Is the Brain Macroscopically Linear?

A System Identification of Resting State Dynamics

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Joint work with Jeni Stiso, Lorenzo Caciagli, Eli Cornblath,
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George Pappas, and Dani Bassett

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" Truth ... is much too complicated to allow anything but approximation "

— von Neumann

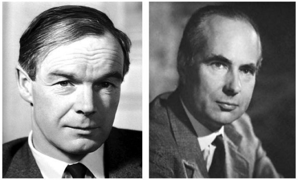
Common points of **tradeoff**:

- **Linear vs. nonlinear**
- Small vs. large dimensional
- Deterministic vs. stochastic
- Stationary vs. time-varying
- ⋮

Nonlinearity: Essential at Microscale

- Fundamental to the HH model

$$
\begin{aligned}
\dot{V}_m &= g_l(V_l - V_m) + g_{\mathrm{K}} n^4 (V_{\mathrm{K}} - V_m) + g_{\mathrm{Na}} m^3 h (V_{\mathrm{Na}} - V_m) + I \\
\dot{n} &= \frac{0.01(10 - V_m)}{e^{1 - V_m/10} - 1}(1 - n) + \frac{e^{-V_m/80}}{8} n \\
\dot{m} &= \frac{0.1(25 - V_m)}{e^{2.5 - V_m/10} - 1}(1 - m) + 4e^{-V_m/18} m \\
\dot{h} &= 0.07 e^{-V_m/20}(1 - h) + \frac{1}{e^{3 - V_m/10} + 1} h
\end{aligned}
$$



A. L. Hodgkin & A. F. Huxley

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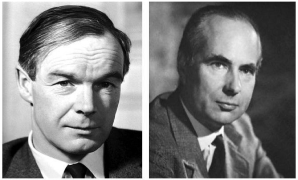

A. L. Hodgkin & A. F. Huxley

✓ **Data-driven**

✓ Functionally, nonlinearity is **essential** for

- Excitable behavior (spiking)
- Limit cycles (rhythmic spiking)
- Logical operations (and, or)
- Bistability
- ⋮

- Seemingly, a network interconnection of billions of nonlinear neurons only explodes in complexity and repertoire of nonlinear behavior!

$\Rightarrow$ Resulting **assumption**: **accurate models** of macroscopic neurodynamics **must be nonlinear**

Nonlinearity: Present at Macroscale?

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$$\tau \frac{dE}{dt} = -E(t) + \big(1 - rE(t)\big) f_E\big[w_{EE}E - w_{EI}I + h_E(t)\big],$$
$$\tau \frac{dI}{dt} = -I(t) + \big(1 - rI(t)\big) f_I\big[w_{IE}E - w_{II}I + h_I(t)\big],$$

(Wilson & Cowan, 1972)

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$$
\begin{aligned}
\dot{y}_0(t) &= y_3(t)\\
\dot{y}_3(t) &= Aa\,\mathrm{Sigm}[y_1(t) - y_2(t)] - 2ay_3(t) - a^2 y_0(t)\\
\dot{y}_1(t) &= y_4(t)\\
\dot{y}_4(t) &= Aa\{p(t) + C_2\,\mathrm{Sigm}[C_1 y_0(t)]\}\\
&\quad - 2ay_4(t) - a^2 y_1(t)\\
\dot{y}_2(t) &= y_5(t)\\
\dot{y}_5(t) &= Bb\{C_4\,\mathrm{Sigm}[C_3 y_0(t)]\} - 2by_5(t) - b^2 y_2(t)
\end{aligned}
$$

(Jansen & Rit, 1995)

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$$\dot{\theta}_n = \omega_n + \frac{1}{N}\sum_{m=1}^{N} K_{mn}\sin(\theta_m - \theta_n)$$

(Kuramoto, 1984)

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$$\dot{x}_i = y_i - a x_i^3 + b x_i^2 - z_i + \left[K_{11}\left(X_1 - x_i\right) - K_{12}\left(X_2 - x_i\right)\right] + IE_i$$
$$\dot{y}_i = c_i - d x_i^2 - y_i$$
$$\dot{z}_i = rsx_i - rz_i - m_i$$

(Stefanescu-Jirsa, 2008)

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(Stefanescu-Jirsa, 2008)

- **Is this true?**

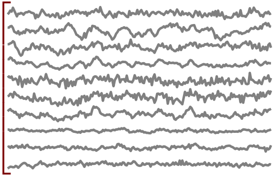
System Identification/Learning of Resting-State Dynamics

Generally-nonlinear ODE models are widespread in comp neuro:

$$\mathcal{M}: \quad \begin{aligned} \dot{\mathbf{x}}(t) &= f(\mathbf{x}(t)) + \mathbf{e}_1(t), \qquad \mathbf{x}(t_0) = \mathbf{x}_0 \\ \mathbf{y}(t) &= h(\mathbf{x}(t)) + \mathbf{e}_2(t) \end{aligned}$$

- $\mathbf{y}(t)$: neuroimaging time series
- $\mathbf{x}(t)$: "internal" state vector (any dimension, could be $= \mathbf{y}(t)$)
- $\mathbf{e}_1(t)$: process noise
- $\mathbf{e}_2(t)$: scanner noise

$$\mathbf{y}(t) = \begin{bmatrix} y_1(t) \\ y_2(t) \\ \vdots \\ y_n(t) \end{bmatrix} =$$



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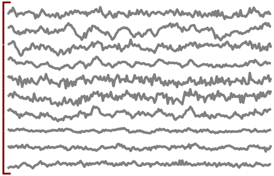
- $\mathbf{y}(t)$: neuroimaging time series
- $\mathbf{x}(t)$:
- $\mathbf{e}_1(t)$:
- $\mathbf{e}_2(t)$: scanner noise

Problem: find the model that best fits the data!

$$\mathbf{y}(t) = \begin{bmatrix} y_1(t) \\ y_2(t) \\ \vdots \\ y_n(t) \end{bmatrix} =$$



System Identification: Prediction Error Framework

- Philosophy: the better a model can **predict** the future of time series from its past ("initial conditions"), the more **accurate** it is

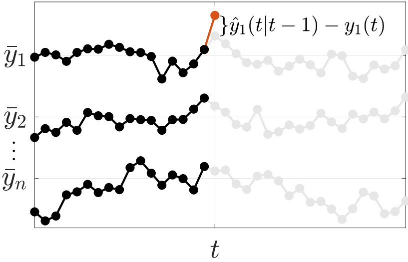
- Simplest: one-step ahead prediction (OSAP)

$$\min_{\mathcal{M}} \sum_{i,t} \left[\hat{y}_i(t|t-1) - y_i(t)\right]^2$$

- Model comparison:

  1. $R_i^2 = 1 - \dfrac{\sum_t [\hat{y}_i(t|t-1) - y_i(t)]^2}{\sum_t [\bar{y}_i - y_i(t)]^2} \leq 1$

  2. Whiteness of residuals (χ^2 test)

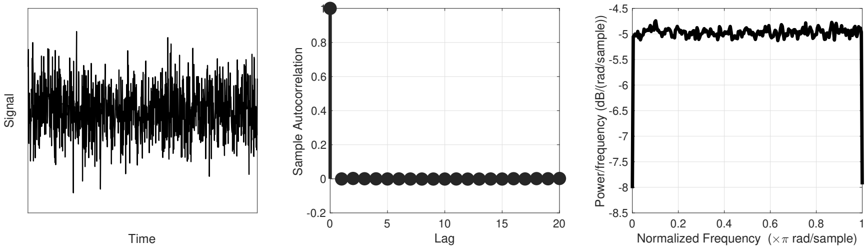


Whiteness of Residuals

- Prediction error (out of sample):

$$\boldsymbol{\varepsilon}(t) = \hat{\mathbf{y}}(t|t-1) - \mathbf{y}(t)$$

- Existence of **"dynamics"** in a signal $\equiv$ **non-white spectrum**



- Can be statistically verified via a χ^2 test: **the smaller the test statistic Q, the better**

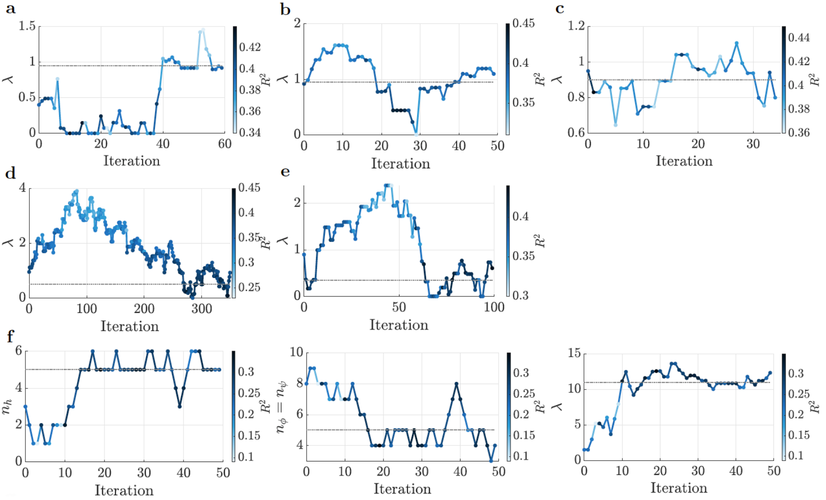
Linear Models

Label	Title	Equation		Parameters
Linear (dense)	Linear models with states at the BOLD/LFP level	$\mathbf{y}(t) - \mathbf{y}(t-1) = \mathbf{W}\mathbf{y}(t-1) + \mathbf{e}(t)$	(4)	None
Linear (sparse)				$\lambda = 0.95$ (fMRI) $\lambda = 1.2$ (iEEG)
AR-2 (sparse)†	Linear autoregressive models	$\mathbf{y}(t) - \mathbf{y}(t-1) = \mathbf{W}\mathbf{y}(t-1) + \mathbf{D}_2\mathbf{y}(t-2) + \mathbf{D}_3\mathbf{y}(t-3) + \cdots + \mathbf{D}_d\mathbf{y}(t-d) + \mathbf{e}(t)$	(5)	$d = 2, \lambda = 0.95$, diagonal $\mathbf{D}_2$
VAR-2 (sparse)†				$d = 2, \lambda = 0.9$
AR-3 (sparse)†				$d=3, \lambda=0.5$, diagonal $\mathbf{D}_2, \mathbf{D}_3$
VAR-3 (sparse)†				$d = 3, \lambda = 0.35$
AR-100 (sparse)‡				$d = 100, \lambda = 1.5$
AR-100 (scalar)‡				$d = 102$
Linear w/ HRF†	Linear models with states at the neural level	$\mathbf{x}(t) - \mathbf{x}(t-1) = \mathbf{W}\mathbf{x}(t-1) + \mathcal{G}_1(q)\hat{\mathbf{e}}_1(t)$ $\mathbf{y}(t) = \mathcal{H}(q)\mathbf{x}(t) + \mathcal{G}_2(q)\hat{\mathbf{e}}_2(t)$	(6a)	$n_h = n_\phi = n_\psi = 5, \lambda = 11$
		$\mathcal{H}(q) = \sum_{p=1}^{n_h} \mathrm{diag}(\mathbf{H}_{:,p})q^{-p}$	(6b)	
		$\mathcal{F}_1(q) = \mathbf{I} - \mathcal{G}_1^{-1}(q) = \sum_{p=1}^{n_\phi} \mathrm{diag}(\mathbf{\Phi}_{:,p})q^{-p}$	(6c)	
		$\mathcal{F}_2(q) = \mathbf{I} - \mathcal{G}_2^{-1}(q) = \sum_{p=1}^{n_\psi} \mathrm{diag}(\mathbf{\Psi}_{:,p})q^{-p}$	(6d)	
Subspace	Linear models with abstract data-driven states	$\mathbf{x}(t) - \mathbf{x}(t-1) = \mathbf{W}\mathbf{x}(t-1) + \mathbf{e}_1(t)$ $\mathbf{y}(t) = \mathbf{C}\mathbf{x}(t) + \mathbf{e}_2(t)$ $\mathrm{Cov}\left(\begin{bmatrix}\mathbf{e}_1(t)\\ \mathbf{e}_2(t)\end{bmatrix}\right) = \begin{bmatrix}\mathbf{Q} & \mathbf{M}\\ \mathbf{M}^T & \mathbf{R}\end{bmatrix}$	(7)	s = 1, r = 3, n = 25 (fMRI) s = 11, r = 49, n = 436 (iEEG)
Zero	Zero model	$\mathbf{y}(t) - \mathbf{y}(t-1) = \mathbf{e}(t)$		None

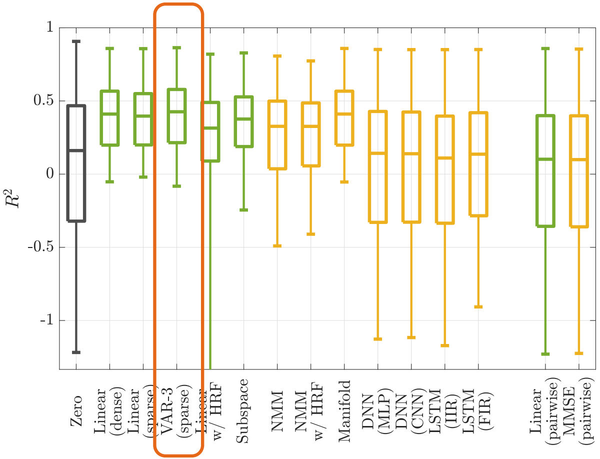
Nonlinear Models

Label	Title	Equation	Parameters
NMM	Nonlinear neural mass models	$\mathbf{y}(t)-\mathbf{y}(t-1)=(\mathbf{W}\psi_{\boldsymbol{\alpha}}(\mathbf{y}(t-1))-\mathbf{D}\mathbf{y}(t-1))\Delta_T+\mathbf{e}(t)$	MINDy default (fMRI) $\lambda_1=\lambda_2=0.2, \lambda_3=2$, $\lambda_4=0.5$ (iEEG)
NMM w/ HRF†		$\mathbf{x}(t)-\mathbf{x}(t-1)=(\mathbf{W}\psi_{\boldsymbol{\alpha}}(\mathbf{x}(t-1))-\mathbf{D}\mathbf{x}(t-1))\Delta_T+\mathbf{e}_1(t)$ (9) $\mathbf{y}(t)=\mathcal{H}(q)\mathbf{x}(t)+\mathbf{e}_2(t)$	MINDy default
DNN (MLP)	Nonlinear models via multi-layer perceptron deep neural networks	$\mathbf{y}(t)-\mathbf{y}(t-1)=f(\mathbf{y}(t-1),\dots,\mathbf{y}(t-d))+\mathbf{e}(t)$ (10)	$d=1, D=6, W=2$ (fMRI) $d=6, D=4, W=26$ (iEEG)
DNN (CNN)	Nonlinear models via convolutional deep neural networks	$\mathbf{y}(t)-\mathbf{y}(t-1)=f(\mathbf{y}(t-1),\dots,\mathbf{y}(t-d))+\mathbf{e}(t)$	$d=17, D=2, l_{\text{filt}}=7$, $n_{\text{filt}}=11, n_{\text{pool}}=4$, $p_{\text{drop}}=0.4$ (fMRI) $d=11, D=7, l_{\text{filt}}=2$, $n_{\text{filt}}=13, n_{\text{pool}}=1$, $p_{\text{drop}}=0.5$ (iEEG)
LSTM (IIR)	Nonlinear models via long short-term memory recurrent neural networks	$\mathbf{y}(t)-\mathbf{y}(t-1)=f(\mathbf{y}(t-1),\dots,\mathbf{y}(0))+\mathbf{e}(t)$	$W=12$ (fMRI) $W=1$ (iEEG)
LSTM (FIR)		$\mathbf{y}(t)-\mathbf{y}(t-1)=f(\mathbf{y}(t-1),\dots,\mathbf{y}(t-d))+\mathbf{e}(t)$	$d=1, W=16$ (fMRI) $d=7, W=1$ (iEEG)
Manifold	Nonlinear manifold-based models	$\mathbf{y}(t)-\mathbf{y}(t-1)=f(\mathbf{y}(t-1),\dots,\mathbf{y}(t-d))+\mathbf{e}(t)$	$d=1, h=830$ (fMRI) $d=7, h=1.2\times10^4$ (iEEG)
MMSE (pairwise)†	Nonlinear minimum mean squared error models (optimal)	$y_i(t)-y_i(t-1)=\mathrm{E}[y_i(t)-y_i(t-1)\mid y_j(t-1)], i,j=1,\dots,n$	$N=280, \beta=0.156$
MMSE (scalar)‡		$y_i(t)-y_i(t-1)=\mathrm{E}[y_i(t)-y_i(t-1)\mid y_i(t-1),\dots, y_i(t-d)], i=1,\dots,n$	$d=15, N=300, \beta=0.007$

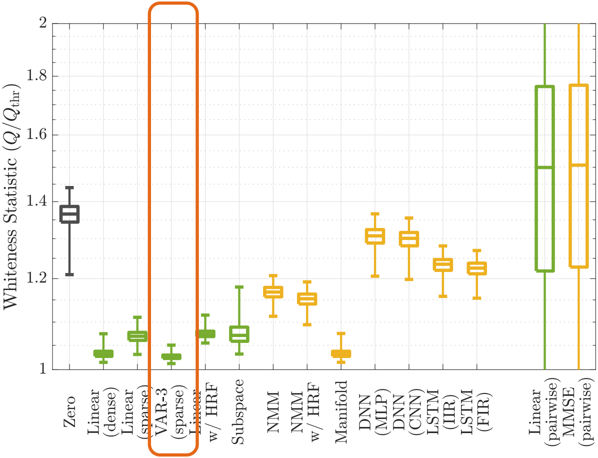
- Simultaneous tuning of each model's hyper-parameters via SGD, until reaching **steady state**



- $R_i^2 = 1 - \frac{\sum_t [\hat{y}_i(t|t-1) - y_i(t)]^2}{\sum_t [\bar{y}_i - y_i(t)]^2} \leq 1$, for any brain region i

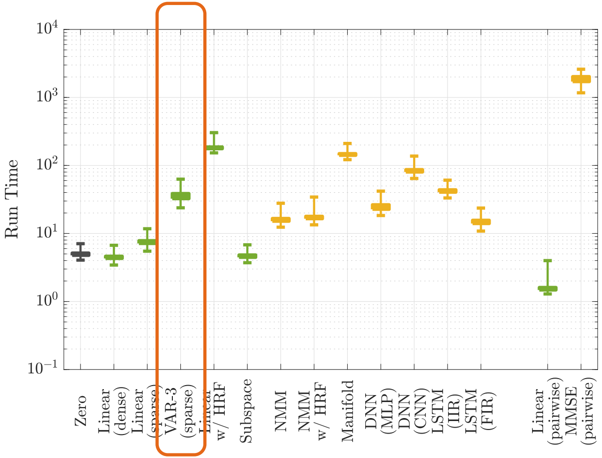


- Same linear VAR-3 model gives the whitest residuals



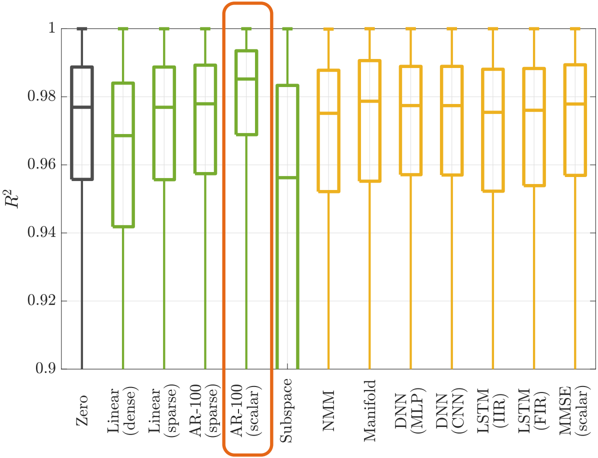
Comparison: Linear Models Are Faster (fMRI)

- Linear models are also faster (training + cross validation time)



Same Story for iEEG

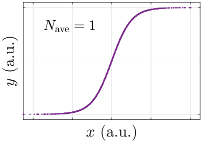
- Same holds true for iEEG



? Why?!

1. Averaging across space

$$y_i(t) = \sigma(x_i(t)), i = 1, \ldots, N$$



Reasons for Linearity

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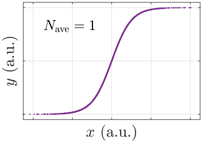
$$\langle x_i \rangle(t) = \frac{1}{N} \sum_{i=1}^{N} x_i(t), \qquad \langle y_i \rangle(t) = \frac{1}{N} \sum_{i=1}^{N} y_i(t)$$



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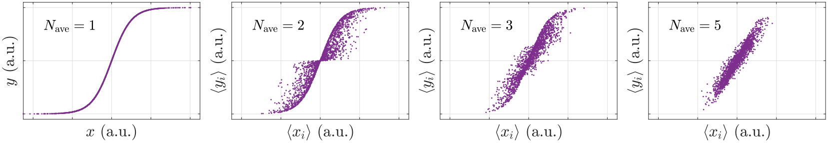

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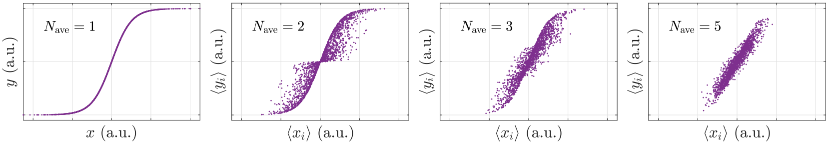
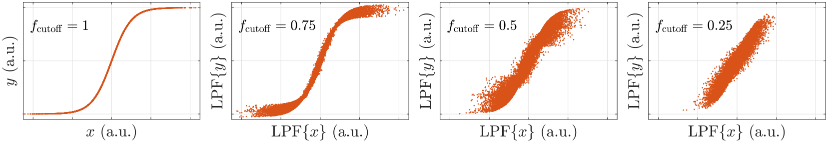
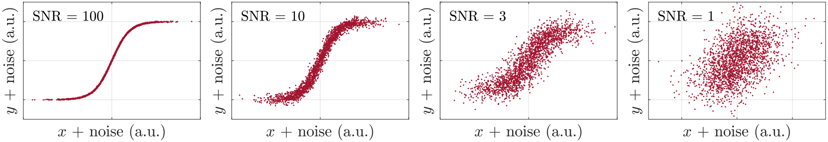


2. Averaging across time (low-pass filtering)



Reasons for Linearity – cont'd

3. Observation noise



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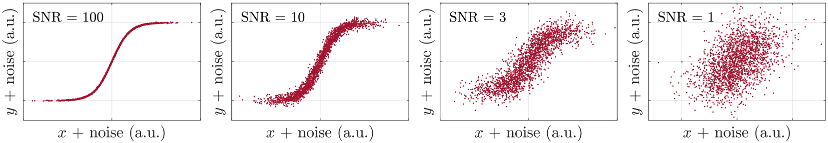
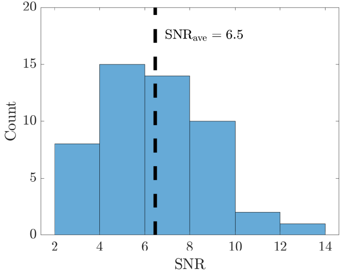


- SNR estimates for our fMRI dataset (upper bound)



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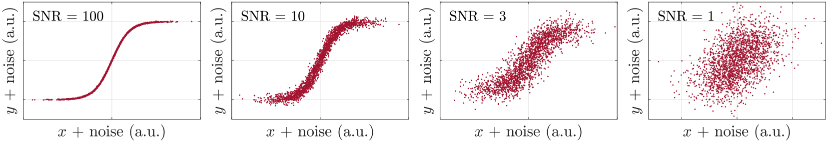
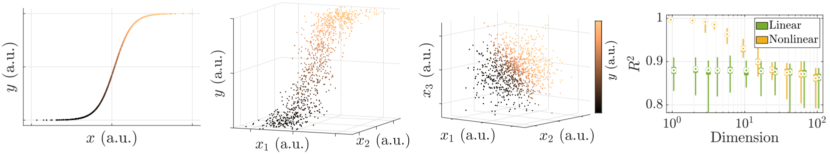


4. Sample scarcity



⋆ What we have is a **combined effect** of 1-4

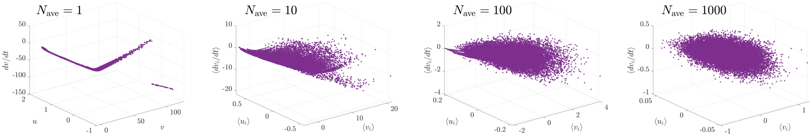
Replication on a Spiking Model

The Izhikevic model:

$$\dot{v}_i = 0.04v_i^2 + 5v_i + 140 - u_i + I, \qquad \text{if} \;\; v_i \geq 30mV : \begin{cases} v_i \leftarrow c \\ u_i \leftarrow u_i + d \end{cases}$$

$$\dot{u}_i = a(bv_i - u_i)$$

1. Averaging across space



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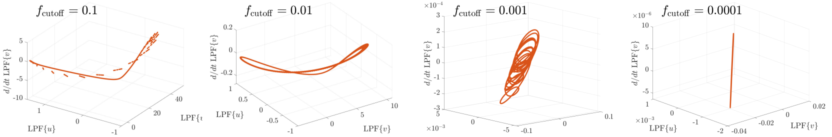


Summary

- ✓ The critical role of scale in computational modeling of neural dynamics
- ✓ The brain is certainly nonlinear at microscale, but apparently linear at the macroscale at rest
- ✓ Potential reasons for (apparent) linearity: spatial averaging, temporal averaging, observation noise, dimensionality

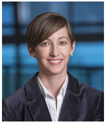
- ? Expanding the families of nonlinear models
- ? Extension of identified models for control
- ? Extensions to include time delays
- ? Are linear models accurate enough?


Scale of Abstraction
Macroscale
Mesoscale
Microscale
Task
Perception
Attention
Decision Making
Rest
Identification
Analysis
Control
Problem

Thank You!

Joint work with

- Prof. Danielle Bassett
- Prof. George Pappas
- Dr. Max Bertolero
- Dr. Jeni Stiso
- Dr. Lorenzo Caciagli
- Dr. Eli Cornblath
- Dr. Xiosong He
- Dr. Arun Mahadevan





and available at

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