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Optimal Control Approach to the Dynamics of a Population of Diabetics

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Abstract

Diabetes is a chronic disease with a huge and growing socio-economic burden affecting individuals, families and the whole society. In this paper, we propose an optimal control approach modeling the evolution from pre-diabetes to diabetes with and without complications. We show the existence of an optimal control and then use a numerical implicit finite-difference method to monitor the size of population in each compartment. Our model shows that, using optimal control, the number of diabetics with and without complications can be significantly reduced in a period of 10 years.

Keywords: Diabetes, mathematical model, stability analysis, simulation, optimal control

1 Introduction

According to the World Health Organisation (WHO), the term of diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Generally, diagnosis of diabetes is based on the level of fasting plasma glucose concentration (FPGC). Normoglecymia, pre-diabetes (also said impaired fasting glucose) and diabetes are respectively defined by a FPGC less than 110mg/dl, between110mg/dl and 126mg/dl, and greater than 126mg/dl [11].

According to the last International Diabetes Federation (IDF) report, more than 370 million people are living with diabetes worldwide (8.5% of adult population) and nearly 300 million people are in the pre-diabetic stage (6.5% of adult population). Consequently, the socio-economic burden of diabetes is huge with nearly five million deaths and more than 470 billion USD spent on healthcare in 2012 [9].

Due to its chronic nature with severe complications (cardiovascular disease, blindness, kidney failure and lower limb amputation), diabetes needs costly and prolonged treatment and care, affecting individuals, families and the whole society. The American diabetes Association estimates that the yearly cost of treating a person with diabetes is over 5 times more than for a person without diabetes [1]. Other studies estimate that the treatment of a diabetic patient with complications is 2 to 5 times higher than for a diabetic without complications but the burden of diabetes goes beyond the limits of economical problems by incurring indirect and intangible costs [3]. Consequently, the burden of diabetes can be reduced by controlling the number of people evolving from the stage of pre-diabetes to the stages of diabetes with and without complications. Following previous mathematical models on diabetes and prediabetes ([4], [5], [6]) the present paper proposes an optimal control approach modeling the dynamics of a population with diabetes.

2 Formulation of the model

We consider the model developed by Boutayeb and Chetouani [4]:

$$\begin{cases} \dfrac{dE(t)}{dt} = & I - (\mu + \beta_3 + \beta_1)E(t) \\ \dfrac{dD(t)}{dt} = & \beta_1 E(t) - (\mu + \beta_2)D(t) + \gamma C(t) \\ \dfrac{dC(t)}{dt} = & \beta_3 E(t) + \beta_2 D(t) - (\mu + \gamma + \nu + \delta)C(t) \end{cases}$$

Where:

- $E = E(t)$ Number of pre-diabetic peopole
- $D = D(t)$ numbers of diabetics without complications
- $C = C(t)$ numbers of diabetics with complications

- $N = N(t) = E(t) + C(t) + D(t)$ denotes the size of the population of diabetics and pre-diabetics at time t
- $I(t)$ denotes the incidence of pre-diabetes
- μ : natural mortality rate,
- β_1 : the probability of developing diabetes ,
- β_2 : the probability of a diabetic person developing a complication,
- β_3 : the probability of developing diabetes at stage of complications ,
- γ : rate at which complications are cured,
- ν : rate at which patients with complications become severely disabled,
- δ : mortality rate due to complications,

The controlled model is given by the following system

$$\begin{cases} \frac{dE(t)}{dt} = I - (\mu + (\beta_3 + \beta_1)(1 - u(t)))E(t) \\ \frac{dD(t)}{dt} = \beta_1(1 - u(t))E(t) - (\mu + \beta_2(1 - u(t)))D(t) + \gamma C(t) \\ \frac{dC(t)}{dt} = \beta_3(1 - u(t))E(t) + \beta_2(1 - u(t))D(t) - (\mu + \gamma + \nu + \delta)C(t) \end{cases} \tag{1}$$

Where u is a control

The objective function is defined as $\mathcal{J}(u) = \int_0^T \left(D(t) + C(t) + Au^2(t)\right) dt$

Where A is a positive weight that balances the size of the terms. U is the control set defined by $U = \{u/u \text{ is measurable, } 0 \leq u(t) \leq 1, t \in [0, T]\}$.

The objective is to characterize an optimal control $u^* \in U$ satisfying

$$\mathcal{J}(u^*) = \min_{u \in U} \mathcal{J}(u)$$

3 The optimal control: existence and characterization

We first show the existence of solutions of the system, thereafter we will prove the existence of optimal control.

3.1 Existence and Positivity of Solutions

Theorem 3.1.
The set $\Omega = \{(E, D, C) \in \mathbb{R}^3/0 \leq C, D, E \leq \frac{I}{\mu}\}$ *is positively invariant under system (1).*

Proof:

$$\begin{aligned}\frac{dE(t)}{dt} &= I - (\mu + (\beta_3 + \beta_1)(1 - u(t)))E(t) \\ &\geq -(\mu + (\beta_3 + \beta_1)(1 - u(t)))E(t)\end{aligned}$$

Then using Gronwall's inequality, $E(t) \geq E(0)e^{\left(-\int_0^T(\mu+(\beta_3+\beta_1)(1-u(t)))dt\right)}$
$\Longrightarrow E(t) > 0$
Assume that there exists some time $t_* > 0$ such that $D(t_*) = 0$, other variables are positive and $D(t) > 0$ for $t \in [0, t_*[$.
Then from $\dfrac{dD(t)}{dt} = \beta_1(1 - u(t))E(t) - (\mu + \beta_2(1 - u(t)))D(t) + \gamma C(t)$ we obtain:

$$\frac{d\left(D(t)e^{(\mu+\beta_2)t}\right)}{dt} = e^{(\mu+\beta_2)t}\left[\beta_1(1 - u(t))E(t) + \beta_2 u(t)D(t) + \gamma C(t)\right]$$

Integrating this Equation from 0 to t_* gives:

$$\int_0^{t_*} \frac{d\left(D(t)e^{(\mu+\beta_2)t}\right)}{dt}dt = \int_0^{t_*} e^{(\mu+\beta_2)t}\left[\beta_1(1 - u(t))E(t) + \beta_2 u(t)D(t) + \gamma C(t)\right]dt$$

$$\Longrightarrow D(t_*) = e^{-(\mu+\beta_2)t_*}\left[D(0) + \int_0^{t_*} e^{(\mu+\beta_2)t}\left[\beta_1(1 - u(t))E(t) + \beta_2 u(t)D(t) + \gamma C(t)\right]dt\right]$$

$\Longrightarrow D(t_*) > 0$ which contradicts $D(t_*) = 0$. Consequently, $D(t) > 0 \quad \forall t \in [0, T]$.
From

$$\begin{aligned}\frac{dC(t)}{dt} &= \beta_3(1 - u(t))E(t) + \beta_2(1 - u(t))D(t) - (\mu + \gamma + \nu + \delta)C(t) \\ \Longrightarrow \frac{dC(t)}{dt} &\geq -(\mu + \gamma + \nu + \delta)C(t)\end{aligned}$$

(because $E(t) > 0$ and $D(t) > 0$)
Then using Gronwall's inequality $C(t) = C(0)e^{-(\mu+\gamma+\nu+\delta)t} > 0$
On the other hand $\dfrac{dN(t)}{dt} = I - \mu N(t) - (\nu + \delta)C(t) \leq I - \mu N(t)$
So $N(t) \leq \frac{I}{\mu} - \left(\frac{I}{\mu} - N(0)\right)e^{-\mu t} \Longrightarrow N(t) \leq \frac{I}{\mu}$

Theorem 3.2.
The controlled system (1) that satisfies a given initial condition $(E(0), D(0), C(0)) \in \Omega$ *has a unique solution.*

Proof: Let $X = \begin{pmatrix} E(t) \\ D(t) \\ C(t) \end{pmatrix}$ and $\varphi(X) = X_t = \begin{pmatrix} \frac{dE(t)}{dt} \\ \frac{dD(t)}{dt} \\ \frac{dC(t)}{dt} \end{pmatrix}$ so the system (1) is rewritten in the following form: $\varphi(X) = X_t = AX + B$ were

$$A = \begin{pmatrix} -(\mu + (\beta_3 + \beta_1)(1-u(t))) & 0 & 0 \\ \beta_1(1-u(t)) & -(\mu + \beta_2(1-u(t))) & \gamma \\ \beta_3(1-u(t)) & \beta_2(1-u(t)) & -(\mu+\gamma+\nu+\delta) \end{pmatrix}$$

and $B = \begin{pmatrix} I \\ 0 \\ 0 \end{pmatrix}$

then $\|\varphi(X_1) - \varphi(X_2)\| \leq \|A\|.\|(X_1 - X_2)\|$. Thus, it follows that the function φ is uniformly Lipschitz continuous. So from the definition of the control $u(t)$ and the restriction on $E(t) \geq 0$, $D(t) \geq 0$ and $C(t) \geq 0$, we see that a solution of the system (1) exists [2].

3.2 Existence of an optimal control

Theorem 3.3.
Consider the control problem with system (1). There exists an optimal control $u^* \in U$ *such that* $\mathcal{J}(u^*) = \min_{u \in U} \mathcal{J}(u)$

Proof: The existence of the optimal control can be obtained using a result by Fleming and Rishel [7], checking the following steps :

- From theorem 3.1 and theorem 3.2 it follows that the set of controls and corresponding state variables is nonempty.

- $\mathcal{J}(u) = \displaystyle\int_0^T \big(D(t) + C(t) + Au^2(t)\big)\, dt$ is convex in u

- The control space $U = \{u/u$ are measurable, $0 \leq u(t) \leq 1, t \in [0,T]\}$. is convex and closed by definition.

- All the right hand sides of equations of system (1) are continuous, bounded above by a sum of bounded control and state, and can be written as a linear function of u with coefficients depending on time and state.

- The integrand in the objective functional, $D(t)+C(t)+Au^2(t)$, is clearly convex on U

- it rest to show that there exists constants $\alpha_1, \alpha_2 > 0$, and $\alpha > 1$ such that $D(t) + C(t) + Au^2(t)$ satisfies $D(t) + C(t) + Au^2(t) \geq \alpha_1 + \alpha_2|u|^\alpha$. The state variables being bounded, let $\alpha_1 = 1/2 \inf_{t\in[0,T]}(D(t), C(t)), \alpha_2 = A$ and $\alpha = 2$ then it follows that: $D(t) + C(t) + Au^2(t) \geq \alpha_1 + \alpha_2|u|^2$

Then from Fleming and Rishel [[7], p 68-69] we conclude that there exists an optimal control.

3.3 Characterization of the optimal control

The necessary conditions for the optimal control arise from the Pontryagin's maximum principle [10]

Theorem 3.4. *Given an optimal control u^* and solutions E^*, C^* and D^* of the corresponding state system (1), there exist adjoint variables λ_1, λ_2 and λ_3 satisfying*

$$\Longrightarrow \begin{cases} \lambda_1' &= (\lambda_1 - \lambda_2)(1-u^*)\beta_1 + (\lambda_1 - \lambda_3)(1-u^*)\beta_3 + \mu\lambda_1 \\ \lambda_2' &= -1 + \beta_2(1-u^*)(\lambda_2 - \lambda_3) + \mu\lambda_2 \\ \lambda_3' &= -1 + (\lambda_3 - \lambda_2)\gamma + \lambda_3(\mu + \nu + \delta) \end{cases}$$

With transversality conditions:$\lambda_1(T) = \lambda_2(T) = \lambda_3(T) = 0$
Moreover the optimal control is given by

$$u^* = \min(1, \max(0, \frac{1}{2A}[E^*\beta_1(\lambda_2 - \lambda_1) + E^*\beta_3(\lambda_3 - \lambda_1) + D^*\beta_2(\lambda_3 - \lambda_2)]))$$

Proof: The Hamiltonian is defined as follows:
$H = D + C + Au^2 + \lambda_1 f_1(E^*, D^*, C^*) + \lambda_2 f_2(E^*, D^*, C^*) + \lambda_3 f_3(E^*, D^*, C^*)$
where :
$f_1(E, C, D) = I - (\mu + (\beta_3 + \beta_1)(1 - u(t)))E(t)$
$f_2(E, C, D) = \beta_1(1 - u(t))E(t) - (\mu + \beta_2(1 - u(t)))D(t) + \gamma C(t)$
$f_3(E, C, D) = \beta_3(1 - u(t))E(t) + \beta_2(1 - u(t))D(t) - (\mu + \gamma + \nu + \delta)C(t)$
The optimal control can be determined from the optimality condition :
$\frac{dH}{du} = 0$
$\Longrightarrow 2Au + \lambda_1(\beta_1 + \beta_3)E(t) + \lambda_2(-\beta_1 E(t) + \beta_2 D(t)) - \lambda_3(\beta_3 E(t) + \beta_2 D(t)) = 0$
$\Longrightarrow u^* = \frac{1}{2A}[\beta_1 E^*(\lambda_2 - \lambda_1) + \beta_3 E^*(\lambda_3 - \lambda_1) + \beta_2 D^*(\lambda_3 - \lambda_2)]$
The adjoint variables λ_1, λ_2 and λ_3 are obtained by the following system:

$$\begin{aligned} \lambda_1' &= -\frac{dH}{dE} = (\lambda_1 - \lambda_2)(1-u^*)\beta_1 + (\lambda_1 - \lambda_3)(1-u^*)\beta_3 + \mu\lambda_1 \\ \lambda_2' &= -\frac{dH}{dD} = -1 + \lambda_2(\mu + \beta_2(1-u^*)) - \lambda_3\beta_2(1-u^*) \\ &= -1 + \beta_2(1-u^*)(\lambda_2 - \lambda_3) + \mu\lambda_2 \\ \lambda_3' &= -\frac{dH}{dC} = -1 + (\lambda_3 - \lambda_2)\gamma + \lambda_3(\mu + \nu + \delta) \end{aligned}$$

$$\Longrightarrow \begin{cases} \lambda_1' &= (\lambda_1-\lambda_2)(1-u^*)\beta_1+(\lambda_1-\lambda_3)(1-u^*)\beta_3+\mu\lambda_1 \\ \lambda_2' &= -1+\beta_2(1-u^*)(\lambda_2-\lambda_3)+\mu\lambda_2 \\ \lambda_3' &= -1+(\lambda_3-\lambda_2)\gamma+\lambda_3(\mu+\nu+\delta) \\ \lambda_1(T) &= \lambda_2(T)=\lambda_3(T)=0 \end{cases}$$

4 Numerical simulation

To solve the system (1) numerically we will use the method Gauss-Seidel-like implicit finite-difference finite-difference method developed by Gumel et al. [8].

The time interval $[t_0, T]$ is discretized with a step h (time step size) such that $t_i = t_0 + ih \quad i = 0, 1, \cdots, n$ and $t_n = T$
So at each point t_i we will note $E_i = E(t_i), \quad D_i = D(t_i), \quad C_i = C(t_i),$
$\lambda_1^i = \lambda_1(t_i), \quad \lambda_2^i = \lambda_2(t_i), \quad \lambda_3^i = \lambda_3(t_i),$ and $u_i = u(t_i)$
For the approximation of the derivative we used simultaneously forward difference for $\frac{dE(t)}{dt}$, $\frac{dD(t)}{dt}$ and $\frac{dC(t)}{dt}$ and backward difference for $\frac{d\lambda_1(t)}{dt}$, $\frac{d\lambda_2(t)}{dt}$ and $\frac{d\lambda_3(t)}{dt}$.
So the derivatives $\frac{dE(t)}{dt}$, $\frac{dD(t)}{dt}$ and $\frac{dC(t)}{dt}$ are approached by the following finite differences: for $i = 0, \cdots, n-1$

$$\frac{dE_{i+1}}{dt} \approx \frac{E_{i+1}-E_i}{h}, \quad \frac{dD_{i+1}}{dt} \approx \frac{D_{i+1}-D_i}{h} \quad \text{and} \quad \frac{dC_{i+1}}{dt} \approx \frac{C_{i+1}-C_i}{h}$$

Similarly, $\frac{d\lambda_1(t)}{dt}$, $\frac{d\lambda_2(t)}{dt}$ and $\frac{d\lambda_3(t)}{dt}$ are approached by finite differences
$\frac{d\lambda_1^{n-i}}{dt} \approx \frac{\lambda_1^{n-i}-\lambda_1^{n-i-1}}{h}$, $\frac{d\lambda_2^{n-i}}{dt} \approx \frac{\lambda_2^{n-i}-\lambda_2^{n-i-1}}{h}$ and $\frac{d\lambda_3^{n-i}}{dt} \approx \frac{\lambda_3^{n-i}-\lambda_3^{n-i-1}}{h}$
for $i = 0, \cdots, n-1$.
Hence the problem is given by the following numerical scheme for $i = 0, \cdots, n-1$

$$\begin{cases} \frac{E_{i+1}-E_i}{h} &= I-(\mu+(\beta_3+\beta_1)(1-u_i))E_{i+1} \\ \frac{D_{i+1}-D_i}{h} &= \beta_1(1-u_i)E_{i+1}-(\mu+\beta_2(1-u_i))D_{i+1}+\gamma C_i \\ \frac{C_{i+1}-C_i}{h} &= \beta_3(1-u_i)E_{i+1}+\beta_2(1-u_i)D_{i+1}-(\mu+\gamma+\nu+\delta)C_{i+1} \\ \frac{\lambda_1^{n-i}-\lambda_1^{n-i-1}}{h} &= (\lambda_1^{n-i-1}-\lambda_2^{n-i})(1-u_i)\beta_1+(\lambda_1^{n-i-1}-\lambda_3^{n-i})(1-u_i)\beta_3+\mu\lambda_1^{n-i-1} \\ \frac{\lambda_2^{n-i}-\lambda_2^{n-i-1}}{h} &= -1+\beta_2(1-u_i)(\lambda_2^{n-i-1}-\lambda_3^{n-i})+\mu\lambda_2^{n-i-1} \\ \frac{\lambda_3^{n-i}-\lambda_3^{n-i-1}}{h} &= -1+(\lambda_3^{n-i-1}-\lambda_2^{n-i-1})\gamma+\lambda_3^{n-i-1}(\mu+\nu+\delta) \end{cases}$$

Then we consider : $E_0 = E(0), D_0 = D(0), C_0 = C(0), u_0 = 0, \lambda_1^n = 0, \lambda_2^n = 0$

and $\lambda_3^n = 0$ so for $i = 0, \cdots, n-1$

$$\left\{\begin{array}{lcl}
E_{i+1} & = & \dfrac{hI + E_i}{1 + h(\mu + (\beta_3 + \beta_1)(1 - u_i))} \\
D_{i+1} & = & \dfrac{D_i + h\beta_1(1 - u_i)E_{i+1} + h\gamma C_i}{1 + h(\mu + \beta_2(1 - u_i))} \\
C_{i+1} & = & \dfrac{C_i + h\beta_3(1 - u_i)E_{i+1} + h\beta_2(1 - u_i)D_{i+1}}{1 + (\mu + \gamma + \nu + \delta)h} \\
\lambda_1^{n-i-1} & = & \dfrac{\lambda_1^{n-i} + \lambda_2^{n-i}(1 - u_i)h\beta_1 + \lambda_3^{n-i}(1 - u_i)h\beta_3}{1 + h\mu + (1 - u_i)h(\beta_1 + \beta_3)} \\
\lambda_2^{n-i-1} & = & \dfrac{\lambda_2^{n-i} + \beta_2(1 - u_i)h\lambda_3^{n-i} + h}{1 + h(\mu + \beta_2(1 - u_i))} \\
\lambda_3^{n-i-1} & = & \dfrac{\lambda_3^{n-i} + \lambda_2^{n-i-1}h\gamma + h}{1 + h(\mu + \gamma + \nu + \delta)} \\
M^{i+1} & = & \dfrac{1}{2A}\left[\beta_1 E_{i+1}(\lambda_2^{n-i-1} - \lambda_1^{n-i-1}) + \beta_3 E_{i+1}(\lambda_3^{n-i-1} - \lambda_1^{n-i-1})\right] \\
& & \quad + \dfrac{1}{2A}\left[\beta_2 D_{i+1}(\lambda_3^{n-i-1} - \lambda_2^{n-i-1})\right] \\
u_{i+1} & = & \min(1, \max(0, M^{i+1}))
\end{array}\right.$$

Different simulations can be carried out using various values of parameters. In the present numerical approach, we use the following parameters values taken from [4]:

Parameter	Value yr^{-1}	Parameter	Value yr^{-1}
μ	0.02	I	2000000
ν	0.05	β_1	0.5
γ	0.08	β_2	0.1
δ	0.05	β_3	0.5

Table 1: Parameter vales used in numerical simulation

$E(0) = 6660000; D(0) = 10200000; C(0) = 5500000;$ $n = 1000; h = 0.01;$ $T = nh = 10$ years $\lambda_1(n) = 0; \lambda_2(n) = 0; \lambda_3(n) = 0;$
Since control and state functions are on different scales, the weight constant value is chosen as follows: $A = 3550000;$

5 Conclusion

As indicated in the introduction section, the burden of diabetes can be reduced at three levels by controlling: 1) the number of people evolving from pre-diabetes to diabetes without complication ($\beta_1(1 - u(t))$), 2) the number of diabetic patients developing complications ($\beta 2(1-u(t))$) and 3) the number of people evolving directly from pre-diabetes to diabetes with complications due to delayed diagnosis ($\beta_3(1-u(t))$). Our model shows that, in a period of ten years, the population of diabetics without complications ($D(t)$) will increase

Initial population (10^6)	$E(0) = 6.66$	$D(0) = 10.20$	$C(0) = 5.50$
Population after 10 years without optimal control (10^6)	$E_1(n) = 1.96$ 70% decrease	$D_1(n) = 14.30$ 40% increase	$C_1(n) = 11.25$ 104% increase
Population after 10 years with optimal control (10^6)	$E_2(n) = 18.72$ 181% increase	$D_2(n) = 14.30$ 24% increase	$C_2(n) = 11.25$ 74% decrease
Difference due to optimal control (10^6)	$E_2(n) - E_1(n) = -16.76$	$D_2(n) - D_1(n) = 1.68$	$C_2(n) - C_1(n) = 9.82$

Table 2: Simulation results and growth rates for $E(T), D(T)$ and $C(T)$

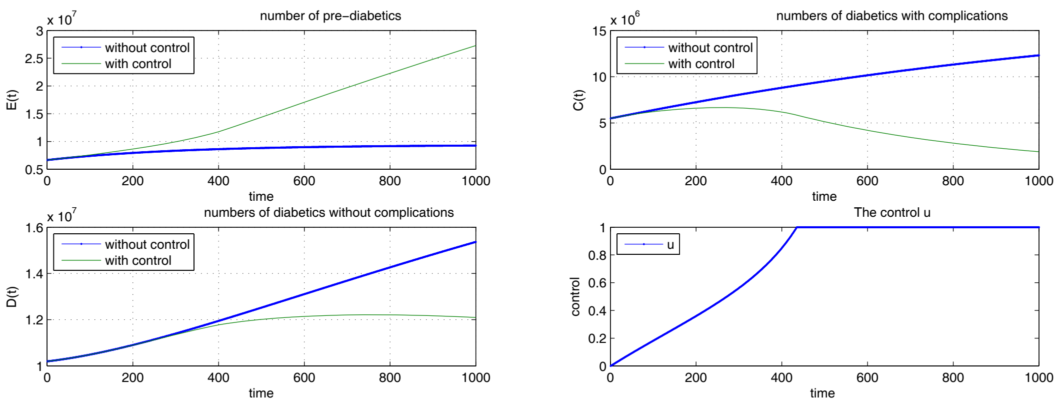

Figure 1: The effect of optimal control on the dynamics of the population of pre-diabetics and diabetics with and without complications

by 26% and 40% with and without control respectively. More importantly, the population of diabetics with complications will increase by 104% without control while it will decrease by 74% in presence of optimal control (Table2, Figure1). This is not a mere mathematical result, pragmatic achievements can be obtained by sensitization for a healthy diet, promotion of physical activity, obesity control and smoking reduction. An optimal strategy will also need early diagnosis of diabetes and affordable treatment and healthcare in order to avoid complications or at least to delay their occurrence as far as possible.

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