rate of drugs in clinical development is leading to an unsustainable business model for the pharmaceutical industry. One reason for this failure rate is the translational disconnect between the outcomes in preclinical animal models and the clinical equivalent.

2 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).





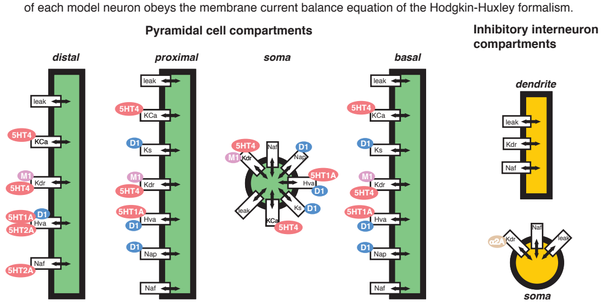
$$\frac{d}{dt}[D_n] = k_{on} \cdot [dop] \cdot [D_f] - k_{on} \cdot K_d \cdot [D_n]$$
$$\frac{d}{dt}[D_d] = k_{on} \cdot [drug] \cdot [D_f] - k_{on} \cdot K_d \cdot [D_d]$$
$$\frac{d}{dt}[D_m] = k_{on} \cdot [metabolite] \cdot [D_f] - k_{on} \cdot K_d \cdot [D_m]$$
$$\frac{d}{dt}[D_t] = k_{on} \cdot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

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

3 Compartemental model of cortical circuitry to represent functional activity

We have constructed a compartmental model that simulates working memory bursts generated in cortex using the neuronal simulation package NEURON (Hines, 1997). Two types of neurons are included in the model: 80 pyramidal cells and 40 inhibitory interneurons (Durstewitz, et al 1999).

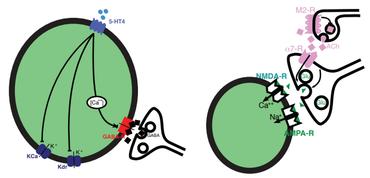
Each cell type is modeled with membrane conductances to simulate their functional role in the circuit, as well as the receptor activations due to the pharmacology that change the spiking activity. Each compartment of each model neuron obeys the membrane current balance equation of the Hodgkin-Huxley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

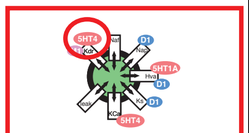


4 Membrane currents of compartments are modulated by receptor activation

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.

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

5 Synaptic currents are modulated by receptors

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

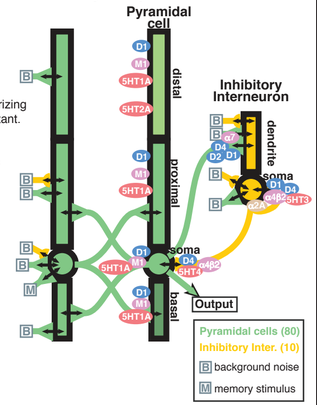
Excitatory synapses include both AMPA and NMDA currents. Parameters include: maximal inward depolarizing conductance, rise time constant, and decay time constant.

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

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

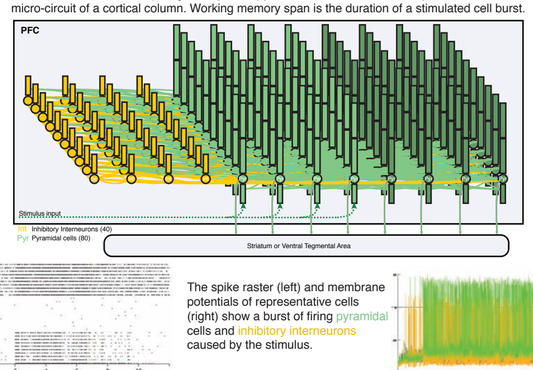
Pyramidal cells receive inhibitory inputs from inhibitory interneutons at the soma and are recurrently coupled through proximal and basal dendrites (Durstewitz, et al 1999)

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



6 Network generates working memory span

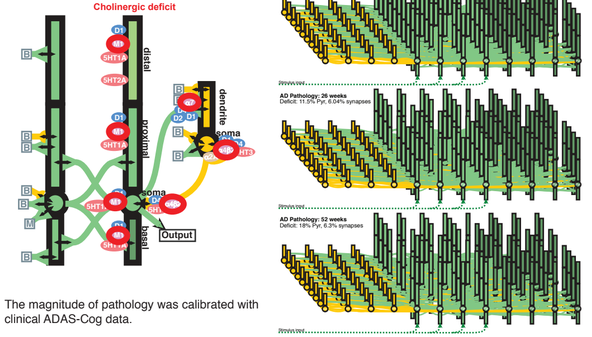
The model simulates the spiking activity of 80 pyramidal cells and 40 inhibitory interneurons in the micro-circuit of a cortical column. Working memory span is the duration of a stimulated cell burst.



The spike raster (left) and membrane potentials of representative cells (right) show a burst of firing pyramidal cells and inhibitory interneurons caused by the stimulus.

7 Implementation of pathology associated with Alzheimer's disease

We implemented the Alzheimer's disease pathology by reducing the cholinergic tone and removing pyramidal cells and synapses from the model.



The magnitude of pathology was calibrated with clinical ADAS-Cog data.

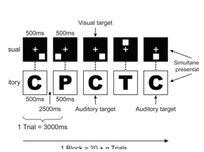
8 Implementation of pathology associated with schizophrenia

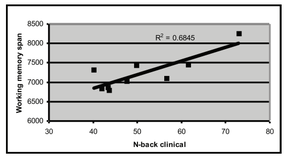
Schizophrenia pathology has been implemented by

1. Decreased the NMDA function (lower the maximum conductance) (Javitt, 1991)
2. Reduction in 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 magnitudes of these pathologies are calibrated to match the change in working memory 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 N-back working memory tasks under stable treatment by antipsychotic drugs.



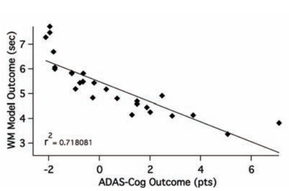


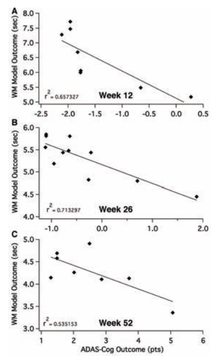
9 clinical interventions, 5 antipsychotics + COMT genotype (Weickert 2003, Bertolino 2004)

17 simulations are combined into 9 data points for calibration of receptor couplings.

9 Calibration of the Alzheimer's pathology

The parameters for the cholinergic deficit and rate of synaptic and neuronal loss was calibrated by comparing changes in the working memory span with the ADAS-Cog clinical scale.





Global correlation (above) between model output and ADAS-Cog outcomes from 28 different therapeutic interventions ($p<0.0001$).

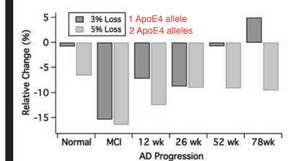
Because ADAS-Cog readouts monitor errors, positive values are associated with shorter working memory spans.

For individual time points (right) there is a good correlation between clinical outcome and corresponding computer model outcome.

10 Model validation and parameter value confirmation

Validation with ApoE4 Genotype

ApoE4 genotype causes additional synaptic loss and cholinergic tone decrease in the AD cortical network causing greater changes in working memory span.



The ApoE4 simulation suggest that the biggest negative effect of synaptic loss is observed in the early stages.

Free parameters

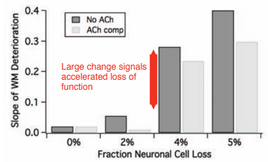
Name	Description	Biological Range	Optimal Value	Reference
Slope % Syn	Slope off raction of synapses disappearing/week	Max 0.075%/week, on top of neuronal loss	0.004	(DeKosky et al., 1996)
Slope % Neuron	Slope of neurons eliminated/week	Max 0.5%/week, leads to 50% neuron loss in 100 weeks	0.025	(Ji et al., 2003)
ACh deficit	Size of the cholinergic N Basalis deficit	Range 5-50% loss	0.175	(Davies and Maloney, 1976, Whitehouse et al., 1983)
5-HT6 e ffect	Relation between 5-HT6 inhibition and free DA, ACH and NE increase	Maximum 0.20	0.025	(Lacroix et al., 2004)
DA increase in 12 wk placebo	DA surge from reward circuit that simulates placebo effect	Maximal 20% (tracer displacement in volunteers)	0.075	(Boileau et al., 2007, Haltia et al., 2008)
Rel α7 vs. α4β2 nAch-R e ffect	Relative e ffect of α7 over α4β2 nAch-R mediated effects	Depends upon dose and nature of enhancement	Range 0.4-2.0	(Zhang et al., 2004)
ACh-E- e ffect on M_1 receptor activation	ACh-E- increases M_1 mAch-R activation level to make pyramidal cells more excitable	Maximal change in membrane resting potential -8 mV (depolarizing)	0.075 / 8 mg Gal or equiv	(Gulledge and Stuart, 2005)

List of 7 free parameters that were calibrated using the relation between clinical outcomes and working model outcomes. We report also the neurophysiological implementation and the biologically realistic boundaries, together with the value determined for the optimal correlation.

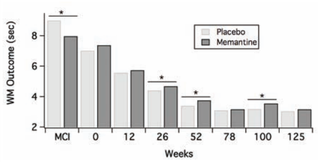
11 Alzheimer's disease stages and treatments

Slope of working memory loss (Δ WM-span/%deleted synapses) with increasing fractions of neuronal cell loss. From 4% the decrease in performance accelerates substantially.

Memantine (weak NMDA-inhibitor) is effective in late stages of AD. Reducing excitation of inhibitory interneurons restores excitatory/inhibitory balance.



Greater cholinergic compensation attenuates the decrease in working memory performance.

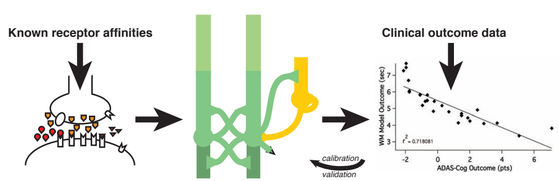


Both excitatory-excitatory (e-e) and excitatory-inhibitory (e-i) synaptic connections are eliminated at the same rate, but because there is an additional pyramidal cell loss, e-e synapses tend to decrease faster.

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 striatal function to predict the effects of pharmaceutical therapies for schizophrenia and Alzheimer's disease.