

First order approximation about $p_{ic} = 0$ is

$$f(0) + f'(0) * (p_{ic} - 0) = p_{ic} \left(\left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right] \right)$$

Where

p_{ic} is the probability of a nonsense error at position i using codon c

p_j is the probability of a nonsense error at position j (using any codon)

$$f(p_{ic}) = \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\frac{p_{ic}}{1-p_{ic}} \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right]$$

So...

$$f(0) = \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right] \left[\frac{0}{1-0} \right]$$

$$f(0) = 0$$

$$\begin{aligned} f'(p_{ic}) &= \frac{\delta}{\delta p_{ic}} f(p_{ic}) = \frac{\delta}{\delta p_{ic}} \left(\left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\frac{p_{ic}}{1-p_{ic}} \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right] \right) \\ &= \left(\left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right] \right) \frac{\delta}{\delta p_{ic}} \left[\frac{p_{ic}}{1-p_{ic}} \right] \\ &= \left(\left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right] \right) \left[\frac{(1-p_{ic})(1) - p_{ic}(-1)}{(1-p_{ic})^2} \right] \\ &= \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right] \left[\frac{1}{(1-p_{ic})^2} \right] \end{aligned}$$

So...

$$\begin{aligned} f'(0) &= \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right] \left[\frac{1}{(1-0)^2} \right] \\ &= \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right] \end{aligned}$$

$$f''(p_{ic}) = \frac{\delta}{\delta p_{ic}} \left(\left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right] \left[\frac{1}{(1-p_{ic})^2} \right] \right)$$

$$f''(p_{ic}) = \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right] \frac{\delta}{\delta p_{ic}} \left[(1-p_{ic})^{-2} \right]$$

$$f''(p_{ic}) = \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right] \left[-2(1-p_{ic})^{-3}(-1) \right]$$

$$f''(p_{ic}) = \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right] \left[2(1-p_{ic})^{-3} \right]$$

So...

$$f''(0) = \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right] \left[2(1-0)^{-3} \right]$$

$$= 2 \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right]$$

Based on what we've talked about with the math, it may be possible that Mike meant to assume $p_{i+1} \approx p_{i+2} \approx \dots \approx p_n$. This feels a little questionable. They are all sufficiently close to 0, but approximating them all at once is suspect. For the first codon in a gene of length 400, p_j incorporates as many as 3^{399} different values.

Regardless, here is the approximation. To keep in the spirit of $p_j \neq p_{j+1}$, I will not simplify $\left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j}\right)\right]$ to $\frac{1}{(1-p_j)^{n-(i+1)}}$, though the calculation actually comes out the same either way.

The final result, the approximation about $p_{i+1}, \dots, p_n \approx 0$ is

$$f(p_j) \approx \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\frac{p_{ic}}{1-p_{ic}} \right] + ((i+1) - n) \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\frac{p_{ic}}{1-p_{ic}} \right] (p_j)$$

$$f(p_j) \approx f(0) + (f(0))(p_j)((i+1) - n)$$

I'm concerned about that last p_j term that is added to the first order term. What is that? We approximated around $p_{i+1} \approx p_{i+2} \approx \dots \approx p_n$

$$f(p_j) = \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\frac{p_{ic}}{1-p_{ic}} \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right]$$

So...

$$f(0) = \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\frac{p_{ic}}{1-p_{ic}} \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-0} \right) \right]$$

$$f(0) = \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\frac{p_{ic}}{1-p_{ic}} \right]$$

$$f'(p_j) = \frac{\delta}{\delta p_j} \left(\left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\frac{p_{ic}}{1-p_{ic}} \right] \left[\prod_{j=i+1}^n \left(\frac{1}{1-p_j} \right) \right] \right)$$

Which I'm going to restate for simplicity as

$$f'(p_j) = (f(0)) \frac{\delta}{\delta p_j} \left(\prod_{j=i+1}^n \frac{1}{1-p_j} \right)$$

$$f'(p_j) = (f(0)) \left(\sum_{j=i+1}^n \frac{-1}{(1-p_j)^2} \right) \left(\prod_{j=i+1, j \neq i}^n \frac{1}{1-p_j} \right)$$

So...

$$f'(0) = (f(0)) \left(\sum_{j=i+1}^n \frac{-1}{(1-0)^2} \right) \left(\prod_{j=i+1, j \neq i}^n \frac{1}{1-0} \right)$$

$$f'(0) = (f(0)) \left(\sum_{j=i+1}^n \frac{-1}{(1-0)^2} \right) \left(\prod_{j=i+1, j \neq i}^n \frac{1}{1-0} \right)$$

$$f'(0) = (f(0)) ((i+1) - n) = ((i+1) - n) \left[\sum_{k=1}^i a_1 + a_2(k-1) \right] \left[\frac{p_{ic}}{1-p_{ic}} \right]$$