The Editor

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Dear Tim

Thank you for your strong encouragement to revise and resubmit our manuscript rsif-2011-0068 entitled "*A formal mathematical framework for physiological observations, experiments and analyses*".

We are very pleased that all three referees think that our approach is important and worth publication. We have addressed all of their comments with changes to the manuscript as outlined below.

**Referee 1** is very positive about our approach, but comments on its possible impact. We have provided a theoretical framework and demonstrated that it can be implemented in real-world applications. This is a key first step, as recognised by all three referees, but of course is only a start. As Referee 1 notes, our framework is “easily extensible”, and we fully anticipate that the impact of our work will derive not only from the start we have made here, but also from many extensions to our ideas by us and others across a wide range of disciplines. In the discussion, we now raise the point that programming language features needed for CoPE are now being implemented in mainstream programming languages.

The referee’s main concern (**comments 1,2 & 4**) relates to our claims about verifiability – particularly as some aspects of an experiment (training regimens of animals, housing conditions, design of recording electrodes) would not usually come under the control of CoPE. We have removed the paragraph dealing with this (last paragraph of the Discussion), and instead suggest possible ways in which our framework can be extended to (a) take advantage of some aspects of mathematical verification such as dimensional unit checking, and (b) incorporate powerful techniques for statistical inference.

The referee’s **third comment** asks whether our framework can deal with stimuli more complex than a cube. It can indeed, and we have now added text to page 9 indicating that natural scenes, for example, can easily be manipulated in CoPE. Given that CoPE is structured around time-varying signals, we anticipate that movies could equally well be implemented with appropriate extensions to our framework.

The referee's fourth comments asks what kinds of meta-data can be described with CoPE. We have added text to page 14 to clarify that CoPE is designed to describe clearly all machine-executable meta-data, not everything that could possibly influence the outcome of the experiment.

The referee’s **final comment** asks whether we could implement dynamic template matching. Dynamic template matching forms an entire area of research in its own right, and commercial software companies devote huge effort to refining their algorithms for it. Implementing this in CoPE is really beyond the scope of this paper, but we have now added a section to the supplementary information demonstrating simple template matching defined as a single function that transform putative spikes to a spike with a goodness-of-fit to a template. An intriguing possibility is that the CoPE framework could be extended to use probabilistic inference to carry out dynamic template matching, as raised in the revised last paragraph of the discussion.

**Referee 2** comments that our approach is “original” and “very clear, even to non-experts”, but thinks that our explanation would benefit from an extended description of the relationship between functional programming and C++ programming. We have added text on page 4 and further discussion on page 14 to address this comment.

The referee’s **second comment** is that unfamiliarity with functional programming may be an obstacle to acceptance of CoPE. This sort of criticism could be levelled at any proposed new technique, and of course, initially, there would be a learning curve for users. We anticipate that the theoretical framework we have developed could be implemented in many ways so that users interact with it through much friendlier user interfaces. Developing such an interface was not a goal of this paper, and indeed, demonstrating its feasibility would significantly dilute the message we wish to disseminate. We now refer to this issue on P XX of the manuscript. We are not quite sure what the referee is getting at in the comment about tools for image generation. We demonstrate that CoPE itself can generate both visual stimuli and electrophysiological feedback signals on standard lab equipment. In our revision we have now described how it can also manipulate natural scenes. We have added text on P XX of the manuscript to briefly discuss the applicability of our framework in a context that is wider than neurophysiology.

The referee’s **final comment** queries the idea of data provenance. We now identify this as the same issue as experimental description rather than an separate issue and have removed the term “equational formulation”

We have corrected the typo and references.

**Referee 3** comments that our approach is “a worthwhile endeavor that has the potential to guide the community...”, but finds some of our notation difficult. We have now simplified our notation by putting lambdas on the left hand sides of equations, so we go from (for example):

smap = \f -> \s -> {: f <: s :> :}

to

smap f s = {: f <: s :> :}

**Comment 2.** F

We now explicitly state the sampling rate of analog-to-ditigal and digital-to-analog converter sources. We have altered the text accordingly on pages 8, 10, 12 and 13 and in the supplementary information.

**Comment 3.** We have altered our use of Real numbers to Float, as suggested.

**Comment 4.** In our first manuscript we followed the convention in presenting Hodgkin-Huxley style neuronal models (except for our new syntax for differential equations). However, we agree that writing activation rate functions like this is inadequate, especially as it does not permit one to take into account uncertainty in the fitted function and merely reports the “best fit.” We have therefore replaced numeric constants with variables, as suggested by the refeee.

**Comment 5.** We now discuss AutoBayes and related statistical programming languages in the revised last paragraph of the Discussion.

**Comment 6.** The referee suggests that we should provide a CoPE description of the additional Methods described in the ‘Materials and Methods’. We now refer to the full CoPE listing for the experiments which are given in the supplemntary information. In addition, we have extended our description of the scope of the meta-data that can be described with CoPE. We make it clear that with CoPE our goal is to describe machine-executable meta-data and not all possible information that could possibly influence an experimental outcome – which we think is not feasible.

**Comment 7.** We have corrected the typos.

**Comment 8.** We think that colour is also essential for Figure 1.

**Comment 9.** We have added text on P 16 and 17 to describe point about the animal ethics.