Case study

Two years of the SyncroPatch 384 in the City of Science

Tools:
SyncroPatch 384

The University of Göttingen
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The University of Göttingen celebrates the second anniversary of the installation of the SyncroPatch 384, a high throughput automated patch clamp device. Funded by the Multiscale Bioimaging Cluster of Excellence (MBExC) at the University Medical Center Göttingen (UMG), the instrument is under continuous use by researchers at the forefront of cardiac and neuronal cellular electrophysiology.

In excitable cells such as cardiomyocytes and neurons, ion channels embedded within cellular membranes conduct minuscule currents into or out of the cell. This maintains cellular homeostasis and facilitates action potential propagation, transferring electrical signals across cardiac muscle or throughout the nerves of the brain. Ion channels, encoded by specific genes, are prone to mutations that can alter their protein structure and function. At the system level such alterations can lead to severe medical conditions, including cardiac arrhythmias or neurological disorders. By understanding the underlying functional pathologies, medical researchers can identify molecular drug targets for pharmacological treatment and clinical management of these diseases.

The patch clamp technique is of profound methodological importance to biomedical research because it allows for precise quantification of the microscopic currents that flow through the ion channels of living cells. This technique was established in the 1970's by Dr Erwin Neher and Dr Bert Sakmann in Göttingen, Germany. They would go on to win the Nobel Prize in Physiology or Medicine in 1991 for their immense body of work which still allows researchers in the present day to understand how cells of the body function.

In the years since the patch clamp technique was invented, the method has been expanded and automated in a way that enables the recording from multiple cells simultaneously, vastly improving ease-of-use and increasing the throughput of data acquisition. The SyncroPatch 384 is a high throughput automated patch clamp instrument for recording from up to 384 cells in parallel. The system is highly flexible and is ideal for drug screening in the pharma industry, and for complex biophysical studies in academic research.[1]

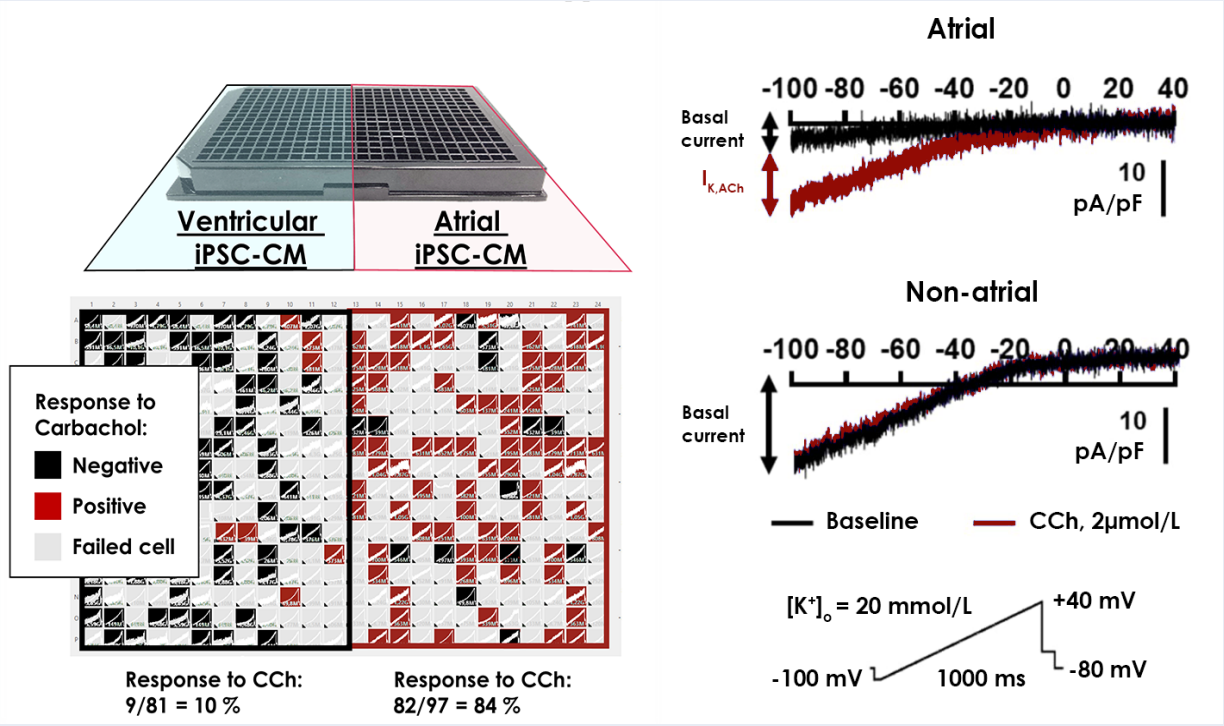
The city of Göttingen, dubbed the City of Science for its many contributions to scientific research over centuries, has continued to be a hub for biophysical research. Realizing the need for high throughput patch clamp measurements to accelerate their electrophysiological research, the Multiscale Bioimaging Cluster of Excellence (MBExC) at the University Medical Center Göttingen (UMG) installed a SyncroPatch 384 at their research campus in July 2022. As an initiative funded by the German Federal and State Governments, the MBExC aims to unravel the structure and function of heart and brain

Nanion's SyncroPatch 384 platform
is a high throughput automated patch-clamp device capable of patching and recording up to 384 cells in parallel. It is highly flexible, making it ideal for complex biophysical studies in academic labs.

> **"Together with Nanion's dedicated researchers, we performed novel experiments on primary cardiomyocytes using the SyncroPatch. These experiments laid the foundation for our exciting future collaboration with Nanion and multiple new projects."**
>
> **Professor Niels Voigt**, University Medical Center Göttingen

cells specifically to understand how to treat cardiac and neurological diseases. Under the umbrella of the MBExC, the SyncroPatch 384 is curated by Prof. Dr. Niels Voigt, an expert in cellular mechanisms of cardiac arrhythmias, and Dr. Thomas Mager, a neuroscientist with extensive expertis e in optogenetics. This case study, written on the two-year anniversary of the Göttingen SyncroPatch 384 acquisition, will summarize the combined projects, collaborations, publications and career opportunities that have been made possible over the last two years.

In the cardiac field, a wide variety of academic projects in Göttingen have made use of the SyncroPatch 384, including the first ever successful measurements of primary cardiomyocytes using high throughput automated patch clamp.[2] The vast amounts of voltage clamp and current clamp data obtained from a small batch of mammalian samples indicate that less animals need to be used in future for scientific purposes while still obtaining large data sets. Popular functional models such as human cardiomyocytes derived from induced pluripotent stem cells (iPSC-CM) also acknowledge the ethical responsibility of reducing animal use by providing theoretically infinite amounts of patient specific cells *in vitro*. In Göttingen, the SyncroPatch 384 acts as both a primary biophysical tool to investigate ion channel function in health and disease, and as a screening platform to determine iPSC-CM batch quality and purity. iPSC-CM differentiation often results in heterogeneous cell populations of nodal, atrial or ventricular subtypes.[3] In studies of chamber-specific diseases such as atrial fibrillation, it is necessary to ensure the cellular substrate is indeed of the desired subtype. Compounds such as the M2 receptor agonist carbachol can be applied to unmask the atrial-specific current $I_{K,ACh}$ and give a readout of atrial purity within a cellular cohort.[4,5] This is an



The SyncroPatch 384 can be used as a functional subtype screening platform to determine the purity of atrial or ventricular induced pluripotent stem-cell derived cardiomyocytes (iPSC-CM). *Flexible distribution of different cell lines or types across the 384 well recording plate allows for simultanous measurement and characterization. M2 receptor agonist carbachol (CCh) can be applied to unmask acetylcholine-activated inward rectifiers ($I_{K,ACh}$) that are only present in atrial cells.[4,5]*

economical method to test each batch "on the side" after crucial measurements to avoid difficult and time-consuming molecular techniques to test for atrial or ventricular-specific genes.

Collaborations involving the Göttingen SyncroPatch 384 have unveiled new potential roles for existing drugs such as the SGLT2 inhibitor Dapagliflozin. Usually prescribed to treat diabetes and kidney failure, recent research has revealed that this drug imparts atrial-specific regulation of cardiac excitability through modulation of the cardiac sodium current.[6] This is particularly important because effective atrial-specific therapies for rhythm control in the absence of proarrhythmic ventricular side effects are severely needed to treat patients with atrial fibrillation. Other major collaborations have identified that gene therapy to restore Plakophilin 2 function in Knock-Out iPSC-CM models reverses the arrhythmic phenotype commonly displayed by patients with mutations in the Plakophilin gene.[7]

The SyncroPatch 384 has also driven important descriptive work optimizing experimental procedures in the iPSC-CM field. For example, through the development of a novel protocol to measure the rapid component of the delayed rectifier current (I_{Kr}) in iPSC-CM using equimolar Cs^+ concentrations,[8] and through long term tracking of ion channel development in iPSC-CM to identify the optimal time window for measurement as cells get older in culture.[3]

In the field of optogenetics, the SyncroPatch 384 in Göttingen has been instrumental in the development of new red-shifted light sensitive ion channels, known as opsins. Derived from microbial organisms, these light sensitive ion channels can be virally inserted into the target organ system and could be used in future for arrhythmia control in the heart and even the clinical restoration of vision or hearing. Much work has been conducted with the Göttingen SyncroPatch 384 combined with the optical stimulation tool to screen immense libraries of new opsins to develop new constructs with a sustained high single channel conductance under continuous illumination conditions. Researchers at the Göttingen campus have been able to show that their new construct, named ChReef (**ChR** [channel rhodopsin] that **e**xcites **ef**ficiently), was successful in partially restoring vision in blind mice following viral insertion of the opsin into retinal ganglion cells.[9] Not only limited to vision restoration, application of ChReef into the spiral ganglion neurons of the inner ear was followed by sustained activation of the auditory pathway under low illumination conditions.

Prof. Niels Voigt (left), Aistė Liutkutė, Dr. Fitzwilliam Seibertz and Dr. Funsho Fakuade with the SyncroPatch 384 at the UMG. *The SyncroPatch 384 is routinely used in the lab to record hiPSC-derived cardiomyocytes to investigate the physiology and pathophysiology of cardiac arrhythmias.*

"The SyncroPatch 384 expands our ability to screen natural variants and follow previously impossible protein engineering approaches for the purpose of advancing optogenetic tools for basic sciences and future medical therapies."

Dr. Thomas Mager, University Medical Center Göttingen

These developments are particularly exciting from a clinical standpoint, as lowering the energy threshold for cochlea activation represents a realistic step closer to wearable optogenetic devices for effective hearing restoration.[9]

In the last two years, the Göttingen SyncroPatch 384 has assayed hundreds of thousands of cells. However, it is not only a platform for scientific discovery. It has also kick-started a teaching programme at the university. Regular seminars and methods courses are offered to masters- and PhD-level students by the Hertha Sponer College within the MBExC. These courses aim to teach students about the automated patch clamp technique and encourage collaborations throughout the university. Within the last two years, key users of the Göttingen device have graduated PhD and medical thesis study programmes, started post-doctoral fellowships, and have joined high level industry positions.

The MBExC has remained on the global frontier of biomedical research into heart and brain function. It is high throughput techniques such as automated patch clamp that add to the growth of this immense program within a historically significant university. At Nanion, we look forward to supporting the ongoing work of the MBExC and following their journey with the SyncroPatch 384.

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