Information Flow in Connectomes II

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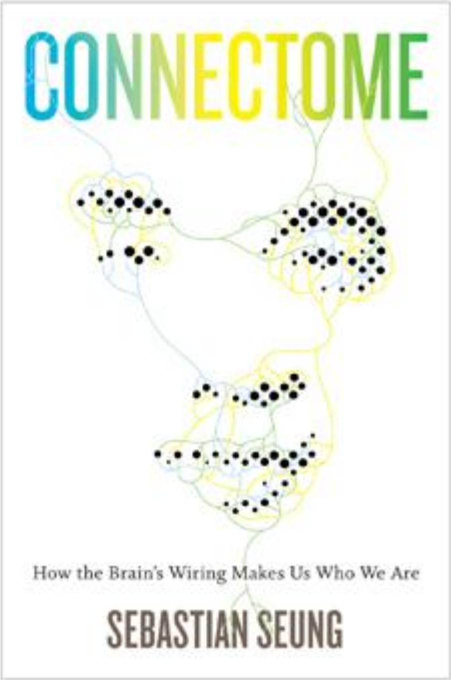
Connectomics: A Grand Challenge of Neuroscience



The theoretical question

- Inferring function from structure
  - What can we say about behavior from the physical structure of the connectome?

Scientific Questions

Question 1 Is it possible to infer functional sub-circuits directly from the anatomical connectome and the electrochemical properties of synapses?

– Eigenmode analysis is a principled method for predicting functional subcircuits

Question 2 Do neuronal circuits allow behaviors to happen as quickly as possible under information flow limitations imposed by synaptic noise properties and synaptic connectivity patterns?

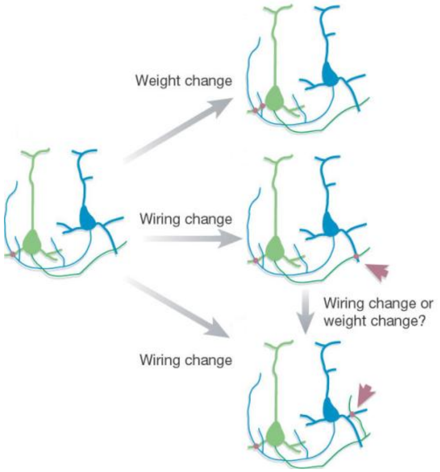
– Informational flow lower bounds are remarkably predictive of experimentally observed behavioral time scales

Question 3 Do synaptic micro-architectures optimize information flow under constraint on number of synapses?

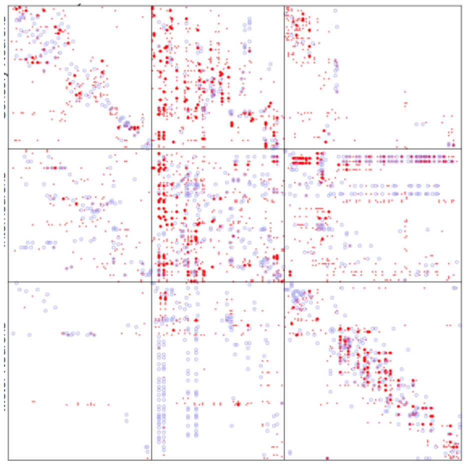
– Hub-and-spoke architectures (as in known chemosensory circuits) optimize bottleneck diameter under synapse number constraint

Vertebrate Memory Recall, Sensory Processing, and Cognition

- Memory stored in connectivity pattern/weights of synapses (Varshney et al., 2006)



- How can these be read out by the brain itself?



A First Step: Experimental Data Analysis

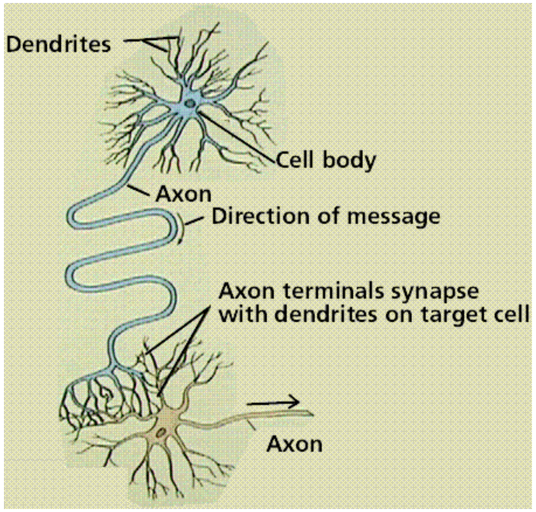
Idea

- Rather than considering the question of how the brain itself can read out the connectome, e.g. for memory recall, let us first consider how a scientist can read out the connectome
- Induce spiking behavior (a form of functional connectivity) to infer anatomical connectivity using Bayesian data analysis methodologies

Outline

- Neural connectivity mapping
  - Multi-neuron excitation and compressed sensing
  - Challenges due to nonlinearities
- Approximate Message Passing:
  - Graphical model approaches
  - A systematic procedure for nonlinear sparse estimation
  - Cortical connectome mapping
- Visual receptive field estimation
  - Hybrid generalized approximate message passing
  - Salamander retinal receptive field: experimental results

Basic Neuron Model

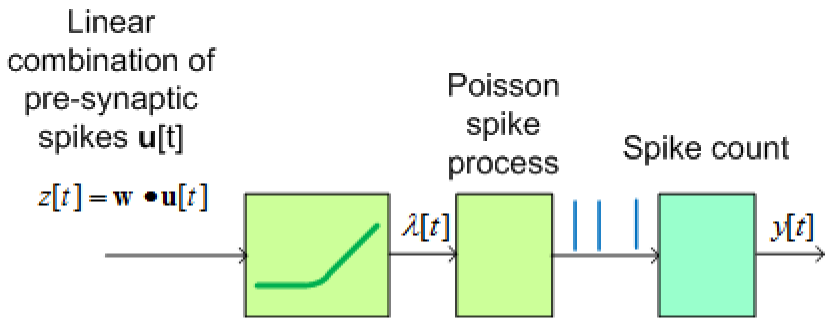


- Neuron: basic information processing cell
  - dendrites receive signals
  - soma processes signals
  - axon outputs signals
  - synapses: electrochemical connections

- Linear nonlinear Poisson (LNP) response model:

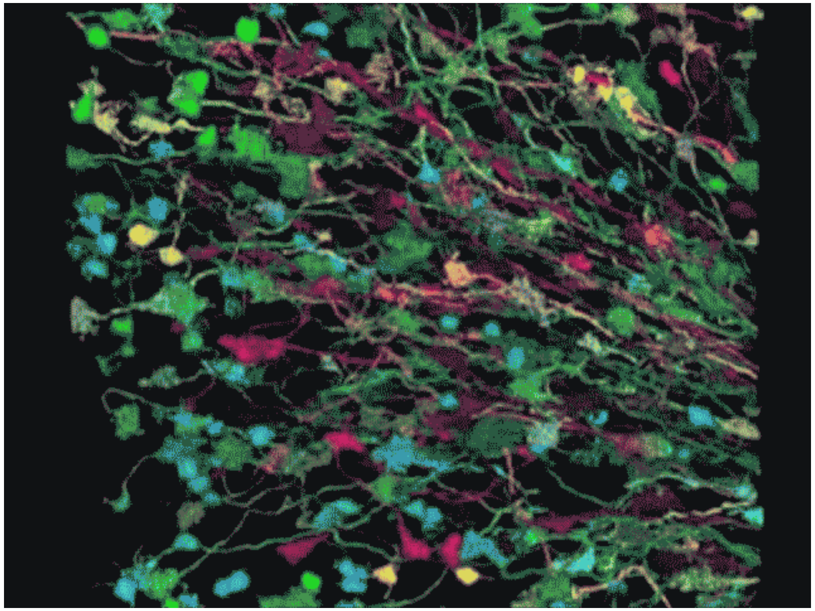
$$z = \sum_{j=1}^{n} a_j x_j \,, \lambda = f(z + d), y = \mathcal{Pois}(\lambda)$$

where λ = Poisson rate and y = number of spikes in interval



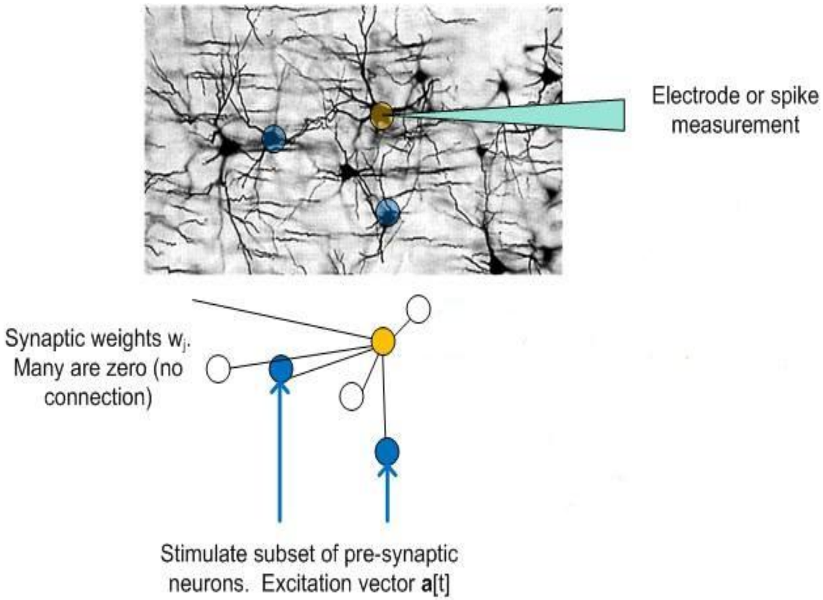
- Feedforward structure (no feedback)

Neural Connectivity Mapping



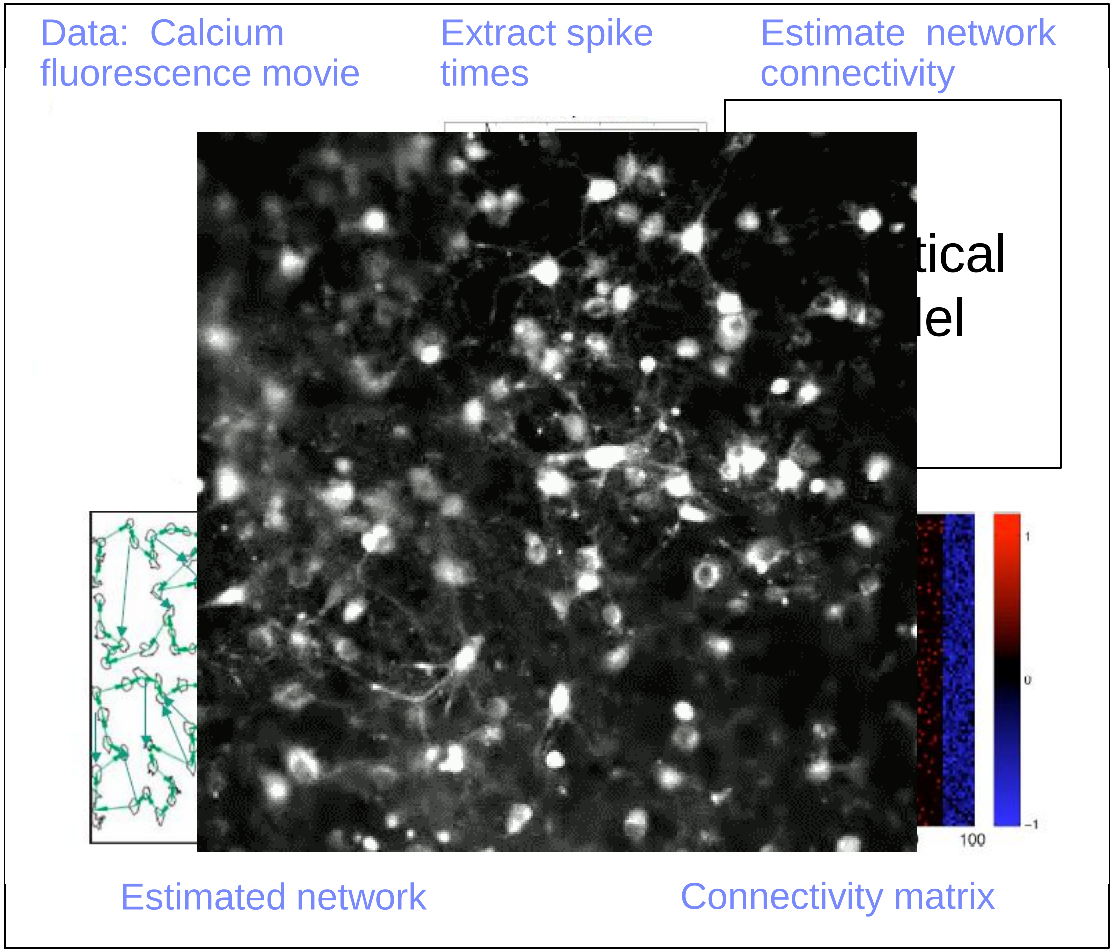
- Mapping neural circuits:
  - Information processing
  - Ensembles of neurons
- Micro-level connectivity
  - Difficult to observe directly *in vivo*
- Staggeringly large data sets
  - Visual cortex ~140 million neurons
  - Connections: ~1000 each
- Are there ways other than electron micrography?
  - (+ machine vision) or (+ crowdsourcing)

Electrophysiology: Single Neuron Excitation



- Excite one pre-synaptic neuron at a time
- Measure response of potentially neighboring post-synaptic neurons
- Estimate synaptic weight w from spike count $y[t]$
- Infer connection between excited and measured neurons if nonzero weight
- Scan through each potential pair of connected neurons

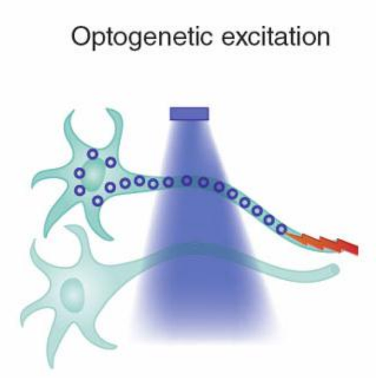
Inferring Neural Connectivity from Calcium Imaging

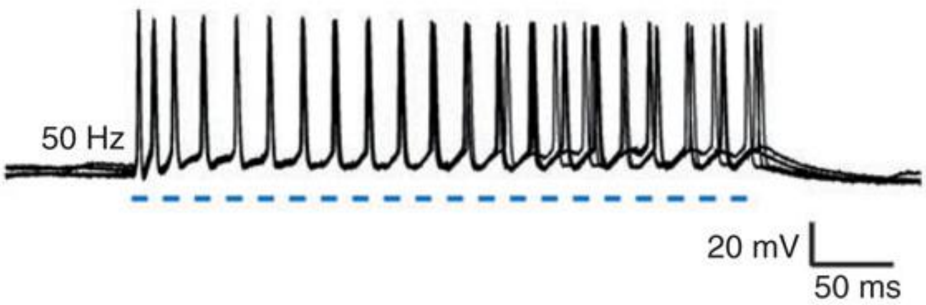


- Genetic modifications
  - Ca^{2+} ion sensitive protein
  - Indicates action potentials
  - Spectrally fluoresce
- Infer network connections statistical correlations in spike rates
- Bayesian / sparse models naturally apply

Optogenetically Controlled Single Neuron Excitation

- Further genetic modifications for optogenetic control using channelrhodopsin-2
  - Light-activated excitation

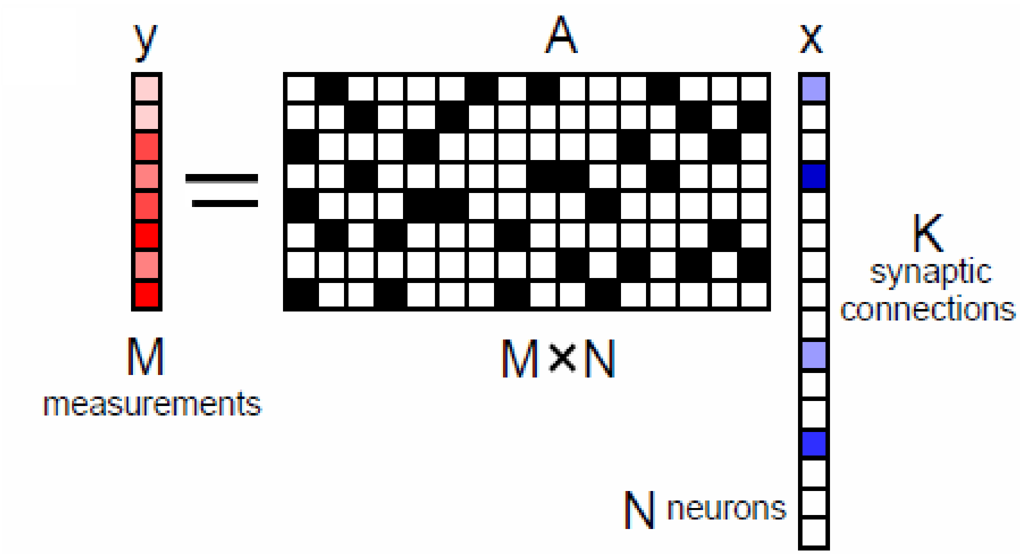




- Optogenetics + Calcium Imaging = all-optical system

- Single neuron excitation: one at a time
  - Ineffficient since connectivity is sparse, even nearby
  - Rare important long-distances hits may be missed
  - Inaccurate and may multiple trials
  - Misses subthreshold connections

Multi-Neuron Excitation: A New Hope



- Excite many neurons simultaneously
  - Row of *A* matrix is a subset of excited neurons
  - Measured response is an entry of *y*
  - The vector x is the unknown weight vector to be inferred: *sparse*

- Canonical compressed sensing with precise anatomical sparsity (Hu & Chklovskii, 2010)

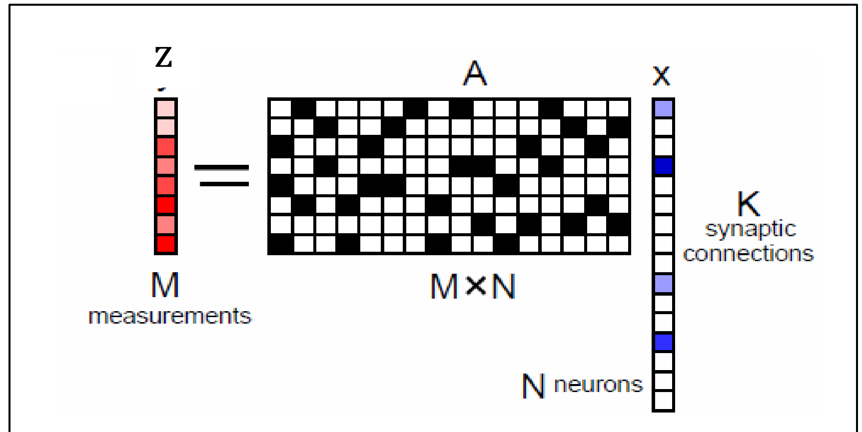
A Challenging Inverse Problem

Nonlinearity & Poisson spiking

Spike count *y*

Non-Gaussian randomness

Unknown mapping



Must incorporate sparsity and other structural information in prior on weight x

- Compressed sensing estimation of weight vector ***x***
  - Place sparse prior on ***x*** to model sparsity in weights
  - Noise is non-additive Gaussian: nonlinearities and Poisson process

Consider a Bayesian formulation

Estimate $\boldsymbol{x}$ from $\boldsymbol{y}$

$\boldsymbol{x}$ variables have prior probability $p(x_1, x_2, \ldots, x_N)$, e.g. sparse/distribution as stretched exponential

$\boldsymbol{y}$ variables are measurements with likelihoods $p(y_1, y_2, \ldots, y_M | x_1, x_2, \ldots, x_N)$, e.g. from LNP model

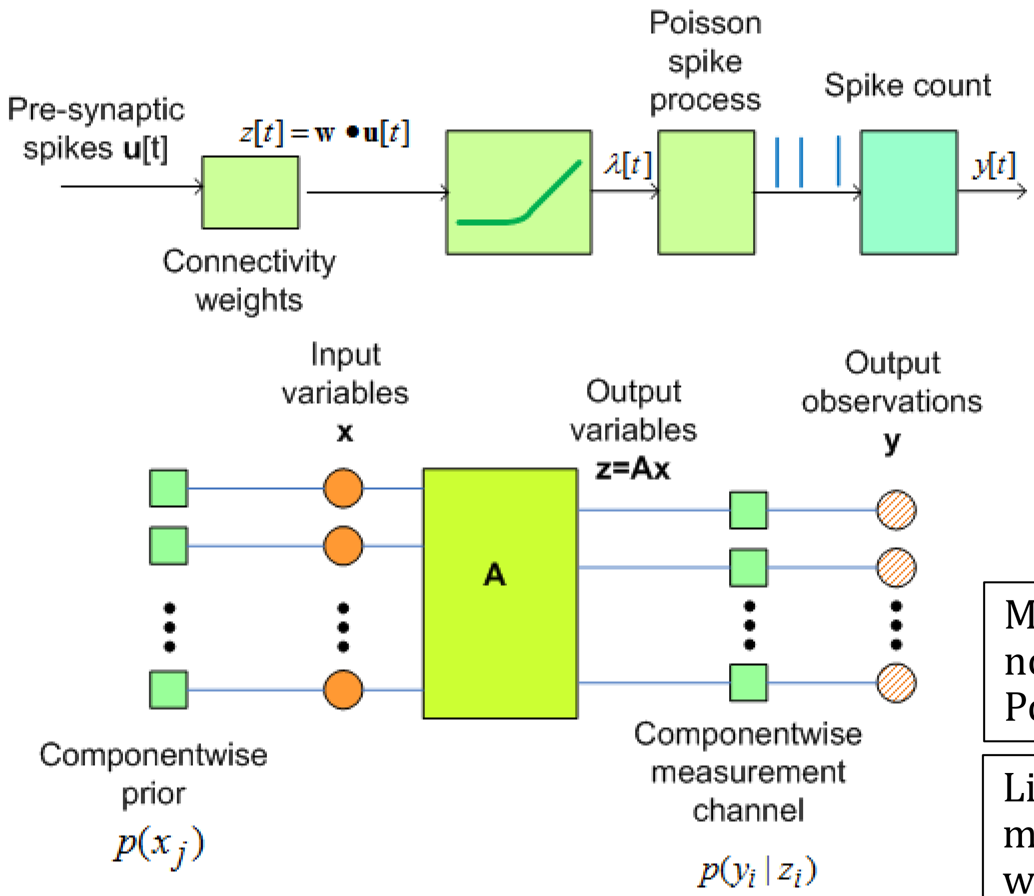
Minimum mean square error (MMSE) estimate:

$$\hat{\boldsymbol{x}} = E(\boldsymbol{x}|\boldsymbol{y})$$

Maximum a posteriori (MAP) estimate:

$$\hat{\boldsymbol{x}} = \arg\max_{\boldsymbol{x}} p(\boldsymbol{x}|\boldsymbol{y})$$

A Graphical Model for Neuronal Connectivity Estimation



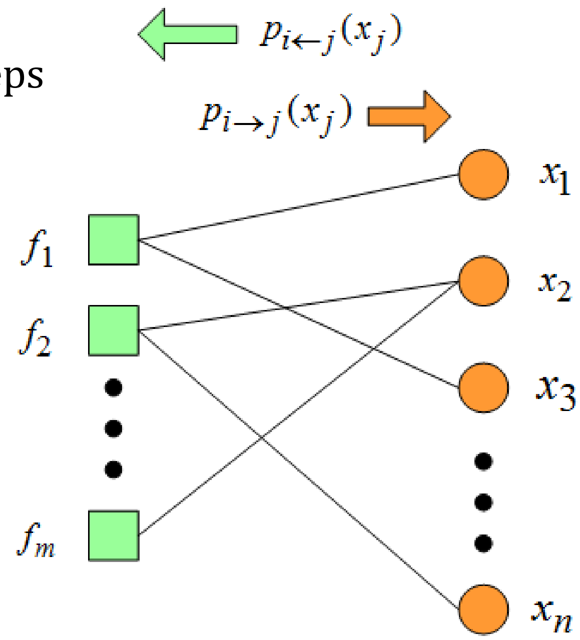
Model for unknown nonlinearity and Poisson process

Linear connectivity matrix with sparse weights

- General separable output channel after linear mixing
- Message-passing algorithm for connectivity estimation for this setting due to Rangan (2010)

Graphical Models and Loopy Belief Propagation

- Computational complexity of MAP or MMSE estimation is exponential in problem size, *N*
- **Belief propagation**: Divide and conquer
  - Factor distribution into smaller terms
  - Iterative algorithm: global inference through local iterative steps
  - Pass *messages* or beliefs/posteriors
  - Message from factor node:
    - current estimate of marginal of that variable
    - based on all other variables
  - Message from variable node to factor node:
    - estimate of the variable from marginals
- General method
  - Exact when graph lacks loops
  - Empirically useful with loops
- Still exponential in number of terms in each factor



Approximate Message Passing: Key Features

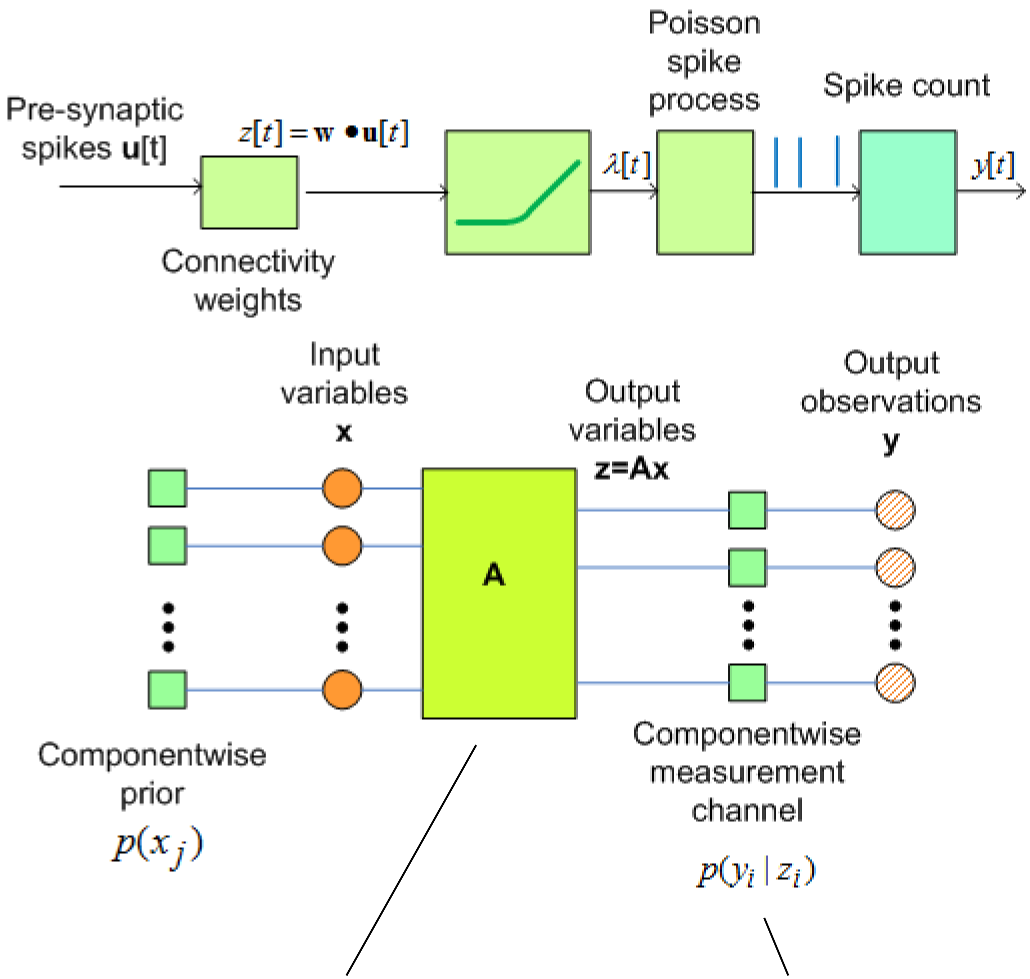
- Approximate iterative method for MMSE and MAP

$$\mathbf{y} = \mathbf{A}\mathbf{x} + \mathbf{w} \qquad \text{Gaussian noise, i.i.d. } \mathbf{A}$$

- Based on Gaussian approximations of loopy BP
  - Approximate messages from variable to factor nodes
  - Justified by Central Limit Theorem
- Computationally fast since no exponential dependence on problem dimensions

- Originally for CDMA multi-user detection (Boutros & Caire, 2001)
- Provable guarantees for sparse i.i.d. matrices (Montanari & Tse, 2005), (Guo & Wang, 2006/2007)
- Recent precise analysis for dense matrices (Donoho, Maleki, & Montanari, 2009), (Bayati & Montanari, 2010)
  - Per iteration estimation error predicted by state evolution equations

GAMP: Neural Connectivity Estimation



Linear connectivity matrix with sparse weights

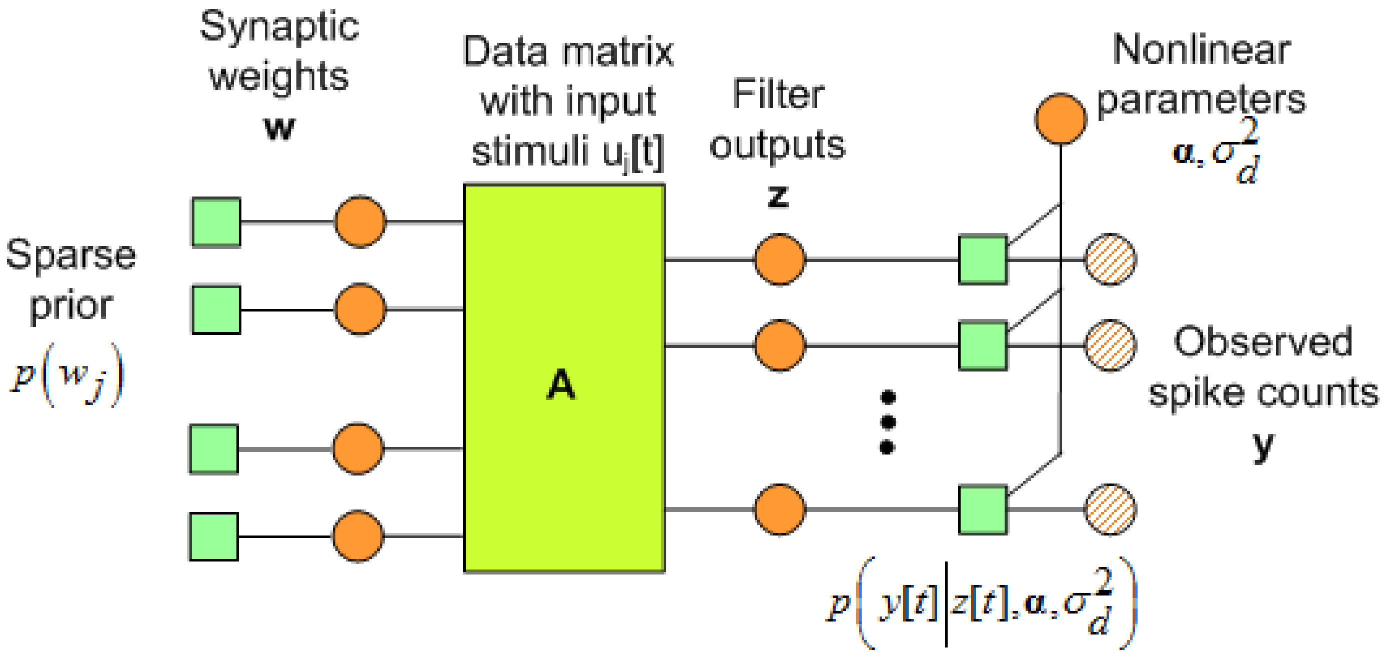
Model for unknown nonlinearity and Poisson process

- Generalized AMP (Rangan, 2010)
  - Allows general separable output channel after linear mixing
  - Quadratic approximation from factor node

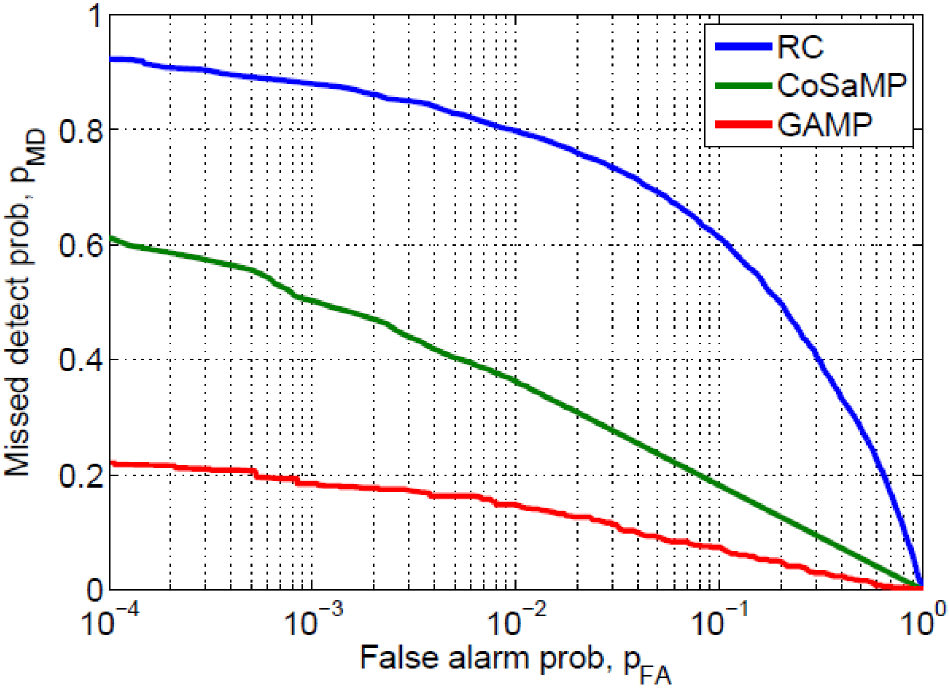
- GAMP perfectly matched to abstraction of connectivity estimation
  - Random neural excitation creates random linear mixing
  - Nonlinear-Poisson spike output captured by output channel $p(y_i|z_i)$
  - Incorporates weight sparsity and nonlinearities

  - Unknown parameters in nonlinearity can be solved iteratively
  - Computationally fast algorithm with testable conditions for optimality under i.i.d. stimulation

Neural Connectivity Estimation via GAMP



Simulation: Connectivity Detection

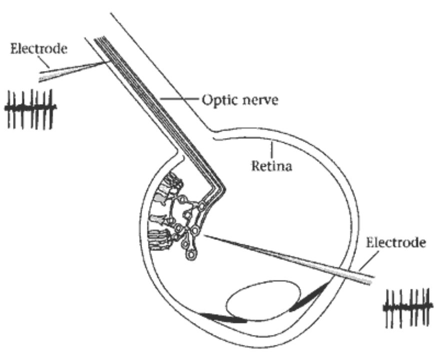


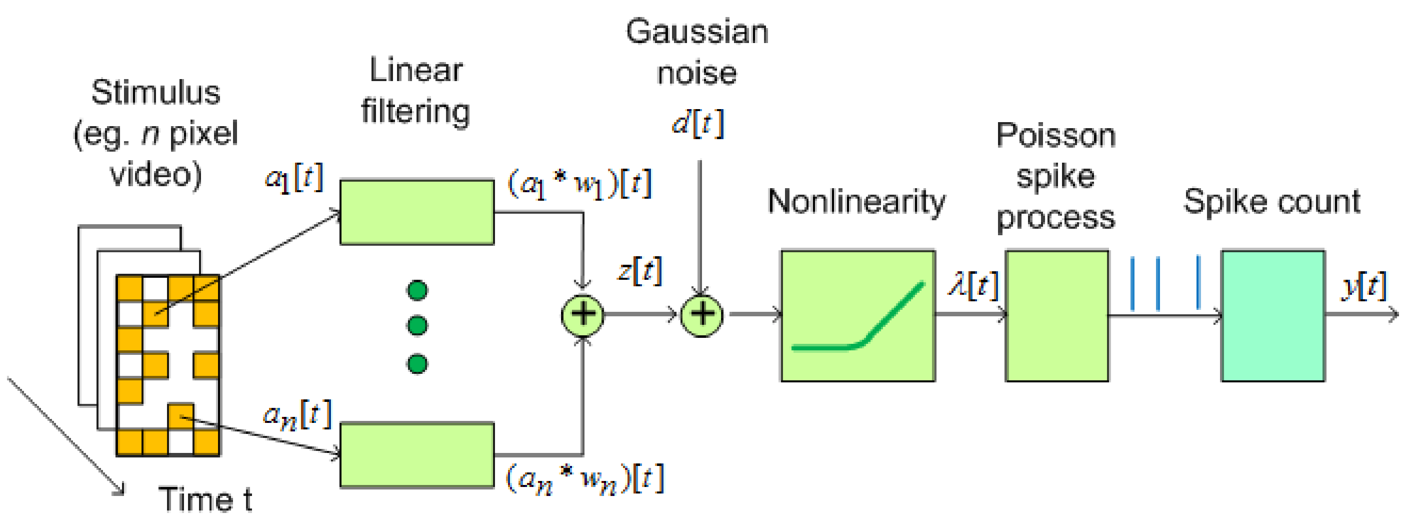
m = 300 measurements
n = 500 pre-synaptic neurons or weights
k = 30 or 6% connected

- Reverse Correlation (RC): linear least-squares estimation, no sparsity
  $$(A^*A + \sigma^2 I)^{-1} A^* \boldsymbol{y}$$
- CoSaMP: greedy convex-optimization-based method for compressed sensing that assumes linear output
- GAMP gives lower missed detection rate for any given false alarm rate

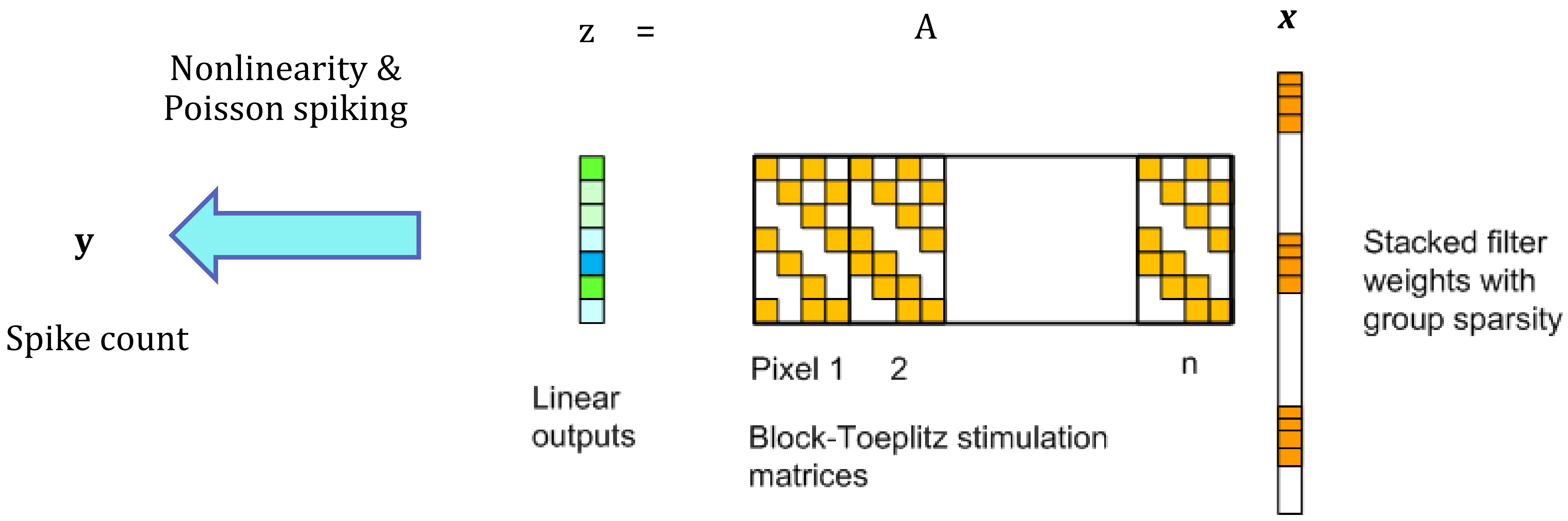
Receptive Field Estimation

- Retinal ganglion cells (RGCs):
  - Sensitive to components of visual image.
  - Typically some local feature (curve, edge, etc.)
- Receptive field estimation:
  - Assume LNP model with filter for each input
  - Expose eye to checkerboard patterns
  - Measure response of RGC
  - Infer linear filters





LNP Model with Group Sparse Structure

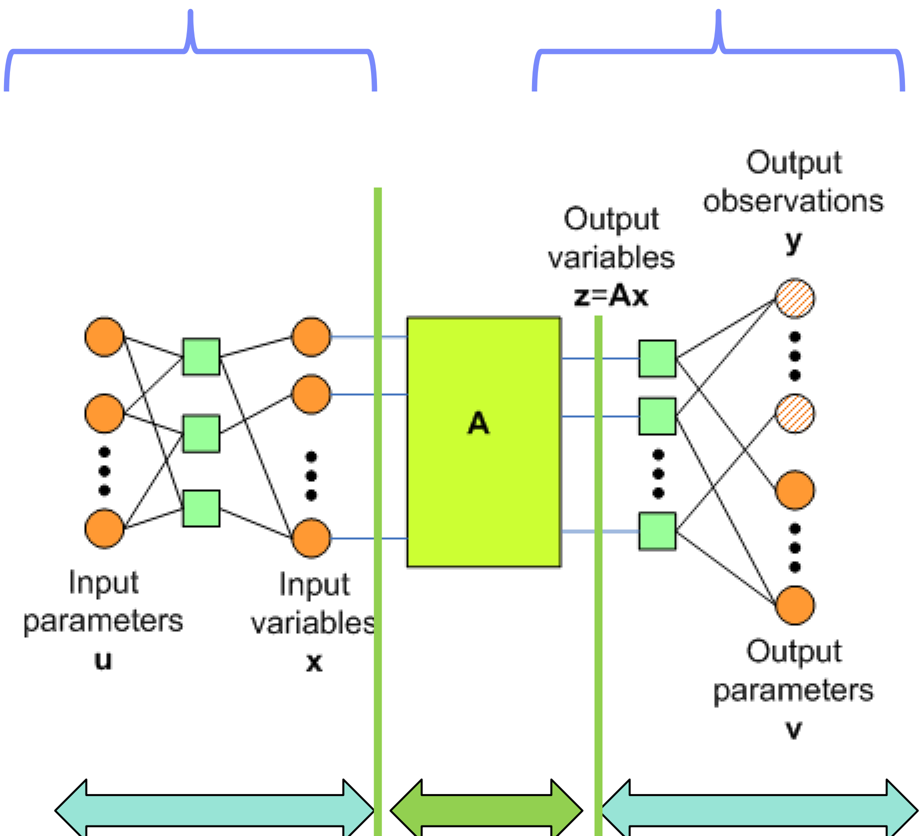


- Linear filter component matrix representation:
  - Each row of stimulation matrix *A* contains *n* pixel values at *L* delays, where *L* = filter length
- Group sparse structure

Hybrid GAMP: Extend to General Graphical Models

Correlations in input x with hidden variables u

Correlations in output y with hidden variables v



Standard BP messages

GAMP messages

Standard BP messages

- Extend AMP-like methodology by adding graphical models for:
  - Correlations between variables or observations
  - Nonlinear observations
  - Unknown parameters in distributions
- Model is a hybrid of standard graphical model and AMP
- Apply GAMP messages only on model with linear relationships

Salamander Receptive Field Estimation Experiment

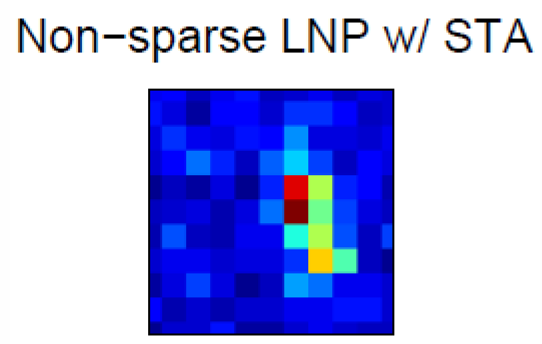
1. Salamander retina exposed to 80×60 i.i.d. black-white pixel image. Spike counts measured in 10 ms intervals.
2. Reduce to a subset of an 11×11 pixel area around pixel with largest response as predicted by STA (Response to other pixels assumed to be zero).
3. Assume $L = 30$ filter taps per response
4. Assume initial nonlinearity $f(v)$
5. Run Hybrid GAMP algorithm with group sparsity prior to compute estimate for filter coefficients
6. Re-estimate nonlinear function $f(v)$ from filter outputs.
7. Return to step 5

NOTE: Use data from Anthony Leonardo, Janelia Farm Research Campus

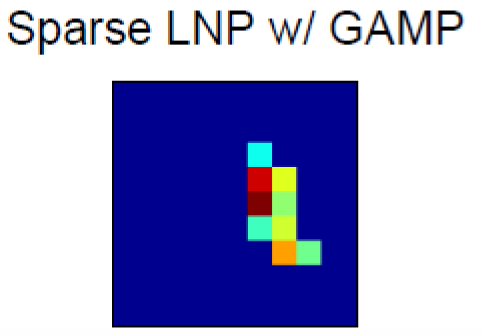
Experimental Results: Salamander Retinal Response

Spatial receptive field

- Figures show estimated 11 × 11 response magnitudes
  - Color indicates magnitude of 30-tap filter for each of the pixels

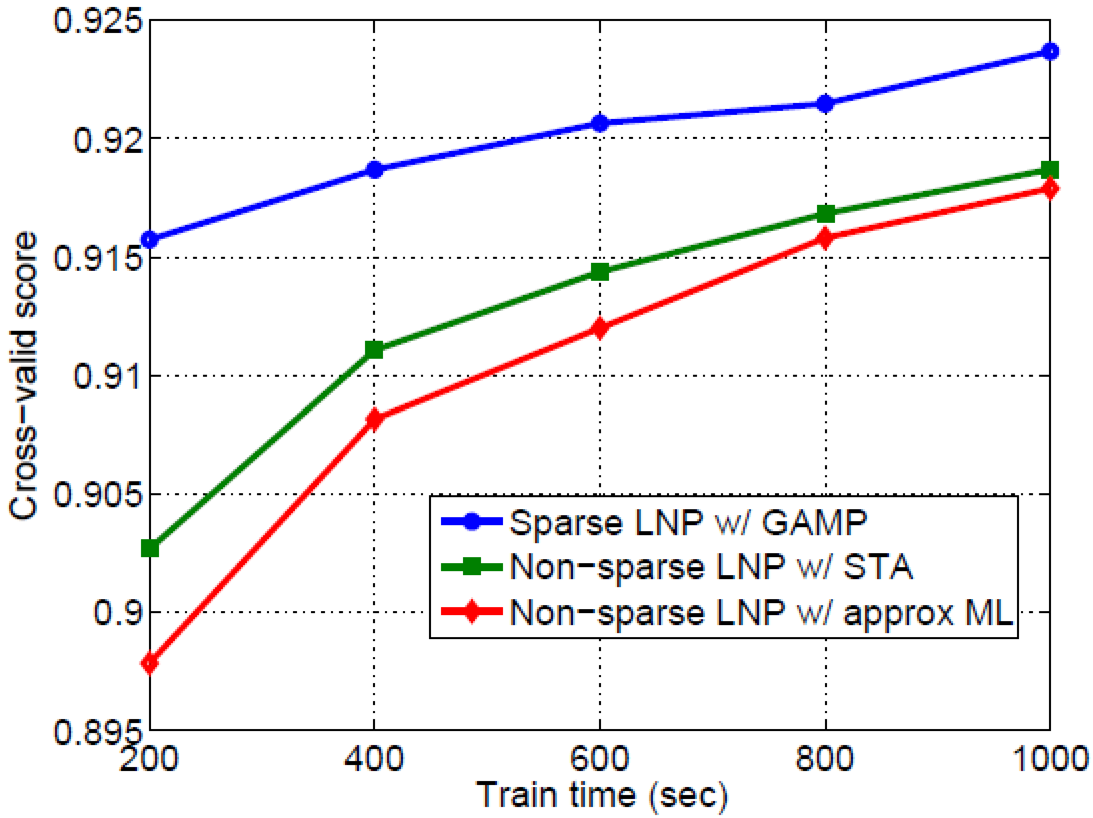


- Standard STA estimate shows noisy (spurious) responses outside center of receptive field



- GAMP method removes significant levels of noise and shows only a response in a small area.

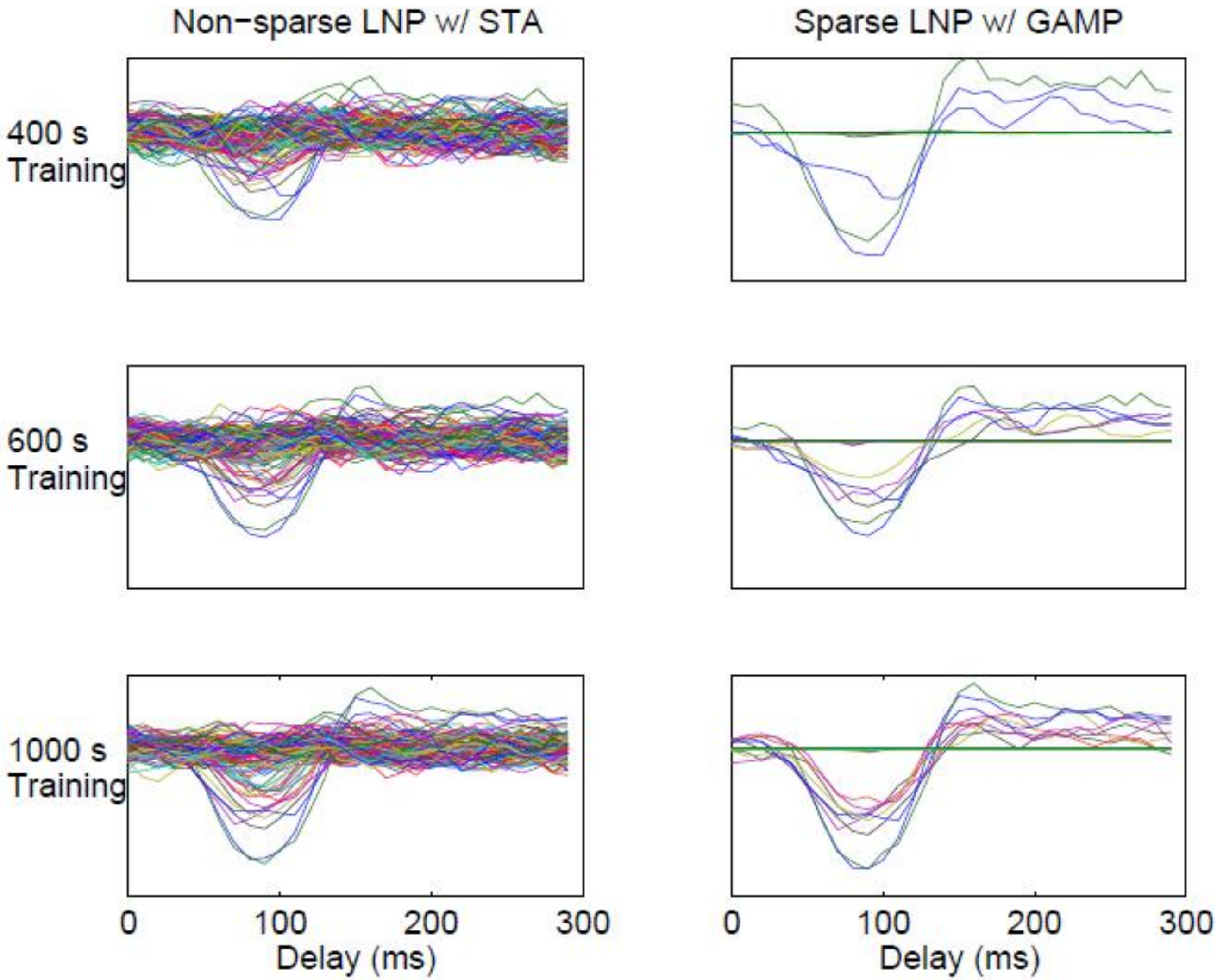
Experimental Results: Cross-Validation



Num training samples	Cross-validation score	
	STA	G-AMP
25000	0.906	0.917
50000	0.914	0.921
100000	0.918	0.923

- Estimates validated on samples not used in training
- Cross-validation score = Geometric mean of the likelihood of the predicted spike rate
- GAMP requires significantly fewer samples for same prediction error

Experimental Results: Salamander Retinal Response



- Hybrid GAMP provides much less noisy estimates of filters
- By imposing sparse priors on the linear weights, GAMP sets many noisy estimates to zero
- Get clean responses even with low number of training samples

Estimated linear responses to 11 x 11 pixels in retinal neurons of a salamander

A First Step: Experimental Data Analysis

Idea

- Rather than considering the question of how the brain itself can read out the connectome, e.g. for memory recall, let us first consider how a scientist can read out the connectome
- Induce spiking behavior (a form of functional connectivity) to infer anatomical connectivity using Bayesian data analysis methodologies

Outline

- Neural connectivity
  - Multi-neuron e
  - Challenges due
- Approximate Mess
  - Graphical mod
  - A systematic pr
  - Cortical connec
- Visual receptive fie
  - Hybrid general
  - Salamander retinal receptive field: experimental results

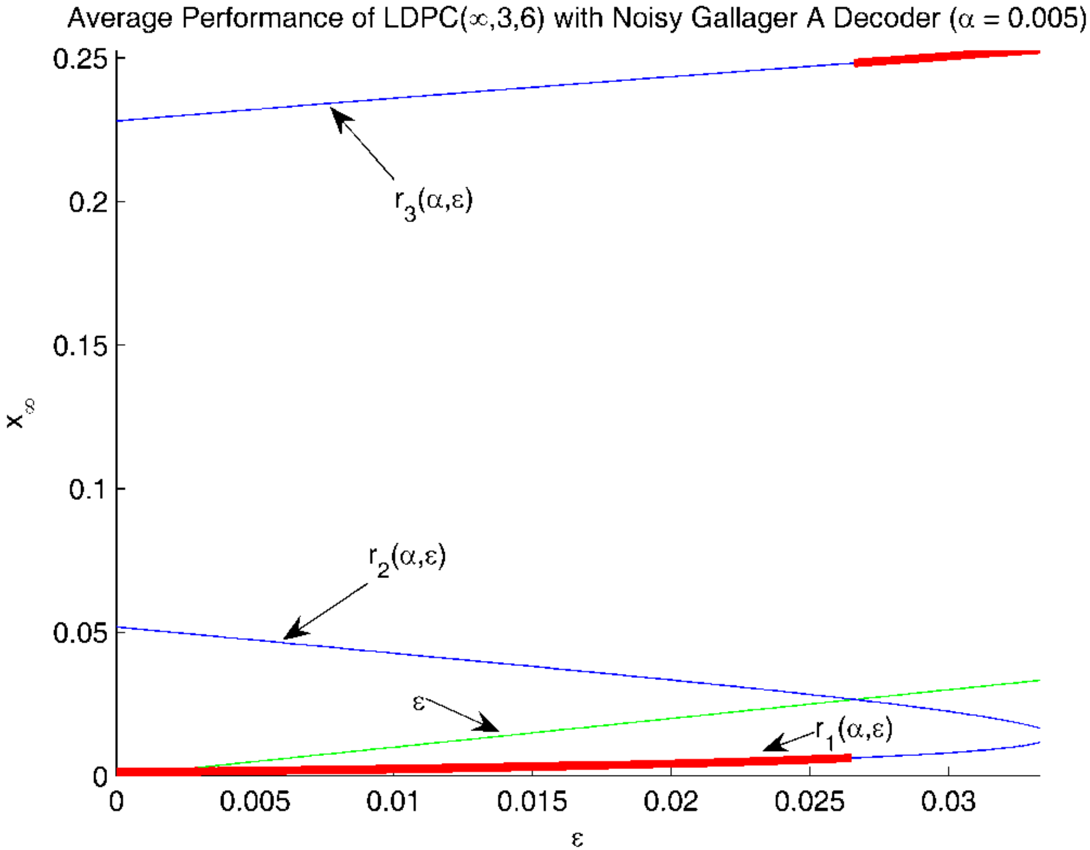
- Thinking technologically rather than scientifically, we can use message-passing Bayesian algorithms for Bayesian inference to reconstruct sensory receptive fields and neuronal connectivity
- Generalized Approximate Message Passing (GAMP) is the best known algorithm for these neuroengineering problems
- Could the brain itself be using message-passing algorithms for Bayesian inference for memory recall and sensory processing?

The Bayesian Brain

- At behavioral level, neural information processing seems to be Bayesian inference
  - (Ernst and Banks, 2002), (Knill and Richards, 1996), (Kording and Wolpert, 2004), (Rao, Olshausen, and Lewicki, 2002), (Stocker and Simoncelli, 2006), (Weiss, Simoncelli, and Adelson, 2002)
- Bounded rationality in economics
  - cf. (Varshney and Varshney, 2008)
- Neurons might be able to implement belief propagation and similar iterative message-passing decoding algorithms for inference in graphical models
  - (Beck and Pouget, 2007), (Dayan, Hinton, Neal, and Zemel, 1995), (Deneve, 2008), (Doya, Ishii, Alexandre, and Rao, 2007), (Hinton and Sejnowski, 1986), (Huys, Zemel, Natarajan, and Dayan, 2007), (Koechlin, Anton, and Burnod, 1999), (Lee and Mumford, 2003), (Ma, Beck, Latham, and Pouget, 2006), (Ott and Stoop, 2006), (Rao, 2005), (Sahani and Dayan, 2003), (Litvak and Ullman, 2009)

How does noise impact message-passing circuits?

- Thermal **noise** strongly affects synaptic transmission (Manwani and Koch, 1999)
- Consider an electronic circuit that uses a (Bayesian) message-passing algorithm to decode a low-density parity check code and that is subject to transient noise/faults
- There are phase transitions in final error probability performance as functions of within-decoder noise

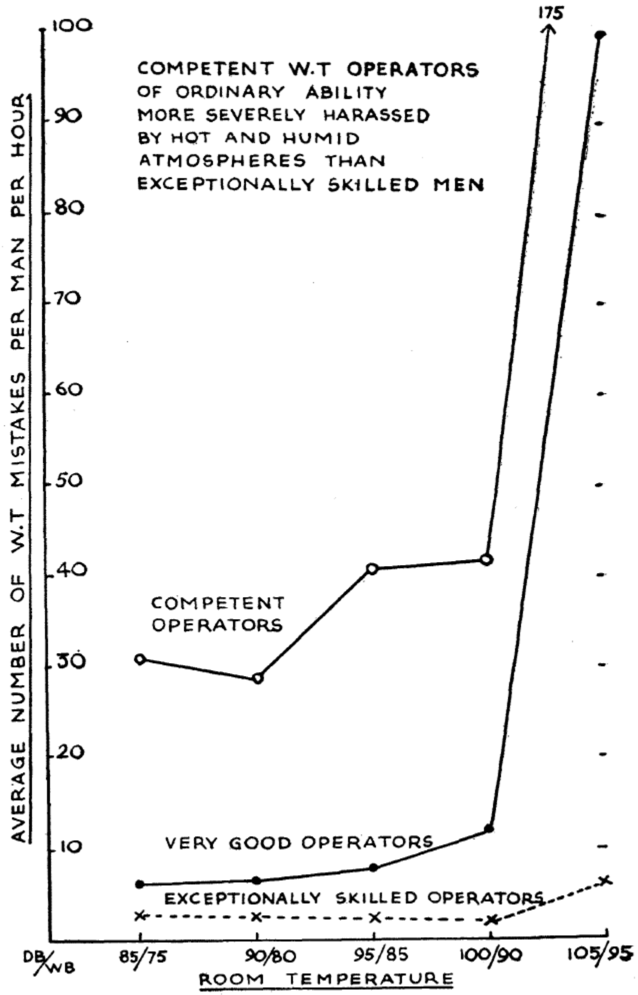


Human Cognitive Work

- People are central in the 'doing of work' and the delivery of services
- People often perform inference tasks similar to decoding and sometimes make errors

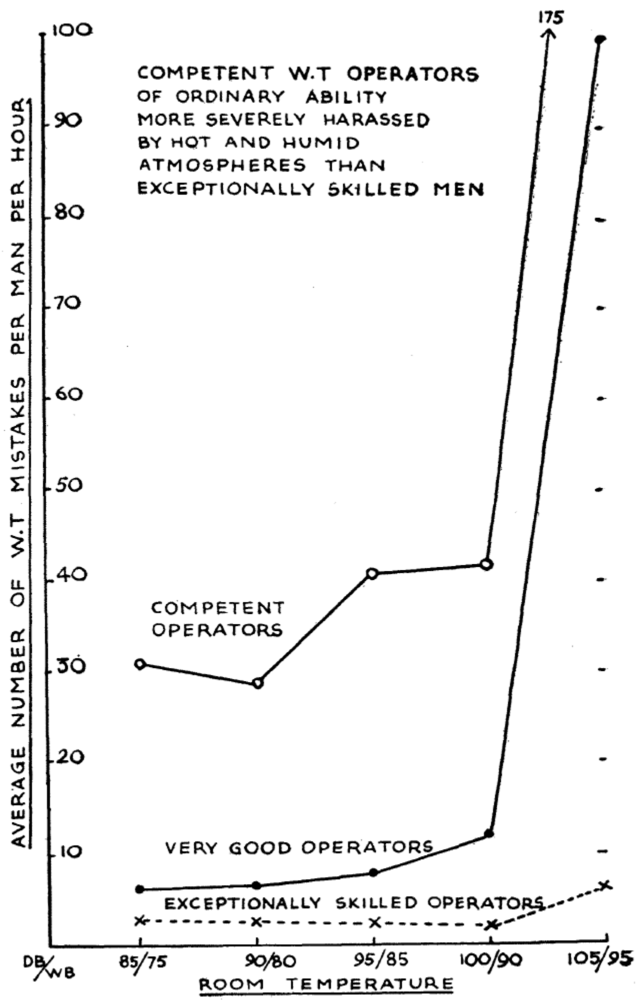
N. H. Mackworth, "Effects of Heat on Wireless Telegraphy Operators Hearing and Recording Morse Messages," *British Journal of Industrial Medicine*, vol. 3, pp. 143-158, July 1946.

Heat Stress on Human Telegraphers

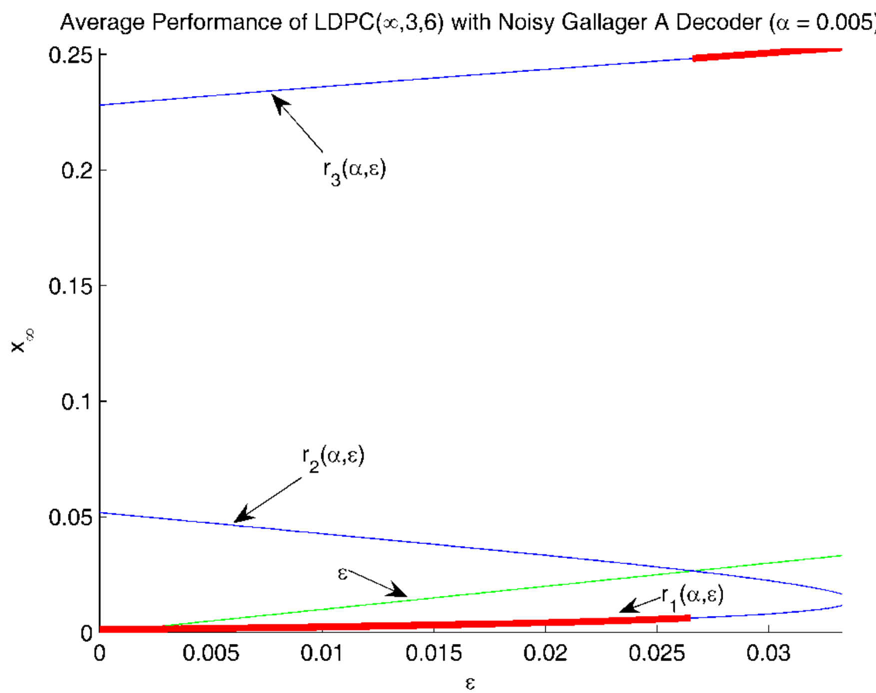


(Mackworth, 1946)

Heat Stress on Human Telegraphers



(Mackworth, 1946)



- Does heat stress increase synaptic thermal noise and cause a phase transition in a message-passing algorithm in the brain?

Closing Remarks

- Presented a state-of-the-art connectome (and receptive field) data analysis method that uses a message-passing algorithm for Bayesian inference, built on models of signal flow in the nervous system.
  - Computationally simple and general procedure
  - Extend compressed sensing paradigm to consider nonlinearities and structured sparsity

  - Experimental validation of connectome reconstruction
  - Integrate-and-fire models, calcium imaging models, etc.

- Does the brain itself use message-passing algorithms internally?
  - There is a great deal of work in the literature that argues for a neuronal implementation of Bayesian message-passing algorithms
  - Human cognitive performance seems to recreate phase transitions that have been characterized in other message-passing inference circuits

References

- Alyson K. Fletcher, Sundeep Rangan, Lav R. Varshney, and Aniruddha Bhargava, “Neural Reconstruction with Approximate Message Passing (NeuRAMP),” in *Proc. Twenty-Fifth Annu. Conf. Neural Information Processing Systems* (*NIPS*), pp. 2555–2563, Dec. 2011.

- Lav R. Varshney, “Performance of LDPC Codes Under Faulty Iterative Decoding,” *IEEE Transactions on Information Theory*, vol. 57, no. 7, pp. 4427–4444, July 2011