The Journal of Physiology

Intrinsic threshold plasticity: cholinergic activation and role in the neuronal recognition of incomplete input patterns

Tuan Pham and Christian Hansel
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Corresponding author(s): Christian Hansel (chansel@bsd.uchicago.edu)

The referees have opted to remain anonymous.

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(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. Depending on transfer agreements, referee reports obtained elsewhere may or may not be included in this compilation. Referee reports are anonymous unless the Referee chooses to sign their reports.)

Dear Dr Hansel,

Re: JP-RP-2022-283094 "Intrinsic threshold plasticity: cholinergic activation and role in the neuronal recognition of incomplete input patterns" by Christian Hansel and Tuan Pham

Thank you for submitting your manuscript to The Journal of Physiology. It has been assessed by a Reviewing Editor and by 2 Referees and the reports are copied below.

Please let your co-authors know of the following editorial decision as quickly as possible.

As you will see, in its current form, the manuscript is not acceptable for publication in The Journal of Physiology. In comments to me, the Reviewing Editor expressed interest in the potential of this study, but much work still needs to be done (and this may include new experiments) in order to satisfactorily address the concerns raised in the reports.

In view of this interest, I would like to offer you the opportunity to carry out all of the changes requested in full, and to resubmit a new manuscript using the "Submit Special Case Resubmission for JP-RP-2022-283094..." on your homepage.

We cannot, of course, guarantee ultimate acceptance at this stage as the revisions required are substantial. However, we encourage you to consider the requested changes and resubmit your work to us if you are able to complete or address all changes.

A new manuscript would be renumbered and redated, but the original referees would be consulted wherever possible. An additional referee's opinion could be sought, if the Reviewing Editor felt it necessary. A full response to each of the reports should be uploaded with a new version.

I hope that the points raised in the reports will be helpful to you.

Yours sincerely,

Katalin Toth
Senior Editor
The Journal of Physiology

EDITOR COMMENTS

Reviewing Editor:

Thank you for submitting the manuscript for consideration for the special JP issue on computational neuroscience. The work raises an interesting question and addresses it through an original combination of computational and experimental approaches. The manuscript was evaluated by two reviewers whose reports raise a number of points that could be addressed in a revised version.

An additional major issue that became apparent during my own evaluation of the manuscript is that a key novel contribution of this work (Fig. 5d-e) rests on experimental data with a very low number of replications and borderline statistical significance. Therefore I find that the number of replications of the key experiments needs to be substantially increased.

REFEREE COMMENTS

Referee #1:

The manuscript combines an abstract neural network with experimental data on changes in intrinsic excitability to argue that changes in firing threshold can be used to move a network from a state adapted to pattern discrimination to one suited to pattern completion/recognition. The main computational conclusion is well-supported, albeit in a slightly esoteric binary model. I have a couple of major and minor comments on the paper.

Major:

Context: There is a body of research on how intrinsic excitability effects the ability of hippocampal cells to separate patterns. An important paper here would be Yim, Hanuschkin, and Wolfart (2015). The system is different, but many of the conclusions, particularly that reducing excitability leads to more distinct outputs, are similar. This manuscript would be better if it could be compared and contrasted to the existing literature on excitability and pattern separation.

True/false positives in Results section 3 and Figure 4: Only the output of the correct output neuron is considered, and that this is likely to understate the rate at which errors appear when that neuron is made more selective (as multiple outputs might activate). Further, the ratio of true to false positives seems a more natural measure than their difference.

Feedforward vs recurrent networks: Recognition of incomplete patterns is a task more often carried out by recurrent networks, going back to at least Hopfield (1982). The manuscript would benefit from a discussion about how the findings might apply in a recurrent network.

Minor:

Line 58: 'therefore unknown'. This ignores a great deal of research on neural connectomes (eg Felleman and van Essen, 1991; Izhikevich and Edelman, 2008) and developmental changes in connectivity (eg Innocenti, 1981; Innocenti 1995).

Lines 167/325: The receiver operating characteristics should be defined.

Figure 1b: Missing scale on the 'distances' arrow.

Line 239/Results section 2/Figure 2: This is a slightly trivial result and might not warrant its own main figure.

Figure 3b: Missing scale on the colour bar.

Referee #2:

I provide further suggestions to improve the presentation of the manuscript.

Line 82: Are all neurons identical in the two-layer feedforward network? or are they

parameterized from a distribution?

Line 174-178: The authors use resting and threshold potentials from V1 neurons in

vivo and S1 neurons in vitro. How do the in vivo and in vitro resting potentials

compare? Did the authors use "activated slice" conditions with low levels of

extracellular Ca2+ to examine any changes in excitability?

Lines 213-215: "It is expected that increased neuronal excitability via a decrease in

spike threshold results in a "merging" of output patterns due to a shared signal

amplification that takes place "downstream" (closer to the soma) of multiple otherwise independent synaptic inputs that target the dendrite." This is a complicated sentence to digest. It also conveys the impression that the authors might have used ball-stick two-compartment model neurons in the neural network model to look at downstream merging of output patterns. This should be further clarified.

Line 412: Discussion: It is known that the dendrites of L2/3 pyramidal neurons express lower levels of the Ih current compared against L5 PCs (doi.org/10.1523/JNEUROSCI.1717-07.2007). The authors should discuss how the IP of L2/3 PCs might contrast with L5 PCs given different levels of Ih and possibly also the expression of cholinergic receptors on dendrites.

Line 428: The authors should comment a bit more on other additional mechanisms contributing to IP. For e.g. serotonergic input, mediated by 5-HT3 receptors, plays an important role in regulating the excitability of apical dendrites of L2/3 PCs (https://doi.org/10.1152/jn.00829.2011)

Line 540: A recent review describes a framework to inform deep neural networks from principles of neuromodulatory systems (https://doi.org/10.1016/j.tins.2021.12.008). The authors could comment on how including neuromodulatory principles in deep networks might improve their training and learning.

ADDITIONAL FORMATTING REQUIREMENTS:

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-A Statistical Summary Document, summarising the statistics presented in the manuscript, is required upon revision. It must be on the Journal's template, which can be downloaded from the link in the Statistical Summary Document section here: https://jp.msubmit.net/cgi-bin/main.plex?form_type=display_requirements#statistics

-Papers must comply with the Statistics Policy https://jp.msubmit.net/cgi-bin/main.plex?form_type=display_requirements#statistics

In summary:

-If n {less than or equal to} 30, all data points must be plotted in the figure in a way that reveals their range and distribution. A bar graph with data points overlaid, a box and whisker plot or a violin plot (preferably with data points included) are acceptable formats.

-If n > 30, then the entire raw dataset must be made available either as supporting information, or hosted on a not-for-profit repository e.g. FigShare, with access details provided in the manuscript.

-'n' clearly defined (e.g. x cells from y slices in z animals) in the Methods. Authors should be mindful of pseudoreplication.

-All relevant 'n' values must be clearly stated in the main text, figures and tables, and the Statistical Summary Document (required upon revision)

-The most appropriate summary statistic (e.g. mean or median and standard deviation) must be used. Standard Error of the Mean (SEM) alone is not permitted.

-Exact p values must be stated. Authors must not use 'greater than' or 'less than'. Exact p values must be stated to three significant figures even when 'no statistical significance' is claimed.

-Statistics Summary Document completed appropriately upon revision

-A Data Availability Statement is required for all papers reporting original data. This must be in the Additional Information section of the manuscript itself. It must have the paragraph heading "Data Availability Statement". All data supporting the results in the paper must be either: in the paper itself; uploaded as Supporting Information for Online Publication; or archived in an appropriate public repository. The statement needs to describe the availability or the absence of shared data. Authors must include in their Statement: a link to the repository they have used, or a statement that it is available as Supporting Information; reference the data in the appropriate sections(s) of their manuscript; and cite the data they have shared in the References section. Whenever possible the scripts and other artefacts used to generate the analyses presented in the paper should also be publicly archived. If sharing data compromises ethical standards or legal requirements then authors are not expected to share it, but must note this in their Statement. For more information, see our Statistics Policy.

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-Please include at least 3 manuscript keywords on the title page of your article file

Confidential Review **11-Mar-2022**

I provide further suggestions to improve the presentation of the manuscript.

Line 82: Are all neurons identical in the two-layer feedforward network? or are they parameterized from a distribution?

Line 174-178: The authors use resting and threshold potentials from V1 neurons in vivo and S1 neurons in vitro. How do the in vivo and in vitro resting potentials compare? Did the authors use “activated slice” conditions with low levels of extracellular Ca2+ to examine any changes in excitability?

Lines 213-215: “It is expected that increased neuronal excitability via a decrease in spike threshold results in a “merging” of output patterns due to a shared signal amplification that takes place “downstream” (closer to the soma) of multiple otherwise independent synaptic inputs that target the dendrite.” This is a complicated sentence to digest. It also conveys the impression that the authors might have used ball-stick two-compartment model neurons in the neural network model to look at downstream merging of output patterns. This should be further clarified.

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Line 540: A recent review describes a framework to inform deep neural networks from principles of neuromodulatory systems (https://doi.org/10.1016/j.tins.2021.12.008). The authors could comment on how including neuromodulatory principles in deep networks might improve their training and learning.

Point-by-point reply to the critiques raised by the reviewing editor and two reviewers

We would like to thank both reviewers and the reviewing editor for their positive, constructive comments. These have helped to revise the manuscript and to significantly improve it. In the resubmitted manuscript, all changes are marked by *italic, underlined text*.

Reviewing Editor:
An additional major issue that became apparent during my own evaluation of the manuscript is that a key novel contribution of this work (Fig. 5d-e) rests on experimental data with a very low number of replications and borderline statistical significance. Therefore, I find that the number of replications of the key experiments needs to be substantially increased.

This is a valid point and we have now added new whole-cell patch-clamp recordings from slices from mouse S1 cortex to reach at least n=9 in each of the three experimental groups shown in Fig. 5b,d-e. Six recordings were added in total, which were performed under the same conditions as described in Gill and Hansel (2020). The results replicate our previous findings and strengthen the statistical significance. We have updated the description of results from the S1 recordings (p. 12-15) as well as their documentation in Fig. 5.

Referee #1:
Major:

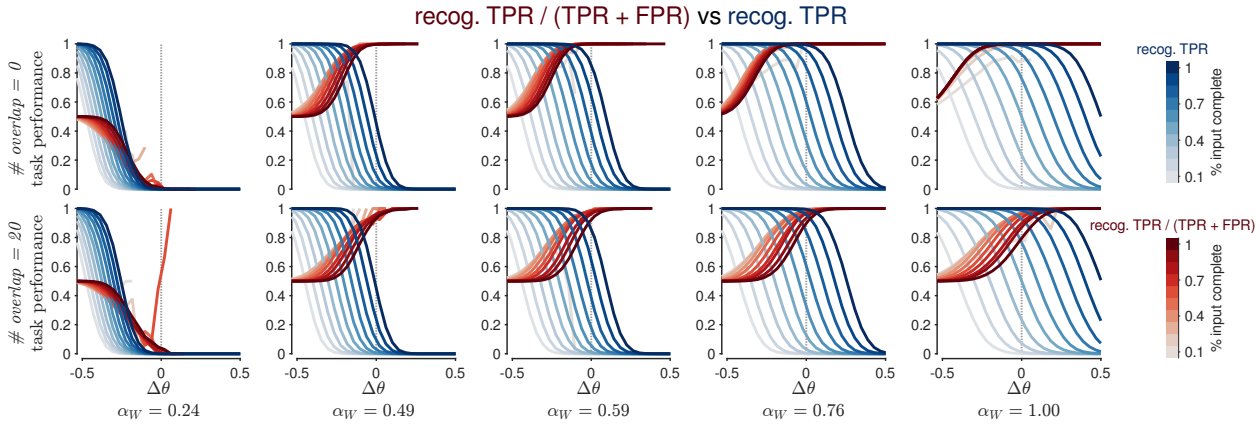
Context: There is a body of research on how intrinsic excitability effects the ability of hippocampal cells to separate patterns. An important paper here would be Yim, Hanuschkin, and Wolfart (2015). The system is different, but many of the conclusions, particularly that reducing excitability leads to more distinct outputs, are similar. This manuscript would be better if it could be compared and contrasted to the existing literature on excitability and pattern separation.

We thank the referee for pointing us toward this phenomenon and this paper in particular. It indeed provides a very good example for the relation between excitability and pattern separation. We discuss this work on p. 16 of the revised manuscript.

True/false positives in Results section 3 and Figure 4: Only the output of the correct output neuron is considered, and that this is likely to understate the rate at which errors appear when that neuron is made more selective (as multiple outputs might activate). Further, the ratio of true to false positives seems a more natural measure than their difference.

We hope that we understood the first part of this comment correctly, and added a caveat to the Methods (p. 5) to note that consideration of threshold changes in multiple output neurons would be expected to lead to different error values.

We agree that there are good reasons to pick the ratio of true to false positives as a measure. However, this approach turned out not to be feasible, as TPR or FPR values of null would not lead to meaningful ratios. The graph below shows this calculation for normalized values and explains why we picked the difference rather than the ratio (ratio saturates when threshold values are enhanced; right side of the plots). We would be open to including this measure, but it would make more sense as a Supplementary Figure, which is not permitted, though, in journal policies.



Feedforward vs recurrent networks: Recognition of incomplete patterns is a task more often carried out by recurrent networks, going back to at least Hopfield (1982). The manuscript would benefit from a discussion about how the findings might apply in a recurrent network.

We decided not to include recurrent network aspects in this work, because we wanted to isolate consequences of excitability changes in the output neuron alone. Nevertheless, this is an important context to establish, and therefore we now reference Hopfield networks and comment on this omission in the Methods section (p. 6).

Minor:

Line 58: 'therefore unknown'. This ignores a great deal of research on neural connectomes (eg Felleman and van Essen, 1991; Izhikevich and Edelman, 2008) and developmental changes in connectivity (eg Innocenti, 1981; Innocenti, 1995).

The original text focused on the lack of knowledge about specific parameter values. We agree, though, that this can be misunderstood as discounting the existing, rich literature on principles of cortical connectivity. We now included and cite the suggested references and added one more (Singer, 1995; which is a great review on functional network architecture). The new text can be found on p. 3 of the revised manuscript.

Lines 167/325: The receiver operating characteristics should be defined.

ROC is now defined and explained (line 205, p. 7).

Figure 1b: Missing scale on the 'distances' arrow.

The scale has been added.

Line 239/Results section 2/Figure 2: This is a slightly trivial result and might not warrant its own main figure.

We agree with the assessment that this is a somewhat trivial result. However, we would prefer to leave it in the manuscript, because it illustrates the problem discussed here well (activation of a target neuron by varying numbers of synaptic input depends on threshold / activation from incomplete input) and therefore makes it easier to read the paper. We suggest to leave it up to the editor to decide one way or the other.

Figure 3b: Missing scale on the colour bar.

The scale has been added.

Referee #2:

Line 82: Are all neurons identical in the two-layer feedforward network? Or are they parameterized from a distribution?

In the two-layer feedforward network used to probe discrimination performance, threshold values are parameterized from a uniform distribution. In the two-layer feedforward model used to probe recognition performance within each layer, all neurons are identical (non-parameterized). The threshold is changed in only one neuron of output layer Y. This is now clarified in the Methods (p. 4+6).

Line 174-178: The authors use resting and threshold potentials from V1 neurons in vivo and S1 neurons in vitro. How do the in vivo and in vitro resting potentials compare? Did the authors use "activated slice" conditions with low levels of extracellular Ca2+ to examine any changes in excitability?

The V1 and S1 datasets are not primarily analyzed and included to allow for a direct comparison. And yet we indeed relate resting and threshold potentials collected from these datasets (p. 13). We now added a brief caveat discussion to make it very clear that there are differences in the recording conditions under which these datasets were obtained. Our in vitro

data were obtained under rather classical conditions (with 2mM extracellular Ca2+), which is now also pointed out (p. 13).

Lines 213-215: "It is expected that increased neuronal excitability via a decrease in spike threshold results in a "merging" of output patterns due to a shared signal amplification that takes place "downstream" (closer to the soma) of multiple otherwise independent synaptic inputs that target the dendrite." This is a complicated sentence to digest. It also conveys the impression that the authors might have used ball-stick two-compartment model neurons in the neural network model to look at downstream merging of output patterns. This should be further clarified.

Oh yes, this was indeed an unnecessarily complicated sentence. We now replaced it with a more simple one that hopefully explains the underlying thought, without evoking incorrect impressions (l. 265, p. 9). No ball-stick model neurons were used in our modeling.

Line 412: Discussion: It is known that the dendrites of L2/3 pyramidal neurons express lower levels of the Ih current compared against L5 PCs (….). The authors should discuss how the IP of L2/3 PCs might contrast with L5 PCs given different levels of Ih and possibly also the expression of cholinergic receptors on dendrites.

In the revised version of the manuscript, we discuss alternative cellular mechanisms in more detail (2nd paragraph of the discussion, p. 16). Here, we now discuss Ih as well as serotonergic signaling (see below). On p. 8 (under 4. Measurement of biological resting and threshold potentials), we now discuss the dendritic location of mAChRs. This was placed in the Methods, to explain what oxo-m bath application is expected to do.

Line 428: The authors should comment a bit more on other additional mechanisms contributing to IP. For e.g. serotonergic input, mediated by 5-HT3 receptors, plays an important role in regulating the excitability of apical dendrites of L2/3 PCs (….).

We now mention serotonergic signaling as a potential candidate mechanism related to IP (p. 16). However, the reference mentioned might not fit well here, because the excitability change seems to indirectly result from a change in dendritic complexity. We did, however, include a review paper on 5-HT receptors and PC excitability.

Line 540: A recent review describes a framework to inform deep neural networks from principles of neuromodulatory systems (…..). The authors should comment on how including neuromodulatory principles in deep networks might improve their training and learning.

We thank the reviewer for this important suggestion. We were not aware of this very interesting paper, but integrated it now into our discussion (last sentence, p. 19-20). We are certain that this is useful for the reader, because it establishes and further deepens the connection between

biological and artificial neural networks regarding cholinergically driven IP as a useful computational tool in pattern recognition and classification.

Dear Dr Hansel,

Re: JP-RP-2022-283473X "Intrinsic threshold plasticity: cholinergic activation and role in the neuronal recognition of incomplete input patterns" by Tuan Pham and Christian Hansel

Thank you for submitting your manuscript to The Journal of Physiology. It has been assessed by a Reviewing Editor and by 2 expert Referees and I am pleased to tell you that it is almost ready for acceptance. Before formal acceptance, however, please provide an abstract figure and legend, as detailed below.

Please advise your co-author of this decision as soon as possible.

The reports are copied at the end of this email. Please address all of the points and incorporate all requested revisions, or explain in your Response to Referees why a change has not been made.

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I look forward to receiving your revised submission.

If you have any queries please reply to this email and staff will be happy to assist.

Yours sincerely,

Katalin Toth
Senior Editor
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REQUIRED ITEMS:

-Please include an Abstract Figure. The Abstract Figure is a piece of artwork designed to give readers an immediate understanding of the research and should summarise the main conclusions. If possible, the image should be easily 'readable' from left to right or top to bottom. It should show the physiological relevance of the manuscript so readers can assess the importance and content of its findings. Abstract Figures should not merely recapitulate other figures in the manuscript. Please try to keep the diagram as simple as possible and without superfluous information that may distract from the main conclusion(s). Abstract Figures must be provided by authors no later than the revised manuscript stage and should be uploaded as a separate file during online submission labelled as File Type 'Abstract Figure'. Please ensure that you include the figure legend in the main article file. All Abstract Figures should be created using BioRender. Authors should use The Journal's premium BioRender account to export high-resolution images. Details on how to use and access the premium account are included as part of this email.

EDITOR COMMENTS

Reviewing Editor:

Thank you for submitting a revised manuscript. The revised version was considered by the original referees who indicated that their original concerns were adequately addressed.

The concern that I raised regarding a small number of replications (the n value) was also addressed, although I would encourage you to increase it further.

Senior Editor:

Please provide an abstract figure and legend.

REFEREE COMMENTS

Referee #1:

The revised manuscript deals with the comments I had about the previous version. I believe that this paper will have an impact on the field as it tightly links an observed physiological change with its computational consequences. As mentioned in my previous review, the computational effect is not entirely novel in a qualitative sense but the modelling here is original and links nicely with the experimental data.

Referee #2:

The authors have addressed all my previous concerns in the revised version.

_____

END OF COMMENTS

Response to Referees:
In the following, we provide a response to the comments by the Reviewing Editor, the Senior Editor as well as the two reviewers.

Reviewing Editor:
The concern that I raised regarding a small number of replications (the n value) was also addressed, although I would encourage you to increase it further.

The first author of this study, Tuan Pham, has left the Hansel laboratory for a position at Brown University at the end of June. He performed all new experiments that were added to the revised version of the manuscript. We hope that the manuscript is acceptable as is, because it would be difficult to schedule additional recordings at this point.

Senior Editor:
Please provide an abstract figure and legend.

An abstract figure and legend are added to the submitted manuscript.

Referee 1:
The revised manuscript deals with the comments that I had about the previous version. I believe that this paper will have an impact on the field as it tightly links an observed physiological change with its computational consequences. As mentioned in my previous review, the computational effect is not entirely novel in a qualitative sense but the modelling here is original and links nicely with the experimental data.

We thank this referee for the constructive criticism provided during the review process, which helped to improve the manuscript significantly.

Referee 2:
The authors have addressed all my previous concerns in the revised version.

We are very grateful for the comments of referee 2 as well. Like those of referee 1, these have been positive, constructive, and helped to make this a better manuscript.

2nd Revision - Editorial Decision **15-Jul-2022**

Dear Dr Hansel,

Re: JP-RP-2022-283473XR1 "Intrinsic threshold plasticity: cholinergic activation and role in the neuronal recognition of incomplete input patterns" by Tuan Pham and Christian Hansel

I am pleased to tell you that your paper has been accepted for publication in The Journal of Physiology.

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Yours sincerely,

Katalin Toth
Senior Editor
The Journal of Physiology

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