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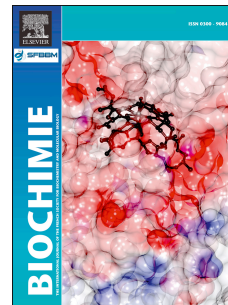
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# Evolution, Energy Landscapes and the Paradoxes of Protein Folding

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## ABSTRACT

Protein folding has been viewed as a difficult problem of molecular self-organization. The search problem involved in folding however has been simplified through the evolution of folding energy landscapes that are funneled. The funnel hypothesis can be quantified using energy landscape theory based on the minimal frustration principle. Strong quantitative predictions that follow from energy landscape theory have been widely confirmed both through laboratory folding experiments and from detailed simulations. Energy landscape ideas also have allowed successful protein structure prediction algorithms to be developed.

The selection constraint of having funneled folding landscapes has left its imprint on the sequences of existing protein structural families. Quantitative analysis of co-evolution patterns allows us to infer the statistical characteristics of the folding landscape. These turn out to be consistent with what has been obtained from laboratory physicochemical folding experiments signalling a beautiful confluence of genomics and chemical physics.

## 1. Introduction

Paradoxically, protein folding has turned out to be easy. How? Why? What's paradoxical? This review is aimed at answering these questions, beginning with the last one [1]. Ever since Anfinsen's groundbreaking experiments, understanding the spontaneous nature of protein folding has been widely viewed as being a difficult problem [2]. Delbrück is quoted by Gunther Stent [3] as saying about protein folding "...the reduction in dimensionality from three dimensional continuous to one dimensional discrete in the genesis of proteins is a new law of physics and one nobody could have pulled out of quantum mechanics without first seeing it in operation." According to Stent, after saying this, Delbrück also immediately quoted Bohr as telling about a man who, upon seeing a magician saw a woman in half, shouts out "It's all a swindle." In a

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