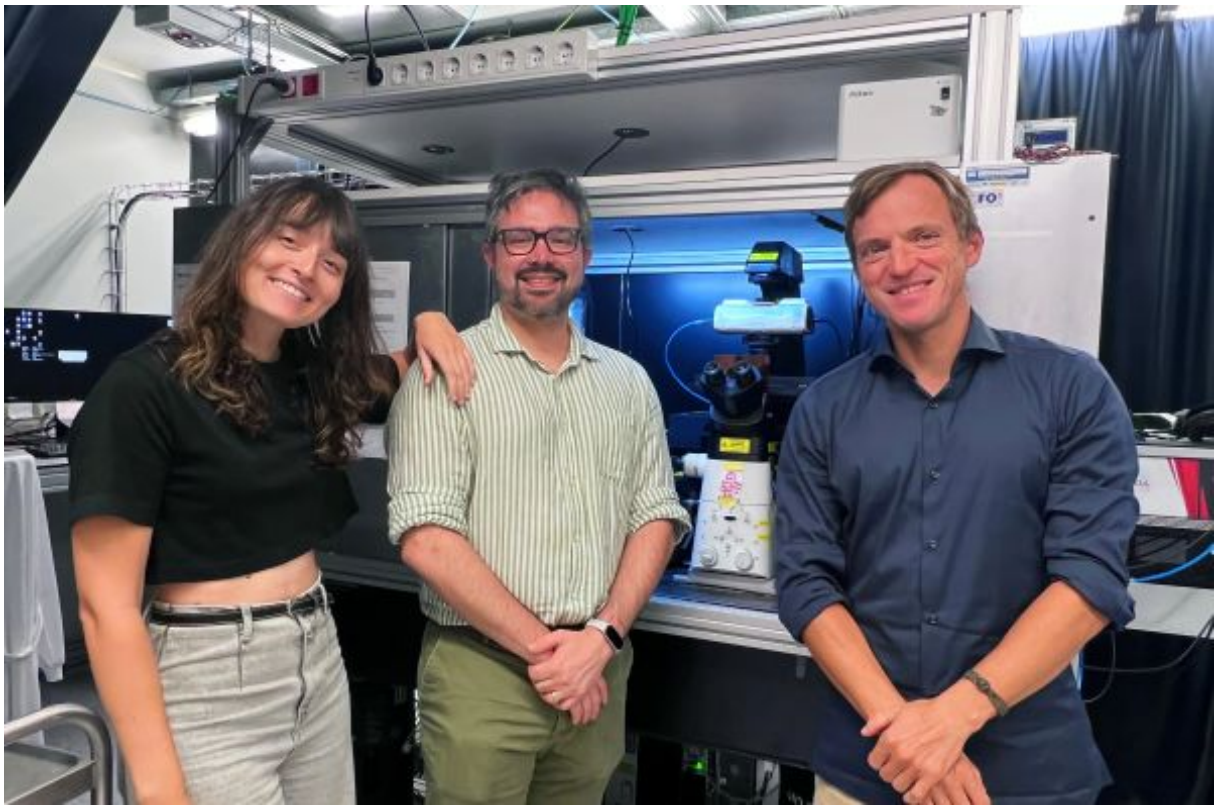

New clues on how physical forces spread in neurons

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 mos detailed description to date of this process, which is key t explaining how several fundamental biological processes unfold from embryo development to the sense of touch.

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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. i¿½Our past work focused on the cytoskeleton, but we began to wond
r whether the plasma membrane could also transmit mechanical information,i¿½ 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 foc
sed laser beams that can both manipulate microscopic objects and measure forces
ith extraordinary precision. In their experiments, the researchers attached two pla
tic microspheres to the axons or neurites of the isolated neurons, pulled them with the opt
cal tweezers, and measured how the generated tension traveled from one to the other
ith exceptional accuracy (at the picoNewton and millisecond scal
s). The results showed that tension propagation is faster in in touch receptors tha
 in proprioreceptors. 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. i¿½The variability of the measurements, cellular heterogeneity a
d stochasticity of the underlying molecular processes imposed significant challenges to t
e interpretation of the results,i¿½ recalls Prof. Krieg. i¿½Developing the 3D model c

anged everything. It gave us the consistency we needed to draw solid conclusions, turning a idea into one exciting insig

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. i¿½It may even be that plas a membrane tension itself regulates obstacles in a feedback/forward loop,i¿½ they specula e. For now, the study already marks a major advance in mechanobiology. Dr. Eva Krey ing, expert in developmental neuroscience from the University of Cambridge who wa not involved in the work, said to the Nature Physics journal: i¿½This is a very timely paper. Giv n the important part that membrane tension has been shown to play in the regulation of ce l function, it is very important to understand how localised this parameter is or how far t propagates.i

?½ The next challenge will be to link these physical insights to specific molecular mechani ms, ultimately bridging the gap between mechanical forces at the membrane and the biolog cal decisions they dr

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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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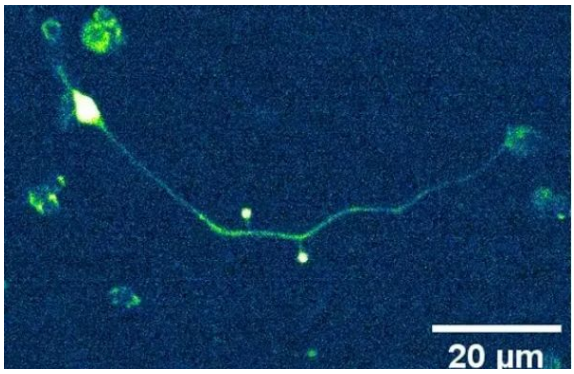

Snapshot of the experiment showing an isolated neuron of the Caenorhabditis elegans with two microspheres attached.