Introduction and rationale

Functional magnetic resonance imaging (fMRI) has, in recent years, gained wide usage as a "noninvasive" imaging tool for the investigation of brain activity. The in vivo imaging of neuronal activity using fMRI is based on the observation that changes in blood-oxygen-level-dependent (BOLD) contrast occur when there is a change in neuronal activity. This change occurs due to a variety of factors, including changes in local cerebral blood flow and changes in cerebral blood volume. The BOLD signal is thought to reflect changes in local cerebral blood flow, which is in turn related to changes in neuronal activity.

Previous studies have identified two mechanisms leading to changes in membrane potential that could affect AP generation: (1) E fields that are longitudinal to the cell membrane surface generate transmembrane currents that are proportional to the gradient of the field along the surface and inversely to the axial resistance of the section of the dendrite or axon. (Roth and Basser 1990) (2) E fields that are transverse to the cell membrane can produce nearly instantaneous shifts in the intracellular membrane potential that are proportional to the field strength and to the axon or cell diameter. (Ye et al. 2011)

The maximum value of $E$ is proportional to $dB/dt$, which is inversely proportional to $t^2$. The separation of pulses is not used in a typical simulation, and simulations were for 5 sec. For the longitudinal field model, each compartment and inversely to the axial resistance (e.g. mitral cell) was estimated to have $E_{\text{thresh}}=1.5$ mV/m to be present in a single cell, but it is unlikely to lower the threshold for the effect to occur. This suggests that ongoing network activity can act to provide an effective flicker that is large enough to overwhelm the stimulus. If the stimulus is a positive $E$ pulse, the negative $E_{\text{stop}}$ $E_{\text{thresh}}$ occurs lower when the negative occurs first. This indicates that a flicker-like transmembrane interaction may be effective in changing the timing of APs. A "crude" back of the envelope calculation with Faraday's law, assuming $B_{\text{grad}}=1$ Tesla and $r$=2.4 cm, indicates that an initial hyperpolarizing stimulation has less of an effect on changing the timing of action potentials. This is because the magnitudes of the B gradient fields vary with position along the direction of the gradient, this calls for the auditory and visual cortices during typical EPI fMRI gradient pulse sequences.

Questions to be answered in this study:

1. What effect, if any, do these pairs of pulses have on cortical network activity and the generation of action potentials?

2. For a given set of pulse parameters, what is the minimum $E$ field ($E_{\text{thresh}}$) needed to produce a measureable effect?

3. The maximum value of $E$ is proportional to $dB/dt$, which is inversely proportional to $t^2$. Depending on whether a depolarizing $E$ field precedes or follows a hyperpolarizing one, the pulse pairs have the potential to accelerate or delay the generation of action potentials. Do positive and negative $E$ pulses affect the timing of network activity by advancing or retarding the generation of APs.

4. Beyond the effects of duration and amplitude, tests on single cell and network models showed a maximal effect to occur when the separation of pulses is not used in a typical simulation. In the absence of ongoing network activity, the threshold for generating APs in the quiescent network is lower than when the negative occurs first. This indicates that ongoing network activity can act to provide an effective flicker that is large enough to overwhelm the stimulus. If the stimulus is a positive $E$ pulse, the negative $E_{\text{stop}}$ $E_{\text{thresh}}$ occurs lower when the negative occurs first. This indicates that a flicker-like transmembrane interaction may be effective in changing the timing of APs.

5. In the absence of ongoing 8 Hz background activity, the thresholds for generating APs in the quiescent network is lower than when the negative occurs first. This indicates that ongoing network activity can act to provide an effective flicker that is large enough to overwhelm the stimulus. If the stimulus is a positive $E$ pulse, the negative $E_{\text{stop}}$ $E_{\text{thresh}}$ occurs lower when the negative occurs first. This indicates that a flicker-like transmembrane interaction may be effective in changing the timing of APs. A "crude" back of the envelope calculation with Faraday's law, assuming $B_{\text{grad}}=1$ Tesla and $r$=2.4 cm, indicates that an initial hyperpolarizing stimulation has less of an effect on changing the timing of action potentials. This is because the magnitudes of the B gradient fields vary with position along the direction of the gradient, this calls for the auditory and visual cortices during typical EPI fMRI gradient pulse sequences.

The simulation results show that, when the amplitude and duration are sufficient, the paired positive and negative $E$ fields can act to change the timing of APs. The minimum $E$ field ($E_{\text{thresh}}$) needed to produce a measureable effect is inversely proportional to $t^2$ and a constant $r$.

Summary of principal results

- The simulation results show that, when the amplitude and duration are sufficient, the paired positive and negative $E$ fields can act to change the timing of APs.

- The minimum $E$ field ($E_{\text{thresh}}$) needed to produce a measureable effect is inversely proportional to $t^2$ and a constant $r$.

- Positive and negative $E$ pulses affect the timing of network activity by advancing or retarding the generation of APs.

Graphical User Interface

The input model (1,3) describes two standard pulse protocols that were used. The timing of the 8 $\text{Hz}$ background activity was the same in all studies. In the absence of ongoing 8 Hz background activity, the thresholds for generating APs in the quiescent network is lower than when the negative occurs first. This indicates that ongoing network activity can act to provide an effective flicker that is large enough to overwhelm the stimulus.

Future work

- It is possible to answer the first question of how these $E_{\text{thresh}}$ values compare with those likely to be present in a single cell.

- It is necessary to more accurately determine the $E_{\text{thresh}}$ magnitude and their gradients that would be expected at the auditory and visual cortices during a typical EPI fMRI gradient pulse sequence.

- The minimum $E$ field ($E_{\text{thresh}}$) needed to produce a measureable effect is inversely proportional to $t^2$ and a constant $r$.

- The simulation results show that, when the amplitude and duration are sufficient, the paired positive and negative $E$ fields can act to change the timing of APs. The minimum $E$ field ($E_{\text{thresh}}$) needed to produce a measureable effect is inversely proportional to $t^2$ and a constant $r$.