Decision Letter

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To: Joshua T Vogelstein <joshuav@jhu.edu>, Liam Paninski <liam@stat.columbia.edu>
From: bj@biophysics.org
Subject: BIOPHYSJ - Revisions Required for BIOPHYSJ/2007/126441
Cc:

MS ID#: BIOPHYSJ/2007/126441

MS TITLE: Model-based optimal inference of spike times and calcium dynamics given noisy and intermittent calcium-fluorescence imaging

Dear Dr. Vogelstein,

I apologize for the very long delay in reaching a decision on your paper, but we needed to chase down an extremely late review. The reviews of your manuscript have now been received. Both reviews were very positive, but both raised the same concern that I had: the paper only uses model data to test the algorithm. Given that real data could be used, this raises a substantial concern as to how dependent the algorithm might be on models for noise, etc. In revising the paper to address the points that were raised, it is very important that real data be tested. The use of real data would not just overcome potential skepticism of the reviewers, but increase the impact that your paper would have on other workers in this area. I once asked a colleague who published an image analysis algorithm why he only used model data, and not real electron micrographs, and he replied that the method did not work with real data! Thus, when an algorithm that is useful does get published using only model data, many people may assume that it does not work with real data (otherwise, real data would have been used). Your

paper will be acceptable for publication in Biophysical Journal after revision to deal with all of the concerns of the reviewers.

To view the comments from the referees for your manuscript, please visit http://submit.biophysj.org, enter the author area, choose "Manuscripts with Decisions", and click on the link that says "Reviews".

The changes that have been made in the revision must be clearly and explicitly explained. We require you to respond to the reviewers comments in the response to reviewers section located on the first page of your revision submission. If the changes are reasonably localized, your changes in the manuscript should be specifically marked (i.e. using colored font, underlined text, highlighted background, italicized font, or marked on the side).

When submitting your revision, download the following form and submit it to the journal office if you haven't done so already:

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If you have not previously submitted this form, please complete the form and fax it back to the editorial office at 301-634-7267. If we do not receive a revised manuscript within ninety days, this paper will be removed from our files. Any revision after that date will be treated as a new submission. Please take care to ensure that your revised manuscript is in final form (double-check figures and references, spelling, grammar, etc.). Excessive galley proof alterations, if the paper is accepted and entered into production, will be invoiced to authors.

Sincerely,

Edward Egelman

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Comments for the Author

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BIOPHYSJ/2007/126441
Model-based optimal inference of spike times and calcium dynamics given noisy and intermittent calcium-fluorescence imaging
Joshua T Vogelstein and Liam Paninski

Decision: Decision: requires minor revision; **Decision Date:** 3 Mar 2008
Date Received: 4 Dec 2007
Editor: Edward Egelman
Article Types: Regular Articles
Editorial Board Area: Section V. Biological Systems, Cellular Processes, Multicellular Dynamics
TOC Category: Biophysical Theory and Modeling
Corresponding Author: Joshua T Vogelstein
Keywords: calcium indicator; fluorescent protein; nonlinear deconvolution; particle filtering; two photon; undersample
Supplemental Files: 0

Reviewer 1 Comments for the Author
Reviewer 2 Comments for the Author

Reviewer 1 Comments for the Author...

[View uploaded comments for the author]

Reviewer 2 Comments for the Author...

The authors present a new method for estimating spike times from noisy calcium imaging data, based on a sequential Monte Carlo Expectation Maximization algorithm. The method performs well in inferring spike times from a range of simulated data. The method is attractive in that it permits spike timing predictions that have a better temporal resolution than the imaging data. In principle, the method could be very useful, particularly for population imaging where temporal resolution has to be sacrificed for spatial resolution.

Major points:

1. The main weakness of the paper is that the authors only use their method on simulated, and not real data. The paper would be far more appealing to experimentalists if they could show an example of how the method could

be applied in a real-world situation. In their introduction they cite several different papers with simultaneous imaging and electrophysiological recordings, i.e. where the imaging signal can be directly calibrated. The authors could easily ask for some of this published data and test their method.

2. The method assumes an instantaneous fluorescence rise after a spike. How would it perform in cases where the calcium signal is temporally filtered (e.g. in somatic - mainly from the nucleus - recordings of OGB1-AM fluorescence)?

3. The model assumes a constant [Ca]-fluorescence-saturation function. How would the algorithm be expected to perform when the AM-loading is very inhomogeneous? In that case one would expect very different concentrations across cells which would result in some cells saturating very early when the indicator concentration is very high.

4. The authors should discuss how the algorithm could be modified to account for in vivo biological noise e.g. originating from heartbeat.

Minor points:

Fig. 1 legend: "Schematic illustration of neuron". This is not a very accurate or descriptive title for the content of the figure.

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In this paper the authors present a mathematically advanced (forward/backward) algorithm that allows them to estimate precise spike times and calcium dynamics on the basis of movies of neurons containing a fluorescent calcium indicator. What makes this approach particularly attractive is the possible incorporation of a stimulus set as a “prior”.

The approach is novel, carries tremendous potential, and benefits from the fact that it is automatic, can take care of a lot of non-linearities and provides the user, due to the automatic approach, with an unbiased prediction of the desired unknowns in most calcium imaging experiments.

The true power of this analysis method is its application to in-vivo calcium imaging experiments where neuronal activity is evoked by specific stimulus sets and where the fidelity of the method can be tested with a few electrophysiological recordings.

If it works this is extremely useful because electrophysiology is usually a pain – especially *in-vivo* – and the promise of being able to get away with a small number of these experiments for analysis verification, and then collect data sets containing hundreds of neurons using functional imaging must be of fundamental importance.

It is a little disappointing that the authors do not provide an example of their analysis method on real data. I would argue that the proof of the pudding still resides in an experimental test, but I realize that the emphasis of the paper is on the computational feasibility – it is a modelling story after all - and as such it is not strictly necessary to include such datasets to make it an attractive manuscript.

It should probably be pointed out in the text more explicitly that this approach of data analysis always requires verification by a few selected e-phys recordings for each given set of neurons in a given preparation to install faith in its application.

All in all I think this is a very nice story that certainly merits publication in the Biophysical Journal.