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BIFURCATION ANALYSIS MATHEMATICAL MODEL FOR THE SPREAD OF EXOGENOUS REINFECTION TUBERCULOSIS

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ABSTRACT

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Tuberculosis can spread in two ways: exogenously and endogenously. A mathematical model is used to analyse exogenous or external tuberculosis transmission in order to predict tuberculosis reinfection. Later, a study based on bifurcation was undertaken on the mathematical model. On the basis of the results, it was determined that the system of exogenous reinfection tuberculosis exhibited a change in stability characteristics and the type of equilibrium point, where the bifurcation parameter is $x = (\mu + k)(\mu + r + d) - \frac{\beta c \wedge k}{\mu N}$. When x is less than zero, the system displays one unstable equilibrium with a saddle point type; when x is equal to zero, the system's stability cannot be determined; and when x is greater than zero, the system of differential equations displays three types of equilibrium: node, star node, and spiral.

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1. INTRODUCTION

Tuberculosis is caused by Mycobacterium tuberculosis, which transmits the disease by direct contact between individuals with active tuberculosis [1]–[3]. The spread of tuberculosis can occur exogenously, endogenously, or both [4]–[6]. Exogenous spread occurs when people with active tuberculosis come into contact with one another. While the endogenous spread is the development of tuberculosis bacteria in individuals who have been previously infected, the individual develops into an individual infected with active tuberculosis [5]. The spread that repeatedly occurs due to contact between latent individuals and active individuals, thereby accelerating the development of bacteria in latent individuals, is called exogenous reinfection.

Globally, in 2020 there were 10 million people in the world suffering from tuberculosis (TB), and 1,2 million people die annually. Indonesia is one of the nations with the largest burden of tuberculosis, with an estimated 845,000 cases of TB-related illness and a death rate of 98.000, or 11 deaths every hour[7]. The transmission of tuberculosis must thereafter be examined.

Using a mathematical model, the spread of exogenous reinfection tuberculosis can be observed. The mathematical model is the process of translating real-world situations into mathematical assertions or mathematical models [8]. Then, a bifurcation-based study of the mathematical model was conducted. Bifurcation is a qualitative change characterized by variations in the number of equilibrium points due to varying parameter values [9]. The equilibrium point is a fixed, constant point with respect to time. The equilibrium point is divided into two parts: the hyperbolic equilibrium point (if the real part of the eigenvalues of the Jacobian matrix at the equilibrium point is not zero) and the non-hyperbolic equilibrium point [10]. Stability properties for hyperbolic equilibrium points are divided based on the type and sign of the eigenvalues.

Some research has been undertaken on modelling, regulating, and analysing the transmission of tuberculosis [11], [12]. Their results show that the spreading can be controlled at the fixed point of the model and show some parameters that should be considered to reduce the case. Liu et al. (2010) give recommendations about preventive programmes for tuberculosis case by case. They show that the spread of tuberculosis has a pattern related to the season. Carlos Castillo-Chaves has had some results on the tuberculosis spreading model in the last two decades. One of them is by including the effect of exogenous reinfection [5], [13], and following the research of Khajanchi et al. [4].

As part of this study, we intend to incorporate a bifurcation analysis into the model provided in [5]. This model has been examined in [5], however the bifurcation approach of R_0 requires additional research. Numerous researchers [14, 15] examined the consequences of backward bifurcation the tuberculosis transmission model. In addition to immunological bistability, they indicate a link with prevalence. This work examines differently the impact of bifurcation on the model of exogenous reinfection tuberculosis at its free infection fixed point.

2. RESEARCH METHODS

The steps to be taken are:

1. Identify the problem raised, namely the problem of the spread of exogenous reinfection of tuberculosis;
2. Collecting references related to the problem of the spread of exogenous reinfection of tuberculosis;
3. Determine and analyze the stability of the equilibrium point of the mathematical model of exogenous reinfection tuberculosis;
4. Analyse the mathematical model of exogenous reinfection tuberculosis with a bifurcation approach;
5. Conduct simulations and conclude.

3. RESULTS AND DISCUSSION

Figure 1 illustrates the mathematical model of external reinfection of tuberculosis. The population is classified into four categories: Susceptible (S), which indicates the number of individuals who are still healthy and vulnerable to illness infection; Exploded (E) indicates the number of passive (latent) infected individuals who cannot transmit the disease to other individuals; Infectious (I) indicates the number of actively infected individuals who can transmit the disease to other individuals; and Treated (T) indicates the number of individuals undergoing treatment and individuals who have recovered but are susceptible to reinfection.

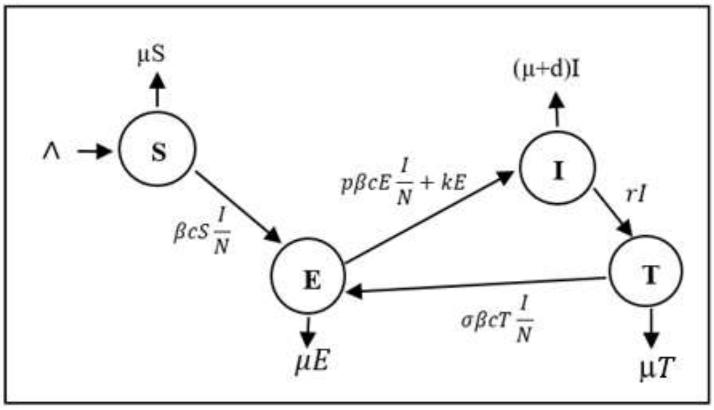

Figure 1. Compartment diagram of exogenous reinfection tuberculosis mathematical model

While the parameters that appear in the diagram are: the recruitment rate of TB (Λ), the natural mortality rate per capita (μ), the average contact per person per unit time (c), the transmission rate (β), the death rate per capita caused by TB (d), the treatment rate per capita (r), the regular progression rate per capita (k), the number of treated individuals infected by one infectious infection per contact per unit time ($\sigma\beta$), and the rate of exogenous reinfection (p). The following system of differential equations is derived from the compartment diagram **[13]**.

$$\frac{dS}{dt} = \Lambda - \beta cS\frac{I}{N} - \mu S \tag{1}$$
$$\frac{dE}{dt} = \beta cS\frac{I}{N} - p\beta cE\frac{I}{N} - (\mu + k)E + \sigma\beta cT\frac{I}{N} \tag{2}$$
$$\frac{dI}{dt} = p\beta cE\frac{I}{N} + kE - (\mu + r + d)I \tag{3}$$
$$\frac{dT}{dt} = rI - \sigma\beta cT\frac{I}{N} - \mu T \tag{4}$$
$$N = S + E + I + T\ . \tag{5}$$

with initial value $S(0) = S_0,\ \ E(0) = E_0,\ \ I(0) = I_0,\ T(0) = T_0$.

To explore the effects of backward bifurcation in the exogenous reinfection tuberculosis model, it is first necessary to discuss the stability near its fixed points. The impact of backward bifurcation is then examined.

3.1. Analysis of Equilibrium Point Stability Mathematical Model of Exogenous Reinfection Tuberculosis

Prior to doing an analysis at the equilibrium point, it is essential to identify the equilibrium point, which is as follows:

$$\frac{dS}{dt} = 0,\ \frac{dE}{dt} = 0,\ \frac{dI}{dt} = 0,\ \frac{dT}{dt} = 0$$

Thus, the following equation holds:

$$\Lambda - \beta cS\frac{I}{N} - \mu S = 0 \tag{6}$$
$$\beta cS\frac{I}{N} - p\beta cE\frac{I}{N} - (\mu + k)E + \sigma\beta cT\frac{I}{N} = 0 \tag{7}$$
$$p\beta cE\frac{I}{N} + kE - (\mu + r + d)I = 0 \tag{8}$$
$$rI - \sigma\beta cT\frac{I}{N} - \mu T = 0 \tag{9}$$

In the epidemic model, there are two sorts of equilibrium points: disease-free equilibrium and endemic equilibrium.

a) Disease-free equilibrium point

The disease-free equilibrium point is the equilibrium point indicating the absence of disease in the population when $I = 0$. By substituting $I = 0$ into System (6)-(9), we got the disease-free equilibrium point $E_0 = \left(\frac{\wedge}{\mu}, 0,0,0\right)$.

To investigate the stability of E_0, we employ linearity using the Jacobian matrix at the point as follows:

$$J\left(\frac{\wedge}{\mu}, 0,0,0\right) = \begin{bmatrix} -\mu & 0 & -\beta c \frac{\left(\frac{\wedge}{\mu}\right)}{N} & 0 \\ 0 & -(\mu + k) & \beta c \frac{\left(\frac{\wedge}{\mu}\right)}{N} & 0 \\ 0 & k & -(\mu + r + d) & 0 \\ 0 & 0 & r & -\mu \end{bmatrix}$$

In addition, the characteristic equation must be applied in order to determine the eigenvalues. Thus, the following is the characteristic equation:

$$V(E_0) = (\lambda + \mu)(\lambda + \mu)(\lambda^2 + (2\mu + r + d + k)\lambda + (\mu + k)(\mu + r + d) - \frac{\beta c \wedge k}{\mu N} = 0.$$

The eigenvalues are negatives $(\lambda_{1,2} = -\mu)$, while the expression $\lambda^2 + (2\mu + r + d + k)\lambda + (\mu + k)(\mu + r + d) - \frac{\beta c \wedge k}{\mu N} = 0$ needs to be solved to get the remaining eigenvalues. We apply the Routh-Hurwitz criteria to find the characteristics of the remaining eigenvalues.

Table 1. Routh-Hurwitz Table of Characteristic Equations for Disease-Free Points

λ^2	1	$(\mu + k)(\mu + r + d) - \frac{\beta c \wedge k}{\mu N}$
λ	$(2\mu + r + d + k)$	0
λ^0	$(\mu + k)(\mu + r + d) - \frac{\beta c \wedge k}{\mu N}$	0

Based on Table 1, the stability requires a positive coefficient. Clearly $1 > 0$ and $(2\mu + r + d + k) > 0$. While in the third row, if $\beta c < \frac{\mu N(\mu + k)(\mu + r + d)}{\wedge k}$ then $(\mu + k)(\mu + r + d) - \frac{\beta c \wedge k}{\mu N} > 0$. Thus, the equilibrium becomes asymptotically stable.

It can therefore be concluded that the disease-free equilibrium point of the mathematical model of the spread of exogenous reinfection of tuberculosis is asymptotically stable or that the disease will disappear if the rate of contact between individuals and infected individuals is reduced.

b) Disease endemic equilibrium point

The endemic equilibrium point will then be identified. This is the point at which the number of people with the disease exceeds zero, indicating that the disease is spreading throughout the community. Endemic disease implies that there are constantly infected individuals in a group. Hence, at the point of endemic equilibrium for the disease I > 0 is reached and is written in notation $E_1 = (S^*, E^*, I^*, T^*)$,

$$S^* = \left(\frac{\wedge N}{I^* \beta c \sigma + N\mu}\right)$$

$$E^* = \left(\frac{\beta c I^*(\beta c \sigma r I^{*2} N + \mu \sigma r I^* N^2 + I^* \beta c \sigma N \wedge + \wedge N^2 \mu)}{(I^* \beta \sigma + N\mu)(I^* \beta c + N\mu)(I^* \beta c p + Nk + N\mu)}\right.$$

$$T^* = \frac{r I^* N}{I^* \beta c \sigma + N\mu}$$

To write I^* in more simpler ways, let

$$A = (-\beta^3 c^3 p \sigma \mu - \beta^2 c^2 \mu^2 N \sigma - \beta^3 c^3 p \sigma d)$$

$$B = (p\beta^3 c^3 \sigma \wedge + k\beta^2 c^2 \sigma r N - \beta^2 c^2 \mu^2 N p \sigma - \beta^2 c^2 N k \sigma \mu - \beta^2 c^2 p \mu^2 N - \beta^2 c^2 N k \sigma r - \beta^2 c^2 N \mu \sigma r - \beta^2 c^2 p N \mu r - \beta^2 c^2 N \mu p \sigma d - \beta^2 c^2 N k \sigma d - \beta^2 c^2 N \mu \sigma d - \beta^2 c^2 p N \mu d)$$

$$C = (p\beta^2c^2 \wedge N\mu + k\beta c\mu\sigma rN^2 + k\beta^2c^2\sigma N \wedge -\mu^2k\beta c\sigma - N^2\mu^3\beta c\sigma - N^2\beta cp\mu^3 - N^2\beta ck\mu^2 - N^2\beta c\mu^3 - N^2\mu k\beta c\sigma r - N^2\mu^2\beta c\sigma r - N^2\mu^2\beta cpr - N^2\beta ck\mu r - N^2\mu^2\beta cr - N^2\mu k\beta c\sigma d - N^2\mu^2\beta c\sigma d - N^2\mu^2\beta cpd - N^2\beta ck\mu d - \beta cdN^2\mu^2)$$

$$D = (k\beta c \wedge N^2\mu - N^3k\mu^3 - N^3\mu^4 - N^3\mu^2kr - N^3\mu^3r - N^3kd\mu^2 - N^3\mu^3d)$$

Hence I^* obtained as follows:

$$I_2^* = \frac{1}{6}\frac{\left(-108DA^2+36CBA+12\sqrt{3}\sqrt{27A^2D^2-18ABCD+4AC^3+4B^3D-B^2C^2A}-8B^3\right)^{\frac{1}{3}}}{A} - \frac{2}{3}\frac{3AC-B^2}{A\left(-108DA^2+36CBA+12\sqrt{3}\sqrt{27A^2D^2-18ABCD+4AC^3+4B^3D-B^2C^2A}-8B^3\right)^{\frac{1}{3}}} - \frac{1}{3}\frac{B}{A}$$

I_2^* satisfy the endemic equilibrium point if $I_2^* > 0$ with

$$\frac{1}{6}\frac{\left(-108DA^2+36CBA+12\sqrt{3}\sqrt{27A^2D^2-18ABCD+4AC^3+4B^3D-B^2C^2A}-8B^3\right)^{\frac{1}{3}}}{A} > \left(\frac{2}{3}\frac{3AC-B^2}{A\left(-108DA^2+36CBA+12\sqrt{3}\sqrt{27A^2D^2-18ABCD+4AC^3+4B^3D-B^2C^2A}-8B^3\right)^{\frac{1}{3}}} + \frac{1}{3}\frac{B}{A}\right)$$

$$I_3^* = -\frac{1}{12}\frac{\left(-108DA^2+36CBA+12\sqrt{3}\sqrt{27A^2D^2-18ABCD+4AC^3+4B^3D-B^2C^2A}-8B^3\right)^{\frac{1}{3}}}{A} + \frac{1}{3}\frac{3AC-B^2}{A\left(-108DA^2+36CBA+12\sqrt{3}\sqrt{27A^2D^2-18ABCD+4AC^3+4B^3D-B^2C^2A}-8B^3\right)^{\frac{1}{3}}} - \frac{1}{3}\frac{B}{A} + \frac{1}{2}I\sqrt{3}\left(\frac{1}{6}\frac{\left(-108DA^2+36CBA+12\sqrt{3}\sqrt{27A^2D^2-18ABCD+4AC^3+4B^3D-B^2C^2A}-8B^3\right)^{\frac{1}{3}}}{A} + \frac{2}{3}\frac{3AC-B^2}{A\left(-108DA^2+36CBA+12\sqrt{3}\sqrt{27A^2D^2-18ABCD+4AC^3+4B^3D-B^2C^2A}-8B^3\right)^{\frac{1}{3}}}\right)$$

$$I_4^* = -\frac{1}{12}\frac{\left(-108DA^2+36CBA+12\sqrt{3}\sqrt{27A^2D^2-18ABCD+4AC^3+4B^3D-B^2C^2A}-8B^3\right)^{\frac{1}{3}}}{A} + \frac{1}{3}\frac{3AC-B^2}{A\left(-108DA^2+36CBA+12\sqrt{3}\sqrt{27A^2D^2-18ABCD+4AC^3+4B^3D-B^2C^2A}-8B^3\right)^{\frac{1}{3}}} - \frac{1}{3}\frac{B}{A} - \frac{1}{2}I\sqrt{3}\left(\frac{1}{6}\frac{\left(-108DA^2+36CBA+12\sqrt{3}\sqrt{27A^2D^2-18ABCD+4AC^3+4B^3D-B^2C^2A}-8B^3\right)^{\frac{1}{3}}}{A} + \frac{2}{3}\frac{3AC-B^2}{A\left(-108DA^2+36CBA+12\sqrt{3}\sqrt{27A^2D^2-18ABCD+4AC^3+4B^3D-B^2C^2A}-8B^3\right)^{\frac{1}{3}}}\right)$$

I_3^* and I_4^* has an imaginary value then I_3^* dan I_4^* not an endemic equilibrium point. Based on the results of the calculation of the endemic equilibrium point, the value is obtained $E_1 = (S_2^*, E_2^*, I_2^*, T_2^*)$.

Similar to the disease-free equilibrium point, the endemic equilibrium point matrix is obtained as follows:

$$J(S^*, E^*, I^*, T^*) = \begin{bmatrix} G & 0 & H & 0 \\ J & K & L & M \\ 0 & O & P & 0 \\ 0 & 0 & Q & R \end{bmatrix}$$

$G = -\beta c\frac{I_2^*}{N} - \mu,\quad H = -\beta c\frac{S_2^*}{N},\quad J = \beta c\frac{I_2^*}{N},\quad K = -p\beta c\frac{I_2^*}{N} - (\mu + k),$

$L = \beta c\frac{S_2^*}{N} - p\beta c\frac{E_2^*}{N} + \sigma\beta c\frac{T_2^*}{N},\quad M = \sigma\beta c\frac{I_2^*}{N},\quad O = p\beta c\frac{I_2^*}{N} + k,\quad P = p\beta c\frac{E_2^*}{N} - (\mu + r + d),$

$Q = r - \sigma\beta c\frac{T_2^*}{N},\quad R = -\sigma\beta c\frac{I_2^*}{N} - \mu$

To analyze the endemic equilibrium point, a characteristic equation is needed, namely

$$|\lambda I - J(E_1)| = 0$$

We get

$$\lambda^4 + U_1\lambda^3 + U_2\lambda^2 + U_3\lambda + U_4 = 0$$

$U_1 = -(G + R + P + K)$
$U_2 = (GR + GP + +PR + GK + KR + PK - LO)$
$U_3 = -(GPR + GKR + GPK + RPK - GLO - RLO + QMO - JOH)$
$U_4 = GRPJ - GRLO + GQMO + RJOH$

Table 2. Routh-Hurwitz Table of Endemic Point Characteristic Equations

λ^4	1	U_2	U_4
λ^3	U_1	U_3	0
λ^2	$\frac{U_1U_2 - U_3}{U_1}$	U_4	0
λ	$\frac{U_1U_2U_3 - U_3{}^2 - U_3{}^2U_4}{U_1U_2 - U_3}$	0	0
λ^0	U_4	0	0

$U_1 = -(G + R + P + K)$
$U_1 = -(-\beta c\frac{I_2^*}{N} - \mu - \sigma\beta c\frac{I_2^*}{N} - \mu + p\beta c\frac{E_2^*}{N} - (\mu + r + d) - p\beta c\frac{I_2^*}{N} - (\mu + k))$
$U_1 > 0$ jika $p\beta c\frac{E_2^*}{N} < \beta c\frac{I_2^*}{N} + \mu + \sigma\beta c\frac{I_2^*}{N} + \mu + (\mu + r + d) + p\beta c\frac{I_2^*}{N} + (\mu + k))$

If the rate of exogenous recurrent infection is large, then the endemic point of the mathematical model of the spread of exogenous reinfection of tuberculosis is asymptotically stable. This is due to the fact that a high rate of exogenous recurrent infection decreases the latent population, since the latent population rapidly transforms into an infection population, resulting in an increase in the infection population. Because there are too many operations on parameters at each value of variable, we can find the stability when the value of parameters is given. By the result, the value of fixed is affected significantly by the value of p and k. It means the exogenous reinfection has a significant role in the spreading of tuberculosis [16], [17].

3.2. Bifurcation Analysis

The characteristic equation of the disease-free equilibrium point is as follows:

$$(\lambda + \mu)(\lambda + \mu)\left(\lambda^2 + (2\mu + r + d + k)\lambda + (\mu + k)(\mu + r + d) - \frac{\beta c \wedge k}{\mu N}\right) = 0$$

It is obtained that the value of $\lambda_{1,2} = -\mu$ or has a negative value, then in the polynomial equation to the power of two from the above equation, namely;

$$\left(\lambda^2 + (2\mu + r + d + k)\lambda + (\mu + k)(\mu + r + d) - \frac{\beta c\wedge k}{\mu N}\right) = 0$$

Suppose $V = 1$

$W = 2\mu + r + d + k$

$X = (\mu + k)(\mu + r + d) - \frac{\beta c\wedge k}{\mu N}$

Then the above equation becomes $V\lambda^2 + W\lambda + X = 0$, so $\lambda_{3,4} = \frac{-W\pm\sqrt{W^2-4VX}}{2V}$.

- For $W^2 - 4X > 0 \rightarrow X < \frac{W^2}{4}$ then $\lambda_{3,4} \in R$

So $\lambda_3 = \frac{-W+\sqrt{W^2-4X}}{2}$ and $\lambda_4 = \frac{-W-\sqrt{W^2-4X}}{2}$

a. If $W > 0,\ X = 0$

$$\lambda_3 = -W + \sqrt{W^2} \quad \rightarrow \quad \lambda_3 = 0$$
$$\lambda_4 = -W - \sqrt{W^2} \quad \rightarrow \quad \lambda_4 < 0$$

Cannot determine stability

b. If $W > 0, 0 < X < \frac{W^2}{4}$

$$\lambda_3 = -W + \sqrt{W^2 - 4X} \quad \rightarrow \quad \lambda_3 < 0$$
$$\lambda_4 = -W - \sqrt{W^2 - 4X} \quad \rightarrow \quad \lambda_4 < 0$$

Asymptotically stable

c. If $W > 0, X < 0$

$$\lambda_3 = -W + \sqrt{W^2 - 4X} \quad \rightarrow \quad \lambda_3 > 0$$
$$\lambda_4 = -W - \sqrt{W^2 - 4X} \quad \rightarrow \quad \lambda_4 < 0$$

Unstable

- For $W^2 - 4X = 0 \rightarrow X = \frac{W^2}{4}$ and $W > 0$ then $\lambda_{3,4} \in R$

  So that $\lambda_{3,4} = \frac{-W \pm \sqrt{W^2-4X}}{2} = -\frac{W}{2} \quad \rightarrow \quad \lambda_{3,4} < 0$
  Asymptotically stable
- For $W^2 - 4X < 0 \rightarrow X > \frac{W^2}{4}$ then $\lambda_{3,4} \in R$

  So that $\lambda_3 = \frac{-W+\sqrt{W^2-4X}}{2}$ and $\lambda_4 = \frac{-W-\sqrt{W^2-4X}}{2}$

  a. If $W > 0, X > \frac{W^2}{4}$

$$\lambda_3 = -W + \sqrt{W^2 - 4X} \quad \rightarrow \quad \lambda_3 \; complex\ number$$
$$\lambda_4 = -W - \sqrt{W^2 - 4X} \quad \rightarrow \quad \lambda_4 \; complex\ number$$

Because of –W is negative, the point stability is asymptotically stable.

So λ_3 and λ_4 will change stability due to changes in the parameter X, where $X = (\mu + k)(\mu + r + d) - \frac{\beta c \wedge k}{\mu N}$.

If:

$X < 0$ → Unstable (saddle point)
$X = 0$ → Cannot determine stability
$0 < X < \frac{W^2}{4}$ → Asymptotically stable (nodes)
$X = \frac{W^2}{4}$ → Asymptotically stable (star nodes)
$X > \frac{W^2}{4}$ → Asymptotically stable (spiral)

Based on the explanation above, the following is the form of the bifurcation

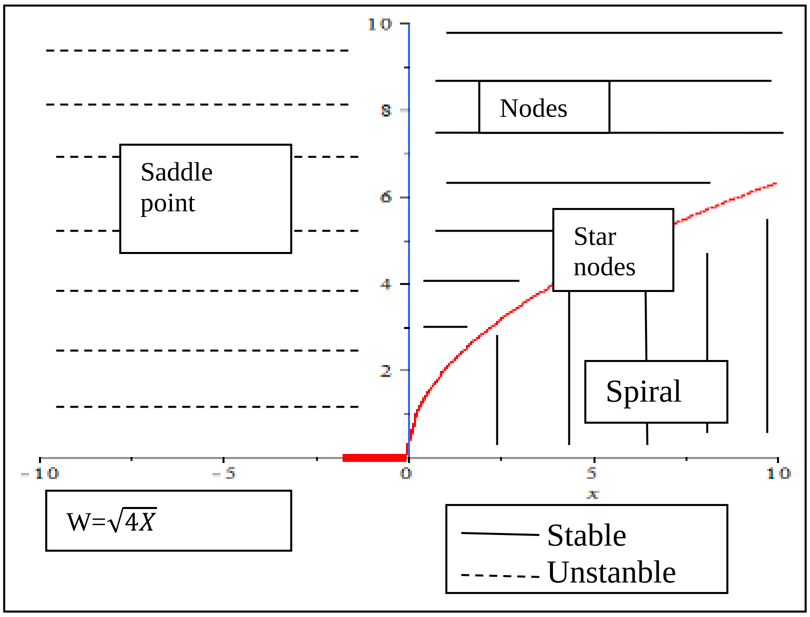

Figure 2. Bifurcation Diagram of Exogenous Reinfection Tuberculosis Model

Based on the figure, it can be concluded that the stability properties change when the value of X changes as shown above. The system of equations for the spread of tuberculosis exogenous reinfection will be stable when $X > 0$ or $(\mu + k)(\mu + r + d) > \frac{\beta c \wedge k}{\mu N}$, which means value $X > 0$ when displacement due to contact between infected individuals is reduced so the disease disappears, which means in the area with a high incidence of tuberculosis, the reinfection model going to unstable **[18]**. By the value of $X > 0$, increasing the value of d also can keep the model stable at its free infection point. One most interesting is the increasing value of k also increases the stability rate of the result. It means that when the primary progression rate (endogenous re-activation) increases, the disease will be eliminated **[19]**.

4. CONCLUSIONS

Based on the discussion, it was found that there was a change in the nature of stability and the type of equilibrium point in the distribution equation system of exogenous reinfection tuberculosis, where the parameter that occurred bifurcation was X, with $X = (\mu + k)(\mu + r + d) - \frac{\beta c \wedge k}{\mu N}$. When the value of X is less than zero, the system of differential equations for tuberculosis exogenous reinfection shows an unstable type with a saddle point type, when the value of X is equal to zero the system of differential equations cannot be determined stability, and when the value of X is greater than zero, the stability of the system of differential equations is asymptotically stable.

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