Reply to the Editor – Misuse of null hypothesis testing: analysis of biophysical model simulations

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Short-title: True interpretation of simulations

Number of words: 362/400

Conflicts of interest: none

We carefully read the letter to the Editor regarding our recent publication[1], in which an experimentally-calibrated population of 173 *in silico* models is used to investigate inter-subject differences in response to L-type calcium current block in atrial fibrillation. The author speculates on the possibility of controlling the sample size of the population for yielding statistical significance in the results[2]. In our study, the sample size is, however, primarily determined by the physiological envelope of the experimental data, rather than being manually imposed. Importantly, our study goes beyond the use of statistical tests, such as p tests, and includes a comprehensive and challenging computational study to evaluate the physiological significance of the findings. Our further analysis demonstrates how the sodium and calcium conductances are the only parameters tested that exhibit high correlations with dominant frequency and rotor meandering in atrial fibrillation, regardless of specific p-values.

Furthermore, the magnitude of differences between groups in our study (sustained versus non-sustained re-entry, and responders versus non-responders to therapy) can be immediately obtained from the figures as the difference of the medians of the distributions. This is of greater significance than the difference of the means in the case of non-symmetric distributions. It additionally represents a further advantage of the experimentally-calibrated population of models approach for the generation of mechanistic insights and hypotheses concerning variability in cardiovascular research, in that the effect sizes obtained from the simulated data can straightforwardly be used as estimates for power calculations. This closes the loop to determine the required sample size to experimentally validate the proposed hypotheses.

In conclusion, our approach is in agreement with the main conclusions of White *et al*[2] who state that “the key insights to be gleaned from simulation models, as with empirical data, must come from interpretation of biological significance.”

References:

1. Liberos A, Bueno-Orovio A, Rodrigo M, Ravens U, Hernandez-Romero I, Fernandez-Aviles F, Guillem MS, Rodriguez B, Climent AM. Balance between sodium and calcium currents underlying chronic atrial fibrillation termination: An in silico intersubject variability study. *Heart Rhythm* 2016;**13**:2358-2365.

2. White JW, Rassweiler A, Samhouri JF, Stier AC, White C. Ecologists should not use statistical significance tests to interpret simulation model results, *Oikos* 2014;**123**:385–388.