



MATHEMATICAL MODELS FOR MONITORING DIABETIC POPULATION WITH MINOR AND MAJOR COMPLICATIONS.

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Abstract

Mathematical model for monitoring diabetic populations with minor and major complications are developed and analyzed in this work. The equilibrium point of the system is shown to be globally asymptotically stable (GAS) using direct Lyapunov method. Some numerical simulations are carried out to demonstrate the

analytical results. It is found that the prevalence/incidence of diabetes is on the rise. Our results are effective in

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monitoring diabetic populations with minor and major complications. The model can be used to monitor global diabetic populations over time.

Introduction

Diabetes is a disorder of metabolism caused by total (or relative) absence of insulin which manifests clinically as an elevated blood glucose. The disorder is usually due to a combination of hereditary and environmental causes [40], resulting in abnormally high blood sugar levels known as hyperglycemia. No one is certain as to what starts the processes that cause diabetes [32]. But scientists believed that genes and environmental factors interact to cause diabetes in most cases [32]. The prevalence of the disease is steadily increasing everywhere, most markedly in the world's middle-income countries.

Unfortunately, effective policies to create supportive environment for diabetic patients are not obtainable in most society. Pursuing such policies is important. This is because when diabetes is uncontrolled, it has dire consequences for health and well-being of the society [13].

Initially, diabetes was considered as a disease with less harm to the society. But in the last few years there has been an alarming increase in the number of people diagnosed with the disease. Report released by World Health Organization (WHO) in 2003 [37] showed that 194 million people were diabetic globally. This represents a global prevalence exceeding three percent of the world’s population. The recent report [38] put the estimated number of people with diabetes at 422 million (representing number of diabetic patients as of 2014). Comparing with 108 million and 194 million in 1980 and 2003 respectively, one can see that the prevalence of the disease has multiplied four times from 1980. Out of this number, 1 person dies every 6 seconds, totaling approximately 5.3 million deaths annually [41]. The ten countries estimated to have the highest number of diabetes in 2000 and 2030 are listed in Table 1 below as presented in [39].

Table 1: *Top ten countries to have highest number of diabetes in 2000 and 2030 [39]*

2000			2030		
Ranking	Country	People with diabetes (in millions)	Country	People with diabetes (in millions)	
1	India	31.7	India	79.4	
2	China	20.8	China	42.3	
3	U.S	17.7	U.S	30.3	
4	Indonesia	8.4	Indonesia	21.3	
5	Japan	6.8	Pakistan	13.9	
6	Pakistan	5.2	Brazil	11.3	
7	Russian	4.6	Bangladesh	11.1	
8	Brazil	4.6	Japan	8.9	
9	Italy	4.3	Philippines	7.8	
10	Bangladesh	3.2	Eqypt	6.7	

Generally, two forms of diabetes are considered: type 1 diabetes, also known as Insulin Dependence Diabetes Mellitus (IDDM), typically occurs

in children and young adults and it represents (10-15) % of the diabetic population, and type 2 diabetes formally known as Non Insulin Dependence Diabetes Mellitus (NIDDM), represents the major part (85-90)% [19]. However, there is third type called gestational diabetes which affects pregnant women and it goes away the moment pregnancy is over. Complications of diabetes are broadly classified into two; minor (acute) and major (chronic) complications [1]. Minor complications of the disease are very serious and have strong health implication. They are usually dangerous complications and are always medical emergency. They include; hyperglycaemia hyperosmolar state, diabetic coma, respiratory infections and periodontal disease. On the other hand, major complications are those complications of disease that continues for a long time and are not easily cured.

From the above statements, it is clear that diabetes aid in developing different kind of diseases. Thus, monitoring the size of the diabetic population is important. Different strategies can be adopted provided they yield the desired results. Our interest is to show that investment in primary health care is necessary and to convince policy makers that bold decisions must be taken for a sustainable development which ensures better quality of life and well-being for the present and future generations of human [13].

Model Formulation

Suppose that $D = D(t)$, $C_1 = C_1(t)$ and $C_2 = C_2(t)$ ($t > 0$) represents the numbers of diabetic patients without complications, with minor complications and with major complications respectively, and let $N = N(t) = D(t) + C_1(t) + C_2(t)$ denote the size of the population of diabetic patients at time t . Let $I = I(t)$ denote the incidence of diabetes.

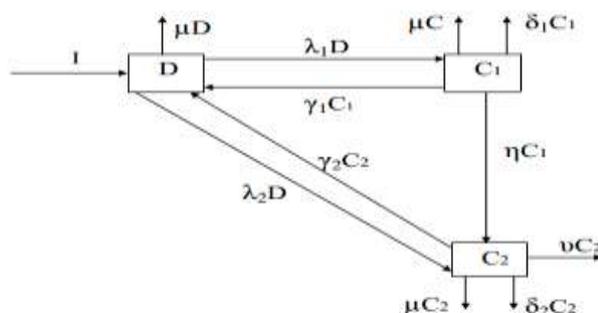


Figure 1: Schematic representation of the model

A person may develop the disease without complications and develop complications with time or die naturally. A diabetic patient with minor complications may die naturally, die as a result of minor complications, develop major complications or have his/her complications cured. A diabetic patient with major complications may die naturally, as a result of the complications, have his/her blood normalized through some control measures and become diabetic patient without complications. On the basis of this, we have the following dynamics; the diagram above shows $I=I(t)$ cases that are diagnosed in a time interval of length t and are assumed to have no complications upon diagnosis. In this same time interval, the number of diabetic patients without complications $D=D(t)$ is seen to increase by the amount $\gamma_2 C_1$ (those who recovered from minor complications) and $\gamma_2 C_2$ (patients who recovered from major complications), and to decrease by μD (patients without complications who die naturally), $\lambda_2 D$ (patients who develop minor complications) and $\lambda_2 D$ (patients who develop major complications). During this same time interval, the number of diabetic patients with minor complications, $C_1=C_1(t)$ is increased by $\lambda_2 D$ (patients who develop minor complications) and decrease by μC_1 (patients with minor complications who die naturally), $\delta_1 C_1$ (patients who die as a result of the minor complications) and ηC_1 (patients with minor complications who develop major complications). On the other hand, the number of diabetic patients with major complications increases by $\lambda_2 D$ (patients who develop major complications) and ηC_1 (patients with minor complications who develop major complications) and decreases by μC_2 , $\delta_2 C_2$, νC_2 , and $\gamma_2 C_2$; patients with major complications who die naturally, patients who die as a result of major complications, patients who are severely disabled and are removed and patients who achieve glucose regulation respectively.

These rates of change are formalized by the ordinary differential equations:

$$\begin{aligned}\frac{dD}{dt} &= -(\lambda_1 + \lambda_2 + \mu)D + \gamma_1 C_1 + \gamma_2 C_2 + I, \\ \frac{dC_1}{dt} &= \lambda_1 D - (\delta_1 + \eta + \gamma_1 + \mu)C_1, \\ \frac{dC_2}{dt} &= \lambda_2 D + \eta C_1 - (\delta_2 + \gamma_2 + \mu + \nu)C_2.\end{aligned}$$

And since $N=D + C_1 + C_2$, the initial value problems (IVP) in term of C_1, C_2 and N are

$$\begin{aligned} \frac{dC_1}{dt} &= -(\xi + \lambda_1)C_1 - \lambda_1 C_1 + \lambda_1 N, \\ \frac{dC_2}{dt} &= (\eta + \lambda_1)C_1 - (\vartheta + \lambda_2)C_2 + \lambda_2 N, \\ \frac{dN}{dt} &= -\delta_1 C_1 - \Lambda C_2 - \mu N + I, \end{aligned} \tag{1}$$

$C_1(0)=C_{10}, C_2(0) = C_{20}, N(0) = N_0, \xi = \delta_1 + \gamma_1 + \eta + \mu, \vartheta = \delta_2 + \gamma_2 + \mu + \nu, \Lambda = \delta_2 + \nu$, and C_{10}, C_{20}, N_0 are the initial values of C_1, C_2 and N respectively.

Table 2: Description of Variables for the Model (1)

Variable	Description
$D(t)$:	number of diabetic patients without complications,
$C_1(t)$:	number of diabetic patients with minor complications,
$C_2(t)$:	number of diabetic patients with major complications,
$N(t)$:	total population of diabetic patients,
t :	time as a continuous variable.

The models are extensions of the models of diabetes considered in [13, 10] by subdividing the compartment for diabetic population with complications into two based on the classification of diabetic complications mentioned in [1].

Basic qualitative properties of the model

Since the model (1) describes human population it is necessary to show that all the state variables C_1, C_2, N are nonnegative for all $t \geq 0$. Solutions with positive initial data remain positive for all $t \geq 0$ and are bounded. Based on biological consideration therefore, the model (1) will be studied in the region:

$$\Omega = \{(C_1, C_2, N) \in \mathbb{R}_+^3 : C_1 \geq 0, C_2 \geq 0, N \leq I/\mu\}.$$

Table 3: Parameters for the Model(1)

Parameter	Description
μ :	natural death,
λ_1 :	probability of developing minor complications,
λ_2 :	probability of developing major complications,

η :	rate of developing major complications from minor complications,
γ_1 :	rate of recovery from minor complications,
γ_2 :	rate of recovery from major complications,
δ_1 :	death induced by minor complications,
δ_2 :	death induced by major complications,
ν :	rate of which diabetic patient with major complications become severely disabled,
I :	incidence of diabetes.

Positivity and boundedness of solutions

Lemma 2.1.

The region Ω is positively-invariant for the model (1) with non-negative initial conditions in \mathbb{R}_+^3 .

Proof.

The system (1) is Lipschitz continuous in Ω , from the standard Theorem in [24], there exists a unique solution to (1). We use the method of contradiction as in [6, 26] to show that Ω is positively-invariant.

Under the initial conditions, assume that there exists a first time t_1 such that

$$C_1(t_1) = 0, \frac{dC_1(t_1)}{dt_1} < 0, C_2(t_1) > 0, N(t_1) > 0 \text{ for } 0 < t < t_1,$$

or there exists a t_2 such that

$$C_2(t_2) = 0, \frac{dC_2(t_2)}{dt_2} < 0, C_1(t_2) > 0, N(t_2) > 0 \text{ for } 0 < t < t_2.$$

$$\text{In the first case } (t_1): \frac{dC_1(t_1)}{dt_1} = -\lambda_1 C_2 + \lambda_1 N = \lambda_1 (N - C_2) > 0,$$

which is a contradiction. Meaning $C_1(t) > 0$.

$$\text{In the second case } (t_2): \frac{dC_2(t_2)}{dt_2} = (\eta - \lambda_2) C_1 + \lambda_2 N = \lambda_2 N + \eta C_1 - \lambda_2 C_1 > 0,$$

which is a contradiction. Meaning $C_2(t) > 0$.

Thus, in any case C_1, C_2 remain positive. Also, since $N(t) \geq C_1(t) + C_2(t)$ and $\frac{dN}{dt} = -\delta_1 C_1 - \eta C_2 - \mu N + I, \leq I - \mu N, \Rightarrow \frac{dN}{dt} + \mu N \leq I.$ (2)

That is to say $\frac{dN}{dt} \leq 0$ if $N \geq \mu I$. Thus, $N \leq \mu I (1 - e^{-\mu t}) + N(0)e^{-\mu t}$. In particular, $N \leq I\mu$.

Thus, the region Ω is positively-invariant. Further, if $N(0) > I\mu$ then either the solution enters Ω in finite time, or $N \rightarrow I\mu$ asymptotically.

Hence the region Ω attracts all solutions in \mathbb{R}_+^3 .

Analysis of the model

In this linear model (1), the probabilities of developing minor and major complications, λ_1 and λ_2 will respectively be estimated to have constant values:

$$\lambda_1 = \frac{C_{10}}{N_0}, \lambda_2 = \frac{C_{20}}{N_0} \quad [13] \quad (3)$$

Local stability analysis of the equilibrium point

The linear model (1) has unique equilibrium point given by:

$$E_l = \left(\frac{\lambda_1 \theta I^*}{\lambda_1 A_1 + \lambda_2 A_2 + A_3}, \frac{(\lambda_1 \eta + \lambda_2 \xi) I^*}{\lambda_1 A_1 + \lambda_2 A_2 + A_3}, \frac{[\lambda_1 (\eta + \theta) + (\lambda_2 + \theta) \xi] I^*}{\lambda_1 A_1 + \lambda_2 A_2 + A_3} \right) \quad (4)$$

$$A_1 = \eta(\mu + \Lambda) + \vartheta(\delta_1 + \mu), \quad A_2 = \xi(\mu + \Lambda), \quad A_3 = \mu\vartheta\xi$$

Lemma 1.

The unique equilibrium point E_l of the model (1) is locally asymptotically stable (LAS).

Proof.

The characteristic polynomial associated to the matrix A of the system (1) is generically

given by

$$p(\chi) = \chi^3 - \tau\chi^2 + (A_{11} + A_{22} + A_{33})\chi - \delta,$$

$\tau = tr(A), \delta = det(A), A_{11}, A_{22}, A_{33}$ are the cofactors of the entries $a_{11}; a_{22}; a_{33}$ respectively of the matrix A and χ denote its eigenvalues.

Thus, the characteristic polynomial for the system is given by

$$\chi^3 + (\lambda_1 + \lambda_2 + B_1)\chi^2 + (\lambda_1 B_2 + \lambda_2 B_3 + B_4)\chi + \lambda_1 A_1 + \lambda_2 A_2 + A_3 = 0, \quad (5)$$

$$B_1 = \mu + \xi + \theta, B_2 = \delta_1 + \mu + \eta, B_3 = \mu + \Lambda + \xi, B_4 = \xi(\mu + \theta) + \mu\theta$$

For the system's equilibrium point (4) to be stable, all the roots of the characteristic equation (eigenvalues) (5) must be negative. We apply Routh stability criterion to achieve that. For convenience, we restate the criterion.

According to the Routh stability criterion, the necessary and sufficient conditions for asymptotic stability are that all the sign of the first column of the Routh table (as below) have the same sign. Thus, the Routh table for the polynomial is given as follows:

χ^n	b_n	b_{n-2}	b_{n-4}
χ^{n-1}	b_{n-1}	b_{n-3}	b_{n-5}
.	c_1	c_2	c_3
.	d_1	d_2	d_3
.

$$c_1 = \frac{b_{n-1}b_{n-2} - b_n b_{n-3}}{b_{n-1}}, \quad c_2 = \frac{b_{n-1}b_{n-4} - b_n b_{n-5}}{b_{n-1}}, \dots$$

$$d_1 = \frac{c_1 b_{n-3} - b_{n-1} c_2}{c_1}, \quad d_2 = \frac{c_1 b_{n-5} - b_{n-1} c_3}{c_1}, \dots$$

If b_n, b_{n-1}, c_1, d_2 have same sign, then the fixed point is stable.

Here, for this system,

$$n = 3, b_3 = 1, b_2 = \lambda_1 + \lambda_2 + B_1, b_1 = \lambda_1 B_2 + \lambda_2 B_3 + B_4, b_0 = \lambda_1 A_1 + \lambda_2 A_2 + A_3$$

We also obtained $c_1 > 0, c_2 = 0, d_1 > 0, d_0 = 0$

Thus, the Routh table for the system is as follows:

χ^3	1	$\lambda_1 B_2 + \lambda_2 B_3 + B_4$	0
χ^2	$\lambda_1 + \lambda_2 + B_1$	$\lambda_1 A_1 + \lambda_2 A_2 + A_3$	0
.	c_1	0	0
.	b_0	0	0
.

Since all the sign of the entries in the first column of the table are positive, then all the roots (eigenvalues) of the characteristic equation (5) are negative.

Hence, the equilibrium point(4) of the system (1) is asymptotically stable. This result shows that the disease establishes itself within certain period of time, but can be controlled at certain level if proper measures are put in place.

Global Stability analysis of the equilibrium point

Having established that the equilibrium point in the linear case is locally asymptotically stable, we prove the global stability of this equilibrium point. to do this we employ the use of Lyapunov functional approach as in [7]. Let us introduce new variables

$$u_1 = C_1 - C_1^*, u_2 = C_2 - C_2^*, u_3 = N - N^* \text{ and } \varphi_1 = I - I^*, u_i = u_i(t), i = 1,2,3, \varphi_1 = \varphi_1(t).$$

Note that $-(\xi + \lambda_1) C_1^* - \lambda_1 C_2^* + \lambda_1 N^* = 0$, $(\eta - \lambda_2) C_1^* - (\vartheta + \lambda_2) C_2^* + \lambda_2 N^* = 0$, $-\delta_1 C_1^* - \Lambda C_2^* - \mu N^* + I^* = 0$. With this change of variables, system (1) becomes

$$\begin{aligned} \frac{du_1}{dt} &= -(\xi + \lambda_1)u_1 - \lambda_1 u_2 + \lambda_2 u_3, \\ \frac{du_2}{dt} &= (\eta - \lambda_2)u_1 - (\vartheta + \lambda_2)u_2 + \lambda_2 u_3, \\ \frac{du_3}{dt} &= -\delta_1 u_1 - \Lambda u_2 - \mu u_3 + \varphi_1, \end{aligned} \tag{6}$$

The global stability of the origin (trivial equilibrium point) of (6) implies the global stability of the equilibrium point to the original system (1).

Theorem 1.

Suppose that (C_1^*, C_2^*, N^*) is below or above (C_1, C_2, N) along the solution curves, the unique equilibrium point E_1 is globally asymptotically stable in the region Ω if the following inequalities hold:

$$\eta < \lambda_2 \text{ and } \Lambda > (1 + \lambda_2).$$

Proof.

Consider the Lyapunov function

$$V(u) = \frac{1}{2} k(u_1 + u_2)^2 + \frac{1}{2} (u_2^2 + u_3^2), u = (u_1, u_2, u_3)$$

where k is a positive constant to be determined later in the course of calculations, with Lyapunov derivative along the solution curves:

$$\begin{aligned} V' &= k(u_1 + u_2)(u_1' + u_2') + u_2 u_2' + u_3 u_3', \quad ' = \frac{d}{dt}, \\ &= k(u_1 + u_2)(-(\xi + \lambda_1)u_1 - \lambda_1 u_2 + \lambda_2 u_3 + (\eta - \lambda_2)u_1 - (\theta + \lambda_2)u_2 + \lambda_2 u_3) + \\ &\quad u_2[-(\xi + \lambda_1)u_1 - \lambda_1 u_2 + \lambda_2 u_3] + \\ &\quad u_3(-\delta_1 u_1 - \Lambda u_2 - \mu u_3 + \varphi_1), \\ &= g_1 u_1^2 - g_2 u_2^2 - \mu u_3^2 + g_3 u_1 u_2 + g_4 u_1 u_3 + g_5 u_2 u_3 + \varphi_1 u_3, \\ g_1 &= k(\eta - \xi - \lambda_1 - \lambda_2), g_2 = k(\theta + \lambda_1 + \lambda_2) + \theta + \lambda_2, \\ g_3 &= k(\eta - \xi - \theta - 2\lambda_1 - 2\lambda_2) + \eta - \lambda_2, \\ g_4 &= k(\lambda_1 + \lambda_2) - \delta_1, \\ g_5 &= k(\lambda_1 + \lambda_2) + \lambda_2. \end{aligned}$$

$$\begin{aligned} \text{Now, } V' &= g_1 u_1^2 - g_2 u_2^2 - \mu u_3^2 + g_3 u_1 u_2 + g_4 u_1 u_3 + g_5 u_2 u_3 + \varphi_1 u_3, \\ &\leq g_1 u_1^2 - g_2 u_2^2 - \mu u_3^2 + g_3 u_1 u_2 + [g_4 u_1 + (g_5 + 1)]u_3, \end{aligned}$$

Clearly, $g_4 < g_5 + 1$.

Letting $g_5 + 1 = 0$, gives $k = \frac{\Lambda - (1 + \lambda_2)}{\lambda_1 + \lambda_2}$, $\Lambda > 1 + \lambda_2$.

Substituting k in g_1, g_2, g_3, g_4 , we have

$$g_1 < 0, g_2 > 0, g_3 < 0, \text{ provided } \eta < \lambda_2, g_4 < 0, \text{ since } g_5 + 1 = 0.$$

Thus, we have

$$\begin{aligned} V' &\leq g_1 u_1^2 - g_2 u_2^2 - \mu u_3^2 + g_3 u_1 u_2 + g_4 u_1 u_3 + g_5 u_2 u_3 + \varphi_1 u_3, \\ &= g_1 u_1^2 - g_2 u_2^2 - \mu u_3^2 + g_3 u_1 u_2 + g_4 u_1 u_3, \end{aligned}$$

Since, at any time, t the equilibrium point (C_1^*, C_2^*, N^*) is either below or above (C_1, C_2, N) along the solution curves, then: either $C_1 - C_1^* > 0$; $C_2 - C_2^* > 0$, $N - N^* > 0$ at a time or $C_1 - C_1^* < 0$; $C_2 - C_2^* < 0$, $N - N^* < 0$. Whichever the case may be, $u_1 u_2$ and $u_1 u_3$ remain positive. And since $g_1 < 0$, $g_2 > 0$, $\mu > 0$, $g_3 < 0$, $g_4 < 0$, therefore $V' < 0$.

Thus, $V' = 0$, if and only if $u_1 = u_2 = u_3 = 0$. This indicates that the largest invariant set in $\{(u_1, u_2, u_3) \in \Omega: V' = 0\}$ is the origin. Therefore, by LaSalle's invariance principle [27], EI is globally asymptotically stable.

This result shows that the disease establishes itself in a community.

Numerical Simulation

This section gives a demonstration of the analytical results in the previous sections. The parameter values are given in table 4. These parameter values were obtained from the source(s) indicated in each case. The global incidence of diabetes used in the simulations is $I = 17000000$. This incidence, is the average of incidences for three years

(2012-2014)[38] [16]. It should also be noted that the death as a result of minor complications of diabetes is slightly higher than that of major complications [38]. Parameter values that we were not able to obtain in the diabetes literature were assumed in the simulations. $C_1(0) = 500000$, $C_2(0) = 600000$, $N(0) = 1500000$ were used as initial conditions. The probabilities of developing minor and major complications were estimated to be $\lambda_1 = 0.33$, $\lambda_2 = 0.40$, (in the linear case) using their definitions given in Subsection (3), while ϑ , ξ and Λ were obtained to be 0.10729142, 0.09379427 and 0.05500572 respectively. With these values of the parameters, the equilibrium point is obtained to be: (143270000, 191880000, 375880000)

Table 4: Parameter values used in the numerical simulations

Parameter	Value	Source
δ_1	0.007508574	Estimated from [29]
δ_2	0.005005716	Estimated from [29]
η	0.03	Assumed
γ_1	0.042	Adopted from [13]
γ_2	0.038	Adopted from [13]
μ	0.0142857	[26]
ν	0.05	Adopted from [13]

The profiles for $C_1(t)$, $C_2(t)$ and $N(t)$ are shown in figures 2. It can be seen from the figure that the fixed point was reached by time $t = 100$ years. It also shows that there is an agreement between the analytical results and the numerical results.

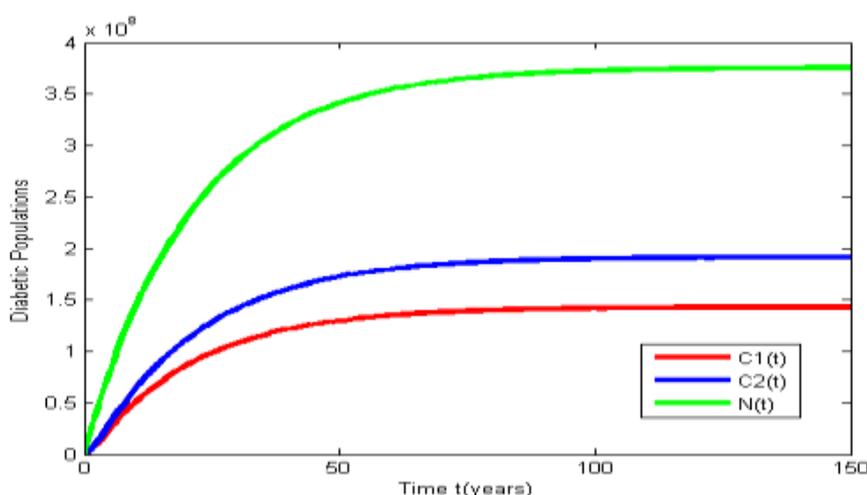


Figure 2: Profile of C_1 , C_2 , N for the full model

A situation where there is no recovery from the complications of the disease (that is $\gamma_1 = 0, \gamma_2 = 0$) is also experimented (see figure 3). The equilibrium point in this case is: (145530000, 194820000, 363230000)

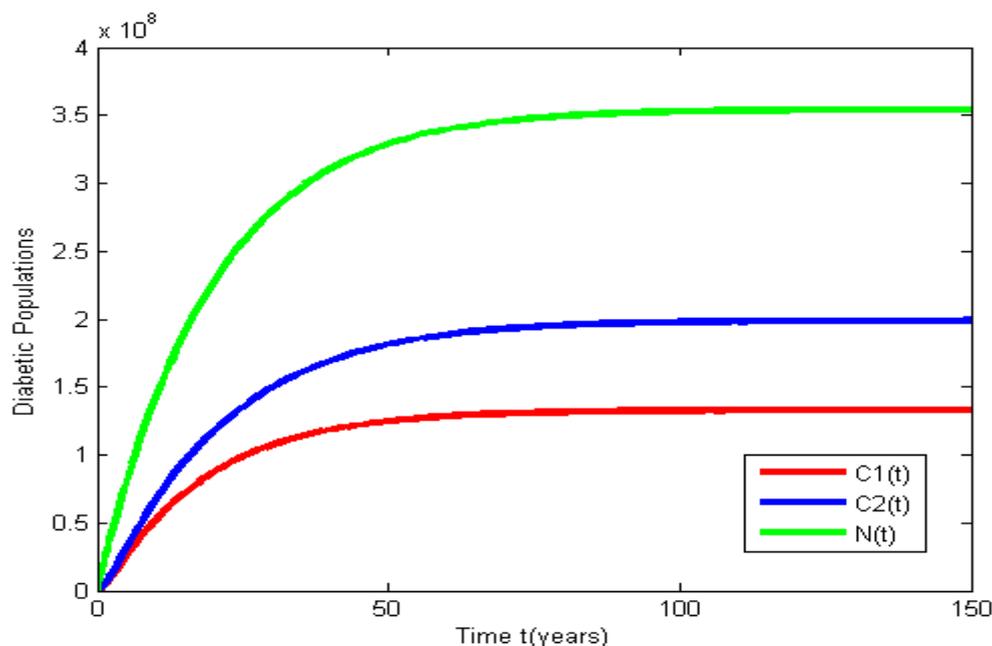


Figure 3: Profile of C1, C2 & N when there is no recovery

Table 4: Parameter values used in the numerical simulations

Parameter	Value	Source
δ_1	0.007508574	Estimated from [29]
δ_2	0.005005716	Estimated from [29]
η	0.03	Assumed
γ_1	0.042	Adopted from [13]
γ_2	0.038	Adopted from [13]
μ	0.0142857	[26]
ν	0.05	Adopted from [13]

Conclusion

This modified models (linear and the nonlinear) is an extension of Boutayeb *et al* model considered in [13] and [10]. This extension was done by subdividing the compartment of diabetic population with

complications into those with minor complications and those with major complications. The extended model shows no any sign of divergence as time increases. In the linear model, a unique equilibrium point was obtained and is found to be globally asymptotically stable unconditionally by the use of direct Lyapunov function. The nonlinear has three positive equilibrium points: *EP 1*, *EP 2* and *EP 3*. *EP 1* and *EP 2* were found to be unstable. *EP 3* is found to be globally asymptotically stable, which is equivalent to the endemic equilibrium point in infectious diseases. It is seen clearly that the absence of the complications of the disease in the population is not guaranteed. However, the central work of the dissertation is to stress the importance of controlling the incidence of the disease and its various complications. It is hitherto important that a better strategy must be put in place to curtail the menace of the disease. The overall results obtained is that the models can monitor diabetic population globally without any condition as to the choice of time of monitoring. In conclusion, we see that our models have given us insight into the various complications of diabetes. This gives a clear signal that health decision makers must invest heavily in health sector so that social and economic costs of uncontrolled diabetes in our societies will be minimal and productivity will be high.

Further study

Nonlinear consideration and analysis of the model can be investigated for more insight into the features or profiles of the model. Also, the effect of treatment of the complications of the disease can be investigated.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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