This notebook contains the proof that MutSel models will always correspond to a dN/dS≤1. The trick is to look at the forward and backward mutational path at the same time, i.e., we show that the total probability weight in going from i to j and going from j to i is always less than or equal to the sum of the frequencies of i and j.

Throughout this document, we write the frequency of amino acid i as x and the frequency of amino acid j as y. Further, we assume that x≤y. The fixation probability from x to y is:

In[81]:=
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p[x_, y_] := (Log[y] - Log[x]) / (1 - x / y)
```

The sum of the probability weights going from x to y and from y to x is:

In[83]:=
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Simplify[x p[x, y] + y p[y, x]]
```

Out[83]= $\frac{2\,x\,y\,(\mathrm{Log}[x]-\mathrm{Log}[y])}{x-y}$

We are going to show that this sum is less than or equal to x+y, i.e.,

$$\frac{2\,x\,y\,(\mathrm{Log}[x]-\mathrm{Log}[y])}{x-y} \leq x+y,$$

for x, y≥0 and x≤y.

To this end, we define the function

$$\mathrm{F}(x,\,y) = x+y-\frac{2\,x\,y\,(\mathrm{Log}[x]-\mathrm{Log}[y])}{x-y}$$

We thus want to show that F(x,y) ≥ 0 for x, y≥0 and x≤y. It is straightforward to show this for x=y:

In[92]:= ~~F[x_, y_] := x + y - (2 x y (Log[x] - Log[y]))/(x - y)~~

~~Limit[F[x, y], x → y]~~

Out[93]= ~~0~~

We now show that the first derivative of F(x, y) is negative throughout x ∈ (0, y), thus proving that F(x, y) has to be monotonically decreasing in this interval and hence has to be ≥ 0 in this interval.

In[108]:=
```
FullSimplify[∂x F[x, y]]
```

Out[108]= $\frac{1}{(x-y)^2}\left((x-3\,y)\,(x-y)+2\,y^2\,(\mathrm{Log}[x]-\mathrm{Log}[y])\right)$

We can rewrite Log[x]-Log[y] as a series:

In[101]:= $\frac{1}{(x-y)^2}\left((x-3\,y)\,(x-y)-2\,y^2\,\mathrm{Sum}[(1-x/y)\text{^}n/n,\,\{n,\,1,\,\infty\}]\right)$

Out[101]= $\frac{(x-3\,y)\,(x-y)+2\,y^2\,\mathrm{Log}\left[\frac{x}{y}\right]}{(x-y)^2}$

If we take only the first two terms of the series, we find that the expression becomes zero:

In[103]:=
```
Simplify[1/(x - y)^2 ((x - 3 y) (x - y) - 2 y^2 Sum[(1 - x / y)^n / n, {n, 1, 2}])]
```
$$\text{Simplify}\left[\frac{1}{(x-y)^2}\left((x-3y)(x-y)-2y^2\,\text{Sum}[(1-x/y)^\wedge n/n,\{n,1,2\}]\right)\right]$$

Out[103]= 0

Thus, we can write the derivative of F(x, y) as:

$$\frac{-2\,y^2\,\text{Sum}[(1-x/y)^\wedge n/n,\{n,3,\infty\}]}{(x-y)^2},$$

which is obviously negative.

Verification that the last statement was true:

In[106]:=
$$\text{FullSimplify}\left[\frac{1}{(x-y)^2}\,{-2}\,y^2\,\text{Sum}[(1-x/y)^\wedge n/n,\{n,3,\infty\}]\right]$$

Out[106]=
$$\frac{(x-3y)(x-y)+2y^2\,\text{Log}\left[\frac{x}{y}\right]}{(x-y)^2}$$

This concludes the proof.

```
(*Plot showing that F[x, y] is positive.*)
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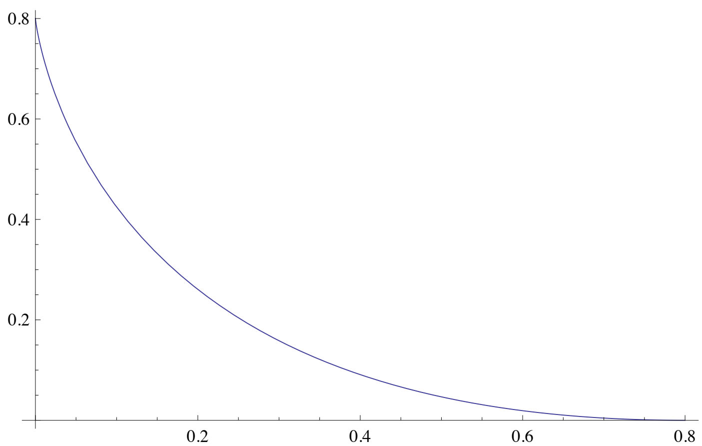
$$\text{Plot}\left[x+y-\frac{2\,x\,y\,(\text{Log}[x]-\text{Log}[y])}{x-y}\;/.\;y\to .8,\;\{x,0,.8\}\right]$$

Out[86]=



In[130]:=
```
(*Plot showing that the derivative of F[x, y] is negative,
and that the partial sums approximate it from above.*)

Plot[{((x - 3 y) (x - y) + 2 y^2 (Log[x] - Log[y]))/(x - y)^2 /. y → .5,
   1/(x - y)^2 (-2 y^2 (Sum[(1 - x / y)^n / n, {n, 3, 3}])) /. y → .5,
   1/(x - y)^2 (-2 y^2 (Sum[(1 - x / y)^n / n, {n, 3, 5}])) /. y → .5,
   1/(x - y)^2 (-2 y^2 (Sum[(1 - x / y)^n / n, {n, 3, 7}])) /. y → .5},
  {x, 0, 0.5`}, PlotStyle → {Black, Blue, Red, Green}, PlotRange → {-5, 0}]
```

Out[130]=