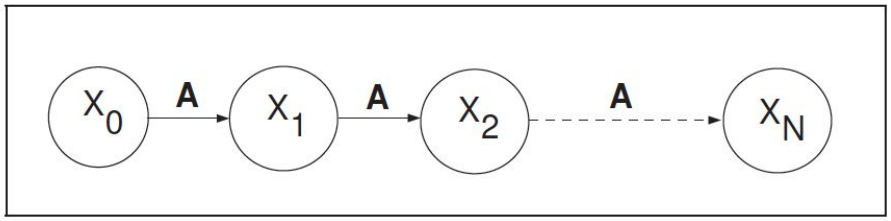
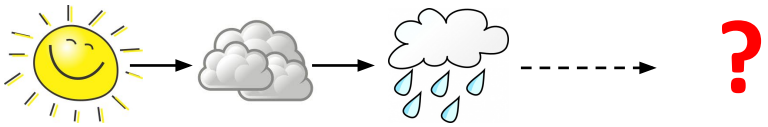
Introducing Hidden Markov Models
First – a Markov Model

A Markov Model is a chain-structured process where future states depend only on the present state, not on the sequence of events that preceded it.



The X at a given time is called the **state**.
The value of Xn depends only on Xn-1.



State : sunny cloudy rainy sunny ?

The Markov Model

State : sunny sunny rainy sunny

?

90 % sunny
10% rainy

State transition probability (table/graph)

(The probability of tomorrow's weather given today's weather)

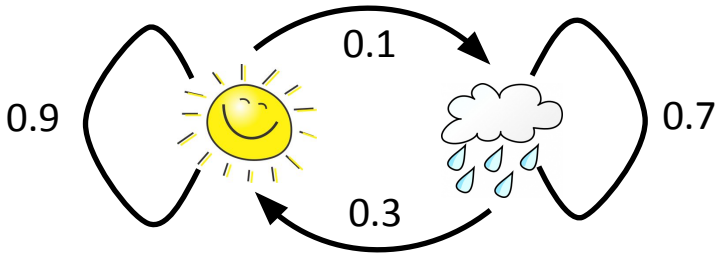
Output format 1:

Today	Tomorrow	Probability
sunny	sunny	0.9
sunny	rainy	0.1
rainy	sunny	0.3
rainy	rainy	0.7

Output format 2:

	sunny	rainy
sunny	0.9	0.1
rainy	0.3	0.7

Output format 3:



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The Markov Model

State : sunny cloudy rainy sunny ?

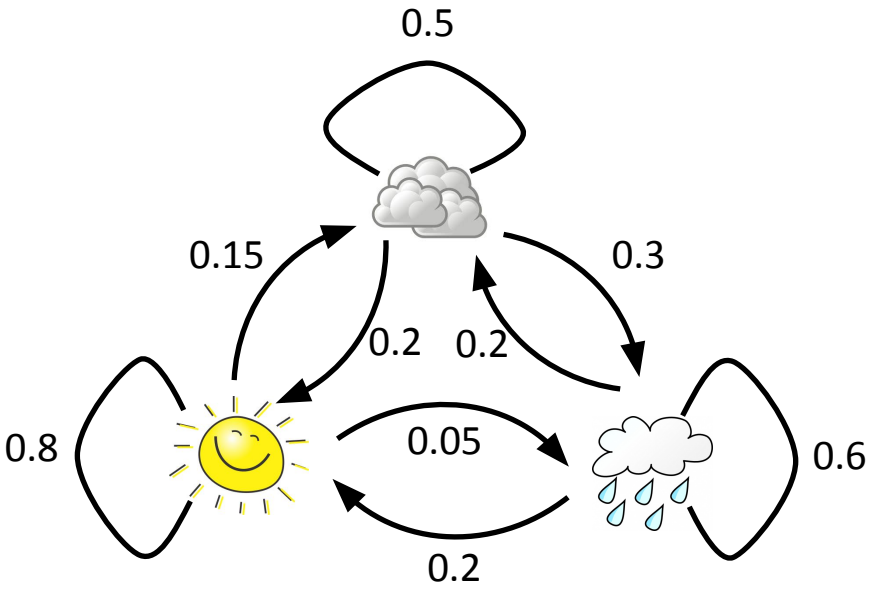
80 % sunny
15% cloudy
5% rainy

State transition probability (table/graph)

Output format 1:

Today	Tomorrow	Probability
sunny	sunny	0.8
sunny	rainy	0.05
sunny	cloudy	0.15
rainy	sunny	0.2
rainy	rainy	0.6
rainy	cloudy	0.2
cloudy	sunny	0.2
cloudy	rainy	0.3
cloudy	cloudy	0.5

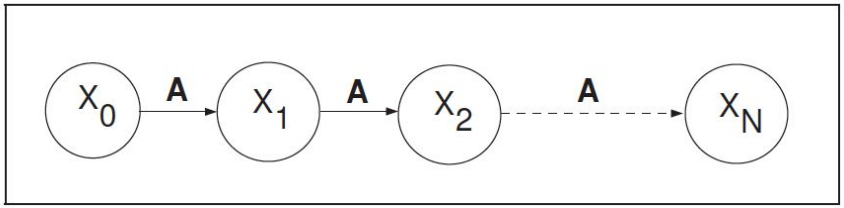
Output format 3:



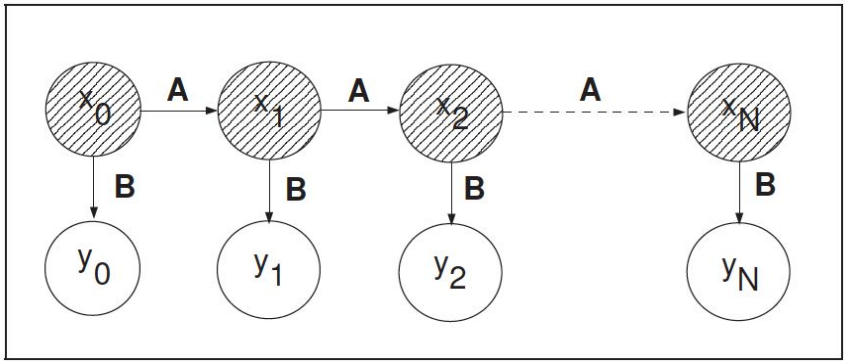
The Hidden Markov Model

A Hidden Markov Model is a Markov chain for which the state is only partially observable.

A Markov Model



A Hidden Markov Model



Hidden states : the (TRUE) states of a system that can be described by a Markov process (e.g., the weather).

Observed states : the states of the process that are `visible' (e.g., umbrella).

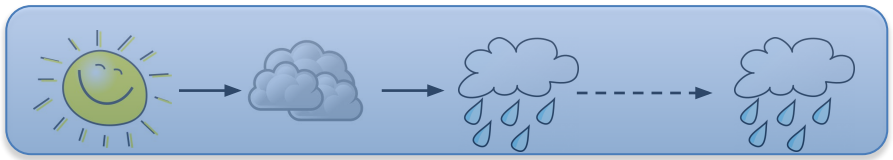
The Hidden Markov Model

	sunny	rainy	cloudy
sunny	0.8	0.05	0.15
rainy	0.2	0.6	0.2
cloudy	0.2	0.3	0.5

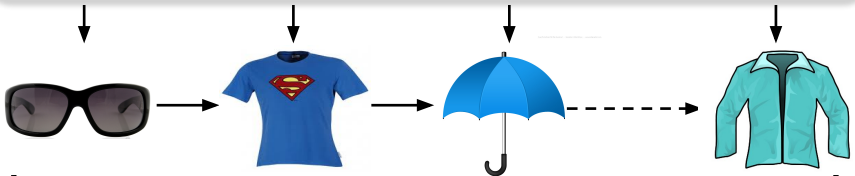
sum to 1

State transition probability table

Hidden States



Observed States



State emission probability table

The probability of observing a particular observable state given a particular hidden state

	sunglasses	T-shirt	umbrella	Jacket
sunny	0.4	0.4	0.1	0.1
rainy	0.1	0.1	0.5	0.3
cloudy	0.2	0.3	0.1	0.4

sum to 1

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The Hidden Markov Model

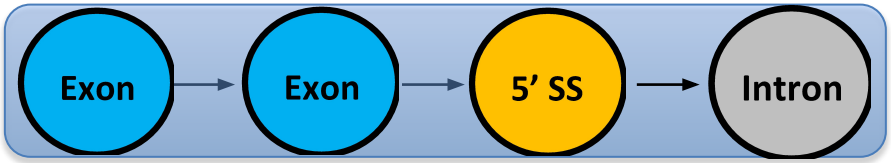
The probability of switching from one state type to another (ex. Exon - Intron).

	exon	5'SS	intron
exon	0.9	0.1	0
5'SS	0	0	1
intron	0	0	0.9

sum to 1

State transition probability table

Hidden States



Observed States

A → C → G → T

State emission probability table

The probability of observing a nucleotide (A, T, C, G) that is of a certain state (exon, intron, splice site)

	A	C	G	T
exon	0.25	0.25	0.25	0.25
5'SS	0	0	1	0
intron	0.4	0.1	0.1	0.4

sum to 1

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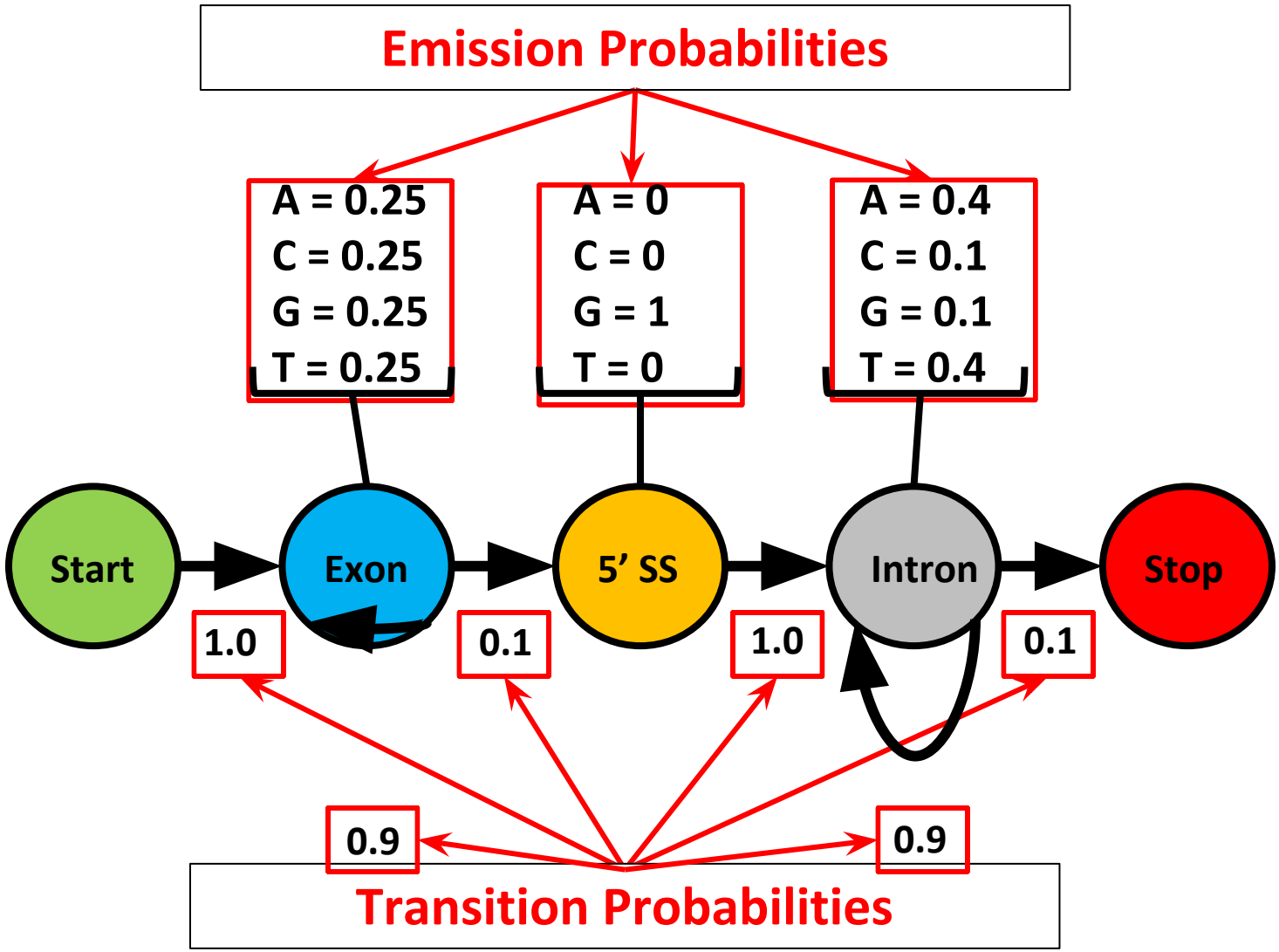
The Hidden Markov Model



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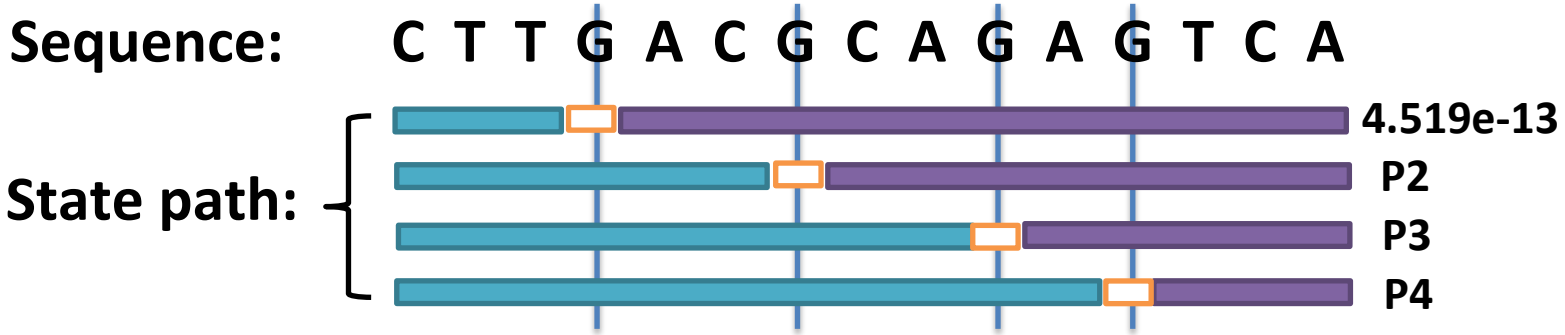
Splicing Site Prediction Using HMMs



To calculate the *probability* of each state path, multiply all transition and emission probabilities in the state path.

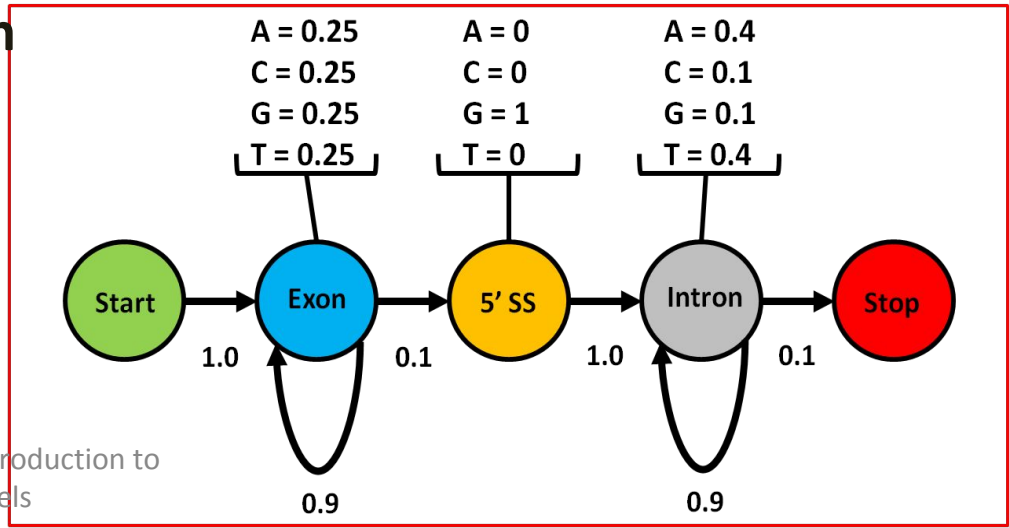
Emission = **(0.25^3)** x 1 x **(0.4x0.1x0.1x0.1x0.4x0.1x0.4x0.1x0.4x0.1x0.4)**

Transition = **1.0** x **(0.9^2)** x **0.1 x 1** x **(0.9^10)** x **0.1**

State path = **Emission** x **Transition**

= 1.6e-10 x 0.00282

= **4.519e-13**



The state path with the highest probability is most likely the correct state path.

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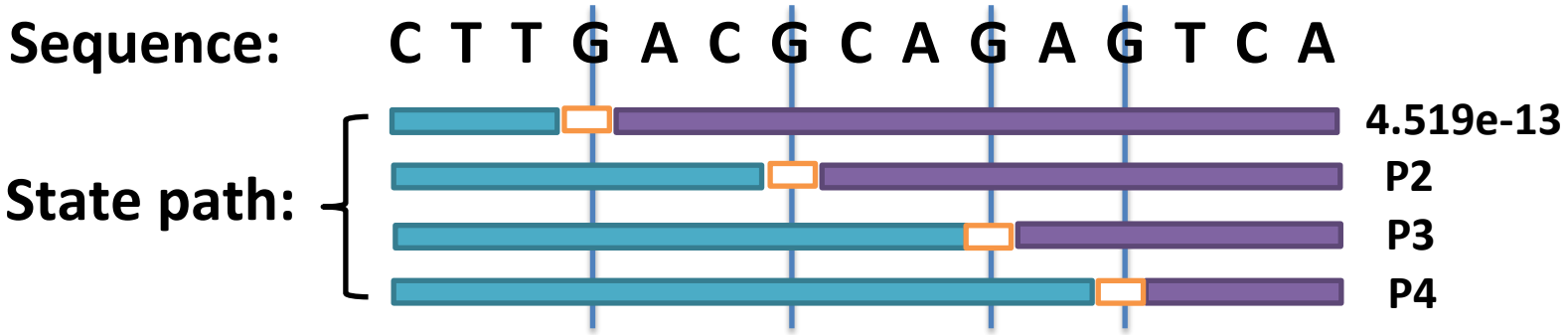
Identification of the Most Likely Splice Site

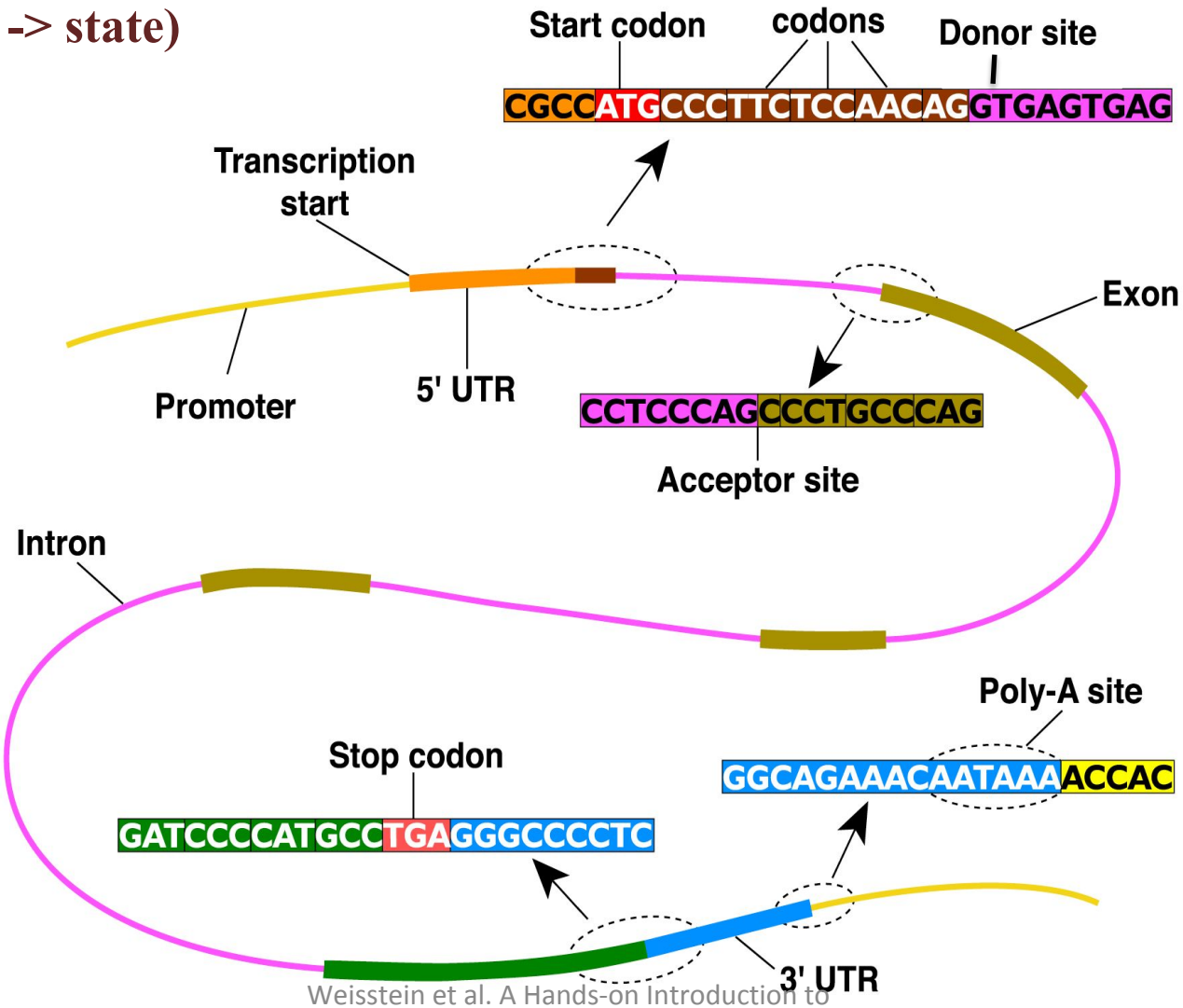


The *likelihood* of a splice site at a particular position can be calculated by taking the probability of a state path and dividing it by the sum of the probabilities of all state paths.

$$\textit{likelihood}\text{ of a splice site in state path \#1} = \frac{\text{4.519e-13}}{\text{4.519e-13 + P2 + P3 + P4}}$$

HMMs and Gene Prediction

(color -> state)

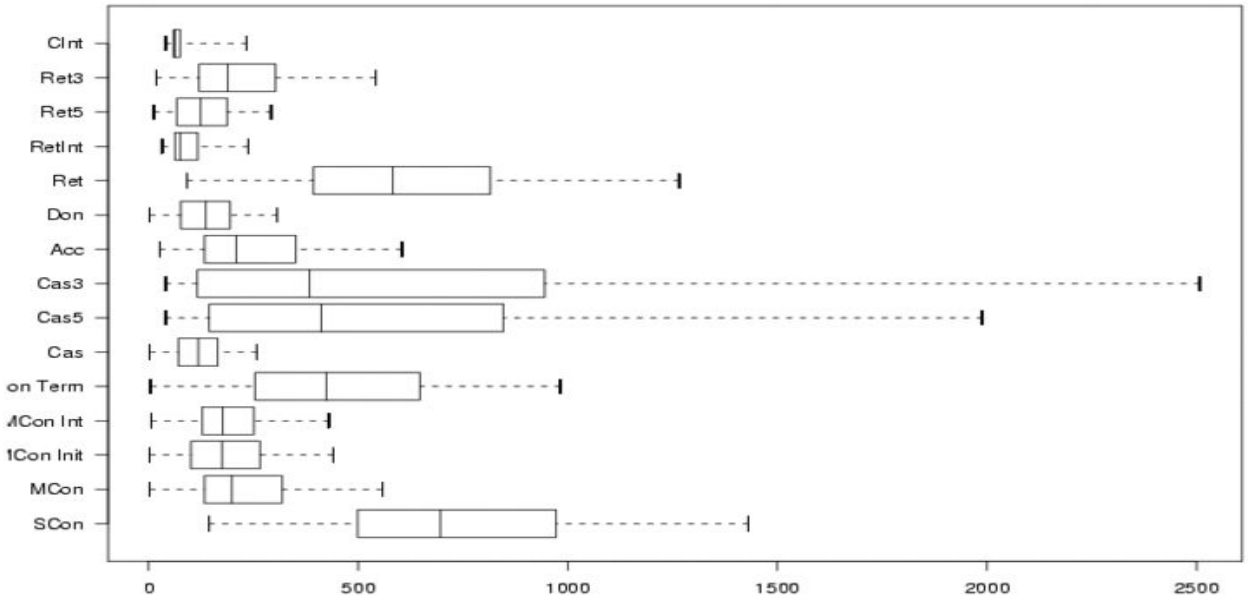


HMMs and Gene Prediction

The accuracy of HMM gene prediction depends on emission probabilities and transition probabilities.

Emission probabilities are calculated based on the base composition in that particular state in the training data.

Transition probabilities are calculated based on the average lengths of that particular state in the training data.



Exon length boxplots (DEDB, *Drosophila melanogaster* Exon Database)

Homework Question: How do transition probabilities affect the length of predicted ORFs?

Conclusions

- Hidden Markov Models have proven to be useful for finding genes in unlabeled genomic sequence. HMMs are the core of a number of gene prediction algorithms (such as Genscan, Genemark, Twinscan).

- Hidden Markov Models are machine learning algorithms that use ***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 which state path is most likely to be correct.