Sparse Bayesian inference and experimental design for synaptic weights and locations

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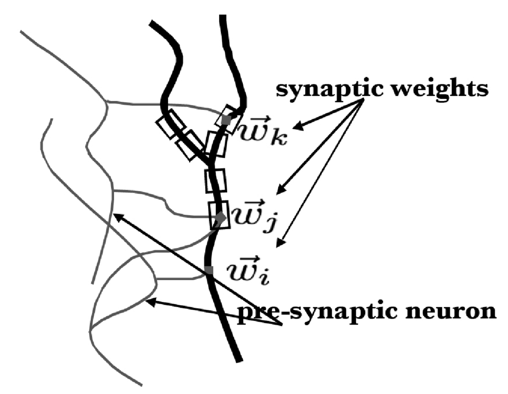
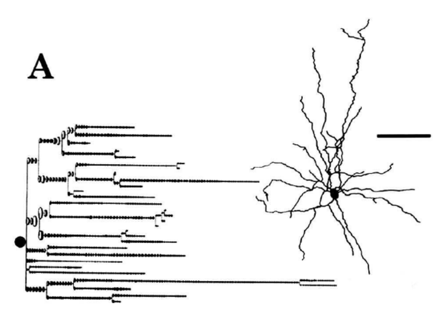
How do neural circuits work?

- Network level: which neurons are interconnected?
- Cellular level:
  - Where are the synaptic inputs in a given dendritic tree?
  - What is their strength?



Basic paradigm: compartmental model

Known anatomy and physical constants of cell (leak coefficient, coupling between compartments) can be encoded in a sparse, symmetric matrix A



The dynamical model

Dynamic Equation: $V_{t+dt} = AV_t + WU_t + \epsilon_t$

Valid in subthreshold regime, may be enforced pharmacologically.

- V_t: Vector of unobserved voltages. $\text{Dim}(V_t) = N \sim 10^3$
- A: Matrix encoding anatomy and electrical constants
- W: Vector of unknown synaptic weights
- U_t: Known presynaptic spike signals
- ϵ_t: Dynamical noise

Observation Equation: $y_t = B_t V_t + \eta_t$

- y_t: Vector of observations. $\text{Dim}(y_t) = S$, $S \ll N$, $t = 1 \dots T$.
- B_t: Observation matrix.
- η_t: Observation noise, Gaussian with covariance C_y.

The Quadratic Log-likelihood:

$$\log p(Y, V|W) = \underbrace{\log p(V|W)}_{\text{From dynamic eq.}} + \underbrace{\log p(Y|V)}_{\text{From observation eq.}}$$

- Marginalize over unobserved voltages:

$$\log p(Y|W) = \log \left[\int p(Y, V|W) dV \right] = r_i W^i + \frac{1}{2} W^i M_{i,i'} W^{i'}$$

Sparse solutions with the Lasso

Solution to sparseness problem: L_1 penalty.

$$\hat{W}(\lambda) = \arg\max_W \left\{ r_i W^i + \frac{1}{2} W^i M_{i,i'} W^{i'} - \lambda \sum_i |W^i| \right\}$$

Convex problem, M negative semi-definite.

Common imaging scheme: scan sampling

Voltages are measured at a small number of compartments that change uniformly with time

$$B_t = \begin{pmatrix} 1 & & & \dots \\ & & 1 & \\ & 1 & & \\ \dots & & & \end{pmatrix}$$

Needs $T \sim O(N)$ measurements to reconstruct signal (Nynquist-Shannon theorem).

New imaging scheme: compressed sensing

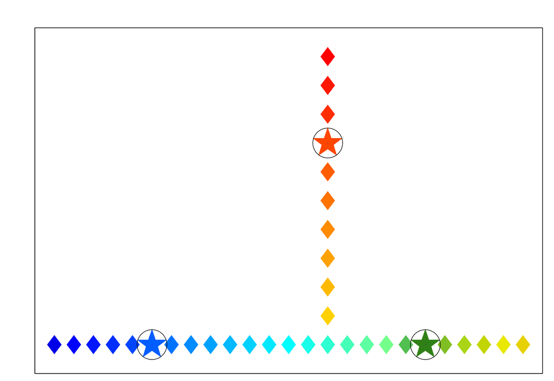
- Measures a linear combination of the voltages at all compartments with random coefficients (Pakman, Huggins & Paninski, 2012)

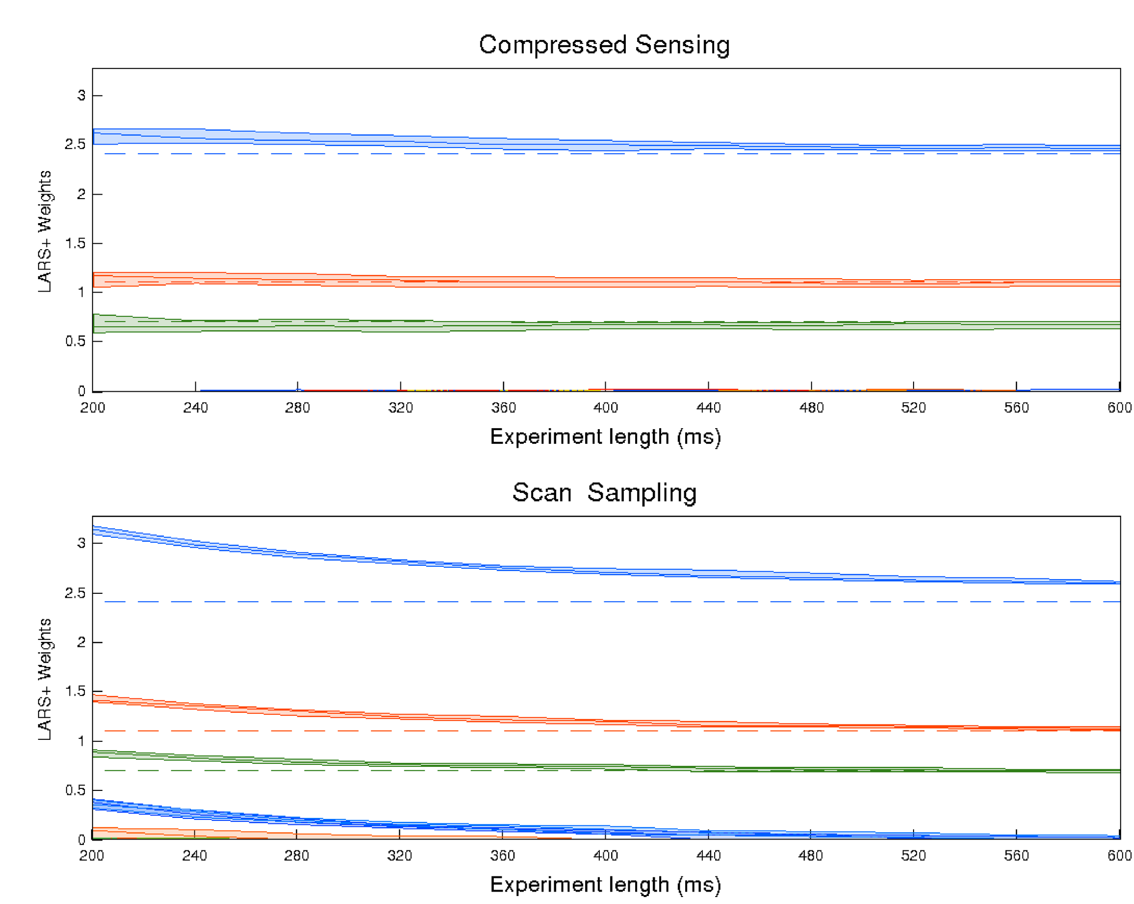
$$B_t = \underbrace{G_t}_{\text{Gaussian entries}} \times \underbrace{(A^{T-2}U_1 + \dots + AU_{T-2} + U_{T-1})^{-1}}_{\text{Offsets neural dynamics}}$$

- Needs $T \sim O(\log N)$ measurements to reconstruct signal with high probability (Candes et. al., 2006).
- Implemented with compressive fluorescence microscopy. (Studer, V. et.al. (2012), Compressive fluorescence microscopy for biological and hyperspectral imaging, PNAS 109(26), E1679-E1687)

Comparison of imaging schemes in toy model

Right: toy neural geometry with 35 compartments and three non-zero synaptic weights at circles. Below: median and .25/.75 quantiles of inferred weights with matching colors, in 100 simulations, as a function of the experiment length. True weights in dashed lines.





Sparse Bayesian inference

- Spike-and-Slab prior (Mitchell & Beauchamp, 1988)

$$s_i | a \sim \text{Bernoulli}(a)$$

$$W_i | s_i, \tau \sim \begin{cases} \delta(W_i) & \text{for } s_i = 0, \\ \mathcal{N}(0, \tau^2) & \text{for } s_i = 1. \end{cases}$$

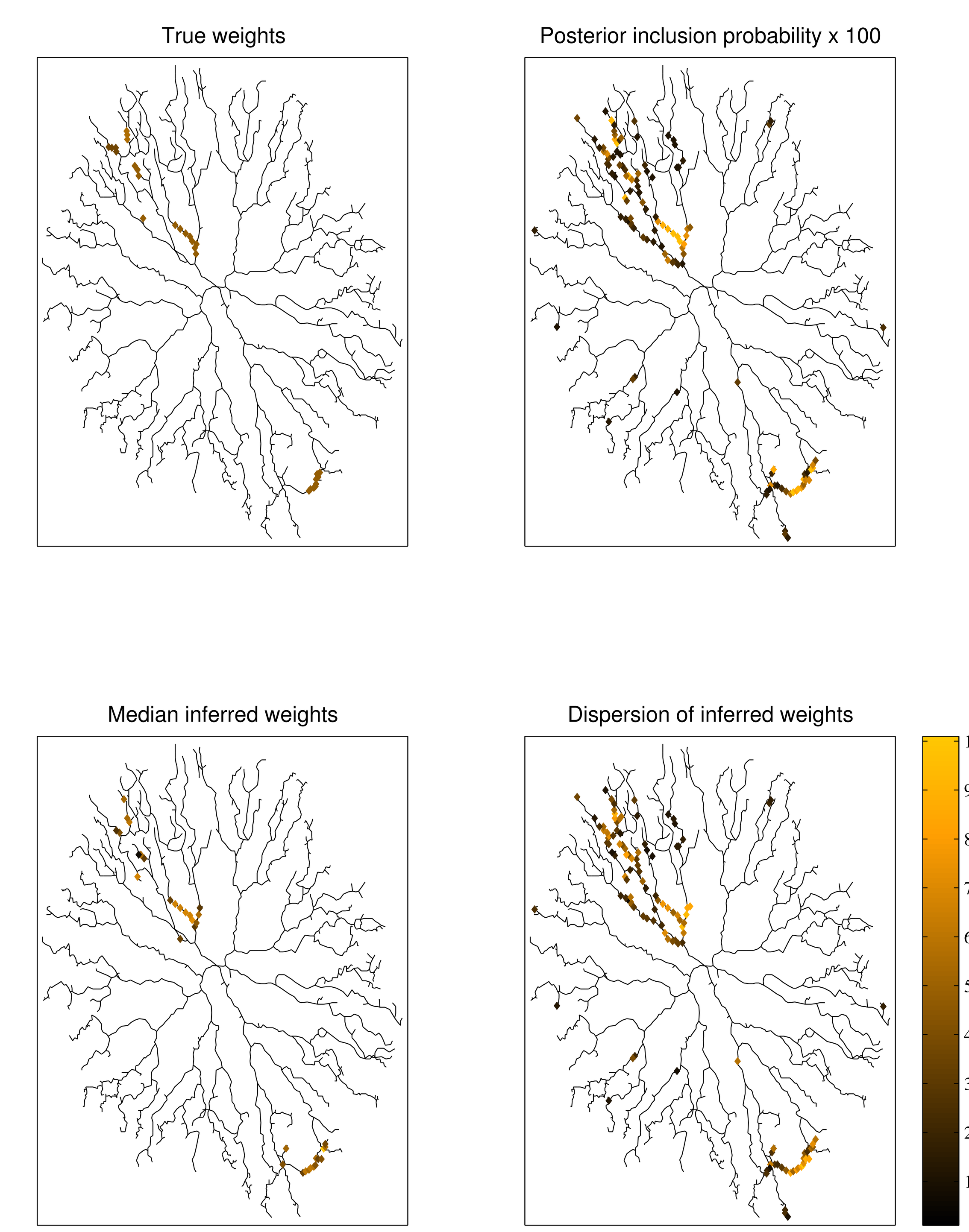
- The parameters a and τ can be determined with an EM algorithm.
- The posterior distribution of the sparsity variables s_i can be Gibbs sampled and each step requires the quotient

$$\frac{p(Y|s_i = 1, S_{-i}, a, \tau)}{p(Y|s_i = 0, S_{-i}, a, \tau)} \qquad (1)$$

where S_{-i} are the sparsity variables without the ith component.
- The probabilities in (1) are Gaussian integrals and can be computed in $O(|S_i|^3)$.
- We developed a method to compute (1) in $O(|S_i|^2)$ as the integral of a Gaussian expectation value.
- Our method allows to use a collapsed Gibbs sampler also when the W_i has a definite sign (Dale's law): the quotient (1) becomes the integral of an expectation value of a truncated multivariate Gaussian.

Simulations in a real reuronal geometry

- $N \sim 10^3$ compartments.
- Optical methods stimulate presynaptic neurons with precision.
- Known dendritic geometry and physical constants.



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