Effects of Transgenic Mosquitoes on the Heterozygous Sickle Cell Population in a Malaria-dense Region

Team 1: Groovy

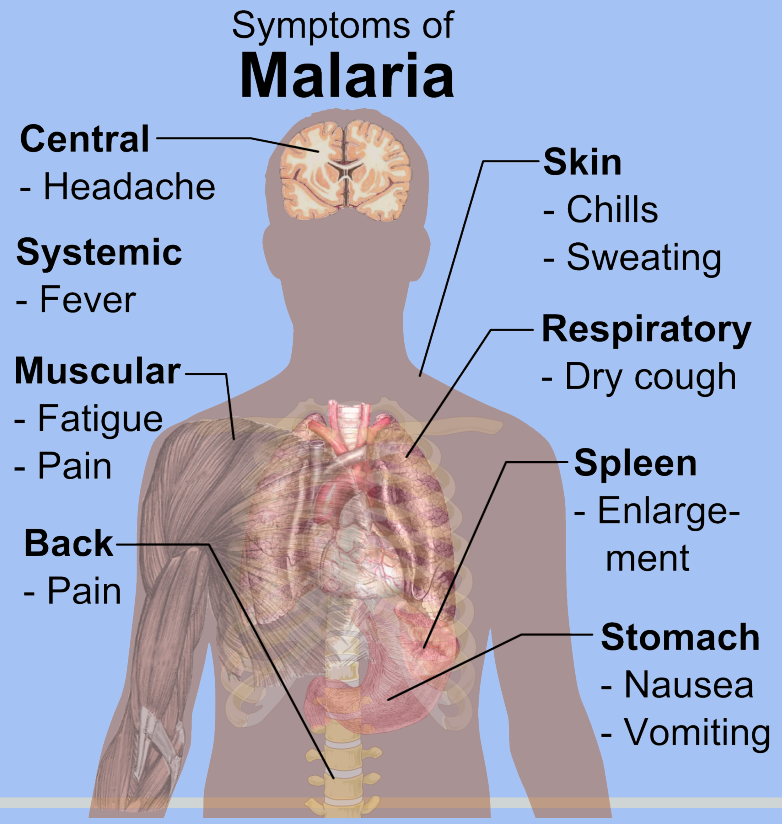
Background - Malaria

- Mosquito-borne infectious disease caused by *Plasmodium*
  - 5 different species
- Female *Anopheles*
- Causes an estimated 207 million cases and 627,000 deaths occurred from malaria in 2012

http://wwwnc.cdc.gov/travel/diseases/malaria

Statistics courtesy of the CDC

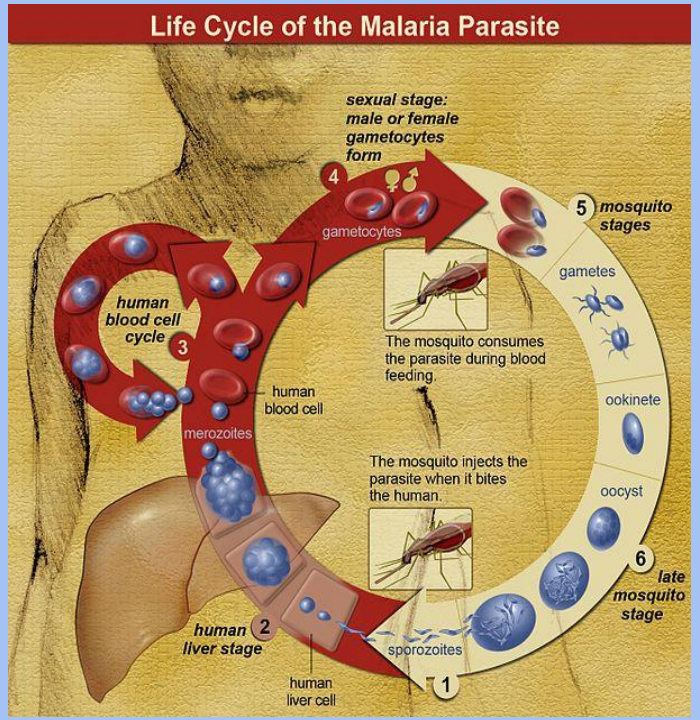
Background - Symptoms of Malaria



http://www.smerete.com/malarial-infection-symbols-curses-and-the-precautions/

Background - Life Cycle of Malaria

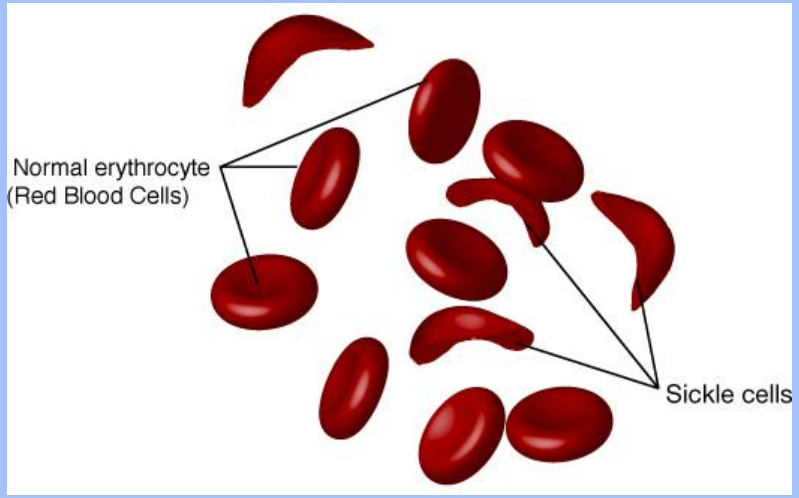
- Sporozoite transmitted into the blood
- Mature and reproduce in the liver
- Merozoites produced re-enter bloodstream and infect new RBC's
  - Thousands of parasite infected cells
- Some merozoites turn into gametocytes
- Mosquito ingests gametocyte
  - Gametes → diploid zygotes → ookinetes → oocysts
  - Growth and division of each oocyst produces sporozoite



http://www.niaid.nih.gov/topics/malaria/pages/lifecycle.aspx

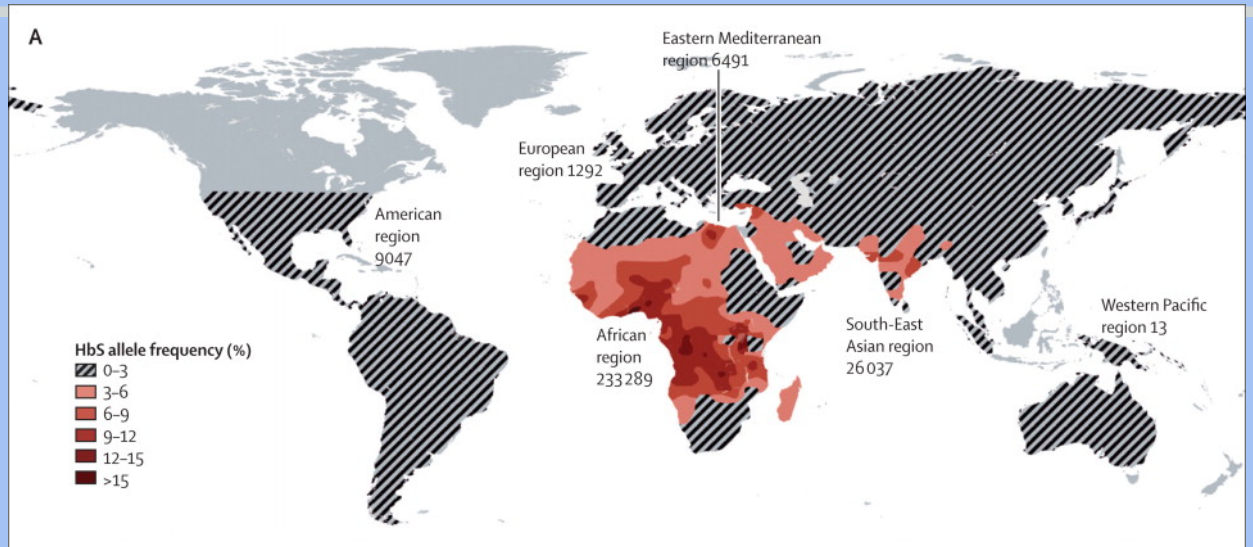
Background - Sickle Cell

- Recessive genetic disease
- Heterozygous individuals show Sickle Cell Trait
    - Have more normal blood cells than people with sickle cell anemia
- Sickle shaped cells cannot use oxygen and have reduced lifespan
- Heterozygous people can still be infectious, they just don't suffer from symptoms
- Strong correlation of areas with high malaria frequency and frequency of heterozygous individuals

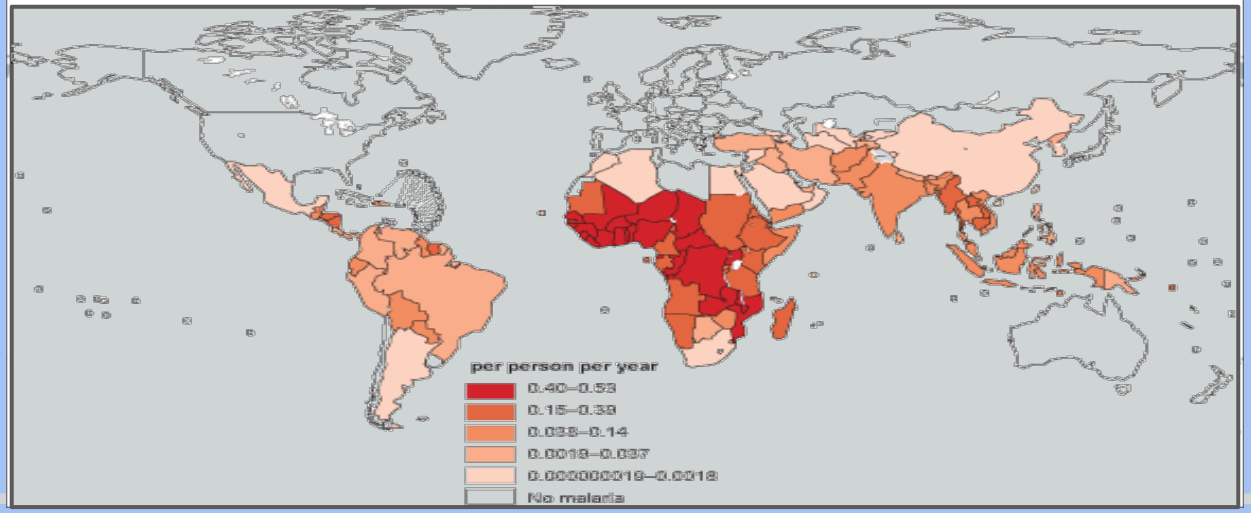


http://geneed.nlm.nih.gov/images/sickle_cell_disease_sm.jpg

http://www.skepticalscience.com/Malaria-biting-climate-change-debate.html



http://runawayjuno.com/wp-content/uploads/2012/02/Malaria_Map.gif



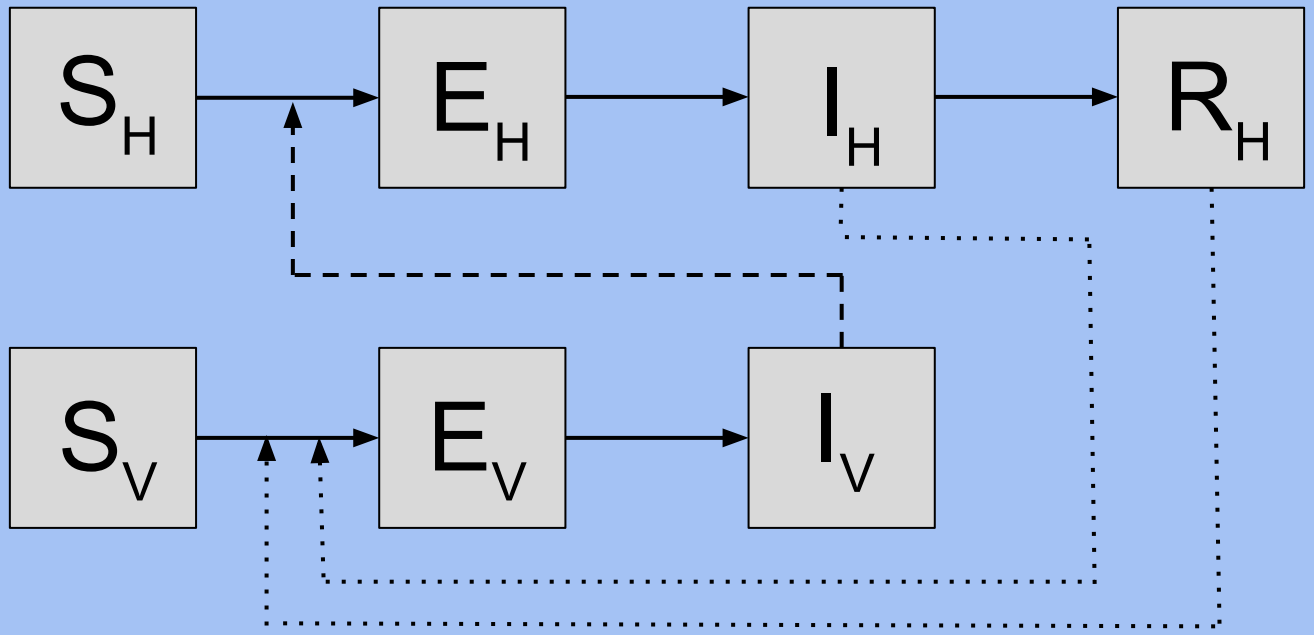
Background - Transgenic Mosquitoes

- Transgenic mosquitoes are artificially engineered to show expression of the SM1 peptide (CCBF3, CCBF6).
  - This creates an environment in their midgut where the plasmodium cannot survive.
- In areas with Malaria,
  - Transgenic mosquitoes exhibit higher fecundity, as a result of not being infected with the plasmodium, which could potentially reduce the incidence of Malaria in the long term.
- In areas without Malaria,
  - Transgenic mosquitoes exhibit no advantage over wild type (WT), non-transgenic mosquitoes.

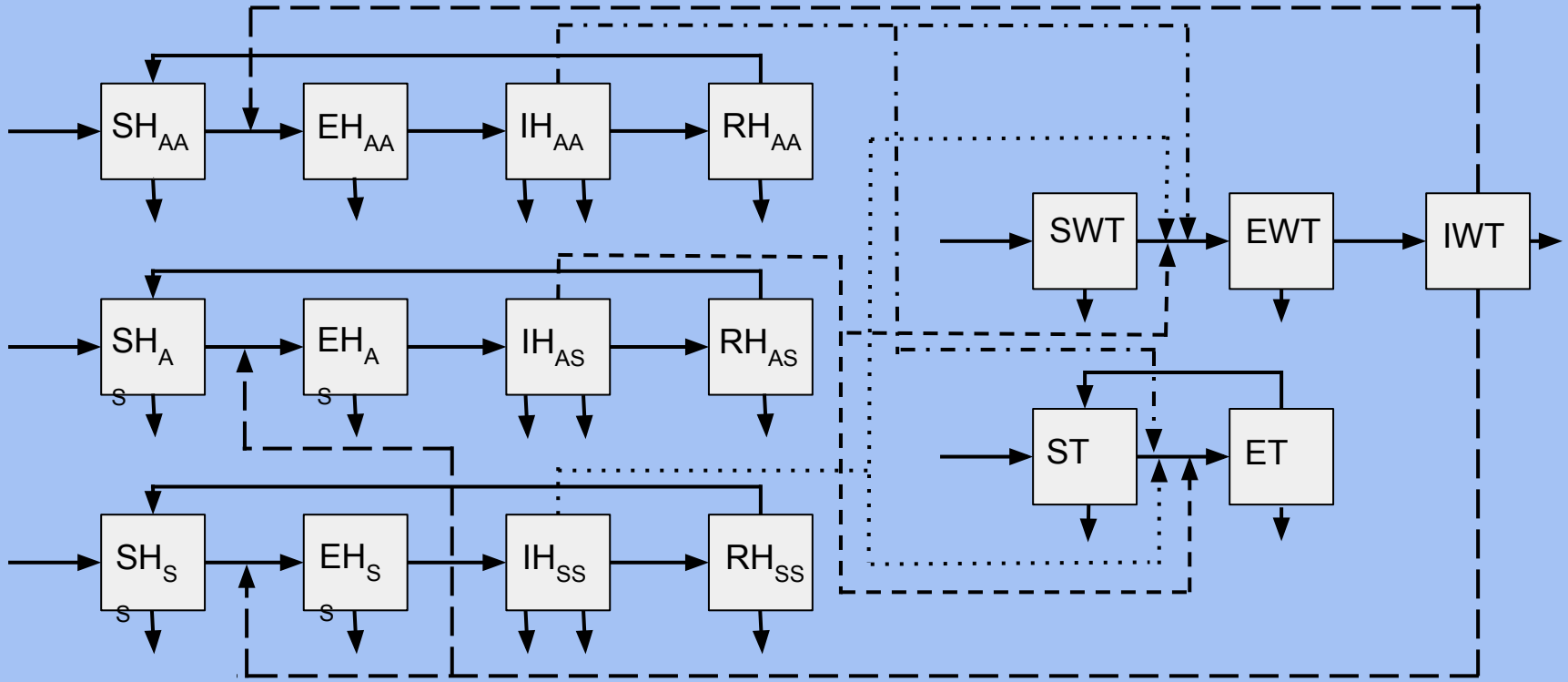
Model Goal

- Introduction of transgenic mosquitoes
  - Infectious population change
- Track change in sickle cell genotypes

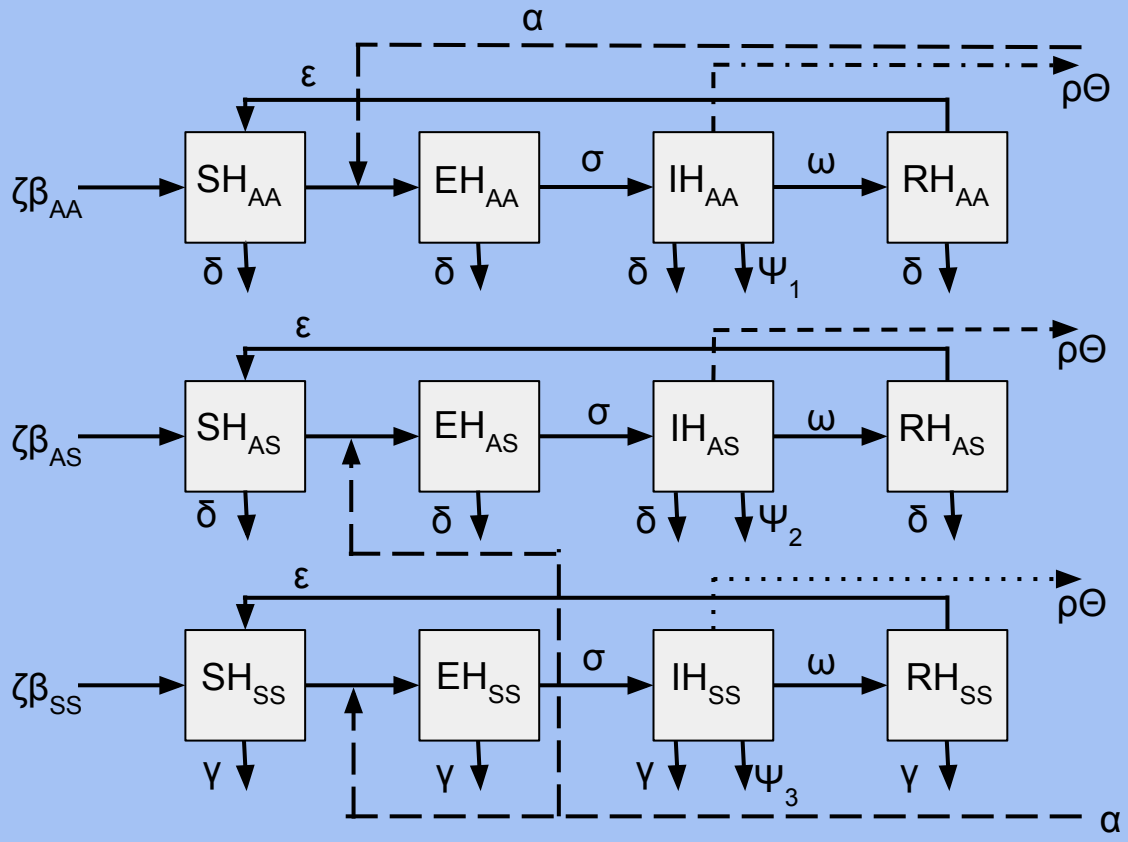
Original Compartment Model



Our Compartment Model



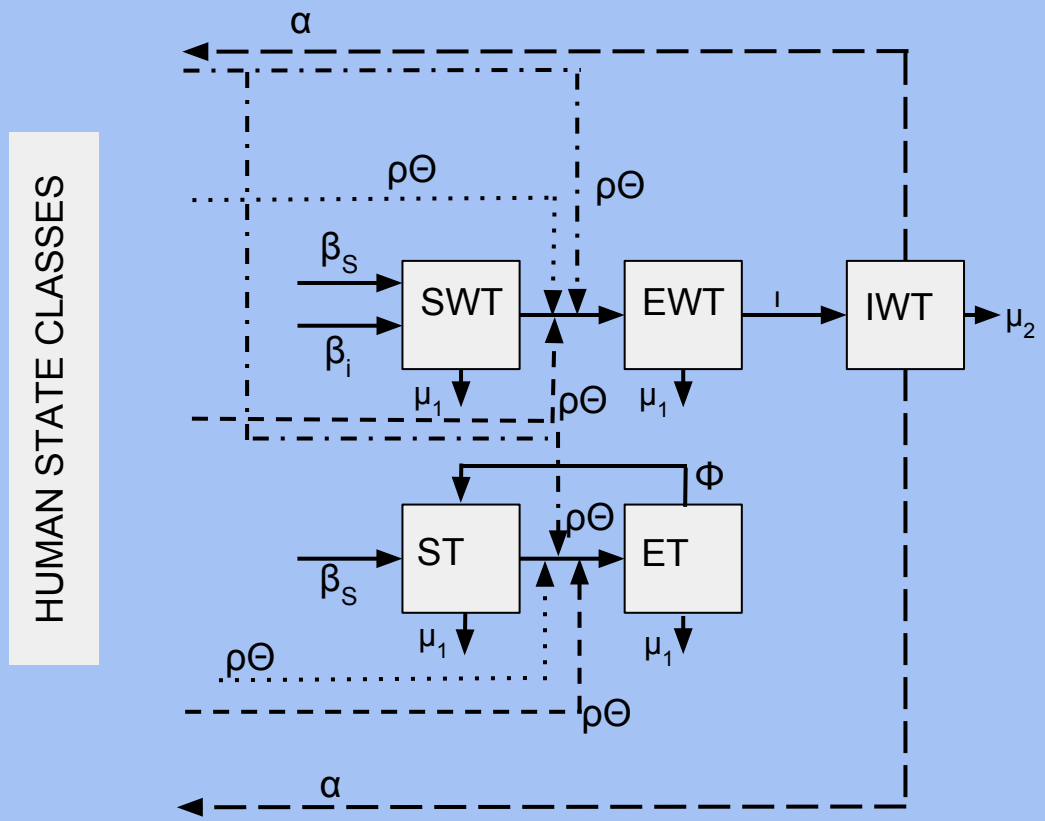
Our Compartment Model: Humans



MOSQUITO STATE CLASSES

α = rate of plasmodia transmission to humans
σ = rate of plasmodia "incubation"
δ = rate of human natural death
γ = rate of death due to sickle cell
ω = rate of recovery from malaria
ψ_1 = rate of homozygous dominant death due to malaria
ψ_2 = rate of heterozygous death due to malaria
ψ_3 = rate of homozygous recessive death due to malaria
ϵ = rate of immunity loss
ζ = human birth rate per day

Our Compartment Model: Mosquitoes



β_S = birth rate of susceptible mosquitoes
β_I = birth rate of infectious mosquitoes
ι = rate of plasmodia incubation in mosquitoes
ϕ = rate of recovery in transgenic mosquitoes
μ_1 = death rate for susceptible mosquitoes
μ_2 = death rate for infectious mosquitoes
ρ = gender ratio
θ = mosquito rate of trasmission

Differential Equations - Humans (AA)

$$\frac{dSH_{AA}}{dt} = \zeta\beta_{AA} + \epsilon RH_{AA} - \alpha SH_{AA}I_{WT} - \delta SH_{AA}$$

$$\frac{dEH_{AA}}{dt} = \alpha SH_{AA} - \sigma EH_{AA} - \delta EH_{AA}$$

$$\frac{dIH_{AA}}{dt} = \sigma EH_{AA} - \omega IH_{AA} - \delta IH_{AA} - \psi_1 IH_{AA}$$

$$\frac{dRH_{AA}}{dt} = \omega IH_{AA} - \epsilon RH_{AA} - \delta RH_{AA}$$

$$\beta_{AA} = \tfrac{1}{4}\left(NH_{AS}\right)^2 + \tfrac{2}{4}NH_{AA}NH_{AS} + \left(NH_{AA}\right)^2$$

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Differential Equations - Humans (AS)

$$\frac{dSH_{AS}}{dt} = \zeta\beta_{AS} + \epsilon RH_{AS} - \alpha SH_{AS}I_{WT} - \delta SH_{AS}$$

$$\frac{dEH_{AS}}{dt} = \alpha SH_{AS}I_{WT} - \sigma EH_{AS} - \delta EH_{AS}$$

$$\frac{dIH_{AS}}{dt} = \sigma EH_{AS} - \omega IH_{AS} - \delta IH_{AS} - \psi_2 IH_{AS}$$

$$\frac{dRH_{AS}}{dt} = \omega IH_{AS} - \epsilon RH_{AS} - \delta RH_{AS}$$

$$\beta_{AS} = \tfrac{2}{4}NH_{SS}NH_{AS} + NH_{SS}NH_{AA} + \tfrac{2}{4}(NH_{AS})^2 + \tfrac{2}{4}NH_{AA}NH_{AS}$$

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Differential Equations - Humans (SS)

$$\frac{dSH_{SS}}{dt} = \zeta\beta_{SS} + \epsilon RH_{SS} - \alpha SH_{SS}I_{WT} - \gamma SH_{SS}$$

$$\frac{dEH_{SS}}{dt} = \alpha SH_{SS} - \sigma EH_{SS} - \gamma EH_{SS}$$

$$\frac{dIH_{SS}}{dt} = \sigma EH_{SS} - \omega IH_{SS} - \gamma IH_{SS} - \psi_3 IH_{SS}$$

$$\frac{dRH_{SS}}{dt} = \omega IH_{SS} - \epsilon RH_{SS} - \gamma RH_{SS}$$

$$\beta_{SS} = \tfrac{2}{4} NH_{SS}NH_{AS} + (NH_{SS})^2 + \tfrac{1}{4}(NH_{AS})^2$$

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Differential Equations - Mosquitoes

$$\frac{dSM_{WT}}{dt} = \beta_S (SM_{WT} + EM_{WT}) + \beta_I IM_{WT} - \mu_1 SM_{WT} - \rho\theta SM_T (IH_{AA} + IH_{AS} + IH_{SS})$$

$$\frac{dEM_{WT}}{dt} = \rho\theta SM_T (IH_{AA} + IH_{AS} + IH_{SS}) - \mu_1 EM_{WT} - \iota EM_{WT}$$

$$\frac{dIM_{WT}}{dt} = \iota EM_{WT} - \mu_2 IM_{WT}$$

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Differential Equations - Mosquitoes

$$\frac{dSM_T}{dt} = \beta_S (SM_T + EM_T) - \mu_1 SM_T - \rho\theta SM_T (IH_{AA} + IH_{AS} + IH_{SS}) + \phi EM_T$$

$$\frac{dEM_T}{dt} = \rho\theta SM_T (IH_{AA} + IH_{AS} + IH_{SS}) - \phi EM_T - \mu_1 E_T$$

β_S = birth rate of susceptible mosquitoes
β_I = birth rate of infectious mosquitoes
ι = rate of plasmodia incubation in mosquitoes
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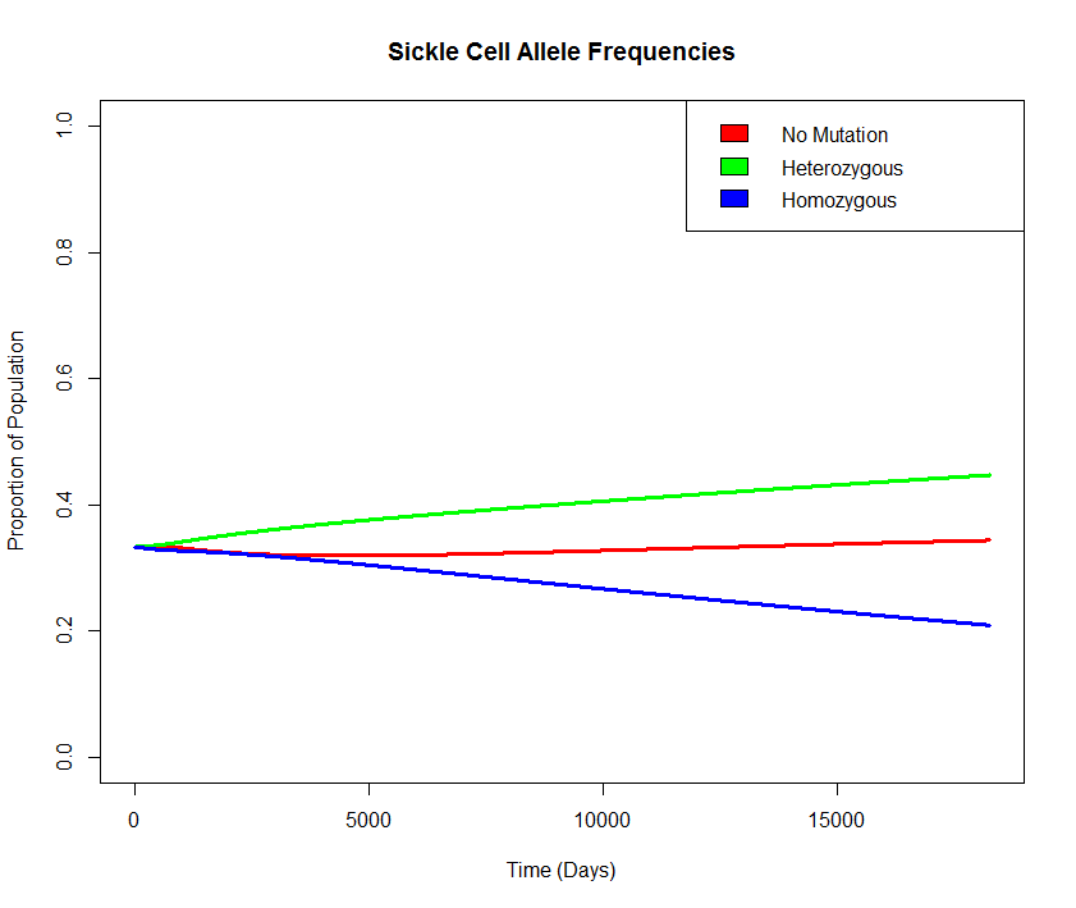
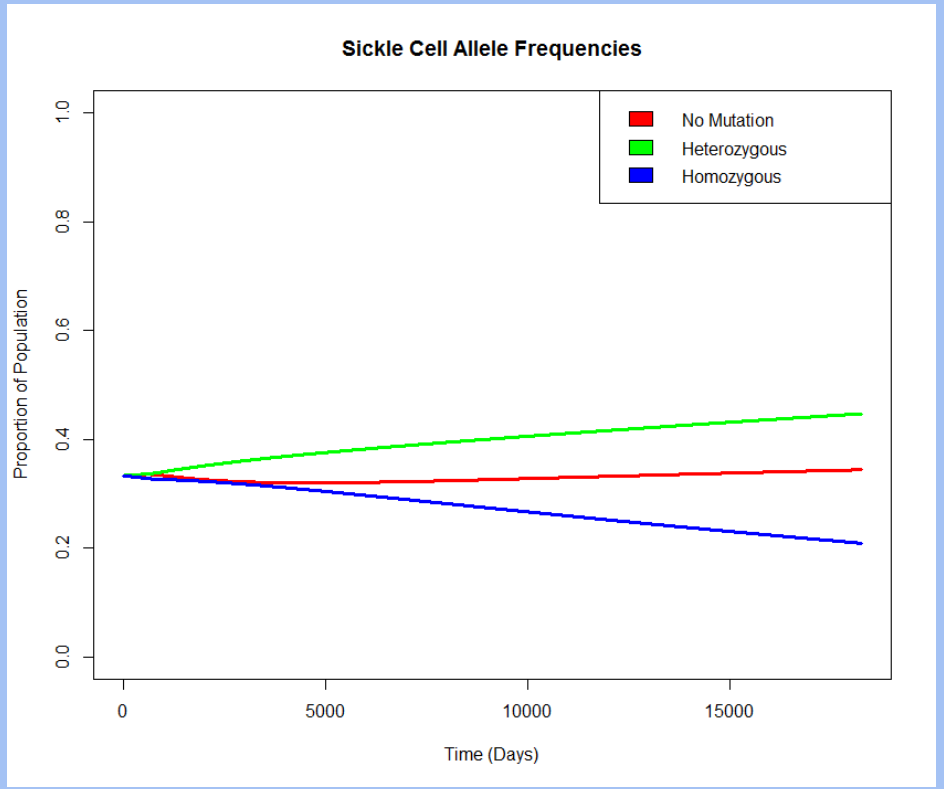
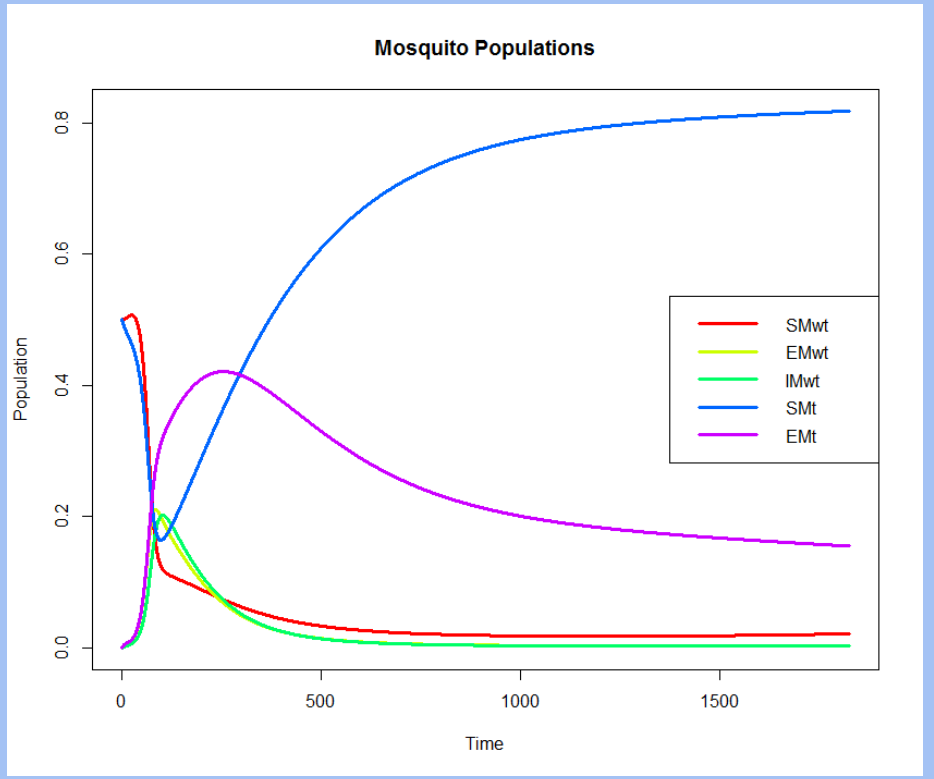
With 100% Wild Type Mosquitoes

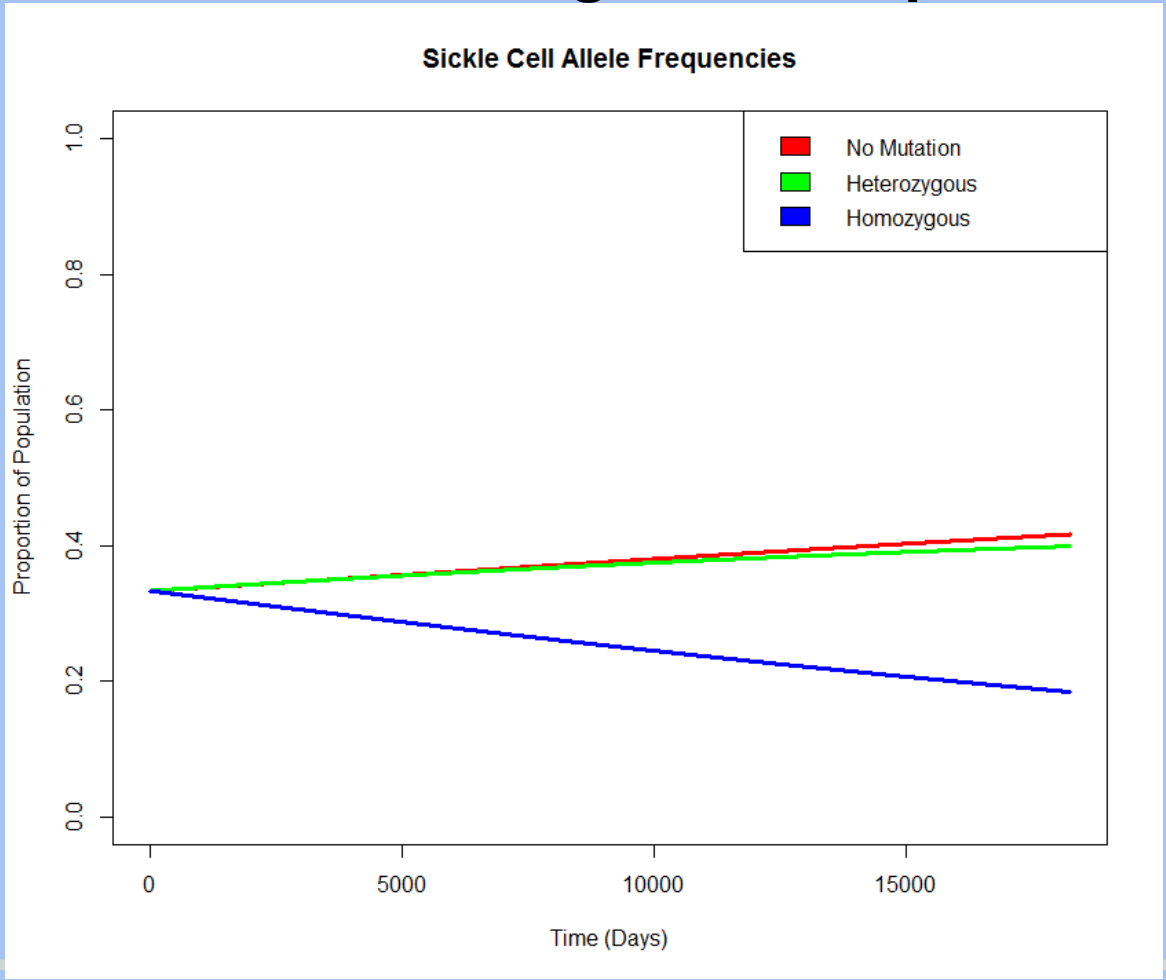


50% Transgenic 50% Wild Type





With 100% Transgenic Mosquitoes



Results

- Heterozygous advantage confirmed
  - Less Heterozygous population with introduction of transgenic mosquitoes
- Transgenic Mosquitoes dominate the population

Conclusions

- Introduction of transgenic to decrease infection
- Biochemical factors from sickle cell

Sources

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