Approximate Bayesian Inference for a Mechanistic Model of Vesicle Release at a Ribbon Synapse

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Introduction

Photoreceptors and bipolar cells in the vertebrate retina are equipped with highly specialized ribbon synapses, able to simultaneously release multiple glutamatergic vesicles in a process known as multivesicular release, contributing to rapid and reliable information transmission.

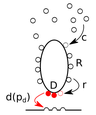
We develop an approximate Bayesian inference scheme for a fully stochastic, biophysically inspired model of glutamate release at this specialised synapse. The model translates known structural features of the ribbon synapse into a set of stochastically coupled equations. We approximate the posterior distributions by updating a parametric prior distribution via Bayesian updating rules.

We show that model parameters can be efficiently estimated for synthetic and experimental data from in vivo two-photon experiments in bipolar cells of zebrafish. Also, we find that the model captures complex properties of the synaptic release such as the temporal precision.

Mathematical description

The vesicle movement at the ribbon is modeled in a discrete way and the changing rates between the three vesicle pools are stochastic:

$$
\begin{aligned}
c(t) &\sim Poisson(\lambda) \\
r(t) &\sim Binomial(R_{t-1}, p_r) \\
d(t) &\sim Beta\text{-}binomial(D_{t-1}, \alpha, \beta) \\
&\text{with } \alpha = f(\rho, p_d(Ca)) \\
&\text{and } \beta = g(\rho, p_d(Ca))
\end{aligned}
$$

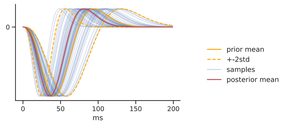


Each rate depends on the current state of the model and is limited by the maximal pool size.

The parameters of r and c are constant over time whereas the distribution of the actual exocytosis d depends on the correlation ρ between vesicles, and in a non-linear way on the calcium concentration:

$$p_d = \frac{1}{(1 + \exp(-k(Ca - h))}$$

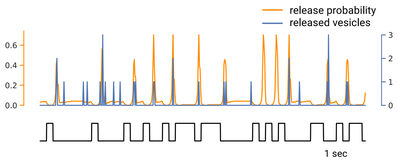
Linear part



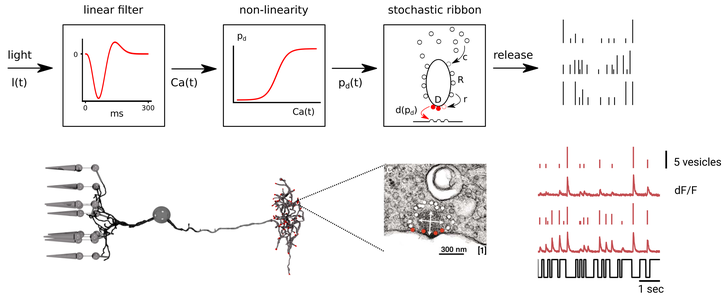
The biphasic kernel of the linear stage of the LNR model is parametrized by one single time stretching parameter γ.

Baseline GLM

We used a GLM as a baselinemodel assuming Poisson noise and a logarithmic link function. The model was trained to predict the release from the last 100 ms of the stimulus as well as 100 ms of the release history. The model is not capable to produce higher quantal events.

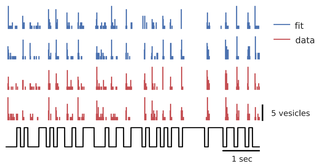


Linear-Nonlinear-Release Model

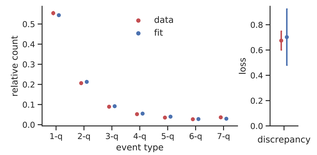


Results

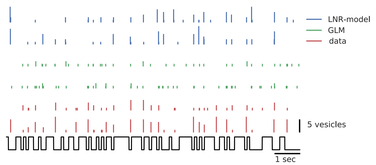
Synthetic data



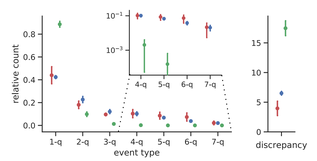
Summary statistics and discrepancy



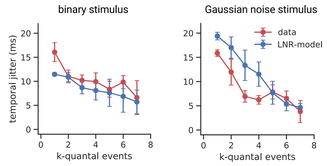
Experimental data and simulations



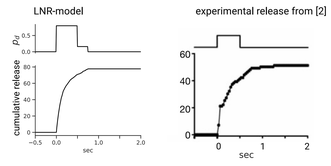
Summary statistics and discrepancy



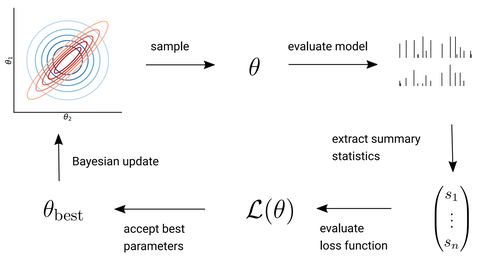
Temporal jitter



Cumulative release



Fitting procedure



Summary statistics:

To compare the different discrete traces summary statistics s_1, ..., s_n are calculated and a weighted euclidean distance between these statistics gives the discrepancy for each parameter set. As summary statsistics we chose the number of *k*-quantal events as well as the totally released vesicles.

Updating rules:

We assumed a Normal distribution as (proposal) prior which is updated by Bayesian updating rules with the best j parameters [3]:

$$\mu_{n+1} = \frac{\kappa_n}{\kappa_n + j}\mu_n + \frac{j}{\kappa_n + j}\bar{\theta},$$

$$\Lambda_{n+1} = \Lambda_n + S + \frac{\kappa_n j}{\kappa_n + j}(\bar{\theta} - \mu_n)(\bar{\theta} - \mu_n)^T,$$

with

$$\bar{\theta} = \frac{1}{j}\sum_{i=1}^{j}\theta_i, \qquad S = \sum_{i=1}^{j}(\theta_i - \bar{\theta})(\theta_i - \bar{\theta})^T,$$

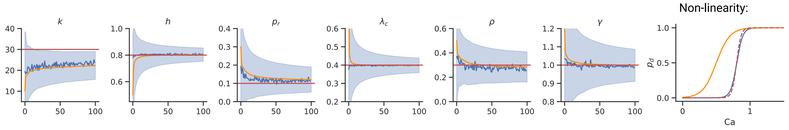
$$\kappa_{n+1} = \kappa_n + j, \qquad \nu_{n+1} = \nu_n + j.$$

Resulting in the following two step sampling procedure:

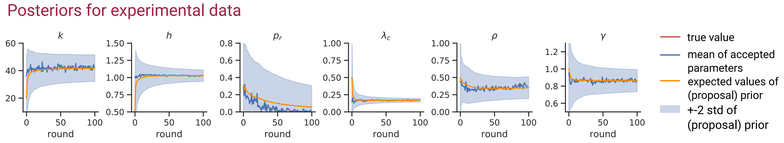
1. Draw covariance $\Sigma_{(n+1)_i} \sim \text{Inv-Wishart}(\Lambda_{n+1}^{-1}, \nu_{n+1}),$
2. Draw samples $\theta_i \sim \mathcal{N}(\mu_{n+1}, \Sigma_{(n+1)_i}).$

Results

Posteriors for synthetic data



Posteriors for experimental data

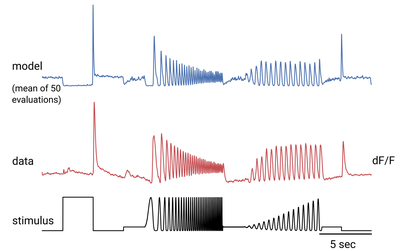


Conclusions

- We developed a framework for linking mechanistic models of neural activity to measured data.
- Combining a system identification approach with a mechanistic, biophysically inspired component enables us to make biologically interpretable predictions.
- The presented linear-nonlinear-release model captures noise of glutamate release at a single synapse.
- Model parameters are infered via an Approximate Bayesian Inference Method.
- LNR model captures well complex features such as temporal precision.
- LNR model outperforms standard GLM.
- Adaption properties of the model show interesting similarities to mouse bipolar cells (outlook).

Outlook

The LNR-model compared to glutamate release of a mouse bipolar cell (BC3b from [3]), after convolution with a "glutamate indicator kernel", shows promising agreement:



References

[1] Holt, M. et al. (2004), Current Biology.
[2] Zenisek, D. et al. (2000), Nature.
[3] Gelman, A. et al. (2013), BDA3.
[4] Franke K. et al. (2017), Nature.

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