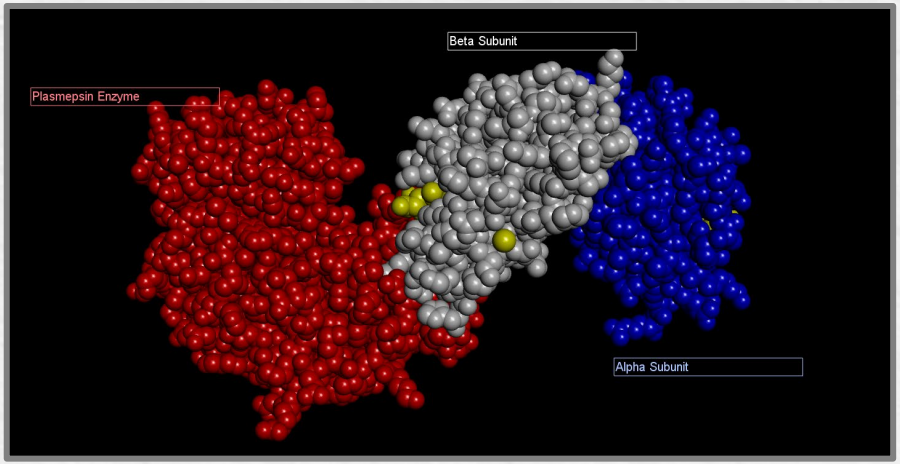
# Why *Malaria* Struggles with Sickle Cell: A Computational Study

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# Understanding Malaria

An overview of the global burden, prognosis, and biomedical significance

# In 2022...

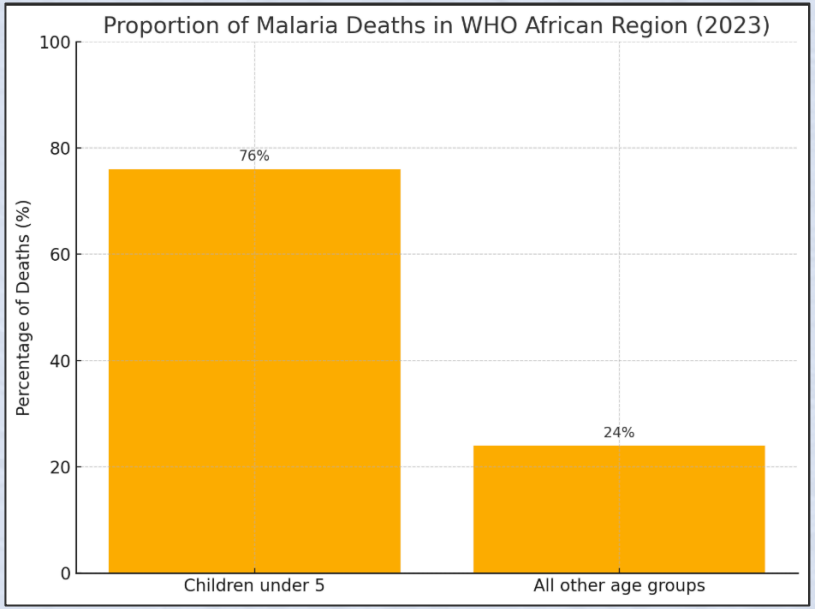
# 249,000,000 Cases

608,000 deaths

Centers for Disease Control and Prevention. (2023, September 18). Impact of malaria interventions. Retrieved April 23, 2025, from https://www.cdc.gov/malaria/php/impact/index.html

**Sub-Saharan African region accounted for 94% of all Malaria cases**

**Children under 5 represented 76% of all Malaria deaths in this region**



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# Relevance of Malaria Research

Bringing the issue “back to home”

# How is Malaria Research Relevant?

- Tourism
- Doctors Without Boarders
- Military

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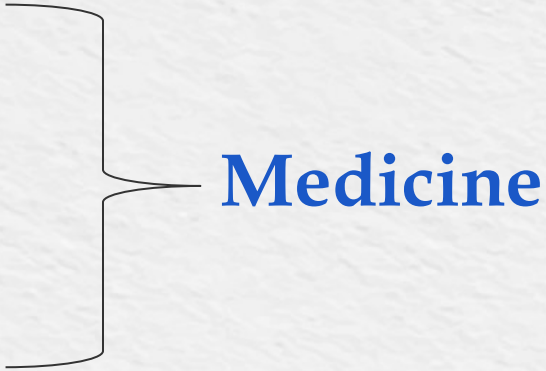
# Interdisciplinary Nature of Study

Connecting Different Disciplines for One Goal

# The Connection Between Fields

- Biology Aspect
- Computer Science Aspect
- Physics Aspect
- Chemistry Aspect



# Malaria: Two Key Players

**Plasmepsin**

-A protein used by Malaria parasite to help degrade hemoglobin

**Hemoglobin**

-Protein in red blood cells – carries oxygen throughout body
-Contains heme – molecule that bounds tightly to oxygen

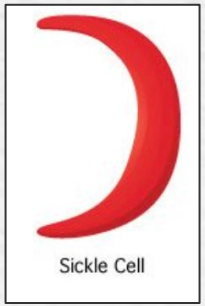
# What is the Sickle Cell Trait

## Normal Hemoglobin

Contains 2 normal alpha-subunits, 2 normal beta-subunits


## Sickle Hemoglobin (HBS)

Contains 2 normal alpha subunits, 2 mutated beta subunits



Hemoglobin

Plasmepsin Enzyme

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# Research Overview: The Big Unknown

What the Research Seeks to Address

# The Big Unknown

*How does the binding of plasmepsin to normal hemoglobin compare with sickle hemoglobin?*

1. What is the binding mode?

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2. What amino acids are involved?

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# Overview of Computational Methods

How the question was addressed

# Computational Methods

Molecular docking simulations via Zdock between **plasmepsin + normal/sickle hemoglobin**

Finding binding location and comparing where plasmepsin bonded for both HBS and normal hemoglobin dimers

Identifying key regions through amino acid interactions (ongoing)

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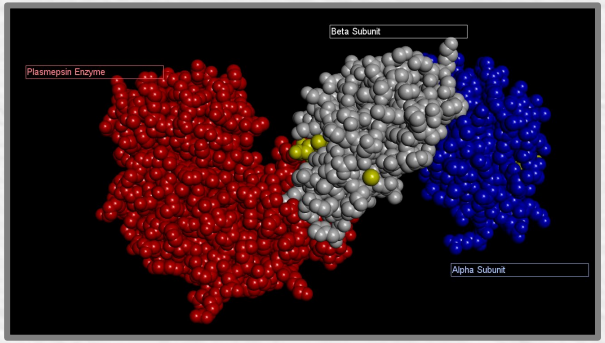
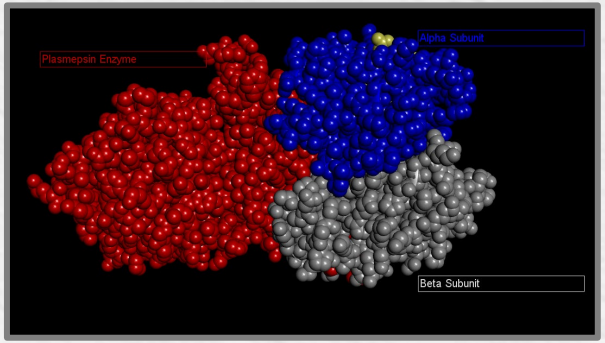
# Results and Addressing the Unknown

Findings and significance for each question

# Binding Mode Results




| | A-monomer | B-monomer | Groove |
|---|---|---|---|
| **Normal hemoglobin dimer w/drug** | 30% | 50% | 20% |
| **Sickle hemoglobin dimer w/drug** | 20% | 40% | 40% |

# Binding Mode Continued

| | Highest Energy |
|---|---|
| Average BE (joules) | -7.23 |
| Standard Dev. | 0.067 |

BE = Binding Energy

| | Highest Energy |
|---|---|
| Average Ki | 5 |
| Standard Dev. | 0.555 |

Ki = Inhibition Constant

# Amino Acid Results

| | |
|---|---|
| VAL1 | LYS7 |
| LEU2 | THR8 |
| SER3 | ASN9 |
| PRO4 | VAL10 |
| ALA5 | LYS11 |
| ASP6 | ALA12 |

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# Summary

Malaria research has regional and domestic relevance

The plasmepsin enzyme degrades hemoglobin

Binding mode results suggest why Malaria struggles in sickle cell (groove)

Amino acid regions were identified

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# Future Research

Next steps and continuing research

# Next Steps

- **Amino Acids**
  Differences in amino acids
- **Drugs**
  New molecular simulations w/ prevalent antimalarial drugs
- **Bonds**
  Understand bond formation for the amino acids
- **Heme**
  Taking advantage of heme’s toxicity to Malaria parasite

# References


- Centers for Disease Control and Prevention. (2023, September 18). *Impact of malaria interventions*. https://www.cdc.gov/malaria/php/impact/index.html

- Solomon, J. (2012, July 25). *During exertion, some blood cells in an athlete with sickle cell trait elongate into sickle shapes that can disrupt blood flow to body organs and lead to health complications* [Image]. AL.com. https://www.al.com/sports/2012/07/athletic_trainers_medical_expe.html

# Thank you

## Questions?

# *What molecular mechanism allows HBS to counter Malaria?*

- **Path A:** Plasmepsin binds too tightly to HBS releasing too much heme (killing itself)
  - Analogous to Venus fly trap
- **Path B:** Plasmepsin binds less effectively to HBS allowing weaker interactions than normal hemoglobin

# What is Gibbs Free Energy

$$\Delta G = \Delta H - T\Delta S$$

- A reaction or process is favorable when ΔG is negative
  - A lower ΔG is more favorable for biological reactions
- Two components:
  - ΔH (enthalpy) → indicates strength
  - ΔS (entropy) → indicates randomness

# Nature of Bonding

## Hydrogen Bonds

Low Entropy
High Selectivity
Very Stable

⇧HB = High enthalpy

## Van Der Waals Force

Weak, random
Attractions between molecules

⇧VDW = High entropy

## *How effective are current antimalarial drugs?*

- Evaluating effectiveness through **stability/frequency** of the drug to the plasmepsin
- Focus on chloroquine drug

# Methods for Q2

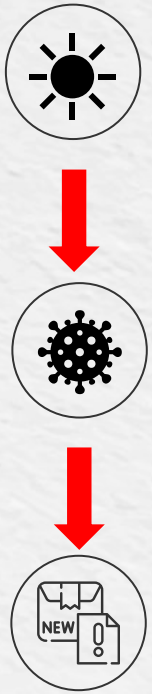
- Most Stable = Lowest Energy = Most Likely in Real Life
- Most Frequent = Highest Biological Relevance
- Finding inhibition constants (Ki)
  - Small Ki: inhibitor is strong (tightly binds to enzyme)
  - Large Ki: inhibitor is weak (doesn’t bind well)

# Sickle Cell: Genetic Resistance to Malaria

- Humid, tropical climates created ideal conditions for Malaria to thrive

- Genetic adaptations emerged: Sickle Cell Trait

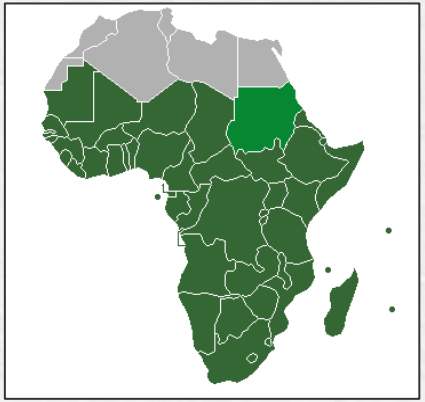
- Biological tradeoffs: anemia, high risk of stroke



# Understanding Malaria

Spreads through bite of infected female *Anopheles* mosquito OR through transfusion of blood

Image Source: CDC / JamesGathany



Primarily present in regions that are humid year-round

- Sub-Saharan Africa
- South America