EXAMINING THE FLEXIBILITY OF TIM BARREL PROTEINS BASED ON THEIR STRUCTURAL TOPOLOGY

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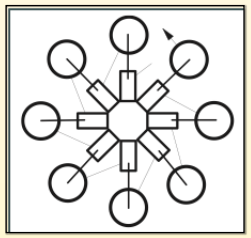
The eight-fold beta/alpha barrel-like fold, first seen in triose-phosphate isomerase (TIM), is a common and versatile fold for proteins. Proteins in this classification have diverse enzymatic functions spanning five of six Enzyme Commission classes[1].

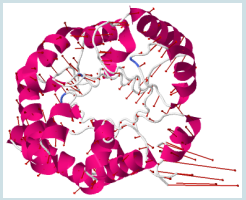


2D representation of beta/alpha barrel fold. The rectangles represent strands while the circles are the flanking helices. Reproduced with permission[2].

Studies have characterized the sequence, structure, localized dynamics and electrostatics of TIM proteins, but the flexibility of the fold is understudied.

We report that **the eight core beta strands behave independently of the eight flanking alpha helices**. The strands and helices repeat in tandem at the sequence level, yet the strands form a core that moves minimally while the helices display greater relative mobility in all of the structures.

Normal mode analysis is a method used to describe global movements in a protein and its flexibility. Each mode is a set of vectors (arrows) at a given frequency. The normal modes produced can be used to describe the atomic fluctuations and the correlations of these movements within the structure. The Bhattacharya coefficient can be used to describe the similarity of these modes between structures.

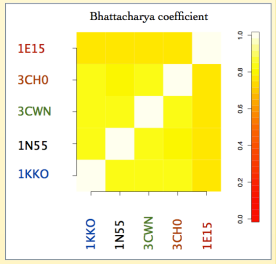


For the coarse-grained normal mode analysis, we used a form of Elastic Network Model defined by the C-alpha forcefield[3], while the all-atom analysis was performed using MMTK using the Amber99 force field[5,6].

Structural alignments were done using Mustang[7].

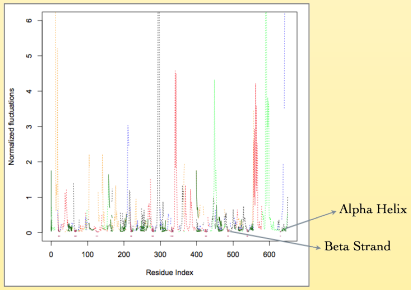
We looked at the principle TIM beta/alpha barrel secondary structure elements of **five structures** from distinct families with **low sequence similarity** between 23 and 38.5 % and low structure similarity.

Despite the low sequence similarity, we found that **the normal modes at the points of structural similarity shows that there is a conservation of dynamics.** This is seen in the score given by the Bhattacharya coefficient[8].

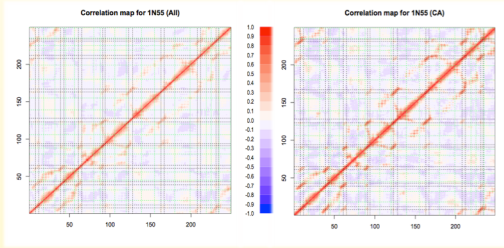


We found that the atomic fluctuations of each of the beta-strands have **a high correlation with its immediate beta-strand neighbour in the core**. Compared to the beta strands, the alpha helices have less correlation with each other and almost none with the strands.

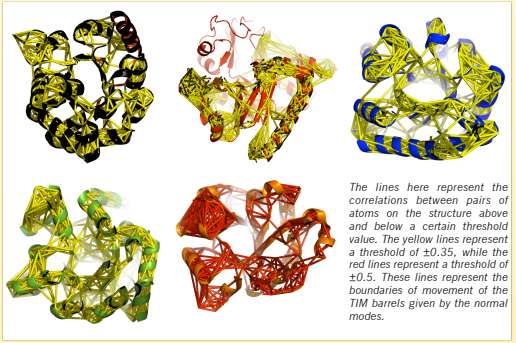
- 1N55
- 1E15
- 1KKO
- 3CWN
- 3CH0



Normalized fluctuations plot from all-atom modes. The dotted lines represent parts of the sequence that does not align, while the solid lines represent parts that do.

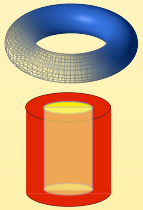


All-atom vs. coarse-grained correlation matrices. The matrix represents the correlation between the atomic fluctuations of pairs of atoms within a structure.



The lines here represent the correlations between pairs of atoms on the structure above and below a certain threshold value. The yellow lines represent a threshold of ±0.35, while the red lines represent a threshold of ±0.5. These lines represent the boundaries of movement of the TIM barrels given by the normal modes.

This core formed by the beta-strands is rigid in all the structures. This is despite the varying loop lengths between them and the presence of accessory secondary structures in some cases. This leads us to hypothesise that the movements of the TIM does not follow its **toroidal** structural description but rather as a **barrel within a barrel**.



In conclusion, the normal modes of TIM are able to characterise its flexibility at the fold level, which gives us insight into its versatility. Our methods can pick out the commonalities between these proteins, such as the rigidity of the beta-barrel core and behave independently of the helices, despite the low sequence and structure conservation.

References
1. Nagano N., Orengo C. A., Thornton J. M., J. Mol. Bio., 2002, (321) 741–7652
2. Taylor, W. R. et al.,Rep. Prog. Phys., 2001, (64)517–590
3. Hinsen K. et al., Chem. Phys. 2000, (261)25– 37
4. Hinsen K., J. Comput. Chem. 2000, (21)79–85
5. Lee M and Duan Y., Proteins, 2004, (55)620–634
6. Hinsen, K. and Kneller, G., 2000, Mol. Simul., (23)275–292
7.Konagurthu, A., et al., 2006, Proteins, 64(3), 559-574
8.Fuglebakk, E., et al., 2012, Bioinformatics, 28(19)2431-40