DAVID BAKER: PROTEIN DESIGN

Key Words: protein design, protein engineering, structure prediction, nanomaterials, epitope-focused vaccine design

Review Part I. Introduction to Protein Design

1. In Part I of the iBiology seminar David introduces two main research problems: protein structure prediction and protein design. What is the purpose of studying these problems? What are some challenges associated with each of these problems?

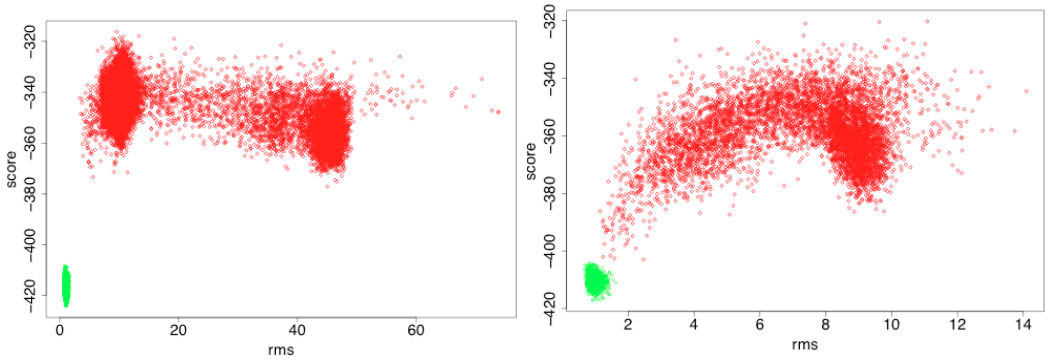
2. What methods does David use to predict protein structure and design new proteins? What are advantages and/or disadvantages of David's approach to protein design? Do you know of any orthogonal approaches?

3. What are some classes of proteins found in nature? What is the purpose of designing the synthetic "idealized" proteins that Baker discusses?

4. How are vaccines traditionally developed for viruses such as influenza? Can protein design overcome roadblocks posed by traditional vaccine development?

5. David discusses a number of protein design projects: ligand-binding proteins, self-assembling proteins, repeat proteins, and other nanomaterials. How might these proteins be useful in other areas of scientific research, i.e. medicine or environmental science? How might protein design be useful in your area of research?

Bonus Challenge Question: Below are two diagrams of Rosetta "folding funnels", each for a unique sequence designed for the same protein structure. On the Y axis is the predicted energy state of each protein structure. On the X axis is the root mean squared distance of each C_a atom from the design model. The green dots are the predicted energy states of the design model. The red dots plot the energy states for all possible conformations of the polypeptide. Which figure describes a polypeptide sequence that is more likely to fold into its design model? Why?



Part II. Discussion Paper (Correia et al. 2014)

1. How does epitope-focused vaccine design work? What are the advantages of this method compared to traditional vaccine design methods?

2. Briefly describe the computational method of protein design discussed in this paper (Fold From Loops). How many FFL designs were ultimately chosen for filtering and human-guided optimization?

3. The authors then did an immunological evaluation of specific FFL designs they optimized. What evidence did the authors have to support and/or go against the clinical relevance of their designed FFL scaffolds?

4. What evidence did the authors have from their antibody characterization that their designed scaffolds can “re-elicit” neutralizing antibodies?

5. Do you think there is enough evidence supporting the efficacy of FFL scaffolds for use as a vaccine against RSV? If no, which additional experiments are required?

6. Comment on the suitability of this approach for developing vaccines against other viruses, i.e. HIV or Ebola.