# High-performance computer provides new insights into the structure and function of ion channels

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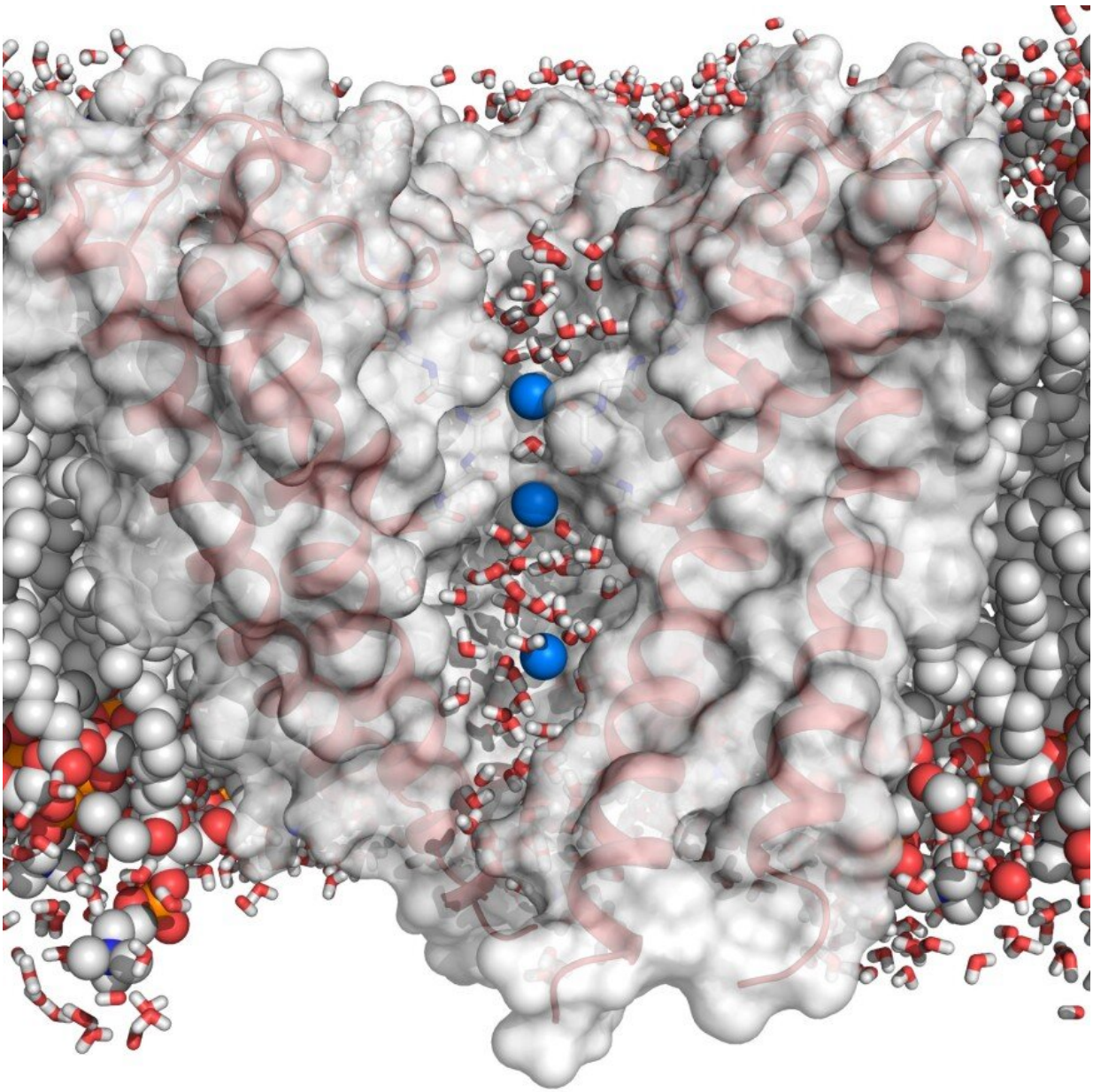


View of the part of the HCN4 channel that is embedded in the membrane. In the protein structure (grey), the transmembrane domains are shown as transparent helices (red). Potassium ions (blue) and water (red/white molecules) can be identified in the central pore. Credit: Technische Universitat Darmstadt

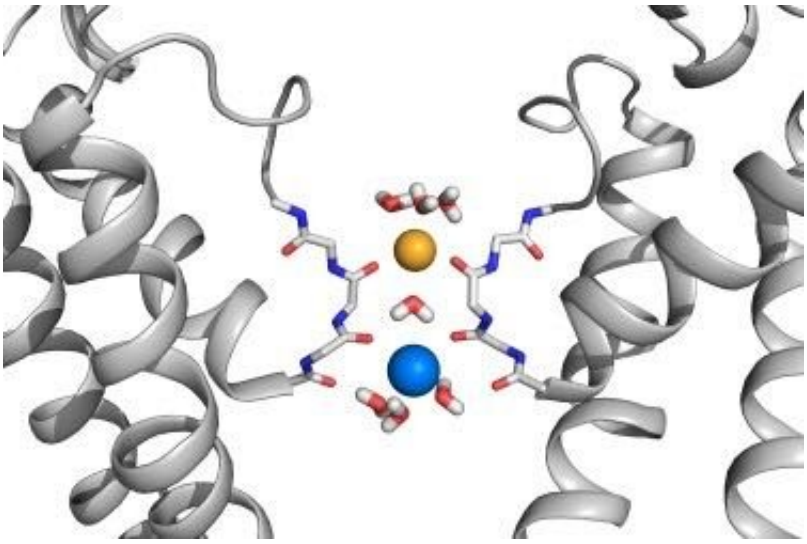
An international team that includes researchers at TU Darmstadt has gained new insights into the protein structure and function of the ion channels that control the heartbeat. The results have now been published in the journal *Molecular Cell*, and could contribute to the development of cardiac drugs with fewer side effects.

We all know the feeling: too much excitement or a strong coffee, and our heart starts thumping. This everyday experience has been very well understood by biologists and physicians at the molecular level for many years. The focus is on special types of ion channels known as the HCN channels, whose activity can be controlled by a variety of cellular signals. The distance between successive action potentials is longer or shorter, depending on the activity of the channel. This increases or decreases the frequency of the heartbeat. HCN channels are of particular importance in human physiology. Cardiac arrhythmia occurs as soon as the channels stop working properly, and in extreme cases an electronic pacemaker has to be fitted to take over the task of the channels.

## Working groups from the Department of Biology involved

With the participation of the working groups of Professor Gerhard Thiel and Professor Kay Hamacher from the Department of Biology at the TU Darmstadt, the laboratories of Professor Anna Moroni (University of

Milan) and Dr. Bina Santoro (Columbia University, New York) present the protein structure and function of the isoforms of the HCN channels that are active in the sinus node of the heart in the latest issue of *Molecular Cell*. The high-resolution structures, which were obtained with the aid of cryo-electron microscopy, show many previously unknown details in the architecture of the channel protein in atomic resolution, and allow conclusions to be drawn with regard to the functional properties. Even more remarkable, however, is the realization that some of the channel structures are in an open, i.e. ion-conducting state.



Enlarged view of the selectivity filter of the HCN4 channel with potassium (blue) and sodium (yellow) ions in their typical binding sites. Individual water molecules can be seen in and around the ions. Credit: Technische Universitat Darmstadt

Using the so-called molecular dynamic simulation on the Lichtenberg computer, the high-performance computer at the TU Darmstadt, Daniel Bauer, doctoral student of the Hamacher working group, investigated the function of HCN channels. This method allows us to watch the protein at

work, as it were.

The insights into the functioning of the channel protein gained from the simulations are remarkable. They show that, unlike the related potassium ion channels ($K^+$ channels), the HCN channels do not have a rigid pore for ion passage, but—depending on whether sodium ($Na^+$) or potassium ions are transported through the channel—dynamically adapt to the size of the transported ion. This is the very first step in explaining the mechanism that allows the HCN channels to transport not only $K^+$ – which is important for their function—but $Na^+$ as well.

The combination of structural experimental insights and computer-based simulations is an ideal approach to a better understanding of the functioning of protein, and to developing specific drugs for the treatment of cardiac arrhythmia. The disadvantages and side effects of currently used drugs could perhaps be prevented with a better understanding of the channels in a new generation of drugs.

**More information:** Andrea Saponaro et al, Gating movements and ion permeation in HCN4 pacemaker channels, *Molecular Cell* (2021). DOI: 10.1016/j.molcel.2021.05.033

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