Computational design of protein-based nanomaterials

Image courtesy of Vikram Mulligan, Ph.D.
Proteins are the workhorses of every living cell

Proteins are the workhorses of every living cell

Proteins consist of long chains of amino acids encoded by sequences of DNA and RNA
Sequence $\Rightarrow$ Structure

Conformation

Energy

Lowest energy state

http://livasperiklis.files.wordpress.com/2012/11/
Sequence → Structure

Conformation

Energy

Lowest energy state

http://livasperiklis.files.wordpress.com/2012/11/
Structure ➔ Function

**Structure**

**Function**
Scaffolding & tracks for transport

http://www.rcsb.org/pdb/education_discussion/molecule_of_the_month/
sequence $\rightarrow$ structure $\rightarrow$ function relationship presents two inversely related challenges

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Amino Acid Sequence</th>
<th>Structure/F</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure prediction</td>
<td>✔</td>
<td>?</td>
<td>Better understand, utilize, and repair natural proteins</td>
</tr>
<tr>
<td>Protein design</td>
<td>?</td>
<td>✔</td>
<td>Engineer new proteins to solve problems not encountered or solved by evolution</td>
</tr>
</tbody>
</table>
sequence ➔ structure ➔ function relationship presents two inversely related challenges

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Amino Acid Sequence</th>
<th>Structure/F</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure prediction</td>
<td>✔</td>
<td>?</td>
<td>Better understand, utilize, and repair natural proteins</td>
</tr>
<tr>
<td>Protein design</td>
<td>?</td>
<td>✔</td>
<td>Engineer new proteins to solve problems not encountered or solved by evolution</td>
</tr>
</tbody>
</table>
sequence $\Rightarrow$ structure $\Rightarrow$ function relationship presents two inversely related challenges

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Amino Acid Sequence</th>
<th>Structure/F Function</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure prediction</td>
<td>✔️</td>
<td>?</td>
<td>Better understand, utilize, and repair natural proteins</td>
</tr>
<tr>
<td>Protein design</td>
<td>?</td>
<td>✔️</td>
<td>Design new proteins to solve problems not encountered or solved by evolution</td>
</tr>
</tbody>
</table>
sequence $\rightarrow$ structure $\rightarrow$ function relationship presents two inversely related challenges

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Amino Acid Sequence</th>
<th>Structure/F Function</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure prediction</td>
<td>✔</td>
<td>?</td>
<td>Better understand, utilize, and repair natural proteins</td>
</tr>
<tr>
<td>Protein design</td>
<td>?</td>
<td>✔</td>
<td>Design new proteins to solve problems not encountered or solved by evolution</td>
</tr>
</tbody>
</table>
Computational protein design: Releasing ourselves from the constraints of evolution

- Method: Energy function + search algorithms
- Goal: Find sequence predicted to produce target structure(s)
Computational protein design: Releasing ourselves from the constraints of evolution

- Method: Energy function + search algorithms
- Goal: Find sequence predicted to produce target structure(s)
Protein-based nanomaterials are particularly intriguing design targets

Delivery vehicles  Signal Transducers  Motors

http://www.rcsb.org/pdb/education_discussion/molecule_of_the_month/
We are developing methods for designing a wide range of protein nanostructures.
New genes are synthesized encoding our designed proteins and used to test our predictions.
A small, but increasing percentage of designs match our predictions.
A small, but increasing percentage of designs match our predictions

Jacob Bale, Neil King, Will Sheffler, Shane Gonen
And when then do match, it is with nearly atomic-level accuracy
We are on the cusp of uncharted territory

- Moving beyond proof-of-principle structures toward functional materials
- Computational modeling and prediction hold the key

Targetted Therapeutics  Clean Energy  Vaccines

Images courtesy of Will Shefler
Thank you!

– Jacob Bale (balej@uw.edu)
  • Baker Group, UW Dept. of Biochemistry
  • UW MCB graduate program
  • UW Institute for Protein Design

– Get involved:
  • Foldit – Free, fun protein structure prediction and design computer game
  • Rosetta@home – Donate your spare CPUs to our calculations

– Acknowledgements:
  • Dr. David Baker, Dr. Neil King, Dr. Will Sheffler, and other Baker Lab members
  • NSF Graduate Research Fellowship, DTRA, AFOSR