Pflügers Archiv - European Journal of Physiology (2020) 472:549–550
https://doi.org/10.1007/s00424-020-02392-3

COMMENTARY

Pacing made easy: dynamic clamp promotes quantitative understanding of cardiac autorhythmicity and boosts the development of new pacemakers

Anatoly Shmygol[1]

Received: 23 April 2020 / Revised: 29 April 2020 / Accepted: 4 May 2020 / Published online: 15 May 2020

Owing to the high morbidity associated with abnormal pacemaker function, much effort has been spent on identifying the mechanisms of cardiac pacemaking and devising strategies for the correction of cardiac arrhythmias. In some cases, a surgical implantation of an electronic pacemaker is often the only choice left to a cardiologist. Although widely used by clinicians, this approach is not ideal because of its invasiveness, which is further exacerbated by the need for periodic replacement of the device due to the finite capacity of its batteries. New developments in the areas of gene transfer and stem cell biology have opened the tantalising prospect of developing biological pacemakers that are capable of replacing the patient's faulty sinoatrial node (SAN) [1].

The current view of cardiac rhythmogenesis is based on a large body of morphological and electrophysiological data painstakingly collected by many research groups over decades (see e.g. [8] for a detailed account). The discovery of a hyperpolarisation-activated cationic current, named "funny" current (I_f), was a major breakthrough [4]. Further work has led to a consensus that the SAN pacing is achieved via an interplay between two molecular mechanisms, namely, the membrane and the calcium clocks [7, 8]. While the former is confined to the surface membrane, the latter is formed by the localised releases of calcium from the submembrane sarcoplasmic reticulum (SR) leading to the generation of depolarising inward current by the sodium/calcium exchanger, thus contributing to the diastolic depolarisation. The two clocks are not mutually exclusive but rather complementary to each other [6]. The final picture, however, remains incomplete and more work is still required. There is a need for new methodological approaches in order to achieve further progress in the development of biological pacemakers. One such approach is the dynamic clamp methodology. The idea of combining an *in silico* model of ionic conductance(s) with the current clamp recording from a living cell in a cell-computer hybrid experiment has been around almost as long as the patch clamp technique itself [5, 12]. For quite some time, it has remained a kind of oddity to most of the cardiac electrophysiology labs owing to the complexity of implementation and strict demands for the computations to be performed in real-time, often at an exceedingly high speed. However, with recent progress in the open-access software and hardware development, the dynamic clamp became accessible to a wider research community and seems poised to become a useful addition to virtually every electrophysiology set-up [3, 9, 10].

A masterclass in the use of dynamic clamp for the bio-pacing research is presented in this issue by V. Valiunas et al. The authors used their previously developed implementation of the dynamic clamp software [2] to inject different values of computed conductances underlying the I_f and I_{K1} into HEK293 cells stably expressing Nav.1.5 channels and observed the appearance of spontaneous action potentials. They succeeded in evaluating the relationship between the magnitude of the above conductances and the initiation, sustenance, and termination of pacing. Having established how pacing depends on the background potassium conductance and pacemaker conductance, the authors proceeded to the evaluation of the simulated coupling conductance on synchronised pacing of the driver and follower cells. Interestingly, the relationship turned out to be bell-shaped, with too low or too high junctional conductance being detrimental to synchronised activity—a result similar to that found in the *in silico* experiments on the smooth muscle syncytium [11]. These results are not only important for the development of bio-pacemakers, but they also provide a new perspective for evaluation of the calcium clock contribution to pacemaking in the near future. Hence, let's keep tuned.

This article is a commentary to the original article https://doi.org/10.1007/s00424-020-02378-1

✉ Anatoly Shmygol
a.shmygol@uaeu.ac.ae

[1] Department of Physiology, College of Medicine and Health Sciences, United Arab University, Al Ain, UAE

References

1. Cingolani E, Goldhaber JI, Marbán E (2018) Next-generation pacemakers: from small devices to biological pacemakers. Nat Rev Cardiol 15:139–150. https://doi.org/10.1038/nrcardio.2017.165
2. Clausen C, Valiunas V, Brink PR, Cohen IS (2013) MATLAB implementation of a dynamic clamp with bandwidth of >125Â kHz capable of generating I^sub Na^ at 37Â °C. Pflügers Archiv - European Journal of Physiology; Heidelberg 465:497–507. https://doi.org/10.1007/s00424-012-1186-8
3. Desai NS, Gray R, Johnston D (2017) A dynamic clamp on every rig. eNeuro 4:ENEURO.0250-17.2017. https://doi.org/10.1523/ENEURO.0250-17.2017
4. DiFrancesco D (1985) The cardiac hyperpolarizing-activated current, if. origins and developments. Prog Biophys Mol Biol 46:163–183. https://doi.org/10.1016/0079-6107(85)90008-2
5. Goaillard J-M, Marder E (2006) Dynamic clamp analyses of cardiac, endocrine, and neural function. Physiology 21:197–207. https://doi.org/10.1152/physiol.00063.2005
6. Lakatta EG, DiFrancesco D (2009) What keeps us ticking: a funny current, a calcium clock, or both? J Mol Cell Cardiol 47:157–170. https://doi.org/10.1016/j.yjmcc.2009.03.022
7. Maltsev VA, Vinogradova TM, Bogdanov KY, Lakatta EG, Stern MD (2004) Diastolic calcium release controls the beating rate of rabbit sinoatrial node cells: numerical modeling of the coupling process. Biophys J 86:2596–2605. https://doi.org/10.1016/S0006-3495(04)74314-3
8. Mangoni ME, Nargeot J (2008) Genesis and regulation of the heart automaticity. Physiol Rev 88:919–982. https://doi.org/10.1152/physrev.00018.2007
9. Nowotny T, Szucs A, Pinto RD, Selverston AI (2006) StdpC: a modern dynamic clamp. J Neurosci Methods 158:287–299. https://doi.org/10.1016/j.jneumeth.2006.05.034
10. Patel YA, George A, Dorval AD, White JA, Christini DJ, Butera RJ (2017) Hard real-time closed-loop electrophysiology with the Real-Time eXperiment Interface (RTXI). PLoS Comput Biol 13:e1005430. https://doi.org/10.1371/journal.pcbi.1005430
11. Sheldon RE, Baghdadi M, McCloskey C, Blanks AM, Shmygol A, van den Berg HA (2013) Spatial heterogeneity enhances and modulates excitability in a mathematical model of the myometrium. J R Soc Interface 10:20130458. https://doi.org/10.1098/rsif.2013.0458
12. Wilders R (2006) Dynamic clamp: a powerful tool in cardiac electrophysiology. J Physiol 576:349–359. https://doi.org/10.1113/jphysiol.2006.115840