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The battle against Malaria

Malaria the final frontier of the world of infectious diseases, Malaria is a disease that has plagued humanity for hundreds if not thousands of years. From the swamps of Africa malaria has been the relentless pursuer of mankind. Essentially malaria is the most widespread and long lived disease. Despite years of trials the nature of malaria and the way it interacts with the human body has made most conventional treatments ineffective. While there are Malaria medication to prevent the initial contraction of the disease there is no medication to cure a person who has already contracted the disease. Essentially while is is possible to partially prevent the initial contraction of Malaria and treat the symptoms of malaria after it is contracted medical technology offers no way to actually cure a person of Malaria.

Sickle cell disease is a wide group of genetic disorders that cause normal red blood cells to become shaped differently. These cells are shaped like sickles and this causes several mild symptoms. Essentially these symptoms are caused by the cells abnormal shapes and how they interact with the walls of the veins. The sickle cells abnormal cells make travel through veins more difficult and the cells often clog inside of the veins creating temporary blocks that stop healthy red blood cells from reaching their destination. Hemoglobin is the internal structure of a red blood cell. Healthy blood cells have an even distribution of hemoglobin. However, sickle blood cells have an abnormal distribution of hemoglobin leading to an abnormal shape.

Red blood cells are the most important part of the human bloodstream. Red Blood cells essentially act as transports for the human body. They move every type of nutrients throughout the bloodstream. For example when a human eats food the food is digested and broken down into its most basic parts in the stomach. The nutrients are absorbed through the stomach lining into the bloodstream. The red blood cells then distribute these nutrients into the the muscles when work is done or the muscles need repair. However more important than the human digestive system or muscular systems red blood cells are an essential actor in the human respiratory system. Oxygen is inhaled and travels to the lungs. Oxygen is important for almost every chemical process in the human body and is needed in order for life.Therefore the oxygen must be distributed to every part of the human body. The oxygen is absorbed by the lungs and transferred to the red blood cells. The red blood cells are shaped like saucers with a small depressions in the the center of the cell. This is important to understand because the depression in the top of the cell allows it to transfer relatively large amounts of both nutrients and oxygen. The shape of red blood cells is essential to their effectiveness in the human body. Without effective red blood cells the human body becomes incompatible with life.

Sickle cells are essentially less effective red blood cells. Their shape does not allow for effective transfer of oxygen or other nutrients. A sickle cell places the same strain on the human body as a healthy cell but has none of the benefits and in fact has some detriments. Humans with the sickle cell disease have an extra amount of strain placed on their bodies in order to sustain sickle cells. According to the CDC about 3.2 million people have Sickle cell disease and about 43 million people have the sickle cell trait. Because Sickle cell disease is a genetic disease it is inherited and follows basic genetic laws for inheritance of genetic traits. Sickle cell disease is a

recessive trait therefore both the mother and the father must carry the trait in order for the gene to become active. If only one parent carries the gene the child carries the gene but does not have sickle cell disease. Because of this Sickle cell disease is relatively sparsely spread and does not actively affect a large volume of people. Furthermore of those populations with active sickle cell disease varies in severity based on how many sickle cells are produced in the body. These factors causes the very few cases of severe Sickle cell disease that can be life threatening.

SIckle cell disease is inaptly named because it is actually not a disease but an evolutionary trait. According to the CDC over 80% of sickle cell disease cases occur in sub-saharan Africa. With another hotspot of the disease in Southern Asia. It seems like there are no common ancestors between these two areas that could have caused the same genetic trait. This is however untrue Southeast Asia and Sub-Saharan Africa are very environmentally similar. Some of the highest rainfalls can be recorded in the areas. In addition to being extremely humid these two areas are both warm tropical regions. These two factors cause the highest concentrations of Malaria in the world in these two regions. It does not seem to be a simple coincidence that sickle cell disease and Malaria are prevalent in the same two regions of the world.

Malaria is a disease that is extremely widespread in Africa for a variety of reasons. One of the most important factors is the environment of the region. According to UWYO a climatology organization Africa averages about 740 millimeters of rainfall every year. This total includes the saharan desert so the rainfall percentage for Sub Saharan Africa is much higher. The majority of Africa below the equator in the tropic of Capricorn. Regions located within either the tropic of cancer or the tropic of Capricorn are considered to be mostly warmer biomes. These

conditions are perfect for the incubation of mosquitos, a vector of Malaria. Furthermore the vast majority of Sub- Saharan Africa has less access to medical supplies than almost any other place on Earth. Many of these same problems are present in both South America and Southeastern asia.

While Southeastern Asia has both a high concentration of Malaria cases and a high concentration of Sickle cell disease. South America is devoid of Sickle cell disease although the environment is almost identical to that of Africa. This is caused by the Columbian exchange. Before European influence South America was devoid of Malaria and therefore the residents did not develop sickle cell disease. This regional comparison is important as it establishes that sickle cell disease is not an evolutionary product of the environment specifically. It is instead a specific evolutionary trait produced in order to give humans partial immunity to the disease.

Humans only evolved genetic traits in order to counteract major environmental challenges. For example changes in skin tone evolved because hours of sunlight varied throughout different regions of the world. This shows how big of a threat Malaria is to humankind. According to the world health organization there were over 214 million cases of Malaria last year. Furthermore the number of new malaria cases has been almost the same for the past decade. This establishes malaria as a larger threat than many larger epidemics. According to the the CDC the Black Plague killed about 200 million people in the middle ages over 60% of humanity's population. However Malaria was a prevalent disease at the time of time black plague. What makes it more deadly is the fact that while the black plague is no longer prevalent at present time but Malaria is. It is this longevity that establishes Malaria as the largest infectious threat.

To understand why Malaria it is important to understand what makes it unique amongst other infectious diseases. Infectious diseases are divided into three major categories, viral, bacterial and parasitic. Viral diseases are diseases that are often airborne or waterborne and are extremely infectious. They enter the human body through the mucus membranes. These diseases are composed of microscopic single cell organisms. These organisms attack the human body by modifying red blood cells to produce more viruses. Many of these diseases are easy to prevent. For example influenza or as it is more commonly known as the “flu” has a yearly vaccine that vastly reduces the chances of infection.The vaccine introduces dead viral cells to the immune system allowing for the body to develop an effective immune response. For the most part all viral diseases can be treated in this manner. This category of disease is the easiest to treat with current medical technology.

The next category of disease is bacterial infections. These infectious diseases are less widespread than viral diseases. They are either introduced to the human body through direct contact or through a break in the skin. These diseases are single cell organisms that reproduce by destroying red blood cells and using the nutrients to reproduce and create colonies. An example of this category of disease is the Strepp infection. Strepp is contracted through direct contact with the disease cells on a surface. While there have been no major outbreaks of Strepp it remains persistent. Most bacterial infections are stopped by antibiotics. Antibiotics essentially destroy the bacterial cells. Each disease has a specific Antibiotic that is specific to it. There is no way to medically prevent the contraction of a bacterial infection with modern technology. Because of this bacterial diseases are harder to treat with medical technology than viral diseases.

The final category are parasitic diseases. This is the category of diseases that Malaria falls under. Parasitic diseases differ from the other two categories of diseases because parasitic diseases are composed of multicell organisms. This makes parasitic diseases much more difficult to treat. Because their multicell organisms the only way to remove parasites is by surgically removing them or by poisoning them. For example tapeworms can be removed either surgically because of their large size or with medication. However Malaria is unique amongst other forms of parasites because. Malaria parasites are individually smaller than red blood cells and use the red blood cells as a host. This is what makes malaria such a difficult disease to combat.

Malaria uses mosquitoes as a vector to carry the disease. Essentially when a mosquito bites an infected human it takes in gametocytes. The gametocytes subsequently infect the mosquitoes cells and create sporozoites. However unlike the exponential growth in number of sporozoites that is seen in humans. The growth of sporozoites in Malaria is stable. Because of this Mosquitos exhibit no symptoms of malaria and essentially act solely for the purpose of a vector. Once an infected mosquito bites a human the sporozoites enter the bloodstream. The sporozoites infect the blood cells. However unlike other disease cells which are either eventually destroyed by the immune system. Or reproduce using the available resources until they are depleted and the host dies. However Malaria does not exhibit these traits on first contraction Malaria causes flu like symptoms. Subsequently after the symptoms recede the disease becomes dormant in red blood cells. The symptoms can then be triggered by being bitten by another infected mosquito or by an immune system reaction. After this the sporozoites start to reproduce breaking down red blood cells causing another flare up of Malaria. This repeated process of flare ups and dormancy makes Malaria seem like a temporary disease. Malaria is actually chronic and

never leaves the blood stream after the initial symptoms are contracted. This is important to understand as it elevates the risk of the disease and the importance of finding an effective defense against it.

Recently a CDC study of infants between 2-16 months of age in sub saharan Africa showed that sickle cell trait is effective at decreasing infant mortality due to Malaria. Young infants are mostly unable to receive any major form of clinical protection in Malaria. Therefore because the subjects were completely unmedicated the results are relevant to showing a correlation between Sickle cell trait and Malaria. Essentially the results of the CDC study show that infants with Sickle cell trait have a slightly lower mortality rate than infants without the trait. However the study also showed that the infants with the Sickle cell disease had by far the highest mortality rate. Unfortunately the study only took into account total mortality. Because of this it is possible to see only that there is a correlation between sickle cell trait and Malaria. It is highly probable that the infants with Sickle cell disease had a higher mortality rate because of the disease and not because they were more likely to contract Malaria. Therefore the only conclusion that can be drawn from these results is that Sickle cell trait is effective at lowering the Malarial infection rate slightly. Therefore the amount of immunity provided by Sickle cell disease against Malaria is still unknown.

Another study done by Gulbenkian Institute of Science used mice in order to test how the difference of hemoglobin present in the blood stream affected rates of Malarial infection. The study found that Sickle cell trait. Does not actually provide immunity to the disease. However it prevents the disease from taking hold after it is contracted. Furthermore the study injected haem which is a component of hemoglobin only found in the blood of people with sickle cell trait and

disease. The researchers then injected the haem into the blood of mice and exposed them to Malaria the mice injected with haem did not develop Malaria. This confirms that sickle cell disease is a protective mechanism against Malarial infection. However although Sickle cell disease has established as protective mechanism for Malaria there are two main reasons why it cannot be used as a widespread defense.

Sickle cell disease is a genetic trait that shows incomplete dominance. This means that the percentage of sickle cells or haem differs from patient to patient. This is problematic because patients with severe sickle cell disease or haem will have symptoms worse than that of a Malarial infection and mortality will rise. Conversely if there is two little haem in the bloodstream it will have no effect on the frequency of malarial infections. This makes the trait impossible to implement as a protective mechanism. In order to find the most effective blood to haem ratio an organization would have to gather individuals with varying severities of sickle cell disease and expose them to Malaria. Which could have lifelong implications. Because of this it is impossible to use Sickle cell Disease as a defense against Malaria.

Another reason that it would be impossible for Sickle cell disease to be a defensive mechanism against malaria is the distribution of the gene. Sickle cell disease is a recessive gene. Relative to world population numbers or even the population of Malarial stricken regions Sickle cell Disease is relatively rare. Furthermore it's nature as a recessive gene makes the future of this gene look much the same as it currently looks. Currently there are around 50 million people with either sickle cell disease or sickle cell trait while the number of Malaria cases is over 240 million. The amount of sickle cell traits in the gene pool will never be enough to counteract the

amount of Malaria cases if the gene continues to spread at its current rate. However this only holds true if the gene is allowed to continue its spread naturally.

In recent years the technology of gene manipulation has become more prevalent in the medical field. A study done by Kunming Biomedical International pioneered gene editing in primates. By manipulating the chromosomes in the sperm and egg the researchers were able to not only artificially fertilize the eggs of an endangered species but also edit the genome of the infant primates. This is a massive step forward previously gene editing was relatively unsuccessful and was only able to edit the genes of an organism which was already living. Essentially the edited genome could not be inherited.

The system used to make these gene edites is named the CRISPR system. The system uses bacteria to edit DNA and RNA. The system can remove selected genes and replace them with different genes. The technology has widespread applications in almost every medical field and environmental study. However moral questions have hindered the progress of this new technology. There are several different potential applications of the CRISPR system in the battle against Malaria.

One of the most widely proposed plans uses the CRISPR system to render female mosquitos sterile after a single generation. This plan suggests altering thousands of mosquitos in a lab setting and then releasing them into the wild. This will decimate the Mosquito population in Malaria stricken areas. However While mosquitoes may seem like simple pest they actually play an important role as a keystone species.

Mosquitos have a complex role in the many ecosystems and removal could result in catastrophic environmental destruction. While best known for their blood meals mosquitos are

actually mostly herbivores. Male mosquitos are pollinators and ingest only nectar. Because of this they can be considered as pollinators. Pollinators are prevalent in almost every terrestrial environment. Furthermore female mosquitos are also pollinators. They only ingest blood during their mating season in order to meet the extra nutrition needs of their mating season. Completely removing mosquitoes from an environment would in some cases be equivalent to removing bees from the environment. The result would be a catastrophic decline in the flora of the region impacting the entire biome. While it is likely that the result would be less severe in most cases the complete removal of a species from a biome would lead to major environmental repercussions. This reason alone is enough to disregard the plan to render mosquitos sterile.

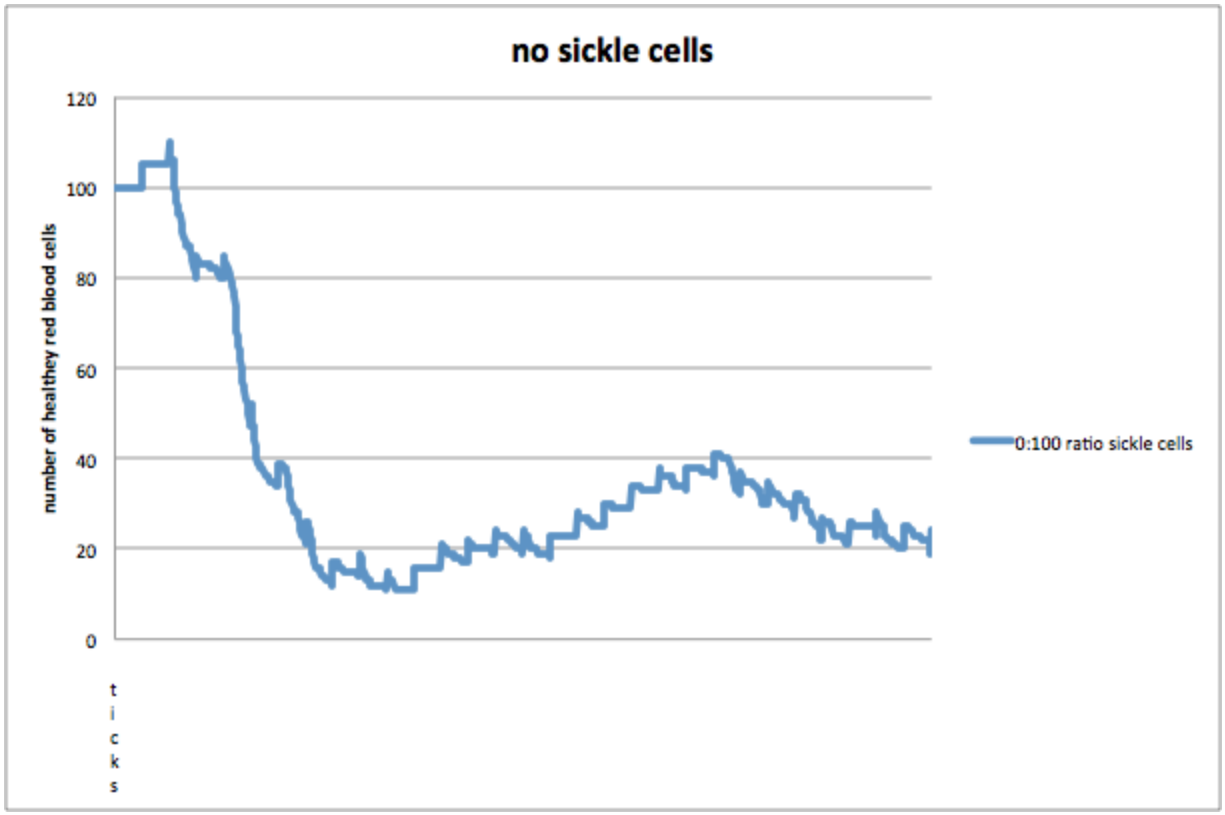
Recently researchers at the University of California have been able to use the CRISPR system in order to edit mosquitos genes allowing them to longer carry Malaria. This seems to be the best possible solution as it allows the survival of mosquitoes in a biome while restricting the spread of malaria. However if this technique was to be implemented the gene of immunity would be a recessive gene and would therefore be ineffective. Even if every mosquitos genes were altered in africa only a quarter of those would survive in the next generation. So this proposal would not be effective as it would only be a temporary measure and have little impact on the rate of Malaria cases in the long run.

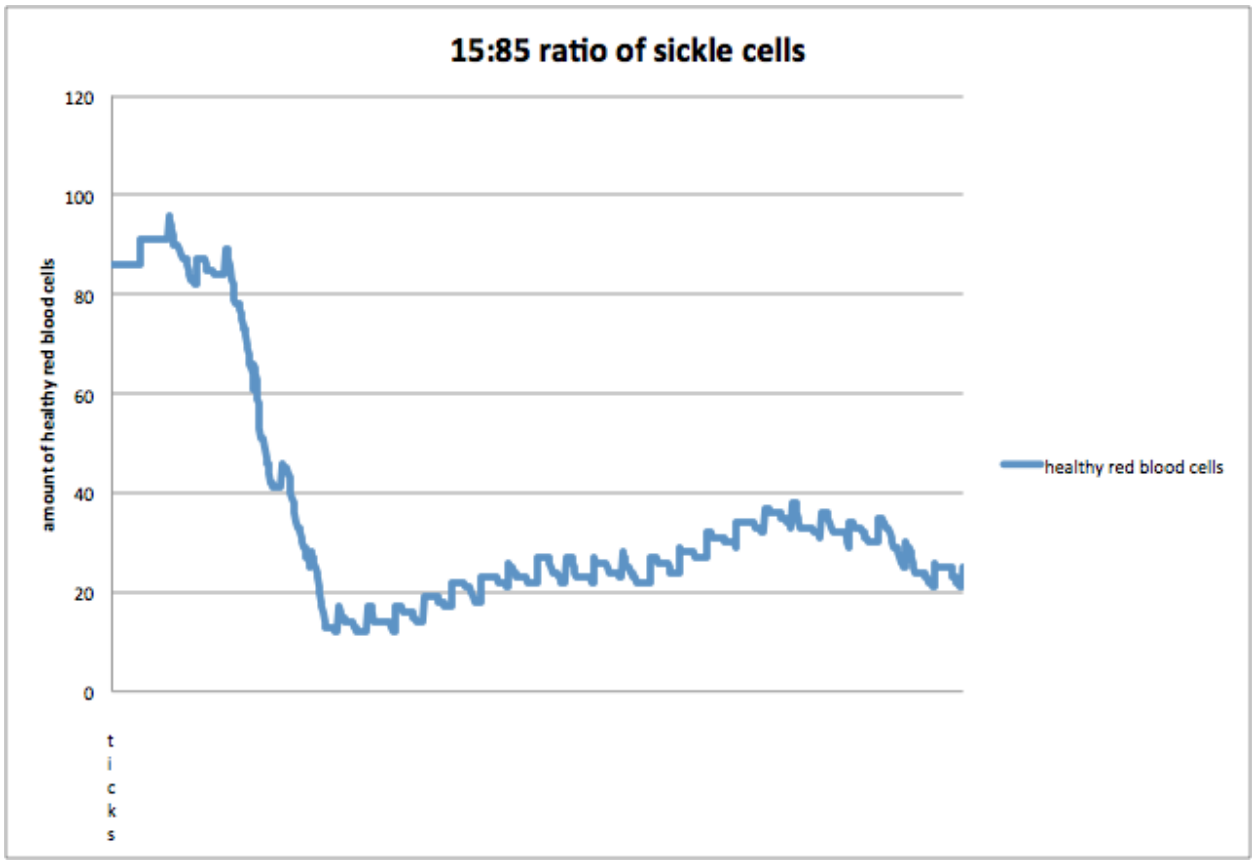
This brings the subject to our project. Essentially because malaria is such a large problem and the human genome has already evolved a genetic defense in order to stop the disease. Instead of changing the vectors of Malaria which could have large environmental repercussions. The Sickle cell trait which is a protective mechanism against Malaria should be changed into a dominant gene to mitigate the effects of Malaria. However since sickle cell trait shows

incomplete dominance and different severities of the disease are present. It is first necessary to find the amount of Haem present in the blood stream that most effectively mitigates malaria. While striking a balance with the symptoms of sickle cell disease. Because this is impossible to experiment in a real world environment because of humane issues. It is necessary to first create a simulation of malaria in the blood stream using agent based modeling to show the relationship between sickle cell disease and Malaria. The program takes into account four different variables to accurately portray the human bloodstream.

After running the program multiple times adjusting the ratio of sickle cells to red blood cells. The most effective protection against Malaria would be to have a ratio of 1:4 healthy blood cells to sickle cells. This ratio provides both a drastically smaller chance of infection than without sickle cells it also mitigates the effects of a malaria flare up. However this ratio of sickle cells also presents increased symptoms of sickle cell disease. Therefore the overall mortality rate would be similar to that of a person with no sickle cell disease. At 15:85 ratio of sickle cells to healthy cells the chance of initial contraction is reduced as is the severity of the malaria flare ups. This ratio also would present few symptoms of sickle cell disease. Because of this this is by far the most effective ratio of sickle cells to healthy blood cells. Overall the more sickle cells and therefore haem is present in the blood stream the higher the resistance is to Malaria.

Results:


no sickle cells
120
100
80
60
40
20
0
number of healthey red blood cells
t
i
c
k
s
0:100 ratio sickle cells


15:85 ratio of sickle cells
120
100
80
60
40
20
0
amount of healthy red blood cells
t
i
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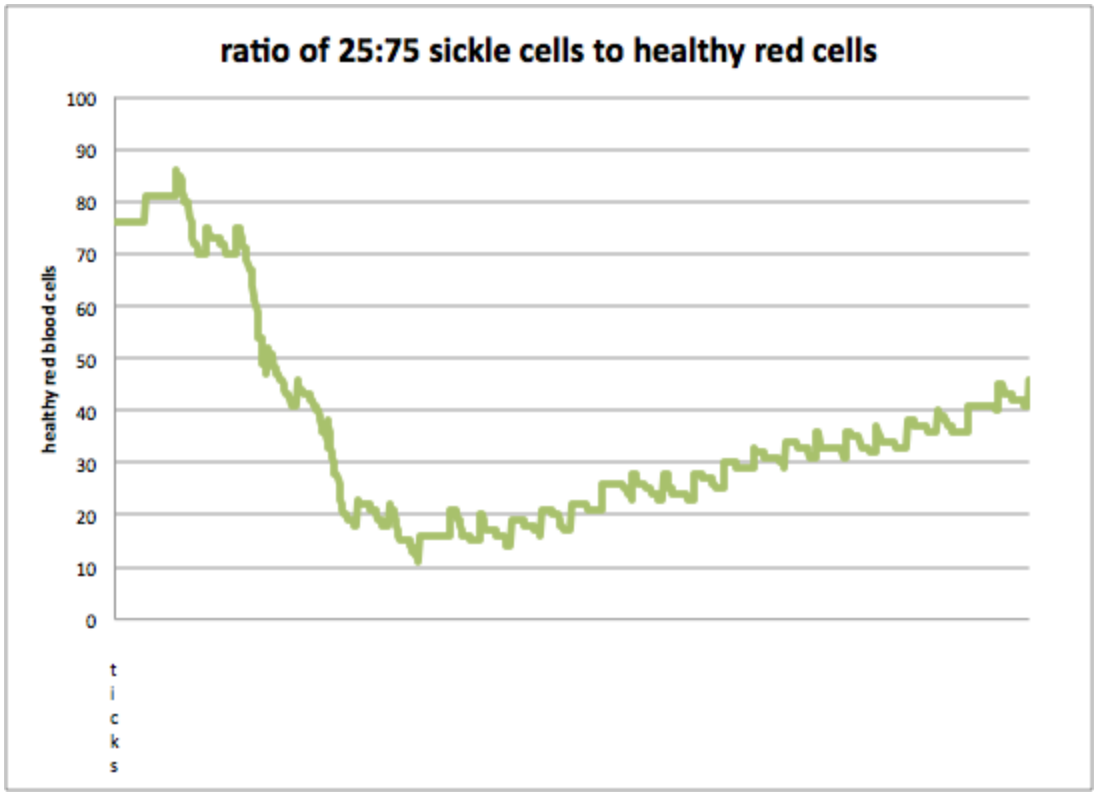
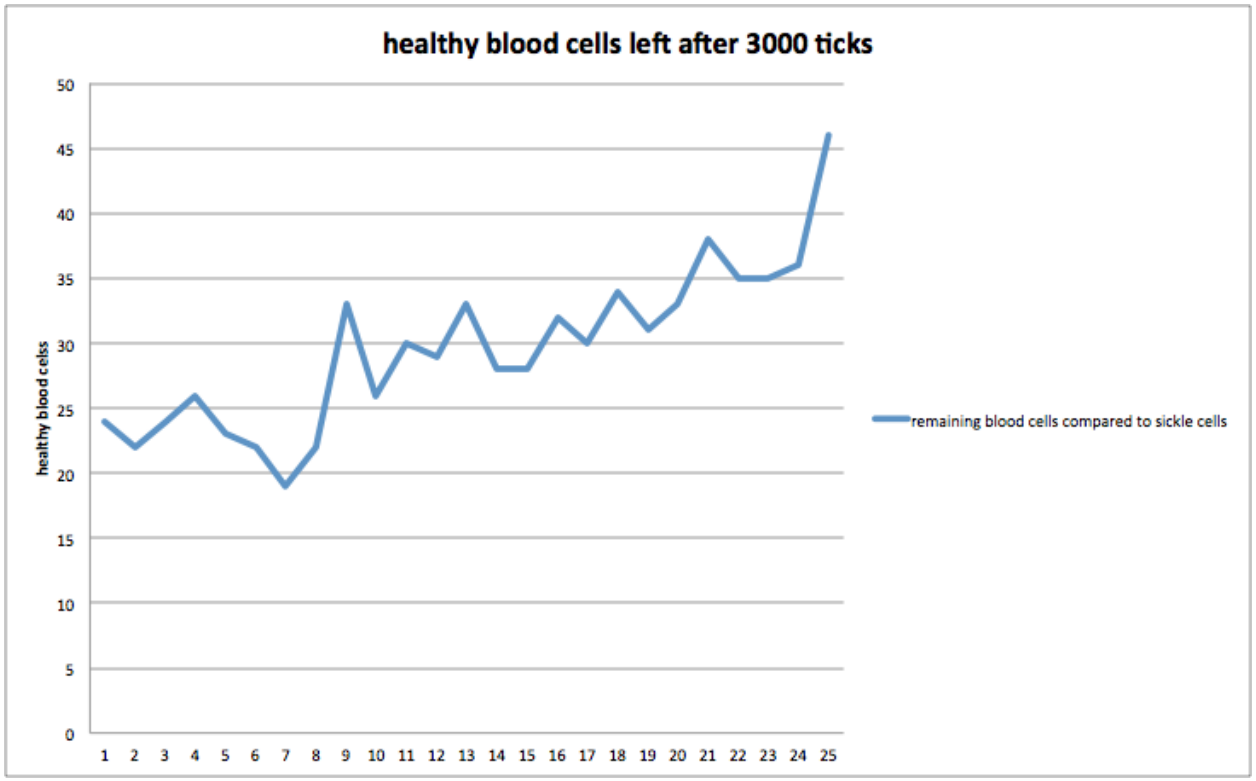
k
s
healthy red blood cells


ratio of 25:75 sickle cells to healthy red cells
healthy red blood cells
100
90
80
70
60
50
40
30
20
10
0
t
i
c
k
s


healthy blood cells left after 3000 ticks
healthy blood celss
50
45
40
35
30
25
20
15
10
5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
remaining blood cells compared to sickle cells

X axis original sickle cells

Code net logo:

```
breed [whitecells whitecell]   ;; randomly move around
breed [redcells redcell]           ;; sit there and get infected by parasite
breed [sicklecells sicklecell] ;; immune to the parasites. dont move
breed [parasites parasite]        ;; when touches white dies. can spawn more

;; controls if the turtles are infected
globals
[
  redcell-spawn
  whitecells-count
  parasites-spawn
  sicklecells-count
]

redcells-own [
  infected?
  redtime                    ;;controls when the infected redcells spawn malaria
]

parasites-own [
```

```
  time                    ;;controls when will randomly spawn more
]


                          ;; Set up the world
to setup
  clear-all
  reset-ticks
  ;;
  ;; Set spawn of the different turtles
  ;; Set coordinates of the cells
  ;;
  create-whitecells spawn-white [
          setxy random-xcor random-ycor
          set size 1.3
  ]
  create-redcells spawn-red [
          setxy random-xcor random-ycor
          set size 1.3
          set redtime 0
          set infected? false       ;;default cells are not infected
  ]
  create-sicklecells spawn-sickle [
```

```
        setxy random-xcor random-ycor
        set size 1.3
]
create-parasites spawn-para [
        setxy random-xcor random-ycor
        set time 0
        set size 1.5
]
;;
;; End of setting the spawn



;; Set up different classes of turtles
set-default-shape whitecells "whitecell"
set-default-shape redcells "redcell"
set-default-shape sicklecells "sickle"
set-default-shape parasites "parasite"
;; End

;;sets the color of the world
ask patches [set pcolor black]
```

```
end ;;END OF SETUP


                        ;; Provides all movement of the program
to Go
  set redcell-spawn redcell-spawn + 1
  set parasites-spawn parasites-spawn + 1
  redmove
  paramove
  sicmove
  whitemove
  tick
end;;END OF GO


to whitemove              ;; movement of the white cells!!!!
  ask whitecells [
        right random 110
        left random 110
        forward 0.4
  ]
end


                        ;; method of movement for the red cells
```

```
to redmove
  spawnredcells
  ask redcells [
        right random 120
        left random 120
        forward 0.5
        if infected? = true
        [
        infectedcell
        ]
  ]
end;;me

to paramove
  parasite-breed
  ask parasites [
        right random 120
        left random 120
        forward 0.3
        let infect one-of redcells in-radius 1
        if infect != nobody [
        ask redcells-here [set infected? true]
```

```
        ]
        ask parasites[
        if any? whitecells in-radius 1 [
        ask parasites-here [die]
        ]
        ]
  ]
end;;me


to sicmove
  ask sicklecells [
        right random 120
        left random 120
        forward 0.5
  ]
end;;me


;; The method for the infected cells
to infectedcell
  set redtime redtime + 1
  if redtime = 200
  [
```

```
        ask redcells-here [
        hatch-parasites random 5
        die
        ]
        set redtime 0              ;; resets the timer of the infected cells
  ]
end
;;end of the infected method

to spawnredcells              ;; spawns more red cells while running
  if redcell-spawn = 100 [
        create-redcells 5[
        setxy random-xcor random-ycor
          set size 1.3
        ]
        set redcell-spawn 0
  ]
end
;;end of the spawn of red cells

to parasite-breed
  if parasites-spawn = 150
```

```
  [
        create-parasites random 5 [
        setxy random-xcor random-ycor
        set size 1.5
        ]
  ]
End
```

Bibliography

"Life Cycle." *Home*. AMCA, n.d. Web. 03 Apr. 2017.

Mosquito Life Cycle (n.d.): 1-2. CDC, 2012. Web. 03 Apr. 2017.

Begley, Sharon. "Mosquito DNA Altered to Block Malaria, Not Spread It." *STAT*. STAT, 08 Aug. 2016. Web. 04 Apr. 2017.

Larson, Christina. "New Tools for Editing the Genome Could Radically Change the Study of Human Diseases." *MIT Technology Review*. MIT Technology Review, 04 Oct. 2016. Web. 04 Apr. 2017.

Lange, Catherine De. "How Sickle-cell Carriers Fend off Malaria." *New Scientist*. New Scientist, 05 May 2011. Web. 04 Apr. 2017.

Admin. "CRISPR Gene-editing Tested in a Person for the First Time." *CRISPR Crispr Genome Editing System*. N.p., 16 Nov. 2016. Web. 04 Apr. 2017.

"Malaria." *Centers for Disease Control and Prevention*. Centers for Disease Control and Prevention, 28 Mar. 2017. Web. 04 Apr. 2017.

"Protective Effect of Sickle Cell Trait Against Malaria-Associated Mortality And Morbidity." *Centers for Disease Control and Prevention*. Centers for Disease Control and Prevention, 08 Feb. 2010. Web. 04 Apr. 2017.

Geerts, B., and E. Lenacre. "Global Precipitation." *Global Precipitation*. N.p., n.d. Web. 04 Apr. 2017.