Our reviewer response follows. The original reviewer comments, where retained, are in shown italics. Our responses are in bold.

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Reviewer #1 (Comments to the Author):

In the revised version of this manuscript, the authors addressed my previous concerns and explained well the details that I asked. By adding the new frequency range to their model, their original claims are more strongly supported. Several clarification troughout the text make the points more clear, specially when comes to the simulation of an artificial oscillation in nature to test their predictions. The discussion makes it more clear now to interpret their results in the context of previous bibliography. Some minor points that I noticed in the text are:

1)   Line 144: "Physiological theta is a GABAergic"
2)   Line 187: "This means our Ca2+ set point (of 0.003 mM) depends on the gL in practice but our choice of of 0.003 mM was arbitrary
3)   Figure 5: Control experiments. A. Change in population hippocampal population rate for different levels of target... B. Change in population synchrony for different levels of target [Ca] (colors) as a function of oscillation...

Thank you.

As I previously stated, I find the data in this manuscript very interesting and believe that will be of the general interest of the readers of the journal.

Thank you!

Reviewer #2 (Comments to the Author):

The manuscript is quite clear now and the results are of interest. Showing that the results can generalize in a number of ways adds to the general importance. I just have a few comments that could be fixed with writing, with no need for new data.

Some confusion could be avoided by for example, omitting all mention of 1000 Poisson neurons and Poisson population (l.67, l. 73) when at the end of the day these neurons are not simulated. Instead an inhomogeneous Poisson spike train is sent to the single neuron being simulated since the sum of 1000 Poisson processes is a single process with 1000 times the rate. I think it is OK to say that you provide such inhomogeneous Poisson input to the single cell and that such input could "represent" the output of 1000 neurons but it is misleading and confusing to suggest that a population of 1000 neurons is included in your model.

e.g. line 77 "instantiation of a randomly generated population" suggests a network with random connections or something. All you did though was instantiated a Poisson process.

The reviewers interpretation of the Poisson rate is not quite right, but the misunderstanding is entirely our fault!

We did simulate 1000 independent Poisson cells, but then connected a randomly chosen 10 percent of these to each cell in the HH population. We did not make this clear. To fix this the text that was line77 now reads:

"[…]Oscillatory input for each cell in the Hodgkin-Huxley population was modeled as a set of about $M=100$ Poisson neurons (Figure~\ref{fig:f1}\textbf{b}-\textbf{c}). With a probability of 0.1 these were randomly drawn from a pool of 1000 Poisson neurons, each of which was independently simulated. To change the level of oscillatory modulation strength, we altered the firing rate of the entire Poisson population."

l.94-96 & Fig. 1: Calcium dynamics arise of 100s of milliseconds so there is confusion here. What you mean is the homeostatic response (via signaling pathways including activation of kinases, transcriptional changes, translation of new proteins, movement of mRNA or proteins in the cell and insertion of receptors) to the changes in calcium dynamics which fluctuate on a timescale of a fraction of a second.

Perfectly right. The text around line 94 now reads:

"Note that in real systems intrinsic homeostasis is thought to happen over minutes or days. However, simulation times that are hours or days long are not computationally feasible. So we follow the field and study a model where Ca^{2+} homeostasis dynamics happen with a 4-second half-life, denoted by τ_h. This might seem like a huge difference. But all that matters mathematically is that homeostasis dynamics happen much slower than all the other synaptic/membrane dynamics. A timescale of $\tau_h > 4$ seconds is a reasonable choice for ensure this. The other major dynamics in the model are synapses with $< 30 ms$ half-lives. This leads to a 133 fold difference between synaptic and homeostatic dynamics."

l.135 "inversion of kappa": I don't think kappa has been defined before this sentence.

Corrected. The text around line135 now reads:

"Note that the inversion in population synchrony, seen in Figure~\ref{fig:f2}\textbf{d} as well as in \ref{fig:f5}\textbf{b}, is a low N effect. As population spiking is suppressed, the total number of spikes declines to the point where the bins used to calculate the Kappa correlation often contain no spikes. This leads to a somewhat misleading increase in synchrony."

l. 156-7 "changes due to K ... can't alter baseline". This is unclear or wrong I think. Any change in K-conductance in a Hodgkin-Huxley like model (like changing the leak conductance) alters both mean firing rate and mean membrane potential depending what is meant by baseline. (A simple simulation reveals this).

K recovery and Na initiation are entangled, as the reviewer correctly states. The text around line 156 now reads:

"The excitability changes we see with homeostasis must be due to the decreases in Na conductance (which initiates spikes) and increases in K conductance (which recovers the voltage following a spike)."

Overall I think some more intuition could be provided into why the main result arises, again, more is needed than a simulation demonstrating an effect. Rather *a clear explanation*.

We have tried to offer a new clear explanation by writing a new part for the Discussion. It reads:

"Oscillations are generally conceived to play a functional role in modulating spiking, by grouping action potentials and improving signal to noise. Absent the effects of homeostasis, our model clearly demonstrates this: with increasing modulation strength, excitatory oscillations

show increased firing rate and synchrony. Given this effect, and the importance of phase coding in the hippocampus, it is reasonable to wonder why hippocampal oscillations are GABAergic. Our model suggests that while this is true for brief, bursty excitatory oscillations, stronger, tonic excitatory oscillations engage homeostatic mechanisms that alter Na and K conductances, driving down the membrane voltage. This, in turn, reduces both the firing rate and spike synchrony in response to inputs."

Typos:
l.23 missing "is"
l.61 "suppresses" is wrong
l.105 "the oscillation's"
l.144 extra "a"
l.158 missing "of"
l. 177 missing "long" after "how"

Thank you.

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Reviewer #3 (Comments to the Author):

Thank you for the improvement over the original submitted manuscript, which has helped me fill in some of the blanks that were previously missing. This is an interesting exploration to consider how homeostatic mechanisms would differently affect AMPAergic versus GABAergic oscillatory inputs. However, there is still room for improvement and clarification to help the reader appreciate and understand details of the work done.

1) Please help the reader by specifying all aspects clearly in the model set-up, equation parameters and interpretation used. Specifically:

(i) I_S referred to only as excitatory in methods (eq 3), but both AMPA and GABA -ergic were examined? It is not clear, largely because parameters are not fully described I think. For example, does g_o, V_o refer to either excitatory or inhibitory and so V_o=V_i or V_e? what is g_x refer to, presumably either but there seem to be too many parameters introduced? I'm guessing the tau_b etc. are excitatory or inhibitory time constants? Could the authors simply fully write out the equations for excitatory or inhibitory oscillatory modulation separately to be clear. Also, parameter values for I_bias (eq 5) are missing - was it varied in the 100 HH models? I'm guessing not as it would add to the variability and synchrony of output to complicate interpretation?

We now better explain all synaptic dynamics and input current in the Methods, addressing we hope the reviewer's questions.

It turns out that I_bias was set to zero in all simulations. We removed it from the paper. The text "I_S referred to only as excitatory in methods" was corrected. It now reads:

"Overall membrane dynamics were governed by these internal ion conductances, and the synaptic input term I_s, which contains both stimulus and oscillatory terms."

(ii) Could the authors expand/improve Fig 1 to help the reader please. In particular, the 'model input' is a bit confusing to me - as I understand it, there are 2 different types of input added at the last 0.5 sec - tonic or bursting oscillation. As presented, one might think this is the top and bottom rows, but it is the 2nd and 3rd rows as given in the caption. So, for the tonic input, there is nothing specifically changed during the last 0.5 sec? That is, it is just an ongoing oscillatory input? I wonder if the

depiction is due to different I_bias values? I hope the authors can make this clear to the reader by fully describing these model input depictions. Model input is a raster plot, right? Expansions are to show that there are no population bursts (top) but there are in 2nd and 3rd panels (?) etc. For the model output in Fig.1c, it would be helpful to also see an expansion of the last 0.5 sec too for the HH cell, perhaps showing an example for the tonic and bursting output.

(iii) With the above point clear, the authors can now provide the reader with a clear description of Fig. 2 and onward regarding oscillation modulation (values of 0-3). As they specify in the revision, this is due to the altering the firing rate of the Poisson population (fixed rate of 6 Hz was changed in the modulation there, to what? etc.?). Perhaps this can be illustrated (akin to revised Fig 1a aspects). I assume that these modulation values are arbitrary values? The authors could specify this clearly in the Methods and/or expanded caption. That is, please 'map' what parameter values in equations to what is specifically plotted. As I understand it from the methods, half of the 1000 Poisson cells have oscillatory aspects (N_o) and the others don't, and presumably they are not connected themselves, right? Is the amplitude A meant to be r_o/2? Not sure why parameter 'A' needs to be introduced?

In freshly looking at Figure 1 we agreed with the reviewer confusions and requests. Her (ii) and (iii), are very good pints. But we also saw broader need to both expand, and simplify, this figure. We have redone this Figure, completely to address the reviewer's concerns and to clarify the model description. Specifically, we have broken out the types of model inputs into (a) the stimulus, and (b) the two types of oscillation (tonic and bursting). We then show examples of the model output for each type of oscillatory input, with and without homeostasis.

Using 'A', as a term, was an artifact from an old draft and we removed it.

2) Fig 4 shows average - what was the variance like? Presumably if this was done with inhibitory oscillatory input, it would not change much from the 'no homeostasis' FI curve? It would be helpful to show this to make their paradoxical result clear.

We will add SE bars to Figure 4. However, the long run times needed to make this data (>10 days) mean we opted to move on with the rest of the response right now, and will add in the error bars before publication.

If the oscillation was inhibitory it would have an FI-curve exactly identical to the no homeostasis condition because there is no oscillation present when calculating these curves. There is a half-second gap between oscillation offset and the impulse current. We updated the methods in the Figure to more clearly explain. They now read,

"To generate this curve the model was equilibrated for 20 seconds, under a 1.5 Hz firing rate and 8 Hz frequency rhythm, after which the current impulse that we described above was applied. During FI-curve estimation these was no oscillation present."

3) It might be interesting to note rodent and human theta hippocampal oscillation differences (e.g., see J.Jacobs Phil Transc. 2014 where intermittent human oscillations described)

We discuss this now in our discussion of Figure 5c.

[….] "It seems an oscillation would need to be present \textit{at least} 10\% of the time to generate a response (Figure~\ref{fig:f5}\textbf{c}). Jacobs \cite{Jacobs2014} estimated the prevalence of hippocampal theta to be about 40\% of the time in rats, and 10\% in humans. So even for humans, who have slower and less stable theta rhythm(s) \cite{Goyal2018}, we'd expect an homeostatic response from AMPAergic theta, if it existed."

Minor:

1) line 52 - "Given that chemical..."
2) line 61 - "suppress..."2) line 61 - "suppress..."
3) lines 133-134 - "...so most probably incomplete at best. Experimental testing is needed". As the authors state, model is 'very simple', one can simply say that it "is" incomplete. What sort of experimental testing do the authors envision?
4) lines 144-5 - not a sentence "Physiological theta….".
5) line 250 - " ...evidence that intrinsic..."
6) lines 263-4 - STG and acronym used and then not on these 2 lines - please fix.
7) line 299 - "... by a sinusoidal..."

Thank you.

We updated the text to both fix the typos above, and we provided a sketch for testing our work in vivo. This now reads,

"While our simple model has been shown by others to recapitulate hippocampal pyramidal cell's activity in laboratory settings \cite{LeMasson1993}, it is a \textit{very simple} model, and validating our work does require new experimental testing. This could be done, for example, by using prolonged excitatory gamma oscillations--arising from direct stimulation of either the medial entorhinal cortex or CA3--to drive a possible homeostatic response in CA1 \cite{Csicsvari2003,Colgin2009}."

Please add some references for this, e.g., Colgin. In their simple model, the authors are presumably assuming that the theta rhythm is primarily due to external oscillatory input (medial septum), but it is of course now clear that there are intra-hippocampal theta rhythms (Williams group, and as notes in Colgin reviews).

We specified the generator of interest in our work, including the requested citation. The text now reads:

"In Figure 2 we compared AMPA and GABAergic models of the theta rhythm (8 Hz). This was done to illuminate their different effects, but was not a biologically realistic model. Hippocampal theta is solely a GABAergic rhythm, at least when driven by medial septum \cite{Colgin2016a}. In hippocampus AMPAergic oscillations are, however, seen in the high gamma range (60-90 Hz). In Figure 3 we confirm AMPAergic oscillations in the gamma range follow the same pattern as theta. And they do. For both 60 and 90 Hz gamma, tonic oscillations suppress excitability and desynchronize firing."

We also discuss the difference in Theta speed and stability in a new small section. It reads:

"Jacobs \cite{Jacobs2014} estimated the prevalence of hippocampal theta to be about 40\% of the time in rats, and 10\% in humans. So even for humans, who have slower and less stable theta rhythm(s) \cite{Goyal2018}, we'd expect an homeostatic response from AMPAergic theta, if it existed."

As I would prefer reviews to not be anonymous, I would like to identify myself (Frances Skinner).

Thank you, Prof. Skinner. Your comments made our work better.