Non-equilibrium stabilization of proteins by chaperones

María Li López Bautista[1], **Paolo De Los Rios**[1,2]

[1] *Institute of Physics, School of Basic Sciences, École polytechnique fédérale de Lausanne (EPFL), 1015 Lausanne, Switzerland*
[2] *Institute of Bioengineering, School of Life Sciences, École polytechnique fédérale de Lausanne (EPFL), 1015 Lausanne, Switzerland*

Within living organisms, proteins are essential components. They are responsible for carrying out almost every function in the cell. Proteins must fold into a specific three-dimensional shape to perform their diverse roles effectively. Indeed, improper folding is the root cause of many diseases [1].

Not surprisingly, there is a specific group of proteins whose function is to assist and safeguard the folding process of other proteins. These are known as molecular chaperones. Here, we focus on the 70 kiloDalton heat shock protein, Hsp70, a molecular chaperone that has been under the spotlight of scientists for decades due to its ubiquitous presence across all living systems and its assistance in a wide range of cellular processes. It is well accepted that the mechanism of action of Hsp70 chaperones consists of a biochemical energy-consuming cycle, which allows them to drive the system out-of-equilibrium and escape the inherent limitations of equilibrium thermodynamics to perform their functions efficiently [2,3].

While Hsp70s have been proven to protect cells from the accumulation of misfolded proteins, how the underlying molecular processes work remains unclear. Considering both the molecular details of chaperones and their client protein, along with a correct inclusion of the energy consumed in each step of the cycle and all relevant conformational transitions, we present a kinetic rate model for the description of the functional cycle of Hsp70 chaperones in protein folding that aims to elucidate the fundamental principles that govern their complex behavior.

References:

[1] Louros, N. et al. (2023). *Nat. Rev. Mol. Cell Biol.*, *24*
[2] Assenza, S. et al. (2019). *eLife*, *8*.
[3] De Los Rios, P., Barducci, A. (2014). *eLife*, *3.*