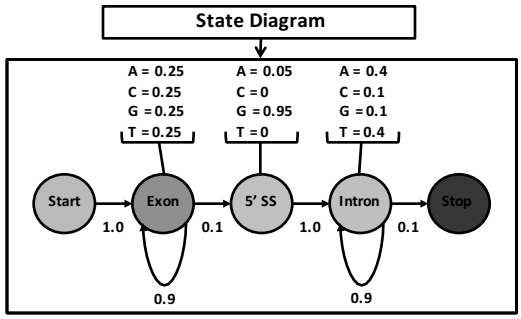
What is a Hidden Markov Model?

- A **Hidden Markov Model (HMM)** is a type of machine learning algorithm.
- With respect to genome annotation, HMMs label individual nucleotides with a ***nucleotide type***. Possible nucleotide types include:
  - Introns
  - Exons
  - Splice Sites (3' and 5')
- HMMs are used in speech recognition, facial recognition and many other applications.

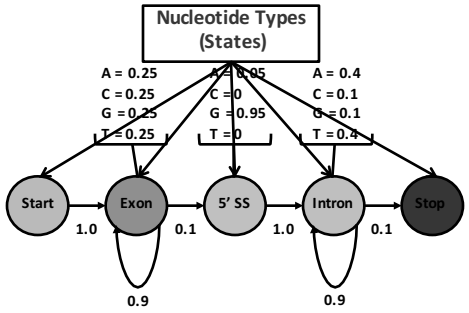
HMM Probabilities

- The probability of switching from one nucleotide type to another (ex. Exon → Intron) is called a ***transition probability.***
- The probability of observing a nucleotide (A, T, C, G) that is of a certain nucleotide type (exon, intron, splice site) is called an ***emission probability***.
- Think of an emission probability as the probability of:
  - Observing an adenine in an exon
  - Observing an adenine in a splice site

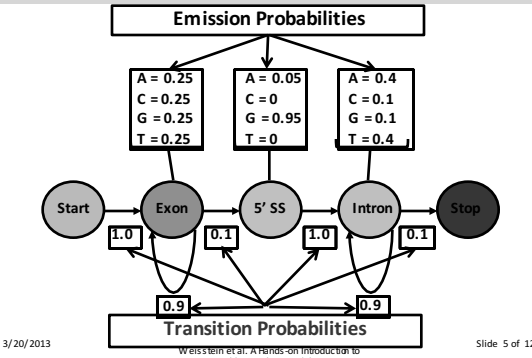
HMM Features



HMM Features



HMM Features



HMM Features

- A ***state path*** is the list of nucleotide type labels assigned to each nucleotide in the sequence.
- An HMM can produce many state paths for a single sequence.

Determining the Correct Splice Site

- A HMM will identify many splice sites for one sequence, but how do we measure which splice site is most likely to be correct?
- One way is to calculate the ***probability*** of each splice site.
- Splice site probabilities are calculated by multiplying all transition and emission probabilities in the state path.
- The splice site with the highest probability is most likely the correct splice site.

Determining the Correct Splice Site

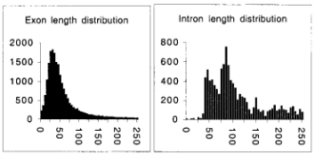
- Each state path has a different annotation for the location of the 5' splice site (white boxes).
- The ***likelihood*** of a splice site at a specific position of the sequence can be calculated by taking the probability of all state paths that assign the splice site to that position and dividing it by the sum of the probabilities of all state paths.

HMMs and Gene Prediction

- Hidden Markov Models are the core of a number of gene prediction algorithms.
  - GENSCAN
  - Augustus
  - GeneId
  - Genemark
  - GRAIL
  - Twinscan

HMMs and Gene Prediction

- Gene prediction algorithm accuracy depends partly on transition probabilities.
- Transition probabilities are calculated based on the distribution of exon and intron lengths in the training data.



Intron–exon structures of eukaryotic model organisms. Michael Deutsch and Manyuan Long* 199[illegible]

Conclusions

- Hidden Markov Models have proven to be useful for finding genes in unlabeled genomic sequence.
- Hidden Markov Models are machine learning algorithms that have ***nucleotide types***, ***transition probabilities*** and ***emission probabilities***.
- Hidden Markov Models label a series of observations with a ***state path***, and they can create multiple state paths.
- It is mathematically possible to determine state paths that are likely to be correct.

Challenges

- How do transition probabilities affect the length of predicted ORFs?
- How do emission probabilities for specific states affect the accuracy of splice site predictions?
- Do gene predictions give the final word on correct splice sites? What other pieces of information would be useful for annotating genes?