

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**

A hand holding a glowing sphere with a complex molecular structure inside, surrounded by a network of lines and nodes.

Week 10, Lecture 1

Putting it all together

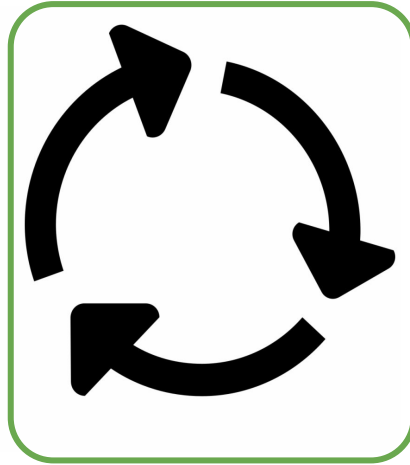
Learning Objectives

1. Evaluate the application of different protein engineering methods in test cases
2. Learn about NIH review panels and grant consideration

Four methods of protein engineering



Rational Design



Directed Evolution



De Novo Design



Machine Learning

Each method has its own advantages and disadvantages



uses prior knowledge, often structure guided to engineer proteins

Advantage	Disadvantage
We're building off of what works → higher chance of success	Limited to what we know
Simpler if you have a good guess	Limited by what exists in nature
Requires fewer resources	You need to know the structure



Each method has its own advantages and disadvantages

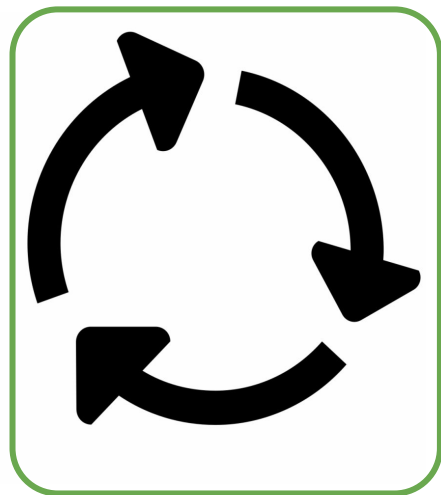


Notes from the class

- Easier to get started with
- Seems like a good starting point
- We're moving from "manual" rational design to computational ones
- It's more interpretable



Each method has its own advantages and disadvantages

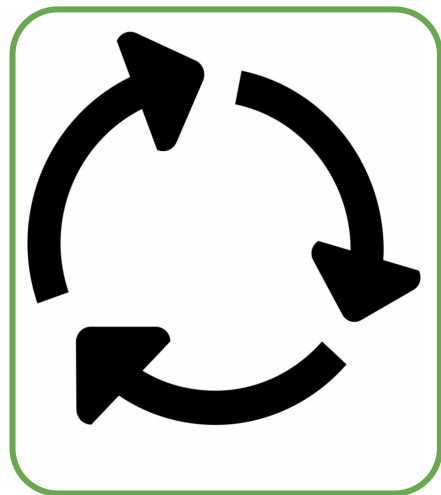


uses a process of mutation and selection,
inspired by evolution

Advantage	Disadvantage
High throughput and can test many things at once	Sequence space is very large and not everything can be sampled
Don't need prior knowledge	Is not interpretable (we don't know why things worked)
Can screen multiple features at once	We're not sure if we're getting the best result
Random mutations = casting a wider net to make sure things work	You need to have a selection/screening method and you have to have some minimal activity



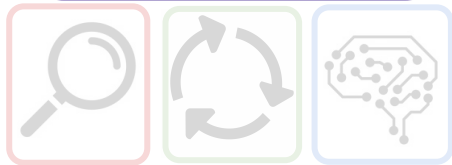
Each method has its own advantages and disadvantages



Notes from class:

- Seems like it is highly used as the last method for improvement in conjunction with other methods
- Continued directed evolution seems exciting
- Use of MSA and evolutionary information helps
- Can be connected with ML for sequence space sampling

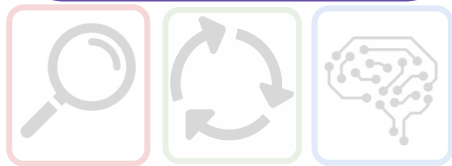
Each method has its own advantages and disadvantages



creates new proteins often by physics-based and heuristic methods

Advantage	Disadvantage
If it works, it generates really good proteins because it considers all the rules	Low success rate
Novelty = less chance of resistance/defense	novel structures → may cause unknown problems downstream
Can create novel function/structure and is not limited to what we know	While not dependent on prior knowledge, still needs the rules
Great for specificity and full control	

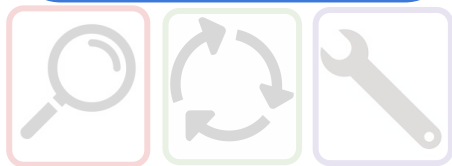
Each method has its own advantages and disadvantages



Notes from class:

- Can be connected with ML to help design or folding prediction
- For a completely new protein, we're not sure about the downstream effects (it's very unknown)
- But the new protein also makes it more selective and less likely to bind to other things

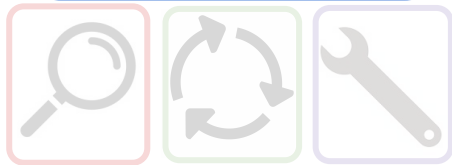
Each method has its own advantages and disadvantages



learns from large databases for prediction, classification, generation

Advantage	Disadvantage
The computational power is getting better	Needs large amount of data
It can uncover new patterns and rules that we can't	Can't be specific/target-based (great for general cases)
Fully reproducible	Can sample new sequences but in the neighborhood of what exist
Can take in multiple considerations into account	

Each method has its own advantages and disadvantages

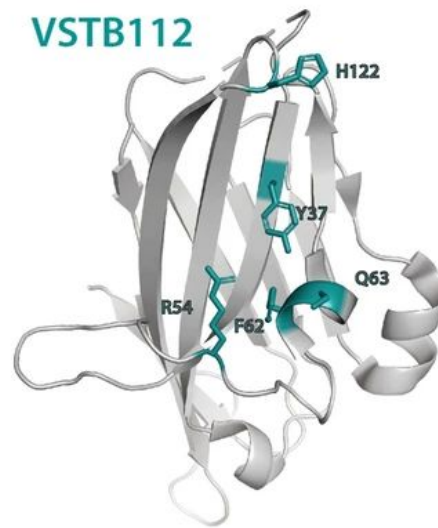
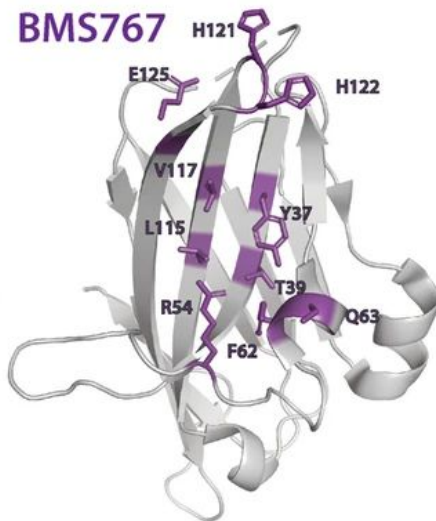
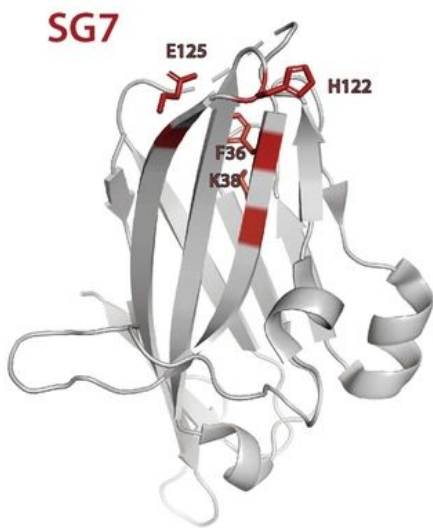


Notes from class:

- It's all about loss function
- ML is the next big thing
- Data is very important and we need more of it
- Hallucination was mind-blowing

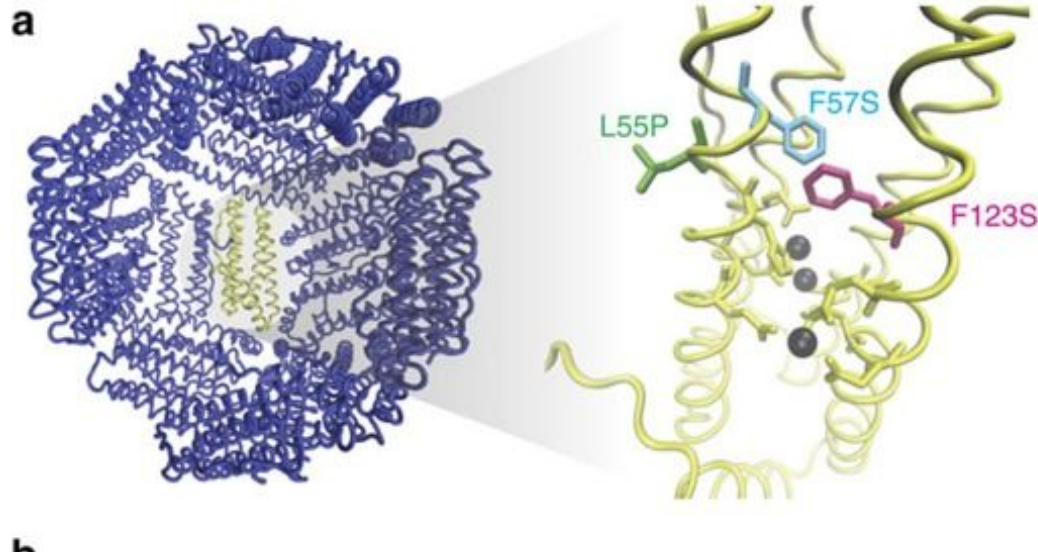
In class activity

Guess which method – scenario 1



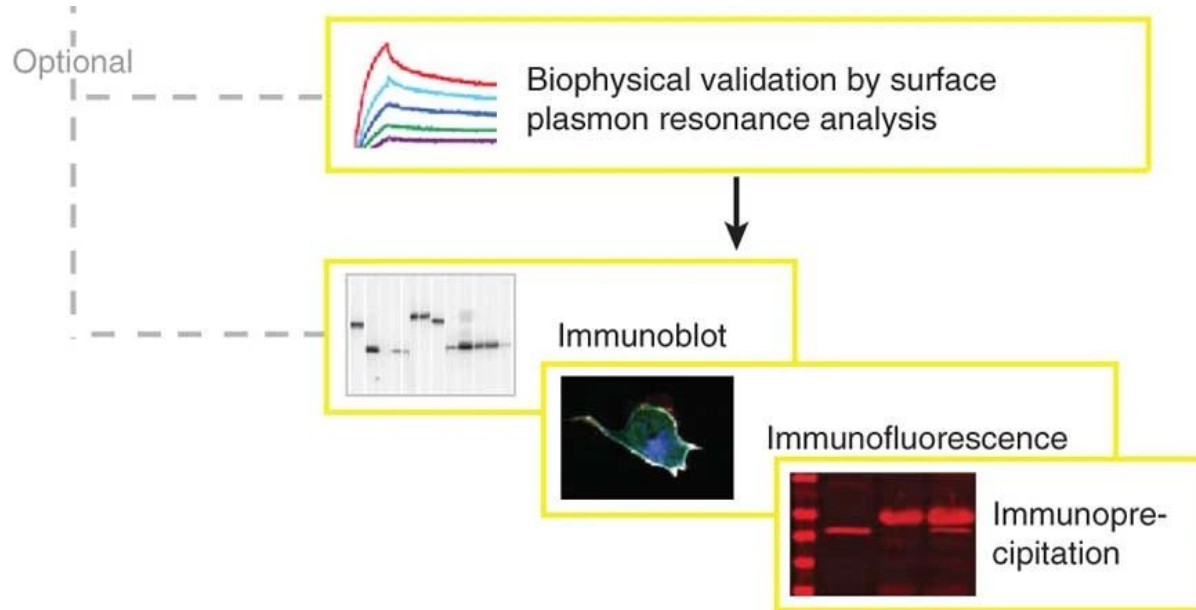
In class activity

Guess which method – scenario 2



In class activity

Guess which method – scenario 3



A quick overview of NIH review panel

Who's on the panel:

Session chair

Reviewers

A quick overview of NIH review panel

What do they discuss:

1. Conflict of interest

A quick overview of NIH review panel

What do they discuss:

1. Conflict of interest
2. Impact scores
 - Significance
 - Innovation
 - Choice of methods
 - Aims
 - Impact
 - Environment
 - Researcher
 - Other documents

A quick overview of NIH review panel

What do they discuss:

1. Conflict of interest
2. **Impact scores**
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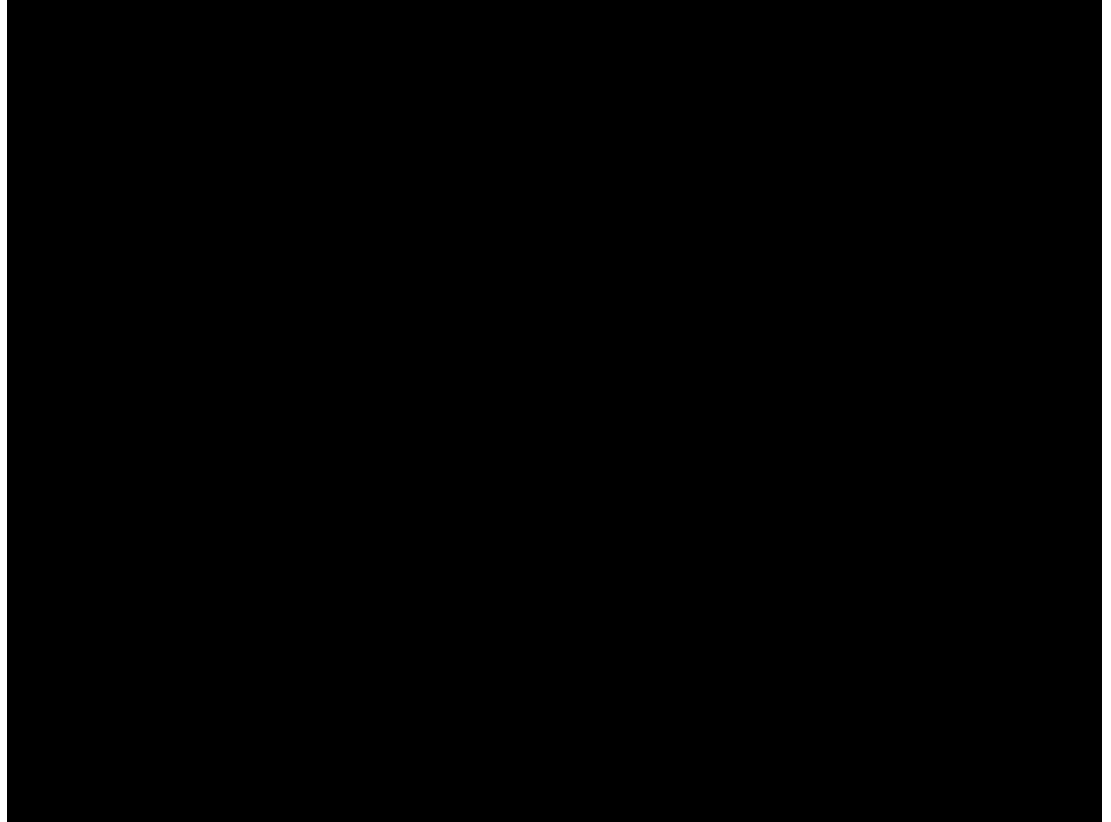
A quick overview of NIH review panel

What do they discuss:

1. Conflict of interest
2. Impact scores
3. Discussion and final score

Inside a mock review session

Minutes 11:11-19
from [NIH mock panel](#)



What'll happen in the next lecture

1. We'll randomly pick a name
2. The person will leave the room
3. The reviewers will share their score and discuss
4. We ask expert opinions from others
5. We mark the final scores
6. We continue until we finish with everyone's application

I'll share the comments in peer review + final scores with everyone

Final grades

Will be reported by Tuesday evening next week

Participation in class	15%
Journal club moderation	15%
Project proposal and write up	30%
Peer review of projects	20%
Assignments	20%
Total	100%

Resources

- Github with all the lecture slides, assignments, and videos
- Zotero library for all the references

Next lecture:
Review!

