Project topics

CS/BioE/CME/Biophys/BMI 279
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Ron Dror

Project Guidelines

- **You are welcome (and encouraged) to pick something that is not mentioned in this presentation**
- Projects should involve structure or spatial organization at a molecular or cellular level
  - Machine learning projects are great, *as long as 3D structure or spatial organization factor in explicitly*
  - Image analysis is great, as long as images are at a molecular or cellular level

Project Guidelines

- Projects can be methods-focused and/or application-focused
  - I.e., you can code/modify software, or apply existing software to a biological problem
  - You could also carefully compare the performance of several algorithms or software packages
- See project assignment sheet on website for details on project writeup and other information
  - Group projects, overlaps with projects for other classes, etc.
  - We expect about as much work (per person) as for the last two assignments.

Protein structure prediction

- Sample codes and servers:
  - Rosetta/PyRosetta (or Robetta webserver)
  - Phyre2 (web server)
  - I-Tasser (web server or download code)
  - Modeller (web server called ModWeb, or download code)
  - SWISS-MODEL (web server)
- Recent deep-learning breakthroughs in protein structure prediction: AlphaFold2 and RoseTTAFold
  - ColabFold package provides a fasts Python-based interface for using both:
    - https://github.com/sokrypton/ColabFold
    - https://www.biorxiv.org/content/10.1101/2021.08.15.456425v2
  - Robbeta webserver allows use of RoseTTAFold, but multiple sequence alignments must be provided (computed separately)

Protein structure prediction

- Topics of interest include
  - Structure prediction methodology
  - Structures of proteins of interest
  - Effects of protein modification (e.g., mutation, phosphorylation)

- Related: RNA structure prediction
  - RNAComposer web server: http://rnacomposer.cs.put.poznan.pl/

Molecular dynamics simulation

- Focus either on simulations of particular molecules, or on methods (e.g., molecular dynamics vs. Monte Carlo)
- Existing software
  - GROMACS, Desmond, NAMD, AMBER (PMEMD module): designed for performance.
    - GROMACS, Desmond, and NAMD are free (for academic use); AMBER is not
    - Desmond can be run through the Schrodinger Maestro graphical user interface
  - Tinker—slow, but designed to be easy to work with the code (also free)
  - Most of these are designed for Linux, but Windows and Mac executables are available for Tinker
- You can write your own code
  - Don’t resubmit code you wrote for BMI/BIOE/GENE 214/CS 274, but you can build on it. For example, increase speed (fast electrostatics methods), improve integrators, add restraints/constraints or other features. Or you could use Tinker for this

Protein Design

- Rosetta software is free for academic use
- Rosetta Design server: http://rosettadesign.med.unc.edu/

Image analysis

- Image classification, segmentation, or denoising; disease diagnosis; cell counting; measurement of protein concentration/localization, and detection of colocalized proteins of different types; or other useful tasks
  - *Project should involve cellular or molecular images* (as opposed to traditional medical MRI or x-ray images, for example)
- Useful software:
  - Matlab (general-purpose; available on LTS machines)
  - ImageJ (free, widely used for biological image processing)
  - CellProfiler (free, includes machine learning applications)
- Or write your own software
  - For machine learning projects, consider using libraries such as TensorFlow or PyTorch

Image analysis

- Sample image sets:
  - https://data.broadinstitute.org/bbbc/
  - http://www.cellprofiler.org/
  - https://www.kaggle.com/iarunava/cell-images-for-detecting-malaria
  - https://www.kaggle.com/paultimothymooney/blood-cells
  - https://www.proteinatlas.org/about/download
  - Please let me know of other good ones you find!

Reaction-diffusion simulation

- Use existing codes:
  - MCell, Smoldyn, Simmune
  - For MCell, consider using CellOrganizer or CellBlender to make models or renderings
- Write your own code
- Build a model of a cellular process, or consider methodological issues

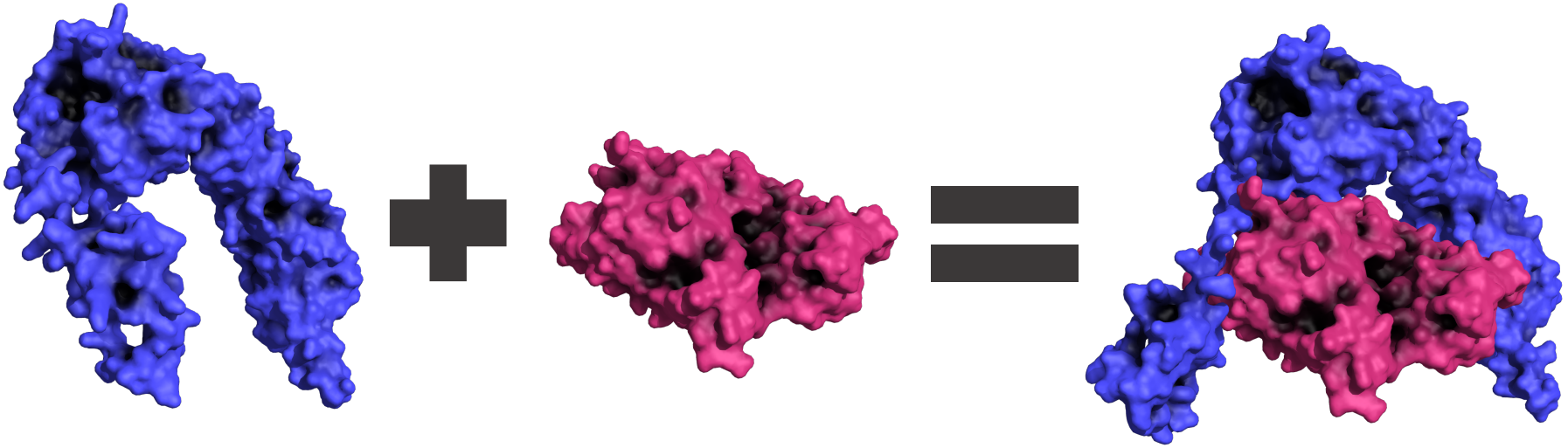
Ligand docking and virtual screening

- Established, free codes and web servers:
  - Autodock Vina
  - SwissDock
- Rosetta Dock (newer; can use in PyRosetta framework)
- GLIDE: Powerful commercial software, for which Stanford now has a university-wide license
  - See https://library.stanford.edu/science/software/schrodinger
  - You can also access other structural modeling software from the same company (Schrodinger); see the link above

- ZINC ligand library: http://zinc.docking.org/

- Related: Protein–peptide docking (e.g., with FlexPepDock or Backrub servers) or protein–protein docking (e.g., with ZDock, Haddock)

Protein-protein and peptide docking



- Starting with existing structures:
  - ZDock, Haddock (use physics-based scoring functions)
- Starting without existing structures:
  - RoseTTAFold (or AlphaFold2)
- Related: docking peptides to a target protein
  - FlexPepDock or Backrub servers. You could also try RoseTTAFold or AlphaFold2

Crystallography

- Structure factors (i.e., primary crystallographic data) are often available in PDB.
  - See http://www.rcsb.org/pdb/101/static101.do?p=education_discussion/Looking-at-Structures/structurefactors.html
- CNS software (http://cns-online.org/v1.3/)

Single-particle electron microscopy

- Software packages:
  - XMIPP: has a graphical user interface, somewhat easier to use
  - Relion: more mathematically sophisticated (Bayesian methods)
- Most use MPI, which complicates installation
- Alternative: implement something yourself
  - Work in two dimensions for simplicity
  - Or tackle early stages in single-particle EM pipeline, such as particle picking

Machine learning

- Protein secondary structure prediction from sequence
  - Some data sets: https://www.princeton.edu/~jzthree/datasets/ICML2014/
- Machine learning on cellular/molecular images (see previous slide)
- ATOM3D
  - A collection of ML tasks and datasets involving 3D molecular structure: https://www.atom3d.ai/
- Learning force fields
  - ANI-1ccx and ANI-1x data sets: https://www.nature.com/articles/s41597-020-0473-z

Other topics

- CellPack (http://www.autopack.org): packing proteins into a cell
- Coarse-grained simulation (e.g., assembly of a viral capsid; consider HOOMD-blue software)
- EVFold (http://evfold.org/): protein structure prediction based on covariation across sequences
  - Also see “Distance-based protein folding powered by deep learning” (https://www.pnas.org/content/116/34/16856.short)