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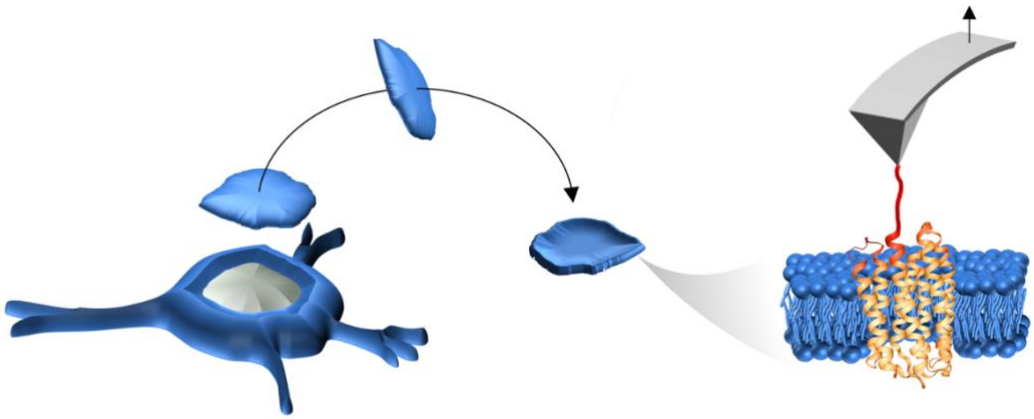
**PRESS RELEASE**

# ‘Unfolding’ membrane proteins to study them

**A new technique developed at SISSA makes it possible to identify cell membrane proteins through the way in which they “unfold”. The new research was recently published in the scientific journal *eLife***



Trieste, 20 October 2022

Of the twenty thousand genes that compose the human genome, around 30% of them code for proteins located in the cell membrane. Moreover, 50% of the drugs in use today precisely target these kind proteins. These biological structures, however, are particularly difficult to study, especially in their native environment. A technique developed at Scuola Internazionale Superiore di Studi Avanzati - SISSA in Trieste, using artificial intelligence and atomic force microscopy, now makes it possible to identify them thanks to the way they 'unfold' directly from their membrane, without having to purify them. This new approach could lead to future interesting developments in the diagnosis of diseases linked to their malfunctioning.

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**‘Unfolding’ proteins to understand their structure**

The atomic force microscope, the instrument at the core of this research, has represented a real revolution in biological analysis: its use has provided much of the current knowledge about the mechanical properties and structure of membrane proteins at room temperature. One of its main advantages is that it enables analysis of samples in conditions that reproduce physiological ones. In particular, the atomic force microscope allows individual proteins to unfold and refold by taking their terminal extremity and gently pulling it. A unique force-distance curve that characterizes the protein is derived from the unfolding of the molecule. Analysis of the sequence of force peaks makes it possible to identify individual membrane proteins.

The SISSA study published in *eLife* demonstrated that it is possible to perform these SMFS (Single Molecule Force Spectroscopy) experiments directly on cell membrane fragments. They allow to study mechanical stability of membrane proteins in physiological conditions without the need to purify them.

**How the technique works**

"As a first step, we used the atomic force microscope to pull the termini of individual proteins in order to unfold them from the cell membrane. This enabled us to record the unfolding of single proteins" explains Nicola Galvanetto of SISSA. The experiment was carried out on various types of cells, mainly neurons.

After assembling the traces, researchers divided them into groups based on their similarities and identified the various proteins in each group by cross-referencing the data with mass spectrometry. With assistance from Professor Alessandro Laio of SISSA, it was possible to classify the various groups of traces in an unsupervised manner. From these data, an algorithm to aid recognition of membrane proteins directly from the unfolding traces was developed. “Years of experiments on different purified proteins have shown that each protein generates its own specific unfolding trace. Therefore it makes sense to classify similar traces for statistical evaluation and then try to identify them using information from various databases" concludes Galvanetto.

**A potentially innovative diagnostic method**

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“The work has resulted in development of a new method for isolating the native membrane which is also suitable for unfolding proteins via AFM” explains Zhongjie Ye of SISSA, adding: "The recently published work represents an important basis for progress in the use of atomic force microscopy to study membrane proteins in their native environment. The process we have developed could potentially also be applied as a diagnostic method in pathologies linked to the malfunctioning of membrane proteins where few cells are available from the patient, thus guiding pathologists’ decisions.”

**USEFUL LINKS**
Full paper: elifesciences.org

**IMAGE**
Credits: Nicola Galvanetto


**SISSA**
Scuola Internazionale
Superiore di Studi Avanzati
Via Bonomea 265, Trieste
**W** www.sissa.it

**Facebook, Twitter**
@SISSAschool

**CONTACTS**
Francesca de Ruvo
→ fderuvo@sissa.it
**T** +39 040 3787231
M +39 329 7453567

Donato Ramani
→ ramani@sissa.it
**T** +39 040 3787513
M +39 342 8022237