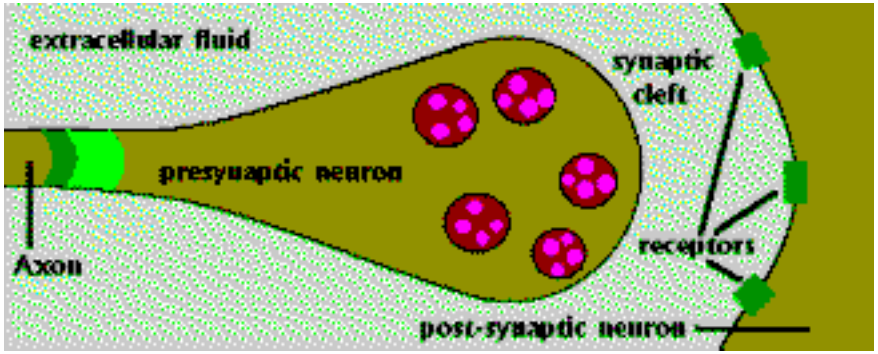
Processing of physiological signals by biochemical systems: emergence of high frequency waves from low frequency inputs in brain receptors.

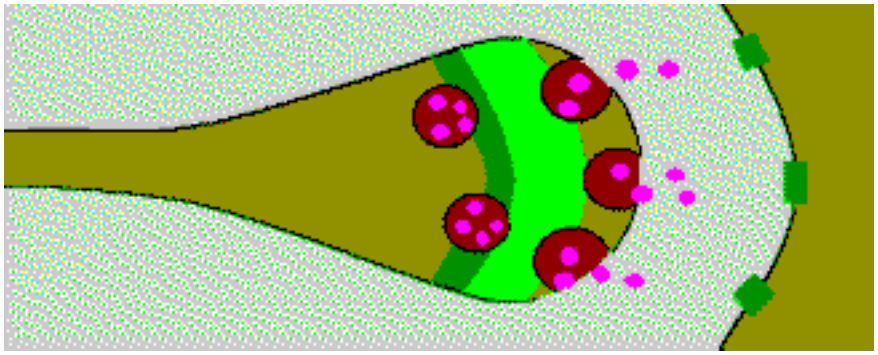
Sanjive Qazi, Parker-Hughes Cancer Center, Roseville, MN55113.

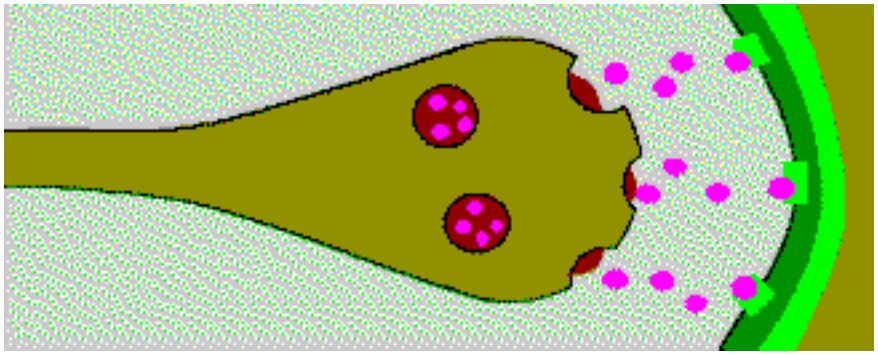
Temporal binding in the brain

How do large numbers of neurons in different areas of the brain communicate to coordinate complex activity ?

- Synchronous gamma oscillations across brain regions (30-100Hz) following sensory stimuli.
- Auditory responses includes brief "40 Hz transient responses", which increase when the subject pays attention and which disappear with loss of consciousness during anaesthesia [Kulli, J. and Koch, C., 1991, Trends Neurosci., 14, 6-10.].
- When people perform simple tasks, slow oscillations in the brain become coupled with the fast, high frequency-gamma oscillations in the same area. Under conditions when different brain areas oscillate together at the same low frequency and phase, the regions tune into the high-gamma oscillations and transfer information between them [Canolty et al., Science, 2006, 1626-8].
- Long-range synchronous oscillations can be generated by a feedback loop between inhibitory neurons in the cortex [Traub et al., 1996, Nature 382, 621-624].
- GABA is the main inhibitory transmitter in the brain.







http://www.fiu.edu/orgs/psych/psb_4003/figures/s_t.htm

Step 1. The neurotransmitter is manufactured by the neuron and stored in vesicles at the axon terminal.

Step 2. When the action potential reaches the axon terminal, it causes the vesicles to release the neurotransmitter molecules into the synaptic cleft.

Step 3. The neurotransmitter diffuses across the cleft and binds to receptors on the post-synaptic cell.

Step 4. The activated receptors cause changes in the activity of the post-synaptic neuron.

Frequency tuning properties of receptors.

- Slow brain oscillations, "tune in" the fast brain oscillations called high-gamma waves that signal the transmission of information between different areas of the brain.
- Slow frequencies synchronize long-range activity.
- High frequencies synchronize short range activity
- Inhibitory neurons required for high frequency waves.
- One intriguing possibility is that the receptors that gate inhibitory potentials may resonate at high frequencies when stimulated at low frequencies.
- This would provide a mechanism for the coupling of brain oscillations required for the coordination of complex tasks.
- Drugs that affect the tuning properties of receptors provides for a more specific mode of action for psycho-active compounds.

Modeling approach

- Transmitter molecules can directly gate ionic conductance through the activation of receptors. The Markov scheme can be represented by a set of bimolecular interactions and state transitions.
- Describe each bimolecular interaction as a function of time, initial ligand, receptor and bound ligand concentration. These functions are analytical solutions which make no assumptions about ligand depletion, and binding can be described during physiological responses.
- Simulate receptor transitions and bimolecular interactions by solving the set of **difference equations.**
- After each time iteration the level of agonist can be changed to any value. Therefore, the input signal can be simulated to include **variation in frequency and amplitude**.

K (On rate)

Receptor (x) + Ligand (y) $\rightleftharpoons$ **Bound ligand (z)**

L (Off rate)

$$\frac{\delta x}{\delta t} = -K \cdot x \cdot y + L \cdot z \qquad \frac{\delta y}{\delta t} = -K \cdot x \cdot y + L \cdot z \qquad \frac{\delta z}{\delta t} = K \cdot x \cdot y - L \cdot z$$

$$\frac{\delta x}{\delta t} = \frac{\delta y}{\delta t} \qquad \frac{\delta z}{\delta t} = -\frac{\delta y}{\delta t}$$

$$x = y - y_0 + x_0 \qquad z = y_0 - y + z_0$$

$$\frac{\delta y}{\delta t} = -K \cdot \left(y - y_0 + x_0\right) \cdot y + L \cdot \left(y_0 - y + z_0\right)$$

$$\frac{\delta y}{\delta t} = -K \cdot y^2 + \left(K \cdot y_0 - K \cdot x_0 - L\right) \cdot y + L \cdot y_0 + L \cdot z_0$$

$$\int \frac{1}{(y - y1) \cdot (y - y2)}\, dy = \int 1\, dt$$

$$y1 = \frac{\left[K \cdot \left(y_0 - x_0\right) - L\right] + \sqrt{\left[K \cdot \left(y_0 - x_0\right) - L\right]^2 + 4 \cdot K \cdot L \cdot y0}}{2 \cdot K}$$

$$y2 = \frac{\left[K \cdot \left(y_0 - x_0\right) - L\right] - \sqrt{\left[K \cdot \left(y_0 - x_0\right) - L\right]^2 + 4 \cdot K \cdot L \cdot y0}}{2 \cdot K}$$

$$y_t = \frac{y1 - \left\{y2 \cdot \frac{y_0 - y1}{y_0 - y2}\right\} \cdot e^{-K (y1 - y2)\, t}}{1 - \left\{\frac{y_0 - y1}{y_0 - y2}\right\} \cdot e^{-K \cdot (y1 - y2) \cdot t}}$$

Bound $z = y_0 - y_t$

Derivation of analytic functions.

K (On rate)

Receptor (R) + Ligand (N) ⇌ **Bound ligand (RN)**

L (Off rate)

$$\frac{dRN}{dt} = K\cdot\left(RN_0 - RN + N_0\right)\cdot\left(RN_0 - RN + R_0\right) - L\cdot RN$$

$$RN(t) = \frac{-\left[z2\cdot RN_0 - z2\cdot z1 - \exp(t\cdot a\cdot(z2 - z1))\cdot z1\cdot RN_0 + \exp(t\cdot a\cdot(z2 - z1))\cdot z1\cdot z2\right]}{\left[-RN_0 + z1 + \exp(t\cdot a\cdot(z2 - z1))\cdot RN_0 - \exp(t\cdot a\cdot(z2 - z1))\cdot z2\right]}$$

Kf (On rate)

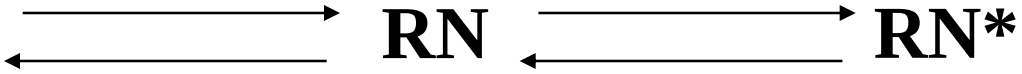
Receptor state 1 (R) ⇌ **Receptor state 2(RR)**

Kr (Off rate)

$$\frac{dRR}{dt} = Kf\cdot\left(R_0 - RR + RR_0\right) - Kr\cdot RR$$

$$RR(t) = \frac{-\left[-\exp(-t\cdot(Kf + Kr))\cdot Kr\cdot RR_0 + \exp(-t\cdot(Kf + Kr))\cdot Kf\cdot R_0 - Kf\cdot R_0 - Kf\cdot RR_0\right]}{(Kf + Kr)}$$

Solving of Difference equations



At time ‘t’; R_t N_t RN_t RN^*_t

R + N ⇌ RN1 (reaction 1) **RN1 = f (R_t, N_t, RN_t)**

RN* ⇌ RN2 (reaction 2) **RN2 = g (RN^*_t, RN_t)**

Change in RN from reaction 1 (RNa) = RN1 - RN_t

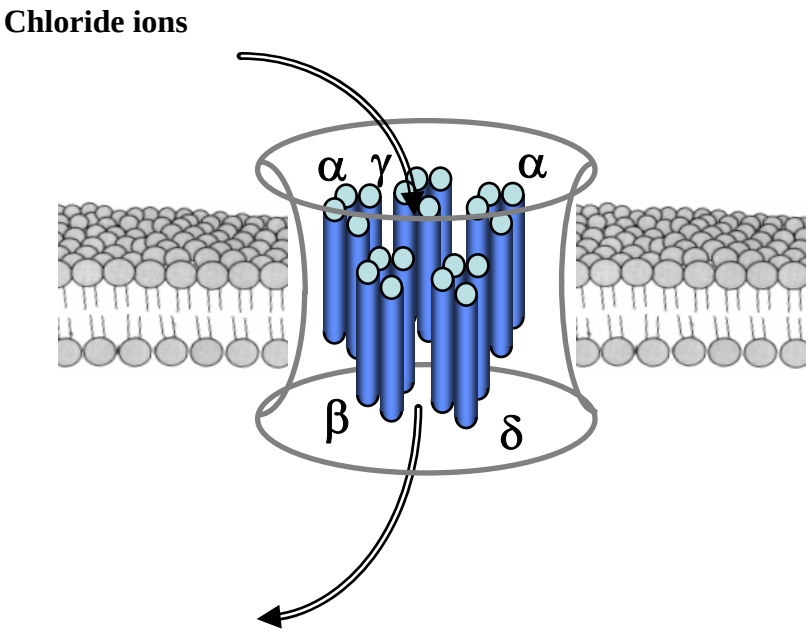
Change in RN from reaction 2 (RNb) = RN2 - RN_t

$RN_{t+1} = RN_t + RNa + RNb$ $RN^*_{t+1} = RN^*_t + RN2 - RN_t$

$R_{t+1} = R_t + RN1 - RN_t$ $N_{t+1} = N^*_t + RN1 - RN_t$

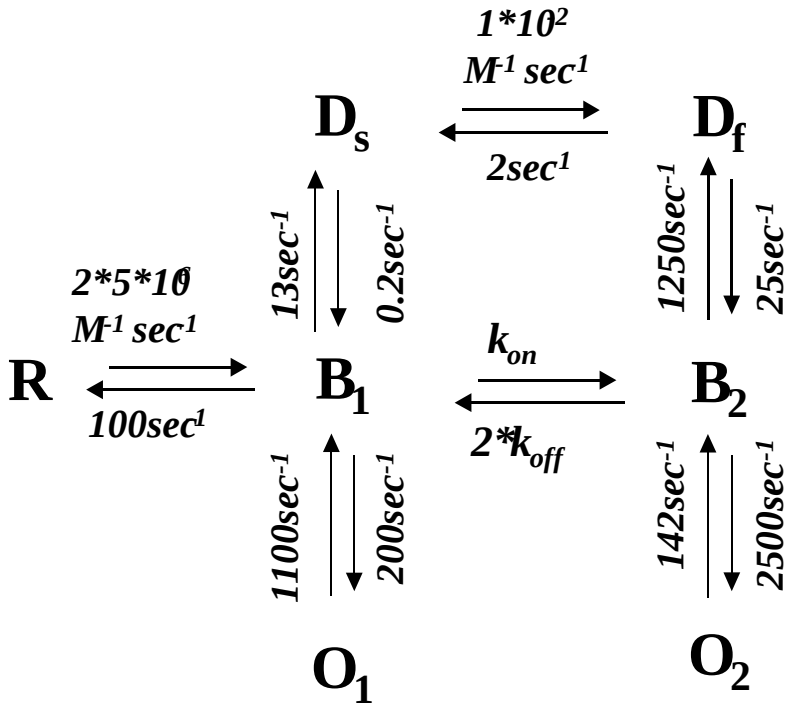
SIGNAL PROCESSING BY THE $GABA_A$ RECEPTOR

$GABA_A$ Receptor



The GABA receptor generates inhibitory potentials in many brain regions and its kinetic scheme has been very well described using patch clamp studies

Kinetic scheme for the $GABA_A$ receptor



Jones *et al*, 1998, *J. Neurosci*, **18**:8590

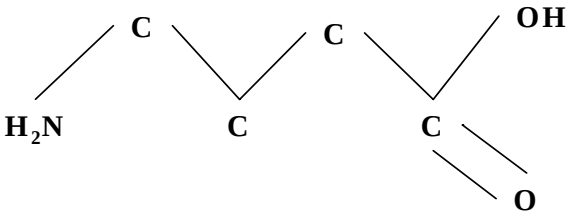
$B_{1/2}$: Bound states
$D_{s/f}$: Desensitized states
$O_{1/2}$: Open states

For GABA activation
k_{on} = 5*10^6 M^{-1} sec^{-1}
k_{off} = 131 sec^{-1}.
d2 = 1250 sec^{-1}.

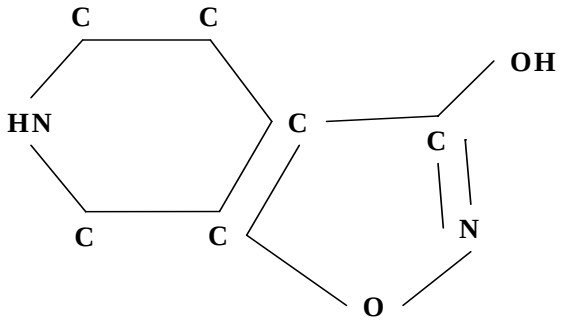
The response to the pulse addition of THIP was also simulated. In this simulation the k_{off} rate was adjusted to 1125 sec^{-1}.

The response to GABA in the presence of an antagonists, pregnenolone (d2 = 4750 sec^{-1}), were also simulated [Shen et al J Neurosci, 2000, 20: p. 3571-9].

GABA



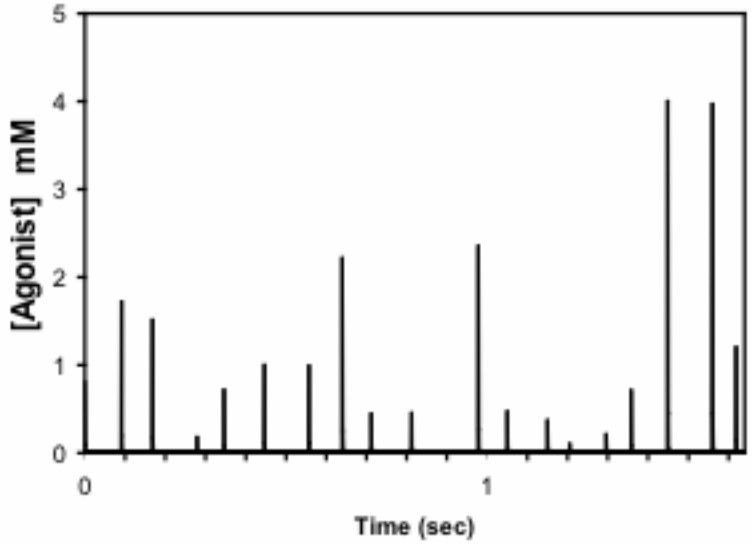
THIP



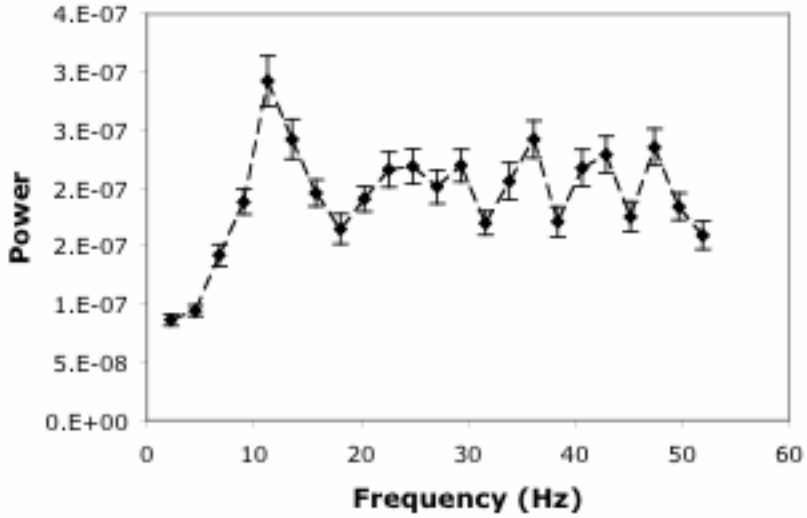
MODELING OBJECTIVES

- Model the processing of frequency information by the GABA receptor when stimulated by different agonists (GABA k_{off} = 131 sec^{-1}; THIP k_{off} = 1125 sec^{-1}).
- Simulate the response of the receptor to a noisy, Poisson distributed, set of agonist pulses.
  - Simulate a noisy train of agonist that better resemble physiological conditions.
  - Measure the linear dependence of the response on the input signal using coherence functions. Values of 1 in the coherence function indicate that the input and the response have strong noise free components in that frequency band. Signal to noise ratio is coherence/(1-coherence).
  - Compare the effects of two agonists (THIP and GABA) and the effect of an antagonist on the GABA response (Pregnenolone).

Simulation of noisy pulsatile release of agonist



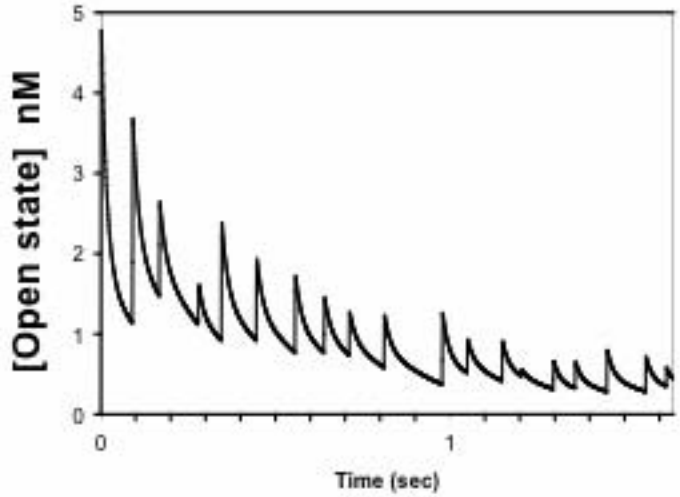
Simulated GABA pulses. Instantaneous release between 1 and 5mM (white noise distribution) over 1.6384 seconds.



The pulses were Poisson distributed with mean frequency of 10Hz. The power of the response at frequency bands of up to 50 Hz was measured for 49 simulations (± SEM).

GABA

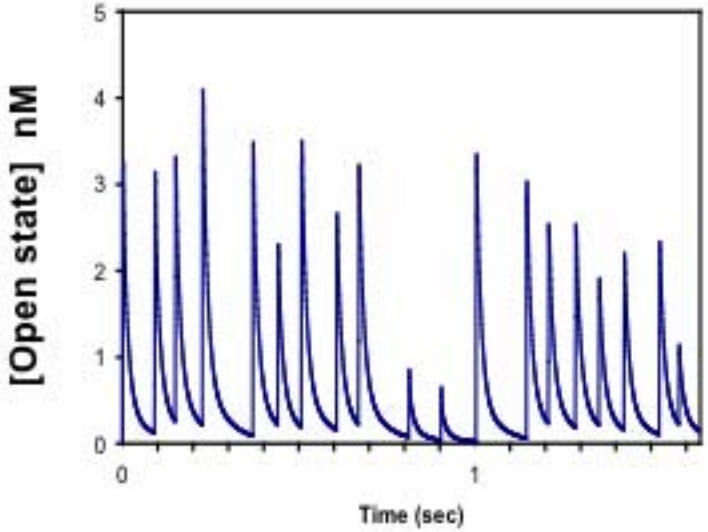
(k_{off} = 131 sec^{-1}, d2 = 1250 sec^{-1})



Receptor Response

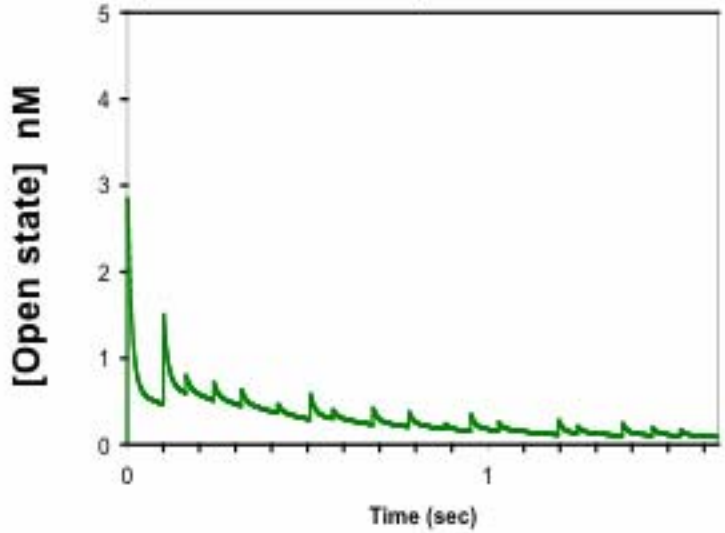
THIP

(k_{off} = 1125 sec^{-1})



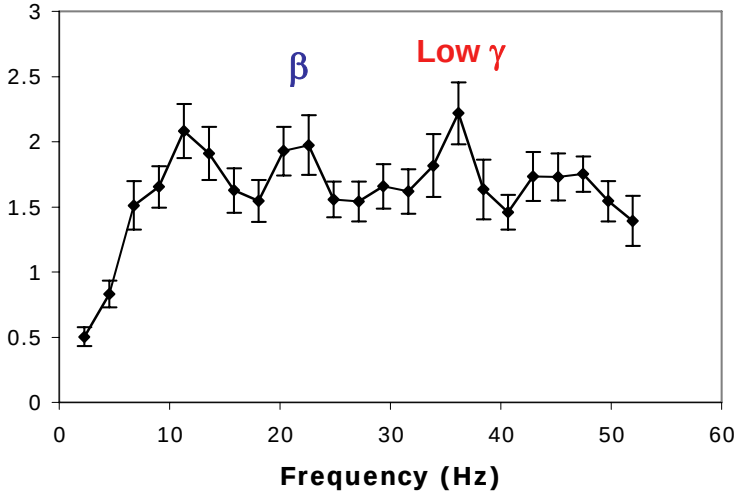
GABA + Pregnenolone

(d2 = 4750 sec^{-1})



GABA

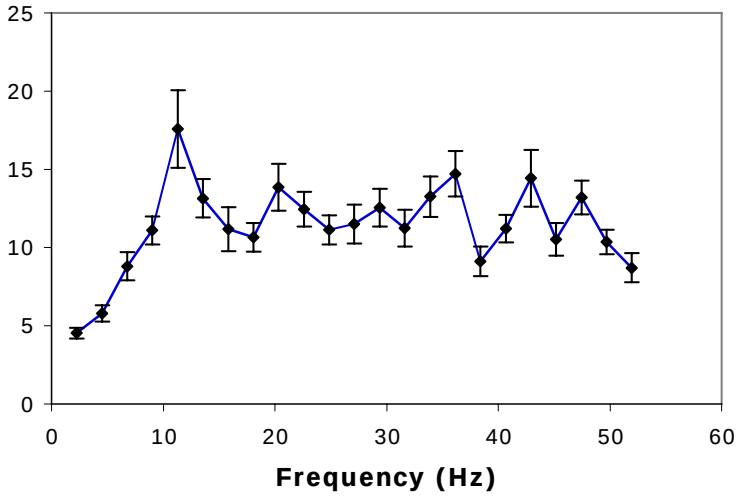
(k_{off} = 131 sec^{-1}, d2 = 1250 sec^{-1})



Signal to Noise Ratio

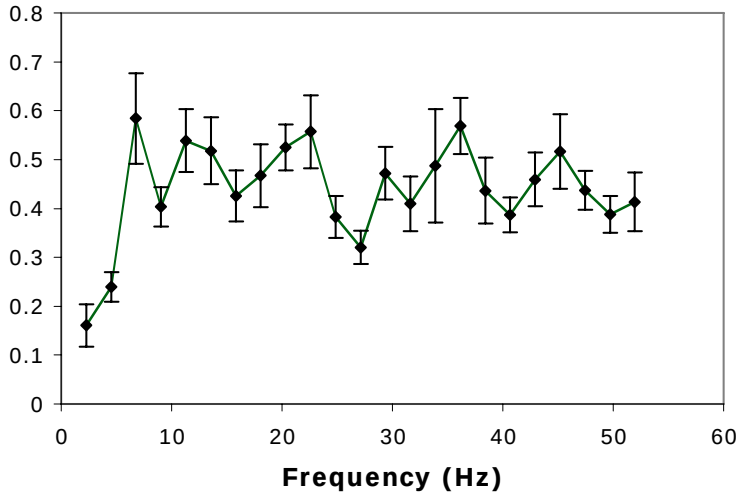
THIP

(k_{off} = 1125 sec^{-1})



GABA + Pregnenolone

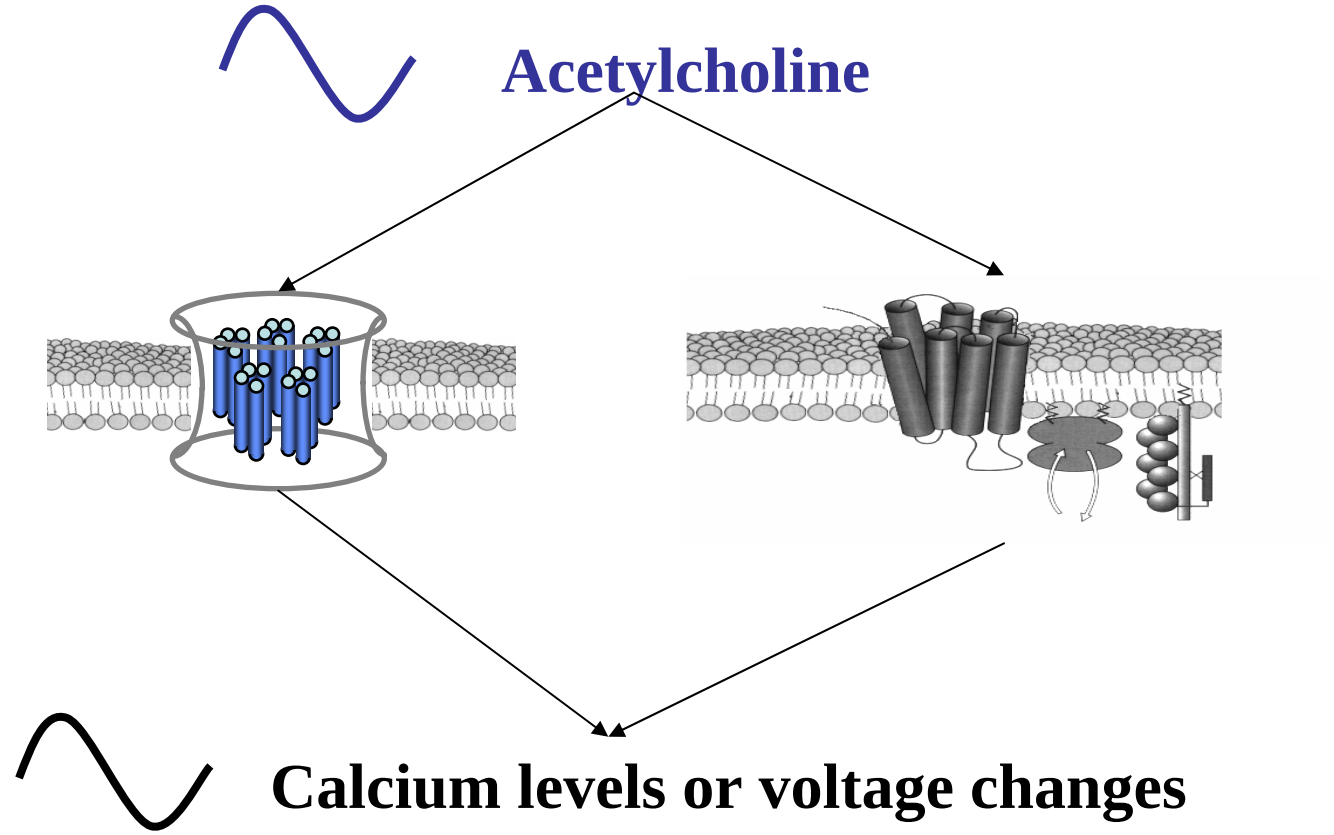
(d2 = 4750 sec^{-1})



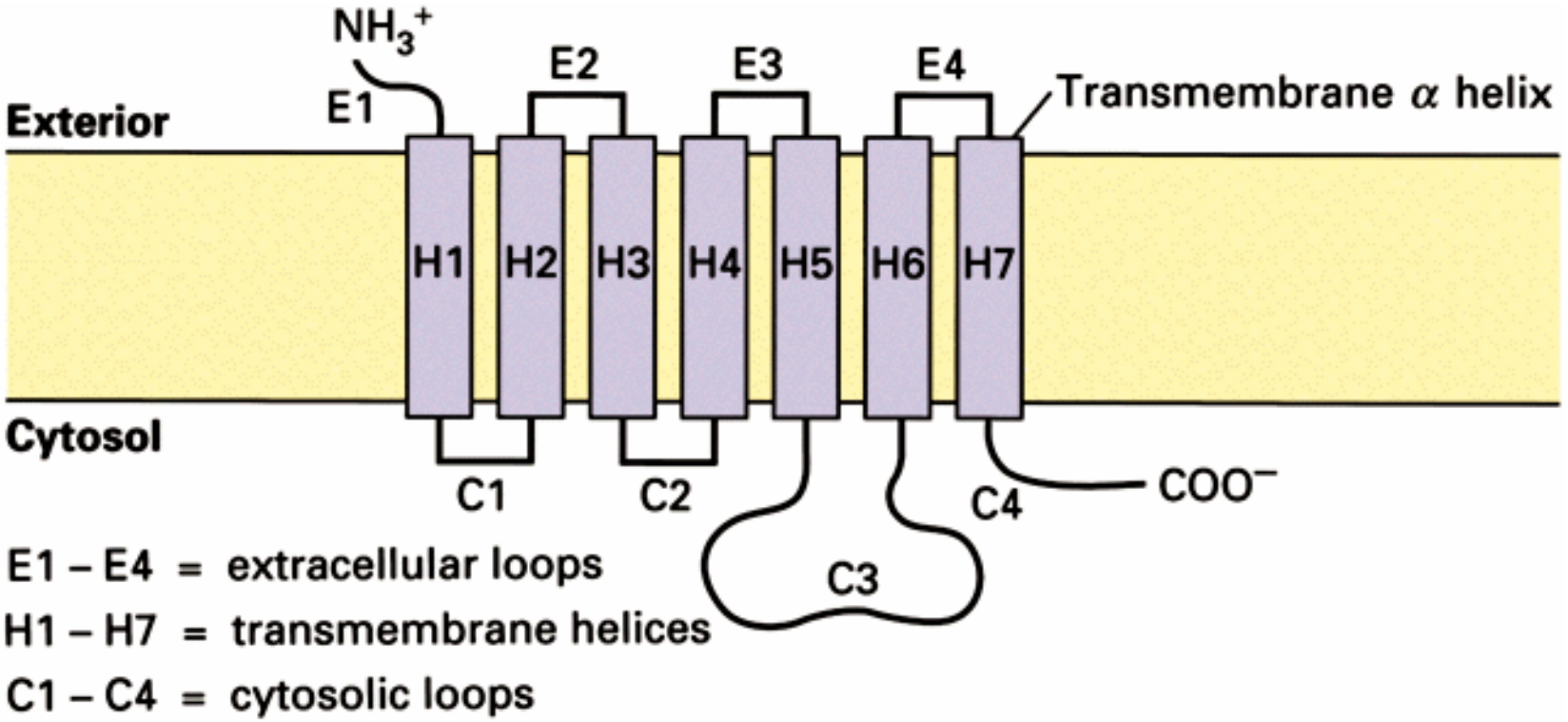
Summary.

- Stimulation with GABA at 10Hz generates two additional frequencies at 20 and 36 Hz.
- Addition of an antagonist, pregnenolone, reduces the signal to noise ratios below 1 at all frequencies.
- Stimulation with an agonist, THIP, increases signal to noise ratios at all frequencies, but the 20Hz and 36Hz frequencies are below that of 10 Hz band.
- Recent studies suggest higher cognitive 'awareness' effects using THIP. Drasbek KR, Jensen K., 2006, 'THIP, a hypnotic and antinociceptive drug, enhances an extrasynaptic GABAA receptor-mediated conductance in mouse neocortex.' Cereb Cortex, 1134-41. Winsky-Sommerer R, Vyazovskiy VV, Homanics GE, Tobler I., 2007, 'The EEG effects of THIP (Gaboxadol) on sleep and waking are mediated by the GABA(A)delta-subunit-containing receptors.' Eur J Neurosci., 25:1893-9.

MODELING MULTIPLE, INTERACTING SIGNAL TRANSDUCTION PATHWAYS:
Determining input output relationships in signaling networks

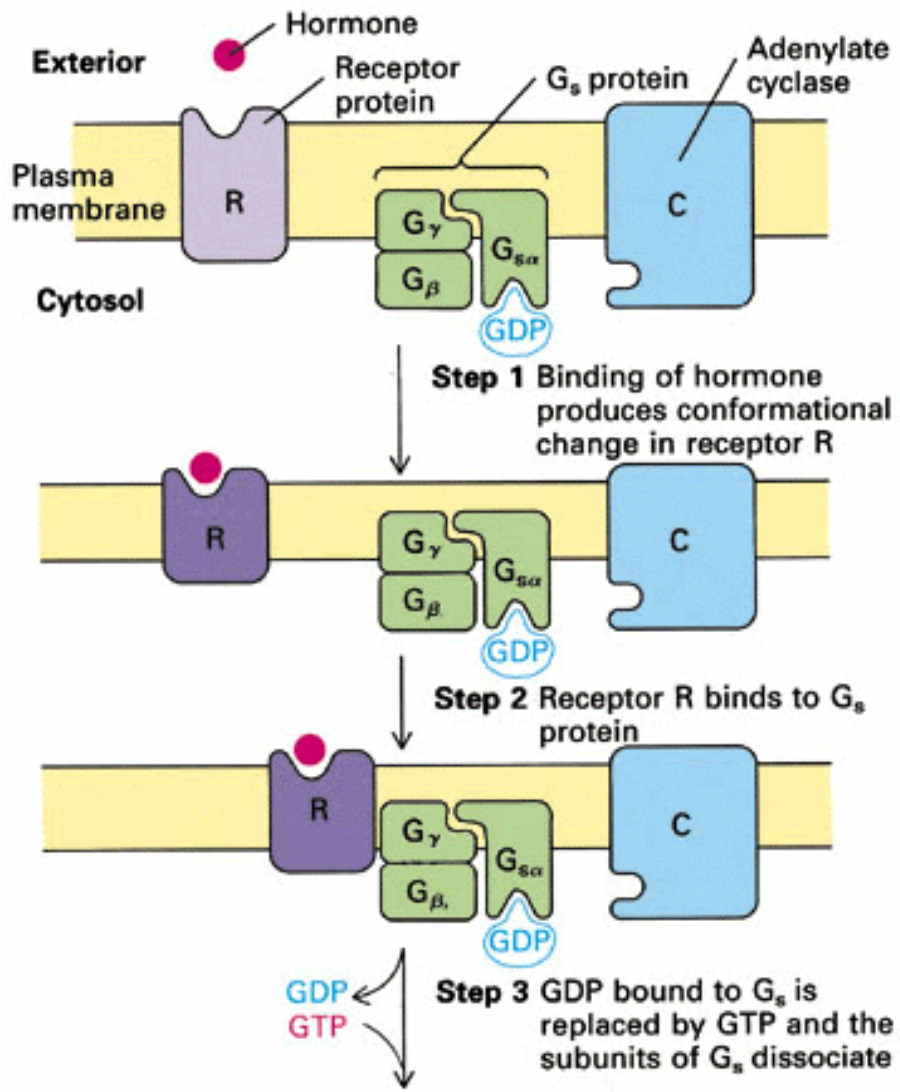


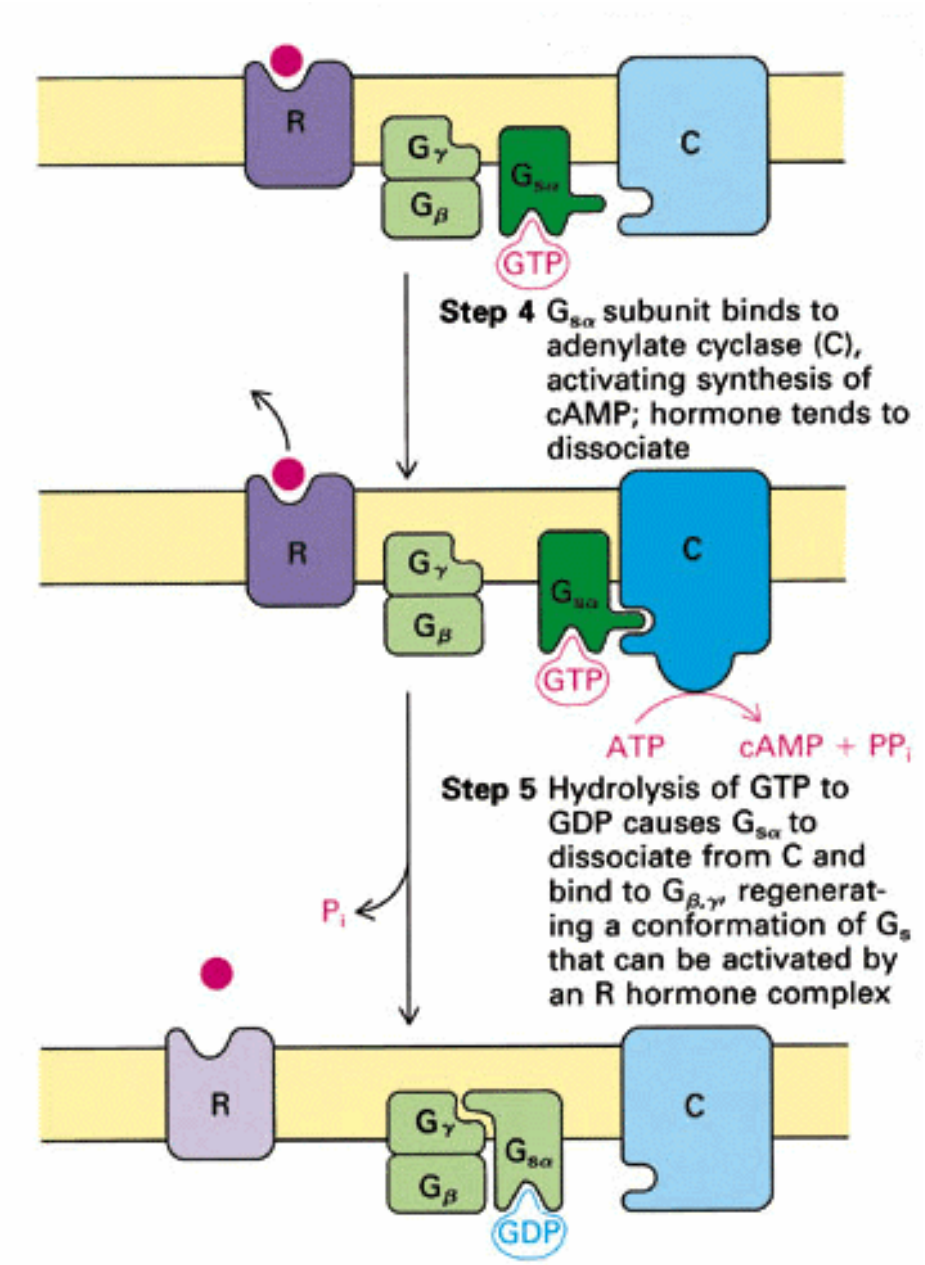
Future Work: Modeling signal transduction pathways.



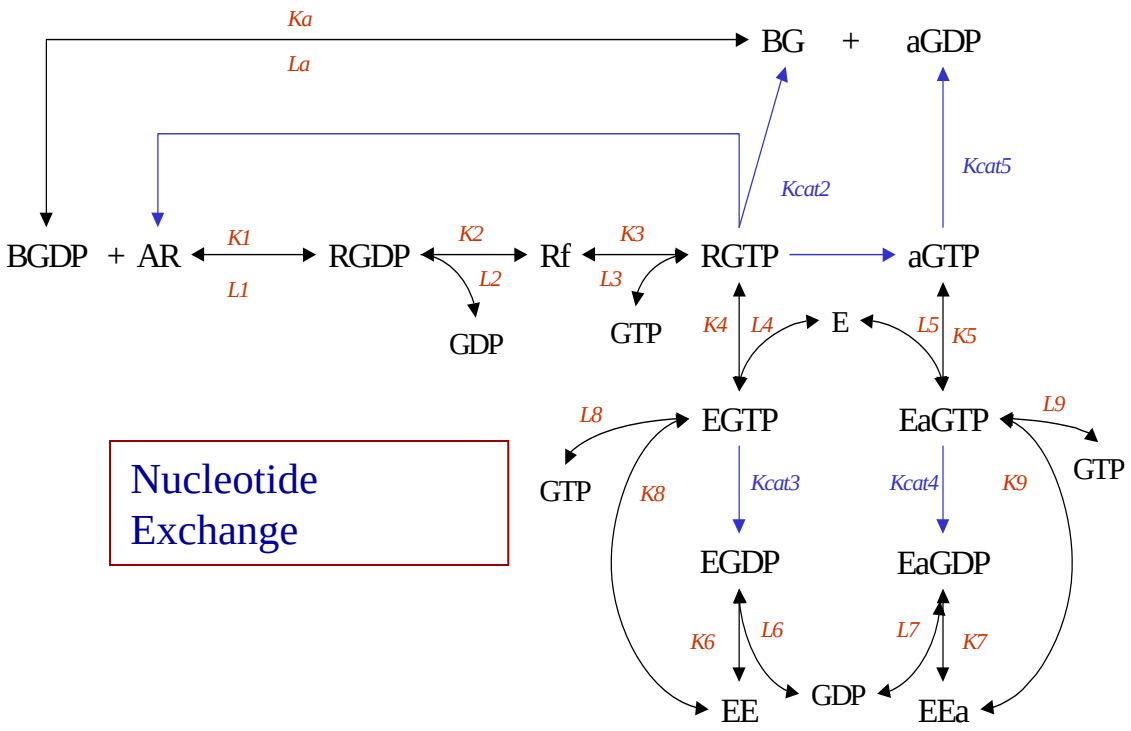
www.pharmacy.ohio-state.edu/homepage/courses/ph410/receptor-3.ppt

Activation pathway of G-protein coupled receptors.




R
G_γ
G_β
$G_{s\alpha}$
C
GTP
Step 4 $G_{s\alpha}$ subunit binds to adenylate cyclase (C), activating synthesis of cAMP; hormone tends to dissociate
R
G_γ
G_β
$G_{s\alpha}$
C
GTP
ATP
cAMP + PP_i
Step 5 Hydrolysis of GTP to GDP causes $G_{s\alpha}$ to dissociate from C and bind to $G_{\beta,\gamma}$, regenerating a conformation of G_s that can be activated by an R hormone complex
P_i
R
G_γ
G_β
$G_{s\alpha}$
C
GDP

MODELING G-PROTEIN INTERACTIONS TO INCLUDE NUCLEOTIDE EXCHANGE AND G-PROTEIN ACTIVATING PROTEINS



Nucleotide Exchange

AR : Agonist receptor complex
BGDP: GDP bound G-protein
E: Phospholiase C
αGTP: GTP bound α subunit

Slow loop | Fast loop

Model the activation of phospholipase C (PLC) by G-proteins.

Investigate the role of the fast and slow nucleotide exchange reactions in the activation of PLC

Simulate complex input signals (change in levels of AR) and examine information flow through the network.