Report on "The dynamic structure underlying subthreshold oscillatory activity and the onset of spikes in a model of medial entorhinal cortex stellate cells"

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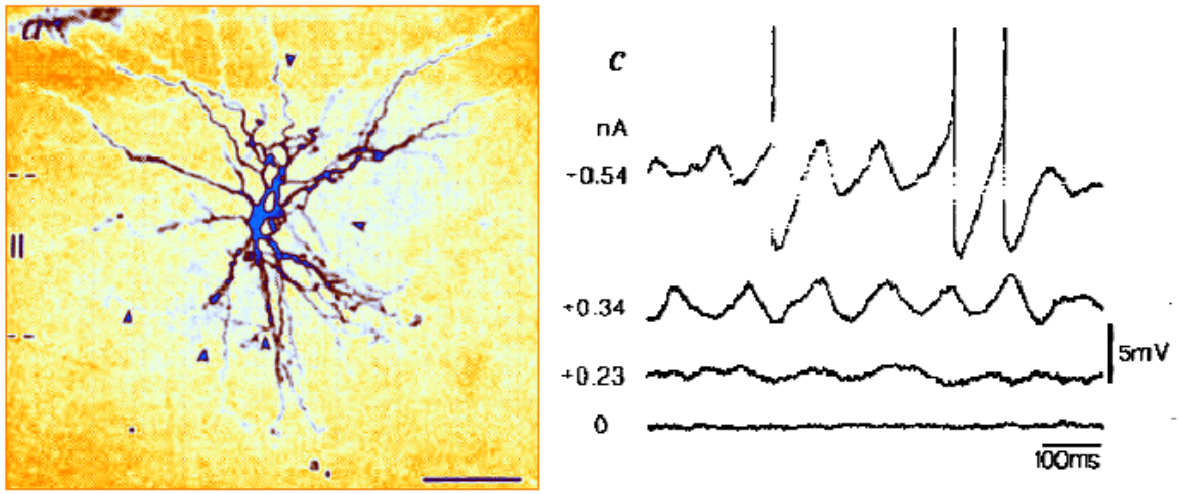
Horacio G. Rotstein, Tim Oppermann, John A. White, & Nancy Kopell
The dynamic structure underlying subthreshold oscillatory activity and the onset of spikes in a model of medial entorhinal cortex stellate cells (2006)
Journal of Computational Neuroscience 21:271-292

Stellate Cells in the Entorhinal Cortex



- Alonso et al. (1989) identify feature in stellate cells from layer II in the entorhinal cortex (ECIIsc): subthreshold oscillation (STO).
- Acker et al. (2003) propose seven-dimensional model of ECIIsc that also display STOs.
- Dynamical cause of STOs not known until Rotstein et al. (2006).

What is the Entorhinal Cortex?

- A major information hub for the hippocampus; plays major role in memory.
- The Entorhinal Cortex (EC) has been found to be the first part of the brain affected by Alzheimer's; it is also the most severely affected.
- Severe pathological damage to this part of the brain occurs in other dementing disorders.
- Young individuals with the Alzheimer's related variant of the ApoE gene are statistically found to have thinner ECs than do controls.

Damage from Alzheimer's disease

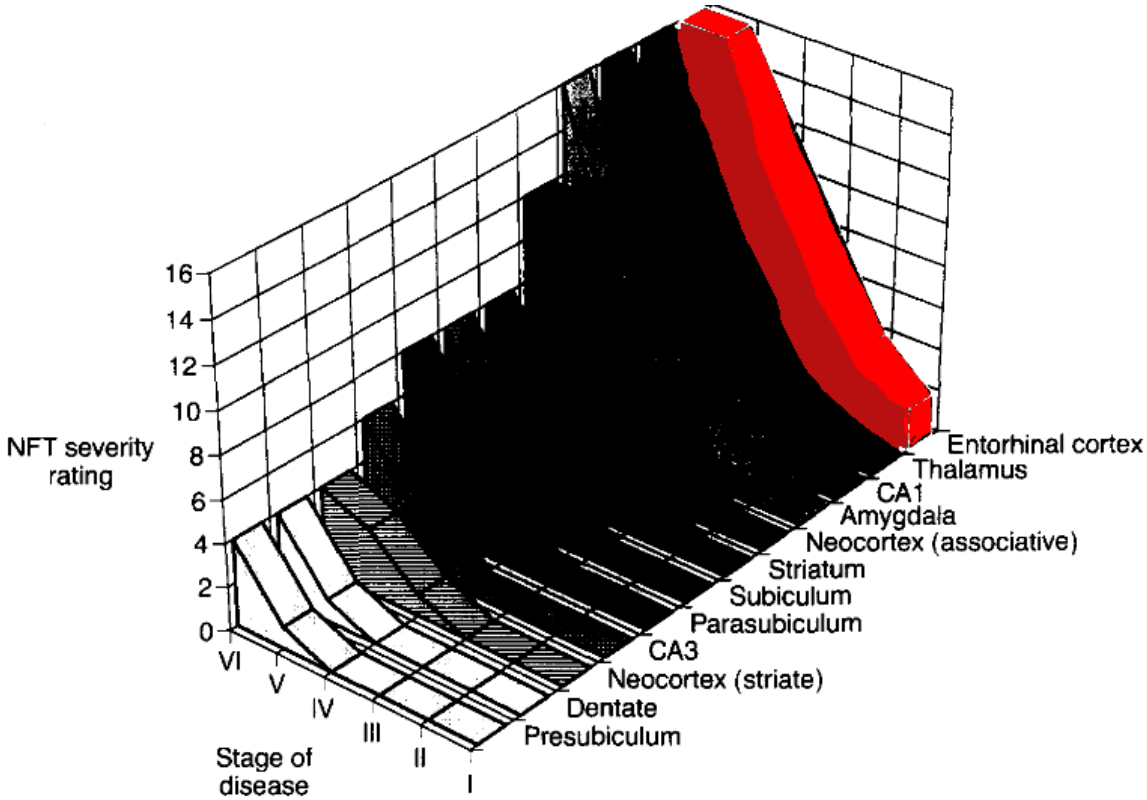


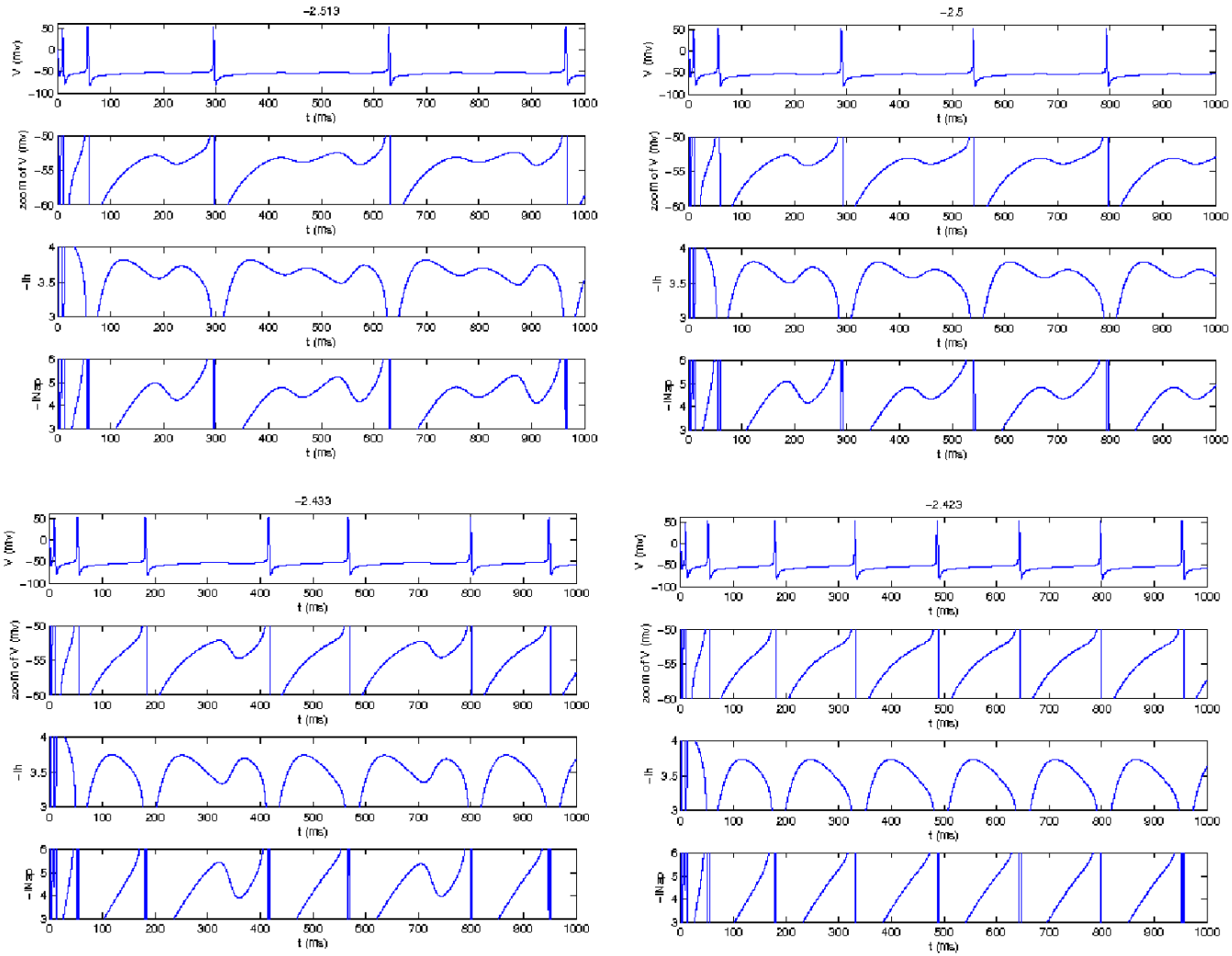
Figure from JONES, R.S.G. (1993) *Entorhinal-hippocampal connections: A speculative view of their function.*
Trends Neurosci. 16: 5864.
Enhanced as best as possible for clarity.

The Acker et al. (2003) model

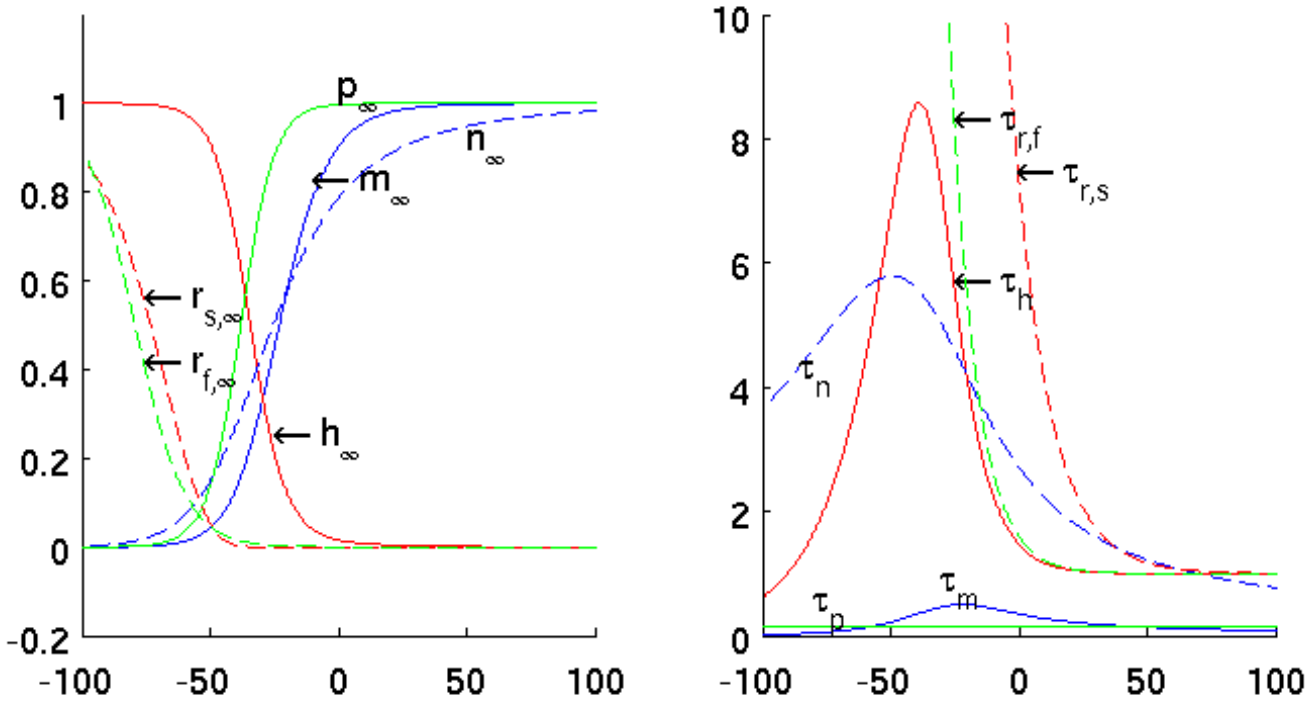
$$
\begin{aligned}
I_{Na} &= G_{Na} m^3 h (V - E_{Na}) \\
I_k &= G_K n^4 (V - E_k) \\
I_L &= G_L (V - E_L) \\
I_{Nap} &= G_p p (V - E_{Na}) \\
I_h &= G_h (0.65 r_f + 0.35 r_s)(V - E_h)
\end{aligned}
$$

$$
\begin{aligned}
C \frac{dV}{dt} &= I_{app} - I_{Na} - I_k - I_L \\
&\quad - I_h - I_{Nap} \\
\frac{dm}{dt} &= \frac{m_\infty(V) - m}{\tau_m(V)} \\
\frac{dh}{dt} &= \frac{h_\infty(V) - h}{\tau_h(V)} \\
\frac{dn}{dt} &= \frac{n_\infty(V) - n}{\tau_n(V)} \\
\frac{dp}{dt} &= \frac{p_\infty(V) - p}{\tau_p(V)} \\
\frac{dr_f}{dt} &= \frac{r_{f,\infty}(V) - r_f}{\tau_{rf}(V)} \\
\frac{dr_s}{dt} &= \frac{r_{s,\infty}(V) - r_s}{\tau_{rs}(V)}
\end{aligned}
$$

The Acker et al. (2003) model

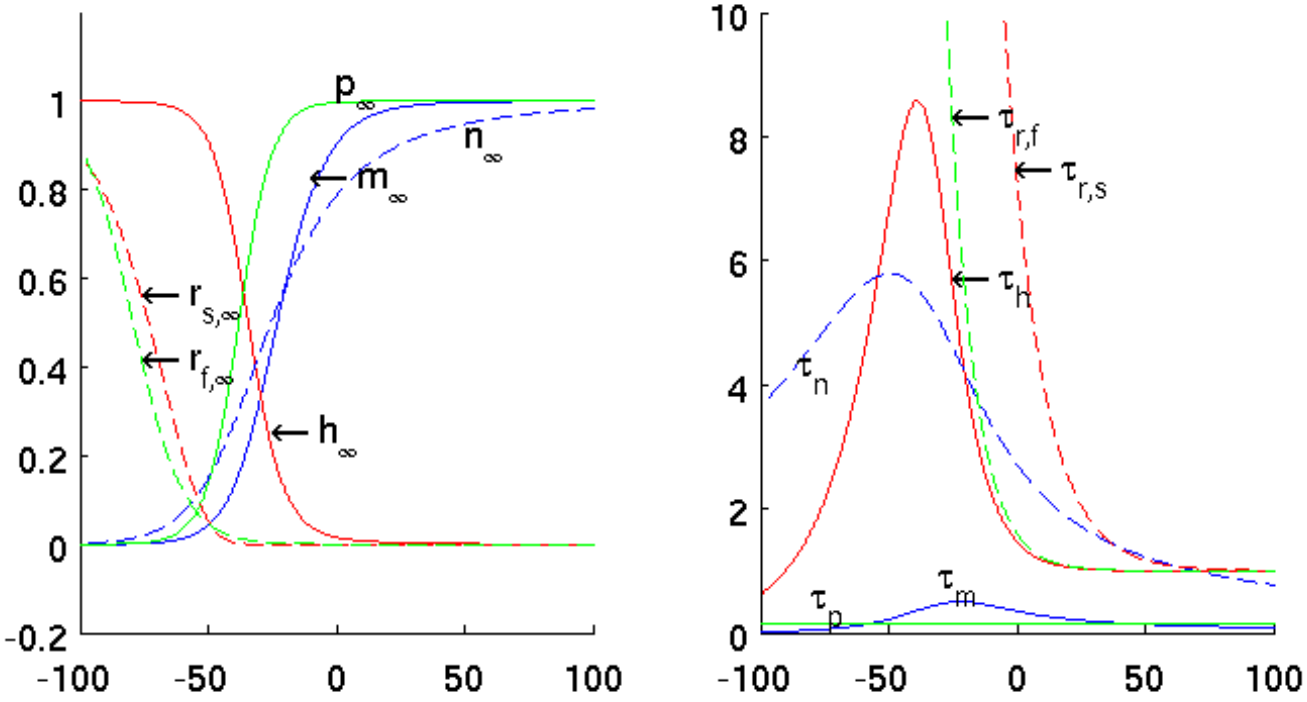


Fast/Slow decomposition?



$\tau_{r,f}$ and $\tau_{r,s}$ are much greater than all other τ_x in the STO regime. Assumption: their evolution in this regime is much slower, and so their dynamics will dominate.

Evolution in STO regime based decomposition?



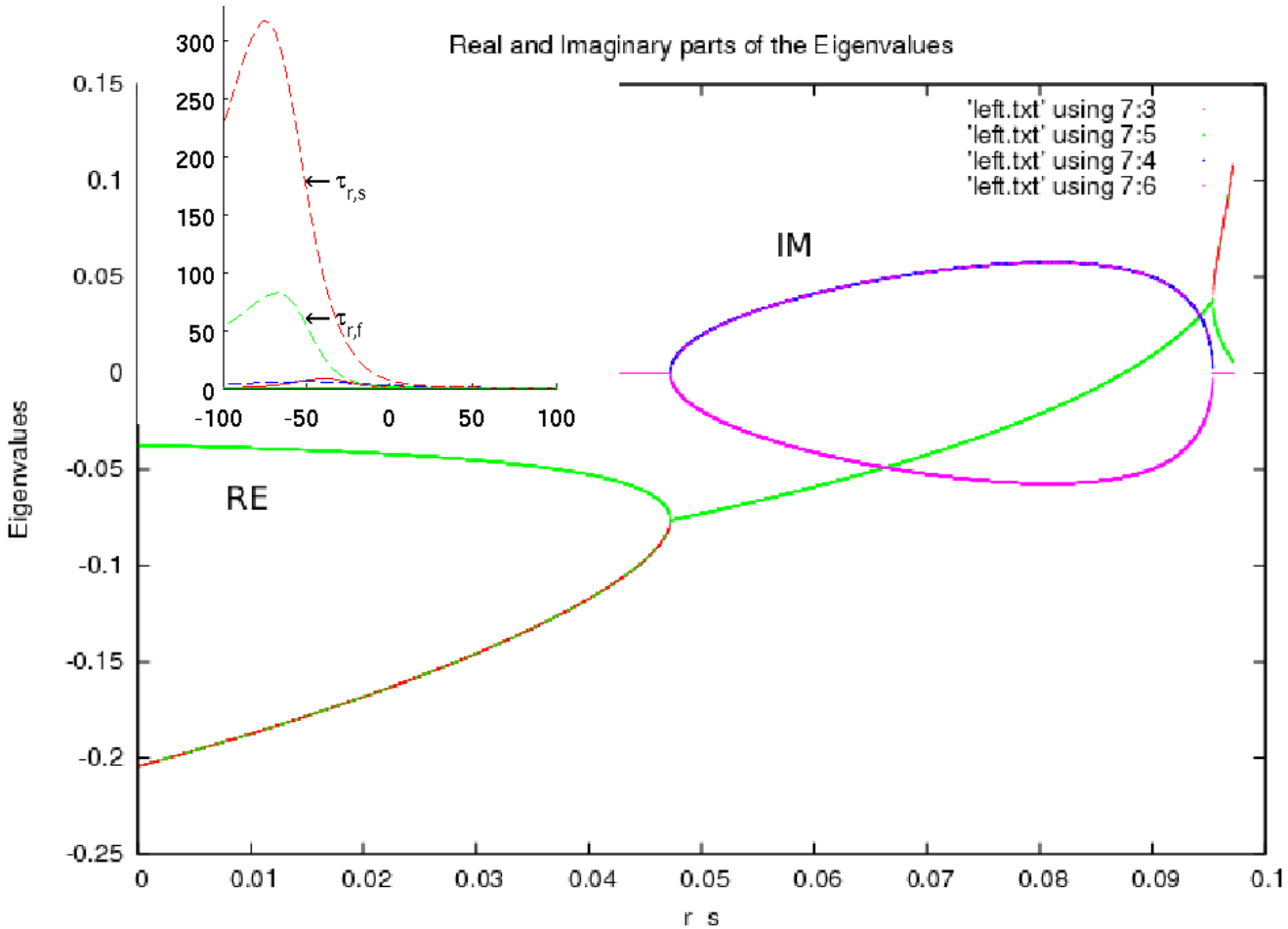
$$
\begin{aligned}
I_{Na} &= G_{Na} m^3 h (V - E_{Na}) \qquad \propto m^3 \approx 0 \text{ in STO regime} \\
I_k &= G_K n^4 (V - E_k) \qquad \propto m^4 \approx 0 \text{ in STO regime} \\
I_L &= G_L (V - E_L) \\
I_{Nap} &= G_p p (V - E_{Na}) \qquad p \propto p_{\text{inf}} \text{ since } \tau_p \text{ small} \\
I_h &= G_h (0.65 r_f + 0.35 r_s)(V - E_h)
\end{aligned}
$$

Reduced System: 3D!

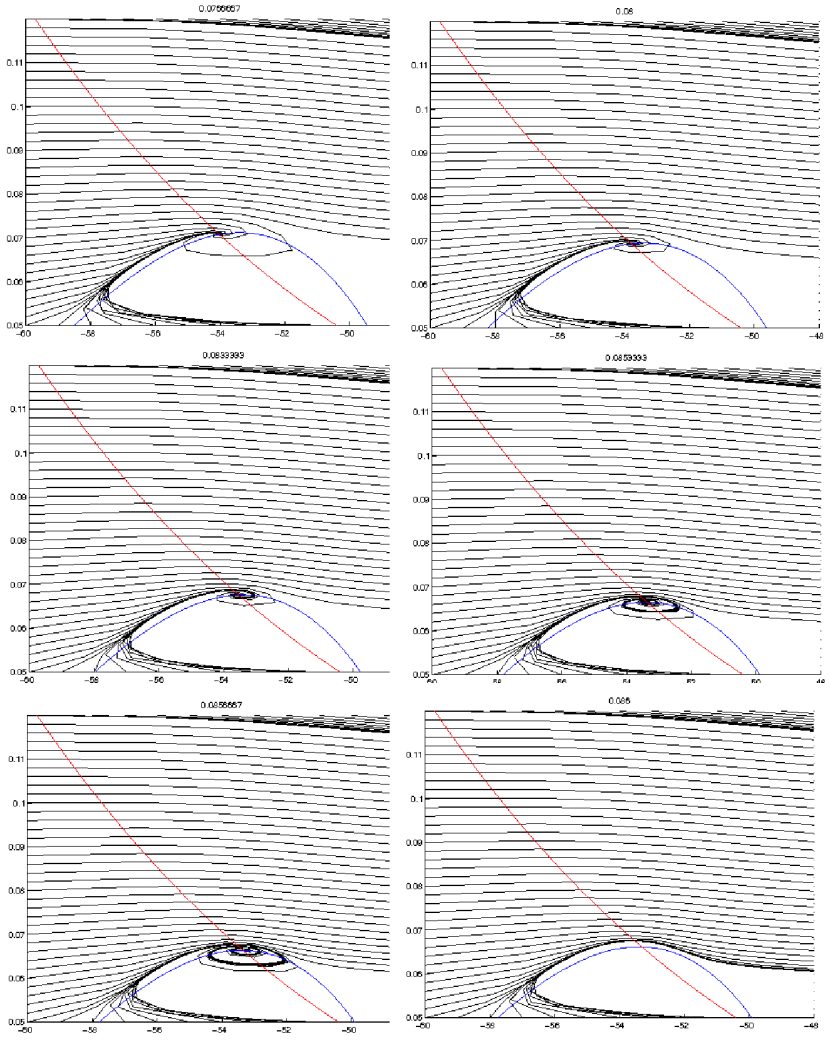
$$
\begin{aligned}
C\frac{dV}{dt} &= I_{app} - G_p p_\infty(V)(V - E_{Na}) - I_L - I_h \\
\frac{dr_f}{dt} &= \frac{r_{f,\infty}(V) - r_f}{\tau_{r_f}(V)} \\
\frac{dr_s}{dt} &= \frac{r_{s,\infty}(V) - r_s}{\tau_{r_s}(V)}
\end{aligned}
$$

Reduced System: Further fast/slow decomposition

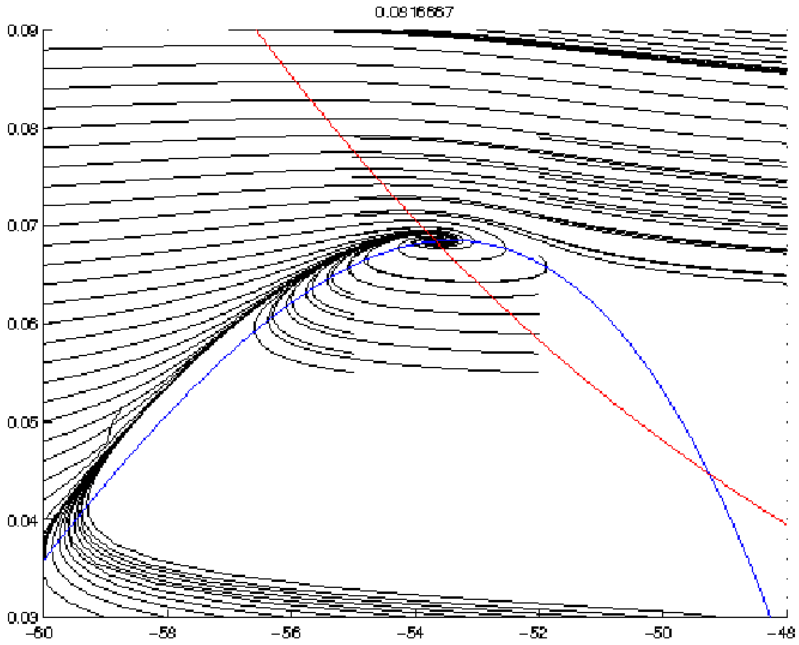
Rotstein et al. further note that in the STO regime, r_s evolves much much slower than r_f due to the relative sizes of the τ. The eigenvalues of the fast system, as a parameter of r_s, indicate an AH bifurcation.

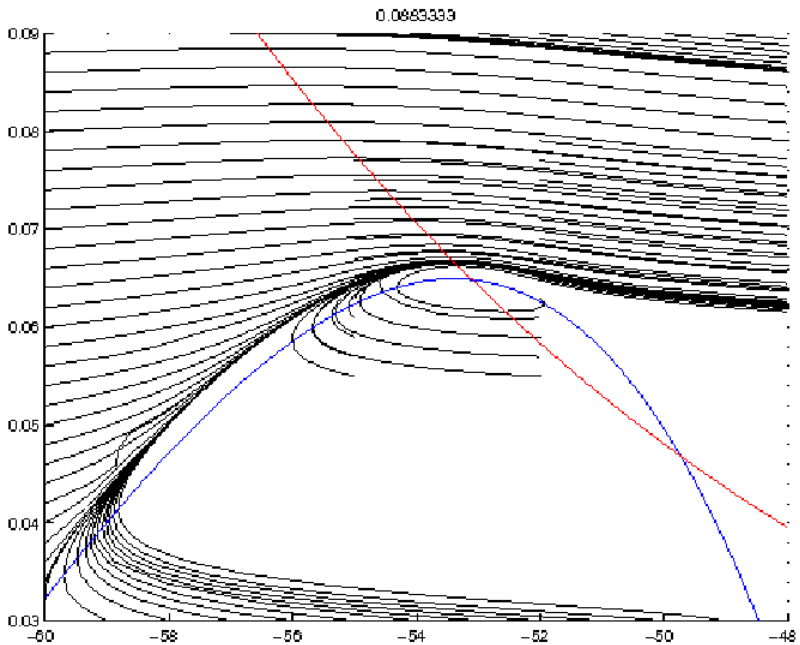


Reduced System: Further fast/slow decomposition

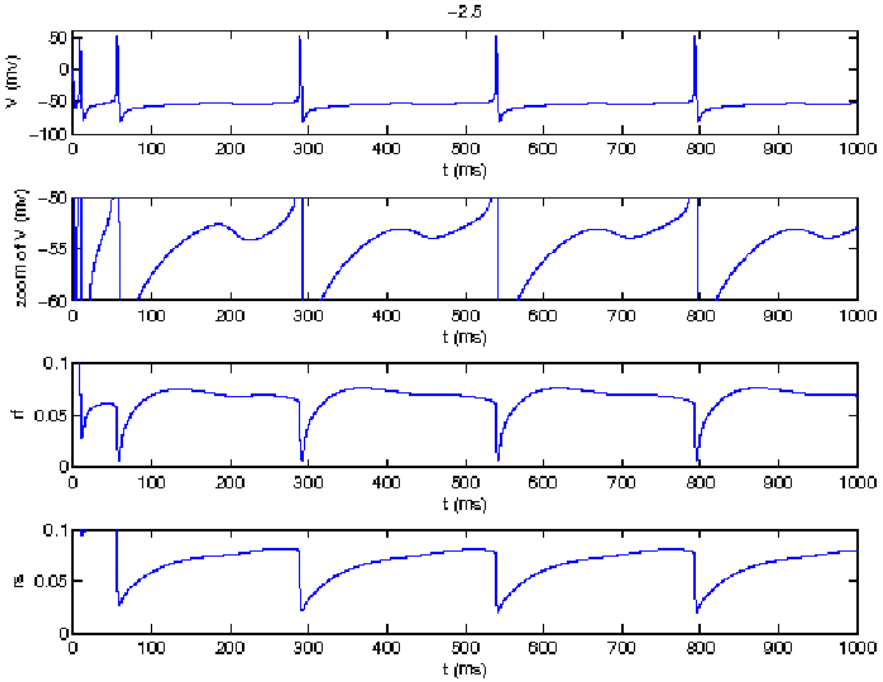


Reduced System: Further fast/slow decomposition





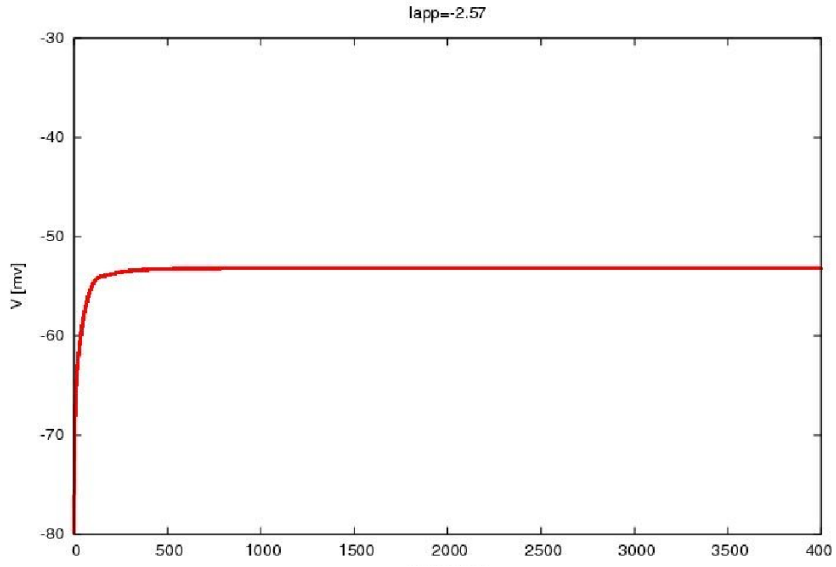
Full reduced system

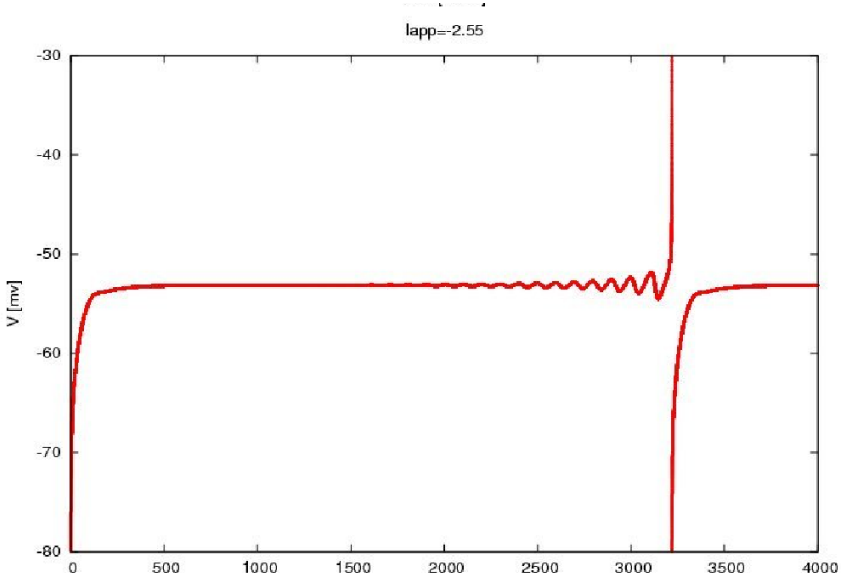


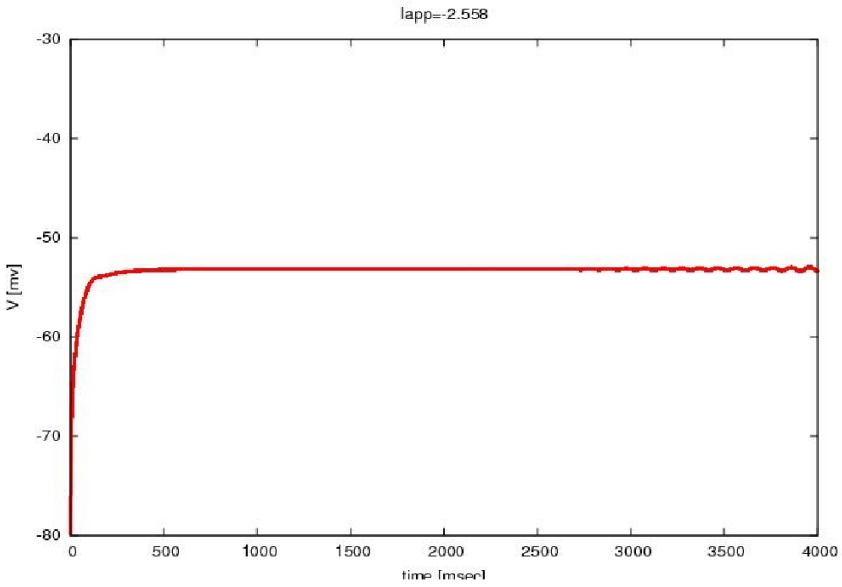
The full reduced system (3D) can be made to imitate the behavior of the 7D system by the introduction of an artificial spike mechanism. Notice that at each action potential, the values of r_f and $_s$ reset to nearly zero. Following Rotstein et al., we model the 3D system with this artificial spiking reset line of code:

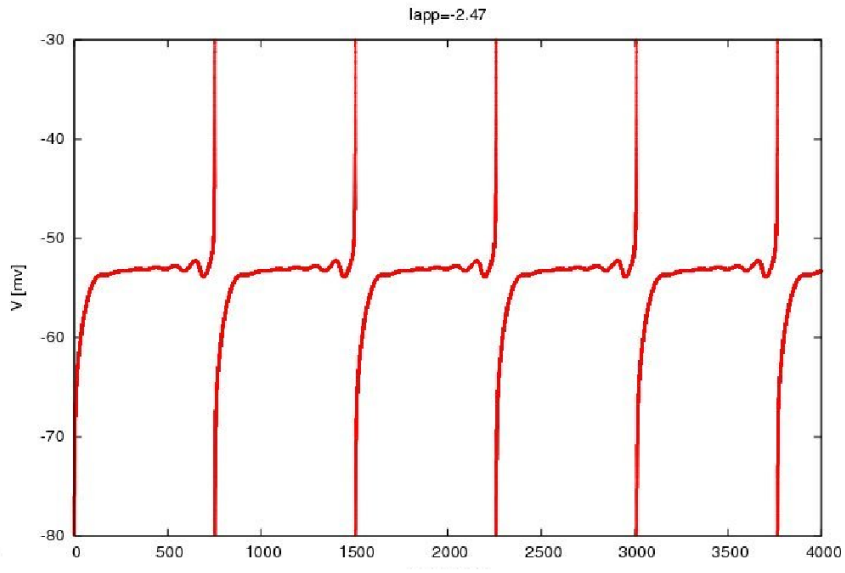
if(y[1]>-30)y[1]=-80; y[2]=0; y[3]=0; flag=0;

Reduced System with artificial spike

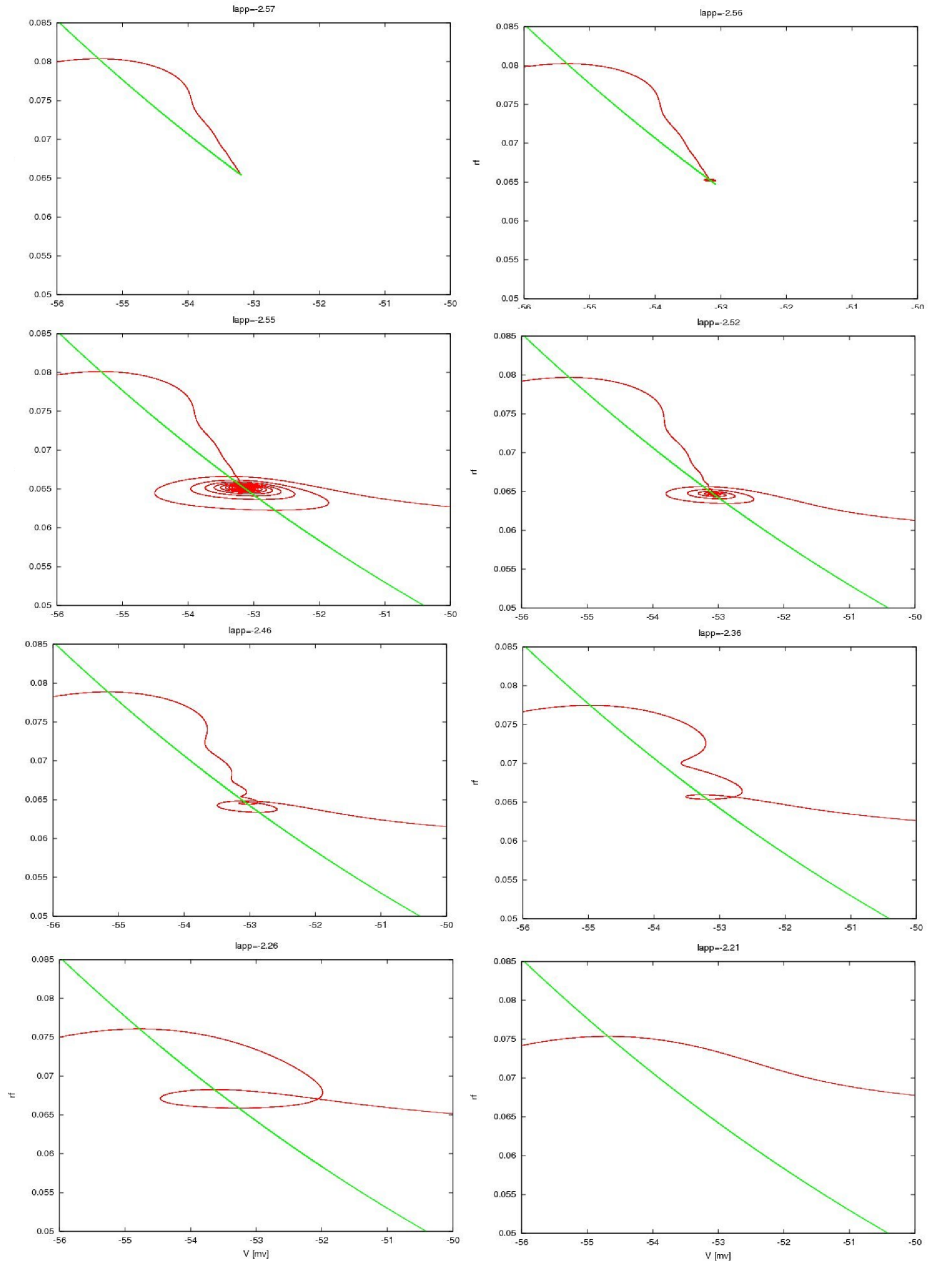




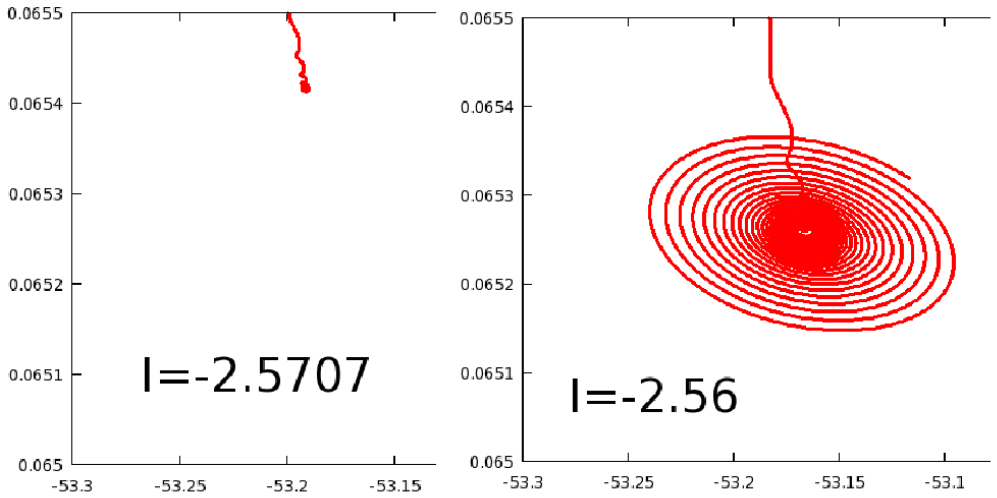


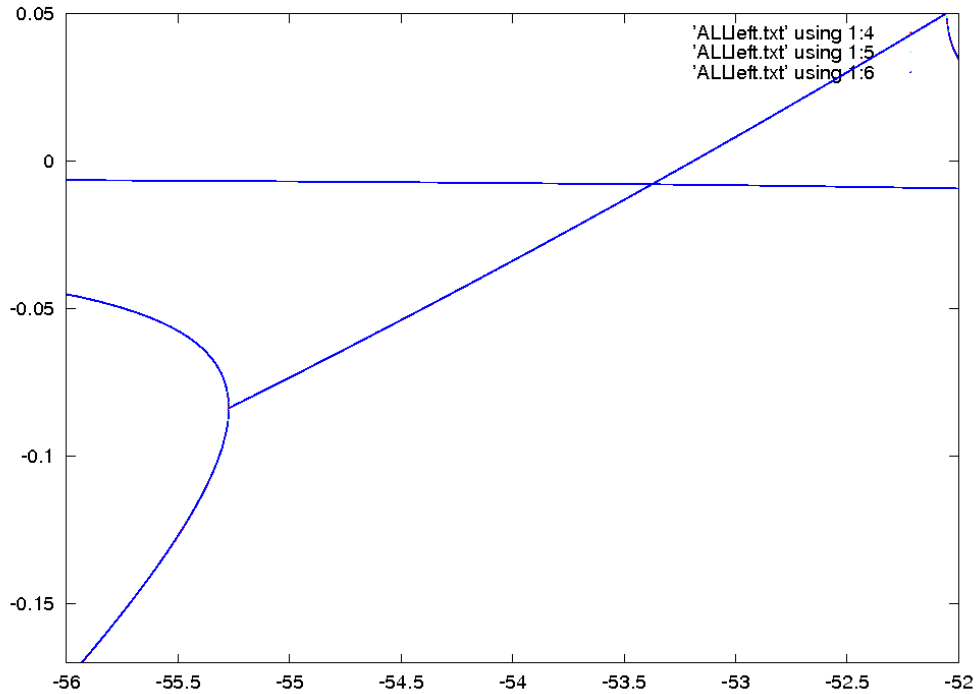


Reduced System



Reduced System





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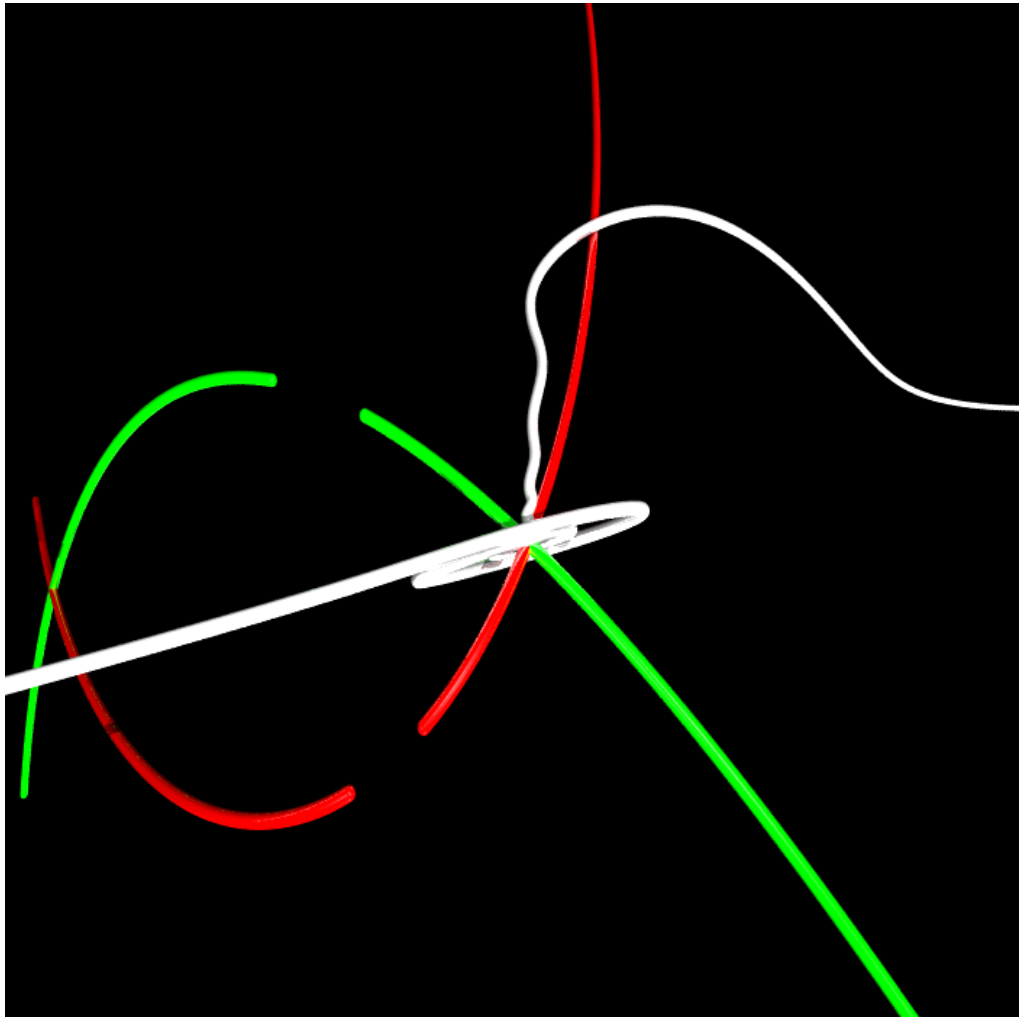
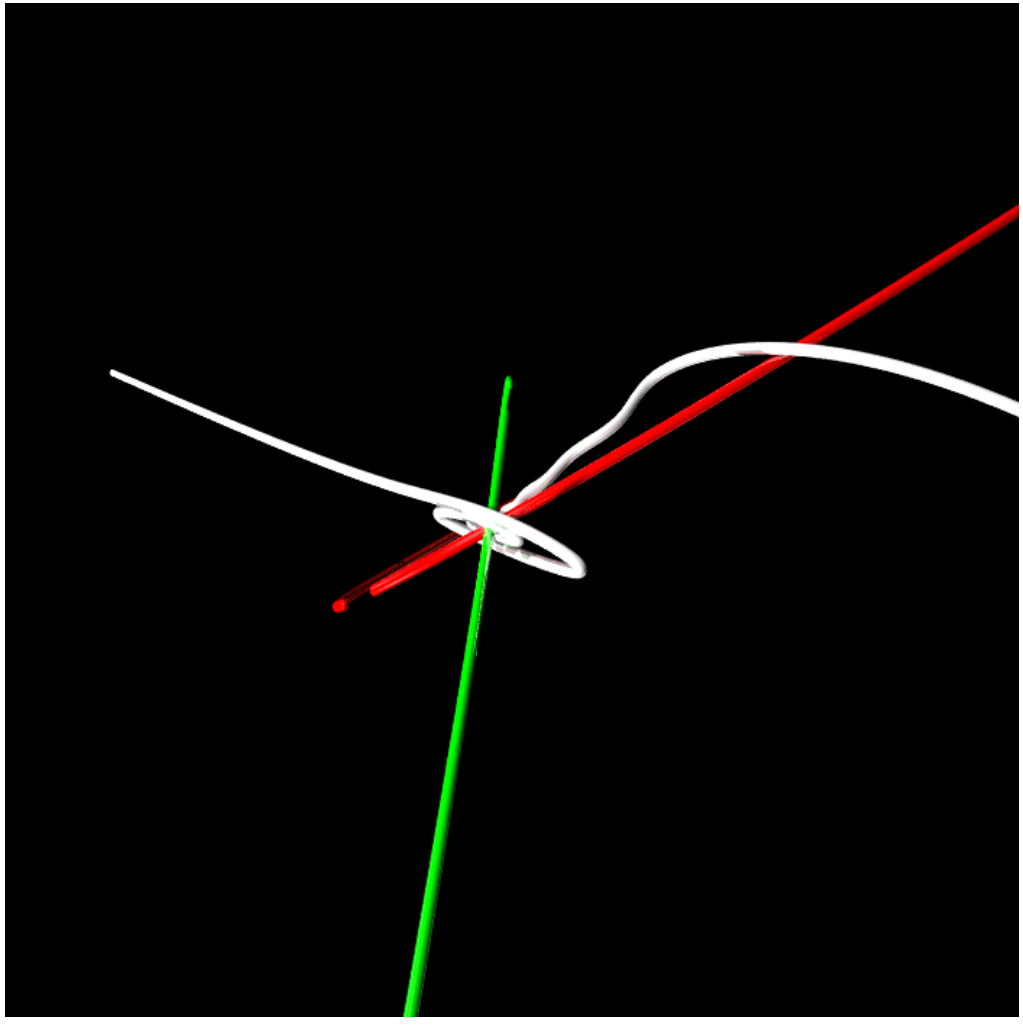


Reduced System



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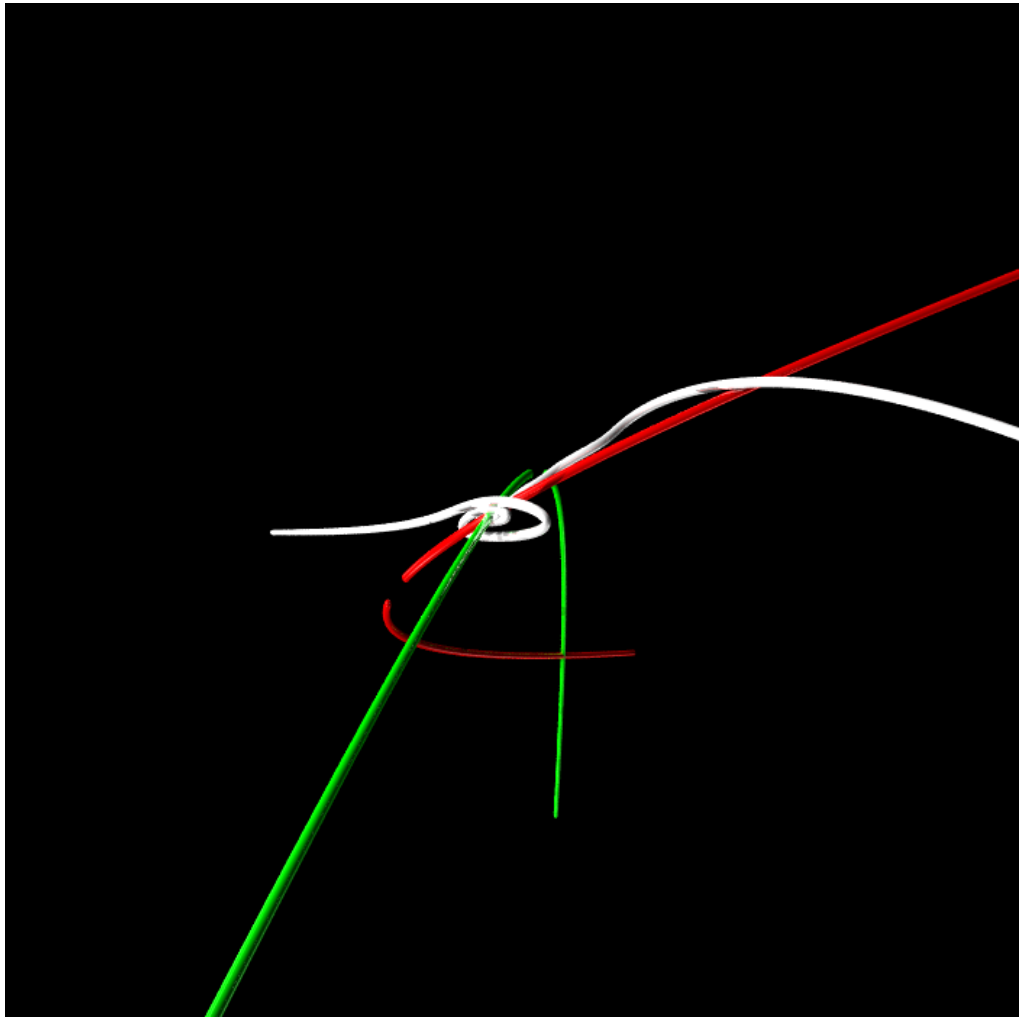

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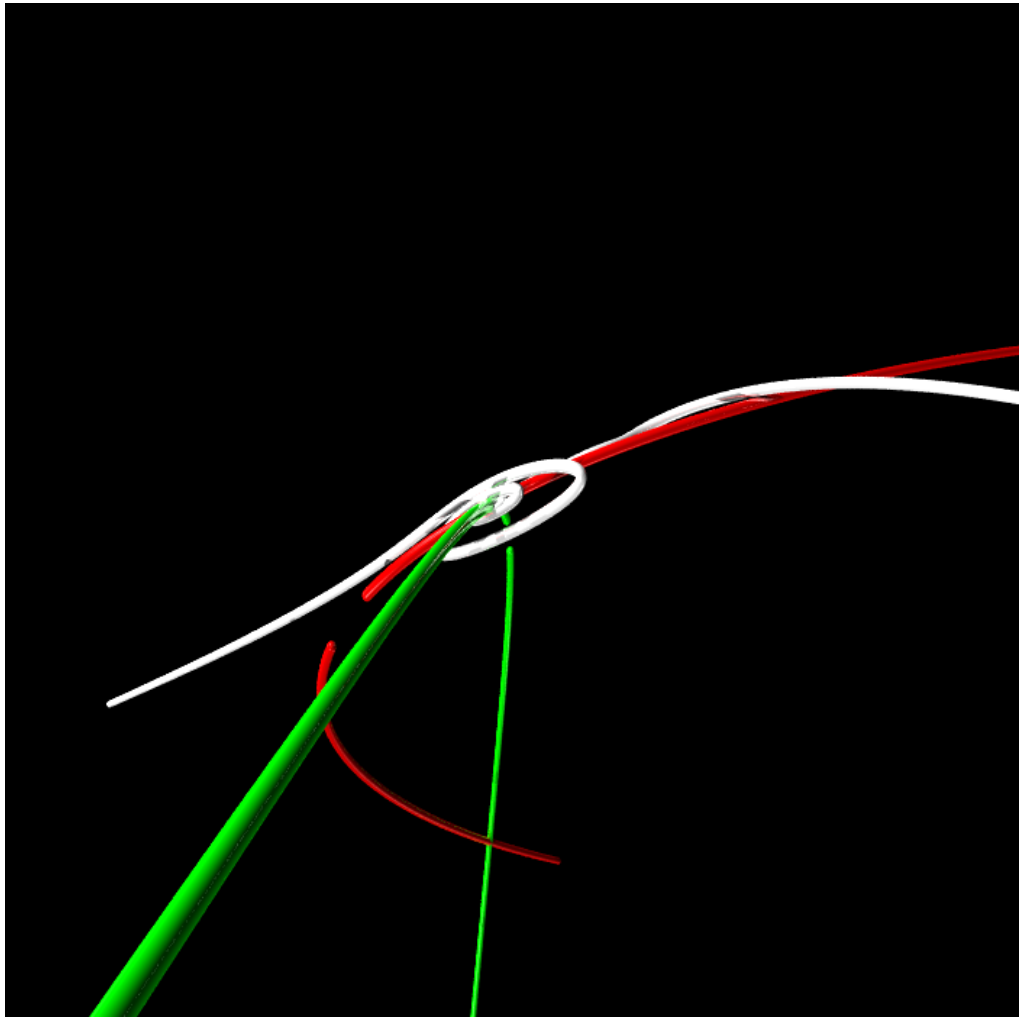

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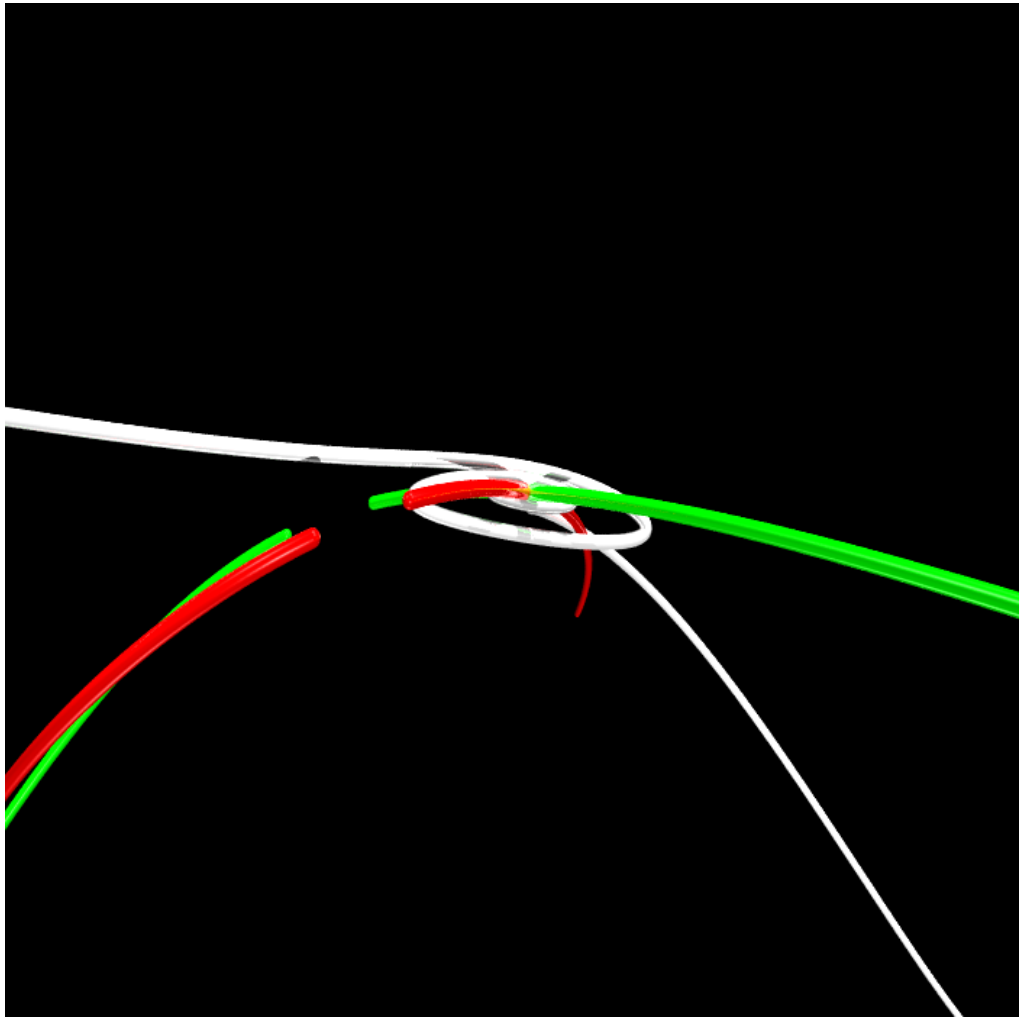

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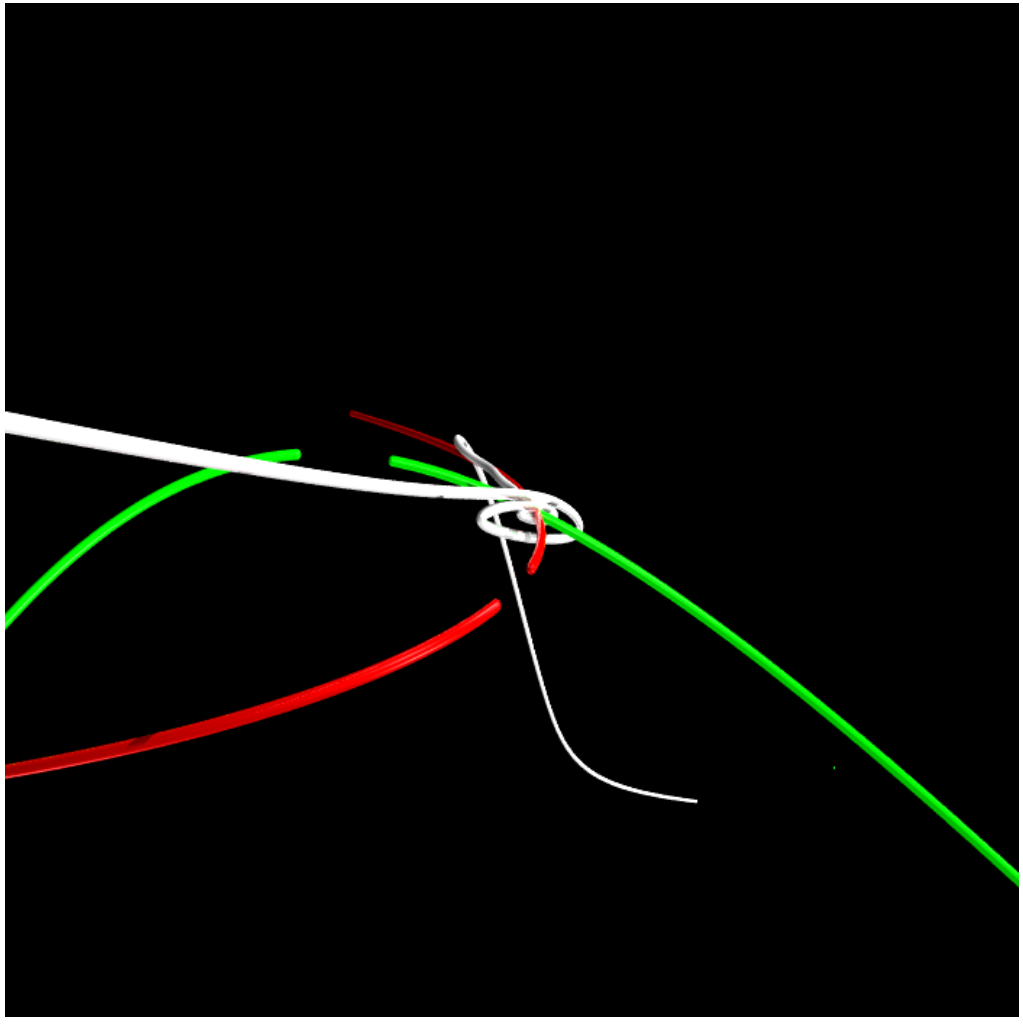

Final slide

Rotstein et al. also showed that the introduction of noise can give the model further verisimilitude with experimental results.

ALONSO, A. & KHLER, C. (1984) *A study of the reciprocal connections between the septum and the entorhinal area using anterograde and retrograde axonal transport methods in the rat brain.* J. Compar. Neurol. 225: 327343.

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Angel Alonso & Rodolfo R. Llinás (1989) *Subthreshold Na+-dependent theta-like rhythmicity in stellate cells of entorhinal cortex layer II* Nature 342, 175 - 177

Horacio G. Rotstein, Tim Oppermann, John A. White, & Nancy Kopell (2006) *The dynamic structure underlying subthreshold oscillatory activity and the onset of spikes in a model of medial entorhinal cortex stellate cells* Journal of Computational Neuroscience 21:271-292

Acker C, Kopell N, White J (2003) *Synchronization of strongly coupled excitatory neurons: Relating network behavior to biophysics.* Journal of Computational Neuroscience 15:71-90

Eugen M. Izhikevich, (2007) *Dynamical Systems in Neuroscience*, The MIT Press, Cambridge