Bridging Rigidity Theory and Normal Modes

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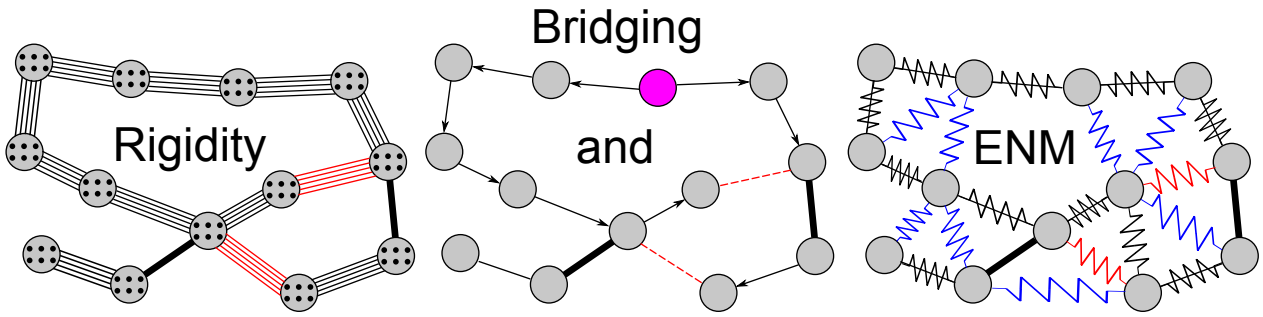

Elastic network models (ENM [1], Figure right) and constraint-based, topological rigidity analysis ([2], Figure left) are two distinct, coarse-grained approaches to study conformational flexibility of macromolecules. Over the last two decades, they have contributed significantly to insights into molecular mechanisms and function. However, despite their shared purpose, the topological nature of rigidity analysis, and the concomitant absence of motion modes, have hindered a direct comparison between them. Here, we present an alternative, kinematic approach to rigidity and flexibility analysis, which eliminates these drawbacks (Figure center). Our analysis of the Jacobian matrix **J**, obtained from treating hydrogen bonds as constraints, bridges results from topological rigidity and ENM: it provides an orthonormal basis for the full spectrum of collective motions, analogous to the eigenspectrum of normal modes, and decomposes proteins into rigid clusters identical to those from topological rigidity [3]. Our hydrogen bond network spectral decomposition allows a detailed comparison of motion modes obtained from both traditional methods. The analysis reveals that collectivity of motions, reported by the Shannon entropy, is significantly lower for rigidity theory versus normal mode approaches. Strikingly, our kinematic approach suggests that the hydrogen bonding network encodes a protein-fold specific, spatial hierarchy of motions, which goes nearly undetected in ENM. The hierarchy uncovers different motion regimes, related to the stiffness of the molecule, that qualitatively agree well with experimental observations and more detailed molecular simulations. For a set of designed, hyper-stable peptides [4], we find a clear shift towards stiffer modes, in agreement with their designed characteristics. Overall, these results suggest that hydrogen bond networks could have evolved to tailor structural dynamics and thus, fold-related function, with broad implications for protein engineering and drug design.

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[2] Jacobs, D. J.; Thorpe, M. F. Generic rigidity percolation: the pebble game. *Phys Rev Lett* **1995**, *75*, 4051.
[3] Budday D, Leyendecker S, van den Bedem H. Geometric analysis characterizes molecular rigidity in generic and non-generic protein configurations. *J Mech Phys Solids* **2015**, *83*, 36-47.
[4] Bhardwaj, G. et al. Accurate de novo design of hyperstable constrained peptides. *Nature* **2016**, *538*, 329–335.