In this manuscript, Schubert et al. present a self-organised recurrent network (SORN) model, in which a recently proposed diffusive homeostatic mechanism is implemented alongside numerous synaptic plasticity mechanisms in previous descriptions of the SORN model. They find that log-normal-like distributions of neural firing rates and synaptic weights can be achieved in this model, as observed experimentally. A prediction that neural firing rates can be related to local neural density is made, as well as observations that these neurons are more likely to be 'driver' neurons with large mean outgoing synaptic weights.

This is a well-written manuscript, and presents some nice analytic approximations for 2D diffusion of NO signal from neuron sources. This study has the potential to be suitable, and of interest, to the plos computational biology readership. However, in it's current form I believe it does not have a sufficiently developed exploration of the network model, nor attempts to experimentally validate predictions arising from the model (see major comments). While it would be well received in a specialised computational neuroscience journal, the scope of the current manuscript is not sufficiently broad/developed to recommend publication.

Finally, it is not clear to me that 'local neuron density predicts firing rates' is the most interesting, or suitable, take home message for the reader. Indeed, this takes away from the finding (Fig3) that driver neurons emerge with diffusive homeostasis, which may have important functional implications that could be explored further.

Major Comments:

- A predominant experimental prediction from this model is that average neural activity should scale inversely with local neural density. The paper would benefit immensely from an attempt to test this prediction, and there may already exist publicly available data which may be somewhat suitable, at least for preliminary analyses. For example, the Allen Institute Brain Observatory contain ~100 calcium imaging sessions from mouse visual cortex, with 100-300 neurons per session. As the position and an activity marker of each neuron is recorded, it would be possible to test the dependence of neural activity on local density (of course, this is a rather crude approach since calcium indicator expression will vary widely across neurons, but it may still be informative). In addition to testing this prediction, this manuscript would be improved with a discussion of alternative mechanisms which may lead to this dependence between firing rates and local density (e.g. a model in which neurons compete for a finite amount of local metabolic resources, which may constrain their activity)

- Fig 3A,line 265,256 "We also tested the case of instantaneous diffusion. Mean weights did not reach as high values as in the case of diffusion at a finite rate"; This seems puzzling. Why is this case so different from the case with normal diffusion, if it was shown that the activity profiles are similar? This should be further investigated and discussed. If it is a robust effect, it would be interesting to explore the functional consequences of having distribution of mean outgoing weights as observed in the

D=10 case, as there is quite a contrast between this and the cases with no/instantaneous diffusion.

- *Fig 2D:* The authors claim that synaptic lifetimes follow a power-law, but this is not entirely substantiated from the data they present and merits more investigation. The linear fits are not that convincing, as the points fall below the line for longer lifetimes. Specifically, the python powerlaw package which they use provides a tool to compare the likilhoods of other distributions describing the synaptic lifetimes, such as exponential (although I haven't used this before so cannot vouch for its reliability). Ideally, longer synaptic lifetime probabilities could be sampled with longer simulations, although I appreciate that this could be limited by computational issues. In addition, it would be interesting to know whether the differences in slope as D is changed are robust and significant, and whether this can be explained.

- Since a significant contribution of this work is that the original formulation of diffusive homeostasis has been studied with more realistic synaptic plasticity, it would be interesting to investigate how network function or capability changes with the different cases explored in this paper, as the authors alluded to at the end of their discussion. Specifically, an interesting avenue of exploration could be how the 'driver neurons' identified by the authors, which occur at low neuron densities, contribute to e.g. the controllability of network dynamics, or play a special role in tasks such as associative learning.

Minor Comments :

Page 3 (network simulation description, table 1): In general, the choice of parameters for the network model isn't backed up by reference or discussion, e.g. connection probabilities, conduction delay etc. While these do seem like reasonable values, it would be good to provide either references of experimental measurements, or point to a previous model which uses similar parameters.

The description of how connections are generated is a bit incomplete. Are connections generated all at once using the distance-dependent probabilities, and then extra ones added on (using the same distance-dependence?) until a target number is reached. Please clarify

Table 2: 'IP' is not defined as far as I can see, so should be defined or replaced with full term (presumably it is intrinsic plasticity, but the casual reader may not know this)

Page 4: Does synaptic generation occur with equal probability between all neurons, or is there a distance dependence?
How sensitive are the network and synaptic dynamics to the choice of synapse generation and pruning? Is it difficult to hand-tune the growth rate to achieve the desired connection fraction? This should be discussed or illustrated, if only briefly.

Page 5: line 113/114; ‘this contrasts …’ . It took a while to understand what separation of timescales the author is discussing here, this could be phrased better.

Page 7: : Neurons placed close to the edge of the sheet have a lower connection 151 probability due to the absence of neighboring neurons in the direction perpendicular to 152 the close-by border - I understood from the model description that the connection probability was fixed during network initialization, and by the synaptic generation mechanism? Please clarify this.

E.q. 10: lambda, D and [NO]_0 are not defined here (although [NO]_0 and D are defined later, but they should be discussed here too).

Fig 2C: The datapoints do not seem to match the gaussian fit very well for small values of the weights. Perhaps this is a feature of their synaptic generation/pruning mechanism; what happens to the distribution if the generation/pruning rates are changed? This should be discussed further; frequencies of such small synaptic weights may anyway be difficult to estimate experimentally.

Fig 2: How exactly is synaptic lifetime measured? Presumably it is the amount of time between the generation of that synapse and its’ pruning?

Page 10
While the derivation for the analytical solution is interesting, and could be useful for readers who wish to adapt it, a significant portion of it could be moved to the methods section.

Page 11,
eq (33): I am a bit lost with what the authors are trying to do here, perhaps phi_0 and phi_point could be defined more clearly? Does phi_point correspond to the analytic approximation and phi_0 the numeric value?

eq (34): K_1 is not defined here, presumably it refers to a modified Bessel function?

Fig 7: There are no legends for this figure, and colors are not consistent with the figure caption.

Page 13, lines 374-380‘ ; it would be interesting to see how changing the density of neurons in either the 2D or 3D cases affect the distribution of firing rates. Since there are a range of neural density value reported experimentally, perhaps different densities also give more skewed or broader distributions in 3D. This may just be trivially similar to changing the diffusion constant, but I am not so sure.

Fig 6: There is not much description of the results of fig 6 in the main text, apart from stating that the prediction is verified. A few sentences describing the results would be helpful to the reader.