

The Protein Trinity: Linking Function and Intrinsic Disorder**Dunker, A. Keith^{*1}, Obradovic, Zoran²****¹Center for Computational Biology and Bioinformatics, Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, USA; ²Center for Information Science and Technology, Temple University, Philadelphia, PA, USA**

Proteins have been shown to exist in at least 3 forms: the ordered state (solid-like), the partially folded state (collapsed, molten globule-like or liquid-like) and the extended state (extended, random coil-like or gas-like). The Protein Trinity Hypothesis has two components: 1. a given native protein can be in any one of the 3 forms for which sequence + environment determines whether the protein is ordered, collapsed-disordered or extended-disordered in the native state; and 2. function can arise from any one of the three forms or from transitions between them.

We have used bioinformatics and data mining to determine the generality and functions of intrinsic disorder. Predictions of intrinsic disorder will be discussed indicating that the Protein Data Bank is highly biased against native disorder and that disorder across the 3 kingdoms follows the ranking eubacteria < archaeobacteria << eukaryota. Indeed, approximately half of eukaryotic proteins are predicted to contain substantial regions of intrinsic disorder. Many of the known disordered regions are involved in signaling, regulation, or control. Involvement of highly flexible or disordered regions in signaling seems to be logical: a flexible sensor could more readily undergo conformational change in response to environmental perturbations than could a rigid one. Thus, the increased putative disorder in the eukaryota is proposed to be the direct result of an increased need for signaling and regulation in nucleated organisms. Application of disorder predictions to cell-signaling, cancer-associated, and various control protein databases support the wide-spread use of intrinsic disorder in protein-based signaling and regulation.

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Further Reading

Vucetic, S., Brown, C. J., Dunker, A.K., and Obradovic, Z. Flavors of Protein Disorder. *Proteins: Structure, Function, and Genetics*. **52**: 573-584 (2003).

(see: <http://www3.interscience.wiley.com/cgi-bin/fulltext/104551103/PDFSTART>)

Dunker, A. K., Brown, C. J., Lawson, J. D., Iakoucheva, L. M., and Obradovic, Z. Intrinsic disorder and protein function. *Biochemistry* **41**: 6573-6582 (2001)

(see: <http://pubs.acs.org/cgi-bin/article.cgi/bichaw/2002/41/i21/pdf/bi012159+.pdf>)