Physics and biology team up to tackle protein folding debate

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A team of researchers from EPFL, (Ecole Polytechnique Fédérale de Lausanne), the University of Lausanne, Northwestern University and Tel Aviv University bring biology and statistical physics together to answer the question of how molecular chaperones fold, unfold and pull proteins around in the cell. Their results appear the week of April 3 in the advance online edition of the *Proceedings of the National Academy of Sciences*.

A series of discussions in a campus café in Lausanne has blossomed into an extraordinary collaboration between EPFL physics professor Paolo De Los Rios and University of Lausanne biology professor Pierre Goloubinoff. Using the principles of statistical physics, they have identified a simple, single mechanism that explains the mechanical role of molecular chaperones in protein folding and translocation, settling at the same time a long-standing controversy over this process.

Molecular chaperones are specialized proteins that help other proteins find their proper conformations and reach their proper places in the cell. For more than two decades, biologists and biochemists have debated how one of these chaperones, Hsp70, manages the mechanical job of unfolding protein aggregates and pulling proteins into the various compartments of the cell. Is it by a "Power Stroke", in which the chaperone would use leverage and produce a mechanical force that pulls the protein, or a "Brownian Ratchet", in which the presence of the chaperone and the thermal fluctuations of the protein itself combine to pull the protein? There is no overwhelming evidence in favor of one

explanation over the other. More importantly, neither theory explains the full range of Hsp70's activity.

Using their prior results from biochemistry, De Los Rios and Goloubinoff turned to molecular geometry, statistical physics and the laws of thermodynamics in an attempt to solve the problem. The result, which they have dubbed "Entropic Pulling", is a modified form of the Brownian Ratchet mechanism. Molecular systems, they explain, must obey the laws of physics and strive for equilibrium. In the process, they increase their entropy. When the Hsp70 molecule, attached to a protein, hits a membrane or an aggregate, a tiny force due to entropy pushes it away again, dragging the protein strand along with it. The collaborators demonstrated that this entropic effect, combined with the protein's own thermal fluctuations, can exert enough force to pull a protein through the narrow pore of a mitochondrial membrane or disentangle an aggregate in the cell.

"Our explanation is so simple," De Los Rios says, "that it almost seems disappointing. We have shown that all the functions of Hsp70 in the cell can be explained by one simple mechanism."

Many diseases – among them mad cow, Parkinson's and Alzheimer's diseases -- are caused by misfolded proteins or aggregates. Goloubinoff emphasizes that understanding how chaperones such as Hsp70 function is important groundwork that must be laid before we can hope to develop strategies to treat these kinds of protein-misfolding pathologies.

Simple, elegant solutions often belie the struggle that went into their creation. The collaborators invested much time, energy (and coffee!) becoming familiar with the culture and language of each other's discipline. Now the effort has borne fruit in an excellent demonstration of the potential of interdisciplinary research in physics and biology.

Source: Ecole Polytechnique Fédérale de Lausanne