The Players

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The Hook

But if \( T \) is some other model we can also write

\[
p(s_0) = \sum_D \Pr(D|T) f(D)
\]

where

\[
f(D) = \frac{\Pr(D|B) \Theta(s(D) \geq s_0)}{\Pr(D|T)}
\]

We can sample sequences according to the model \( T \) and average their corresponding \( f(D) \) values. This is called importance sampling. If \( T \) is well chosen, only a few hundred sequences are needed for a good estimate.

The Tale

What model \( T \) should I use?

Toward calculating \( \Pr(D|T) \), we use a HMM/HBM forward algorithm with all the HMM/HBM-software transition and emission probabilities raised to some power \( 1/T \). Specifically, we define the model for parameter \( T \) as

\[
\Pr(D|T) \propto \Pr(D|B) \text{HMM}(D|p^{1/T})
\]

We compute the normalization factor

\[
Z(T) = \sum_D \Pr(D|B) \text{HMM}(D|p^{1/T})
\]

as we would compute \( \text{HMM}(D|p^{1/T}) \), but using the mean emission probability of an emitter \( E \)

\[
\sum_d \Pr(d|B)p_E(d)^{1/T}
\]

in lieu of any specific emission probability \( p_E(d)^{1/T} \) for letter \( d \).

To sample, we perform a stochastic backtrace through the \( Z(T) \) calculation. We sample the path as usual, and at each encounter with each emitter \( E \) we sample a letter \( d \), with probability

\[
\frac{\Pr(d|B)p_E(d)^{1/T}}{\sum_{d'} \Pr(d'|B)p_E(d')^{1/T}}
\]

For each sequence thus sampled, we compute

\[
f(D) = \frac{Z(T) \Theta(s(D) \geq s_0)}{\text{HMM}(D|p^{1/T})}
\]

The Set-Up

The statistical significance for some score \( s_0 \) is defined to be

\[
p(s_0) = \sum_D \Pr(D|B) \Theta(s(D) \geq s_0)
\]

where the sum is over sequences \( D \), \( \Pr(D|B) \) is the probability of the sequence under some background model \( B \), the score \( s(D) \) is from the software, and \( \Theta \) is a function that is 1 if its argument is true or 0 if it is not.

The Wire

Statistical significance of HMMER profile-HMM scores for a random module model of length \( M=100 \), scanning a sequence of length \( L=200 \).

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