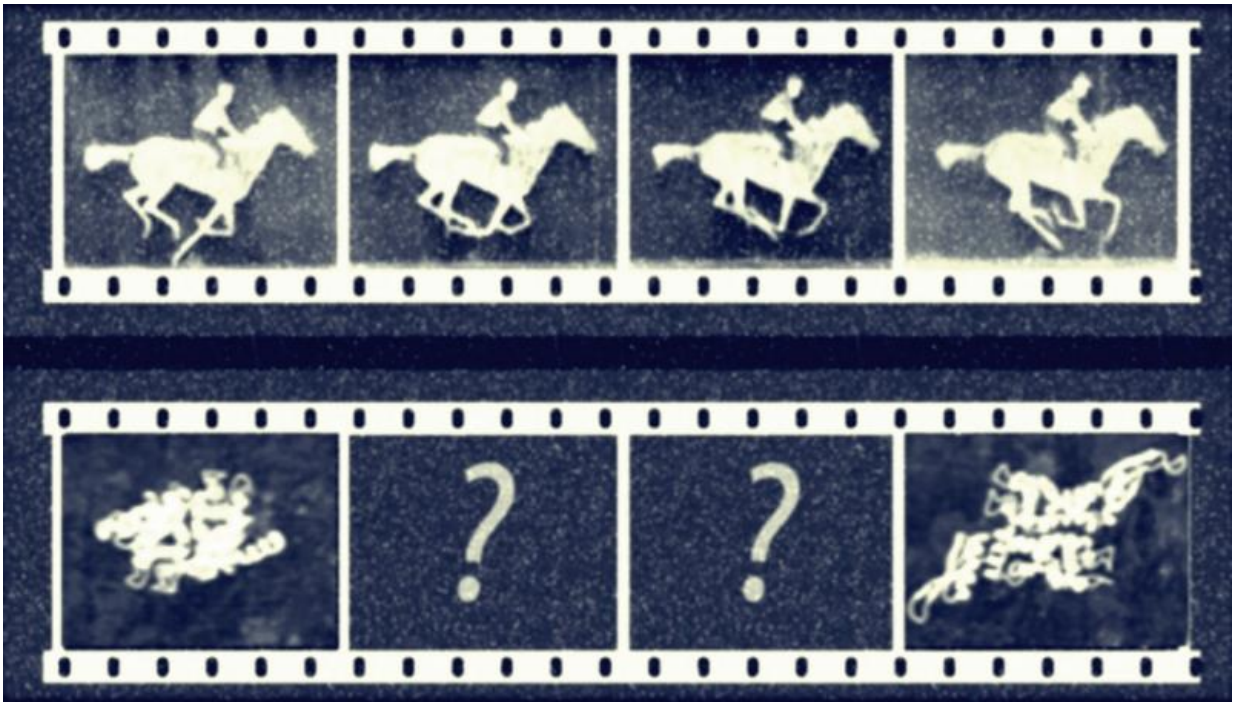
A minimalist theory to predict protein movements

September 6 2016



Eadweard Muybridge's pictures of a galloping horse enabled detailed analysis of animals and humans in motion. Today's protein research is faced with a similar situation when trying to understand how proteins move. Credit: L. Orellana

Proteins are large molecules that carry out all basic cell functions. In order to achieve this, they continually change shape by expanding or contracting parts; they hide surfaces or reveal them to interaction with other molecules. However, these changes are very difficult to observe

and the methods used by scientists to study them involve costly simulations performed in supercomputers. A joint study between scientists at the Institute for Research in Biomedicine (IRB Barcelona) and the KTH Royal Institute of Technology in Stockholm has now allowed the development of a much simpler method that permits equally precise predictions and can be done on a standard pc. The results have been published in *Nature Communications*.

The changes in protein shape occur extremely fast and are almost unperceivable. "Unless you "photograph" the changes that a protein undergoes and understand its movement and therefore the underlying molecular mechanism, this process is a mystery," explains Laura Orellana, first author of the article. Until now, to overcome the experimental difficulties behind "photographing"proteins, scientists used theoretical models to simulate protein movements, atom by atom. "Given that proteins generally hold thousands of atoms, the calculations are lengthy and costly, and they call for the use of supercomputers for weeks and even months."

To overcome this issue, Orellana and her colleagues used several low resolution proteins models called coarse-grained models, which greatly simplify the structure of a protein. "It is like an impressionist painting, in which you can appreciate the general picture but without many details. Using these models, we get a global view of the entire molecule and they also allow us to study changes in large proteins using a laptop in only a few minutes," explains Orellana. "There is a huge saving in resources."

Called eBDIMS, this novel simulation technique was developed by Orellana during her doctoral thesis under Modesto Orozco, head of the Molecular Modelling and Bioinformatics Lab at IRB Barcelona, and pioneer in coarse-grained simulations in Spain. Now, during her postdoctoral training in Erik Lindahls lab at the KHT Royal Institute of Technology in Stockholm, Orellana has perfected and tested the

algorithm through a novel analysis in order to test its validity. "Until now coarse-grained models were considered a secondary approach, but we wanted to demonstrate that they are as precise as the most advanced simulations," she says. The researchers measured the validity of the algorithm using widely studied proteins for which the movements have been analysed experimentally. "It was highly satisfying to see that our model precisely predicted the transition of proteins when they changed from one shape to another. We demonstrated that what is important is not the number of variables that you have but rather their quality."

In addition to shedding light on protein dynamics, the study has potential applications for the development of new drugs that cannot be addressed using current techniques. "Our validation alone has already produced new data on a protein used to study neuronal transmission. I am sure that, on the basis of known structures, eBDIMS will be able to generate new hypotheses and will pave the way to a new generation of therapeutic targets."

More information: Laura Orellana et al. Prediction and validation of protein intermediate states from structurally rich ensembles and coarse-grained simulations, *Nature Communications* (2016). DOI: 10.1038/ncomms12575

Provided by Institute for Research in Biomedicine (IRB Barcelona)