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Diabetes, Complications And Limit Cycles*

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Abstract

In this paper, we consider a population of diabetics and divide it into two subcategories, one of diabetics with complications and another one of diabetics without complications. From a model examining the complications of individuals diagnosed with diabetes, we associate a nonlinear optimal control problem. Considering this last one, we prove that there is no cyclical behavior between diabetics with complications, diabetics without complications and the rate at which complications are cured. Moreover we characterize the state equilibrium via Hopf bifurcation theorem adapted to optimal control problem.

1 Introduction

Diabetes is a chronic disease caused by a combination of hereditary and acquired bad factors. The treatment is based on medication, strict diet and physical exercises. The population of diabetics grows significantly in the world and more precisely in developing countries and this disease with its complications are an important cause of death. Consequently it is important to understand the efficiency of the treatments, the effects of external factors on the disease and its evolution. The reader could find in the literature many mathematical models focused on these challenges [1, 2, 3, 4, 5, 8, 9, 10].

To our knowledge, the contributions via the optimal control theory for diabetes are not very wide. In [5], J. R. Faria showed that there is a cyclical behavior between the weight and the consumption of a diabetic created by the medical treatment, by using the Hopf bifurcation theorem adapted to optimal control problem. In [2], the authors considered an optimal control problem for the evolution of numbers of pre-diabetics and diabetics with and without complications and showed that the population of diabetics with complications decreases in presence of optimal control. In [1], S. Bernard and A. Piétrus considered a new model of regulation adapted to the one introduced in [10] and studied it in the framework of ordinary differential equation and optimal control theory. By controlling the external glucose food intake, they proved that the plasma glycemia level can be minimized.

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In this work, we consider a population of diabetics, divided into two subcategories, one of diabetics with complications and another one of diabetics without complications as in [3]. From the model examining the complications of individuals diagnosed with diabetes, we associate a nonlinear optimal control problem. Considering this last one, we prove that there is no cyclical behavior between diabetics with complications, diabetics without complications and the rate at which complications are cured. Moreover, we are placed in the framework of a nonlinear optimal control problem with a scalar control and two states for which necessary conditions of an optimal control are well known [7]. We can thus characterize the equilibrium point by using an adaptation of Hopf bifurcation theorem to optimal control models as it has been done in [6, 13, 14, 15].

Consequently, section 2 is devoted to the two dimensional nonlinear optimal control problem. From a control chosen as the rate at which complications are cured and a concave performance index chosen as a combination of the control and the two subcategories of diabetics, we show the existence of an optimal control and characterize it via the Pontryagin's maximum principle. In section 3, we prove that there is an equilibrium state and that there is no cyclical behavior between the number of diabetics with complications, the one of diabetics without complications and the rate at which complications are cured. The equilibrium state is characterized in section 4 with the help of computations on Maple that we describe in the appendix. We finish by some concluding remarks and perspectives.

2 The Optimal Control Problem

In this section, we are going to use some results on the optimal control theory for a model examining the complications of individuals diagnosed with diabetes. This theory is very wide and we refer the reader to [7, 11, 12] for more details about it.

We begin with the mathematical model of [3] in which we choose all the parameters depending on the time:

$$\begin{cases} D'(t) = I - (\lambda(t) + \mu(t))D(t) + \gamma(t)C(t), \\ C'(t) = \lambda(t)D(t) - (\gamma(t) + \mu(t) + \nu(t) + \delta(t))C(t), \end{cases} \tag{1}$$

where

- t is the time,
- $D(.)$ the number of diabetics without complications,
- $C(.)$ the number of diabetics with complications,
- I the incidence of diabetes,
- $\lambda(.)$ the probability of developing a complication,
- $\mu(.)$ the natural mortality rate,
- $\gamma(.)$ the rate at which complications are cured,
- $\nu(.)$ the rate at which patients with complications become severely disabled,

- $\delta(.)$ the mortality rate due to complications.

In this work, the chosen control is $u(t) = \gamma(t)$, the rate at which complications are cured. Is is natural to make this choice regarding the following but other choices of control could be interesting.

THEOREM 1. For all fixed control $u = \gamma$, there exists one and only one maximal solution $([0, t_m(u)], D_u(.), C_u(.))$ of the Cauchy problem (1) with the initial conditions $D(0) = D_0 \in \mathbb{R}$, $C(0) = C_0 \in \mathbb{R}$ and $t_m(u) \in \mathbb{R}_+ \cup \{+\infty\}$.

PROOF. It follows from the application of Cauchy-Lipschitz's theorem for the problem (1) since all the functions λ, μ, γ, ν and δ are in $L^\infty(I, R_+)$.

For a fixed discount rate $r > 0$, we define a concave performance index

$$F(\gamma, D, C) = \alpha \ln \gamma + \ln C + D,$$

with $\alpha > 0$ which will be well chosen later, and our aim is to maximize

$$\int_0^{+\infty} \exp(-rt) F(\gamma(t), D(t), C(t)) dt.$$

THEOREM 2. Let (D_0, C_0) be in $I\!R^2$ such that there is a control $u(.)$ satisfying (1) with the initial conditions $D(0) = D_0$ and $C(0) = C_0$. There exists an optimal control u defined on $[0, +\infty[$ such that the associated trajectory $(D_u(.), C_u(.))$ satisfies (1), the initial conditions and which maximizes

$$\int_0^{+\infty} \exp(-rt) F(\gamma(t), D(t), C(t)) dt.$$

PROOF. We are in the framework of [7, 13] that is a nonlinear optimal control problem with a scalar control $u(t) = \gamma(t)$ and two states $D(t)$ and $C(t)$ where the present value of a concave performance index $F(\gamma, D, C)$ has to be maximized. We conclude by following the gait of [13].

In order to characterize this optimal control, we are going to apply as usual the Pontryagin's maximum principle. We refer the reader to [7, 11, 12, 13] for more details about this principle and more precisely on the necessary conditions for an optimal control.

THEOREM 3. With previous assumptions, there exists an application $P(.) = (P_D(.), P_C(.)) : [0, +\infty[\longrightarrow \mathbb{R}^2$ absolutely continuous called adjoint vector, such that, for almost all $t \geq 0$,

$$\begin{cases} P'_D(t) = (r + \lambda(t) + \mu(t)) P_D(t) - \lambda(t) P_C(t) - 1, \\ P'_C(t) = (r + \mu(t) + \nu(t) + \delta(t)) P_C(t) - (C(t))^{-1} + \gamma(t)(P_C(t) - P_D(t)), \end{cases}$$

with the limiting transversality conditions

$$\begin{cases} \lim\limits_{t\to+\infty} \exp(-rt)P_D(t)D(t) = 0, \\ \lim\limits_{t\to+\infty} \exp(-rt)P_C(t)C(t) = 0. \end{cases}$$

And the optimal control $\bar{\gamma}$, whose existence has been proved in previous theorem, is given by

$$\forall t \geq 0,\ \bar{\gamma}(t) = \frac{\alpha(t)}{(P_C(t) - P_D(t))C(t)}.$$

PROOF. The associated Hamiltonian is defined from the state equations and the integrand of the objective function $F(\gamma, D, C)$ as

$$\begin{aligned} H(\gamma, D, C, P_D, P_C) &= \alpha \ln \gamma + \ln C + D + P_D\left[I - (\lambda+\mu)D + \gamma C\right] \\ &\quad + P_C\left[\lambda D - (\gamma + \mu + \nu + \delta)C\right]. \end{aligned}$$

We just apply the Pontryagin's maximum principle and the fact that the optimal control has to maximize the Hamiltonian with respect to u. We omit all the t in order to relieve the writing and we do it from now.

3 Existence of Equilibrium State

THEOREM 4. If $\mu = 0$, $\alpha < 1 - \sigma^{-1}I$ and $r > I(1 - \alpha - \sigma^{-1}I)^{-1}$, then there is an equilibrium state for the system

$$\begin{cases} D'(t) = I - (\lambda(t) + \mu(t))D(t) + \gamma(t)C(t), \\ C'(t) = \lambda(t)D(t) - (\gamma(t) + \mu(t) + \nu(t) + \delta(t))C(t), \\ P_D'(t) = (r + \lambda + \mu)P_D(t) - \lambda P_C(t) - 1, \\ P_C'(t) = (r + \mu + \nu + \delta)P_C(t) - (C(t))^{-1} + \gamma(P_C(t) - P_D(t)). \end{cases}$$

PROOF. The equilibrium state (D^*, C^*, P_D^*, P_C^*) if it exists, is solution of the following system that we are going to solve:

$$\begin{cases} I - (\lambda+\mu)D + \bar{\gamma}C = 0, \\ \lambda D - (\bar{\gamma} + \mu + \nu + \delta)C = 0, \\ (r + \lambda + \mu)P_D - \lambda P_C - 1 = 0, \\ (r + \mu + \nu + \delta)P_C - C^{-1} + \bar{\gamma}(P_C - P_D) = 0. \end{cases}$$

In order to simplify the writing, let us set $\rho = \lambda+\mu$, and $\sigma = \mu+\nu+\delta$, and $T = P_C - P_D$. By replacing $\bar{\gamma}$ by $\alpha(TC)^{-1}$, the use of the first equation gives

$$D = \frac{IT + \alpha}{\rho T}$$

and the use of the second one gives

$$C = \frac{\lambda}{\sigma}D - \frac{\alpha}{\sigma T}.$$

Consequently,

$$C = \frac{\lambda(\alpha + IT) - \alpha\rho}{\sigma\rho T}.$$

Moreover, by using the fourth equation, we obtain

$$P_C = \frac{1-\alpha}{(r+\sigma)C}$$

so

$$P_C = \frac{(1-\alpha)\sigma\rho T}{(r+\sigma)[\lambda IT + \alpha(\lambda-\rho)]}.$$

The third equation implies that

$$P_D = \frac{\lambda}{r+\rho}P_C + \frac{1}{r+\rho}$$

so

$$P_D = \frac{\lambda T[\sigma\rho(1-\alpha) + I(r+\sigma)] + \alpha(r+\sigma)(\lambda-\rho)}{(r+\sigma)(r+\rho)[\lambda IT + \alpha(\lambda-\rho)]}.$$

Thus

$$T = \frac{(r+\rho)(1-\alpha)\sigma\rho T - \lambda T[\sigma\rho(1-\alpha) + I(r+\sigma)] - \alpha(r+\sigma)(\lambda-\rho)}{(r+\sigma)(r+\rho)[\lambda IT + \alpha(\lambda-\rho)]}.$$

We obtain

$$\begin{aligned} & T(r+\sigma)(r+\rho)[\lambda IT + \alpha(\lambda-\rho)] \\ = \quad & (r+\rho)(1-\alpha)\sigma\rho T - \lambda T[\sigma\rho(1-\alpha) + I(r+\sigma)] - \alpha(r+\sigma)(\lambda-\rho), \end{aligned}$$

that is

$$\begin{aligned} & \lambda I(r+\rho)(r+\sigma)T^2 + [\alpha(\lambda-\rho)(r+\rho)(r+\sigma) - (r+\rho)(1-\alpha)\sigma\rho \\ & +\lambda\sigma\rho(1-\alpha) + \lambda I(r+\sigma)T] + \alpha(r+\sigma)(\lambda-\rho) = 0. \end{aligned}$$

But $\mu = 0$ that is $\lambda = \rho$ so

$$T = \frac{\sigma(1-\alpha)r - I(r+\sigma)}{I(r+\lambda)(r+\sigma)},$$

since λ and T are non equals to zero. Consequently

$$P_C^* = \frac{(1-\alpha)\sigma}{(r+\sigma)I}, \quad P_D^* = \frac{\lambda(1-\alpha)\sigma + (r+\sigma)I}{(r+\sigma)(r+\lambda)I},$$

$$C^* = \frac{I}{\sigma}, \text{ and } \quad D^* = \frac{I}{\lambda} + \frac{\alpha I(r+\lambda)(r+\sigma)}{\lambda[\sigma(1-\alpha)r - I(r+\sigma)]}.$$

It follows that

$$\gamma^* = \frac{\alpha\sigma(r+\lambda)(r+\sigma)}{\sigma(1-\alpha)r - I(r+\sigma)}$$

and $\gamma^* > 0$ if and only if $r[\sigma(1-\alpha) - I] > \sigma I$. At this stage, we have to discuss about possible values of α and r to ensure the existence of equilibrium state.

- If $\alpha > 1$ then $\gamma^* < 0$,
- if $\alpha = 1$ then $\gamma^* < 0$,
- if $\alpha < 1 - \sigma^{-1} I$ then $\gamma^* > 0$ if and only if $r > \frac{\sigma I}{\sigma(1-\alpha)-I}$,
- if $1 - \sigma^{-1} I < \alpha < 1$ then $\gamma^* < 0$.

There is only the third case which leads us to conclude, since γ^* is a rate so has to be non negative.

4 Stability Analysis

In this part we are going to classify the equilibrium state defined in the previous section.

THEOREM 5. There is no limit cycle between the number of diabetics with complications, the one of diabetics without complications and the rate at which complications are cured.

PROOF. Let us define the Jacobian by

$$J = \begin{pmatrix} \partial D'/\partial D & \partial D'/\partial C & \partial D'/\partial P_D & \partial D'/\partial P_C \\ \partial C'/\partial D & \partial C'/\partial C & \partial C'/\partial P_D & \partial C'/\partial P_C \\ \partial P'_D/\partial D & \partial P'_D/\partial C & \partial P'_D/\partial P_D & \partial P'_D/\partial P_C \\ \partial P'_C/\partial D & \partial P'_C/\partial C & \partial P'_C/\partial P_D & \partial P'_C/\partial P_C \end{pmatrix}$$

and the term K by

$$K = \begin{vmatrix} \partial D'/\partial D & \partial D'/\partial P_D \\ \partial P'_D/\partial D & \partial P'_D/\partial P_D \end{vmatrix} + \begin{vmatrix} \partial C'/\partial C & \partial C'/\partial P_C \\ \partial P'_C/\partial C & \partial P'_C/\partial P_C \end{vmatrix} + 2 \begin{vmatrix} \partial D'/\partial C & \partial D'/\partial P_C \\ \partial P'_D/\partial C & \partial P'_D/\partial P_C \end{vmatrix}.$$

In order to study the existence of a limit cycle, it is necessary to know the sign of the determinant of the Jacobian J and of the term K calculated at the state equilibrium point. For our problem, we have

$$J = \begin{pmatrix} -(\lambda+\mu) & \gamma & 0 & 0 \\ \lambda & -(\gamma+\mu+\nu+\delta) & 0 & 0 \\ 0 & 0 & r+\lambda+\mu & -\lambda \\ 0 & C^{-2} & -\gamma & r+\gamma+\mu+\nu+\delta \end{pmatrix}$$

and

$$K = \begin{vmatrix} -(\lambda+\mu) & 0 \\ 0 & r+\lambda+\mu \end{vmatrix} + \begin{vmatrix} -(\gamma+\mu+\nu+\delta) & 0 \\ C^{-2} & r+\gamma+\mu+\nu+\delta \end{vmatrix} + 2 \begin{vmatrix} \gamma & 0 \\ 0 & -\lambda \end{vmatrix}.$$

Consequently,

$$\det J = [(\lambda+\mu)(\gamma+\mu+\nu+\delta) - \lambda\gamma] \begin{vmatrix} r+\lambda+\mu & -\lambda \\ -\gamma & r+\gamma+\mu+\nu+\delta \end{vmatrix},$$

that is

$$\det J = [(\lambda+\mu)(\gamma+\mu+\nu+\delta)-\lambda\gamma]\,[(r+\lambda+\mu)(r+\gamma+\mu+\nu+\delta)-\lambda\gamma]$$

and

$$\begin{aligned}\det J &= [\lambda(\mu+\nu+\delta)+\mu(\gamma+\mu+\nu+\delta)]\,[(r+\mu)(r+\gamma+\mu+\nu+\delta)\\ &\quad +\lambda(r+\mu+\nu+\delta)],\end{aligned}$$

which implies that $\det J \geq 0$. Moreover,

$$K = -(\lambda+\mu)(r+\lambda+\mu)-(\gamma+\mu+\nu+\delta)(r+\gamma+\mu+\nu+\delta)-2\gamma\lambda,$$

that is $K \leq 0$. Since $\det J \geq 0$ and $K \leq 0$, we can say that there is no limit cycle between diabetics with complications, diabetics without complications and the rate at which complications are cured.

Let us notice that this result occurs without using the equilibrium state and does not depend on the form of F.

THEOREM 6. The equilibrium state defined in previous section is a saddle point.

PROOF. In order to classify the state equilibrium, we have to know the sign of $Q = \det(J) - \frac{1}{2}K^2$. Because of the complications of the calculus, we use Maple. We write Q as a polynomial function of degree 4 in γ and evaluate the coefficients of the powers of γ to note that there are negatives, which allows us to conclude that Q is negative, since γ is positive. The reader can find the different orders in the following appendix. Consequently, we can say that one has a saddle point stability, real roots, two are negative and two are positive, and local monotonicity, according to the classification of equilibria from $\det(J)$ and K of [6].

5 Concluding Remarks

In this paper, we proved that by controlling the rate at which complications are cured, we can maximize the number of diabetics with complications which are cured and those without complications. Moreover we showed that the evolution of complications of diabetics does not stabilize around the equilibrium state which is in fact a saddle point. All these results seem to conform to the reality. For the sequel, it will be interesting to see the influence of physical exercises, consumption and treatment on the number of diabetics with complications. For this, the first challenge would be to introduce these parameters in the models and the second one would be to control them in order to reduce the number of diabetics with complications.

6 Appendix

For the sake of simplicity, we have set $d := \delta$, $g := \gamma$, $l := \lambda$, $m := \mu$, $n := \nu$ et $x := r$ in the Maple command lines.

First, we introduce, the formulas of $\det(J)$ and K by typing:

```
> det(J) := ((x + m) * (x + g + m + n + d) + l * (x + m + n + d)) * (l * (m + n + d
  +m * (g + m + n + d));
> K := -(l + m) * (x + l + m) - (g + m + n + d) * (x + g + m + n + d) - 2 * g * l;
```

After, we evaluate $Q = \det(J) - \frac{1}{2}K^2$ by typing

```
> Q := evala(det(J) - K^2/4);
```

Our goal is to develop the polynomial function Q as a power series of the variable g. The polynomial function Q is of fourth degree and clearly, the coefficient of g^4 is $-\frac{1}{4}$. That is why we introduce

```
> coeff_g4 := -1/4;
```

In order to determine the coefficient of g^3, we use the following command line:

```
> isolate(Q - coeff_g4 * g^4, g^3);
```

which leads us to set

```
> coeff_g3 := -m - n - d - l - 1/2 * x;
```

With the same method, we determine the coefficient of g^2, by using the following command line:

```
> isolate(evala(Q - coeff_g4 * g^4 - coeff_g3 * g^3), g^2);
```

which leads us to set

```
> coeff_g2 := -3/2 * x * n - 3/2 * l * x - 2 * l * n - 2 * l * d - 3/2 * x * d - x * m
  -3 * m * n - 3 * n * d - 3 * m * d - 3 * l * m - 3/2 * l^2 - m^2 - 1/4 * x^2 - 3/2 * n^2
  -3/2 * d^2;
```

Still in the same way, we determine the coefficient of g, using this command line:

```
> isolate(evala(Q - coeff_g4 * g^4 - coeff_g3 * g^3 - coeff_g2 * g^2), g);
```

which leads us to set the command line

```
> coeff_g1 := -2 * x * m * n - x * l * n - 2 * m * l * d - 2 * x * l * m - 6 * m * n * d
  -2 * m * l * n - x * l * d - 2 * x * m * d - l^3 - n^3 - d^3 - 3/2 * l^2 * x - 1/2 * x^2 * d
  -3 * l^2 * m - 3 * m * n^2 - 1/2 * l * x^2 - l^2 * d - 3/2 * x * d^2 - 1/2 * x^2 * n
  -2 * m^2 * l - 3/2 * x * n^2 - 2 * m^2 * n - n^2 * l - d^2 * l - 3 * n^2 * d
  -3 * n * d^2 - 3 * m * d^2 - 2 * m^2 * d - l^2 * n - 3 * x * n * d - 2 * n * d * l;
```

Finally, we calculate the coefficient of zero order of Q (in the expansion of Q as a power series of the variable g) with the command line

```
> coeff_g0 := evala(Q - coeff_g4 * g^4 - coeff_g3 * g^3 - coeff_g2 * g^2
  -coeff_g1 * g);
```

To find the sign of coeff_g0, we expand it as a second order power series of variable x. Using the following sequence of command

```
> isolate(evala(coeff_g0), x^2);
> simplify(1/2 * l * n + 1/2 * l * d - 1/2 * n * d - 1/4 * l^2 - 1/4 * n^2 - 1/4 * d^2
  +(l - n - d)^2/4);
```

leads us to set

```
> coeff_g0_x2 := -(l - n - d)^2/4;
```

as the coefficient of x^2. By the same method as before, we are able to set the command line

```
> coeff_g0_x1 := -(l^2 - (n + d)^2) * (l - (n + d))/2 - m * (l - n - d)^2;
```

as the coefficient of x, and

```
> coeff_g0_x0 := -(l^2 - (n + d)^2)^2/4 - (m^2) * (l - n - d)^2 - m * (l^2 - (n + d)^2)
```

$*(\mathsf{l} - \mathsf{n} - \mathsf{d})$;
as the constant coefficient with respect to the variable x.

Using the fact that all the parameters are nonnegative numbers, one can see that all the coefficients of the previous expansion of Q are non positive numbers. This leads us to conclude that $Q \leq 0$.

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