Identification of Parameter Existence and Stability of Treated Diabetes Mellitus Prognosis Model

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Abstract. Diabetes mellitus (DM) is a prognosis disease, preceded by overweight and obese, and followed by chronics and metabolic syndrome if the sufferer is not treated. The transition from such vulnerable person to overweight, obese, diabetes mellitus, chronics and metabolic syndrome is driven by interaction among its population. This paper considers two kinds of interaction, namely positive and negative interaction. The positive interaction impacts the person in such group population moving to the higher level of prognosis, while the negative interaction turns to the lower one. A mathematical model that represents its prognosis is governed regarding to two different treatments. The model is developed by consider the transition of every group of population due to the prognosis process. The existence of an endemic implicit critical point of the model is guaranteed in such parameter interval. The stability of the critical point is identified from the Jacobian matrix of the represented nonlinear system. The identification notices some parameter requirement that determined the local stability of the critical point. The simulations show that the diabetes mellitus population is not easy to be reduced.

1. Introduction
Diabetes mellitus is a metabolic disorder of multiplenaetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both [1], [2]. A more simple definition found in [3], that is a general term for heterogeneous disturbances of metabolism for which the main finding is chronic hyperglycaemia [3]. The fact that obesity was found in the patients with a type 2 DM diagnosis [2] comes to consider obese as the cause of DM. In the long term, effects of diabetes mellitus include progressive development of specific complication. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease, even the metabolic syndrome [3], that is diabetes mellitus and/ or insulin resistance together with two or more of the other listed component [1]. Another reference stated it as a known cluster of risk factors for ischaemic heart disease, stroke and peripheral vascular disease [2]. Epidemiological studies confirm that this syndrome occurs commonly in a wide variety ethnic groups including Caucasians, Afro-Americans, Asian Indians, Chinese, Australian Aborigines, Polynesians and Micronesians [4], [5]. The pathogenesis of the syndrome is strongly linked to central obesity and tissue resistance to insulin action arising from genetic pre-disposition or acquired factors, such as obesity and physical inactivity.

Usually called prognosis, In the scope of medic, prognosis is known as predicting of the progress or outcome of the disease [6]. Hippocrates was stated that it speaks of predicting “things present, things past, and things to come;” [7]. Prognosis is also found in DM paradigm [8] that could be seen from its
several stages. Considering DM as the things present, there are vulnerable, over weighted and obese stages that could be considered as the things past and chronics and metabolic syndrome as the things to come. The governed model [9] considered obese as the risk factor and metabolic syndrome of DM and discussed its prognosis. The model was developed from [10] that consider where the prognosis is driven by people interaction. The positive interaction impacts the person in such group population to move to the higher level of prognosis, i.e from obese to DM, while the negative interaction turns to the lotewer one, i.e from DM to obese.

Many diabetes managements are stated in [2], [11], [12], [13], the efforts is to improve the quality of life and productivity of people with diabetes. One if its treatment is using medications to treat DM. This paper discuses a mathematical model of DM that represents its prognosis in such community of people. The prognosis of DM makes the dynamic of the population, divided into vulnerable, overweight, obese, DM, chronics and metabolic syndrome subpopulations, is very interested to be studied. The dynamic is observed by analyzing the stability of the represented system at the critical point using the Routh Hurwitz criteria [14].

2. Mathematical models

2.1. The Preview Models

Interaction of people is consider as the main cause of the transition of people from such closed population classification of people into another, that are health, overweight and obese [10]. There are two kinds of interaction, namely positive and negative interaction. The positive interaction impacts the person in such group population moving to the higher level of prognosis, while the negative interaction turns to the lower one. Considering obesity as the trigger factor and metabolic syndrome as the risk factor of type 2 DM, [9] developed the model by added two compartments to the preview model and studied the dynamic of vulnerable, overweight, obese, DM and metabolic syndrome that caused by the interaction among peoples in the population.

The stability of the endemic critical point analysis shows that we have to pay attention to the transition rate of overweight to obese, more over the transition rate of obese to type 2 DM. Moreover, because the unstable condition of type 2 DM is easier to achieve because of the tightness of the parameter stability interval, it is needed to control the unbounded obese population that easily to reach. As a consequence, it stimulates the transition revolving of DM and metabolic syndrome and that need an appropriate diabetes management, especially for medication treatment.

![Compartments Diagram of Obesity, DM and Metabolic Syndrome Prognosis](image-url)
2.2. The Governed Model
This paper developed the model of [9] by involve biguanide (metformin) for peoples who have type 2 DM, that help to decrease the amount of glucose made by liver, and sulfonylureas for peoples who have type 1 DM, that help pancreas to make more insulin to have lower blood glucose [15]. Fig.1 shows the population that consist of vulnerable($S_N$), overweight($S_o$), obese($O$), DM($D$), chronics ($K$) and metabolic syndrome (M) subpopulations. The vulnerable subpopulation grows a number of new born baby as much that comes from $S_N, S_o$ and $O$ with $r, p$ and $q$ are the probability of normal weighted baby born of $S_N, S_o$ and $O$ subpopulations respectively and $\theta$ is the annual natural growth rate and a number of $S_N$ subpopulation that belongs to $S_N$ because of $\omega$ negative interaction rate and $\tau$ self motivation rate. Some of the $S_N$ sub population that has positive interaction with $S_o$ and $O$ belong to $S_o$ because of gain weight, some other proportion $r^*\theta$, $r^* = (1 - r)$, directly belongs to $D$ because of type 1 DM suffering and some of them are not alive anymore with $\mu_1$ natural death rate will make the vulnerable subpopulation decreases.

It is assumed that no new born baby are obese and normal weight baby are born from $S_N$ and $S_o$ subpopulations, such that the overweight subpopulation grows a number of overweight new born baby as much that comes from $S_o$ and $O$ with $1 - p$ and $1 - q$ are the probability of over weighted baby born from $S_o$ and $O$ subpopulations respectively and a number of $O$ subpopulation that belongs to $S_o$ because of $\omega$ negative interaction rate. Some of the $S_N$ subpopulation that have positive interaction $\alpha$ with $S_o$ belong to $O$ because of gain weight and some of them are not alive anymore with $\mu_1$ natural death rate will make the overweight subpopulation decreases.

The obese subpopulation grows because of some of the $S_N$ subpopulation that have positive interaction $\alpha$ with $S_o$ belong to $O$, while some of them are not alive anymore with $\mu_1$ natural death rate and the transition $\gamma$ to DM subpopulation will make the obese subpopulation decreases. In this paper DM sufferer are treated uses biguanid with 500 mg (IR) dosage strength/ product with maximum approved daily dose refer to [12]. As a consequence a controlled parameter $u_2$ is influenced, instead of another controlled parameter $u_2$ that influences the growth of the DM subpopulation. The growth of this population will decrease because of the accumulation of natural death rate and the death rate caused by the disease and the transition of the DM to the chronics subpopulation. This transition makes the metabolic syndrome subpopulation grows and finally decreases because of the accumulation of natural death rate and the death rate caused by the disease.

The governed model could be represented by the following dynamic system:

\[
\begin{align*}
\frac{dS_N}{dt} &= \theta (rS_N + pS_o + qO) + (\omega S_N + \tau)S_o - \alpha (S_o + O)S_N - \mu_1 S_N \\
\frac{dS_o}{dt} &= \alpha (S_o + O)S_o + \theta ((1 - p)S_o + (1 - q)O) + \omega (S_N + S_o)O - \mu_1 S_o - (\alpha O + \beta)S_o \\
\frac{dO}{dt} &= (\alpha O + \beta)S_o - \mu_1 O - \gamma u_2 O \\
\frac{dD}{dt} &= \gamma u_2 O + (1 - r)\theta u_2 D - (\mu_1 + \mu_2)D - \delta D \\
\frac{dK}{dt} &= \delta D - (\mu_1 + \mu_2)K - \varepsilon K \\
\frac{dM}{dt} &= \varepsilon K - (\mu_1 + \mu_2)M
\end{align*}
\]

(1)

The descriptions of the parameters are stated in Table 1.

| Symbol | Description |
|--------|-------------|
| $\theta$ | The natural death rate |
| $r, p, q$ | The probability of normal weighted baby born from $S_N, S_o$ and $O$ subpopulations respectively |
| $\alpha$ | The successness of negative interaction between $S_N$ and $S_o$, and or $O$ to transition the people from $S_N$ to $S_o$, and from $S_N$ to $O$ |
| $\beta$ | The transition rate of overweight people being obese |
| $\gamma$ | The transition rate of obese people being DM |
| $\delta$ | The transition rate of DM people being chronics |
| $\varepsilon$ | The transition rate of chronics people being metabolic syndrome |
| $\omega$ | The successness of positive interaction between $O$ and $S_o$ and $S_N$ to transition the people from $O$ to $S_o$ and between $S_N$ and $S_o$ to transition the people from $S_o$ to $S_N$ |
Symbol | Description
--- | ---
\( \tau \) | The transition rate of overweight people being vulnerable because of self motivation
\( \mu_1 \) | The natural death rate
\( \mu_2 \) | The death rate because of the diseases
\( u_1 \) | The number of oral medication: Sulfonilurea/ day
\( u_2 \) | The number of oral medication: Biguanid/ day

The critical point of the system is investigated by considering the system in a stagnant condition. The expression of the implicit critical point is given by:

\[
T = (S_N, S_o, O, D, K, M)
\]

such that:

\[
S_o = \frac{(\mu_1 + \gamma u_2)O}{\alpha O + \beta}
\]

\[
S_N = \frac{A + B}{\alpha(\mu_1 + \gamma u_2) + \alpha(\alpha + \omega)O + (\alpha + \omega)\beta}
\]

where:

\[
A = \theta(p - 1)(\mu_1 + \gamma u_2) + \theta(q - 1)(\alpha O + \alpha \beta)
\]

\[
B = 2O(\alpha - 1)(\mu_1 + \gamma u_2) + \mu_1(\mu_1 + \gamma u_2 + \beta)
\]

\[
D = \frac{\theta(r - 1)u_1 + \mu_2 + \rho}{\gamma u_2 \delta O}
\]

\[
K = \frac{\theta(r - 1)(\mu_2 + \epsilon)u_1 + \mu_2 + \rho}{\gamma u_2 \delta O}
\]

\[
M = \frac{\theta(r - 1)u_1 + \mu_2 + \rho}{\gamma u_2 \delta O}
\]

\[
O > 0 \quad \omega > \alpha
\]

**Table 2. Critical Point Existence Requirements**

| Critical Point | Existence Requirement |
|---------------|-----------------------|
| \( T = (S_N, S_o, O, D, K, M) \) | \( \theta(1 - p - q) - 2(\tau + \mu_1) < u_1 \) |
| \( S_o = \frac{(\mu_1 + \gamma u_2)O}{\alpha O + \beta} \) | \( 2\gamma \frac{\mu_2 + \delta}{\theta(1 - r)(\mu_2 + \epsilon)} \) |
| \( S_N = \frac{A + B}{\alpha(\mu_1 + \gamma u_2) + \alpha(\alpha + \omega)O + (\alpha + \omega)\beta} \) | \( \frac{\theta(1 - r)}{\mu_2 + \delta} \) |

### 3. Stability analysis

The stability of the implicit critical point is determined from the Jacobian matrix of the system that being evaluated at the critical point. The characteristic equation is the following sixth order polynomial of \( \lambda \):

\[
P(-\lambda) = (\lambda + (r - 1)\theta \mu_1 + \mu_2 + \rho)(\lambda + \mu_2 + \epsilon)(\lambda + \mu_2)(a_o \lambda^2 + a_1 \lambda + a_2)
\]

where:

\[
a_o = (\omega \alpha^2 + \alpha^3)O^2 + (\mu_1 + \beta + \alpha^2 \gamma u_2)\alpha^2 O + (\alpha + \omega)\beta^2 + (2 \omega O + \alpha \mu_2)\beta
\]
where $\alpha$, $\alpha_1$, $\alpha_2$, $\alpha_3$ and $\alpha_4$ are respectively fourth or third order of polynomial in $O$.

The first and second negative eigen values, i.e. $\lambda = -(\mu_2 + \varepsilon)$ and $\lambda = -\mu_2$ are derived without any requirement, while the third eigen value is lead to $\theta < \frac{\mu_3 + \beta}{\mu_1(1-r)}$ that restricted the natural death rate. Using the assumption, identification of the other stability requirements of the other two eigen values is tabulated in Table 3.

### 4. Numerical simulations

The dynamic (Fig.2) of the vulnerable, overweight, obese, DM, chronics and metabolic Syndrome are simulated for some values of initial conditions and parameters (Table 4). The simulation in the short time period in Fig.3 shows that the transition of vulnerable people makes the overweight subpopulation increasing in a very short time. Its increasing doesn’t make the obese subpopulation increase but push the DM subpopulation growth (Fig. 4). This phenomena convinces that obese is the trigger factor of DM.

### Table 3. Critical Point Stability Requirements

| Stability Requirements | Description |
|------------------------|-------------|
| $a_1 = (p - r)(O\alpha + 2\beta)\alpha \theta \omega + (p - \omega)\theta \omega \beta^2 + (p - q)\alpha \beta^2$ | Stable |
| $(\mu_1 - \theta r)(\gamma u_2 + \mu_1)\beta \alpha + 2(3\mu_1 - \theta r)O\beta \alpha^2 + (2\mu_1 - \theta r)O\mu_1 \alpha^2$ | $\mu > 0$ |
| $(4\mu_1 - 2\theta r)\omega \beta O + (2\mu_1 - O) \alpha \beta^2 + (4\mu_1 - \theta \omega) \alpha^2 O^2$ | $\mu > 0$ |
| $(\beta - \theta r)(\alpha \beta^2 + \omega \beta^2) + (2\beta - \theta r)O\gamma u_2 \alpha^2 + (5\beta - \theta r) \alpha^2 O^2$ | $\mu > 0$ |
| $- (2\beta - \omega O)O^2 \alpha^2 + (2\alpha - 1)O^3 + (2\mu_1 - O) \omega \beta^2 + (5\alpha - 2) \omega \beta \alpha O^2$ | $\mu > 0$ |
| $(2\alpha - \omega)\alpha \omega \mu_1 O^2 + (2\alpha - \omega)(2\alpha + \omega) O^2 \alpha^2$ | $\mu > 0$ |
| $(4\alpha \beta - \mu_1 \omega)\omega \beta O + (\sqrt{2\alpha} \omega - \mu_1)(\sqrt{2\alpha} \omega + \mu_1) \alpha \omega O$ | $\mu > 0$ |
| $+ (\sqrt{3} \mu_1 \alpha - \sqrt{3} \beta \omega) \gamma u_2 O + 2(2\beta + (p - q) \omega) \beta \omega O^2$ | $\mu > 0$ |
| $+ \frac{\alpha^2 (\gamma^2 u_2^2 + (p - q) \theta \alpha O)}{\gamma^2 u_2^2 + (p - q) \theta \alpha O} \alpha_2 = P(\alpha) = \alpha_0 \alpha^4 + \alpha_1 \alpha^3 + \alpha_2 \alpha^2 + \alpha_3 \alpha + \alpha_4$ | $\mu > 0$ |

The critical point stability requirements are tabulated in Table 3.
\[a_1^* = (p - r)(0\alpha + 2\beta\alpha\theta\omega + (p - \omega)\theta\omega\beta^2 + (4\mu_1 - 2\theta)\omega\beta\alpha\theta + (2\mu_1 - 0)\alpha\beta^2
+ (5\beta - \theta r)\alpha^20^2 + (2\alpha - 1)0^3 + (2\mu_1 - 0)\omega\beta^2 + (5\alpha - 2)\omega\beta\alpha0^2
+ (2\alpha - \omega)\alpha\omega\mu_10^2 + (\sqrt{2}\alpha - \omega)(\sqrt{2}\alpha + \omega)0^2\alpha\gamma u_2 + (4\alpha\beta - \mu_1\omega)\omega\beta\theta
+ (\sqrt{2}\alpha0 - \mu_1)(\sqrt{2}\alpha0 + \mu_1)\alpha\omega\theta + (\sqrt{3}\mu_1\alpha - \sqrt{\beta}\omega)\gamma u_20
\]

\[a_2^* = (p - q)\alpha\beta^2 + (\mu_1 - \theta r)(\gamma u_2 + \mu_1)\beta\alpha + 2(3\mu_1 - \theta r)0\beta\alpha^2 + (2\mu_1 - \theta r)0\mu_1\alpha^2
- (2\beta - \omega0)0^2\alpha^2 + 2(2\beta + (p - q)\theta)\beta\alpha^2 + 0\alpha^2(\gamma^2u_2^2 + (p - q)\theta\alpha0)
\]

\[
\max \left\{ \frac{\theta(1 + 3r) - (6\mu_1 + \tau)}{2\gamma}, \frac{\theta(1 - p - q) - 2(\tau + \mu_1)}{2\gamma} \right\} < u_2
< \min \left\{ \frac{1 + \sqrt{2}}{\gamma}, \frac{\theta(1 - p - q) - 2\tau\mu_1}{2\gamma} \right\}
\]
Figure 4. The Role of Obese to The DM Growth

Table 4. Parameters and Variables

| Variables/Parameter | Initial Value/Value       | Source |
|---------------------|--------------------------|--------|
| $\theta$            | 1.62/365                 | [16]   |
| $r, p, q$           | 2/3, 2/5, 1/5            |        |
| $\alpha$            | 1/2                      |        |
| $\beta$             | 1/3                      |        |
| $\gamma$            | 1/4                      |        |
| $\delta$            | 1/8                      |        |
| $\epsilon$          | 1/6                      |        |
| $\omega$            | 53/(240.365)             | [17]   |
| $\tau$              | 78/(240.365)             |        |
| $\mu_1$             | 1.5/365                  | [16]   |
| $\mu_2$             | 0.045                    |        |
| $u_1$               | 12, 20 and 40            | [12]   |
| $u_2$               | 1500, 2001 nd 2550       |        |
| $S_N$               | 113                      | [18]   |
| $S_0$               | 33                       |        |
| $D$                 | 14                       |        |
| $O$                 | 68                       |        |
| $K$                 | 8                        |        |
| $M$                 | 12                       |        |

5. Discussion

Figure 4 shows a peak to peak time of DM, chronics and metabolic syndrome, for the value of $u_1 = 20$ and $u_2 = 1500$, where the time needed for the peak obese to come to the peak chronics is 4.5 years and the time needed for the peak chronics to come to the peak metabolic syndrome is 11.5 years. Varying the value of $u_1$ and $u_2$ indicates the changing of the peak to peak time interval (Table 5). For a such value of $u_1$, varying the value of $u_2$ will not impact the peak to peak time. While for a such value of $u_2$, in case of raising the value of $u_1$, varying the value of $u_1$ makes the peak to peak time becomes longer. The starting points of the DM, chronics and metabolic syndrome that longer indicates the successes of the treatment of $u_1$ to makes a longer life time of the type 1 DM sufferers.
Table 5. The contribution of treatment to peak time of DM, chronics and metabolic syndrome

| O  | K  | M  | C to O (year) | C to M (year) | \( u_1 \) and \( u_2 \) |
|----|----|----|--------------|---------------|------------------|
| 3.05 | 7.73 | 18.86 | 3.68 | 11.13 | \( u_1 = 10, u_2 \in [1500,2000,2550] \) |
| 3.51 | 8.08 | 19.56 | 4.5 | 11.48 | \( u_1 = 12, u_2 \in [1500,2000,2550] \) |
| 4.33 | 9.37 | 22.72 | 5.04 | 13.35 | \( u_1 = 20, u_2 \in [1500,2000,2550] \) |

6. Concluding Remarks
The treated DM prognosis model that represents the prognosis of vulnerable, overweight, obese, DM, chronics and metabolic syndrome has been derived. The model shows that obese is the crucial stage for DM prognosis that have to be pay attention to hold the prognosis. If this crucial stage is passed, the medication treatment is only worked to postpone the life time expectation.

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