PROTEINS
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PERSPECTIVES

Conformational and connotational heterogeneity: A surprising relationship between protein structural flexibility and puns

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ABSTRACT

Protein structures are often thought of as static objects, and indeed, the bulk of a protein's sequence forms α-helices, β-sheets, and other generally well-ordered substructures. These portions of the molecule pre-pay the entropic price of maintaining a globally unique fold, freeing other regions to adopt multiple alternative conformations. In many cases, this localized flexibility is biologically interesting: it may be important for catalytic turnover or for conformational selection before forming an intermolecular complex, for example. Similarly, most of written language is carefully tuned to avoid ambiguity and convey a singular meaning, a cohesive message. This linguistic scaffolding in some sense pre-pays a rhetorical price, paving the way for punctuated instances in which a given word or phrase can simultaneously adopt multiple alternative connotations—in other words, for puns.

Proteins 2015; 00:000–000.

Key words: protein structure; protein dynamics; evolution; language; rigidity.

Despite powerful experimental and computational advances over the past half-century, protein crystallography has largely maintained a consistent goal: deciphering "the structure" of whichever particular protein strikes one's scientific fancy. The endeavor almost always focuses on a singular conformation of the protein molecule—if not blindly, at least with tunnel vision. To be sure, there has always been and continues to be room for creativity: a crystallographer may need idiosyncratic leaps of logic to grow her requisite crystals, clever experiments may be needed to decipher the mutual synchronicities of the thousands of X-rays that bounce off protein copies within the crystal, and so on. Yet the name of the game remains largely unchanged: estimate one position for each of the thousands of atoms that comprise the protein.

However, growing recognition of "conformational heterogeneity" in proteins[1–3] has set the stage for a subtle rebellion against this staid perspective. A new, more multifaceted perspective has arisen that denies the dogma of unique, rigid protein structures, instead positing that some atoms adopt multiple different positions at

All work performed at University of California, San Francisco
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Received 11 December 2014; Revised 5 January 2015; Accepted 9 January 2015
Published online 23 January 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/prot.24765

different times. In other words, the elemental building blocks of proteins are in some cases degenerate in terms of their structures and, in turn, their functions.

This notion of multifarious building blocks amidst an otherwise rigid backdrop in proteins is surprisingly reminiscent of another (sadly) underappreciated construct: puns. Puns are excursions from singular meaning in prose: they represent "connotational heterogeneity". The overarching goal of vast swaths of writing—articles, magazines, even much of fiction—is to convey an idea and convey it clearly, without ambiguity. Puns, on the other hand, are poised for surprise attacks on the reader amidst text that is otherwise painstakingly refined to convey a single intended meaning, much as alternative conformations are concentrated not in the more rigid "load-bearing" regions of a protein, but in specialized areas such as enzyme active sites[4] where they can impart the greatest functional (in the biochemical sense) advantage.

Neither protein conformational heterogeneity nor puns can be safely overdone, though. In both writing of text (which encodes semantic meaning) and evolution of protein sequences (which encode protein conformations), the primary battle is against entropy: writing is a continuous struggle against entropy of syntactic structure and conveyed meaning, and evolution of globular protein structure is an uphill battle against conformational chaos and functional impotence. For both the greatest prose and the most biochemically adept proteins, then, the author—be that the writer via her pen or Nature via natural selection—has achieved a balance between rigidity and flexibility, between unyielding meaning and pure meaninglessness. The result in both cases is a carefully metered dosage of delightfully unresolved tension, of potential rendered less fleeting.

Is this analogy ultimately meaningful? Can other useful connections be drawn between the evolution of biological macromolecules, language, and other complex systems? Perhaps so, and perhaps not, but metaphors can be powerful drivers of insight and creativity, and I hope this one "crystallizes" other provocative ideas from the reader.

ACKNOWLEDGMENT

The author thanks James Fraser for inspiring many thoughts about protein conformational heterogeneity and supporting him exploring the connection to language.

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