Sickle cell refers to an allele that affects the β-chain of hemoglobin. The allele, S, confers resistance to malaria, but there is a pleiotropic effect of the allele when homozygous that causes severe anemia.

Actually, there are 3 alleles at the β locus: A - "normal", susceptible to malaria when AA, S - "sickle-cell", C - recessive, gives high resistance when homo.
**Fitnesses of Genotypes Given Below**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Fitness</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>0.9</td>
<td>Susceptible</td>
</tr>
<tr>
<td>As*</td>
<td>1.0*</td>
<td>Resistant</td>
</tr>
<tr>
<td>SS</td>
<td>0.2</td>
<td>Anemia</td>
</tr>
<tr>
<td>Ac</td>
<td>0.9</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Sc</td>
<td>0.7</td>
<td>Anemia</td>
</tr>
<tr>
<td>CL*</td>
<td>1.3*</td>
<td>Highly Resistant</td>
</tr>
</tbody>
</table>

**Note:** Overdominance for fitness

**Note:** Highest fitness
When Bantu-speaking peoples of Africa expanded into West-Central Africa, malaria was not a problem. However, with their introduction of slash-and-burn agriculture they established a "new" environment ripe for malaria.

Initial (before slash-and-burn) allele freq.

- A, near unity
- S, very rare
- C, very rare

Let

- \( p = \text{freq of } A \)
- \( q = \text{freq of } S \)
- \( r = \text{freq of } C \)
Now, remember our old friend, $\Delta \theta$?

For two alleles we had

$$\Delta \theta = \theta' - \theta = 8 \frac{\sum p \omega_{12} + 8 \omega_{22}}{\bar{w}} - \bar{\theta}$$

Where $\bar{w} = p^2 w_{11} + pq w_{12} + q^2 w_{22}$

Expanding to 3 alleles gives

$$\Delta \theta = \theta' - \theta = 8 \frac{\sum p \omega_{AS} + 8 \omega_{SS} + r \omega_{SSS}}{\bar{w}} - \bar{\theta}$$
Simplifying from the previous page, we get

\[ A_q = \frac{g}{\bar{w}} \left[ p \text{WAS} + g \text{Wss} + r \text{Wsc} - \bar{w} \right] \]

**WHERE** \( \bar{w} = p^2 \text{WAA} + 2pg \text{WAS} + g^2 \text{Wss} \)
\[ + 2gr \text{Wsc} + r^2 \text{Wcc} + 2pr \text{Wac} \]

Now: let \( A_s = p \text{WAS} + g \text{Wss} + r \text{Wsc} - \bar{w} \)

And think of \( A_s \) as the **Ave Excess of the S Allele**

---

**AND NOTE THAT** \( A_s \) **GIVES THE DIFFERENCE**

**IN FITNESS BETWEEN A GAMETE BEARING S**

**AND THE POPULATION MEAN**
Given this definition of $G_s$, we get:

$$\Delta g = \frac{g}{\omega} G_s$$

Note that $\Delta g = 0$ when $G_s = 0$.

Also note that the direction of $\Delta g$ (+ or -) depends only on the sign of $G_s$.

Similarly:

$$\Delta p = \frac{p}{\omega} Q_A$$

$$\Delta r = \frac{r}{\omega} Q_c$$

$$Q_c = p_w a + g \omega s + r \omega a c - \bar{w}$$

$$Q_A = p_w a + g \omega s + r \omega a c - \bar{w}$$
From prev.: $A_g = \frac{a_0}{w}$

$dr = \frac{r}{w} q_e$

For our initial gene freq. Before slash-and-burn
$p \approx 1; q \approx 0, r \approx 0$

we get

$\overline{w} = p^2 w_{AA} + 2pq w_{AS} + q^2 w_{SS}$

$\downarrow [0.9] + \downarrow 0 + \downarrow 0$

$+ 2qr w_{Sc} + r^2 w_{cc} + 2pr w_{Ac}$

$\downarrow 0 + \downarrow 0 + \downarrow 0$
\[
\begin{align*}
q_8 &= p_8w_{4s} + q_7w_{3s} + r_7w_{5c} - \bar{w} \\
&= \downarrow \quad \downarrow \quad \downarrow \quad \downarrow \\
&= 1[1.0] + 0 + 0 - 0.9 \\
&= 0.1
\end{align*}
\]

Hence \( q_8 > 0 \), and the \( S \) allele should \( \uparrow \) when rare.
Consider now the $c$ allele

$$\Delta r = \frac{r}{w} \Delta c$$

Under the same initial conditions \((p^{21}; g^{20}; r^{20})\)

$$\bar{w} = 0.9 \text{ (as shown prev page)}$$

$$\Delta c = p\Delta wc + g\Delta wc + r\Delta wc = \bar{w}$$

$$= [0.9] + 0 + 0 - 0.9$$

$$= 0.9 - 0.9 = 0$$

Hence: The response to malaria was

1) rapid increase in $\Delta s$
2) no change in $c$ [even though the $cc$ genotype is most fit!]
Thus dominance in the S allele and recessiveness in C plays a critical role!

At equilibrium ($\Delta p = \Delta q = \Delta r = 0$)

1) $p \approx 0.89$  
2) $q \approx 0.11$  
3) $G_S = (0.89)(1.0) + (0.11)(0.2) + (0.0)(0.7) - 0.91 = 0$
4) $G_C = (0.89)(1.0) + (0.11)(0.7) + (0.0)(1.3) - 0.91 = -0.03$

Hence C can't increase in the polymorphic population.
HENCE (and this is the take-home message)

The course and end point of selection requires knowledge of

1) starting conditions
and 2) dominance

Is this (ie 1 & 2 above) enough?
The inbreeding coefficient, \( f \), is the probability that the allele originated in the same ancestor, say grandma. The allele is then “identical by descent” (IBD).
Now suppose we allow slight inbreeding: $f = 0.05$.

Then for $p^2 = 1$, $q > 0$, $r > 0$

\[ q_s = (1-f)pW_{As} + \left( f + (1-f)g \right) W_{ss} + (1-f)rW_{sc} - \overline{w} \]

\[ = (0.95)(1)(1) + [0.05]0.2 + (0.95)(0)(0.7) - 0.9 \]

\[ = 0.06 \]

**Hence $\Delta q > 0$; $s^r$ when rare**

\[ q_c = (1-f)pW_{Ac} + (1-f)gW_{sc} + \left[ f + (1-f)r \right] W_{cc} - \overline{w} \]

\[ = (0.95)(1.0)(0.9) + (0.95)(0)(0.7) + [0.05 + 0](1.3) - 0.9 \]

\[ = 0.02 \]

**Hence $\Delta r > 0$; $c^r$ when rare**
Thus in-breeding would allow for the C allele to increase, whereas out-breeding would not.

Hence: in addition to starting conditions and dominance relationships, we need to know breeding system to predict the course and endpoint of selection.

What is the endpoint for $f=0.05$?

As $c \uparrow a_s + q_A$ acquire negative values and the C allele is fixed at $r=1.0$
THIS GRAPH IS FOR BEFORE MALARIA. Note: here Was=Wac=1.0
After Malaria. $f = 0.0$. No inbreeding
After Malaria. $f = 0.05$
After Malaria. \( f = 0.10 \). Discussion: why does the fitness surface change?
see sickle cell simulation.

\[ F = 0.05 \]