11: Catchup II

Machine Learning and Real-world Data (MLRD)

Ann Copestake

Lent 2020

Last session: HMM in a biological application

- In the last session, we used an HMM as a way of approximating some aspects of protein structure.
- Today: catchup session 2.
- Bit more about cell membranes and proteins.
- Data and domain knowledge.
- Very brief sketch of protein structure determination:
  - including **gamification** and **Monte Carlo methods**: related ideas are used in many very different machine learning applications.
  - and a very little about AlphaFold.

What happens in catchup sessions?

- Lecture and demonstrated session scheduled as in normal session.
- Lecture material is non-examinable.
- Time for you to catch-up in demonstrated sessions or attempt some starred ticks.
- Demonstrators help as usual.

A biological application: the data

```
#MNQGKIWTVVNPAIGIPALLGSVTVIAILVHLAILSHTTWFPAYWQGGVKKAA
 iiiiiiiiiiiiiiMMMMMMMMMMMMMMMMMMMMMoooooooooooooooooo
```

- top line records the amino acid sequence (one character per amino acid)
- bottom line shows the states:
    - i: inside the cell
    - M: within the cell membrane
    - o: outside the cell

Domain knowledge

Is this possible?

```
#MNQGKIWTVVNPAIGIPALLGSVTVIAILVHLAILSHTTWFPAYWQGGVKKAA
 iiiiiiiiiiiiiiiiiiiiioooooooooooooooooooooooooooooooo
```

Domain knowledge

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#MNQGKIWTVVNPAIGIPALLGSVTVIAILVHLAILSHTTWFPAYWQGGVKKAA
 iiiiiiiiiiiiiiiiiiiiioooooooooooooooooooooooooooooooo
```

What about?

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#MNQGKIWTVVNPAIGIPALLGSVTVIAILVHLAILSHTTWFPAYWQGGVKKAA
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```
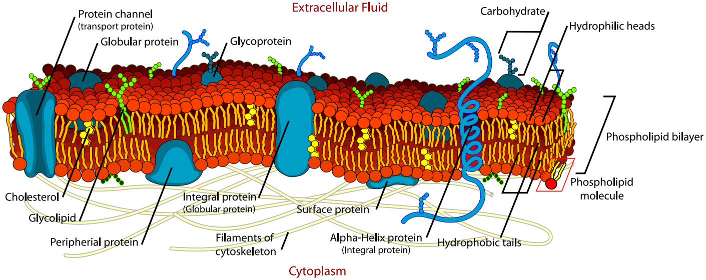

And this?

```
#MNQGKIWTVVNPAIGIPALLGSVTVIAILVHLAILSHTTWFPAYWQGGVKKAA
 iiiiiiiiiiiiiiMMMMMMMMMMMMMMMMMMMMMiiiiiiiiiiiiiiiiii
```

Cell membranes and proteins



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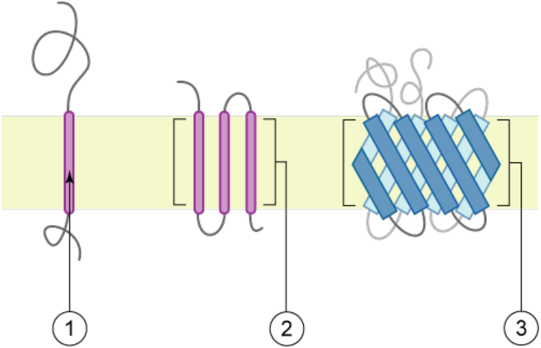
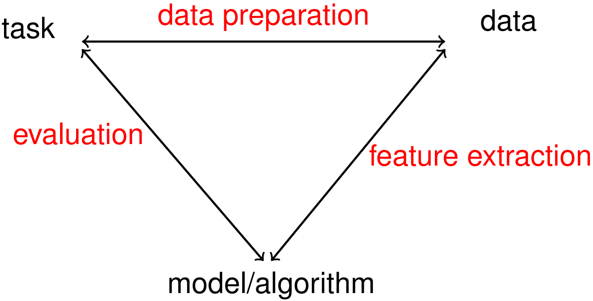
Transmembrane protein: schematic diagram



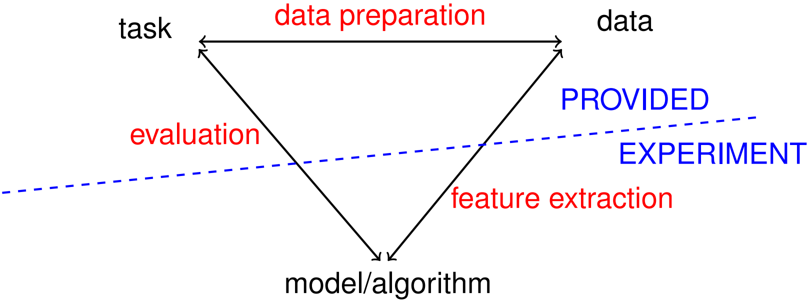
1. a single transmembrane α-helix (bitopic membrane protein)
2. a polytopic transmembrane α-helical protein
3. a polytopic transmembrane β-sheet protein

By Foobar - self-made by Foobar, CC BY 2.5, https://commons.wikimedia.org/w/index.php?curid=802476

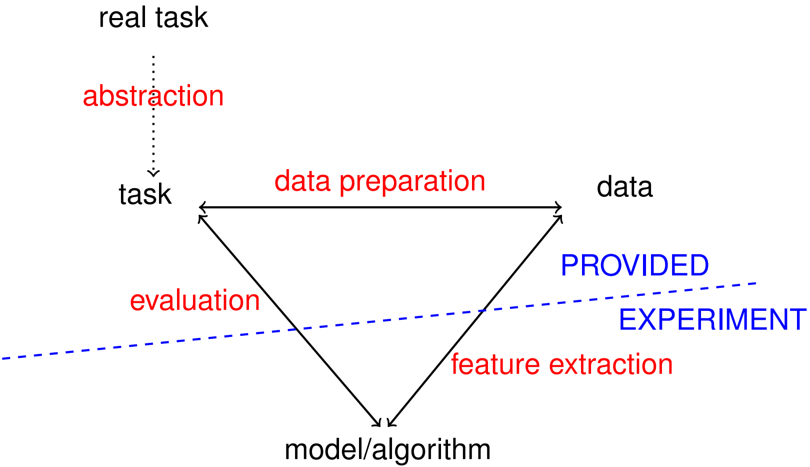
Machine learning, abstractly



Standard tasks



And actually . . .



Tasks, data and domain knowledge

- Most ML researchers and textbooks ignore issues relating to data collection and task definition.
- Lots of examples of tasks that bear little resemblance to real applications.
- Real data is noisy and sometimes systematically biased.
    - Deep learning techniques are extremely good at exploiting data biases.

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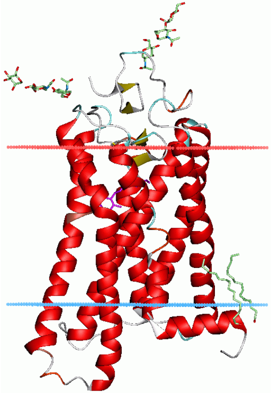
- Domain expertise is required to define the task and evaluation and to collect and check data.
- ML expert plus domain expert: is ML approach modelling constraints? HMMs and membrane proteins?

Transmembrane protein example: (bovine) rhodopsin



- rhodopsin: one of the visual pigments
- accurate structure via x-ray crystallography: difficult and time-consuming, membrane location not determined

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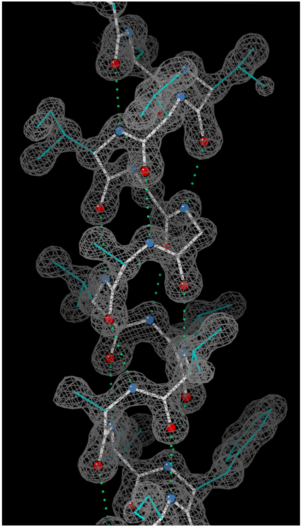
Protein structure

- Levels of structure:
  - Primary structure: sequence of amino acid residues.
  - Secondary structure: highly regular substructures, especially α-helix, β-sheet.
  - Tertiary structure: full 3-D structure.
- In the cell: an amino acid sequence (as encoded by DNA) is produced and folds itself into a protein.
- Secondary and tertiary structure crucial for protein to operate correctly.
- Some diseases thought to be caused by problems in protein folding.

Alpha helix



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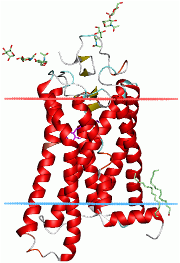
Bovine rhodopsin



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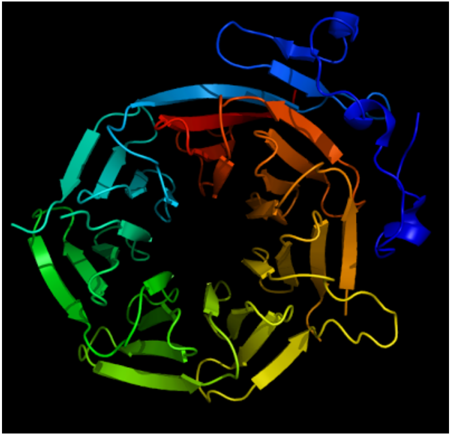
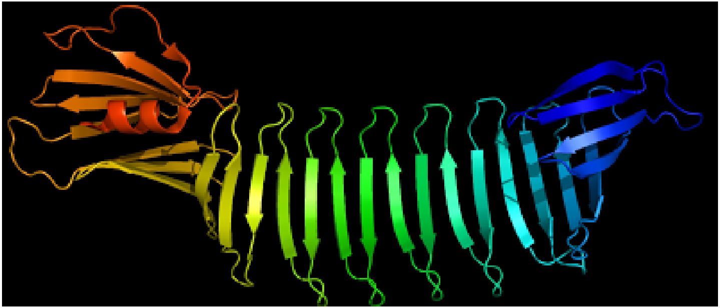
- found in the rods in the retina of the eye
- a bundle of seven helices crossing the membrane (membrane surfaces marked by horizontal lines)
- supports a molecule of **retinal**, which changes structure when exposed to light, also changing the protein structure, initiating the visual pathway

7-bladed propeller fold (found naturally)



http://beautifulproteins.blogspot.co.uk/

Peptide self-assembly mimic scaffold (an engineered protein)



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Protein folding

- Anfinsen's hypothesis: the structure a protein forms in nature is the **global minimum** of the free energy and is determined by the animo acid sequence.
- Levinthal's paradox: protein folding takes milliseconds — not enough time to explore the space and find the global minimum. Therefore kinetic function must be important.

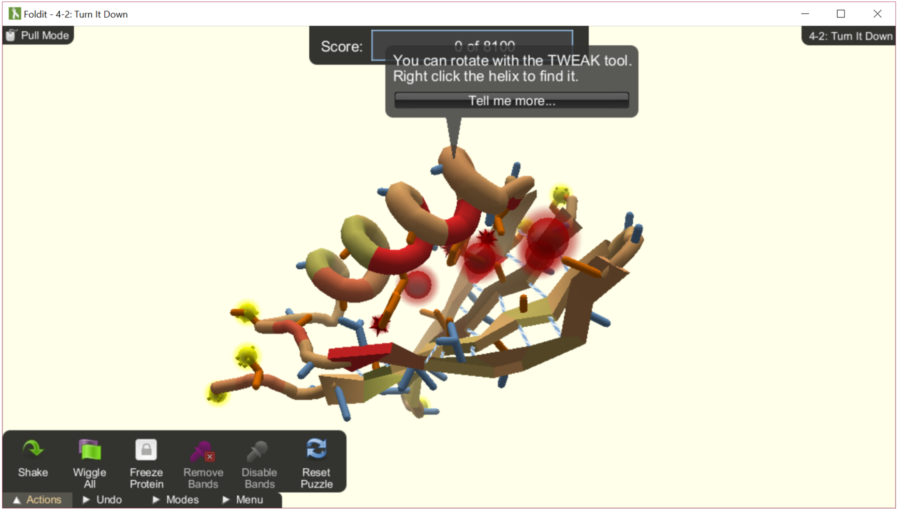
Protein structure determination and prediction

- Primary structure may be determined directly or from DNA sequencing: relatively easy.
- Secondary and tertiary structure can be determined by x-ray crystallography and other direct methods, but difficult, expensive, time-consuming.
- Given amino acid sequence, can we predict the structure? i.e., determine how the protein will fold.
- Secondary structure prediction is relatively tractable: various prediction methods, including HMMs.
- Tertiary structure prediction is very difficult.

Protein tertiary structure prediction

- Modelling protein structure fully is hugely computationally expensive. Ideally, should model all the water molecules too …
- Several approaches, including:
  1. Molecular Dynamics (MD): modelling chemistry. folding@home: use home computers to run simulations.
  2. Foldit: get lots of humans to work on the problem (an example of **gamification**). `https://fold.it/portal/`
  3. Use **Monte Carlo methods** (repeated random sampling) to explore possibilities.
  4. Use additional information either a) previously determined structures or b) **evolutionary coupling** (e.g., DeepMind's AlphaFold)

2: Foldit: combined human-computer intelligence



Foldit - 4-2: Turn It Down

Score: 0 of 8100

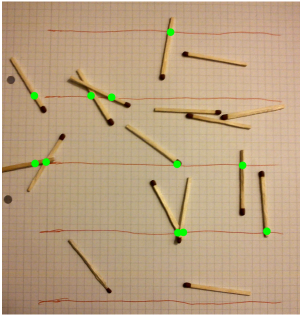
You can rotate with the TWEAK tool. Right click the helix to find it.

3: Monte Carlo methods in protein structure prediction

- Objective: find lowest energy state of protein.
- Idea: start with secondary structure, try (pseudo)random move, see if result is lower energy and repeat.
- Problem: **local minima** — locally good move may not be part of best solution.
- So: also sometimes accept a move that increases energy.
- Specific approach **Metropolis-Hastings**: a type of **Markov Chain Monte Carlo** method (e.g., **Rosetta**).

Monte Carlo methods in general

- Using random sampling to solve intractable numerical problems.
- Buffon's needle problem used for estimating π ('experiment' by Lazzarini 1901).



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Monte Carlo methods

- Physicists developed modern Monte Carlo methods at Los Alamos: programmed into ENIAC by von Neumann.
- Bayesian statistical inference not until 1993 (Gordon et al): essential for many modern machine learning approaches.
- Gibbs sampling is a special case of Metropolis-Hastings.
- Much more about this in later courses.
- Practical introduction by Geyer in

  http://www.mcmchandbook.net/HandbookTableofContents.html

4: Using additional information in protein folding

1. use previously determined structures of similar proteins.
2. **evolutionary couplings**: databases of proteins in an evolutionary relationship, mutations tend to be correlated if amino acids are physically close in folded protein:
   - generate likely contacts (nowadays using deep learning), feed info into folding program;
   - Deep Mind's AlphaFold: produce full probability distribution of distances, statistical potential function which is directly minimized by **gradient descent**.
     `https://deepmind.com/blog/alphafold/`
     `https://moalquraishi.wordpress.com/2018/12/09/alphafold-casp13-what-just-happened/`
     (updated version in Bioinformatics)

Conclusions

Protein structure prediction is still unsolved.
Possible approaches involve several techniques used elsewhere in machine learning:

- gamification: an example of human-computer collaboration
- Monte Carlo methods
- using additional information sources (domain knowledge)

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General discussion in deep learning: constraints/priors vs **tabula rasa** approaches (also question as to what counts as tabula rasa . . .)