FM-Sim: Protocol Definition, Simulation and Rate Inference for Neuroscience Assays

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Abstract. Synaptic vesicle recycling at the presynaptic terminal of neurons is essential for the maintenance of neurotransmission at central synapses. Among the tools used to visualise the mechanics of this process is time-series fluorescence microscopy. Fluorescent dyes such as FM1-43, or engineered fluorescent versions of synaptic vesicle proteins such as pHluorins, have been employed to reveal different steps of this key process [3, 5]. Predictive *in silico* modelling of potential experimental outcomes would be highly informative for these time consuming and expensive studies.
We present FM-Sim, a user-friendly tool for defining and simulating fluorescence microscopy experimental assays, with the following features:

- Intuitive user definition of experimental protocols.
- Automatic conversion of protocol definitions into time series rate value changes.
- Domain-specific simulation model of a synaptic terminal.
- Experimental data used for model parameter value inference.
- Automatic Bayesian inference of parameter values [1, 4].
- Reduction of inferred parameter set size for Bayesian inference.

1 Biological Background

Within chemical synapses of central nervous system (CNS) neurons, neurotransmitter is released from the presynaptic terminal to propagate the neural signal to the postsynaptic terminal of the following neuron. This neurotransmitter is stored in vesicles within the presynaptic terminal, which are exocytosed in response to an incoming action potential. To prevent vesicle depletion, compensatory endocytosis of plasma membrane allows regeneration of these vesicles.

2 FM-Sim: Neuroscience Assay Simulation

FM-Sim uses a hybrid stochastic model with delays of the vesicle cycle for simulation and inference. The kinetic rates and associated time delays of state transition are the parameters of the model.

FM-Sim allows the definition of experimental protocols. These are timed sequences of events, including reagent addition, and electrical or chemical stimulation of neurons. Each protocol event can have rate parameter values set manually, inferred from observations, or inherited from protocol events already active. Once defined, the protocol events are converted into rate change events for stochastic simulation. At each rate change event, the rate values in effect are calculated, accounting for value inheritance. A single value is used for each inferred protocol event parameter when generating Bayesian inference proposals, ensuring consistency if that parameter value is used in multiple rate change events.

Protocols are simulated stochastically using the Delayed Stochastic Simulation Algorithm (DSSA) [2] with hybrid extensions, and the results of multiple simulation runs aggregated to provide mean and variance of the simulated model results. These results show both the expected fluorescence level, and the numbers of vesicles and endosomes at each stage of the synaptic vesicle cycle. Rate parameters for a experimental protocol that have not been fixed by the user can be inferred from attempts to match experimental data. A Bayesian approach to parameter inference is used, based on a Particle Marginal Metropolis-Hastings scheme using Sequential Monte Carlo estimates of marginal likelihoods [1, 4].

FM-Sim is available at http://homepages.inf.ed.ac.uk/s9269200/software/.

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