

Available online at www.sciencedirect.com**SciVerse ScienceDirect**

Physics of Life Reviews ••• (••••) •••–•••

**PHYSICS of LIFE
reviews**www.elsevier.com/locate/plrev

Comment

On the evolutionary conservation of protein dynamics

Comment on “Comparing proteins by their internal dynamics: Exploring structure–function relationships beyond static structural alignments” by Cristian Micheletti

Julian Echave

Escuela de Ciencia y Tecnología, Universidad Nacional de San Martín, Martín de Irigoyen 3100, 1650 San Martín, Buenos Aires, Argentina

Received 17 October 2012; accepted 19 October 2012

Communicated by E. Di Mauro and E. Shakhnovich

The comparison of protein sequences launched the field of Molecular Evolution in the 1960s [1]. The next breakthrough in our understanding of protein evolution came at the beginning the 1980s with the comparison of protein structures [2], which allowed the study of more distant evolutionary relationships and is at the basis of current evolutionary classifications of proteins [3,4]. More recently, a number of groups independently started working on comparing protein motions and a field of “comparative protein dynamics” is emerging [5–7]. Cristian Micheletti, one of the founders and principal contributors to this field, has written a timely and comprehensive review of its state of the art [8], which I here comment. I will focus on two questions that are fundamental for the study of protein evolution.

First, is protein dynamics evolutionarily conserved? As reviewed in [8], a variety of properties related to dynamics have been found to be conserved, including C_α mean square fluctuations, C_α – C_α distance fluctuations, Essential Dynamics spaces, and individual normal modes. Moreover, not only are such properties conserved, but also several cases exist for which dynamics-based comparisons find similarities even in the absence of significant structural similarity. In a word, protein internal dynamics is evolutionarily conserved.

Second, why is protein dynamics conserved? In accordance with most comparative dynamics studies performed so far, in [8] it is considered implicitly or explicitly that protein dynamics is conserved for functional reasons. For the cases studied, conserved motions are qualitatively interpreted in terms of the known function and their consistency with other features such as observed conservation of structural and sequence functional features.

However, before moving on to explain the conservation of a given property in terms of its functional relevance, which implies the assumption that conservation results from selective constraints, we should study the effect of unselected mutations. For example, for the case of protein motions, normal modes are differentially conserved: the lowest-energy, collective and coherent normal modes are more conserved than the higher-energy, localized ones [9]. Even though we may be tempted to interpret this as evidence of the functional importance of the conserved modes, a simple perturbative model shows that the observed pattern of conservation is just the expected response of the protein to random mutations [10]. In other words, the lowest normal modes are not more conserved because of selective constraints on function, but because they are more robust with respect to mutations; physics, not biology, explains

DOI of original article: <http://dx.doi.org/10.1016/j.plrev.2012.10.009>.E-mail address: julian.echave@gmail.com.

1571-0645/\$ – see front matter © 2012 Elsevier B.V. All rights reserved.

<http://dx.doi.org/10.1016/j.plrev.2012.10.006>

Please cite this article in press as: Echave J. On the evolutionary conservation of protein dynamics. *Phys Life Rev* (2012), <http://dx.doi.org/10.1016/j.plrev.2012.10.006>

the observed pattern of conservation. This issue should be further studied before drawing any definitive conclusions regarding the reasons underlying the observed conservation of protein motions.

References

- [1] Zuckerkandle E, Pauling L. Molecules as documents of evolutionary history. *J Theor Biol* 1965;8:357–66.
- [2] Lesk AM, Chothia C. How different amino-acid sequences determine similar protein structures – structure and evolutionary dynamics of the globins. *J Mol Biol* 1980;136:225–70.
- [3] Orengo CA, Michie AD, Jones S, Jones DT, Swindells MB, Thornton JM. CATH – a hierarchic classification of protein domain structures. *Structure* 1997;5:1093–108.
- [4] Murzin AG, Brenner SE, Hubbard T, Chothia C. SCOP – a structural classification of proteins database for the investigation of sequences and structures. *J Mol Biol* 1995;247:536–40.
- [5] Maguid S, Fernandez-Alberti S, Ferrelli L, Echave J. Exploring the common dynamics of homologous proteins. Application to the globin family. *Biophys J* 2005;89:3–13.
- [6] Pang A, Arinaminpathy Y, Sansom MSP, Biggin PC. Comparative molecular dynamics – similar folds and similar motions? *Proteins* 2005;61:809–22.
- [7] Carnevale V, Raugei S, Micheletti C, Carloni P. Convergent dynamics in the protease enzymatic superfamily. *J Am Chem Soc* 2006;128:9766–72.
- [8] Micheletti C. Comparing proteins by their internal dynamics: exploring structure–function relationships beyond static structural alignments. *Phys Life Rev* 2012 [in this issue].
- [9] Maguid S, Fernandez-Alberti S, Echave J. Evolutionary conservation of protein vibrational dynamics. *Gene* 2008;422:7–13.
- [10] Echave J. Why are the low-energy protein normal modes evolutionarily conserved? *Pure Appl Chem* 2012;84:1931–7.