Biological Sequence Analysis (Ch 1. Introduction)

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Motivation of computational biology

- Organize, classify and parse the sequence data
- Behind the string of bases or amino acids is the whole complexity of molecular biology
- Capturing some of this complexity
- Direct experimentation is the most reliable way to determine a biological molecule's structure or function
- Obtaining DNA sequence of the gene for an RNA or protein is far easier than direct experimentation
- Biological information can be inferred from sequence alone.
- HMM is used for statistical analysis of sequence

Sequence similarity, homology, and alignment

- Two sequences are homologous
  - New sequences are adapted from pre-existing sequences rather than invented de novo.
  - Nature is a tinkerer and not an inventor [Jacob 1977]
  - We are transforming information by homology.
- Alignment between two strings
  - Evolving sequences accumulate insertions, deletions, substitutions
  - Scoring of alignment can be very complex.
  - Probabilistic modeling methods

Overview of the book

- Pairwise alignment
  - Pairwise alignment (2),
  - Markov chains and hidden Markov models (3),
  - Pairwise alignment using HMMs (4)
- Multiple alignment
  - Profile HMMs for sequence families (5)
  - Multiple sequence alignment methods (6)
- Phylogenetic trees
  - Building phylogenetic trees (7)
  - A probabilistic approach to phylogeny (8)
- RNA structure
  - Transformational grammars (9)
  - RNS structure analysis (10)

Probabilities and probabilistic models (1)

- Model: a system that simulates the objects (or sequences) under consideration
- Probabilistic model: one that produces different outcomes with different probabilities
  - (Example 1) A model of a roll of a dice have six parameters
  - (Example 2) A model of a sequence of three consecutive rolls [1, 6, 3]
- Biological sequences: a strings from a finite alphabet (4 nucleotides or 20 amino acids)

Probabilities and probabilistic models (2)

- Maximum likelihood estimation : maximize $P(D \mid \theta)$
- Overfitting: from a limited amount of data the model is well adapted to the training data but not generalize well to a new data (Ex) [*TTT*] : *p(H)*=0, *p(T)*=1
- Conditional, joint and marginal probabilities
  - Probability of rolling *i* given dice 1 : $p(i \mid D_1)$
  - Probability of picking dice j and rolling an *i* :

$$p(i, D_j) = p(D_j)\, p(i \mid D_j)$$

  - Probability of rolling *i* : $p(i) = \sum_j p(D_j)\, p(i \mid D_j)$

Probabilities and probabilistic models (3)

- Bayes theorem and model comparison
  - Testing of fair dice : Pick a dice at random and roll it for 3 times,

$$p(\textit{unfair dice} \mid (5,5,5)) = \frac{p((5,5,5) \mid \textit{unfair dice})\, p(\textit{unfair dice})}{p((5,5,5))}$$

  - Protein sequence: extracellular proteins have a slightly different amino acid composition than intracellullar proteins.

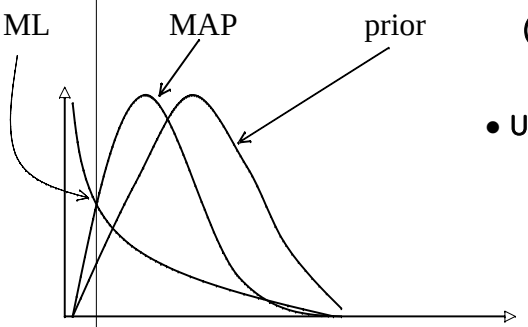
    Test whether a new sequence is extracelluar or not:

$$p(ext \mid x) = \frac{p(x \mid ext)\, p(ext)}{p(x)} = \frac{p^{ext} \prod_i q_{x_i}^{ext}}{p(x)}$$

Probabilities and probabilistic models (4)

- Bayes theorem and parameter estimation (MAP)

$$p(\theta \mid D) = \frac{p(\theta)\, p(D \mid \theta)}{\int_{\theta'} p(\theta')\, p(D \mid \theta')}$$



(E.g.) Roll a dice to have (1,3,4,2,4,6,2,1,2,2):

MLE (P5)=0

- Use of pseudo-count for the insufficient data