Webinar - Modelling Paper Synthesis and Reviews

Synthesis of Reviews:

Editor's synthesis:

A note on reviewers' identity of this version: R1 here was R2 of the previous version. R2 here is a postdoc of R1 of the previous version, who also participated in generating the report. Hence your ms was evaluated by the same reviewers and me.

Final decision: Revise and re-review. Both reviewers recognize the manuscript may advance the field yielding some interesting new insights on the generic processes underlying normal and abnormal forms of hippocampal high-frequency oscillations. While authors have addressed most of our concerns for the previously rejected submission (requiring more than 2 months' work) and the ms is substantially improved, there are still several remaining. I therefore would reconsider a revised version.

In particular, major points that still require some work are:

1) The ms is lengthy and poorly concise. It would benefit from some focus and emphasis on novelty. Regarding HFOs, the merit of the article is to conceptualize in generic terms the basic processes underlying: 1) ambiguity of the ripple range (100-250Hz) for dissecting IPSP-based and AP-based forms of HFOs, including their different spectral features; 2) fluctuations in the ripple and fast ripple range (>250 Hz) of individual events, resembling experimental data and 3) how AP-based HFOs could arise from asynchronous firing. This is done in the abstract and Introduction but it is somehow diluted along the text and specifically in Discusssion. Some suggestions include:

- We feel the ms would benefits from revision to avoid reiteration. For instance, section 'Pathological' HFOs are generic...' in Discussion is somehow reiterative and can be synthetized into the previous section 'Mechanisms of normal and pathological HFOs'. (see my point 23)
- We suggest moving the section 'Conclusions' to the first paragraph of Discussion to provide a succinct summary of your major novel findings, as suggested by R1.
- In addition, since some predictions are not really new authors should consider comments 2 and 3 by R2 and revise the whole ms accordingly. Regarding R2's comments on interneuronal firing rate, we discussed the picture is not crystal clear. For physiological ripples in vivo, work by Klausberger and Somogyi shows PV-basket cells can fire at stereotyped high frequency rate, but axoaxonic cells did not, neither O-LM cells. In vitro, Hajos et al found similarly for PV-basket but not for axoaxonic nor O-LM cells. Marchioni and Macaferri found some variability for epileptiforms events, as did Spampanato and Mody. So, you can take this into consideration when addressing points 2 and 3 by R2.
- We also agreed that the analytical/math section of 'Analytical proof of HFOs from asynchronous firing' in Methods is still an issue, as we commented for your previous submission. First, it breaks the narrative and advance results making the whole story difficult to follow. Second, we find this part would better fit in a more theoretical study that authors could further exploit. Finally, we would need feedback from a theoretician with expertise in neuroscience which would make the revision process longer and difficult. I would therefore ask removing this part; together with the corresponding paragraph in Results (see my points 7, 16). If the authors still feel this is an essential part of their work they should try integrating this part into the result section in a more compact manner.
- Results regarding the reconstructed LFP model could be headed independently in a new section (see my point 16). We also suggest that Fig.9, for the reconstructed LFP model, should come earlier, since it introduces the generic LFP model for both AP (left) and IPSPs (right). Then Fig.8 (AP) and Fig.9 (IPSP) could follow. This hopefully would make the narrative shorter and smoother. See my point 17
- The whole ms would benefits from carefully reading to make it a little more compact and smooth to read. See some of my comments along the pages.

2) While authors made an effort in clarifying parameters used and model definition there are some omissions:

- See point 2 by R1. In particular, we further discussed about this point in the consultation session and this is what R1 clarified about this point:
"Regarding my point 2: The parametric studies they present in Figures 8-9 has to do with how they distribute their spikes or IPSPs over time. Not the waveform itself of APs and IPSPs. This is only very briefly studied in Figure 10 where they give a few examples of t_rise and t_decay for their IPSPs. My point is that the readers should know the basic and important synaptic and AP parameters of their biophysical model (which are then also used in the constructed LFP one). We shouldnt have to reach Figure 10 to find out their default GABA decay time for example. And synaptic conductance or any AMPA-related parameter is never given in the text. These basic numbers should be

presented at Methods"
- Please provide parameters used for simulations in Fig.4, as obtained from data shown in Fig.2 and 3. (See my point 11)
- Regarding justification/meaning of satellite cells, see my point 4
- Regarding LFP signals, see my points 5 and 6
- Regarding justification of parameter ranges, see my points 9, 10, 11, 13, 14
- See points 3 and 4 by R1 regarding data presentation
- Please consider whether showing representative intracellular traces for the biophysical model will help to better appreciate the role of AP, IPSPs and depolarizing block in HFOs. See my points 11 and 15
- There are some unclear sentences in the text. See minor points by R2 and my points 12, 21,
- For some clarifications and references, see my points 1,2,3, 18, 19, 20 and 22
Regarding point 1 by R2 on the need for experimental validation: we discussed and agreed this is not strictly required.

Editor's comments:

1. Page 1, first para of Introduction: 'HFOs are brief oscillations of the local field potentials..'
2. Page 2, first para: Useful to make a note that clinical HFOs have been typically recorded with macroelectrodes (Jirsh, Urrestarazu) but also with microelectrodes (Bragin, Le Van Quyen, Worrell).
3. Page 2, second para: sparse pyramidal cell firing during ripples was described by Csicsvari and it should be cited (either the JN 1999 paper or the Neuron 2000)
4. Page 3, third para: I would like to insist on the idea that when connectivity ratios (pyr-interneurons; pyr-pyr) and the % of active cells (80/3080=2.5%), satellite and pyramidal cells can be conceptualized as the same population of pyramidal cells. Maybe a note could be helpful.
5. Page 4, biophysical model, LFP equation: It seems authors estimate laminar LFP profiles along all modeled somatodendritic compartments. However, only one LFP channel is reported at 50 um from the cell layer (according to Fig.1B). How is that LFP signal derived from the laminar LFP obtained from equation (1)? Is this reflecting a micro- or a macro-electrode? (An hippocampal pyr cell somata has about 20 um diameter, hence 3080 pyr cells would yield about 60 mm)
6. Page 4, constructed LFP model: the basic assumption for convoluting signal waveforms is linearity. This should be stated. Also useful to cite Bazelot et al J Physiol 2010 (for how micro-field IPSPs and EPSPs are generated) and Gold et al. JNeuroPhysiol 2006 for extracellular AP waveforms.
7. Page 6, section on 'Analytic proof...': I found this part breaks the rational flow, makes the ms more difficult to follow and represent a more theoretical derivation. Without this part the ms still keeps focused. I would consider leaving it out.
8. Page 8, first result section: May be useful to recall the reader the noise is uncorrelated. Also here, it may be useful to define fast ripple when calling to Fig.2A. Actually the sentence "(The peak frequency in the fast ripple band had to have higher spectral power than the peak frequency in the ripple band for at least 25% of the duration of the sharp wave in order to count as a fast ripple event.)" in page 9, second para, should probably come earlier in the first section of Results.
9. Fig.2A and 3A, why is noisy intensity range different? Can fast ripples (i.e. HFO > 250 Hz) be generated for pyr cell simulation with larger noise intensity as in Fig.2?
10. Page 9, section Effects of compromised inhibition: It would be useful to the reader to identify what is the connection with the previous set of simulations. For instance: 'We therefore investigated the effects of compromising network inhibition on fast ripple generation...starting from model shown in Fig.3 for xxx (parameters)'
11. Fig.4. Please, clarify the parameter settings used for each simulation. Maybe useful to use similar time scale in all figures. Is there any relationship between HFO spectral characteristics (or parameter regime) and duration? I also find useful to show one representative example of the intracellular signal in both pyr cell types for each simulation.
12. Page 9, same section, second para: '...until at extreme levels the network is completely uncoupled, leading to asynchronous pyramidal cell spiking. Yet, as shown in Fig. 5B, even asynchronous networks ...' Not sure where the asynchronous nature can be seen.
13. Fig.5 caption: clarify what parameter range is used (as mentioned in previous fig) to generate this simulation.
14. Page 9, section Generation of ripples...: 'To address the first question, we ran simulations in which uncorrelated noisy input was delivered to the 80 active pyramidal cells, with no other cells in the network and no coupling between pyramidal cells.' Again, it would be useful to the reader to identify what is the connection with the previous set of simulations. How does it relate to previous simulations (i.e. Fig.3 versus Fig.6)?
15. Fig.6: ? Useful to show one representative example of the intracellular signal to appreciate the nature of intracellular firing and depolarizing block.
16. Page 10, second para: This relates to the mathematical derivation that I suggest to remove. A new section for the reconstructed LFP should better follow. The word agnostic seems to be weird when referring to the model. Was not blind a better usage?

17. Fig.8,9 and 10: I suggest that Fig.9, for the reconstructed LFP model, should come earlier, since it introduces the generic LFP model for both AP (left) and IPSPs (right). Then Fig.8 (AP) and Fig.9 (IPSP) could follow. This hopefully would make the narrative shorter and smoother.
18. Page 10, last para: The evolution of the network preferred HFO frequency would depend on the intrinsic firing rate of individual cells, and this was examined in Ibarz et al.
19. Page 11 and Fig. 8: The results that the lower the jitter the larger the fast ripple occurrence seems to contradict experimental data (Foffani et al. 2007). This may be due to the nature of the generic model that considers asynchronous stationary firing, in contrast to the transient all-or-none nature of population bursts that compose HFOs. To me this just reflects the epiphenomenalism of HFOs.
20. Page 11, second para: for AP contribution to HFO the work by Csicsvari should be quoted.
21. Page 12, first para, last sentence: '...LFP are unlike to produce fast ripples..' Not sure I understand this sentence.
22. Page 13, second para: A note should be added on the major caveat with the reconstructed LFP model, i.e. that it doesn't take into account the complex spatiotemporal non-linear relationship between different somatodendritic sinks and sources that buildup LFP signals.
23. Page 14, section Pathological HFOs are generic..., could be integrated into section Mechanisms of normal and pathological..' to avoid reiteration.
24. Useful to check Schlingloff et al. JN 2014

R1's comments:

Advances the Field (Required):
Through a series of simulations of biophysical networks or generic spiking patterns the authors explore how normal and abnormal ripple oscillations can emerge in the LFP through the network's structure or lack thereof. This yields some interesting basic insights on the underlying nature of these LFP rhythms.

Comments to the Authors (Required):
The authors have done substantial work to expand and improve the analysis of their simulations and the scope of their manuscript. I find the narrative still non-linear and somewhat convoluted (e.g. the story would perhaps be easier to follow if they would start from the constructed LFP model and then moved up in complexity with the full biophysical one instead of the other way around). This makes the line of results slightly difficult to follow conceptually. Nevertheless I believe the main results, as presented in the revised manuscript, have substantially increased the significance of the work and I would at this point support its publication.

Please take into consideration the following minor points:

1) Due to the complicated nature of the analysis and the length (and wordiness) of the manuscript itself, I think the Discussion would benefit by starting off with a brief list of main findings.

2) Since APs and IPSP waveforms are key to the both models, the authors should describe their dynamics in the Methods section (rise time, decay time, half-width duration, amplitude, synaptic conductance).

3) No error bars are ever described. Please indicate what they represent in corresponding figure legends.

4) I think Figure 5A would benefit if it was reversed and the x-axis read "Percent removed inhibitory connections" so that the curve is an increasing one. That way Panels B-D would be presented in reversed order so that the effect becomes more and more pronounced as the reader moves forward through the panels, instead of the other way around.

R2's comments:

Advances the Field (Required):
Mitigated. Possible mechanisms able to generate a transient switch from ripple into pathological fast-ripples are particularly interesting and are an important question.

But this study is fully computational. Predictions of the model are not really new. None of the predictions were experimentally verified.

Comments to the Authors (Required):
This article is a re-submission. The authors have answered most issues raised by previous reviewers.

Using a detailed model comprising one type of interneuron (mimicking perisomatic projecting basket cell) and pyramidal cells, this study shows that action potential and IPSP can both contribute to ripples in LFPs. The model also predicts that HFOs can be produced either by coherent firing of basket cells or pyramidal neurons. Pathological ripples emerge when generated by APs and arise when synaptic input overcomes network inhibition enough to allow out of phase firing. Feed forward inhibition limits HFO in the gamma/ ripple band. Interestingly Fast Ripples could be evoked only in case of impairment of inhibitory feedback connections, inducing asynchronous firing of pyramidal neurons. FRs emerge briefly and spontaneously from asynchronous activity in an uncoupled network.

The possible mechanisms able to generate a transient switch from ripple (produced by action potentials and the loss of inhibitory network) into pathological fast ripple are particularly interesting and are an important question. The document is well referenced. Although very simplified, the hippocampus network comprises feedforward /collateral excitation and feedforward inhibition.

However some concerns remain.

1- This study is fully computational. None of the prediction was experimentally verified.
Considering that thousands of distinct configurations of detailed computational model can produce plausible biological signals (Marder E1, Taylor AL Multiple models to capture the variability in biological neurons and networks. Nat Neurosci. 2011 Feb;14(2):133-8.), produced by a very simple neuronal network, it seems important to check experimentally at least some predictions of the model. This would considerably strengthen the article.

2- From all the results cited above, most of them confirm previously published results. Several points have been already pointed out by the previous reviewers (IPSP/AP vs HFO, how inhibition shape ripple activity, role of AP in Ripple) so I just add three more:

a) "fast ripple episodes occurred due to two out-of-phase spiking clusters" as the author indicate themselves that this was already published by (Foffani et al., 2007; Ibarz et al., 2010) and also (Demont-Guignard et al., 2012).

b) Pathological ripples emerge when enhance pyramidal cells activity is coupled with a decrease of inhibitory IPSP. This result is somehow similar to the fact that an increase of excitation of glutamatergic cells coupled to a decrease of GABAergic inhibition would generate FR as reported in (Bragin et al J Neurosci 2002 and Wendling et al, EJN2012).

c) Conditions leading to either ripple or fast ripple in the hippocampus, see (Aivar et al., JNeurosci, 2014)
Therefore, the authors should clearly emphasize the novel predictions and minor the already known points.
3- The authors show that in the model, HFOs were elicited through coherent firing of 20 BC cells. Peak network frequency (reaching fast ripple frequency >250Hz in the LFP) closely matches the mean basket cell firing frequency (1-300 Hz). The authors therefore explain that this LFP signal reflects IPSP due to BC firing. However, experimental data tends to show that fast spiking interneurons (as basket cells or chandelier cells of rat or monkey) barely fire above 100 Hz, when recorded in current clamp mode (Massi et al., 2012; Povysheva et al., 2013). This is an important issue. The author should provide references , contradicting the references cited above, showing that in vivo, or at least in brain slices,(in epileptic condition ?) basket cells (or other perisomatic targeting interneurons) could sustain a firing rate >150Hz.
Note that, in epileptic or non-physiologic conditions, CA3 pyramidal cells could fire at 150-300Hz as shown with simultaneous patch-clamp and field recording in hippocampal slices by (Aivar P, Valero M, Bellistri E, Menendez de la Prida L.J Neurosci 2014).

What happens when interneuronal gap junctions are suppressed in the model? Does it change the interneuronal firing rate or the emergence of ripple / FR in the LFP? It might be interesting to know if the presence interneuron gap junctions is able to change the frequency of HFO.

Minor:
P9: Results: "However, in contrast to the prior case (Fig. 2), at higher frequencies the lower frequency peak, produced by pyramidal cell action potentials, dominated."
This sentence doesn't sound clear to me.

P9: "Thus, this model shows the transition from what are likely normal to epileptic HFOs. However, with this configuration (all connections intact) it was impossible to elicit fast ripples for two reasons [...]"

Did the author mean that "epileptic HFO" that are pathologic ripple (i.e<250Hz) ? How can the authors be sure that these oscillations are "pathologic"?