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REVIEW

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Advances in ion channel high throughput screening: where are we in 2023?

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ABSTRACT

Introduction: Automated Patch Clamp (APC) technology has become an integral element in ion channel research, drug discovery and development pipelines to overcome the use of the highly time-consuming manual patch clamp (MPC) procedures. This automated technology offers increased throughput and promises a new model in obtaining ion channel recordings, which has significant relevance to the development of novel therapies and safety profiling of candidate therapeutic compounds.

Areas covered: This article reviews the recent innovations in APC technology, including platforms, and highlights how they have facilitated usage in both industry and academia. The review also provides an overview of the ion channel research endeavors and how APC platforms have contributed to the understanding of ion channel research, pharmacological tools and therapeutics. Furthermore, the authors provide their opinion on the challenges and goals for APC technology going forward to accelerate academic research and drug discovery across a host of therapeutic areas.

Expert opinion: It is clear that APC technology has progressed drug discovery programs, specifically in the field of neuroscience and cardiovascular research. The challenge for the future is to keep pace with fundamental research and improve translation of the large datasets obtained.

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1. Introduction

Ion channels are pivotal physiological proteins, facilitating ionic fluxes that underpin a compendium of biological processes [1]. With the discovery of these ion channel proteins came the need to gain access to real-time data to record the functional passage of ions through these channels. In 1978, Neher and Sakmann made the practical demonstration with the invention of the patch clamp technique that enabled researchers to measure tiny currents in biological membranes [2]. Twenty years later, using X-ray crystallography on Actinobacteria, scientists provided a three-dimensional molecular structure of an ion channel [3]. The world of electrophysiology has grown since then and now plays a critical role in both fundamental, primary ion channel research and applied research in drug discovery programs in both academia and industry. This has provided data for FDA-approved medicines with some 18% targeting human ion channels to offer their therapeutic potential [4]. Further, all new chemical entities (NCEs) – irrespective of their physiological target in the body – are tested for cardiac liability and safety against a panel of ion channels that make up the cardiac action potential [5]. This underlies the importance of real-time data from human ion channels, as the drive for better medicines continues. However, the experimental technique was rate limiting in data acquisition, particularly problematic in the high throughput screening (HTS) that is needed for drug discovery and development.

Historically, patch clamp experiments have been time consuming with manually operated 'rigs' routinely used since the development of the patch clamp technique. This led to the exploration of automating the process to scale up ion channel screening of candidate molecules from low throughput (i.e. data points per day, d.p./day) to high throughput. The first automated patch clamp (APC) platform to market was in 2002 (IonWorks, Essen Instruments; for a detailed history of APC and its development, see [6]). In that first decade of APC technology, adoption was primarily in industrial labs, but in the last decade, academic users are adopting automated workflows to support their physiology, pharmacology, and toxicology research. There is now widespread evidence of their use in the published literature (Figure 1) which is testament to their successful deployment in global primary ion channel research and drug discovery and development pipelines.

2. State of play

2.1. Technological advances

For an historical perspective covering the key technological APC developments – including planar patch clamp, multiple compound additions, internal perfusion, costs per data point – see reviews by Bell and Dallas [6] and Bell & Fermini [7]. In this section, we aim to update the more recent developments (within the last 5 years) that are driving and advancing the capabilities of APC recordings. Since 2018, three new or updated APC platforms have come to market: QPatch II (Sophion Bioscience [8], SyncroPatch 384i [9], and the 'semi-APC' QPatch Compact (Sophion Bioscience; see https://sophion.com/products/qpatch-compact/). However, beyond the brief overview given in Table 1, this section is not meant as a detailed comparison of these latest platforms; this section aims to provide more generic technological

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Article highlights

- Automated Patch Clamp (APC) technology is rapidly evolving and becoming embedded in academia and industry research settings.
- Significant barriers have been identified that have required optimization of APC platforms to full exploit their potential.
- Neuroscience and cardiovascular research have benefited greatly from APC technologies.
- The ion channel community is now looking to used iPSC-derived cells to improve translation of research; this presents its own challenges to using APC platforms.
- APC platforms have a role to play in academia and industry spanning fundamental ion channel research through to drug discovery pipelines.

developments that are making APC platforms more useful in a broader range of capabilities and applications.

2.1.1. Temperature control

Temperature has multiple, significant effects on protein physiology and pharmacology, including their modulation by drugs. Ion channels are no different in this respect and temperature is of critical importance (e.g. safety pharmacology testing of compounds on cardiac ion channels [10]). This is demonstrated by the hERG channel and the evidence that channel biophysical properties are temperature dependent; further, drug-specific interactions are also temperature dependent [11–13]. These significant effects on ion channel biophysics and drug–ion channel interactions (e.g. drug binding/unbinding events) clearly show that controlling the accuracy, stability, and consistency of temperature is a critical environmental factor in ion channel experimentation.

Considering this critical importance of temperature in all biological processes, it is surprising that temperature control has only come to the fore in APC in the last few years. Part of this slow adoption is research driven (i.e. the research need and advocacy for temperature control in experimentation), part is due to the engineering problem controlling temperature causes. A key engineering problem to overcome in consistently accurate temperature control on APC platforms is the significant heat generated by having 8–384 individual electrode connectors (dubbed the bed-of-nails or BoN) in circuit with patch clamp amplifiers, all in close proximity to the cell recording sites. The heat generated at the BoN and recording sites is significant, resulting in "room temperatures" for APC measured at approximately 25–27°C (versus standard lab room temperatures of 20–23°C). For instance, Lei et al. [14] estimated the SyncroPatch 384PE APC system generated heat at the BoN and recording sites to be at least + 3°C; consequently, the authors reported that temperature could not be kept below 25°C, even when the temperature controller was set to temperatures lower than 25°C. Similarly, Sophion found levels of amplifier heat generation in both the QPatch II & the Qube to be ~+2–3°C (in-house data, not shown).

To address this problem of BoN heat generation, APC designers and engineers have settled on two ways of controlling experimental recording temperatures. The first method is via ambient temperature control, whereby the APC *macro-environment*, consisting of cabinet and/or perfusate solution temperature, is used to set and control the experimental temperature (e.g. see APC comparison Table 1). The second method is by setting the temperature directly at the *recording site micro-environment* (i.e. directly at the BoN; see APC comparison Table 1). The second format of controlling temperature at the BoN micro-environment poses a greater technical challenge: it requires the snaking of heating/cooling fluid tubing throughout the bed of electrodes in the BoN. In doing so, this fluid thermal tubing decouples the micro-environment of the recording sites from heat generated by amplifiers, making both cooling and heating possible. By insulating the recording sites from the amplifier heat and through the efficient heat coupling between BoN and recording plate, this format enables accurate control of temperature from + 10°C to + 42°C with an accuracy of ±0.5°C. The temperature versus time plots obtained on the QPatch II system shown in Figure 2 illustrate the very tight and controlled temperatures achievable using this method: the experimentally set command temperatures (T_{Set}) are accurately tracked by the BoN temperatures (T_{BON}).

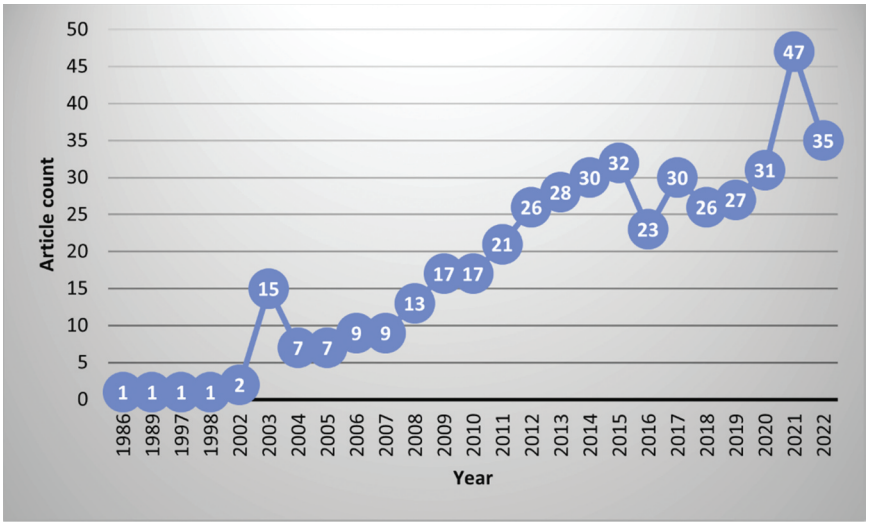

Figure 1. Automated patch clamp adoption. Timeline from PubMed indicating the number of articles per year returned when searching for "automated and patch clamp." Search undertaken August 2023. Note some articles may be reviews and not original primary research and this will undoubtedly not capture all automated research.

Table 1. Key features of developments in APC (in blue) and semi-APC (in yellow) platforms in the last decade (2013–2023). A comparison of key features of the second generation of APC platforms. Abbreviation: d.P./day – data points per day; PDMS – poly-dimethyl-siloxane; BoN – bed-of-nails. Adapted from [7] with permission of Elsevier.

Feature	Qube (Sophion, Denmark)	IonFlux Mercury/Ultra (Fluxion, USA)	QPatch II (Sophion, Denmark)	SyncroPatch 384i (Nanion, Germany)	QPatch Compact (Sophion, Denmark)
Recording sites	384	64 / 256	16 / 48	384 / 768 (2nd module)	8
Throughput (d.p./day)	~ 16 k	~ 5 k / 18 k	~ 3-5 k	~ 20 k / 40 k	200-400
Substrate	Planar, silicon/glass	Lateral, PDMS	Planar, silicon/glass	Planar, glass	Planar, silicon/glass
Seal resistances	> 1 GΩ	> 1 GΩ	> 1 GΩ	>1 GΩ	>1 GΩ
Amplifier compensation	Yes	Yes	Yes	Yes	Yes
Internal perfusion	Yes (offline)	No	No	Yes (online)	No
Temperature control	Yes - BoN	Yes - ambient	Yes - BoN	Yes - ambient	Yes - BoN
Multiple compound additions	Yes	Yes	Yes	Yes	Yes
Recording well format	Microfluidics fed	Microfluidics fed	Microfluidics fed	Fixed well	Microfluidics fed
External solution exchange cycle	Add-displace-replace	Continuous	Add-displace-replace	Add-dilute-remove	Add-displace-replace
Current clamp	Yes	Yes	Yes	Yes	Yes

2.1.2. Current clamp, dynamic and adaptive current clamp capability

Manual patch clamp amplifiers allow researchers to obtain recordings in both voltage clamp mode and current clamp mode. APC amplifiers are no different and capable of both voltage- and current-clamp recordings. As such, current-clamp provides the testing of cardiac safety of drug effects on an ion channel current to be directly measured via their effects on membrane voltage e.g. by measuring action potentials (APs). For instance, current-clamp recordings made upon cardiac cells or cardiac model cells (e.g. human induced pluripotent stem cells derived cardiomyocytes, hiPSC-CMs; see "Cardiovascular drug discovery" section below) contain the complement of cardiac ion channels: the resulting assays can be used to determine the effects of drugs in this cardiac AP current-clamp mode [15,16].

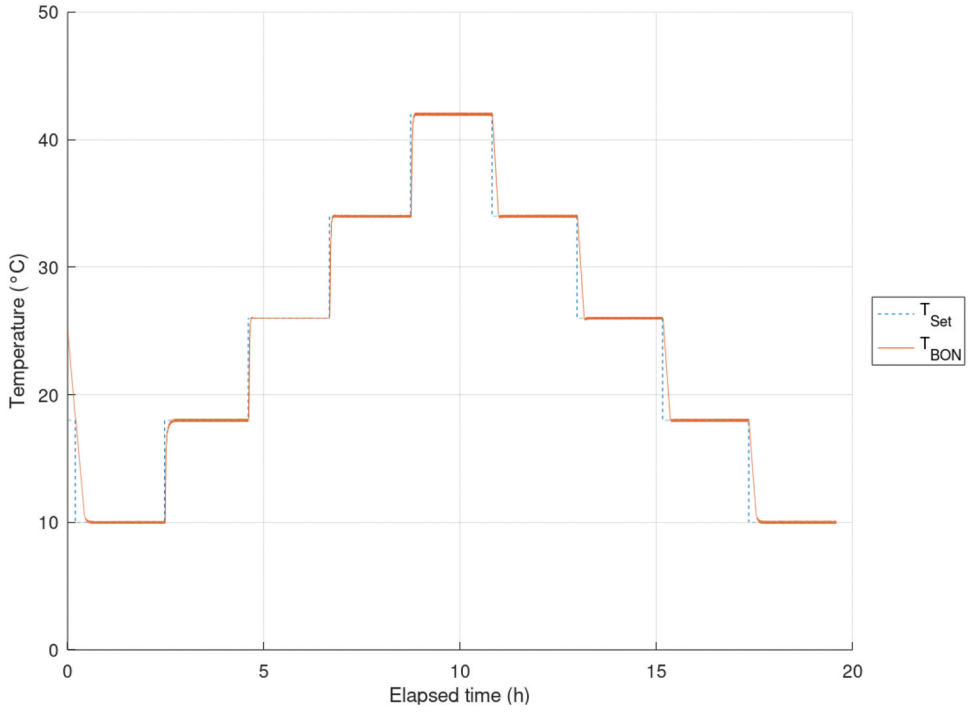

Figure 2. Temperature regulation in APC platforms. QPatch II temperature-time plots for set command temperature (TSet) & the temperature recorded at a temperature sensor embedded in the BoN housing (TBON). Following equilibration of TBON temperatures (orange plot) to the TSet command temperature (dotted blue plot), the TBON temperatures consistently tracked TSet temperatures from +10°C to +42°C with an accuracy of ± 0.5°C. Reproduced from [7] with permission of Elsevier.

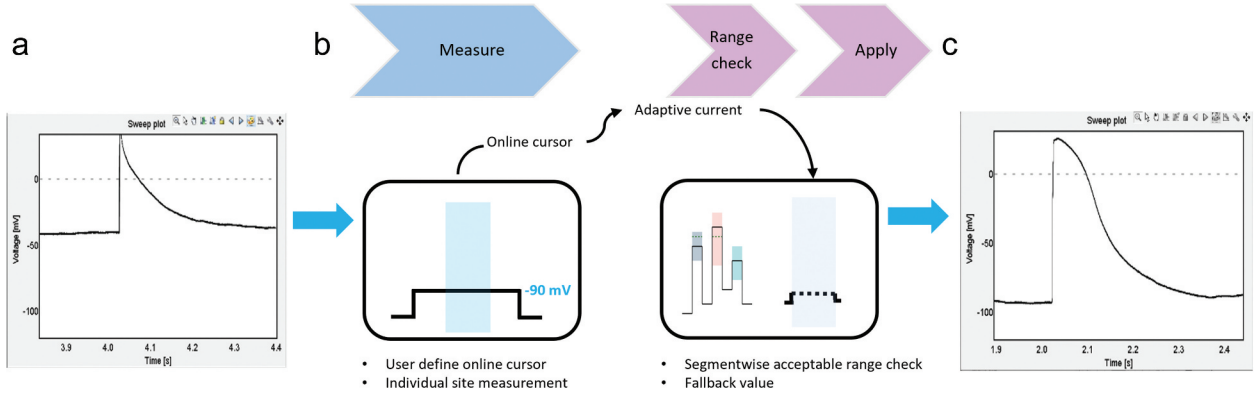

Figure 3. Adaptive Current clamp (IAdapt) schematic. (a) Representative trace showing an action potential measured without the IAdapt feature applied in current clamp configuration on QPatch II. (b) The workflow illustrates how the system measures the current required to be injected for the individual cells to hold the resting membrane potential at a certain voltage (here −90 mV) using the IAdapt feature. (c) Representative trace showing the improvement of action potential shape with application of IAdapt feature to the action potential recording shown in (a).

Developing the capability of current-clamp further, "dynamic clamp" has been applied to APC current clamp recordings. In dynamic clamp, additional cell-by-cell currents can be modeled and added into the cell's existing complement of channel currents. An example might be: the inward rectifier potassium current, IK1, is modeled and electronically added into an hiPSC-CMs' mixed population of channel currents, thereby enhancing maturation of these cardiomyocytes by computer modeled currents, since the IK1 current is often lacking in "immature" hiPSC-CMs and artificially replicates the more mature primary cardiac ventricular cells [17].

Another recent development that is furthering current clamp recordings on APC platforms is "adaptive current clamp." As covered above, cardiac action potential measurements are a useful tool for biophysical and pharmacological characterization of cardiac myocytes. However, hiPSC-CMs often display a depolarized resting membrane potential (in part due to the reduced or absent IK1 current, see text above), limiting the quality of action potential measurements in drug screening or disease modeling studies. A way to overcome this limitation is by using adaptive current clamp (e.g. QPatch II, Sophion). As .shown in Figure 3(a), the action potential measurement from a hiPSC-CM shows depolarized resting membrane potential (RMP) around −40 mV with a very short action potential duration (APD). Adaptive current clamp measures RMP individually for each cell, then "adapts" an injecting the current (Figure 3(b)) required to hold each cell's RMP at a potential closer to expected typical levels for a mature CM (e.g. −90 mV in Figure 4(c)). Using adaptive current clamp significantly improved the upstroke velocity and the action potential duration (APD), as shown in Figure 3(c).

2.2. Advances in drug discovery

The role of ion channels in drug discovery is critical to evaluate therapeutic effects but also remains pivotal in safety screening of new drug candidates or new chemical entities (NCEs). Therefore, there is scope for a diverse range of therapeutic areas to benefit from the adoption of automated platforms for functional ion channel studies. This review aims to highlight two key areas of physiology and pathophysiology where significant progress using automated technology has been made to support drug discovery (see Figure 4).

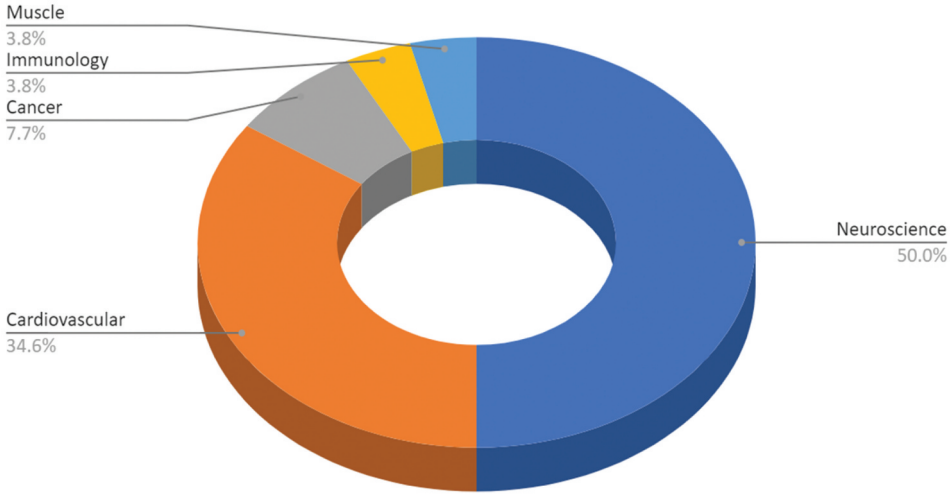

Figure 4. APC applied ion channel drug discovery research by disease area. This chart reveals the identified therapeutic areas that authors state within the APC publications from 2022. Where no direct therapeutic area was cited, this was extrapolated from the ion channels under investigation.

2.2.1. Neuroscience drug discovery

Electrophysiology has long been a vital tool in neuroscience, where the required tools are needed to interrogate the activity of neurons and surrounding glia as they communicate using electrical signals. As exemplified in Figure 4, there is an increasing need to achieve HT screening capabilities in neuronal ion channels. This is particularly relevant in epilepsy where around 25% of genes identified in epilepsy encode ion channels [18]. It is not surprising then that epilepsy researchers have adopted APC technology into their translational pipelines. Drug discovery and development routinely employs mammalian cell lines (e.g. HEK293, CHO) overexpressing the target ion channel(s) to define the activity of test compounds against these targets. Neuroscience-based drug discovery also calls for more physiological *in vitro* models, ultimately to achieve more translatable ion channel research from bench to bedside. This has seen the development and routine use of rodent brain slice electrophysiology, which retains some physiological parameters but limits translation advances. There have been some interesting technological advances to improve and automate the use of electrophysiology in brain slices [19]; however, this does not adequate upscale the data output to what is available using the APC HTS platforms described in this review. Consequently, animal and human iPSC derived neuronal cell lines or primary, acutely isolated neurons are the *in vitro* models that researchers increasingly turn to for use in HT APC assays.

iPSC-derived neurons, which can be derived from diseased animal models or from human patients, can provide neuronal subtype and disease-specific cells. In recent years, there have been significant improvements in reprogramming, induction, and maturation and growth cycles, leading to more consistent and matured iPSC-derived neurons. There are many techniques to achieve this consistency and maturity, which aim to increase the physiological and translatable relevance of these cells [20,21]. Further, a second element that has come on leaps and bounds in the last couple of years are the growth, dissociation, and handling procedures of iPSC cultures, making for healthier and significant improvements in the cell suspensions needed for successful ion channel recordings in APC [22]; these developments are also applicable to iPSC-cardiomyocytes (see "Cardiovascular drug discovery" section, below).

An alternative *in vitro* model for APC recordings is to use primary, acutely isolated neurons taken from animals and/or human tissue biopsies (e.g. of diseased tissues). In a groundbreaking study published earlier this year, the Waxman lab at Yale described dissociation, purification, and Qube (Sophion Bioscience) APC voltage- and current-clamp techniques for nociceptive dorsal root ganglia (DRG) [23]. The authors show that the increased throughput of recordings (1–10 via MPC vs up to ~ 200 via APC) allows for the possibility of sub-population characterization, unbiased neuronal selections, and without the need for overnight coverslip incubation. This efficient, increased throughput of ion channel recordings from primary neuronal cells will surely provide methodological guidelines and incentives to adopt these techniques in many more neuronal subtypes and other tissues around the body.

2.2.2. Cardiovascular drug discovery

Cardiovascular research has also benefited from the implementation of APC platforms, in both the characterization of mutations in ion channels driving pathology (e.g. Long QT syndrome) and also from a safety screening point of view. To bring about translational research, induced pluripotent stem cell-derived cardiomyocytes (iPSC-CM) have emerged as a promising *in vitro* model for investigating cardiac drug effects and safety pharmacology (for a review see [7]). This innovative approach has gained substantial traction and exhibits a developmental trajectory akin to advancements witnessed in neuroscience research (see section 2.2.1).

Despite the notable progress, it is important to acknowledge that many iPSC-CM express ion channel populations that are considered "immature." These populations often encompass the pacemaker If current, which is prevalent in immature cardiomyocytes but diminishes as cells mature. Additionally, iPSC-CM frequently exhibits insufficient levels of the IK1 current, as highlighted by [17,18]. To rectify these deficiencies, diverse techniques have been employed to restore the lacking ion channel currents. For instance, one adopted method involves augmenting the expression of deficient channel currents through viral transfection, as demonstrated by [20,21]. Moreover, innovative approaches such as dynamic clamp and adaptive current clamp (refer also to section 2.1.2) have been employed in action potential characterization. These methods simulate and electronically introduce ion currents into iPSC-CM, effectively compensating for the absent ion channel currents, such as IK1, as evidenced by Becker et al. [24] and Verkerk et al. [25].

As seen in neuronal *in vitro* assay developments, acutely isolated, primary cardiomyocyte (CM) ion channel recordings have also seen substantial progress in recent years. This direct recording from fully matured CM also overcomes the potential immaturity of iPSC-CM described above, another step toward more physiological recordings that make for more medically relevant and translatable *in vitro* models. Due to the size and morphology (10–130 µM rod-like cells), auto-contractile nature, and mixed populations of atrial and ventricular cells, CMs are particularly challenging cells to make patch-clamp recordings from. Much like neuronal cell recordings, the throughput for CM recordings via MPC is very low (routinely less than the 1–10 recordings made on DRG neurons per day per experienced electrophysiologist given by Ghovanloo et al. [21], see "Neuroscience drug discovery" section 2.2.1 above). Again, this low level of throughput hampers cardiac research, drug discovery, and safety pharmacology. To address this research bottleneck, great progress was made earlier this year by developing methods of isolation, purification, and handling to make recordings from acutely isolated, primary CM on APC, increasing throughput dramatically [26].

However, it is pertinent to note a correction that needs to be made in the discourse. Seibertz et al. [24] deserve acknowledgment for their commendable work in overcoming significant challenges associated with CM ion channel recordings using automated patch-clamp (APC) platforms. Nonetheless, it is necessary to rectify the assertion made in their paper, lacking experimental support, that APC platforms featuring microfluidic-fed recording sites (e.g. those offered by Sophion and Fluxion, see

Table 1) would be unsuitable for CM recordings due to their large, rod-like morphology. This contention posits that CMs would encounter physical obstructions within the microfluidic channels. Contrarily, it is important to emphasize that microfluidic channels in Sophion's recording plates possess a minimum width of approximately 300 µm, thereby facilitating unhindered rotation of even the largest CMs along their principal axes (up to ~130 µm). Furthermore, experimental evidence attests to the feasibility of conducting ion channel recordings from acutely isolated mammalian CMs on APC platforms featuring microfluidic channels (in-house data from Sophion). This physical dimension and experimental evidence serves to debunk the aforementioned assumption.

3. Expert opinion

The ease and high throughput that APC affords are clear advantages over time-consuming, technically challenging MPC techniques. This efficiency of ion channel recordings when combined with long-standing capabilities on select APC platforms (see Table 1 for platform capabilities comparison), such as: low volume, rapid exchange of recording solutions via microfluidic channels and current clamp, makes for a compelling case and explains the growing adoption as a standard technique in ion channel recordings in multiple research environments. As outlined here, further capabilities like temperature control and innovative advances in current clamp (e.g. dynamic clamp and adaptive current clamp) and the significant progress the field has made in high-throughput recordings on iSPC and primary, acutely isolated cells, are all driving ion channel research and drug discovery faster and further than ever before. While not exclusive to APC platforms, there needs to be a wider discussion and implementation of standard protocols across research groups and APC platforms as evidence highlights the variability in pharmacological readouts, which could have an impact on safety margins reported for candidate molecules [27]. This will involve a community wide effort to standardize approaches and share best practices to improve reproducibility in APC research.

Whilst APC provides high quality, high throughput, and concordant statistical power (increased n) for measuring action potentials via current clamp (see Current Clamp section 2.1.2 above), further efficiencies (greater throughput and cheaper) recordings for cardiac safety, neuronal drug discovery would be welcomed in the field. Kilfoil et al. [28] made a comparison between a high sampling rate fluorescent plate reader (the Photoswitch Bolt platform, <1 ms sampling, i.e. giving sufficient time resolution to definition of AP kinetics), Qube (Sophion Bioscience) APC and hERG binding assays. APC technology was well regarded, and, alongside the Bolt, provided sufficient time-resolved data to efficiently measure and define AP pharmacology. Such complementary technologies are likely the way forward that such drug testing may be best generated in future drug discovery and safety pharmacology studies.

The single cell suspension that planar patch clamp requires does mean that recordings that require networked or synapsing neurons or electrically connected CMs (e.g. *in vivo* or *ex vivo* slice recordings) will always be a gap in APC capabilities. This is also coupled by the increasing awareness and understanding of the relevance of 3D cell systems; typical monolayer and cellular suspension recordings do not provide the structural architecture that is observed *in vivo*. Here, both manual and automated platforms need to evolve if they are to interrogate 3D cellular environments. Some progress has been made on manual platforms with recordings for cell aggregates or spheroids reported [29–31]. How physiologically relevant these recordings are remain to be seen as there may be an inherent element of preselection of the outer cells that provide the data outputs at present. However, given the advances reported here, we may see further progress in this field in the next decade. Consequently, APC should be seen as complementary – not competing – technology to the vast scope of recording capabilities and environments that MPC offers.

In summary, it is clear that automated platforms have made a significant contribution to ion channel research across the physiological spectrum (for reviews, see Bell & Dallas [6], Liu et al. [15], McGivern & Ding [32], and Obergrussberger et al. [9]). Initially pioneered and adopted by industry for the clear need for higher throughput requirements in drug discovery, development and cardiac safety screening, academia is quickly catching up and embedding platforms within institutes from both research and scholarship perspective goals [33–36].

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Declaration of interest

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Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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