

# New Concept and Algorithms to Reveal Protein Dynamics and Intramolecular Interaction Network and Their Application for Protein Design

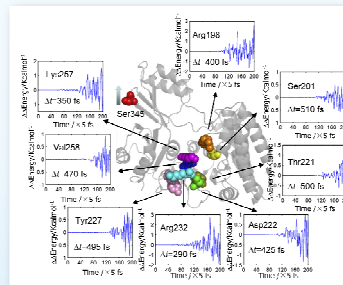
Cheng-Wei Ma and An-Ping Zeng<sup>1</sup>

## Introduction

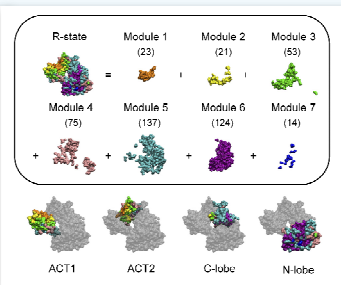
Protein dynamics is essential for its function, especially for intramolecular interactions during signal transduction or when immobilized on surface or in structured materials.

## Energy dissipation model [1]

We have recently proposed a new concept, energy dissipation model, to systematically reveal protein dynamics upon effector binding and energy perturbation. The concept has been successfully applied to better understand the intramolecular signal transduction during allostery of enzymes (Fig. 1). We further introduced the term “protein dynamical modules” based on the residue response time upon energy disturbance (Fig. 2). Different from protein structural modules which merely provide information about the structural stability of proteins, protein dynamical modules could reveal protein characteristics from the perspective of dynamics.



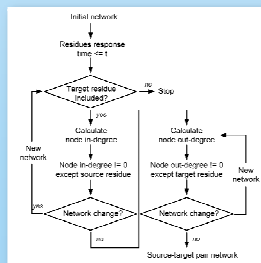
**Figure 1.** Energy dissipation upon energy perturbation using *E. coli* aspartokinase III as the model system.  $\Delta t$  is the time point when the residue responds to the energy perturbation.



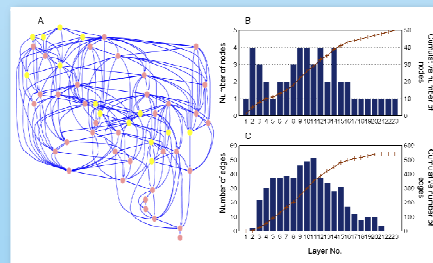
**Figure 2.** Protein dynamical modules of *E. coli* aspartokinase III. Modules are differently colored and numbers of residues within each dynamical module are given in brackets.

## Intramolecular interaction network [2]

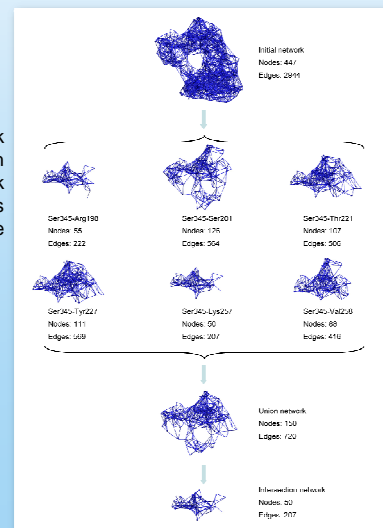
To reveal intramolecular interaction (signal transduction) network, a new algorithm of network construction has been developed based on the new concept (Fig. 3). A key feature of this approach is that direction information is specified after inferring protein residue-residue interaction network involved in the process of molecular interaction and signal transduction (Fig. 4). This enables fundamental analysis of the regulation hierarchy and identification of regulation hubs of the signaling network (Fig. 5).



**Figure 3.** Algorithm proposed to construct source-target pair networks from the Initial network.



**Figure 5.** (A) Hierarchical layout of the core signal transduction network. Residues that have been experimentally proved are colored in yellow. (B) The number of nodes for each layer (histogram) and the cumulative number of nodes (line). (C) The number of edges passing through each layer (histogram) and the cumulative number of edges (line).



**Figure 4.** Signal transduction networks constructed based on the new protein dynamics model of energy dissipation and the novel algorithm of network construction.

## Application for protein design [3]

We are working to extend the concept for better understanding the interactions and functionality of enzyme complexes and for rational design of proteins. In particular, we aim to extend the concept and methods for designing fusion proteins and technical protein scaffolds for multistep enzymatic biocatalysis processes.

## References:

- [1] Ma, et al. (2011a) A new concept to reveal protein dynamics based on energy dissipation. *PLoS ONE* 6, e26453.
- [2] Ma, et al. (2011b) Discovery of intramolecular signal transduction network based on a new protein dynamics model of energy dissipation. *PLoS ONE* (Under revision).
- [3] Ma et al. (2011c) Exploring signal transduction in heteromultimeric protein based on energy dissipation model. (Submitted).

## Contact

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## We look for:

- Experimental methods to study protein dynamics
- Partners for structure determination and for application of our methods

## We offer:

- Molecular dynamics simulation of proteins
- Modeling of molecular interactions
- Suggestions for rational protein design