

New clues on how physical forces spread in neurons

In a project originally launched to pilot a new idea sparked by curiosity, ICFO researchers and collaborators have now uncovered new insights into how physical stresses (which might encode mechanical information) spread across the membranes of neurons. In a Nature Physics article, the team presents the most detailed description to date of this process, which is key to explaining how several fundamental biological processes unfold from embryo development to the sense of touch.

The study focuses on two different sensory receptors in the neurons of the roundworm *Caenorhabditis elegans*, showing that they propagate tension differently. More surprisingly, the researchers discovered that not only the presence of obstacles in the cell's membrane, but also their arrangement, affects how far the tension propagates. This arrangement acts as a regulatory switch: it can keep signals concentrated and localized or let mechanical information travel over extended distances further

through the neuron.

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How do embryos develop? Why does the cortex of the mammalian brain fold? How do we feel touch at our fingertips? These and other fundamental biological questions remain unsolved. Yet, scientists know they all rely on a common principle: the conversion of a physical stimulus into a biochemical signal.

The field of mechanobiology has recently gained new insights into which physical signals travel across cells and how far they spread. One key finding is that the rheological properties of the cell membrane (how it deforms and flows under stress) play a key role in such propagation. Still, many details of this intricate mechanism remain unclear.

ICFO researchers **Dr. Frederic Catala-Castro** and **Dr. Neus Sanfeliu-Cerdan**, led by **Prof. at ICFO Michael Krieg**, together with the group of Prof Padmini Rangamani at the University of California San Diego, have now shed more light on **how neurons transmit strains and stresses through their membranes**. In a Nature Physics article, they present **the most detailed description to date of the molecular processes underlying this phenomenon**. The study focuses on two different mechanoreceptors in the roundworm *Caenorhabditis elegans*: touch receptors, which respond very quickly to contact, and proprioceptors, which sense rapid deformations of the body itself during movement.

From curiosity to a valuable insight

Interestingly, this research began as a side project, sparked by previous conflicting reports in the literature. *Our past work focused on the cytoskeleton, but we began to wonder whether the plasma membrane could also transmit mechanical information,* explains P of. Michael Krieg, lead author of the st

dy. To investigate this, they used an optical tweezer apparatus, a tool based on highly focused laser beams that can both manipulate microscopic objects and measure forces with extraordinary precision. In their experiments, the researchers attached two plastic microspheres to the axons or neurites of the isolated neurons, pulled them with the optical tweezers, and measured how the generated tension traveled from one to the other with exceptional accuracy (at the piconewton and millisecond scales). The results showed that tension propagation is faster in touch receptors than in proprioceptors. Even more intriguingly, the researchers found **that propagation is influenced** not just by the presence of obstacles in the membrane -mainly embedded proteins- but also **by how these obstacles are arranged**.

Mathematical modeling, together with experimental data, revealed that when obstacles are aligned in a regular pattern, they restrict propagation to shorter distances. According to the researchers, a controlled, limited spread of tension may not be a limitation. Instead, it may

help neurons pinpoint where a force is applied, distinguish between different stimuli, and generate localized responses without affecting the entire cell. This, in turn, could enhance the neuron's ability for sensory processing or produce more adaptive motor responses. In contrast, a random arrangement of obstacles allows tension to travel much farther, potentially helping cells distribute mechanical information across longer distances. The 3D modeling set up in Rangamani's lab was crucial to reveal the role of obstacle arrangement, since it allowed the researchers to finally bring their multiple observations into a common framework. The variability of the measurements, cellular heterogeneity and stochasticity of the underlying molecular processes imposed significant challenges to the interpretation of the results, recalls Prof. Krieg. Developing the 3D model changed everything. It gave us the consistency we needed to draw solid conclusions, turning an idea into one exciting insight.

Toward fully understanding membrane tension propagation

Looking ahead, the researchers plan to explore other interactions of the cell with its environment, many of which have been largely ignored, as well as to discern the molecular identity of the obstacles and how they are regulated. It may even be that plasma membrane tension itself regulates obstacles in a feedback/forward loop, they speculate. For now, the study already marks a major advance in mechanobiology. Dr. Eva Kreyling, expert in developmental neuroscience from the University of Cambridge who was not involved in the work, said to *Nature Physics* journal: This is a very timely paper. Given the important part that membrane tension has been shown to play in the regulation of cell function, it is very important to understand how localised this parameter is or how far it propagates.

The next challenge will be to link these physical insights to specific molecular mechanisms, ultimately bridging the gap between mechanical forces at the membrane and the biological decisions they drive.

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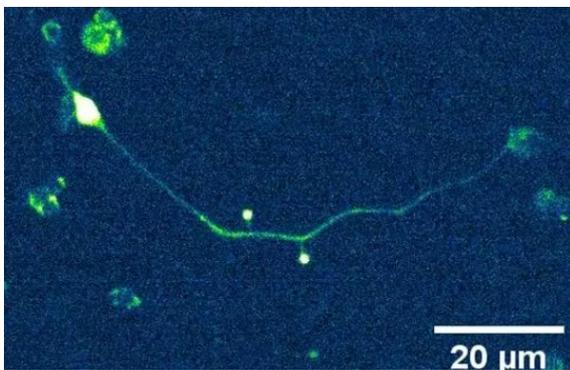
Reference:

F. Catala-Castro, M. Bonilla-Quintana, N. Sanfeliu-Cerdan, P. Rangamani, M. Krieg, Periodic Obstacles Regulate Membrane Tension Propagation to Enable Localized Mechanotransduction.
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Snapshot of the experiment showing an isolated neuron of the *Caenorhabditis elegans* with two microspheres attached.