

## Preface

In July 2011, I gave a lecture at the University of Toronto, in Canada. In that lecture, I said among other things that hydrophilic interactions in fact bring us as close as we can hope for to the solution of the protein folding problem (*PFP*).

After the talk, a guy who is engaged in protein folding calculations came to me and asked: "Can you actually fold a protein with hydrophilic interactions?"

"Yes, of course," I snappily replied. "In fact, I do it every second and in every cell of my body." We both smiled. He had obviously expected a different answer.

This anecdotal story was not the only occasion where I have experienced something like this. For quite some time, I've realized that different people have different views on what the protein folding problem (*PFP*) is. This book presents my views on the main questions associated with protein folding, as well as the possible answers. Before starting to write this book, I asked my friends and colleagues about their views on the main problem associated with the phenomenon of protein folding. I will discuss the result of this query in Chapter 1. The consensus "average" *PFP* consists of essentially three problems:

- A. What is the relationship between a sequence of amino acids and the structure of the native protein?

- B. What are the main factors that speed up the folding of proteins?
- C. What are the main contributing factors to the stabilization of the native structure?

As I shall discuss in Chapter 1, problem A does not have a general answer. In other words, there exists no general “code” that translates from a *sequence* to a *structure*. The second and third problems do have general answers.

The reader who is familiar with the biochemical literature might well be astonished upon reading the last paragraph. Open any textbook, review articles, or a specific article on protein folding, and you are likely to find a statement describing the *PFP* as the most challenging problem in molecular biology.

It is the purpose of this book to prove the contentions that problems B and C have a general solution whereas problem A does not. I hope that this book will contribute to demystifying the whole *PFP*.

The reader might wonder as to why, in spite of its simplicity, the *PFP* is still considered to be the most challenging, difficult, daunting, formidable, and a host of other intimidating descriptions.

The answer to this question is lengthy and is discussed in detail in Chapter 2. Here, I shall briefly state that the *PFP* reminds me of the story, or perhaps the joke, about a man who lost his keys while walking along a dark street. Instead of looking for them at the spot where they must have fallen, he goes to the nearest lamp post and searches there. This is what has happened with problems B and C. People have searched for the solution (the “key” to understanding the *PFP*) in the wrong places, where it was virtually impossible to find it, thus rendering

the search the most challenging, daunting, formidable, as well as futile endeavor. What is even more ironic is that even when light had already shone brightly on the solution, people continued to search where it could not be found. Some claimed to have found the key, but alas, it was the wrong key...

As for the first problem (A), people have searched not only where the key cannot be found, but more fundamentally, they have looked for a "key" that does not even exist.

I am aware of the enigmatic flavor of what I have said above. I am also sure that some will raise an eyebrow, and perhaps stop reading the book at this point. I know for sure that such people exist, having received so many contemptuous comments from reviewers of articles which I sent for publication.

I offer this book to those readers who are open minded and are not fixated with the old paradigms such as the dominance of hydrophobic effects. I hope that this book will not only demystify the *PFP* but also open the reader's mind to other applications of the rich and powerful repertoire of hydrophilic effects.

This book is organized in such a way that it can be read by anyone who knows what proteins are and has some knowledge of basic thermodynamics. To keep the flow of ideas smooth and not to get bogged down by technical issues, I have collected all these in the Notes section, and in the Appendices at the end of the book.

Contrary to many statements made in the literature, understanding the *PFP* and its solution does not depend on understanding statistical mechanics. It is true that statistical mechanics is essential for the understanding of solvent-induced interactions and forces. Once one is familiar with these, there is no need to apply statistical mechanical methods for "solving" the *PFP*.