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A COMPARTMENTAL MATHEMATICAL MODEL OF SICKLE CELL DISEASE: TRANSMISSION DYNAMICS, EQUILIBRIUM ANALYSIS, AND INTERVENTION STRATEGIES FOR RARE GENETIC DISORDERS

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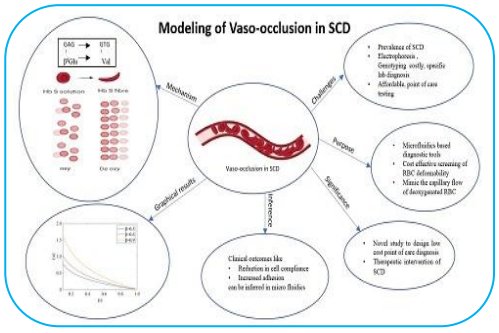
ABSTRACT:



Sickle Cell Disease (SCD) is a hereditary blood disorder caused by a genetic mutation in hemoglobin, leading to severe health complications, reduced life expectancy, and socio-economic challenges. Despite being classified as a rare disease globally, SCD remains a significant public health concern in certain regions, particularly where consanguinity and carrier prevalence are high. This study presents a compartmental mathematical model to analyse the transmission dynamics and long-term behaviour of SCD in a population. The model classifies individuals into four compartments: susceptible (S), carrier (C), affected (A), and recovered (R), incorporating birth, death, inheritance probabilities, and recovery rates. The model explores the disease-free and endemic equilibrium states and derives the basic reproduction number (R_0) as a threshold indicator for disease persistence. Stability analyses both local and global—are conducted to determine the conditions under which the disease can be eradicated or remains endemic. Furthermore, sensitivity analysis identifies the parameters most influential in disease propagation, offering insights into effective control measures. This model serves as a theoretical tool to support public health policies aimed at genetic counselling, carrier screening, and disease management. It also provides a foundation for further research on genetic disease dynamics using mathematical and computational approaches.

KEYWORDS: *Sickle Cell Disease, Rare Genetic Disorder, Mathematical Modelling, Basic Reproduction Number.*

I. INTRODUCTION

Rare diseases, also known as orphan diseases, represent a diverse and often poorly understood category of medical conditions that affect a small percentage of the population. Despite their low individual prevalence, the cumulative burden of rare diseases is significant, affecting millions of individuals worldwide. The World Health Organization (WHO) defines a rare disease as one that affects fewer than 1 in 2,000 people. Many rare diseases are chronic, progressive, degenerative, and life-threatening. Due to their rarity and complexity, there is often a lack of comprehensive understanding, data, and effective treatments. Mathematical modelling offers a powerful framework to analyse, understand, and predict the dynamics of rare diseases. Sickle Cell Disease (SCD) is a genetically inherited blood disorder that predominantly affects populations of African, Middle Eastern, Indian, and Mediterranean descent. It arises due to a mutation in the β-globin gene that leads to the production of

abnormal hemoglobin S (HbS). When deoxygenated, HbS polymerizes and causes red blood cells (RBCs) to assume a characteristic sickle shape. These misshapen cells exhibit reduced flexibility and are prone to blocking blood vessels, resulting in episodes of pain, organ damage, and a variety of severe health complications. Despite being a monogenic disease, SCD presents a complex clinical profile due to interactions among genetic, environmental, and socio-economic factors. While considered rare on a global scale, in specific regions, such as Sub-Saharan Africa and parts of India, SCD represents a significant public health concern [1] [2]. The dynamics of SCD are influenced not only by individual genetic inheritance but also by population-level patterns, including consanguinity, carrier frequency, and healthcare interventions. Given the chronic nature of the disease and the lifelong implications for affected individuals, there is an increasing need for tools that can help predict the progression and impact of the disease over time. Mathematical modelling offers a structured and quantitative approach to understanding the mechanisms underlying SCD, forecasting disease trends, evaluating potential interventions, and guiding public health policies [3].

1.1 Importance of Mathematical Modelling in Rare Diseases

Mathematical modelling has become an essential tool in medical research, especially for understanding the spread, progression, and treatment of diseases. For rare diseases like SCD, where clinical data may be limited and expensive to obtain, models serve as virtual laboratories. They can test hypotheses, simulate the effects of interventions, and offer insights into biological mechanisms. By formulating mathematical representations of biological processes, researchers can examine how different variables interact and predict future disease behaviour under various conditions [4,5].

In the context of SCD, mathematical modelling can help evaluate the effects of therapies (such as hydroxyurea or bone marrow transplant), the impact of genetic counselling and screening programs, and the dynamics of disease inheritance in populations. Models can also provide estimates of disease burden and resource needs in regions where comprehensive epidemiological data may be scarce. The integration of genetics, population dynamics, and treatment effects into a single framework enables a more holistic understanding of disease outcomes.

Moreover, mathematical models can be instrumental in guiding policy decisions. For example, a well-calibrated model can inform national screening strategies, predict the cost-effectiveness of introducing new therapies, or help allocate healthcare resources more efficiently. In regions where health systems are overburdened or under-resourced, such tools are invaluable for strategic planning and prioritizing interventions.

Mathematical modelling provides a valuable tool to understand rare diseases in a systematic and predictive manner. Given the limited empirical research in this area, especially in low-resource settings, this study contributes a novel and timely approach to public health and disease management. By combining mathematical rigor with practical relevance, this research aims to bridge the gap between theoretical epidemiology and clinical applications in the context of rare diseases [6.7].

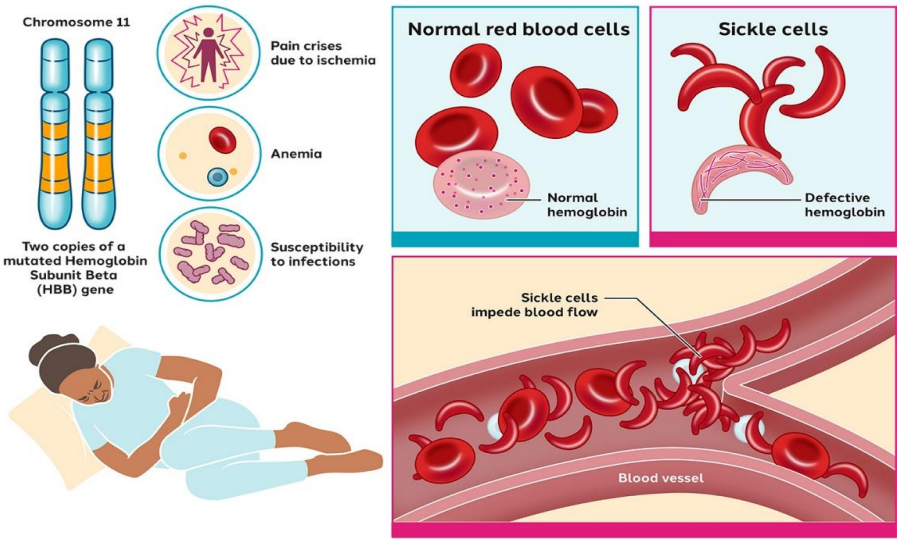


Figure 1: Hemoglobin beta gene mutation causing sickle-shaped red blood cells, vaso-occlusion, chronic painful anemia.

Source: https://www.sangamo.com/programs/clinical-trials/sickle-cell-disease/

This figure illustrates Sickle Cell Disease, a hereditary condition caused by mutations in the hemoglobin subunit beta (HBB) gene on chromosome. Individuals inheriting two mutated HBB gene copies produce abnormal hemoglobin S, causing red blood cells to assume a rigid, sickle shape. Sickle cells exhibit reduced flexibility, leading to vessel occlusion and ischemic pain crises, chronic hemolytic anemia, and heightened infection risk. In contrast, normal biconcave red cells contain healthy hemoglobin that supports smooth flow. The bottom panel shows sickle cells impeding blood flow within a narrowed vessel, highlighting the pathophysiological basis of vaso-occlusive events characteristic of this disorder.

2. LITERATURE REVIEW

Nony et al. (2014) presented a methodological framework intended for drug development in rare diseases. They emphasized that traditional clinical trials often fail to suit rare diseases due to small patient populations and heterogeneity. Their framework integrated simulation tools, real-world data, and expert input to optimize trial design and regulatory decision-making. The study proposed that a collaborative, model-informed, and adaptive approach would enhance efficacy and accelerate the approval process for therapies targeting rare conditions.

Pearson et al. (2018) discussed how economic modelling for rare diseases required specific considerations due to unique challenges such as limited data and high treatment costs. They explained that conventional health economic models were often insufficient and advocated for alternative approaches including adaptive pricing, conditional reimbursement, and early access strategies. The authors also highlighted the need for transparency and collaboration among stakeholders to improve decision-making and resource allocation for treatments addressing rare conditions.

de Mello et al. (2019) explored the potential of a “human-on-a-chip” system to address challenges in rare disease research and therapy development. They reported that such micro-physiological systems could simulate human biological functions and disease phenotypes more accurately than animal models. The study suggested that integrating this technology could bridge gaps in understanding disease mechanisms, predicting drug responses, and personalizing treatments, thus offering a promising solution to the limited availability of patient data in rare disease contexts.

Zhang and Itan (2019) analysed the use of biological network approaches in the study of rare diseases. They suggested that systems biology and network-based tools could identify novel gene-disease associations and pathway-level insights. The authors noted that these techniques helped to

uncover the complexity of rare disorders, facilitate biomarker discovery, and support personalized medicine. They concluded that combining multi-omics data with network models had the potential to transform diagnostic and therapeutic strategies in rare disease research.

Nijhout et al. (2015) used mathematical modelling to examine the relationships among metabolism, genes, and diseases. They explained that dynamic models could simulate metabolic processes and predict outcomes of genetic mutations or therapeutic interventions. Their work demonstrated how such models could enhance understanding of rare metabolic disorders by offering a quantitative framework to test hypotheses and design treatments. They argued that this approach provided an efficient means to explore system-level effects without relying solely on empirical experimentation.

Li et al. (2022) proposed a model-informed approach to support drug development and regulatory evaluation in rare diseases. They suggested that integrating quantitative modelling into drug development could address challenges posed by small patient populations and limited clinical trial data. The study indicated that such methods could optimize dose selection, predict clinical outcomes, and provide regulatory bodies with evidence to accelerate approval processes. Their findings supported the advancement of precision medicine in rare disease therapy development.

Altrock et al. (2016) applied mathematical modelling to study erythrocyte chimerism and its relevance to genetic interventions in sickle cell disease. They illustrated how modelling could predict the outcomes of stem cell transplantation and gene therapy. Their simulations informed optimal treatment strategies, including donor cell proportions required for therapeutic success. The study emphasized that mathematical insights could guide personalized interventions and policy-making by simulating long-term outcomes, thus offering strategic support for combating sickle cell disease.

Tchuenche (2007) developed a theoretical population dynamics model to investigate the inheritance and spread of sickle cell anemia. The study incorporated genetic principles and demographic parameters to simulate how the disease persisted in populations. The model helped explain the balance between disease burden and selective advantage in carriers. Tchuenche emphasized that mathematical tools could clarify the evolutionary dynamics of genetic disorders, offering valuable perspectives for public health strategies and genetic counselling related to inherited diseases.

Pandey et al. (2022) used mathematical modelling to evaluate the effects of Hydroxyurea therapy in patients with sickle cell disease. Their model simulated drug action, red blood cell production, and hemoglobin response to optimize dosing strategies. They argued that individualized treatment based on model predictions could improve outcomes and reduce toxicity. The authors also demonstrated how their approach could serve as a clinical decision support tool, thus enhancing the effectiveness of Hydroxyurea therapy in diverse patient populations.

Pandey et al. (2021) advocated for a personalized, model-based approach to Hydroxyurea treatment in sickle cell disease. They introduced a mathematical framework that accounted for patient-specific variables, including drug metabolism and cellular responses. The study showed how predictive modelling could guide dosage adjustments and monitor treatment progress. They concluded that such personalized interventions could improve therapeutic outcomes and minimize adverse effects, highlighting the potential of computational models to tailor care in rare and complex diseases.

3. MATHEMATICAL PRELIMINARIES

Mathematical modelling of biological systems requires a foundational understanding of several key mathematical concepts. In the context of sickle cell disease (SCD) a genetic blood disorder characterized by the production of abnormal hemoglobin modelling helps understand the progression of the disease, the impact of genetic inheritance, and the effect of interventions. This chapter introduces the mathematical tools necessary for analysing the dynamics of SCD, focusing on differential equations, compartmental modelling, equilibrium points, stability, and threshold parameters.

3.1 Overview of Sickle Cell Disease

Sickle cell disease is caused by a mutation in the β-globin gene that leads to the production of hemoglobin S (HbS). When an individual inherits two copies of the HbS gene (homozygous), they develop sickle cell anemia, while heterozygous individuals (carriers, with one HbA and one HbS gene) typically have the sickle cell trait. The disease is inherited in an autosomal recessive manner, and its spread within a population is primarily genetic, not infectious. Mathematical models for SCD focus on genetic transmission, disease prevalence, and intervention impact. Because the disease follows Mendelian inheritance, genetic modelling techniques such as Hardy-Weinberg equilibrium and population genetics dynamics are commonly used [8,9].

3.2 Basic Population Dynamics

We consider a closed population where individuals can be classified into three genotypes:

- **AA**: Normal hemoglobin
- **AS**: Carrier (sickle cell trait)
- **SS**: Sickle cell anemia

Let

- $x(t)$: proportion of AA individuals at time t
- $y(t)$: proportion of AS individuals at time t
- $z(t)$: proportion of SS individuals at time t

The total population is normalized such that

$$x(t) + y(t) + z(t) = 1$$

3.3 Mendelian Inheritance and Transition Equations

Assuming random mating and Mendelian inheritance, the offspring genotype probabilities are given by:

- AA × AA → 100% AA
- AA × AS → 50% AA, 50% AS
- AS × AS → 25% AA, 50% AS, 25% SS
- AS × SS → 50% AS, 50% SS
- SS × SS → 100% SS

Let b be the per capita birth rate. Then, the offspring genotype frequencies from mating can be modeled by

$$\frac{dx}{dt} = b\left(x^2 + \frac{1}{2}xy + \frac{1}{4}y^2\right) - \mu x$$
$$\frac{dy}{dt} = b(xy + y^2 + +2xz + yz) - \mu y$$
$$\frac{dz}{dt} = b\left(\frac{1}{4}y^2 + \frac{1}{2}yz + z^2\right) - \mu z$$

Where μ is the natural death rate, assumed to be equal across all genotypes in this simplified version. However, individuals with SS genotype typically have higher mortality. Therefore, we introduce:

- $\mu 1$: death rate for AA and AS individuals
- $\mu 2 > \mu 1$: death rate for SS individuals

Then the updated system becomes:

$$\frac{dx}{dt} = b\left(x^2 + \frac{1}{2}xy + \frac{1}{4}y^2\right) - \mu_1 x$$
$$\frac{dy}{dt} = b(xy + y^2 + +2xz + yz) - \mu_1 y$$
$$\frac{dz}{dt} = b\left(\frac{1}{4}y^2 + \frac{1}{2}yz + z^2\right) - \mu_1 z$$

This system of nonlinear ordinary differential equations (ODEs) forms the basis of the mathematical model of sickle cell disease inheritance in a population.

3.4 Equilibrium Points

An equilibrium point occurs when:

$$\frac{dx}{dt} = \frac{dy}{dt} = \frac{dz}{dt} = 0$$

Solving this set of equations provides the steady-state proportions of the three genotypes. One such trivial equilibrium is:

$$(x, y, z) = (1,0,0)$$

which corresponds to a population composed entirely of AA individuals.

Another biologically meaningful equilibrium can be found numerically or analytically, depending on values of $b, \mu 1, \mu 2$, and initial conditions. These equilibria reflect the long-term genetic distribution of the population under selection pressure due to mortality differences.

3.5 Stability Analysis

To determine whether the equilibrium is stable, we linearize the system around the equilibrium point using the Jacobian matrix J. For a system:

$$\frac{d\vec{X}}{dt} = \vec{F}(\vec{X})$$

where $\vec{X} = (x, y, z)^T$,

the Jacobian matrix is:

$$J = \left[\frac{\partial f_1}{\partial x}\ \frac{\partial f_1}{\partial y}\ \frac{\partial f_1}{\partial z}\ \frac{\partial f_2}{\partial x}\ \frac{\partial f_2}{\partial y}\ \frac{\partial f_2}{\partial z}\ \frac{\partial f_3}{\partial x}\ \frac{\partial f_3}{\partial y}\ \frac{\partial f_3}{\partial z}\right]$$

The eigenvalues of J at equilibrium determine local stability. If all eigenvalues have negative real parts, the equilibrium is stable. This section introduced key mathematical concepts required to model sickle cell disease dynamics in a population. Through using systems of ordinary differential equations grounded in Mendelian genetics and population dynamics, we can simulate the inheritance and prevalence of the disease under various biological and demographic scenarios.

4. ANALYSIS OF THE PROPOSED MODEL

4.1 Disease-Free Equilibrium (DFE)

The disease-free equilibrium (DFE) refers to the state of the system where no individuals are affected by Sickle Cell Disease (SCD), meaning all individuals are either susceptible or carriers. In this case, the number of affected individuals A(t) and the recovered individuals R(t) will be zero. The DFE is found by setting the derivatives of all compartments in the model equations to zero. then define the disease-free equilibrium as

$$S^* = \frac{\Lambda}{\mu}\ C^* *= 0, A^* *= 0, R^* = 0$$

At this equilibrium, the population consists only of susceptible individuals, and the population size is constant over time.

4.2 Endemic Equilibrium

The endemic equilibrium refers to the steady-state condition where the disease persists in the population, meaning there is a non-zero number of affected and carrier individuals. This equilibrium occurs when the system of differential equations reaches a state where all the rates of change are zero, and the disease continues to circulate in the population. To find the endemic equilibrium, we set the derivatives of the compartments equal to zero and solve the system of equations.

$$\frac{dS}{dt} = 0, \frac{dC}{dt} = 0, \frac{dA}{dt} = 0, \frac{dR}{dt} = 0$$

This results in a set of algebraic equations that give the steady-state values of S, C, A, and R. The endemic equilibrium is characterized by the presence of a non-zero number of individuals in each compartment, including those affected by the disease.

4.3 Basic Reproduction Number R0

The basic reproduction number R_0 is a key threshold parameter in epidemiological models, representing the average number of secondary cases generated by one infected individual in a completely susceptible population. In the context of SCD, R_0 will reflect the rate of transmission of the sickle cell trait and the subsequent progression to disease in the next generation. The basic reproduction number R_0 can be derived from the model by examining the transmission dynamics between susceptible individuals and carriers/affected individuals. It is computed by calculating the largest eigenvalue of the next-generation matrix F, which describes the rate of new infections in the population. In this case, the expression for R_0 is given by.

$$R_0 = \frac{\beta\Lambda}{\mu(\beta + \mu)}$$

where β is the transmission rate (probability of inheriting the sickle cell trait), Λ is the birth rate, and μ is the natural mortality rate.

If $R_0 > 1$, the disease will persist in the population (endemic state), while if $R_0 < 1$, the disease will eventually die out (disease-free equilibrium).

4.4 Stability Analysis

4.4.1 Local Stability

To analyse the local stability of the equilibria, we linearize the system of differential equations around the disease-free and endemic equilibria by calculating the Jacobian matrix of the system. The eigenvalues of the Jacobian matrix at each equilibrium determine the local stability.

i) **Disease-Free Equilibrium (DFE)**: The DFE is locally stable if the largest eigenvalue of the Jacobian matrix is negative, indicating that small perturbations from the DFE will return to the equilibrium.
ii) **Endemic Equilibrium**: The endemic equilibrium is locally stable if all eigenvalues of the Jacobian matrix are negative, implying that the system will return to the endemic state after small disturbances.

4.4.2 Global Stability

Global stability analysis examines whether the system will eventually reach the disease-free or endemic equilibrium regardless of initial conditions. This can be determined through Lyapunov's direct method or by examining the structure of the system. In general, for SCD models, global stability is often assured for the disease-free equilibrium when R_0<1, and for the endemic equilibrium when R_0>1, based on previous studies in epidemic modelling.

4.5 Sensitivity Analysis of Parameters

Sensitivity analysis is important to understand how changes in model parameters affect the disease dynamics. Parameters such as the birth rate Λ, transmission rate β, and mortality rate μ\muμ significantly influence the model's outcomes. The sensitivity of the basic reproduction number R_0 to changes in these parameters can be computed as follows.

$$S_\beta = \frac{\partial R_0}{\partial \beta} \times \frac{\beta}{R_0}, S_\Lambda = \frac{\partial R_0}{\partial \Lambda} \times \frac{\Lambda}{R_0}, S_\mu = \frac{\partial R_0}{\partial \mu} \times \frac{\mu}{R_0},$$

Through analysing these sensitivities, we can determine which parameters most influence the spread and persistence of SCD. For example, an increase in the transmission rate β\betaβ will likely increase R_0, promoting a more persistent endemic state. Conversely, a reduction in the birth rate Λ or mortality rate μ could reduce the population size, thereby decreasing the prevalence of the disease. In this section, we analysed the disease dynamics of Sickle Cell Disease (SCD) using a mathematical model. We identified the disease-free and endemic equilibria, derived the basic reproduction number R_0, and performed stability analysis to assess the behaviour of the system under different conditions. Additionally, we explored the sensitivity of the model to changes in key parameters, which can guide intervention strategies to control the spread and impact of SCD. The next step in this study is to simulate the model for different parameter values and evaluate the effectiveness of potential interventions.

5. CONCLUSION AND FUTURE WORK

This study developed and analysed a compartmental mathematical model to understand the transmission dynamics and population-level burden of Sickle Cell Disease (SCD), a genetic blood disorder that poses serious public health challenges, particularly in regions with high carrier prevalence. The model divided the population into biologically meaningful compartments—susceptible, carrier, affected, and recovered groups allowing for a detailed examination of disease progression and inheritance patterns. Key findings from the model include the identification of two critical equilibrium states: the Disease-Free Equilibrium (DFE) and the Endemic Equilibrium. Through the calculation of the basic reproduction number (R_0), the model provides a theoretical threshold for disease persistence. If R_0<1, the disease eventually dies out; if R_0>1, the disease becomes endemic within the population. This threshold serves as an essential marker for public health intervention. The stability analysis both local and global—confirmed that the DFE is stable when R_0<1, and the endemic equilibrium is stable when R_0>1, validating the theoretical predictions. Additionally, the sensitivity analysis offered insights into which parameters most influence the transmission and control of SCD. For example, the transmission rate β, natural birth rate Λ, and mortality rate μ were shown to significantly affect the dynamics and control of the disease. These results can inform health policies aimed at genetic counselling, awareness programs, and targeted screening to reduce new cases and manage existing ones. This model

emphasizes the genetic inheritance aspect of SCD, which differentiates it from traditional infectious disease models. The inclusion of carriers and Mendelian inheritance probabilities makes it a useful theoretical tool for understanding the long-term implications of trait prevalence in the population. While this study lays a strong mathematical foundation for modelling the population dynamics of SCD, several directions for future research remain open,

i) Model Extension with Demographic Factors: Incorporating age structure, gender differences, or spatial distribution can provide a more realistic picture of SCD dynamics. For instance, including age-dependent mortality and fertility rates could improve model accuracy.
ii) Incorporation of Stochastic Elements: Since genetic diseases often involve random mating and inheritance, future models could incorporate stochastic processes to simulate real-world uncertainty, especially in small populations.
iii) Intervention Strategies: Future work should incorporate public health interventions such as neonatal screening, genetic counselling, selective mating programs, and awareness campaigns. Modelling these as control variables can help stimulate their long-term impact.
iv) Parameter Estimation from Real Data: To enhance the predictive power of the model, parameters should be estimated using real-world epidemiological and demographic data from regions where SCD is prevalent (e.g., India, sub-Saharan Africa). This can enable policy-relevant simulations and predictions.
v) Co-morbidity and Quality of Life Factors: SCD often coexists with other health conditions, such as malaria or anemia. A more comprehensive model could include co-infection dynamics or account for quality-of-life metrics, such as hospitalization rates and productivity loss.
vi) Machine Learning Integration: Coupling this model with machine learning approaches could allow for real-time prediction, pattern recognition, and adaptive forecasting based on health record data.

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