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OPTIMAL CONTROL OF INCIDENCE OF MEDICAL COMPLICATIONS IN A DIABETIC PATIENTS' POPULATION

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ABSTRACT
Considering the increasing number of morbidity and mortality associated with diabetes, there is dire need for a consistent and effective management of patients' living with diabetes in order to ameliorate the social and economical consequences on the affected individuals and the society at large. We propose a deterministic model for effective health - management of patients' living with diabetes using the management of the patients before developing complications and the thorough management of patients with complications to ensure that they stay out of complications as two different controls strategies. We formulate a fixed time optimal control problem subject to the model dynamics with the goal of finding the optimal combination of the control strategies that will minimize the cost of the implementing the proposed strategies as well as the incidence of complications within the population. We use Pontryagin's maximum principle to derive the problem optimality system and solve the system numerically. Results from our simulations are discussed.
Keywords: Diabetes, Optimal control, Pontryagin's maximum principle, Optimality system, Hamiltonian.

INTRODUCTION

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin (i.e. the hormone that regulates the blood sugar) or when the body cannot effectively use the insulin it produces (IDF, 2004; WHO and IDF, 2004; WHO, 2014). There are two major types of diabetes; these are the type-1 and the type-2 diabetes. The type-1 diabetes is characterized by deficient insulin production and requires daily administration of insulin while the type-2 diabetes is due to body's ineffective use of insulin often caused by excess body weight and physical inactivity. Moreover, there is also one other form of diabetes called Gestational diabetes (GDM). It is usually as a result of high blood glucose levels during pregnancy. GDM places affected women and their children at an increased risk of developing type 2 diabetes later in life (IDF, 2004, WHO, 2014).

Diabetes can eventually results in the damage of patient's heart, blood vessels, eyes, kidneys, and nerves. These complications increase the patient's risk of heart disease and stroke, foot ulcer and limb amputation, blindness, kidney failure, and premature death. Globally, 347 million people have diabetes and 3.2 million deaths are attributable to diabetes every year (WHO and IDF, 2004; WHO, 2014) . Worse still, the World Health Organization projected that diabetes will be the 7th leading cause of death by the year 2030. Therefore, there is the need to put series of effective measures in place to minimize the social and economic impact of the disease on patients and the society. Obviously, effective management of diabetic patients to delay or prevent complications and thorough management of patients with complications to get out of complications is one guaranteed way of consistently reducing the incidence of these complications.

Mathematical modelling and predictive biosimulations have been applied extensively in the treatment and control of spread of diseases like Diabetes, HIV/AIDS, Cancer, Tuberculosis, etc. In particular, a number of models have been developed to study diabetes as reviewed in the paper by Kansal (Kansal, 2004). Based on this critique, he concluded that each of the model is well suited for the purpose for which they are developed but there are limitations on how each of the model can be utilized.

In a related research work, Boutayeb *et al.* (2004) proposed a mathematical model for the dynamics of the population of diabetes patients with or without complications using a system of ordinary differential equations. The model was solved numerically and the results confirm diagnosis and recommendations given by specialists and experts in the field of diabetes and health management. The authors demonstrated that adequate investment in health care is a cost-effective strategy in controlling the incidence of diabetes and its complications (Boutayeb *et al.*, 2004).

Recently, optimal control theory has been used extensively in series of real-life applications. For instance, it was used in deriving control strategies for mitigating the spread of different infectious diseases (Joshi *et al.*, 2006; Yan, Zou and Li, 2007; Gaff and Schaefer, 2009; Blayneh *et al.*, 2010). Also, the theory was used to evolve effective treatment strategies for the treatment of some deadly or terminal ailments/infections (Kirschner *et al.*, 1997; Nanda *et al.*, 2007; Fister and Donnelly, 2005).

In this paper, we applied optimal control theory to minimize the incidence of medical complications among diabetic patients using two different control strategies. In section two, we described the proposed model and its parameters. In section three, we formulated the modelled problem as an optimal control problem, derived the adjoint equations, characterized the optimal controls and obtain the optimality system. In section four, we numerically solved the resulting optimality system and discussed our findings.

THE MATHEMATICAL MODEL

We consider the model proposed by Boutayeb *et al* (Boutayeb *et al.*, 2004) with some modifications and incorporate two control strategies. The model subdivides the diabetic patients' population into diabetics without complications D(t) and diabetics with complications C(t); where D(t) represents number of patients having diabetes without complications while C(t) represents number of patients having diabetes with complications. Thus, the total diabetic patients' population under consideration is given by N(t)= C(t) + D(t). Suppose Λ denote the incidence of diabetes in the society which implies the average number of newly diagnosed diabetic cases per unit time and it is assumed that these detected cases are without complications.

Thus, the diabetic patients' population dynamics is given by the following system of ordinary differential equations:

$$\left.\begin{aligned}\frac{dD}{dt} &= \Lambda + u_2\gamma C - (1-u_1)\nu D - \mu D \\ \frac{dC}{dt} &= (1-u_1)\nu D - u_2\gamma C - \mu C - \delta C\end{aligned}\right\} \quad (1)$$

and the total population N(t) satisfies the equation

$$\frac{dN}{dt} = \Lambda - \mu N - \delta C$$

The parameters for the model are defined in Table 1 below:

Table 1: Description of parameters used in the model

Parameter	Description
Λ	average annual incidence of diabetes without complications
μ	natural mortality rate
ν	probability of a diabetic developing complications
γ	rate at which complications are cured
u_1	effective rate of medical management D class per unit time
u_2	effective rate of medical management of C class per unit time
δ	Diabetes complications induced - death rate

Note that $\lim_{t\to\infty} N(t) \le \frac{\Lambda}{\mu}$ However, under the dynamics described by (1), the region Ω defined by $\Omega = \{(D,C) \in \Re^2_+ \mid D + C \le \frac{\Lambda}{\mu}\}$ is positively invariant.

OPTIMAL CONTROL

We define our objective functional as

$$Z = \min_{u_1,u_2} \int_0^{t_f} (k_1 C + \tfrac{1}{2}k_2 u_1^2 + \tfrac{1}{2}k_3 u_2^2)dt \quad (2)$$

subject to system of equations (1) with appropriate states initial conditions and t_f is the final time while the control set U is Lebesgue measurable and it is defined as

$$U = \{(u_1(t), u_2(t)) \mid 0 \le u_i \le 1,\ i = 1..2,\ t \in [0, t_f]\} \quad (3)$$

and the weight constants k_1, k_2, k_3 are the relative weights and helps to balance each terms in the integrand so that any of the terms does not dominate. Here, it is important to note that k_2, k_3 are relative measures of the cost or effort required to implement each of the associated control strategies while k_1 is the relative measure of the importance of reducing the number of patients in the C(t) class.

The upper bound for each of the controls u_{1max}, u_{2max} will depend on the budget allocated for the execution of each of the control strategies. For instance, we shall hypothetically set u_{1max} =0.75, u_{2max} =0.5 in our subsequent simulations. We wish to determine the optimal combination of controls u_1 and u_2 that will be adequate to minimize cost of implementing the two control strategies as well as reduce the incidence of medical complications among diabetic patients over a fixed time period.

Existence of an optimal control strategy for the problem

We examine the sufficient conditions for the existence of a solution to the optimal control problem.

Theorem 1 : There exists an optimal control set (u_1, u_2) *; with corresponding solution* (D^*, C^*) *to the model system (1)), that minimize Z over U.*

Proof 1:

The existence of the optimal control is guaranteed by the compactness of the control and the state space and the convexity in the problem based on Theorem 4.1 of Chapter III and its corresponding Corollary in (Fleming and Rishel, 1975) . The following non-trivial requirements from Fleming and Rishel's theorem are stated and verified below:

(1) The set of all solutions to the (1) and its associated initial conditions together with the corresponding control functions in U is non empty.

(2) The state system can be written as a linear function of the control variables with coefficients dependent on time and state variables.

(3) The integrand L in equation (2) is convex on U and additionally satisfies

$$L(t, D, C, u_1, u_2) \geq c_1 \,|\,(u_1, u_2)\,|^{\alpha} - c_2, \ \ where\ c_1, c_2 > 0\ \ and\ \alpha > 1.$$

We refer to Theorem 3.1 by Picard-Lindelof in (Coddington and Levinson, 1955). Based on this theorem, if the solutions to the state equations are a priori bounded and if the state equations are continuous and Lipschitz in the state variables, then there exists a unique solution corresponding to every admissible control set in U. Using the fact that for all $(D, C) \in \Omega$, all the model states are bounded below and above; then the solutions to the state equations are bounded.

In addition, it is direct to show the boundedness of the partial derivatives with respect to the state variables in the system and this shows that the system is Lipschitz with respect to the state variables. Thus, the condition 1 holds. As we can observe from the state equations (1), the state equations are linearly dependent on the controls u_1 and u_2. Thus, condition 2 also holds. To establish condition 3, we observe that the integrand L in our objective functional is convex since it is quadratic in the controls. We only then need to prove the bound on L. This is shown as below:

$$\begin{aligned} L &= \tfrac{1}{2}(k_2 u_1^2 + k_3 u_2^2) + k_1 C, \\ &\geq \tfrac{1}{2}(k_2 u_1^2 + k_3 u_2^2), \qquad \sin ce\ k_i > 0,\ \ i = 1..3, \\ &\geq \tfrac{1}{2}(k_2 u_1^2 + k_3 u_2^2) - (k_2 + k_3), \quad \sin ce\ k_2 u_1^2 - k_2 \leq 0\ \ and\ k_3 u_2^2 - k_3 \leq 0, \qquad (4) \\ &\geq \min(\tfrac{1}{2}k_2, \tfrac{1}{2}k_3)(u_1^2 + u_2^2) - \beta, \quad where\ \ \beta = k_2 + k_3 > 0, \\ &\geq k \,\|\,(u_1, u_2)\,\|^2 - \beta, \quad where\ \ k = \min(\tfrac{1}{2}k_2, \tfrac{1}{2}k_3) > 0. \end{aligned}$$

Characterization of the optimal controls

We characterize the optimal controls (u_1, u_2) which gives the optimal levels for each of the two control strategies and the corresponding states (D^*, C^*). The necessary conditions for the optimal controls are obtained using the Pontryagin's maximum principle (Pontryagin *et al.*, 1986) while the terminal conditions on the adjoint variables are obtained based on the transversality condition (Hartl and Sethi, 1982).

Theorem 2 (Necessary conditions): *Let* $(u_1, u_2) \in U$ *be an optimal control with the corresponding states* D^* *and* C^**: Then, there exist the adjoint variables* λ_1 *and* λ_2 *which satisfy:*

$$\left.\begin{aligned} \frac{d\lambda_1}{dt} &= \nu(1-u_1)\lambda_1 + \mu\lambda_1 - \nu(1-u_1)\lambda_2, \\ \frac{d\lambda_2}{dt} &= -k_1 - u_2\gamma\lambda_1 + (u_2\gamma + \mu + \delta)\lambda_2. \end{aligned}\right\} \qquad (5)$$

and the transversality conditions yields

$$\lambda_1(t_f) = 0, \;\; \lambda_2(t_f) = 0. \qquad (6)$$

with the optimal controls defined as follows

$$\left.\begin{aligned} u_1^* &= \min\;\{\max\;(0, \frac{(\lambda_2 - \lambda_1)\nu D}{k_2}),\;\; u_{1\max}\}, \\ u_2^* &= \min\;\{\max\;(0, \frac{(\lambda_2 - \lambda_1)\gamma C}{k_3}),\;\; u_{2\max}\} \end{aligned}\right\}$$

Proof 2

Using Pontryagin's maximum principle, we obtain (5) from

$$\lambda_1' = -\frac{\partial H}{\partial D}, \quad \lambda_2' = -\frac{\partial H}{\partial C}. \qquad (7)$$

where the Hamiltonian H is given by

$$\begin{aligned} H &= k_1 C + \tfrac{1}{2}k_2 u_1^2 + \tfrac{1}{2}k_3 u_2^2 + \lambda_1(\Lambda + u_2\gamma C - (1-u_1)\nu D - \mu D) \\ &\quad + \lambda_2(1-u_1)\nu D - u_2\gamma C - \mu C - \delta C) \end{aligned} \qquad (8)$$

The transversality condition have the form (6), since all the states are free at the terminal time. As regards $u^* = (u_1^*, u_2^*)$, we differentiate *H* with respect to u_1 and u_2 on *U.*

Thus, the Hamiltonian *H* is maximized with respect to the controls at the optimal control $u^* = (u_1^*, u_2^*)$, to obtain

$$\left.\begin{aligned} \frac{\partial H}{\partial u_1} &= k_2 u_1 + \lambda_1 \nu D - \lambda_2 \nu D = 0, \quad at\;\; u_1 = u_1^*, \\ \frac{\partial H}{\partial u_2} &= k_3 u_2 + \lambda_1 C - \lambda_2 C = 0, \quad at\;\; u_2 = u_2^*. \end{aligned}\right\} \qquad (9)$$

Hence, solving for u_1^* *and* u_2^* on the interior sets gives:

$$\left.\begin{aligned} u_1^* &= \frac{(\lambda_2 - \lambda_1)\nu D}{k_2}, \\ u_2^* &= \frac{(\lambda_2 - \lambda_1)\gamma C}{k_3}. \end{aligned}\right\} \quad (10)$$

We can now impose the bounds $0 \le u_1 \le u_{1\max}$ and $0 \le u_2 \le u_{2\max}$ on the controls to get

$$\left.\begin{aligned} u_1^* &= \min\ \{\max\ (0, \frac{(\lambda_2 - \lambda_1)\nu D}{k_2}),\ u_{1\max}\}, \\ u_2^* &= \min\ \{\max\ (0, \frac{(\lambda_2 - \lambda_1)\gamma C}{k_3}),\ u_{2\max}\} \end{aligned}\right\} \quad (11)$$

Thus, we now have the below optimality system to solve:

$$\left.\begin{aligned} &D(t)' = \Lambda + u_2^*\gamma C - (1-u_1^*)\nu D - \mu D, \\ &C(t)' = (1-u_1^*)\nu D - u_2^*\gamma C - \mu C - \delta C, \\ &D(0) = 564.0,\ C(0) = 47.0, \\ &\lambda_1'(t) = \nu(1-u_1^*)\lambda_1 + \mu\lambda_1 - \nu(1-u_1^*)\lambda_2, \\ &\lambda_2'(t) = -k_1 - u_2^*\gamma\lambda_1 + (u_2^*\gamma + \mu + \delta)\lambda_2, \\ &\lambda_1(t_f) = 0,\ \lambda_2(t_f) = 0. \end{aligned}\right\} \quad (12)$$

SIMULATION OF RESULTS AND DISCUSSION

We solved the resulting optimality system numerically using a forth order iterative Runge-Kunta scheme. This method solves the model state equations with an initial guess for u_1 and u_2 forward in time; after which it solves the adjoint equations backward in time while the controls are continuously updated based on control equations (11). The computational procedure is done iteratively until results converges (Lenhart, 2007). Using the parameter values Λ = 6.0 million, ν = 0.05, μ =0.02, ∂ = 0.05, γ = 0.08, taking from (Boutayeb *et al.*, 2004) with u_1, $u_2 \in$ [0,1],
and the initial population for each of the compartments to be D(0)=564.0 million and C(0)=47.0 million. We simulated the optimality system; assuming the following maximum levels of effectiveness for each of the control strategies: $u_1 = 0.75$ and $u_2 = 0.5$. We investigated three scenarios: the situation where the resources are inadequate to fully manage all diabetics patients with or without complications, so preference are given to patients with complications (i.e. the weight constants are $k_1 = 1.0,\ k_2 = 1000,\ k_3 = 1.0$; the situation where there is inadequacy of resources with the preference given to patients without complications(i.e. the weight constants are $k_1 = 1.0,\ k_2 = 1.0,\ k_3 = 1000$); the situation where there is abundance of resources with all diabetic patients medically managed without preference (i.e.

the weight constants are $k_1 = 1.0,\ k_2 = 1.0,\ k_3 = 1.0$).

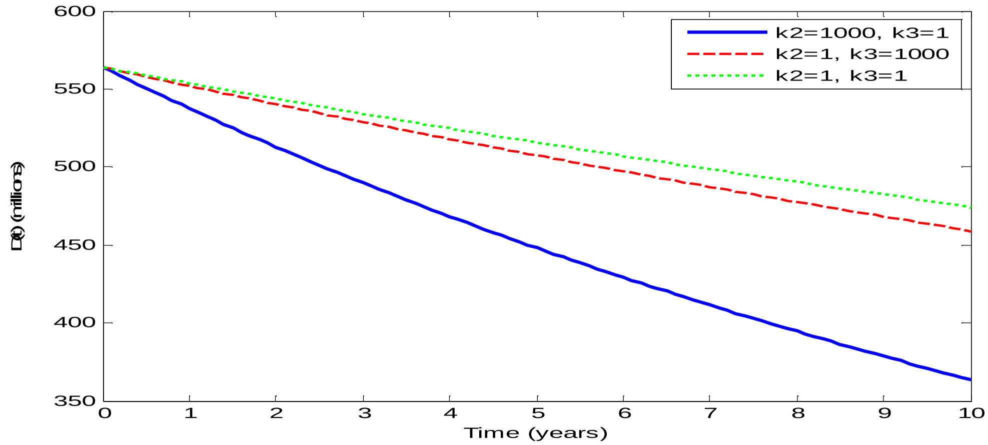

Figure 1: Number of Diabetic patients without Complication.

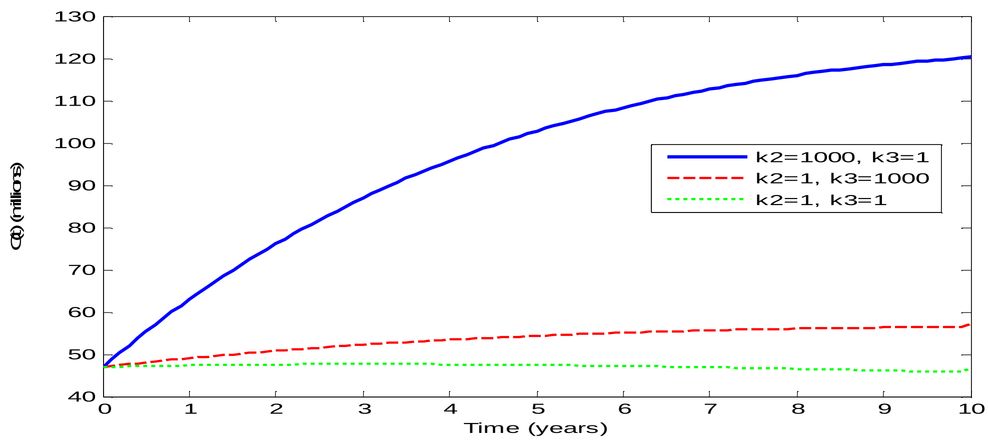

Figure 2: Number of Diabetic patients with Complications.

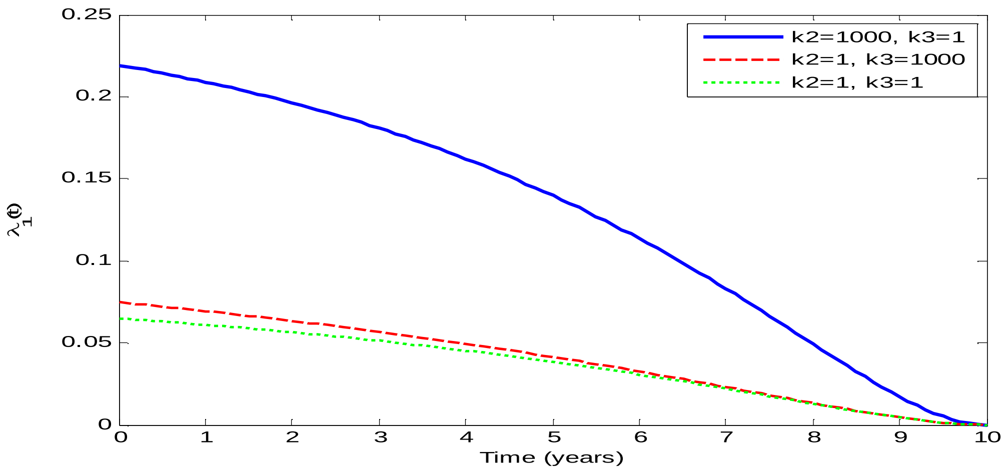

Figure 3: The marginal cost for the D(t) Class.

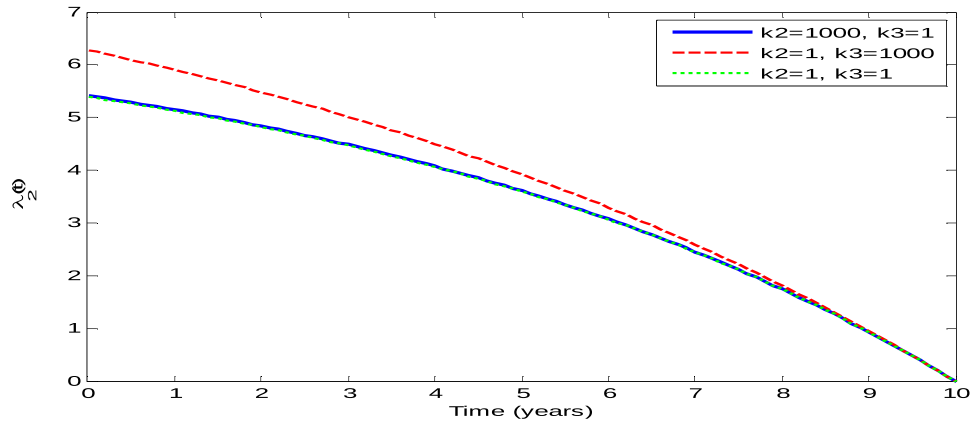

Figure 4: The marginal cost for the C(t) Class.

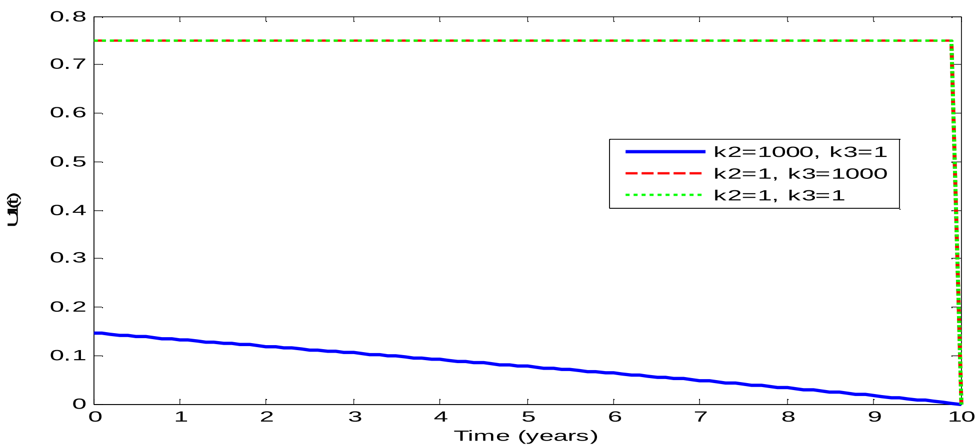

Figure 5: Required Effective rate of $u_1(t)$ per unit time.

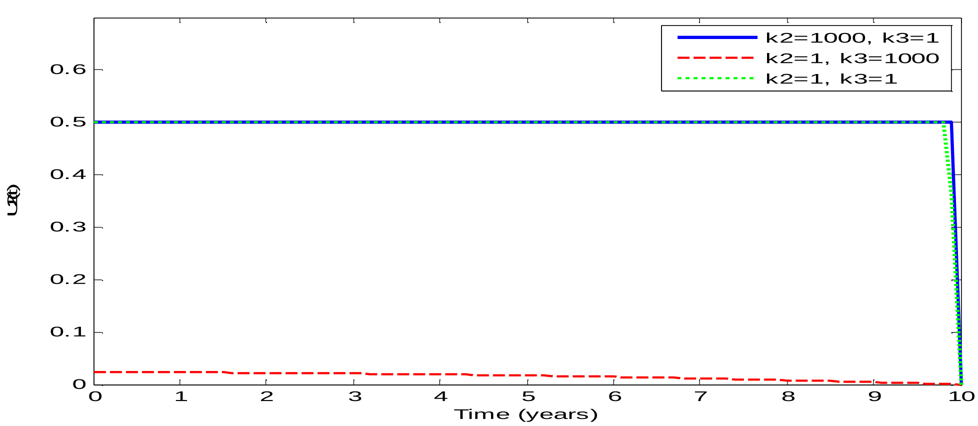

Figure 6: Required Effective rate of $u_2(t)$ per unit time.

Figures 1 and 2 show the dynamics of the diabetic patients' population without and with complications respectively under the three scenarios investigated. We observe that D(t) continues to decrease over time in each of the three scenarios . More importantly, the scenario where preference is given to patients with complications yielded a remarkable reduction in the D(t) class population over the ten year period. However, there is no significant difference in the D(t)class population for the other scenarios. As for the C(t) population, it grows conspicuously under the first scenario, it increases marginally under the second scenario and it remains relatively stable under the third scenario. Aside, there is a marked difference in the C(t) population profile for each of the three scenarios. Figure 3 shows that the additional cost/effort needed to achieve a single patient reduction in population of the D(t) class is reducing over time for the three scenarios, though this marginal cost per unit time for the first scenario is more than double that for the second and third scenario. Similarly, figure 4 shows that the additional cost/effort needed to achieve an additional single patient reduction in the C(t) class population is decreasing over time for the three scenarios. Although, this cost/effort is relatively higher in the second scenarios than any of the other two scenarios.

The two control graphs

Figures 5 and 6 showed that the maximum effectiveness of each of the control strategies that would be needed to attain optimal outcomes in each of the three scenarios. For instance, under the first scenario, we need to use maximum possible effective rate for control u_1 and as low as 4.0% of the maximum possible effective rate for the control u_2 in order to achieve optimal outcome. In general, the results show that the scenario where the resources available is enough to medically manage all diabetics patients with or without complications gives the best optimal outcome. This is so because it yielded the least number of patients in the C(t) class, with not too high population in D(t) class while the marginal costs of achieving an additional single patients reduction in D(t) and C(t) is decreasing over time. Nevertheless, for situation where the resources are inadequate, our results show that the scenario where preference are given to patients without complications yielded the better optimal outcome.

CONCLUSION

We presented a modified deterministic model for controlling the incidence of medical complications in a diabetic patients' population. We, then formulated an optimal control problem subject to the model dynamics with the goal of minimizing the number of diabetic patients with complications together with the cost of managing diabetic patients with/without complications using two different control strategies. We proved the existence and uniqueness of the optimal control and characterized the controls based on Pontryagin's Maximum principle. We solved the resulting optimality system numerically.

Our results showed that in a situation where the resources are inadequate to medically manage all the patients, preference should be giving to those without complications to ensure that they stay out of complications. This however requires the maximum possible effectiveness for the control strategies targeting the patients without complications while the required effectiveness for the control strategy for managing diabetic patients with complications remains relatively low. This notwithstanding, the best optimal outcome is accomplished when all diabetic patients with or without complications are medically managed. This later outcome requires that resources are in abundance to implement the control strategies and that the maximum possible effectiveness of each of the two control strategies are met almost all-through the time period under consideration.

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