

A Mathematical Modeling on the Stability Analysis of Heart Disease Dynamics

Christiana Ene Agbo^{1*}, Roseline Toyin Abah², and Ayinde Muhammed Abdullahi³

^{1,2,3}Department of Mathematics, University of Abuja, Nigeria

*Corresponding author: agbo.ene@uniabuja.edu.ng

ABSTRACT Heart disease, pose a significant global health challenge, demanding innovative approaches for prevention and control. This research develops a sophisticated mathematical model that integrates lifestyle, and environmental exposure to enhance our understanding of heart disease dynamics. The model integrates the of interconnected ordinary differential equations to elucidate population-level dynamics in disease transmission and agent-based modeling to simulate individual-level variations in lifestyle, genetic predispositions, and environmental exposures. The model assumes linear additive of risk factors, homogeneity within populations, and stable parameters over time. It incorporates lifestyle modifications, genetic predispositions, and environmental exposures as key components, recognizing their impact on heart disease risk. In this paper, a model incorporating the reproduction number, endemic equilibrium, and disease-free equilibrium has been developed utilizing stability analysis methods, including the Hurwitz stability criterion and linear stability analysis.

KEYWORDS: Heart disease, Cardiovascular System (CVS), Stability analysis, reproduction number, Endemic and Equilibrium.

I. INTRODUCTION

Heart disease encompasses any pathology that impacts the heart and vascular system, including but not limited to Coronary Artery Disease (CAD), arrhythmias, and heart failure. Such conditions may lead to myocardial injury, manifesting symptoms such as angina pectoris and arrhythmias, as reported by the American Heart Association (2019). Based on reports from the World Health Organization, cardiovascular disease remains the foremost cause of mortality on a global scale. Furthermore, for practically all countries, its rising tendency over the previous thirty years is still continuing by Cai et al. (2023). In the year 2019, cardiovascular diseases were responsible for over 18 million mortalities globally, representing 32% of total deaths; myocardial infarctions and cerebrovascular accidents constituted 85% of these fatalities. by World Health Organization (2021). This fact has stimulated research into models of the heart disease and cardiovascular system (CVS), where studies using mathematical and computational models are considerably easier and less expensive to conduct than in vivo or in vitro studies. The cardiovascular system's primary functions include supplying the body with oxygen and other nutrients and barring metabolic waste products. The pulmonary rotation, which moves blood through the lungs, and the systemic rotation, which moves blood throughout the body, are the two vascular circuits that the heart pumps tube through in order to negotiate their functions by Batzel et al. (2007).

Since the heart diseases is a relatively complex system that requires knowledge from multiple physics and chemistry disciplines to fully comprehend its behavior, models or simulators that vary in detail have been developed in an effort to provide a comprehensive understanding of the system's functioning. Numerous models have been proposed and examined in this regard from various angles, including the study of gas exchange, neuro-regulation mechanisms, and the system's hemodynamics of the heart; however, the latter approach has consistently drawn more attention because of its potential physiological or clinical applications by Simaan (2009). The two primary approaches utilized for this kind of approach are (1) lumped parameter 2 models, which summarize the main behaviors of each of the heart components in a simplified way by Ortiz-Rangel et al (2022). The (2) distributed parameter models, which use finite element software to describe the cardiovascular system CVS in one, two, or three dimensions by Alastruey et al. (2007) or modeling using a hydraulic approach by Rosalia et al. (2021).

The rise in computing power has drawn a lot of attention, in particular, to three-dimensional distributed parameter models in recent decades. However, because these models are more complex and concentrate on partial vascular zones, they require longer simulation times and simpler models to define their boundary conditions by Roy et al (2021). According to Keshavarz-Motamed (2020), the models provide the ability to diagnose or forecast how the CVS will behave in a patient experiencing cardiovascular malfunction or pathology. They may also be used to examine the functionality of auxiliary devices by Liu et al. (2020). The existing literature provides a solid foundation for understanding heart disease epidemiology, risk factors, and the role of mathematical modeling. However, a critical gap exists in comprehensive models that integrate lifestyle and environmental factors. Using stability analysis methods including Hurwitz stability criteria and linear stability analysis, a model based on reproduction number, endemic equilibrium, and disease-free equilibrium will be designed in this study.

II. METHODOLOGY

The model will employ a compartmental structure to represent the population dynamics in relation to heart disease. The population is stratified into distinct compartments, each capturing a specific aspect of the individual's health status.

A. MODEL VARIABLE DESCRIPTION

- (a). Susceptible (S): Individuals who are free from heart diseases and have not experienced heart disease mortality.
- (b). Exposed (E): This compartment represents individuals exposed to different levels of heart disease. Exposure levels are determined based on dietary patterns, considering factors such as processed food consumption and traditional dietary habits.
- (c). Infected (I): Individuals in this compartment have experienced changes in cardiovascular health. This compartment accounts for individuals with elevated heart disease or other cardiovascular risk factors.
- (d). Recovered (R): Individuals who have either recovered from the heart disease impact. This compartment considers lifestyle modifications, medical interventions, or other factors influencing recovery.

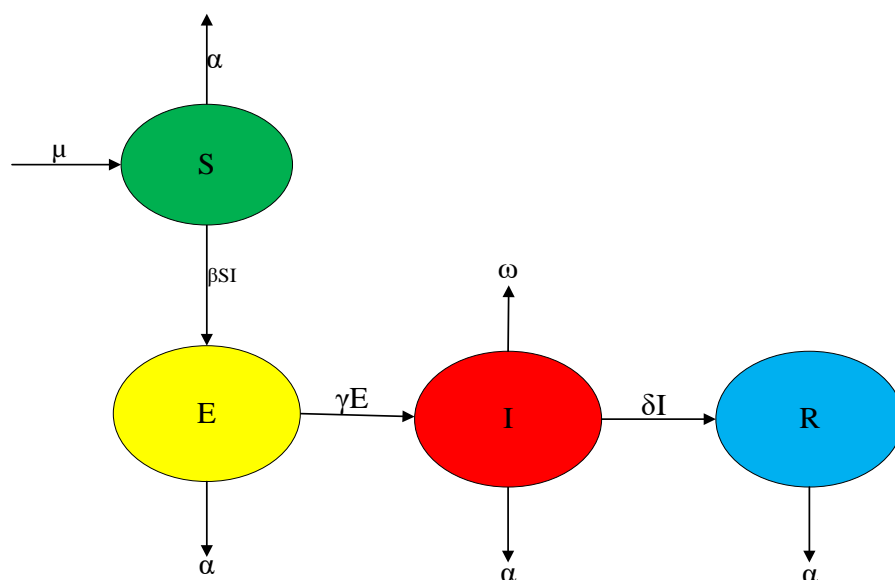


Figure 1: Model Design

S/NO	PARAMETERS	DESCRIPTION
1	μ	Per capita Birth rate
2	σ	Natural death rate
3	β	Transmission rate of heart diseases
4	γ	Progression rate of exposed class into infected class
5	ω	Mortality rate due to heart diseases
6	δ	Recovery rate

B. MODEL FORMULATION

Temporal rates of change inside each compartment are captured by a series of ordinary differential equations that hinder transitions between these compartments. The formulation of the model incorporates the intrinsic progression of cardiac health, alongside factors such as adaptation, recovery, and mortality, which serve as the driving forces that influence these transitions.

The model equations are as follows:

$$\frac{dS}{dt} = \mu - \beta SI - \alpha S \quad (1)$$

$$\frac{dE}{dt} = \beta SI - \gamma \cdot E - \alpha E \quad (2)$$

$$\frac{dI}{dt} = \gamma \cdot E - (\alpha + \delta + \omega)I \quad (3)$$

$$\frac{dR}{dt} = \delta \cdot I - \alpha R \quad (4)$$

as

$$P(t) = S(t) + E(t) + I(t) + R(t) \quad (5)$$

III. MODEL ANALYSIS

A. INVARIANT AND FEASIBILITY ANALYSIS

For equation (1) - (4) we investigate solutions with $S_0 \geq 0$, $E_0 \geq 0$, $I_0 \geq 0$ and $R_0 \geq 0$ as initial condition. First, we demonstrate that the population as a whole does not change. If (1- 4) are sum up we have

$$(S + E + I + R)' = \mu - \mu(S + E + I + R) \quad (6)$$

If we let a $P_0 = S_0 + E_0 + I_0 + R_0$ then $P(t)$ implies

$$(1 - P)' = -\mu(1 - P) \quad (7)$$

which can be solved to yield

$$1 - P(t) = (1 - P_0)e^{-\mu t}, t \in \mathbb{R}^4 \quad (8)$$

Based on this relationship, it is possible to draw the following conclusions:

(1) if $P_0 = 1$, then $P(t) = 1$ for every t and total population $P = 1$ if it holds true for every t .

(2) if $P_0 = 1$ then $P(t) \rightarrow 1$ exponentially as $t \rightarrow \infty$.

Consequent to these deductions, we are able to infer that all limit sets as $t \rightarrow \infty$ of solutions to equations (1-4) are confined within the compartment $S + E + I + R = 1$, which also maintains invariance. Should our focus be directed towards the limiting behaviors of solutions, it becomes essential to confine our analysis to the invariant plane $S + E + I + R = 1$. The invariance of this plane implies that the total population $P(t)$ remains constant at 1 for all t if $P_0 = 1$. The constant total population P has been normalized to 1 for the sake of simplicity. The conservation of the total population permits us to streamline model equations (1-4) by effectively reducing the number of variables by one. For example, we can implement the substitution.

$$R(t) = 1 - S(t) - E(t) - I(t) \quad (9)$$

The system is analyzed with a focus exclusively on the equations pertaining to S , E , and I . Upon comprehending the dynamics of $S(t)$, $E(t)$ and I the dynamics of $R(t)$ can subsequently be derived from the linear relationship articulated in equation (9). Given that equation (1) does not incorporate the variable R , we may initially disregard the R equation and examine the ensuing three-dimensional system of differential equations.

$$S' = \mu - \beta SI - \alpha S \quad (10)$$

$$E' = \beta SI - \gamma \cdot E - \alpha E \quad (11)$$

$$I' = \gamma \cdot E - (\alpha + \delta + \omega)I \quad (12)$$

In the subsequent portion of this section, we concentrate our theoretical examination on the mathematical frameworks delineated in equations (10-12). The findings we present can be efficiently adapted to correspond with those articulated in equations (1-4). Initially, we establish the inherent feasible domain associated with equations (10-12).

$$\mathbb{R}^3 = \{(S, E, I) | S \geq 0, E \geq 0, I \geq 0\} \quad (13)$$

Is positive invariant and belongs to equation (10-12). It is possible to check whether the vector field of (11-12) at the boundary of \mathbb{R}^3 is either tangential to the boundary or pointing to the interior of \mathbb{R}^3 . Similarly, for equation (1-4) we can also show that the non-negative orthant of \mathbb{R}^4 is invariant. The positive invariance of \mathbb{R}^4 is synonymous with the assertion that non-negative initial conditions yield non-negative solutions for $t \geq 0$, a crucial characteristic given that all variables denoted by $S(t)$, $E(t)$ and $I(t)$, $R(t)$, and correspond to the populations of individuals and must inherently be non-negative. Under these circumstances, we assert that the model is deemed well-posed. It is noteworthy that there is no necessity to examine all possible initial conditions in \mathbb{R}^3 . letting $S + E + I + R = 1$ and $R(t) \geq 0$ and $S(t) + E(t) + I(t) \leq 1$ for all t . Hence only the initial conditions at the bounded region are considered.

$$\nabla = \{(S, E, I) \in \mathbb{R}^3 | S + E + I \leq 1\} \quad (14)$$

We can confirm that ∇ is positively invariant for equation (10-12) by taking into account the direction of the vector field on the plane $S + E + I + R = 1$. Solutions beginning ∇ in will stay in ∇ , proving that the solution is feasible.

B. STABILITY ANALYSIS

The equilibrium points for endemic and disease-free conditions are ascertained using stability analysis.

Each of the two equilibrium points (10–12) must equal zero or $\frac{dS}{dt} = 0$, $\frac{dE}{dt} = 0$, $\frac{dI}{dt} = 0$ thus obtained

$$\mu - \beta SI - \alpha S = 0 \quad (15)$$

$$\beta SI - \gamma \cdot E - \alpha E = 0 \quad (16)$$

$$\gamma \cdot E - (\alpha + \delta + \omega)I = 0 \quad (17)$$

consequently, the equilibrium points of S , E , and I is determined.

C. DISEASE FREE EQUILIBRIUM

The equilibrium point for a disease-free state is the point at which no disease exists, indicating

$$E = 0, I = 0 \quad (18)$$

Then

$$S = \frac{\mu}{\alpha} \quad (19)$$

in equation (15)

Then, the disease-free equilibrium for the heart disease model is:

$$K_0 = (S, E, I) = \left(\frac{\mu}{\alpha}, 0, 0\right) \quad (20)$$

D. ENDEMIC EQUILIBRIUM FOR HEART DISEASE MODEL

The endemic equilibrium point indicates the potential for disease transmission. To sustain the disease among the population, the model necessitates that the values of $S \neq 0$, $E \neq 0$, $I \neq 0$, and $R \neq 0$ from equation (10 – 12). The endemic equilibrium point for this model is obtained

$$S = \frac{(\omega + \delta + \mu)(\gamma + \alpha)}{\beta\gamma} \quad (21)$$

$$E = \frac{\beta\gamma\mu - (\omega + \delta + \alpha)}{\beta\gamma} \quad (22)$$

$$I = \frac{\beta\gamma\mu - (\omega + \delta + \alpha)(\gamma + \alpha)}{\beta(\omega + \delta + \alpha)(\gamma + \alpha)} \quad (23)$$

Then, endemic equilibrium points for the model are

$$K_e = (S, E, I) = \left(\frac{(\omega + \delta + \mu)(\gamma + \alpha)}{\beta\gamma}, \frac{\beta\gamma\mu - (\omega + \delta + \alpha)}{\beta\gamma}, \frac{\beta\gamma\mu - (\omega + \delta + \alpha)(\gamma + \alpha)}{\beta(\omega + \delta + \alpha)(\gamma + \alpha)} \right) \quad (24)$$

E. BASIC REPRODUCTION NUMBER (R_0)

The number which corresponds to the number of newly infected people followed by only one infected individual in a totally susceptible population is termed as the basic reproduction number of an infectious disease by Diekmann et al. (2010). The basic reproduction number is computed using the next-generation matrix method using vector variables. Writing the subsystem in matrix form as:

$$\frac{d}{dt}x = f(x) - v(x) \quad (25)$$

where the vectors f and v are defined below, with the partial derivatives of f and v evaluated

at K_0 being given by

$$F = Df = \frac{\partial f}{\partial x} \text{ and } V = Dv = \frac{\partial v}{\partial x} \quad (26)$$

The fraction of susceptible individuals at the endemic level or the reduced reproduction number based on the vectors f and v that are selected can be determined by Yang (2014).

Diagonal matrix V is taken into consideration to determine the fundamental reproduction number R_0 . Thus, the f and v vectors are

$$f = \begin{pmatrix} \beta S \\ 0 \end{pmatrix} = \begin{pmatrix} \beta \frac{\mu}{\alpha} \\ 0 \end{pmatrix} \quad (27)$$

and

$$v = \begin{pmatrix} -(\gamma + \alpha) \\ \gamma - (\alpha + \delta + \omega) \end{pmatrix} \quad (28)$$

Result in F and V is given by

$$F = \begin{pmatrix} 0 & \beta \frac{\mu}{\alpha} \\ 0 & 0 \end{pmatrix} \quad (29)$$

and

$$V = \begin{pmatrix} -(\gamma + \alpha) & 0 \\ \gamma & -(\alpha + \delta + \omega) \end{pmatrix} \quad (30)$$

$$V^{-1} = \begin{pmatrix} \frac{-1}{(\gamma + \alpha)} & 0 \\ \frac{\alpha}{(\gamma + \alpha)(\alpha + \delta + \omega)} & \frac{-1}{(\alpha + \delta + \omega)} \end{pmatrix} \quad (31)$$

so that

$$\begin{aligned} FV^{-1} &= \begin{pmatrix} 0 & \beta \frac{\mu}{\alpha} \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{-1}{(\gamma + \alpha)} & 0 \\ \frac{\alpha}{(\gamma + \alpha)(\alpha + \delta + \omega)} & \frac{-1}{(\alpha + \delta + \omega)} \end{pmatrix} \\ &= \begin{pmatrix} \frac{\beta\mu}{(\gamma + \alpha)(\alpha + \delta + \omega)} & \frac{\beta\mu}{(\alpha + \delta + \omega)} \\ 0 & 0 \end{pmatrix} \end{aligned} \quad (32)$$

Then the basic reproduction number R_0 , given by $\sigma(FV^{-1})$ where σ denoted the dominant eigenvalue is

$$R_0 = \frac{\beta\mu}{(\gamma+\alpha)(\alpha+\delta+\omega)} \quad (33)$$

F. LOCAL STABILITY ANALYSIS

The basic reproduction number is used as a threshold parameter in the preceding section to determine the number of equilibria in the model equation (1–4). We will show in this section that it also establishes the equilibria's local stability.

Theorem 1

- (a). If $R_0 < 1$, then the equation (15- 17) of the disease-free equilibrium is locally asymptotically stable.
- (b). If $R_0 > 1$, then equation (15-17) of the disease-free equilibrium becomes unstable and the endemic equilibrium K_e is asymptotically stable.

Proof

Equation (15-17) found the Jacobian matrices

$$J(K_0) = \begin{bmatrix} -(\beta I + \alpha) & 0 & -\beta S \\ \beta I & -(\gamma + \alpha) & \beta S \\ 0 & \gamma & -(\alpha + \delta + \omega) \end{bmatrix} \quad (34)$$

And the eigenvalue of the Jacobian matrix in Eq. (4.1) is

$$\det(\lambda I - J(K_0)) = \begin{vmatrix} \lambda + (\beta I + \alpha) & 0 & -\beta S \\ \beta I & \lambda + (\gamma + \alpha) & \beta S \\ 0 & \gamma & \lambda + (\alpha + \delta + \omega) \end{vmatrix} = 0 \quad (35)$$

Substituting the value $S = \frac{\mu}{\alpha}$ and $I = 0$ obtained

$$\begin{bmatrix} \lambda + \alpha & 0 & -\beta \frac{\mu}{\alpha} \\ 0 & \lambda + (\gamma + \alpha) & \beta \frac{\mu}{\alpha} \\ 0 & \gamma & \lambda + (\alpha + \delta + \omega) \end{bmatrix} = 0 \quad (36)$$

$$(\lambda + \alpha) \left[(\lambda + (\gamma + \alpha))(\lambda + (\alpha + \delta + \omega)) - \frac{\beta\gamma\mu}{\alpha} \right] = 0 \quad (37)$$

Let $A = \alpha$, $B = (\gamma + \alpha)$ and $C = (\alpha + \delta + \omega)$ so that (4.4) becomes

$$(\lambda + A)[(\lambda + B)(\lambda + C) - D] = 0 \quad (38)$$

The characteristics equation (4.5) is

$$(\lambda + A)[\lambda^2 + (B + C)\lambda + BC - D] = 0 \quad (39)$$

From equation (4.6) the eigenvalue $\lambda_1 = -A < 0$. Then the eigenvalue λ_2 and λ_3 satisfy

$$\lambda^2 + (B + C)\lambda + BC - D = 0 \quad (40)$$

Since

$$\lambda_2 + \lambda_3 = -(B + C) < 0 \quad (41)$$

$$\lambda_2\lambda_3 = BC - D = BC(1 - R_0) \quad (42)$$

If $R_0 < 1$ and $\lambda_2\lambda_3 > 0$, then λ_2 and λ_3 are either both real numbers possessing identical signs or complex numbers that serve as conjugates of one another. The stipulated condition $\lambda_2 + \lambda_3 < 0$ indicates that they are either both negative real numbers or complex numbers characterized by negative real components. Consequently, K_0 is deemed asymptotically stable in accordance with the Routh-Hurwitz stability criterion as articulated by Michael (2018). If $R_0 > 1$, then $\lambda_2\lambda_3 < 0$, and therefore λ_2 and λ_3 possess contrasting signs, leading to the conclusion that K_0 is unstable. The Jacobian matrix at K_e is

$$J(K_e) = \begin{bmatrix} -(\beta I_e + \alpha) & 0 & -\beta S_e \\ \beta I_e & -(\gamma + \alpha) & \beta S_e \\ 0 & \gamma & -(\alpha + \delta + \omega) \end{bmatrix} \quad (43)$$

If $R_0 > 1$ so that $K_e \in \nabla$.

The characteristic equation of $J(K_e)$ using the Routh–Hurwitz condition by Michael (2018) follows as:

$$\text{tr}J(K_e) = -(\beta I_e + \alpha)(\gamma + \alpha)(\alpha + \delta + \omega) < 0 \quad (44)$$

$$\begin{aligned} \det(J(K_e)) &= -(\beta I_e + \alpha)(\gamma + \alpha)(\alpha + \delta + \omega) - \beta I_e \beta S_e \gamma + (\beta I_e + \alpha)\gamma \beta S_e \\ &= -(\beta I_e + \alpha)(\gamma + \alpha)(\alpha + \delta + \omega) + \gamma \beta S_e \\ &= -(\beta I_e + \alpha)(\gamma + \alpha)(\alpha + \delta + \omega) + \alpha(\gamma + \alpha)(\alpha + \delta + \omega) \\ &= -\beta I_e(\gamma + \alpha)(\alpha + \delta + \omega) < 0 \end{aligned} \quad (45)$$

The sum of minor matrix of $J(K_e)$ is

$$\begin{aligned} H &= (\beta I_e + \alpha)(\gamma + \alpha) + (\beta I_e + \alpha)(\alpha + \delta + \omega) + (\gamma + \alpha)(\alpha + \delta + \omega) - \gamma \beta S_e \\ &= (\beta I_e + \alpha)(2\alpha + \gamma + \delta + \omega) \end{aligned} \quad (46)$$

since

$$(\gamma + \alpha)(\alpha + \delta + \omega) - \gamma \beta S_e = 0 \quad (47)$$

hence

$$\begin{aligned} \text{tr}J(K_e)H &= -(\beta I_e + \gamma + 3\alpha + \delta + \omega)(\beta I_e + \alpha)(2\alpha + \gamma + \delta + \omega) \\ &< -\beta I_e(\gamma + \alpha)(\alpha + \delta + \omega) = \det(J(K_e)) \end{aligned} \quad (48)$$

This follows that K_e is asymptotically stable when $R_0 > 1$.

IV. RESULTS AND DISCUSION

The study formulated a mathematical framework to scrutinize the dynamics of heart disease, emphasizing both population-level dynamics and individual risk determinants, including lifestyle choices, genetic susceptibility, and environmental influences. The framework employs a compartmental SEIR (Susceptible, Exposed, Infected, Recovered) configuration alongside ordinary differential equations to depict transitions among compartments, thereby accounting for disease advancement, recovery, and mortality. The invariant and feasibility assessments indicated that the population dynamics remain confined within the feasible domain of the model, thereby ensuring realistic behavior; furthermore, the model equation was demonstrated to be positively invariant, signifying that all variables (which denote populations) remain non-negative and within predetermined bounds over time. A stability analysis was conducted utilizing the Hurwitz criterion and the basic reproduction number to ascertain equilibrium states. A disease-free equilibrium was identified, characterized by the absence of heart disease transmission. It was demonstrated that this state exhibits local asymptotic stability when the basic reproduction number (R_0) < 1 , while an endemic equilibrium materializes when the reproduction number (R_0) > 1 , indicating persistent disease transmission. This equilibrium was established to be asymptotically stable.

The basic reproduction number (R_0) serves as a threshold parameter, with stability transitions occurring contingent upon whether the value of the reproduction number is below or above the critical threshold. The Jacobian matrix and its corresponding eigenvalues were employed to validate the stability criteria for both equilibrium states. The outcomes are congruent with theoretical anticipations, as disease-free conditions become unstable when the reproduction number surpasses 1. The incorporation of lifestyle and environmental determinants within the model constitutes a novel methodology, effectively addressing the deficiencies present in existing cardiovascular disease frameworks. The model furnishes a theoretical underpinning for evaluating interventions aimed at diminishing the prevalence of heart disease. These findings underscore the paramount significance of preventive strategies to sustain a disease-free equilibrium and alleviate the risk associated with endemic disease states.

V. CONCLUSION

In this scholarly article, we have introduced an SEIR epidemic model specifically designed for heart disease and examined the dynamics associated with this model utilizing theoretical methodologies. Initially, the parameter conditions pertaining to the invariant and feasible analyses of both the disease-free equilibrium and the endemic equilibrium are derived through rigorous analysis. Within the context of this model, we have established the basic reproduction number R_0 , which serves to delineate the dynamical behavior of model equations (1-4). when $R_0 < 1$, as delineated in Theorem 1, the disease-free equilibrium is locally asymptotically stable; furthermore, when $R_0 > 1$ Theorem 1 indicates that the disease-free equilibrium K_0 transitions to an unstable state while the endemic equilibrium K_e is characterized as asymptotically stable. Subsequently, by employing qualitative theory, we ascertain the potential stability states of the system that correspond to various equilibrium points, taking into account different parameters under a range of

parameter conditions. In conclusion, the study provides significant revelations regarding the complexities of heart ailments through the application of mathematical modeling, thereby enhancing the comprehension of the potential impact of interventions on disease prevalence

REFERENCES

- Alastruey, J., Parker, K., Peiro, J., Byrd, S., & Sherwin, S. (2007). Modelling the circle of Willis to assess the effects of anatomical variations and occlusions on cerebral flows. *Journal of Biomechanics*, 40(8), 1794–1805. <https://doi.org/10.1016/j.jbiomech.2006.07.008>
- American Heart Association. (2019). Cardiovascular diseases affect nearly half of American adults, statistics show.
- Batzel, J. J., Kappel, F., Schneditz, D., & Tran, H. T. (2007). *Cardiovascular and respiratory systems: Modeling, analysis, and control*. Society for Industrial and Applied Mathematics.
- Cai, L., Wang, R., & Zhang, D. (2023). Cardiac disease modeling with engineered heart tissue. In Kuehn, M. H., & Zhu, W. (Eds.), *Human iPSC-derived disease models for drug discovery. Handbook of Experimental Pharmacology* (Vol. 281). Springer. https://doi.org/10.1007/164_2023_681
- Diekmann, O., Heesterbeek, J. A. P., & Roberts, M. G. (2010). The construction of next-generation matrices for compartmental epidemic models. *Journal of the Royal Society Interface*, 7(47), 873–885. <https://doi.org/10.1098/rsif.2009.0386>
- Keshavarz-Motamed, Z. (2020). A diagnostic, monitoring, and predictive tool for patients with complex valvular, vascular, and ventricular diseases. *Scientific Reports*, 10, 6905. <https://doi.org/10.1038/s41598-020-63616-6>
- Liu, H., Liu, S., Ma, X., & Zhang, Y. (2020). A numerical model applied to the simulation of cardiovascular hemodynamics and operating condition of continuous-flow left ventricular assist device. *Mathematical Biosciences and Engineering*, 17(6), 7519–7543. <https://doi.org/10.3934/mbe.2020388>
- Li, M. Y. (2018). *An introduction to mathematical modeling of infectious diseases. Mathematics of Planet Earth*. Springer. <https://doi.org/10.1007/978-3-319-72122-4>
- Ortiz-Rangel, E., Guerrero-Ramírez, G. V., García-Beltrán, C. D., Guerrero-Lara, M., Adam-Medina, M., Astorga-Zaragoza, C. M., Reyes-Reyes, J., & Posada-Gómez, R. (2022). Dynamic modeling and simulation of the human cardiovascular system with PDA. *Biomedical Signal Processing and Control*, 71, 103151. <https://doi.org/10.1016/j.bspc.2021.103151>
- Rosalía, L., Ozturk, C., Van Story, D., Horvath, M. A., & Roche, E. T. (2021). Object-oriented lumped-parameter modeling of the cardiovascular system for physiological and pathophysiological conditions. *Advanced Theory and Simulations*, 4, 2000216. <https://doi.org/10.1002/adts.202000216>
- Roy, D., Mazumder, O., Sinha, A., & Khandelwal, S. (2021). Multimodal cardiovascular model for hemodynamic analysis: Simulation study on mitral valve disorders. *PLoS ONE*, 16(8), e0256467. <https://doi.org/10.1371/journal.pone.0256467>
- Simaan, M. A. (2009). Rotary heart assist devices. In *Springer handbook of automation* (pp. 1409–1422). Springer. https://doi.org/10.1007/978-3-540-78831-7_67
- Yang, H. M. (2014). The basic reproduction number obtained from Jacobian and next-generation matrices: A case study of dengue transmission modeling. *BioSystems*, 126, 52–75. <https://doi.org/10.1016/j.biosystems.2014.01.005>
- World Health Organization. (2021, October 11). Cardiovascular diseases (CVDs). *World Health Organization*. [https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds))