Improvements on a Linear Controller for Seizure Suppression in a Human Cortical Model

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Outline

• Model Summary
• Dynamics of the model
• Original seizure suppression controller
• Modified seizure suppression controller
• Conclusions and areas for future research
Model Overview – Anatomical

- Two columns of cortical neurons interconnected
  - Excitatory (pyramidal)
  - Inhibitory
- Diameter ~0.3–1 mm
- Depth ~2-3 mm

Figure Credit: Steyn-Ross, et. al. PHYSICAL REVIEW E 60(6) 7299(13).
Model Overview - Analytical

- Model originally developed to model EEG response during anesthesia.
- EEG is aggregate current flow across the surface of the cortex – in this model “h_e”.
- Experimentation showed that the model could also be used in seizure research [1,2].

Figure Credit: Bojak and Liley. PHYSICAL REVIEW E 71, 041902 r2005d
Model Equations

• Steyn-Ross 1999 model consists of 14 stochastic partial DEs with 29 parameters [1]
  – Cumbersome to solve
  – What parameter values are physiologically valid

• Bojak 2005 used Monte-Carlo type simulation to determine >70,000 parameter sets that fit physical data [3]
  – Still 29 dimensional parameters and SPDEs

• Kramer 2006 approximated model with 14 ODEs and 20 parameters through dimensional analysis [4]
Model Implementation

d\text{He}/dt = 1 - \text{He} + \gamma_e (\text{hoe} - \text{He}) \text{Iee} + \gamma_i (\text{hoi} - \text{He}) \text{Iie}

d\text{Hi}/dt = 1 - \text{Hi} + \gamma_e (\text{hoe} - \text{Hi}) \text{Iei} + \gamma_i (\text{hoi} - \text{Hi}) \text{Iii}

d\text{Iee}/dt = \text{Jee}

d\text{Jee}/dt = (-2 \tau_e \text{Jee} - \tau_e^2 \text{Iee} + \tau_e^2 (\eta \beta_e \text{sehe}(\text{He}) + \phi_e + \rho_e))

d\text{Iei}/dt = \text{Jei}

d\text{Jei}/dt = (-2 \tau_e \text{Jei} - \tau_e^2 \text{Iei} + \tau_e^2 (\eta \beta_e \text{sehe}(\text{He}) + \phi_i + \rho_i))

d\text{Iie}/dt = \text{Jie}

d\text{Jie}/dt = (-2 \tau_i \text{Jie} - \tau_i^2 \text{Iie} + \tau_i^2 (\eta \beta_i \text{sihi}(\text{Hi}) + \phi_e + \rho_i))

d\text{Iii}/dt = \text{Jii}

d\text{Jii}/dt = (-2 \tau_i \text{Jii} - \tau_i^2 \text{Iii} + \tau_i^2 (\eta \beta_i \text{sihi}(\text{Hi}) + \phi_i + \rho_i))

d\text{Psie}/dt = \text{Psie}

d\text{Psie}/dt = (-2 \lambda_e \text{Psie} - \lambda_e^2 \phi_e + \lambda_e \eta \beta_e \text{diffsehe}(\text{He}) + \lambda_e^2 \eta \beta_e \text{sehe}(\text{He}))

d\text{Psii}/dt = \text{Psii}

d\text{Psii}/dt = (-2 \lambda_i \text{Psii} - \lambda_i^2 \phi_i + \lambda_i \eta \beta_i \text{diffsehe}(\text{He}) + \lambda_i^2 \eta \beta_i \text{sehe}(\text{He}))

\text{sehe}(\text{He}) = 1 / (1 + \exp(-\text{ge}(\text{He} - \text{thetae})))

\text{sihi}(\text{Hi}) = 1 / (1 + \exp(-\text{gi}(\text{Hi} - \text{thetai})))

\text{diffsehe}(\text{He}) = 0 \times \text{He}
Model Implementation

- Model parameters from [4]
- Kramer notes that the parameters were verified as within normal physiological values per [3]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Seizure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>gammae</td>
<td>1.42E-03</td>
<td>1.30E-03</td>
<td>Influence of inputs on mean soma membran potential</td>
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<td>gammiai</td>
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<td>0.0774000</td>
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<tr>
<td>hoe</td>
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<td>-0.643000</td>
<td>Cell reversal potential</td>
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<tr>
<td>hoi</td>
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<td>1.290000</td>
<td></td>
</tr>
<tr>
<td>te</td>
<td>12</td>
<td>12.00</td>
<td>Neurotransmitter rate constant</td>
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<tr>
<td>ti</td>
<td>2.6</td>
<td>2.60</td>
<td></td>
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<tr>
<td>lambdae</td>
<td>11.2</td>
<td>11.20</td>
<td>Corticocortical length</td>
</tr>
<tr>
<td>lambdai</td>
<td>18.2</td>
<td>18.20</td>
<td></td>
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<tr>
<td>pee</td>
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<td>548.07</td>
<td>Subcortical inputs</td>
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<td>16.00</td>
<td></td>
</tr>
<tr>
<td>pei</td>
<td>16</td>
<td>16.00</td>
<td></td>
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<tr>
<td>pii</td>
<td>11</td>
<td>11.00</td>
<td></td>
</tr>
<tr>
<td>nalphae</td>
<td>4000</td>
<td>4000.00</td>
<td>Total distant synaptic connections</td>
</tr>
<tr>
<td>nalphi</td>
<td>2000</td>
<td>2000.00</td>
<td></td>
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<tr>
<td>nbetae</td>
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<td>3034.00</td>
<td>Total local synaptic connections</td>
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<td>536.00</td>
<td></td>
</tr>
<tr>
<td>ge</td>
<td>-19.6</td>
<td>-19.600</td>
<td>Transfer function (sigmoid slope)</td>
</tr>
<tr>
<td>gi</td>
<td>-9.8</td>
<td>-9.800</td>
<td></td>
</tr>
<tr>
<td>thetai</td>
<td>0.857</td>
<td>0.857</td>
<td>Transfer function (inflection point)</td>
</tr>
<tr>
<td>thetai</td>
<td>0.857</td>
<td>0.857</td>
<td></td>
</tr>
</tbody>
</table>

Subscript e = excitatory, i = inhibitory
Model Simulation

- XPP used to solve system of equations
- Data from XPP at various parameter values stored for generation of bifurcation diagrams
- Model simulation consistent with dynamics from Kramer in [4]
Top = Kramer [4], Bottom = XPP Simulation

Bifurcation Diagram of He vs. gammae

he (mV) vs. time (s)
Making the model have a Seizure

- Model parameters adjusted so that $\gamma_e$ was slightly less than its value at bifurcation
- Impulse function used in XPP to perturb the model and induce a seizure
- 40ms duration, 70mV amplitude
Seizure Suppression

- Kramer illustrates a linear gain controller capable of controlling seizures (n.b he also evaluated several other controllers)
  - He also demonstrated that application of this type of linear controller works at reducing seizure like activity in rat hippocampal slices in vitro.
- The controller works by applying negative gain to He (-1.97 used as gain) [4]

\[
\frac{dH_e}{dt} = 1 - H_e + \gamma_{ae}(H_{oe} - H_e)I_{ee} + \gamma_{ai}(H_{oi} - H_e)I_{ie} + H_e\cdot\text{hegain}
\]

\[
\frac{dH_i}{dt} = 1 - H_i + \gamma_{ae}(H_{oe} - H_i)I_{ei} + \gamma_{ai}(H_{oi} - H_i)I_{ei} + H_i\cdot\text{hgain}
\]
Kramer linear He controller

- He gain method controls seizures at correct tunings; but induces seizures at insufficient negative gain.
- Could present a problem in application
Kramer linear He controller

- He gain method effects cortical activity even if there is no seizure
  - Cortical activity should be unaffected unless prevention of a seizure is required
- Both graphs are at the same “non-seizure” parameters
  - Left = hegain = -1.97 without seizure
  - Right = no controller
  - Normal he level reduced from 1.2 to 0.7
Why normal dynamics are effected

- Since the He is multiplied by a factor (hegain) and added back to He, if He varies with other parameters during normal behavior, the controller will effect normal dynamics.
- Solution: Find a parameter to use for gain that does not vary significantly with parameter values unless there is a seizure.
  - Gain or offset can be chosen to limit effects on dynamics during normal behavior.

\[
\frac{dHe}{dt} = 1 - He + gammae(hoe-He)*lee + gammai(hoi-He)*lie + He*hegain
\]
Finding a new parameter...

- $\Psi_e$ has almost zero slope with changing $\gamma_e$
- $\Psi_e$ is the derivative of excitatory input from outside the modeled column
Psie as a seizure suppression controller

• ODE for He modified to include Psie as a linear controller with gain

\[ \frac{dHe}{dt} = 1 - He + \gammae(eo - He)\alphae + \gammai(oi - He)\alii + psiegain*Psie \]

• Same method used to test this controller as was used for the controller developed by Kramer [4]
Psie based controller

- Psie controller works very well at very low and positive gain (why?!)

![Graphs showing different gain settings for Psie controller](image)
Psie based controller – closer look

- Figure is Psie scaled and translated to similar scale with He
- Psie is out of phase with He
  - Allows gain to be positive
- But does Psie control effect base dynamics?
Comparison of control types

- Psie control does not change the dynamics of the system unless a seizure event occurs.
- Psie control value cannot induce a seizure.
- Better for clinical application.

\[ \text{hegain} = -1.97 \]

\[ \text{psiegain} = 1 \times 10^{-3} \]
Conclusions and Future Research

• A model was implemented to simulate cortical activity during a seizure
• The model exhibited the behavior consistent with the literature
• A previously reported controller (He gain, [4]) was implemented that reduced seizures; but altered the normal dynamics of the model
• A new controller was conceived (Phie gain) that uses the derivative of long-range cortical input to suppress seizure activity
• The new controller was effective at controlling seizure activity and does not change the normal dynamics of the model

• Potential future research could involve:
  – Verification that the new control parameter (Phie) can be measured in vitro and is effective at reducing seizures
  – Investigation of new control schemes based on other parameters or algorithms
References

# Parameters

- \( \text{par ampl}=0, a=50, b=100 \)
- \( \text{par psiegain}=0 \)
- \( \text{par hegain}=0 \)
- \( \text{par hoe}=-0.643 \)
- \( \text{par ho}=1.29 \)
- \( \text{par te}=12 \)
- \( \text{par ti}=2.6 \)
- \( \text{par pear}=-0.643 \)
- \( \text{par pier}=16 \)
- \( \text{par pii}=11 \)
- \( \text{par nalp}e=4000 \)
- \( \text{par nabetae}=3034 \)
- \( \text{par nbetai}=536 \)
- \( \text{par ge}=-19.6 \)
- \( \text{par gi}=-9.8 \)
- \( \text{par thetae}=0.857 \)
- \( \text{par thetai}=0.857 \)

# initial conditions

- \( \text{init He}=1.2 \)
- \( \text{init Hi}=1.19 \)
- \( \text{init lee}=19.42 \)
- \( \text{init Jee}=0 \)
- \( \text{init lei}=22 \)
- \( \text{init Jie}=0 \)
- \( \text{init lli}=36.11 \)
- \( \text{init Jii}=0 \)
- \( \text{init Phi}=4.79 \)
- \( \text{init Pse}=0 \)
- \( \text{init Phi}=2.39 \)
- \( \text{init Psii}=0 \)

# Stim parameters

- \( \text{par ampl}=0, a=50, b=100 \)
- \( \text{par psiegain}=0 \)
- \( \text{par hegain}=0 \)
- \( \text{par hoe}=-0.643 \)
- \( \text{par ho}=1.29 \)
- \( \text{par te}=12 \)
- \( \text{par ti}=2.6 \)
- \( \text{par pear}=-0.643 \)
- \( \text{par pier}=16 \)
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- \( \text{par nalp}e=4000 \)
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- \( \text{par gi}=-9.8 \)
- \( \text{par thetae}=0.857 \)
- \( \text{par thetai}=0.857 \)

# Model equations

\[
\frac{dH_e}{dt} = 1 - H_e + g_0 * (H_0 - H_e) * I_e + g_1 * (H_0 - H_e) * I_i + g_0 * (H_0 - H_e) * I_e + g_1 * (H_0 - H_e) * I_i + \text{Psiegain} * P_s + \text{stim}(t) + H_e * h_e g a i n
\]

\[
\frac{dH_i}{dt} = 1 - H_i + g_0 * (H_0 - H_i) * I_e + g_1 * (H_0 - H_i) * I_i
\]

\[
\frac{dI_e}{dt} = -2 * t_e * J_e + t_e^2 * I_e + t_e^2 * \left( n_b e t a_e * s e h e(H_e) + P_s + p_e e \right)
\]

\[
\frac{dI_i}{dt} = -2 * t_i * J_i + t_i^2 * I_i + t_i^2 * \left( n_b e t a_i * s i h i(H_i) + p_i \right)
\]

\[
\frac{dJ_e}{dt} = -2 * t_e * J_e + t_e^2 * I_e + t_e^2 * \left( n_b e t a_e * s e h e(H_e) + P_s + p_e e \right)
\]

\[
\frac{dJ_i}{dt} = -2 * t_i * J_i + t_i^2 * I_i + t_i^2 * \left( n_b e t a_i * s i h i(H_i) + p_i \right)
\]

\[
\frac{dP_s}{dt} = -2 * \lambda_e * P_s + \lambda_e * nalpha_e * \text{diffsehe}(H_e) + \lambda_e * nalpha_e * \text{sehe}(H_e)
\]

\[
\frac{dP_i}{dt} = -2 * \lambda_i * P_i + \lambda_i * nalpha_i * \text{diffsehe}(H_e) + \lambda_i * nalpha_i * \text{sehe}(H_e)
\]

\[
\text{sehe}(H_e) = 1 / \left( 1 + \exp(-g_e * (H_e - \theta e)) \right)
\]

\[
\text{sihi}(H_i) = 1 / \left( 1 + \exp(-g_i * (H_i - \theta_t)) \right)
\]

\[
\text{diffsehe}(H_e) = 0 * H_e
\]

# Function for seizure control via voltage stimulation

\[
\text{stim}(t) = \text{ampl} * \text{heav}(t-a) * \text{heav}(b-t)
\]