From the Evans function to deep brain stimulation and back

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Mission for speakers: address

(i) definition of the field,

(ii) research highlights in the field,

(iii) critical considerations for someone wanting to enter the field today,

(iv) ideal type(s) of training, and

(v) suggested changes and directions for the field.

My background:

Ph.D. in Applied Mathematics, Brown University

Q:

1. **How do we attract bright undergraduates to graduate studies in mathematical neuroscience?**
2. **How do we convey to students what this field is all about?**

A:

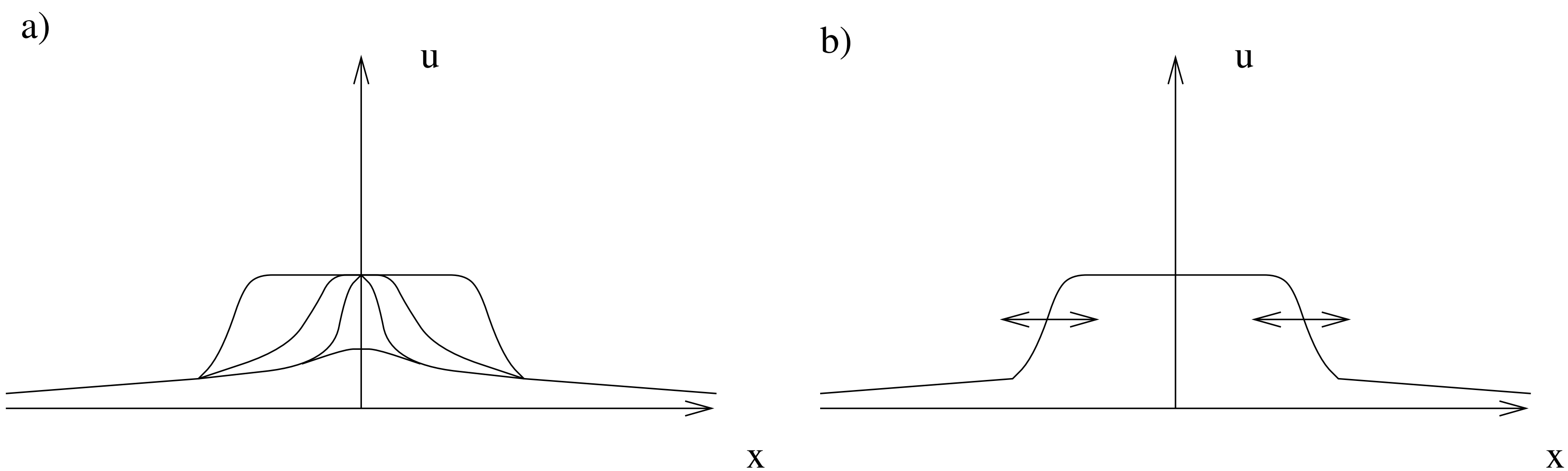
1. **recruit undergraduates for research**
2. **faculty research presentations**
3. **research posters in the halls**
4. **talks to undergraduates on visits to campuses**
5. **publications to mail to smaller colleges (*What's Happening in the Mathematical Sciences*)? how to coordinate?**
6. **REU/RTG**

My thesis: ***The Generation of Edge Oscillations in an Inhomogeneous Reaction-Diffusion System***

$$\begin{cases} u_t = u_{xx} + I(\epsilon x)W(u,w) - u, \\ w_t = D(w_{xx} + \epsilon^2(u - \gamma w)) \end{cases}$$

Fabry-Pérot interferometer

→ supports standing wave solutions $(u(x), w(x))$ that could destabilize ⇒ perform stability analysis



Evans function for linear stability analysis:

- linearization about $\Phi(\xi), \xi = x - ct \Rightarrow$ eigenvalue equation

$$\lambda P = B P_{\xi\xi} + c P_\xi + DF(\Phi(\xi))P =: \mathcal{L}P$$

- rewrite $\mathcal{L}P = \lambda P$ as $Y' = M(\xi, \lambda)Y, Y \in \mathbb{R}^{2n}$, with solutions $Y(\xi) = \Psi(\xi, \lambda)Y(0)$

- define

$$E_-^u(\lambda) = \{Y(0) \in \mathbb{R}^{2n} : \Psi(\xi, \lambda)Y(0) \longrightarrow 0 \text{ as } \xi \rightarrow -\infty\} \; : \; k - \dim$$

$$E_+^s(\lambda) = \{Y(0) \in \mathbb{R}^{2n} : \Psi(\xi, \lambda)Y(0) \longrightarrow 0 \text{ as } \xi \rightarrow +\infty\} \; : \; (2n - k) - \dim$$

- take bases $Y_1^-(\lambda), \ldots, Y_k^-(\lambda)$ of $E_-^u(\lambda)$, $Y_1^+(\lambda), \ldots, Y_{2n-k}^+(\lambda)$ of $E_+^s(\lambda)$

- let

$$E(\lambda) = |Y_1^-(\lambda) \ldots Y_k^-(\lambda) \; Y_1^+(\lambda) \ldots Y_{2n-k}^+(\lambda)|,$$

  such that $E(\lambda) = 0 \; \Leftrightarrow \; \lambda$ is an evalue of $\mathcal{L}$

Since then...

- sleep rhythms and related epilepsy: synchronization and clustering of synaptically coupled oscillators

$$\begin{cases} C_m v' = -\Sigma I_{ion} - g_{syn} s(v - E_{syn}), \\ s' = \alpha(v_{pre})(1-s) - \beta s \end{cases}$$

- spike-timing dependent plasticity: computational implications and biological mechanisms
- persistent, localized activity patterns in neuronal network models
- modeling the basal ganglia and a possible mechanism underlying deep brain stimulation for Parkinson's disease
- traveling waves in spiking neural field models
- oscillations in heterogeneous networks/effects of synaptic coupling
- noise and bursting in single neuron models
- canards and mixed-mode oscillations in single neuron models
- deriving information about coupling architecture from activity patterns
- the efficacy of synaptic inputs at inducing neuronal firing

Q: What is the best training for tackling such problems?

Claims:

1. Specialized training in neuroscience topics is not a requirement for a success in mathematical neuroscience.
2. Training in applied mathematics provides tools that are useful for tackling mathematical neuroscience problems (mechanisms).

Downside:

entropy	information theory
spike-frequency adaptation	filter
Nernst potential	principal components
(un)supervised learning	Hebbian plasticity
bursting oscillations	Hodgkin-Huxley equations

Also, how to:

- generate good problems?
- communicate across fields?

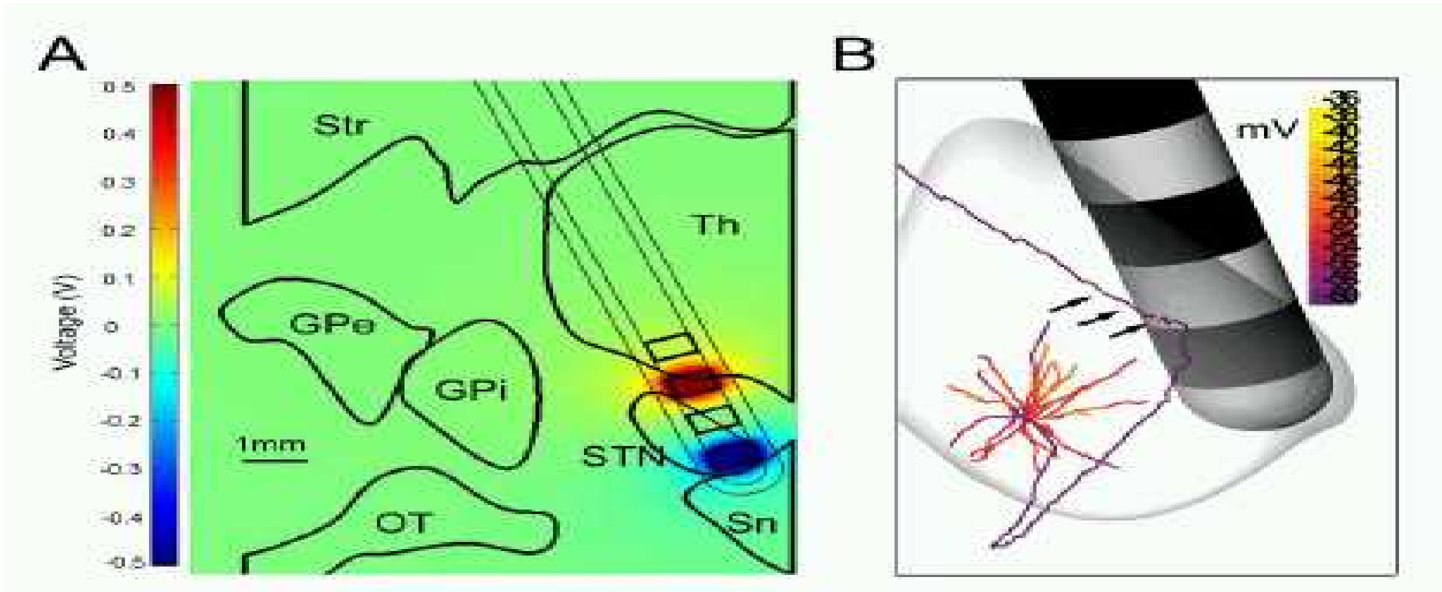
Challenges:

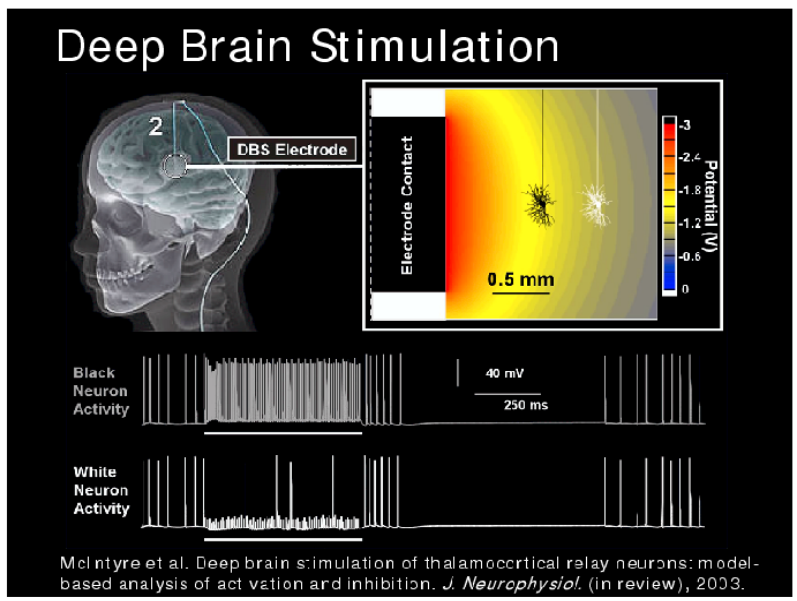
1. **Develop training that integrates mathematics and neuroscience.**
2. **Develop training that integrates students with diverse backgrounds.**

Ideas:

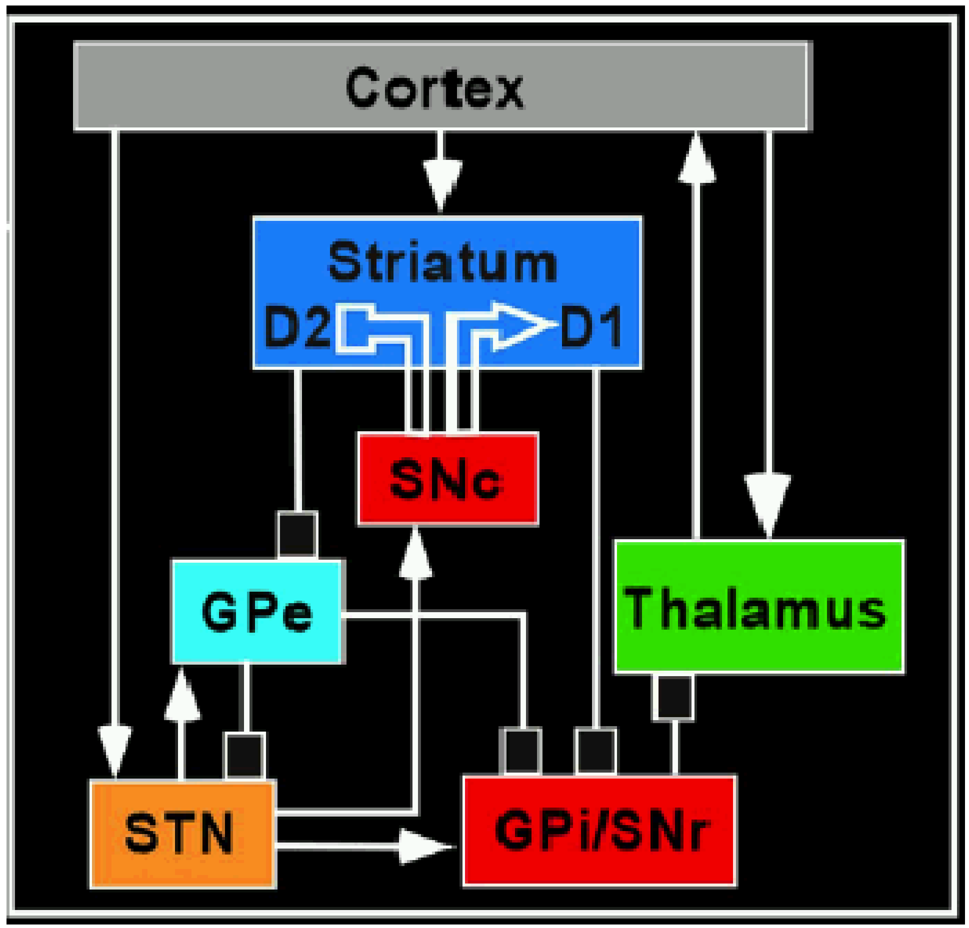
1. **computational neuroscience vs. mathematical neuroscience**
2. **semi-unified courses**
3. **journal clubs: within and between departments**
4. **working groups**
5. **experimental rotations?**

Deep brain stimulation (DBS):





Box and arrow diagram:



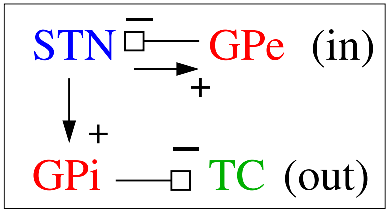
—□ = inhibition

—▷ = excitation

Note: **VL thalamus relays outputs between cortical areas, modulated by inhibition from basal ganglia.**

Biophysical basal-ganglia-thalamocortical network model:

Individual thalamic (TC) equations:



$$
\begin{aligned}
C_m v' &= -I_L - I_{Na} - I_K - I_T - I_{GPi\to TC} - I_{signal} \\
h_T' &= (h_{T_\infty}(v) - h_T)/\tau_{h_T}(v) \\
h' &= (h_\infty(v) - h)/\tau_h(v) \\
s' &= \alpha(1-s)exc(t) - \beta s, \quad exc(t) = \Sigma H(t-t_{on})(1-H(t-t_{off}))
\end{aligned}
$$

$$
\begin{aligned}
I_L &= g_L(v - v_L) & I_T &= g_T m_{T_\infty}^2(v) h_T (v - v_{Ca}) \\
I_{Na} &= g_{Na} m_\infty^3(v) h (v - v_{Na}) & I_{GPi\to TC} &= g_{GPi}(v - v_{inh}) \Sigma_j (s_{GPi})_j \\
I_K &= g_K n^4 (v - v_K) & I_{signal} &= g_{signal} s (v - v_{exc})
\end{aligned}
$$

$$
X_\infty(v) = (1 + \exp(v - \theta_X)/\sigma_X)^{-1}; \quad X \in \{m, h, m_T, h_T\}
$$

STN voltage equation:

$$
C_m v_{STN}' = -I_L - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} - I_{GPe\to STN} + DBS
$$

GPe voltage and synaptic equations (GPi is similar):

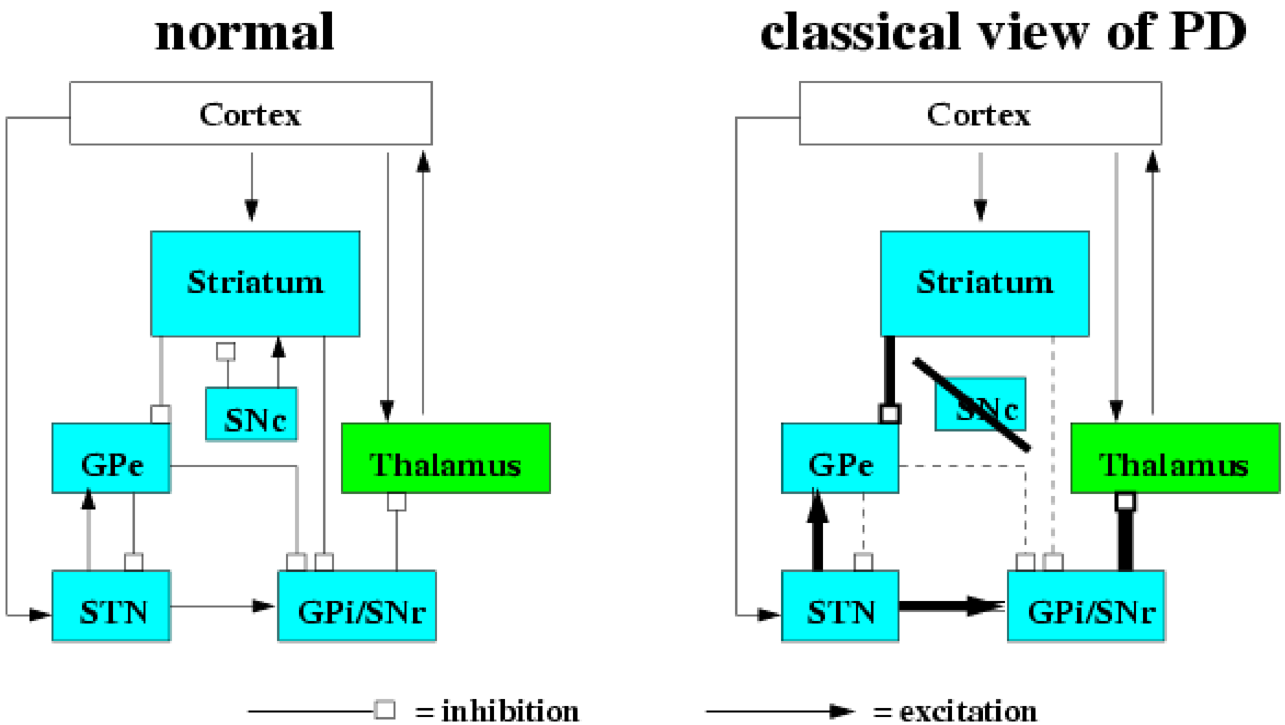
$$
\begin{aligned}
C_m v_{GPe}' &= -I_L - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} - I_{STN\to GPe} - I_{GPe\to GPe} \\
s_{GPe}' &= \alpha_{GPe}(1 - s_{GPe}) inh(v_{GPe}, t) - \beta_{GPe} s_{GPe}
\end{aligned}
$$

Some important directions for the field:

1. **Automation of parameter estimation techniques, optimized for neuronal network structure and data**

2. **Scale-up: from small networks where mechanisms can be analyzed to larger-scale networks *with complex coupling architectures***

An interesting paradox:



- PD: ↑ inhibition from GPi to thalamus associated with motor symptoms
- DBS: data (e.g. Hashimoto et al., 2003) and simulations (e.g. McIntyre et al.) show GPi activity ↑ further
- *Why should this ↑ in inhibition* relieve *PD symptoms?*

Idea:

- **In PD, GPi outputs become *rhythmic*, not just stronger. This compromises thalamic relay.**
- **DBS cuts the rhythmicity and restores relay: *stronger inhibition is less of a nuisance if it's more regular.***

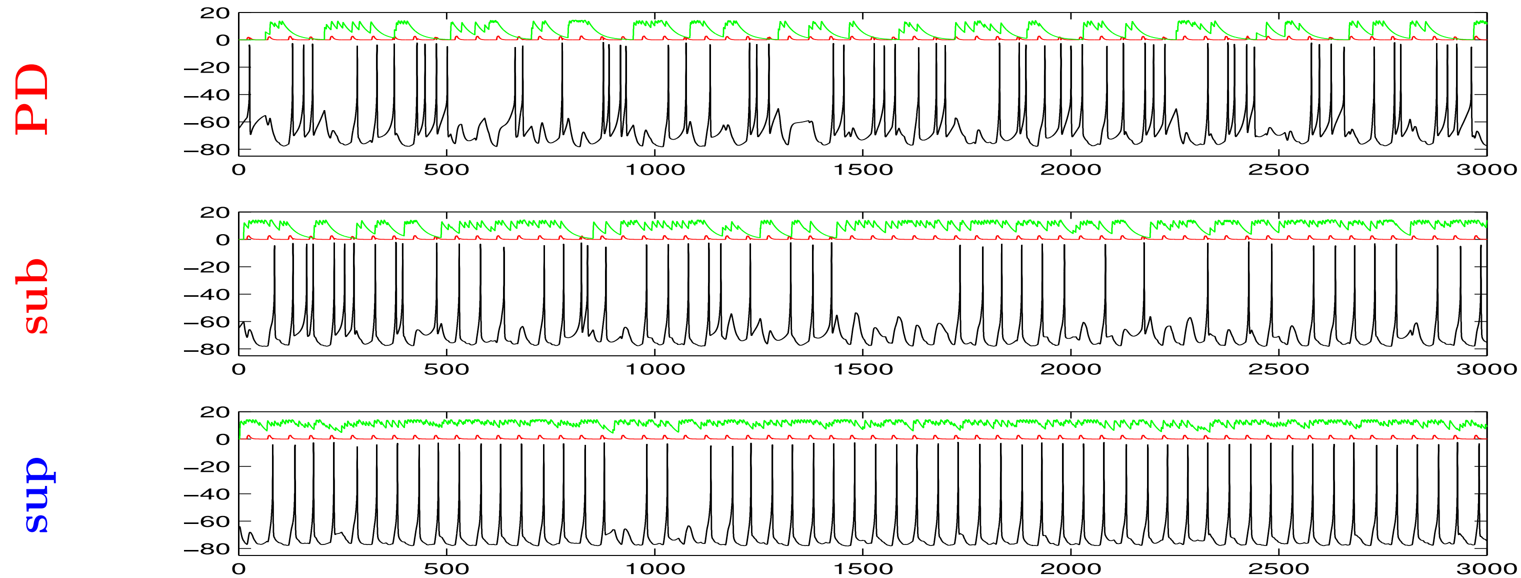
Papers:

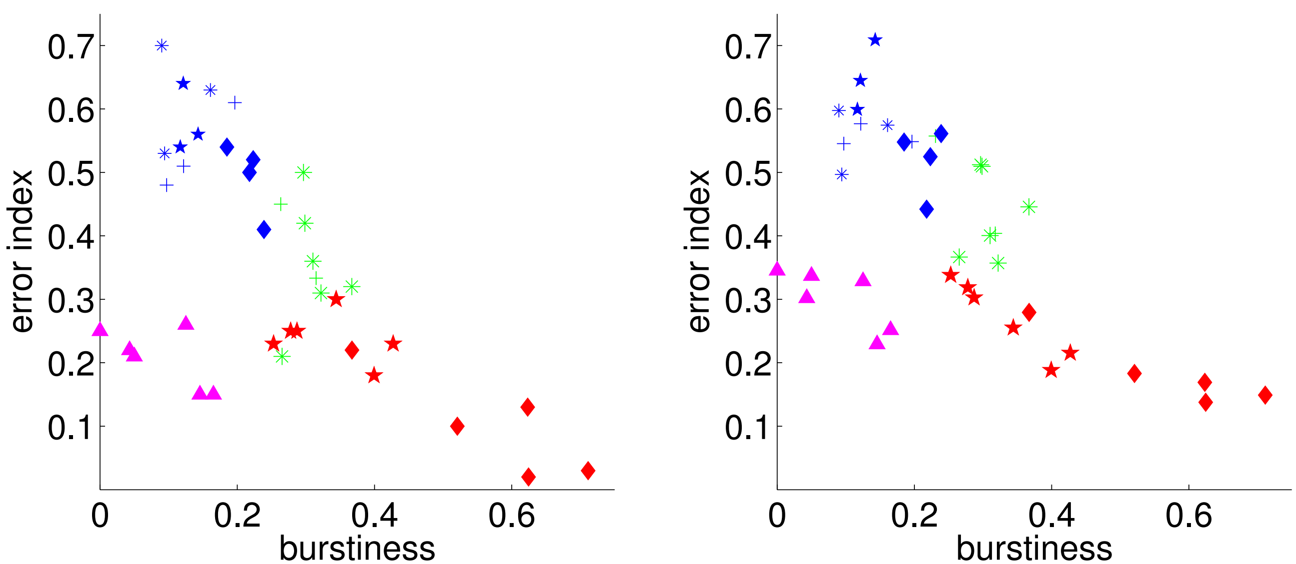
- **Terman et al., J. Neurosci., 22(7):2963-2976, 2002**
- **Rubin and Terman, J. Comp. Neurosci., 16:211-235, 2004**
- **Rubin and Josić, Neural Comp., 19:1251-1294, 2007**
- **Guo et al., *in preparation***

Test of prediction: GPi data into thalamic model!

use GPi recordings from primates in PD/DBS as input:

green=GPi signal, red=cortical inputs, black=TC response





Observation:

- **Mathematicians are trained to derive precise statements of assumptions under which particular results can be proved to hold.**
- **Assumptions play a much different role in applied mathematical neuroscience problems.**

A final question:

How does this work fit into a mathematics department?

- **valued by colleagues?**
- **tenure credit?**
- **student thesis work?**