

Multifunctional Proteins

Objective: To give a presentation of about 60 minutes at the end of the week covering the key aspects of the comparison of protein with multiple functionalities.

Many cases of proteins with multiple functions are now known. The extra function has almost always come as a surprise and was discovered serendipitously. The true extent of multiple functionalities is unknown and would be of great interest to evaluate. Proteins consist of many atoms and have complex movements of time spans of a μ -second to a second, so theoretically it would be possible pack many actions into one protein. To exemplify, describing the action of 1 protein could entail the positions of 10^4 atoms and to describe its motion in 1 μ -second would need 10^9 time steps, in total 10^{13} coordinates. Its function might be summarized by one action (such as hydrolyzing 1 bond) in this time period. However, designed machines are different from evolved machines and these numbers also illustrate that there could be room for several functions, possibly many. Moonlighting proteins are clearly understudied and could be extremely important in the biology of an organism. A series of question could be addressed by standard methods of molecular evolution. However, hard questions would remain and could not be solved by computational methods alone – hard experimental evidence on many more moonlighting proteins would be needed.

It is of interest to

1. Tabulate known cases of moonlighting proteins
2. Evolutionary modeling the phenomena of moonlighting
3. Measuring selection strength of known moonlighting proteins
4. If possible to separate the selection into component stemming from the two functionalities?
5. Is it possible to assign functional constraint to individual positions from the two functionalities with homologous proteins that have combinations of the functionalities
6. Dating the acquisition of a newest function
7. Detecting multiple functions from structure, molecular evolution and molecular dynamics

The Big Questions Are:

How do you define function and make a statement that a protein has several functions?

How do multiple functionalities arise?

How widespread is multifunctionality in proteins?

How do you prediction function for a protein?

Are there examples of multifunctionality higher than two?

Is it found in other molecules/structures than proteins?

Which principles could be used to detect multifunctionality?

How frequent is an extra functions gained/lost?

Is there a trend in which of function can be gained/lost?

Maximal Contents of Presentation

The scientific history of multifunctionality in proteins

Description of key examples of multifunctionality

How is multifunctionality detected?

How is multifunctionality predicted?

Recommended literature

Hawkins T, Kihara D. Function prediction of uncharacterized proteins. *J Bioinform Comput Biol.* 2007 Feb;5(1):1-30.

Constance J. Jeffery Moonlighting proteins *TIBS* 24.8- – *JANUARY 1999*

Constance J. Jeffery Moonlighting proteins: old proteins learning new tricks *TRENDS in Genetics* Vol.19 No.8 August 2003 415-

Carlos Gancedo* and Carmen-Lisset Flores Moonlighting Proteins in Yeasts *MICROBIOLOGY AND MOLECULAR BIOLOGY REVIEWS*, Mar. 2008, p. 197–210

Hult K, Berglund P. (2007) Enzyme promiscuity: mechanism and applications. *Trends Biotechnol* 25(5):231-8.

Kannan S, Hauth AM, Burger G. (2008) Function prediction of hypothetical proteins without sequence similarity to proteins of known function *Protein Pept Lett.* 15(10):1107-16.

Khersonsky O, Roodveldt C, Tawfik DS (2006) Enzyme promiscuity: evolutionary and mechanistic aspects. *Curr Opin Chem Biol.* 10(5):498-508.

McCauley, S. & Hein, J. (2006) Using hidden Markov models (HMM) and observed evolution to annotate ssRNA viral genomes. *Bioinformatics*, 22(11), 1308–1316

Pedersen, et al. (2004) A comparative method for finding and folding RNA secondary structures in protein-coding regions. *Nucleic Acids Research*, 32, 4925–4936

Pedersen et al. (2004) An evolutionary model for protein-coding regions with conserved RNA structure. *Mol. Biol. Evol.*, 21, 1913–1922.

Taglieber A, Höbenreich H, Carballera JD, Mondière RJ, Reetz MT. 2007 “Alternate-site enzyme promiscuity” *Angew Chem Int Ed Engl.*;46(45):8597-600.

Whisstock JC, Lesk AM. 2003 Prediction of protein function from protein sequence and structure. *Q Rev Biophys.* 36(3):307-40.