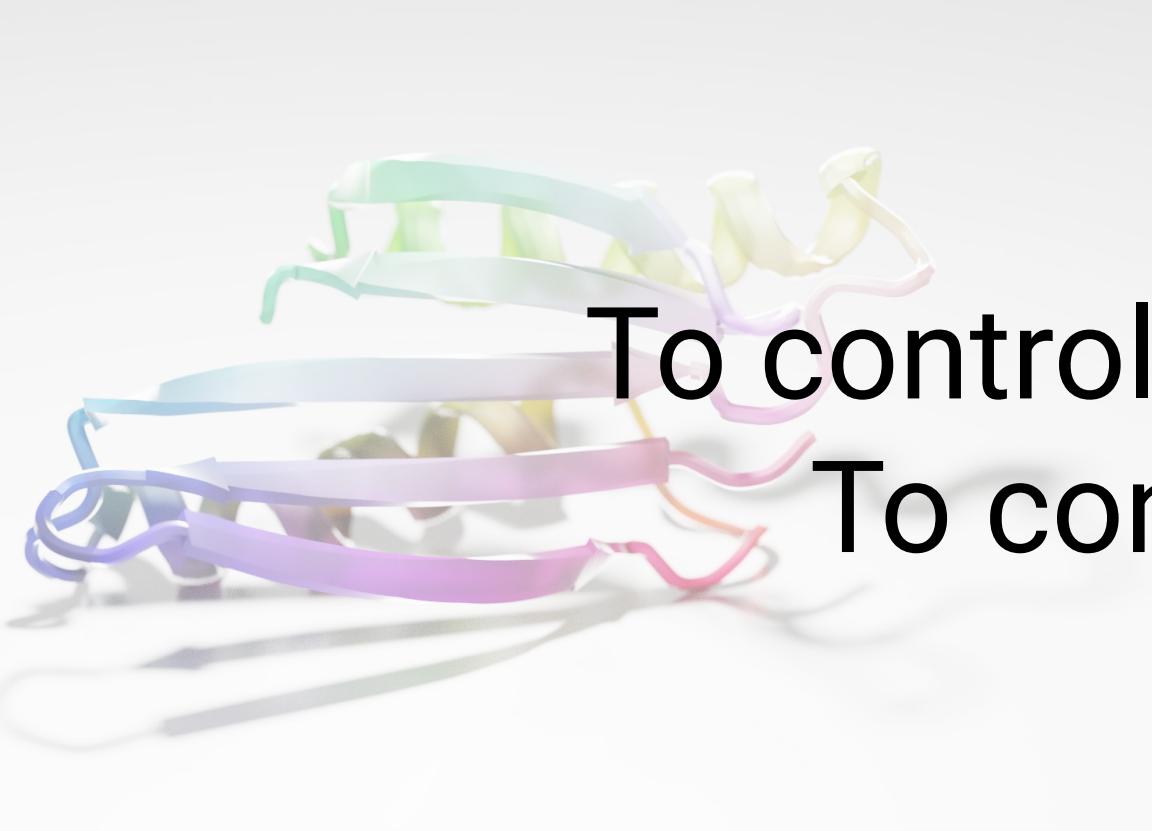


Class core values

1. Be **respectful** to yourself and others
2. Be **confident** and believe in yourself
3. Always do your **best**
4. Be **cooperative**
5. Be **creative**
6. Have **fun**
7. Be **patient** with yourself while you learn
8. Don't be shy to **ask "stupid" questions**



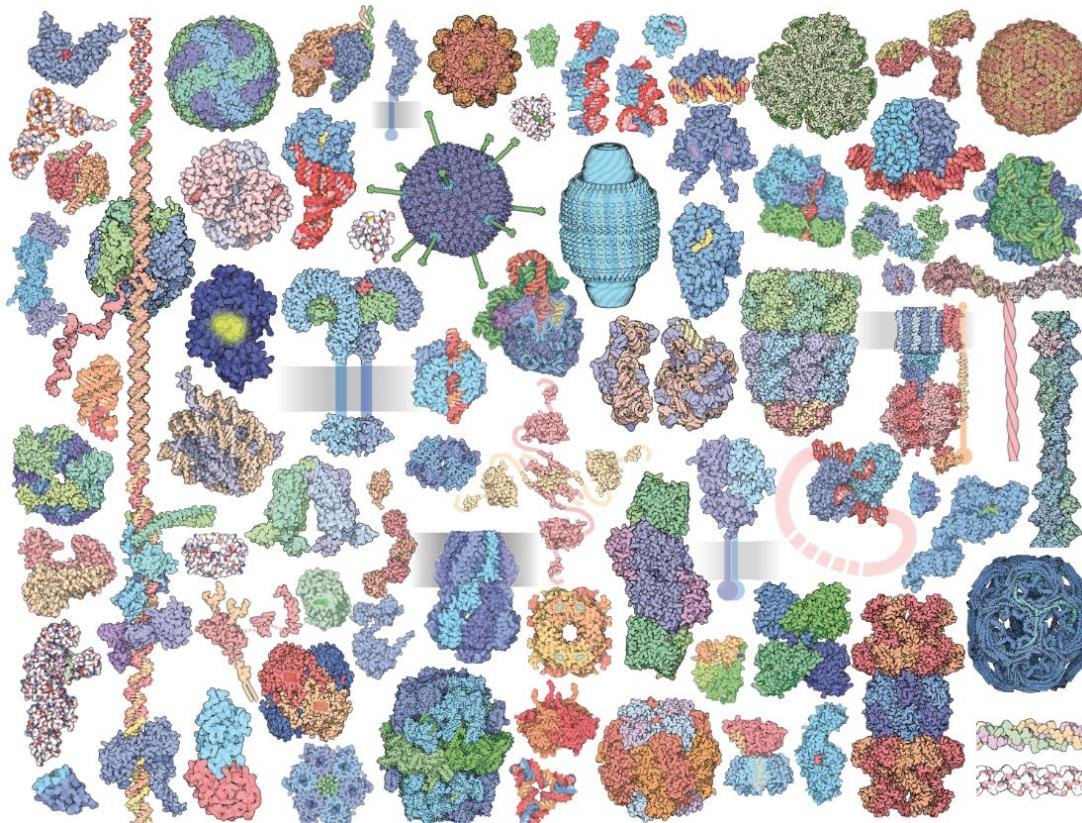
Week 6, Lecture 2

To control function =
To control shape

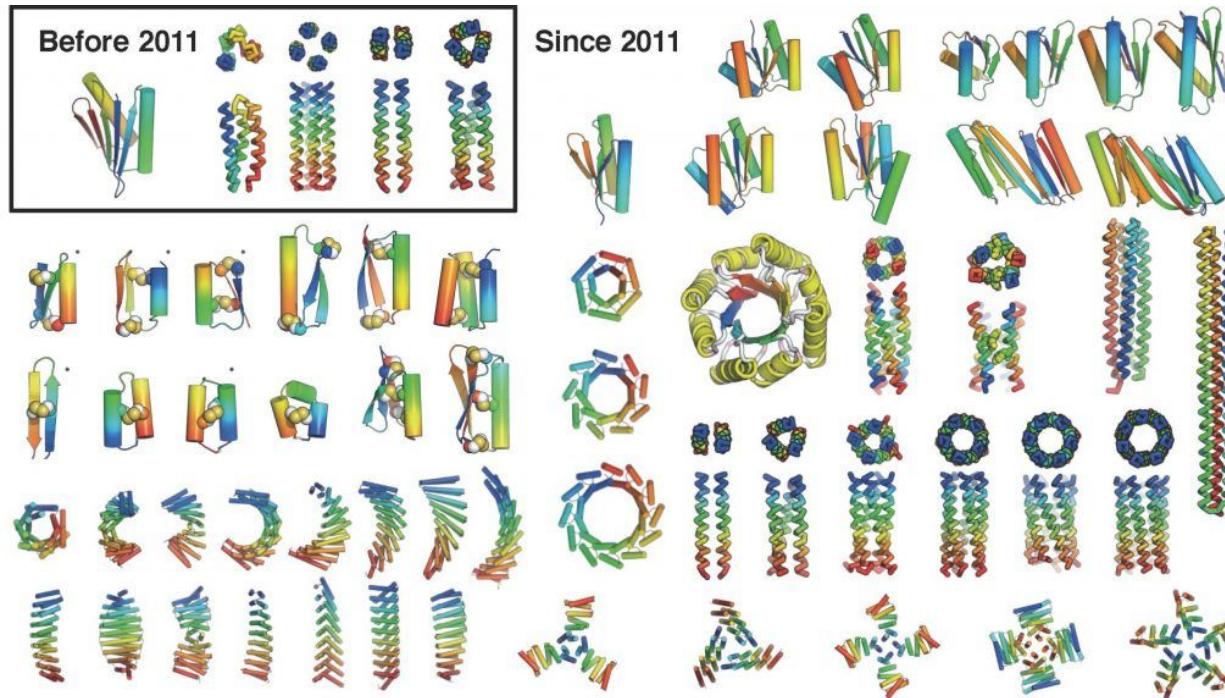
Learning Objectives

1. Describe the underlying process of de novo design of shape
2. Identify the challenges in designing shapes using computational methods
3. Describe methods used for de novo design of shape
4. Apply Crick's parameters to design helical bundles

Function of proteins is controlled by their shape

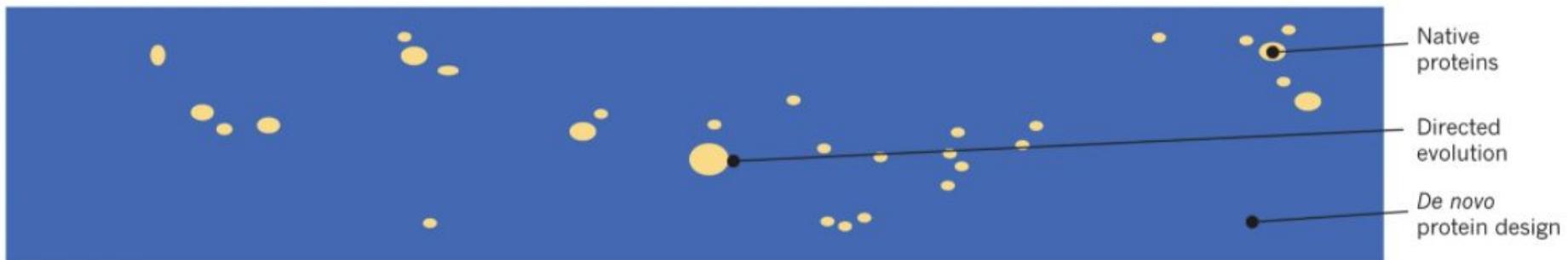


Q1. Can we precisely control the shape?



Q1. Can we precisely control the shape?

Q2. Can we sample the entire structure space?

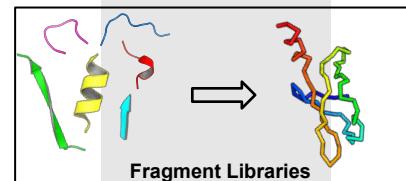


Design of shape = finding sequences for a defined backbone shape

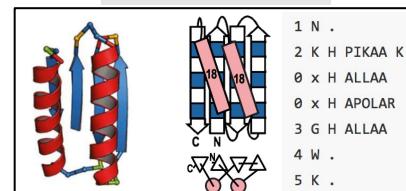
...TRGEEGCQETSQTGRDKNQVEGEVQIVS
TATQTFLATSINGVLWTVYHGAGTRTIASP...
Final Sequence

Scoring based on
structural features

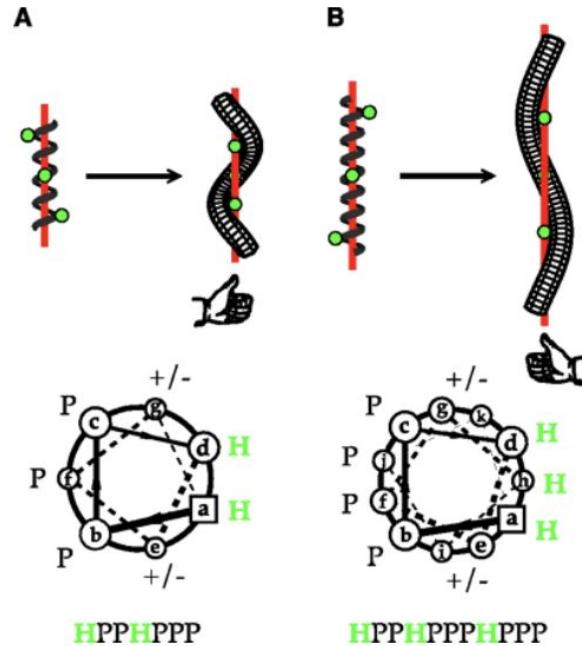
Sidechain assignment
to stabilize structure



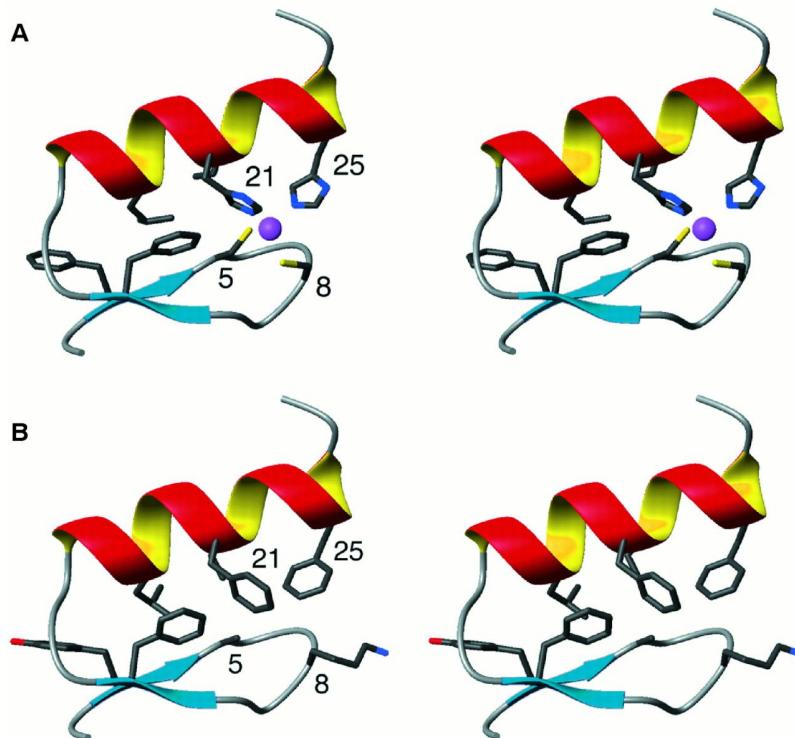
Fragment assembly



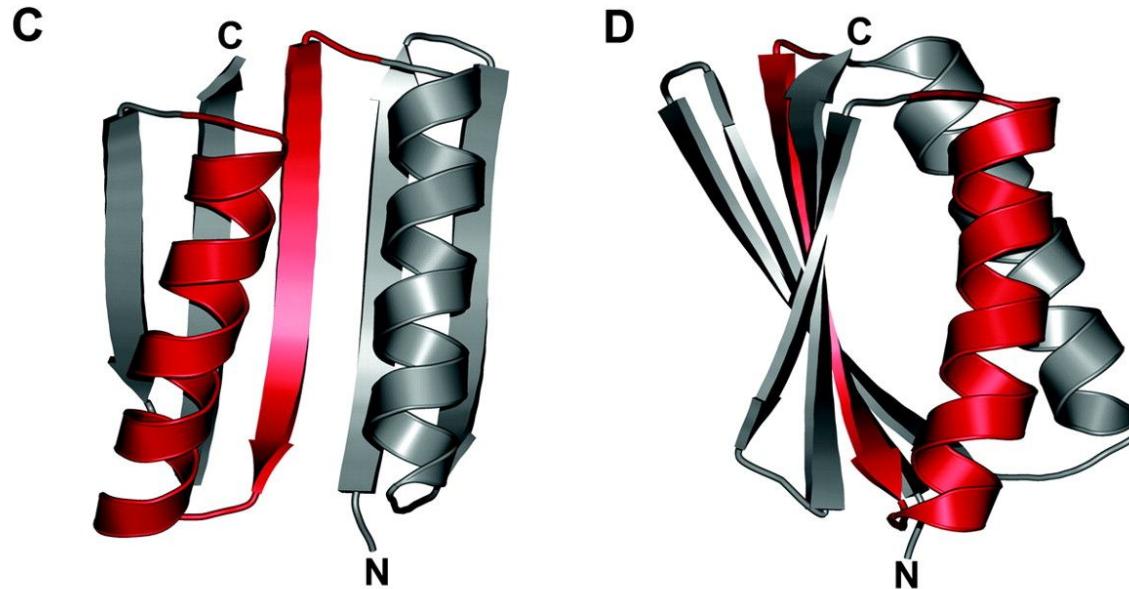
Early designs focused mostly on statistical information and observations



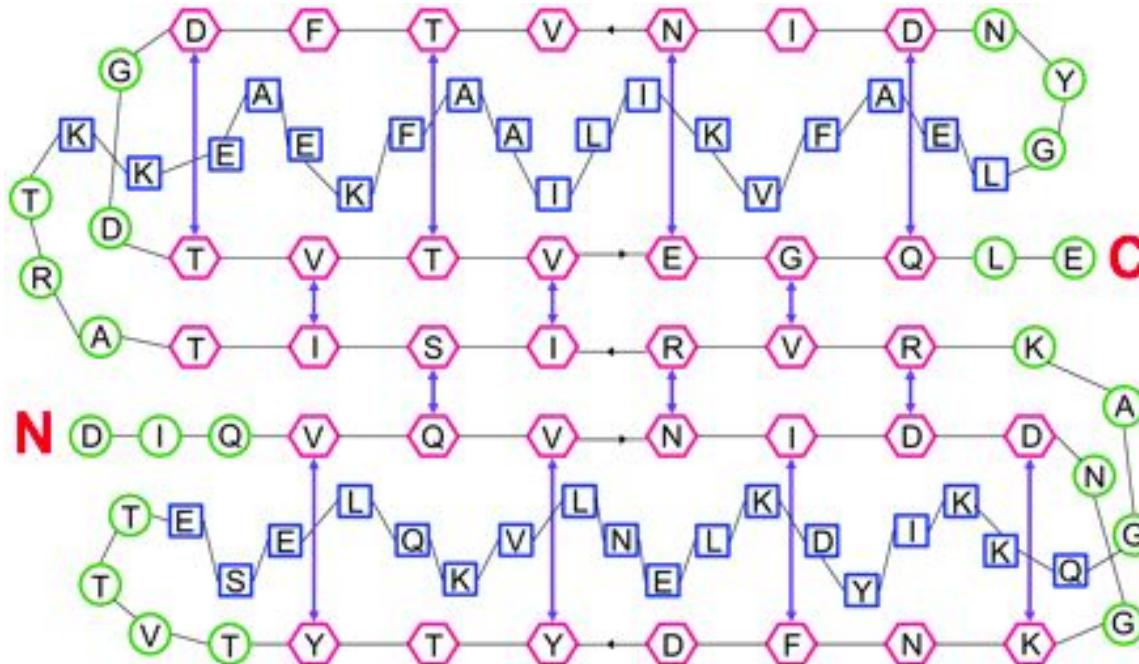
Others realized that design can be poised as a computational problem



Assembling fragments from PDB help with starting the process

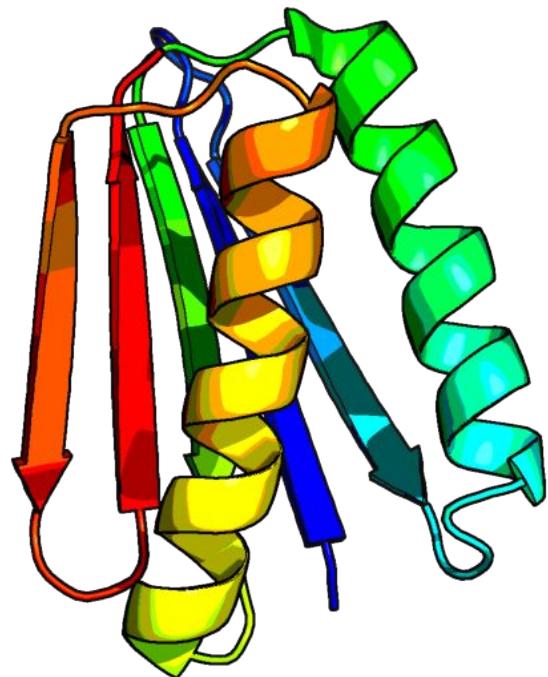


Sequences are selected to minimize the score function

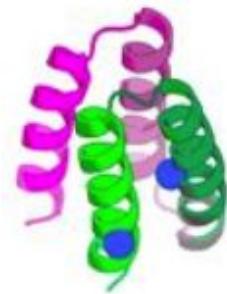


In class activity:

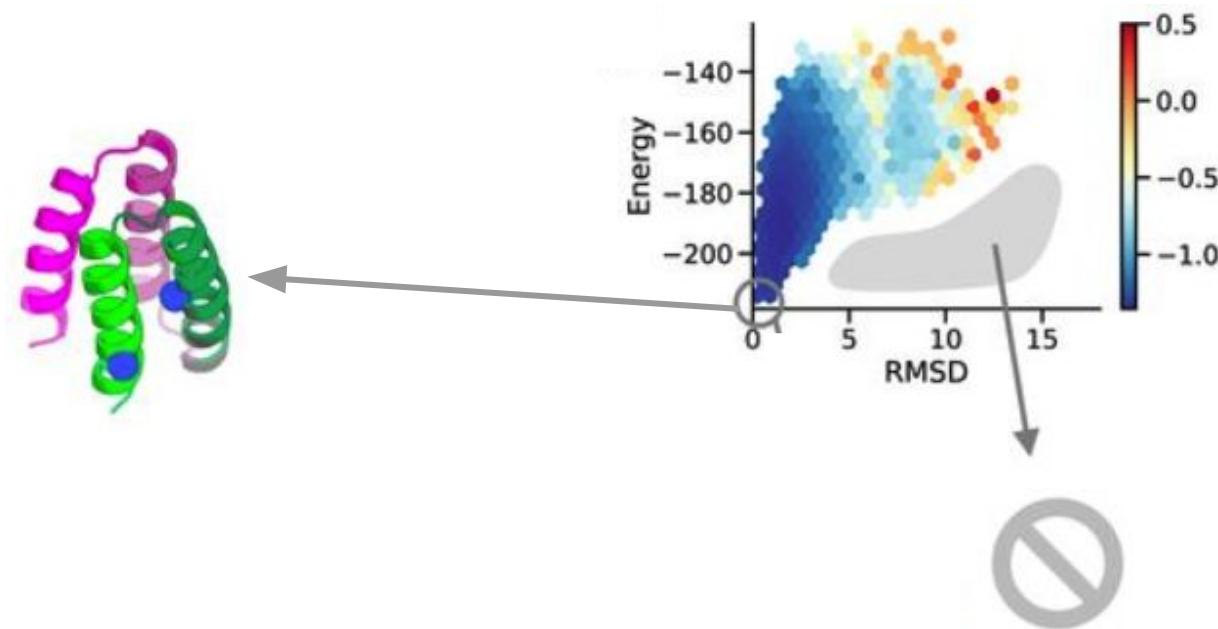
Build your own protein!



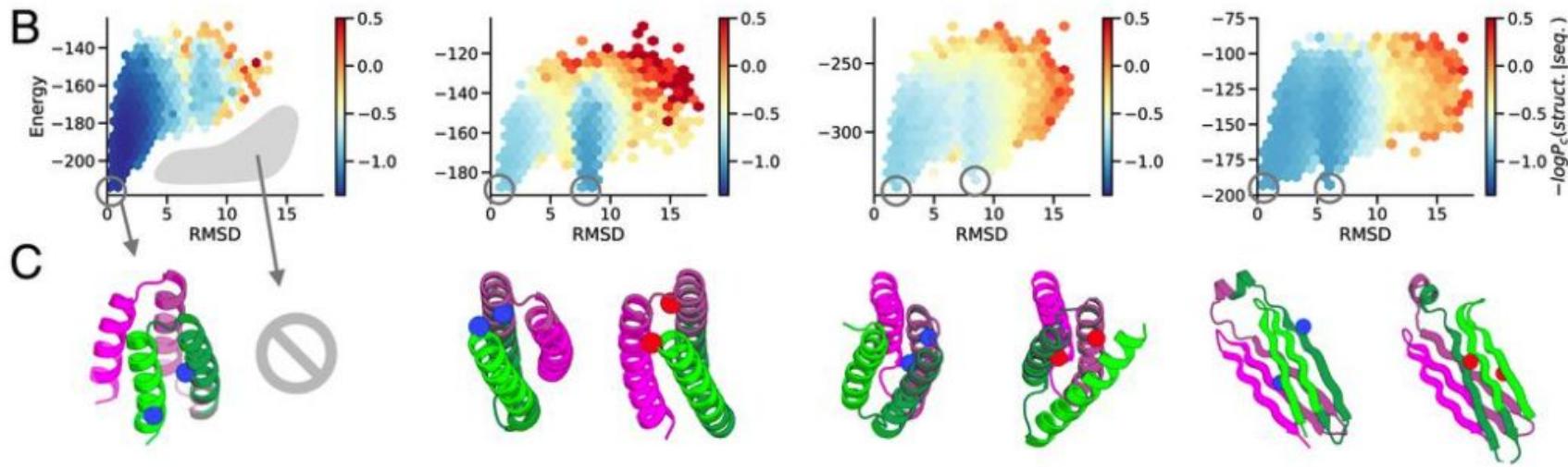
Sequence design only has a local view of the energy landscape



Sequence design only has a local view of the energy landscape



Sequence design only has a local view of the energy landscape → ab initio folding is needed



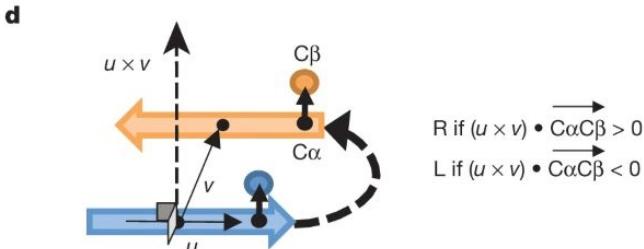
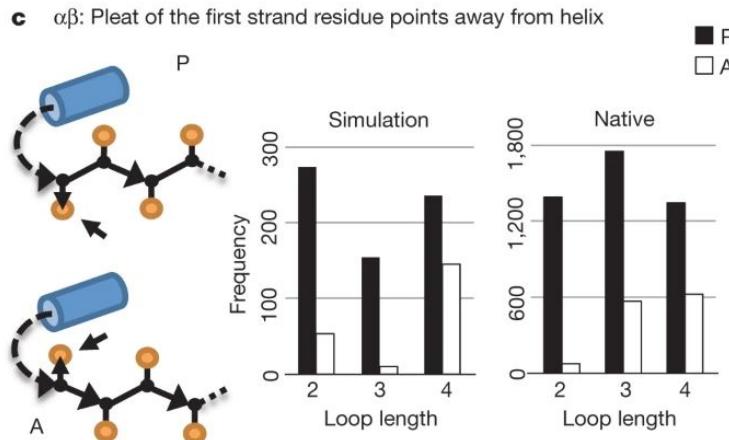
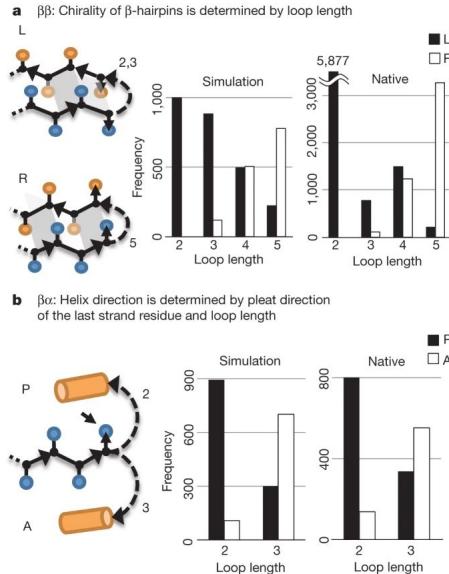
Often guidance from the designer is required to overcome the limitations of the score function

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1. Good turns = good designs

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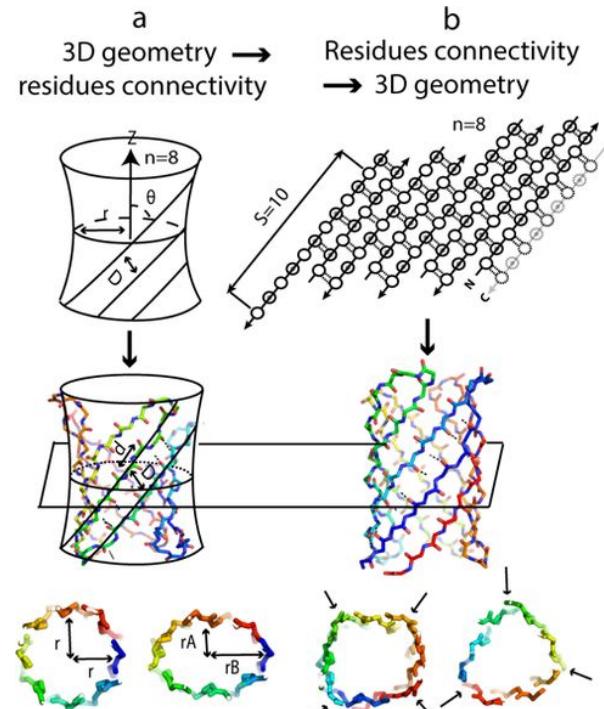


Often guidance from the designer is required to overcome the limitations of the score function

1. Good turns = good designs
2. Glycines exist for a reason

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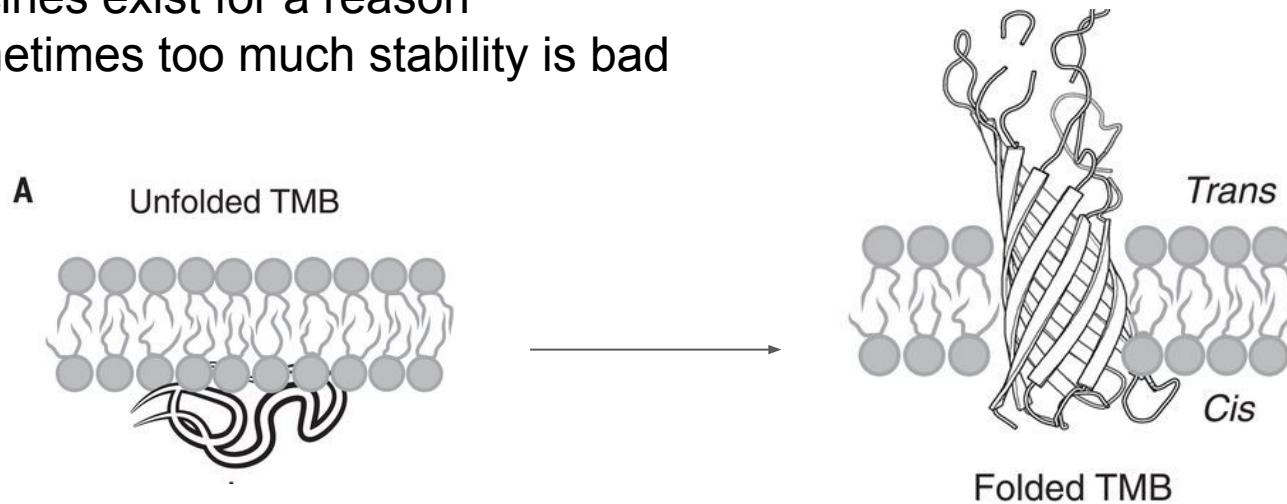


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1. Good turns = good designs
2. Glycines exist for a reason
3. Sometimes too much stability is bad

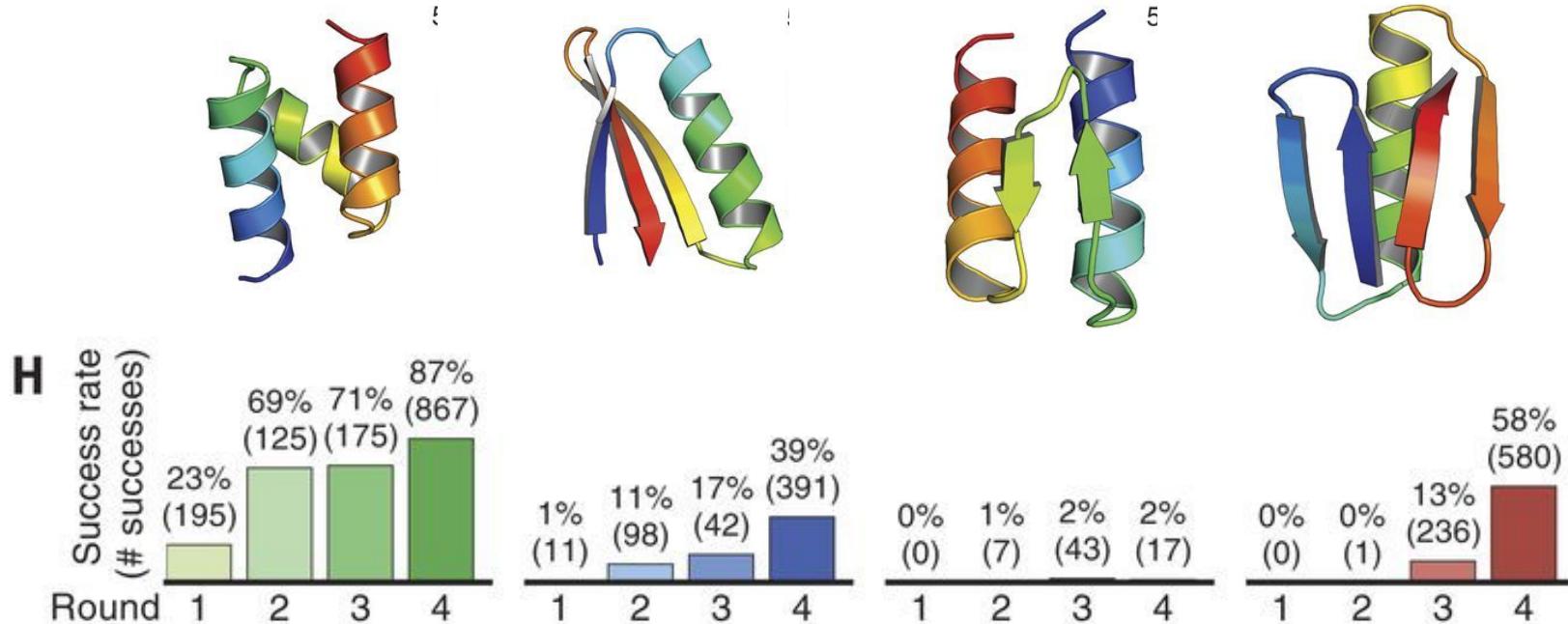
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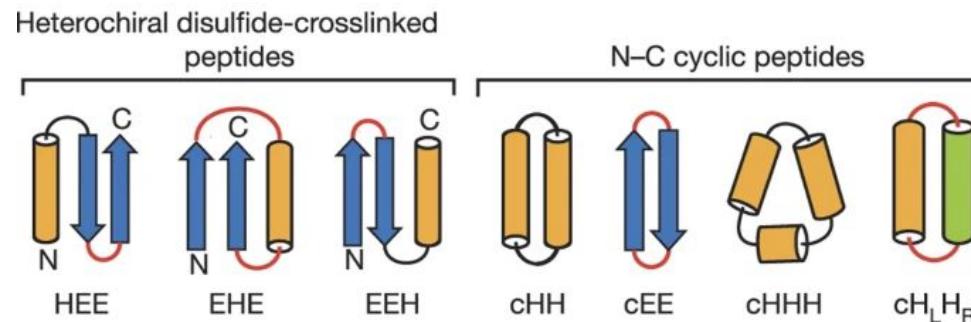


Repeating a design cycle can result in better designs and help learn new features

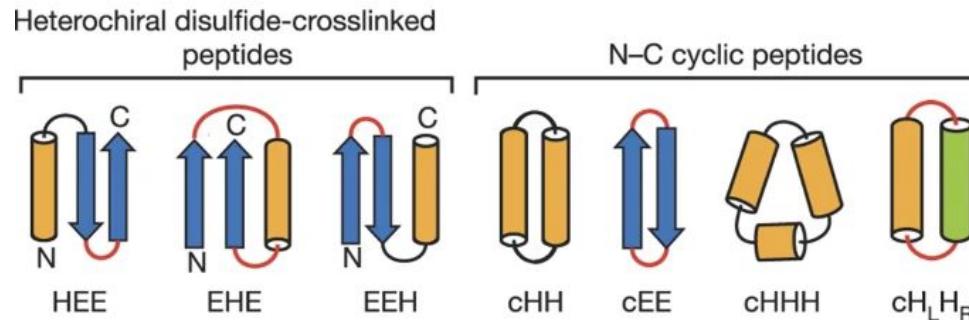
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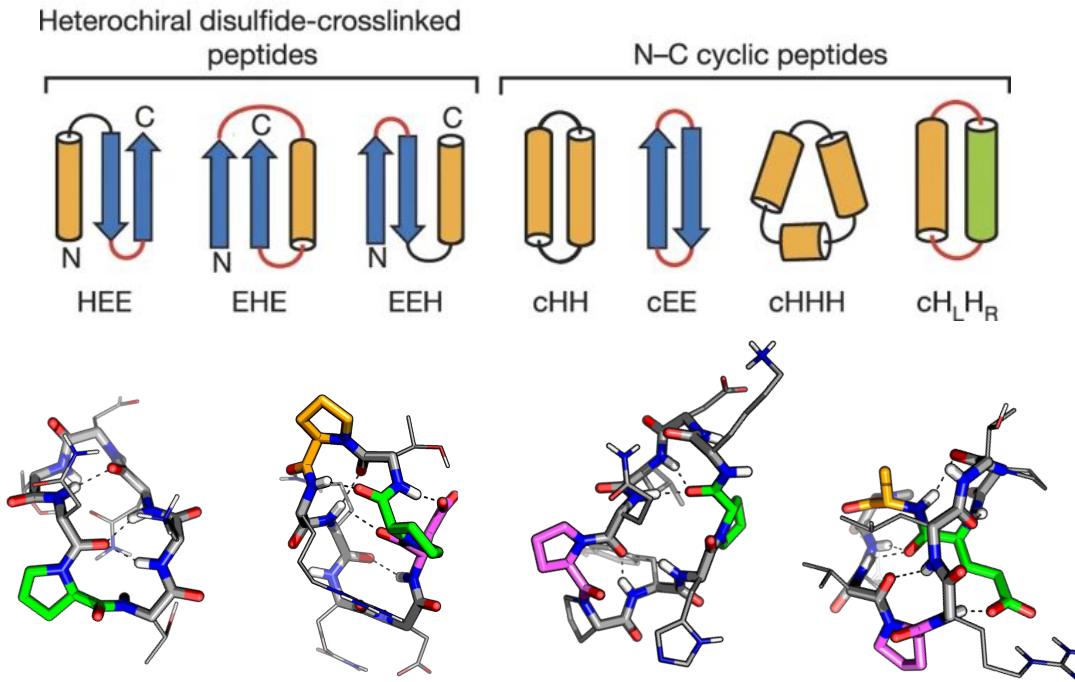
Folds that don't exist in nature



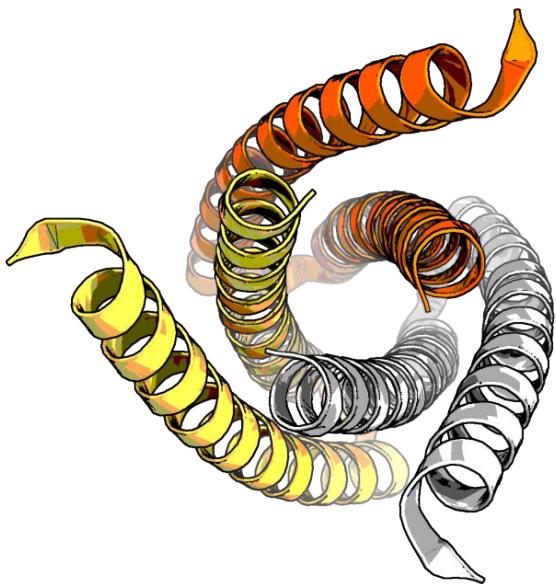
Folds that don't exist in nature can be built using fragment-free systems



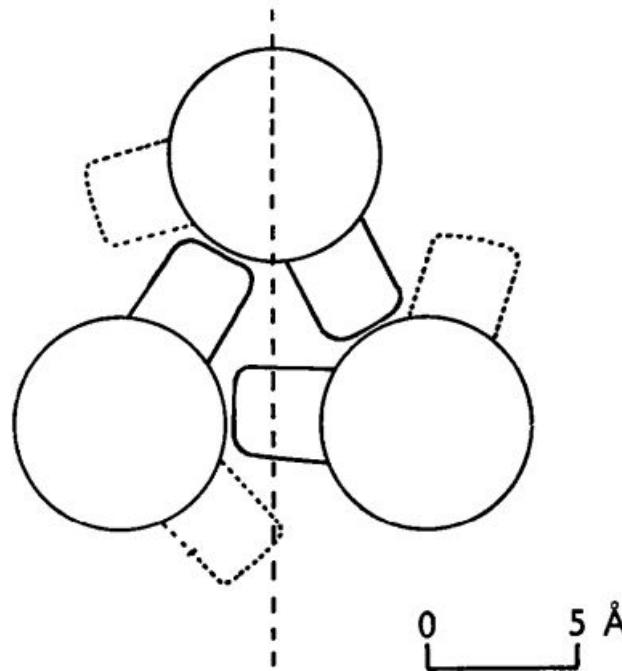
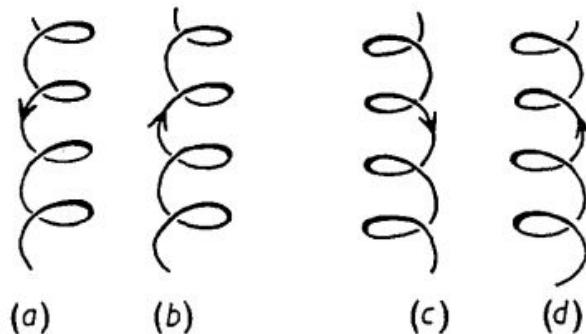
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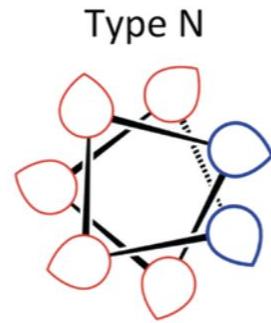
The special case of helical bundles



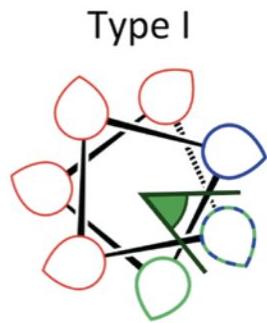
The features of α -helices and how they pack has been of interest from their early discovery



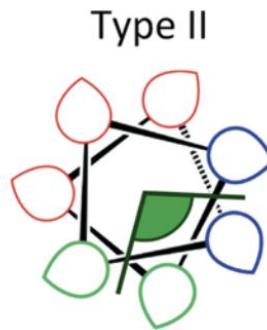
Patterns of packing and arrangement have been used to generate bundles of different size/shape



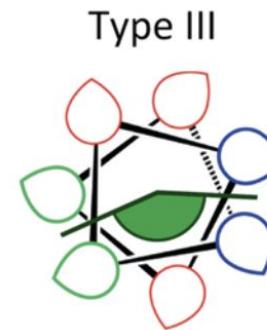
hphhphh



offset $\approx 51^\circ$
hphhphh

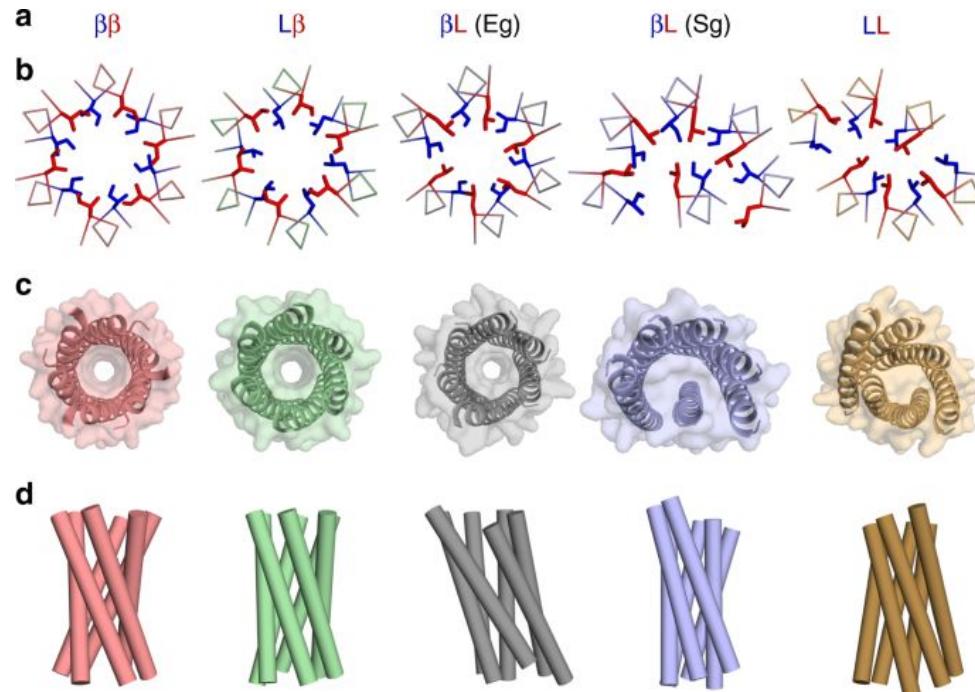


offset $\approx 103^\circ$
hhphhhph

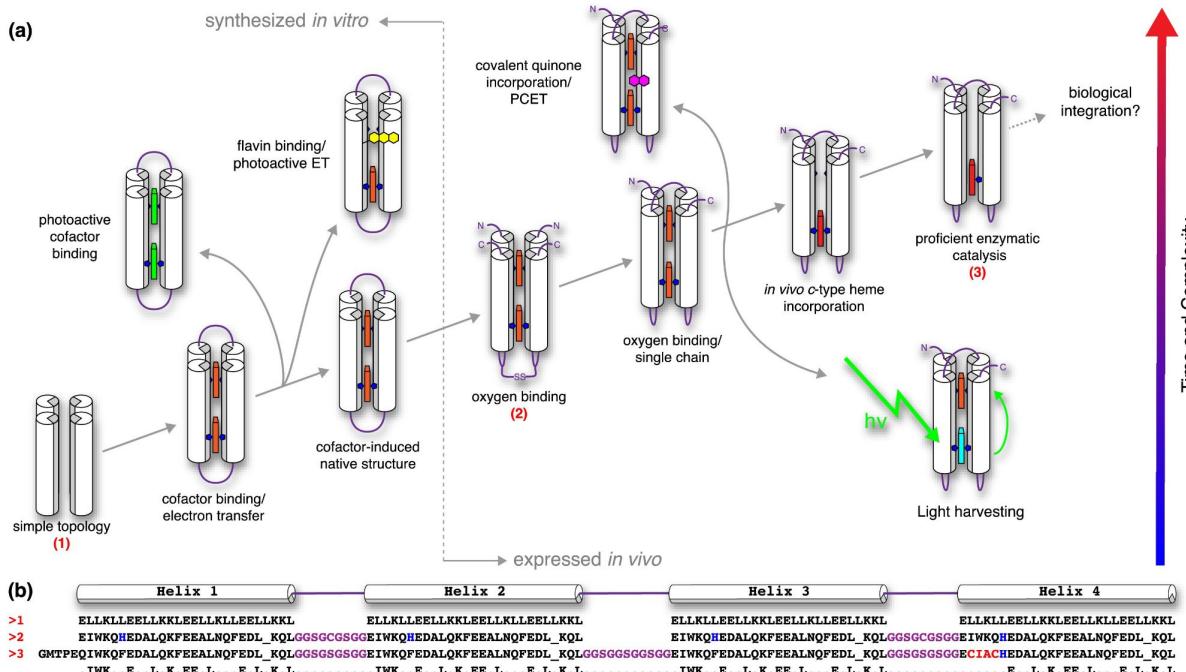


offset $\approx 154^\circ$
hhphphph

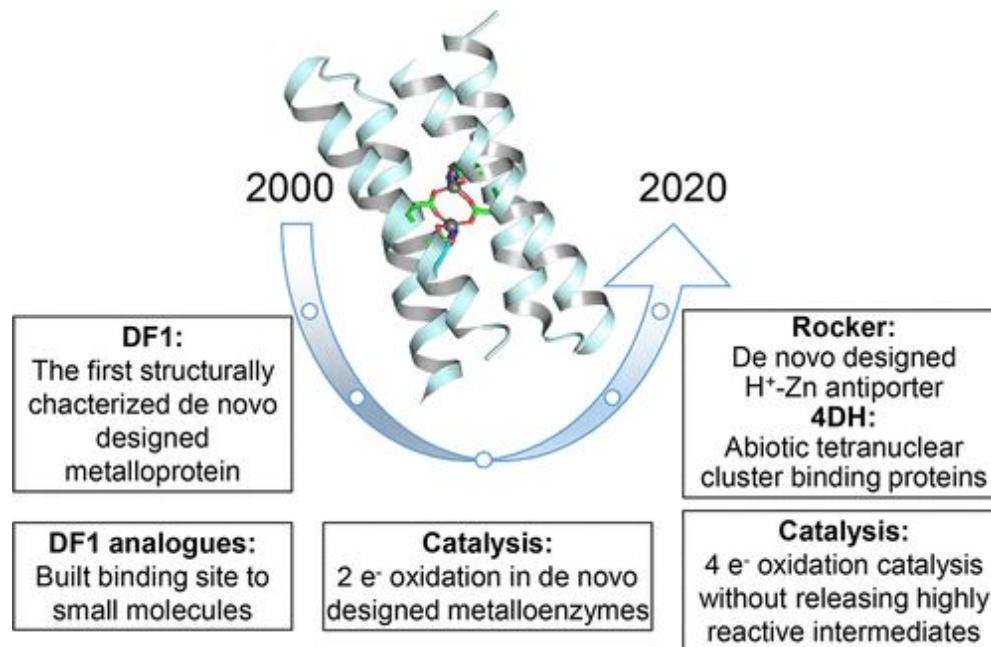
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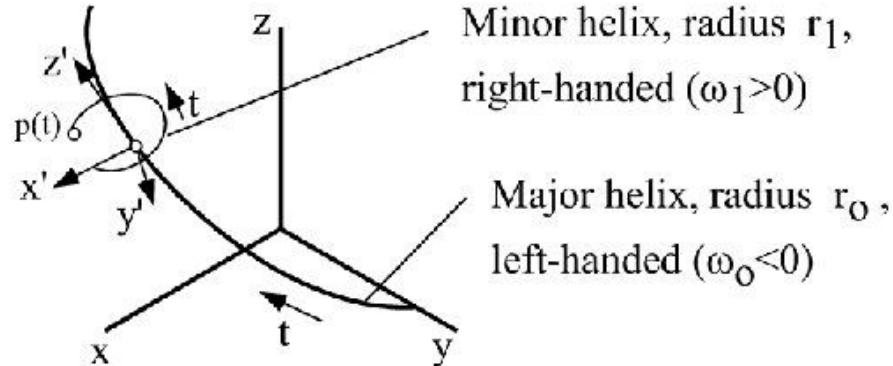
Helical bundles have been used as scaffolds for electron transfer and enzymatic activities



Four helix bundles were used as a versatile scaffold for many activities



Helical bundles can be parametrically designed



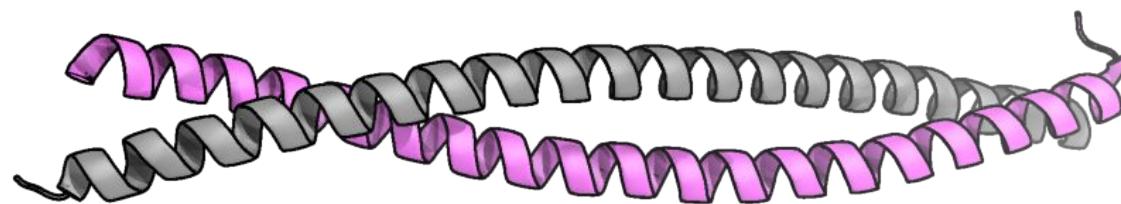
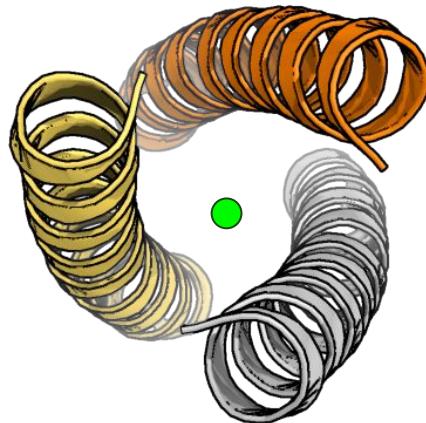
$$\begin{aligned}x(t) &= r_0 \cos \omega_0 t + r_1 \cos \omega_0 t \cos \omega_1 t - r_1 \cos \alpha \sin \omega_0 t \sin \omega_1 t \\y(t) &= r_0 \sin \omega_0 t + r_1 \sin \omega_0 t \cos \omega_1 t + r_1 \cos \alpha \cos \omega_0 t \sin \omega_1 t \\z(t) &= p_0(\omega_0 t) - r_1 \sin \alpha \sin \omega_1 t \\ \alpha &= \tan^{-1}(2\pi r_0 / p_0)\end{aligned}$$



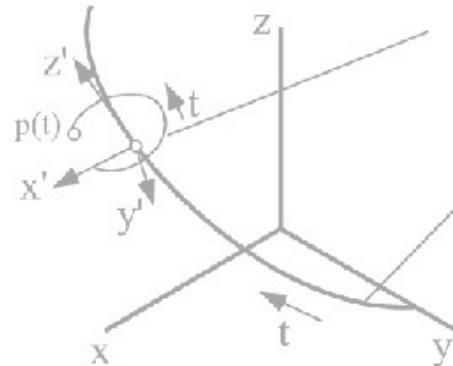
F.H.C. Crick, "The Fourier Transform of a Coiled-coil",
Acta Cryst. (1953), **6**, 685-689

In class activity

Parametric design of helical bundles

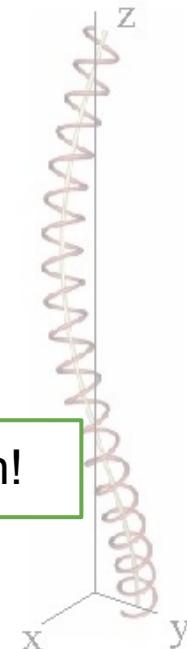


Helical bundles can be parametrically designed



Minor helix, radius r_1 ,
right-handed ($\omega_1 > 0$)

Major helix, radius r_0 ,
left-handed ($\omega_0 < 0$)



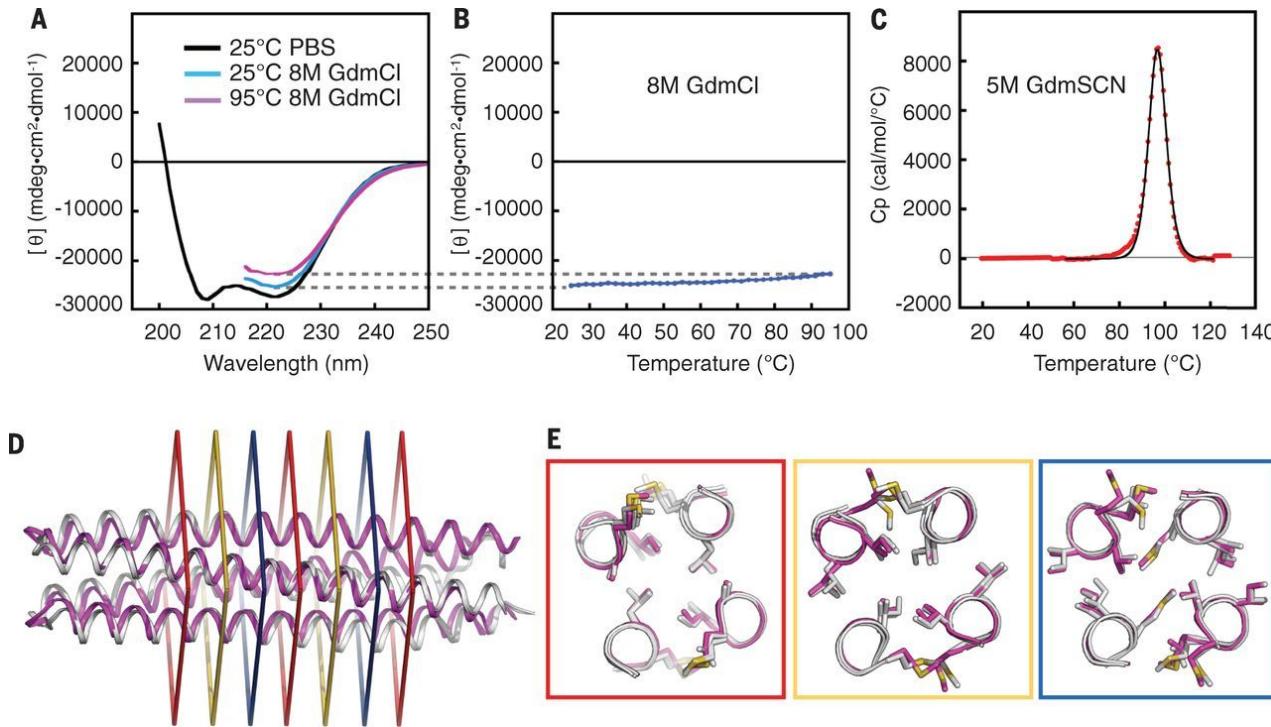
And that opened the door to so much!

$$y(t) = r_0 \sin \omega_0 t + r_1 \sin \omega_0 t \cos \omega_1 t + r_1 \cos \omega_0 t \sin \omega_1 t$$
$$z(t) = p_0(\omega_0 t) - r_1 \sin \alpha \sin \omega_1 t$$

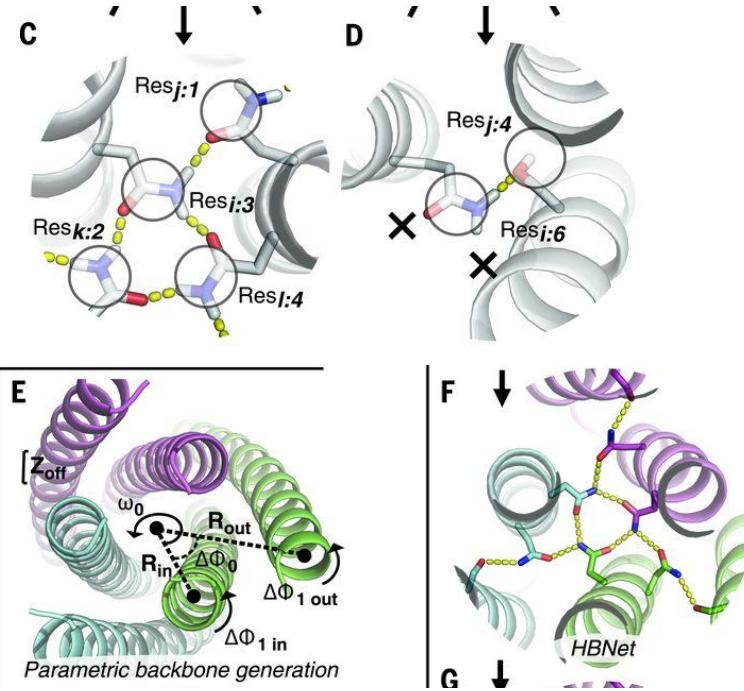
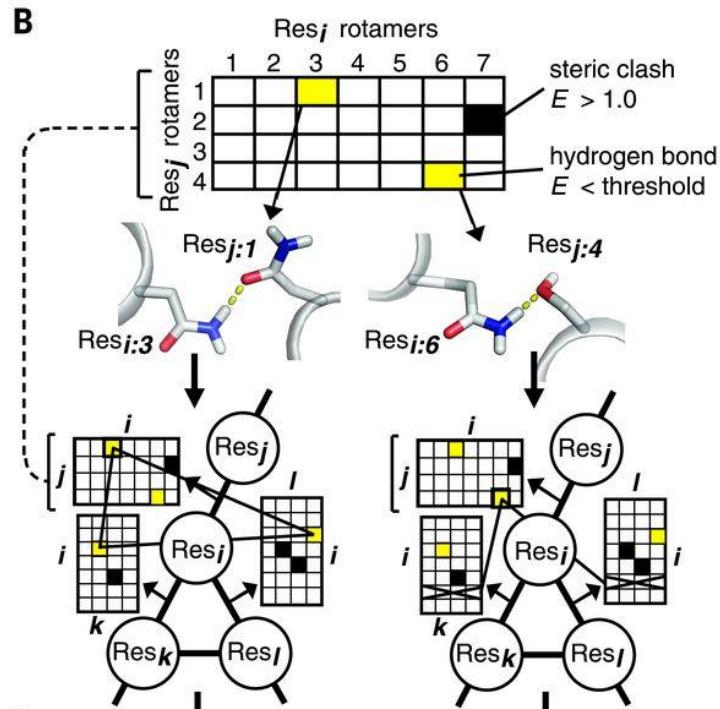
$$\alpha = \tan^{-1} (2\pi r_0 / p_0)$$

F.H.C. Crick, "The Fourier Transform of a Coiled-coil",
Acta Cryst. (1953), 6, 685-689

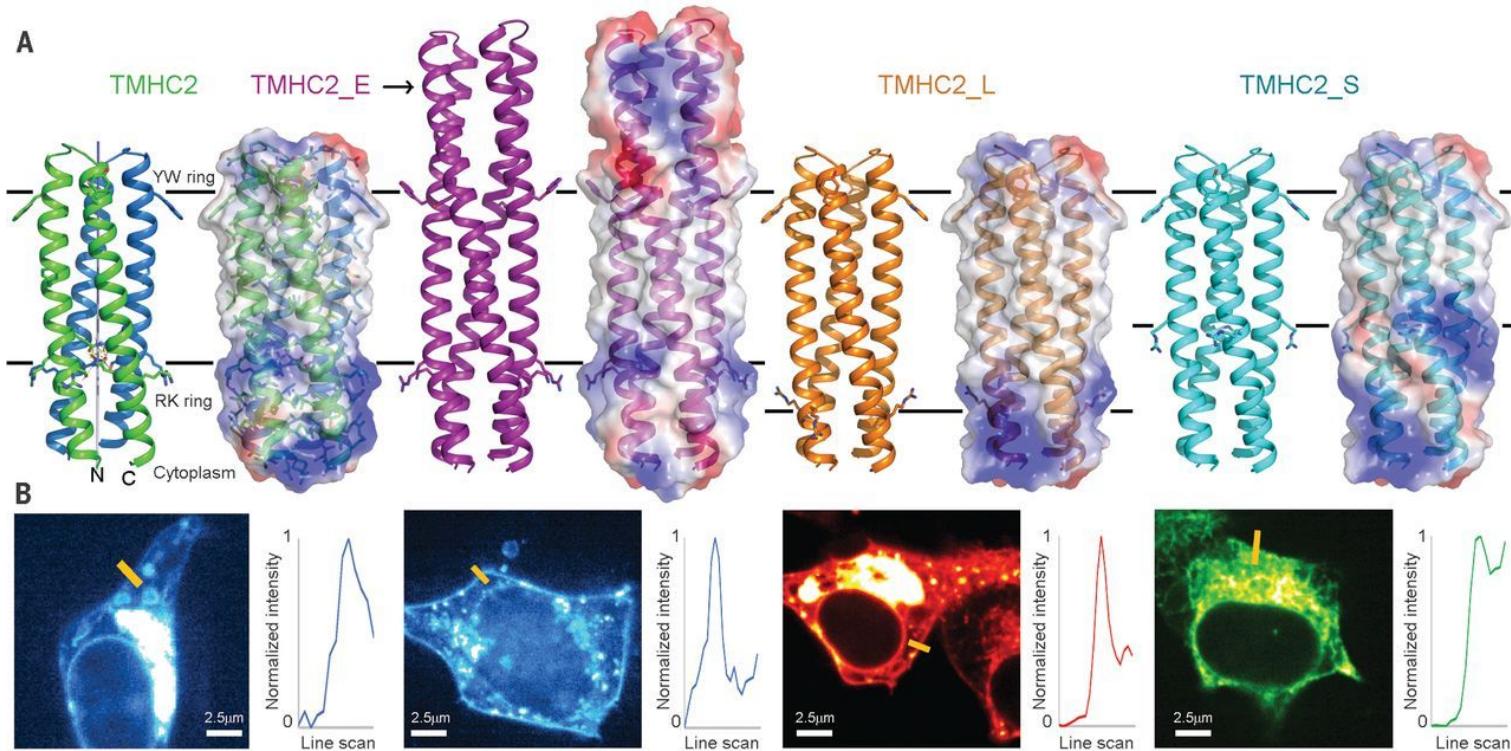
Hyperstable helical bundles



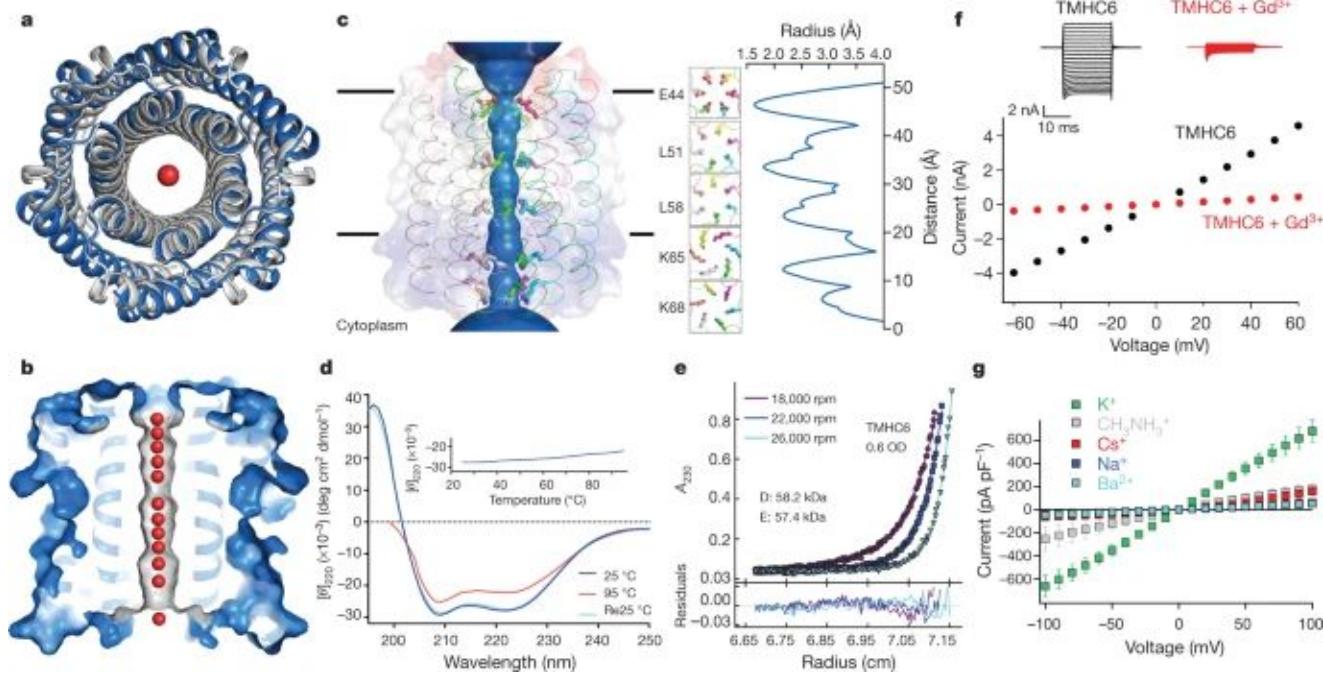
Hydrogen bonds at helical interface



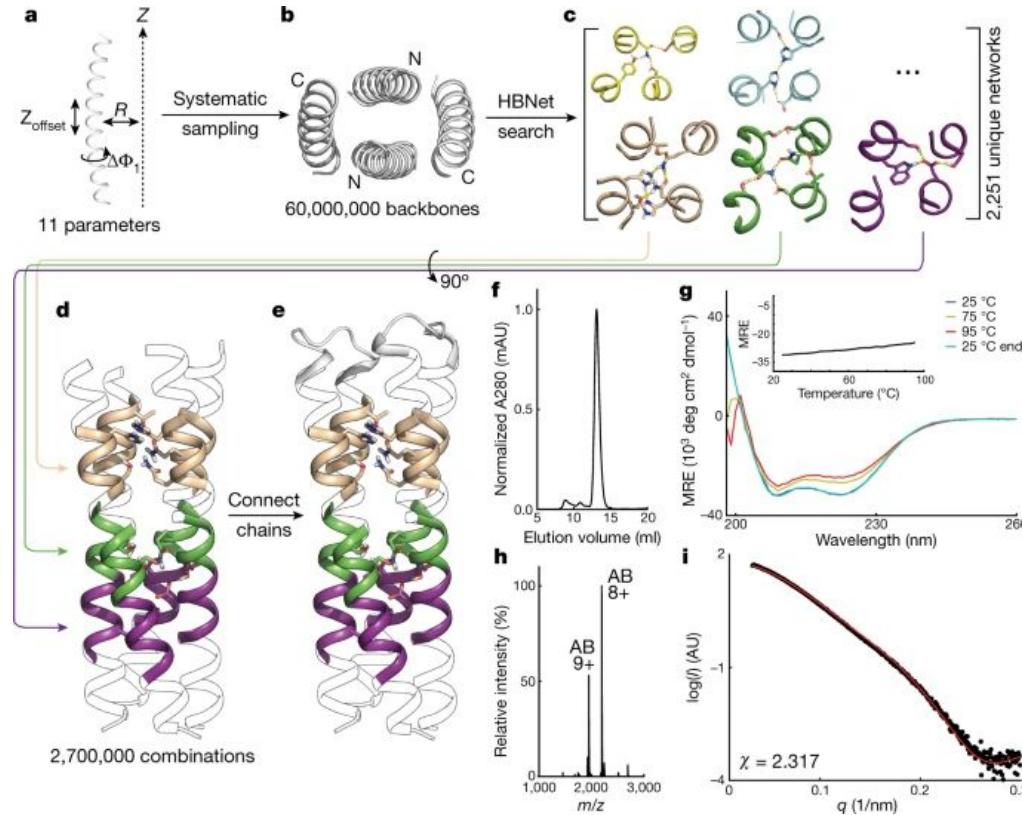
Membranous helical bundles



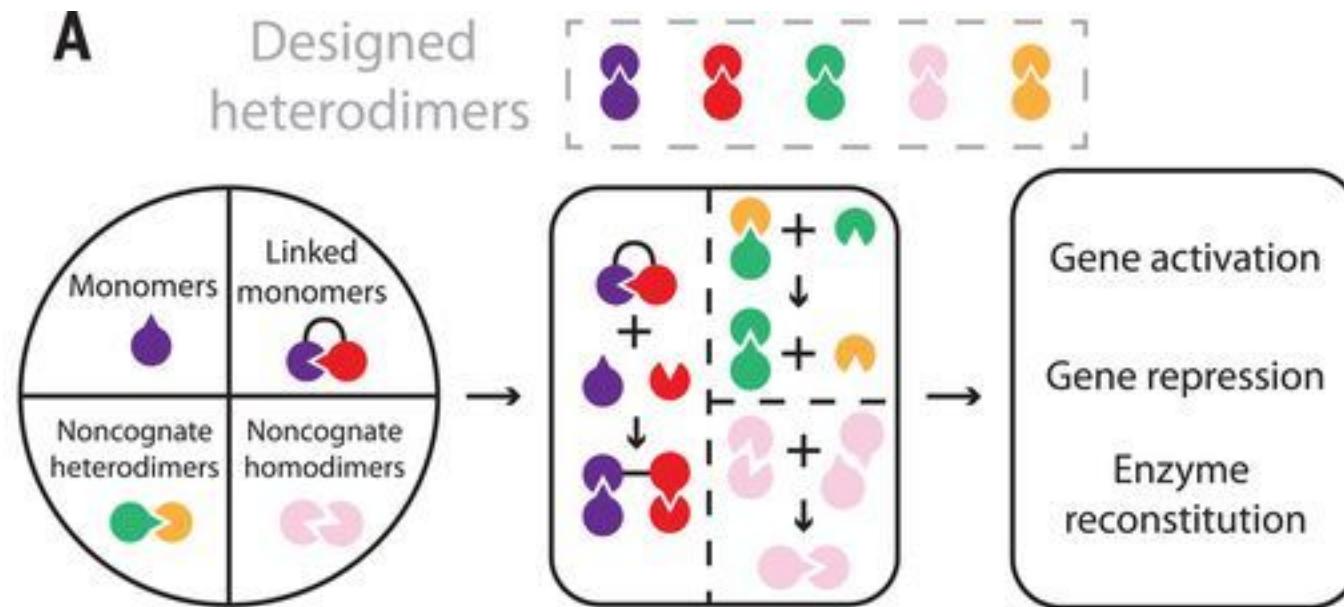
Membrane pores



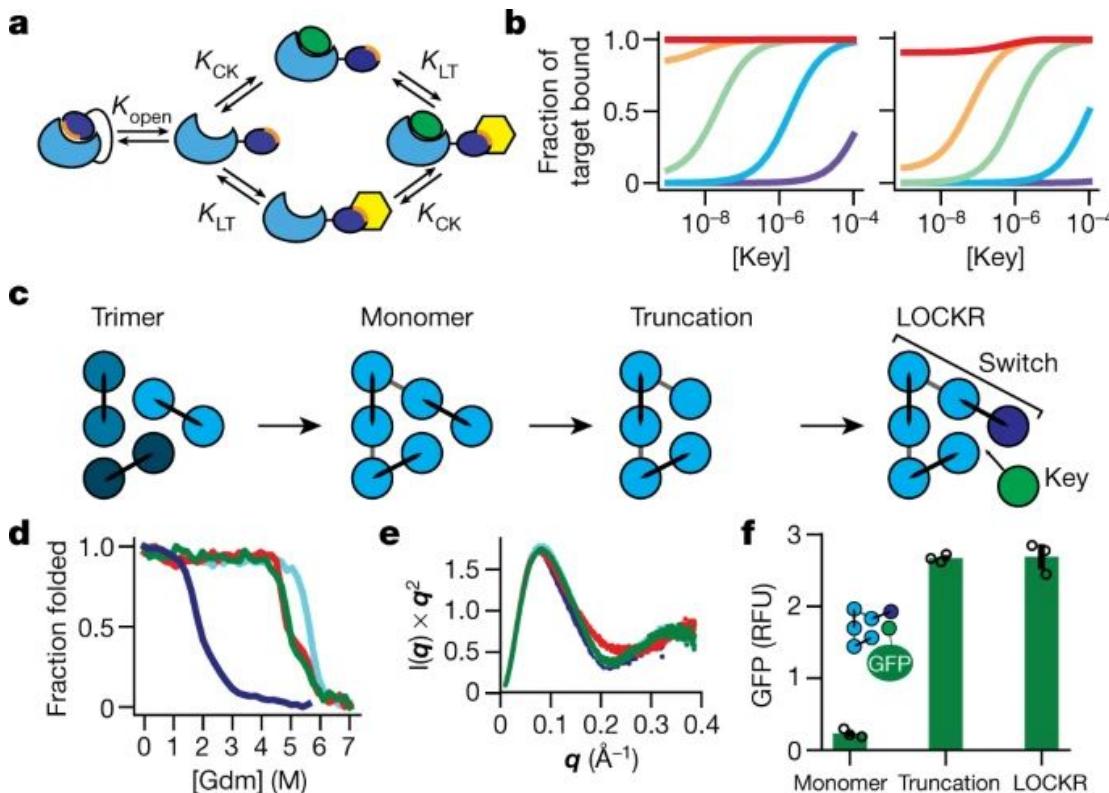
Tons of orthogonal dimers



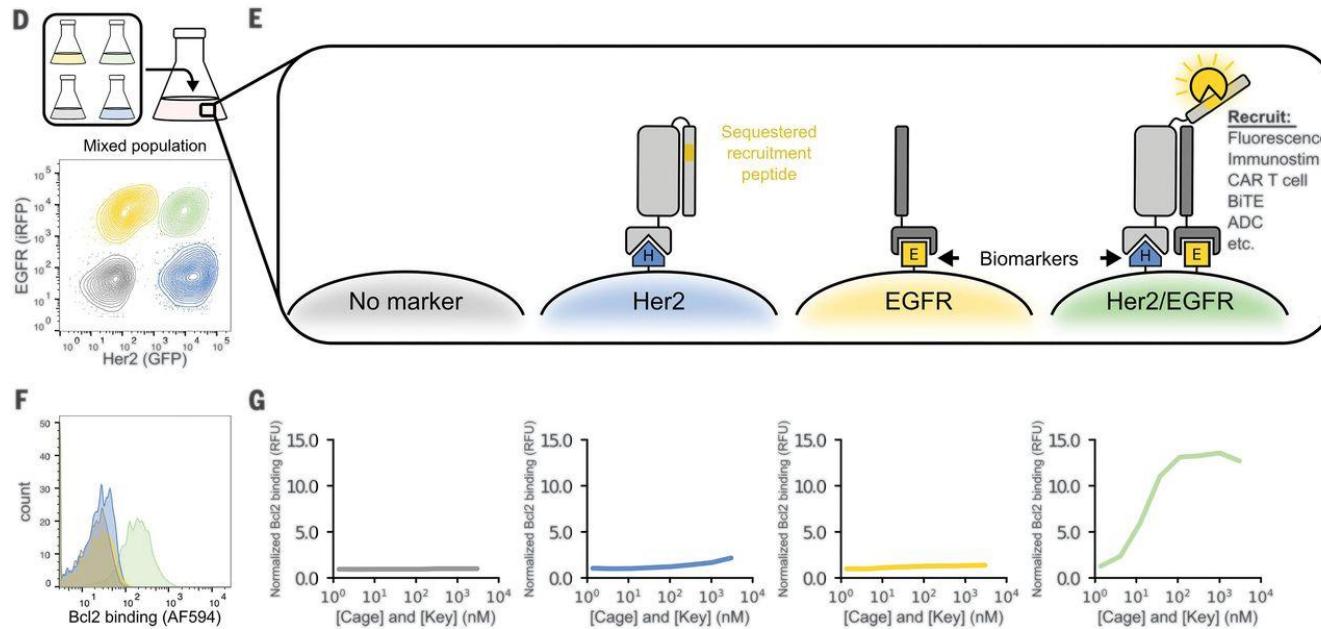
And logic gates based on them



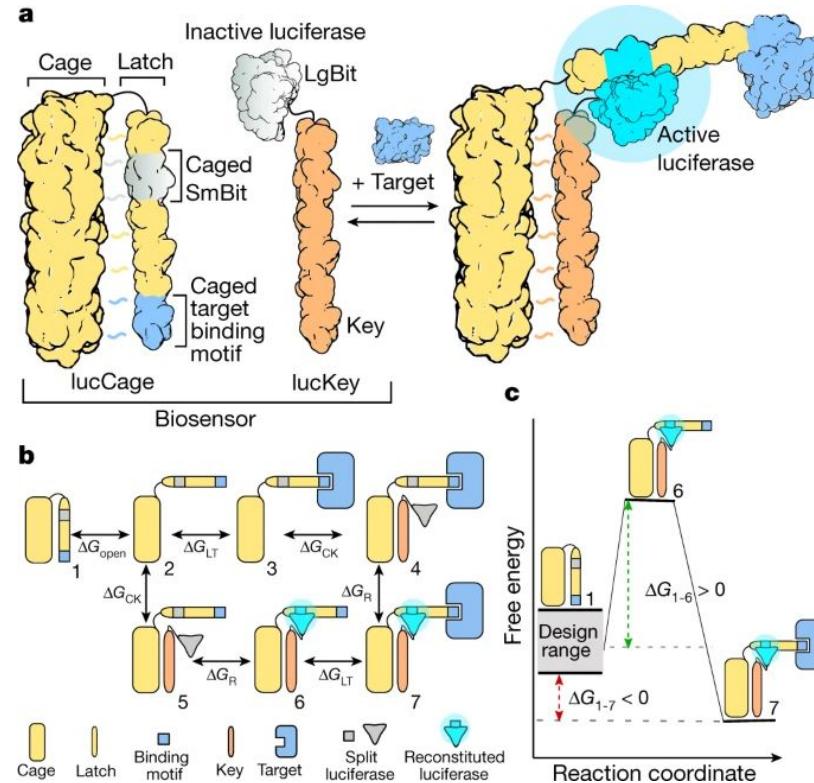
Bioactive protein switches



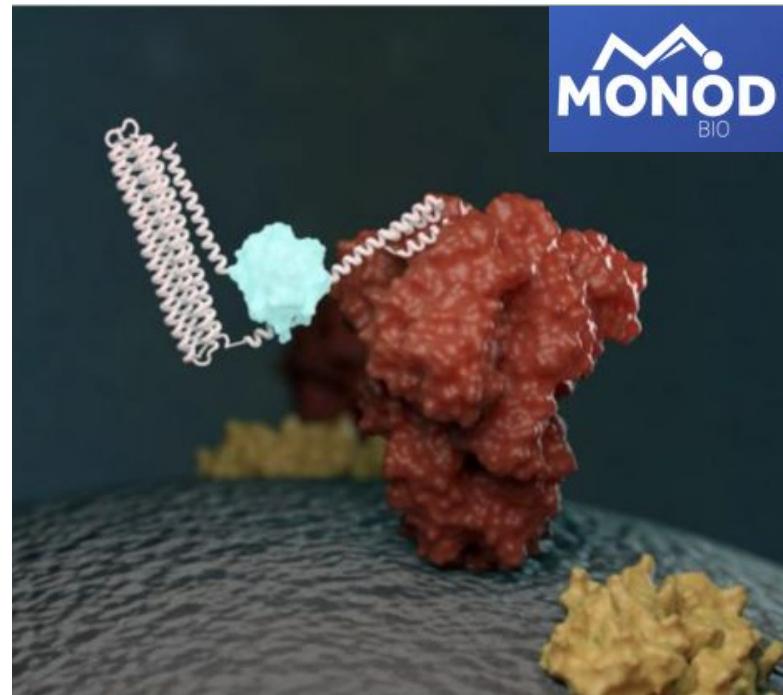
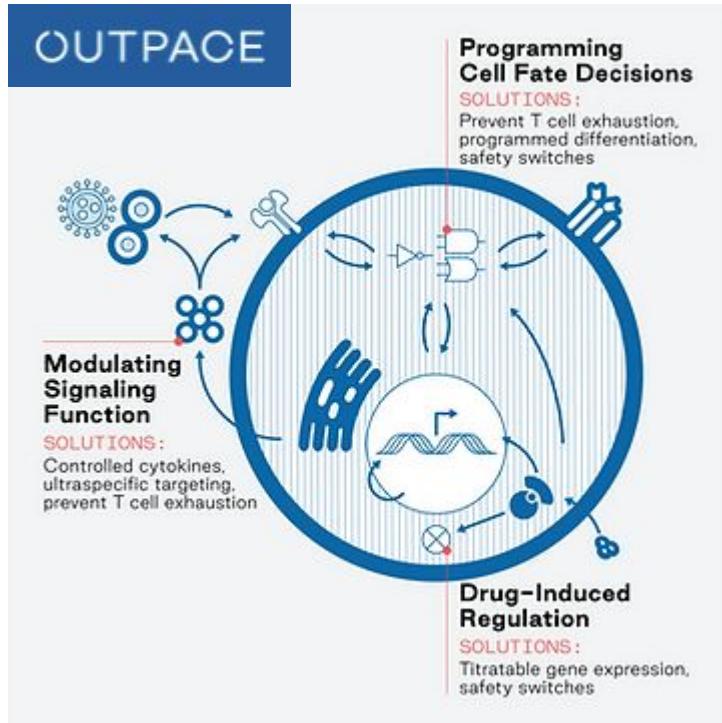
And their use to detect diseased cells



Or to accurately detect targets



And change the world



For the next lecture:

1. Read journal for the next lecture
 - a. Moderated by **group III**
2. Post-class assignment
Due a week from now

Next lecture:

From structure to function

