The Journal of Physiology

Caution: Merging Ion Channel Traffic Ahead

Brian P Delisle and Don E Burgess
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The referees have opted to remain anonymous.

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Reviewing Editor: Eleonora Grandi

Transaction Report:

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Dear Brian,

Re: JP-P-2023-284497 "Caution: Merging Ion Channel Traffic Ahead" by Brian P Delisle and Don E Burgess

Thank you for submitting your manuscript to The Journal of Physiology. It has been assessed by a Reviewing Editor and by 1 expert referee and we are pleased to tell you that it is acceptable for publication following minor revision.

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

The referee reports are copied at the end of this email.

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We look forward to receiving your revised submission.

If you have any queries, please reply to this email and we will be pleased to advise.

Best wishes

Natalia Trayanova
Senior Editor
The Journal of Physiology

EDITOR COMMENTS

Reviewing Editor:

Thank you for a nice commentary. There are a few suggestions from the reviewer that the authors are invited to consider and incorporate in the revision at their discretion.

REFEREE COMMENTS

Referee #1:

We thank the authors first and foremost for their constructive comments and excellent suggestions during the review process, which have greatly improved our manuscript. We are honoured to have our work highlighted in this perspective article.

We read the perspective with great interest and appreciate the detailed and very clear explanation of our modelling methodology, which may make the work easier to understand to the diverse readership of the Journal of Physiology.

We did not find any major factual inaccuracies in the perspective article, although it might be relevant to note that we used both stochastic single-channel simulations (when comparing to results investigating single-channel properties such as recycling rates) and equivalent deterministic models for all whole-cell simulations. The exact same model structure and parameters can be used for both approaches, which produce the same results for a sufficiently large number of channels, but the deterministic implementation is significantly more computationally efficient.

Finally, we were wondering whether the perspective should not also briefly mention that in fact all ion channels are regulated by dynamic trafficking processes, which are modulated by various physiological factors and numerous drugs, and may constitute novel therapeutic targets, as the authors have themselves investigated in the past. In general, such a broader perspective about potential future implications of the concepts addressed in our manuscript would likely be of particular interest to readers of the journal (perhaps even more so than the theoretical details of our methods).

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Confidential Review **28-Feb-2023**

Response to the editor and referee:

Reviewing Editor:

Thank you for a nice commentary. There are a few suggestions from the reviewer that the authors are invited to consider and incorporate in the revision at their discretion.

Thank you for the kind note. We have incorporated the referee's suggested changes in the revised document.

REFEREE COMMENTS

Referee #1:

We did not find any major factual inaccuracies in the perspective article, although it might be relevant to note that we used both stochastic single-channel simulations (when comparing to results investigating single-channel properties such as recycling rates) and equivalent deterministic models for all whole-cell simulations. The exact same model structure and parameters can be used for both approaches, which produce the same results for a sufficiently large number of channels, but the deterministic implementation is significantly more computationally efficient.

Thank you for this comment. We hope we made this point clearer on P4.

"Meier and colleagues use stochastic simulations to determine the rate constants for Kv11.1 channels by optimizing agreement with experimental results for Kv11.1 channel trafficking. Since they can use the same model structure for deterministic simulations, they are able to integrate the model with a Markovian model of I_{Kr} and the ORd AP model."

Finally, we were wondering whether the perspective should not also briefly mention that in fact all ion channels are regulated by dynamic trafficking processes, which are modulated by various physiological factors and numerous drugs, and may constitute novel therapeutic targets, as the authors have themselves investigated in the past. In general, such a broader perspective about potential future implications of the concepts addressed in our manuscript would likely be of particular interest to readers of the journal (perhaps even more so than the theoretical details of our methods).

Thank you for suggestion. We worked make this point clearer. We modified the text on P5.

"A strength and limitation are the model's simplicity and its sole focus on Kv11.1 channels. All the cardiac ion channels are regulated by dynamic cytoplasmic processes, which are also modulated by various physiological factors (temperature, ionic conditions, and drugs). These limitations reflect the need for more experimental data on the cytoplasmic processes that regulate the trafficking of Kv11.1 and the other cardiac ion channels."

1st Revision - Editorial Decision 08-Mar-2023

Dear Brian,

Re: JP-P-2023-284497R1 "Caution: Merging Ion Channel Traffic Ahead" by Brian P Delisle and Don E Burgess

Thank you for a nice perspective!

We are pleased to tell you that it has been accepted for publication in The Journal of Physiology.

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Reviewing Editor Comments:

Thank you for a nice perspective!

1st Confidential Review 07-Mar-2023