The Dynamics of Thalassemia Management in the United Arab Emirates

Hamda Al Dhaheri
Dept. of Mathematical Sciences
United Arab Emirates University
Al Ain, UAE
201200255@uaeu.ac.ae

Sehjeong Kim*
Dept. of Mathematical Sciences
United Arab Emirates University
Al Ain, UAE
sehjung.kim@uaeu.ac.ae

So-Yeun Kim
Dept. of Finance and Insurance
Hongik University
Sejong-si, South Korea
s22kim@hongik.ac.kr

***Abstract*—We consider a genetic disease called Thalassemia. Thalassemia is a genetic blood disorder caused by abnormal hemoglobin. Hemoglobin is a composite of proteins in red blood cells that carries oxygen and is made of two proteins from four alpha-globin genes and two beta-globin genes. Individuals with thalassemia have defects in one or more of such genes. The treatment of thalassemia requires a life-long blood transfusion and removal of excessive iron in the blood stream from the frequent blood transfusion. These life-long treatments demand a strong personal commitment and a constant supply of blood stock that leads to a high medical cost, which can be a burden on a health care system in some countries like the United Arab Emirates. To reduce thalassemia major population, various forms of thalassemia control measures have been used and hence, the substantial reduction of thalassemia major population has been achieved. However, the prevalence of thalassemia carrier population still remains high, which leads to a potential growth of thalassemia major population through carrier-carrier marriages.**

Thus, in this paper, we investigate a long term effectiveness of thalassemia control measures. We develop a mathematical model including three age groups and thalassemia control measures, and analyze the stability of two types of equilibrium points that reflect the eventual status of thalassemia prevention. Through the stability analysis of the two types of equilibrium points, we reveal that control measures are positively effective only in the short term to reduce the prevalence of the disease but not enough to eradicate thalassemia in the long term. We illustrate our stability results via computer simulations by using the demographic data of the United Arab Emirates.

***Index Terms*—Thalassemia management, mathematical modeling, compartment model, stability analysis**

I. Introduction

Thalassemia is a genetic disease in which the body makes an abnormal form of hemoglobin. The disorder results in excessive destruction of red blood cells, which leads to anemia. In general, hemoglobin is the protein in red blood cells that carries oxygen and is made of two proteins from four α-globin genes and two β-globin genes. A defect in one or more of such genes causes α or β-thalassemia. Genetically, for example, β-thalassemia major occurs when both of β-globin genes are affected, otherwise, β-thalassemia carrier (minor) will occur [1]–[6]. Most forms of thalassemia cause a chronic and lifelong anemia that can begin in early childhood and often must be treated with frequent blood transfusions due to the deformity of red blood cells for the patient's entire life unless he or she can receive 100% matched bone marrow transplant, which is a low possibility. Thus, the blood consumption of thalassemia treatment outranks that of any other treatments requiring blood use.

Thalassemia has mostly occurred in Mediterranean area, the Middle Eastern and North African region, Transcaucasia, Central Asia, the Indian subcontinent, and Southeast Asia [7], [8]. However, due to the migration of people from these regions, thalassemia populations have become a public health concern even in North America [7]. As a result, worldwide, 56,000 conceptions cause thalassemia; of these, approximately 30,000 are affected by β-thalassemia and 3,500 succumb perinatally from the hydrops fetalis syndrome, a type of α-thalassemia. It has also been estimated that, worldwide, 9 million thalassemia carrier women become pregnant annually and 1.33 million pregnancies are at risk of a thalassemia major condition [8], [9].

One of main causes is known to be a consanguineous marriage practice, an inter-family marriage. In particular, the Middle East and North Africa regions show a high prevalence of thalassemia major and carrier populations due to a consanguineous marriage tradition [10]–[16]. In particular, the government of the United Arab Emirates (UAE) has pursued thalassemia control measures such as thalassemia screening at various levels, genetic counseling service, public campaign and so on to reduce thalassemia major population [17]–[20]. For example, in 2008, the UAE government launched a nationwide campaign to promote premarital screening and from 2010 most newborn babies are screened. Also, premarital screening has been mandatory for all about-to-marry couples [21] since 2012 in order to screen possible diseases including genetic diseases like thalassemia.

As a result, today, the number of affected births has been almost halved or close to zero compared to the time before the introduction of the prevention in the UAE. Although the number of thalassemia major has been substantially reduced, the thalassemia carrier population has steadily increased as the whole population increased in the UAE [22]. The high prevalence of thalassemia carrier population is still a public health concern since there will be a 25% chance of having

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∗ Corresponding author

a thalassemia major child if a carrier-carrier marriage occurs. The carrier-carrier marriage is a major contributor of a potential growth in thalassemia major population.

Thus, in this paper, we would like to qualitatively investigate whether or not the current thalassemia control measures such as *newborn baby screening*, *premarital screening*, and *education about thalassemia* could achieve the eradication of thalassemia in the long term in the UAE via mathematical model at a population level. We study the stability of two types of equilibrium points of the model that reflect the thalassemia major and carrier population free status and thalassemia major only free status. In fact, these equilibrium points are the eventual goal of thalassemia control. We will construct a compartment model that divide the whole population into subpopulation groups including three age groups and thalassemia control measures mentioned above, and analyzes the stability of two types equilibrium points. Then, we illustrate the stability results of two equilbirum points with the UAE demographic data via computer simulations. The organization of the paper is as follows. In Sec. II, we describe our mathematical model, and explain variables and parameters. In Sec. III we show the stability of the two types of equilibrium, and in Sec. IV we present computer simulations of our model with the UAE demographic data. Finally, discussion and future work are presented in Sec. V.

II. Model Formulation

Since a genetic disease is inherited through marriage, we divide the whole UAE population into male and female groups (subpopulations) in our model. Also, to investigate the effect of education about thalassemia, we also, divide the male and female groups into educated and uneducated groups further. Then, we classify the population in the UAE into

- Children population under the age 12: Normal children G_K and (thalassemia) carrier children G_K^C
- Young adult population who are single and between 12 and 25 years old: Educated normal S_K^E and not educated normal S_K; educated carrier C_K^E and uneducated carrier C_K groups
- Adult marriageable populations over the age 25 who are single: Educated adult normal S_K^{AE}, uneducated adult normal S_K^A; educated adult carrier C_K^{AE} and not educated adult carrier C_K^A groups
- Married group: U
- Thalassemia major males and females: T_M and T_F

for $K = \{M, F\}$, where M for male and F for female. Here, normal population indicates individuals who inherit no thalassemia genes from both of their parents. Carrier population means individuals who carry a thalassemia gene inherited from only one of their parents and hence can live a normal life. Thalassemaia major population is a group of individuals who carry thalassemia genes inherited from both of their parents and show symptoms of thalassemia. With the population groups (compartments), we will construct a compartment model and the describe the dynamics between compartments by differential equations. For the model, we assume the following:

A1. Thalassemia control measures are newborn baby screening, premarital screening and education about thalassemia.

A2. The newborn baby screening is given to almost every newborn babies, the premarital screening is provided to the adult marriageable groups who are above the age of twenty, and the education about the thalassemia will be conducted in some schools to children under the age of 20.

A3. From the newborn baby screening, there may be concerned parents about their carrier babies. These parents may indirectly or directly inform the carrier status to their babies, which can be considered as education about the thalassemia as well.

A4. People who receive the thalassemia control measure can reconsider their marriage decision.

A5. Thalassemia major class has a very low chance of marriage due to prolonged treatments. Hence, the marriage rate of the thalassemia major class is negligible.

A6. Since carrier-carrier marriage can produce thalassemia major population in their next generation, the marriage reconsideration rates of carrier groups will be in focus.

A7. Educated carrier single populations may have a higher rate of marriage reconsideration comparing to uneducated carrier single populations

A8. Except for the thalassemia major class, all other groups can marry with certain marriage rates.

A9. The chances of marriages among single males and females are

- normal male $\times$ normal female
- normal male $\times$ carrier female or carrier male $\times$ normal female
- carrier male $\times$ carrier female

As we can notice, the marriage between carrier populations will produce thalassemia major population. Thus, the control of the spread of thalassemia will depend on how to manage the carrier population and the reproduction of the carrier-carrier marriages. In order to see the effect of thalassemia control measures on a given population, we construct a mathematical model at a population level as follows:

Children and thalassemia groups:

$$\frac{dG_M}{dt} = b_M U - \zeta\eta_T^M\beta_S^M G_M - \zeta\eta_{CG}^M\beta_S^M G_M - \gamma_M G_M - d_M^G G_M$$

$$\frac{dG_F}{dt} = b_F U - \zeta\eta_T^F\beta_S^F G_F - \zeta\eta_{CG}^F\beta_S^F G_F - \gamma_F G_F - d_F^G G_F$$

$$\frac{dG_M^C}{dt} = \zeta\eta_{CG}^M\beta_S^M G_M - \gamma_M G_M^C - d_M^G G_M$$

$$\frac{dG_F^C}{dt} = \zeta\eta_{CG}^F\beta_S^F G_F - \gamma_F G_F^C - d_F^G G_F$$

$$\frac{dT_M}{dt} = \zeta\eta_T^M\beta_S^M G_M - \left(\frac{\kappa(1-\zeta\eta_T^M)\gamma_M(G_M+G_M^C)}{\gamma_M(G_M+G_M^C)+\gamma_F(G_F+G_F^C)}\right)T_M$$

$$-d_T T_M$$

$$\frac{dT_F}{dt} = \zeta\eta_T^F\beta_S^F G_F - \left(\frac{\kappa(1-\zeta\eta_T^F)\gamma_F(G_F+G_F^C)}{\gamma_M(G_M+G_M^C)+\gamma_F(G_F+G_F^C)}\right)T_F$$

$$-d_T T_F$$

Single young adult male:
Normal and carrier groups with/without education

$$\frac{dS_M}{dt} = (1-\varepsilon)\gamma_M G_M - \alpha_S^M S_M - d_M S_M$$

$$\frac{dS_M^E}{dt} = \varepsilon\gamma_M G_M - \alpha_S^M S_M^E - d_M S_M^E$$

$$\frac{dC_M}{dt} = (1-\rho)\gamma_M G_M^C - \tilde{\varepsilon} C_M - \alpha_S^M C_M - d_M C_M$$

$$\frac{dC_M^E}{dt} = \rho\gamma_M G_M^C + \tilde{\varepsilon} C_M - \alpha_S^M C_M^E - d_M C_M^E$$

Single marriageable male:
Normal and carrier groups with/without education

$$\frac{dS_M^A}{dt} = \alpha_S^M S_M - \alpha_M S_M^A \frac{(S_F^{AE}+C_F^{AE}+S_F^A+C_F^A)}{N^A} - d_M S_M^A$$

$$\frac{dS_M^{AE}}{dt} = \alpha_S^M S_M^E - \alpha_M S_M^{AE} \frac{(S_F^{AE}+C_F^{AE}+S_F^A+C_F^A)}{N^A} - d_M S_M^{AE}$$

$$\frac{dC_M^A}{dt} = \alpha_S^M C_M - \alpha_M C_M^A \frac{(S_F^{AE}+C_F^{AE}+S_F^A+C_F^A)}{N^A}$$

$$+\nu_M\alpha_M C_M^A \frac{(C_F^A+C_F^{AE})}{N^A} - d_M C_M^A$$

$$\frac{dC_M^{AE}}{dt} = \alpha_S^M C_M^E - \alpha_M C_M^{AE} \frac{(S_F^{AE}+C_F^{AE}+S_F^A+C_F^A)}{N^A}$$

$$+\tilde{\nu}_M\alpha_M C_M^{AE} \frac{(C_F^A+C_F^{AE})}{N^A} - d_M C_M^{AE}$$

Single young adult female:
Normal and carrier groups with/without education

$$\frac{dS_F}{dt} = (1-\varepsilon)\gamma_F G_F - \alpha_S^F S_F - d_F S_F$$

$$\frac{dS_F^E}{dt} = \varepsilon\gamma_F G_F - \alpha_S^F S_F^E - d_F S_F^E$$

$$\frac{dC_F}{dt} = (1-\rho)\gamma_F G_F^C - \tilde{\varepsilon} C_F - \alpha_S^F C_F - d_F C_F$$

$$\frac{dC_F^E}{dt} = \rho\gamma_F G_F^C + \tilde{\varepsilon} C_F - \alpha_S^F C_F^E - d_F C_F^E$$

Single marriageable female:
Normal and carrier groups with/without education

$$\frac{dS_F^A}{dt} = \alpha_S^F S_F - \alpha_F S_F^A \frac{(S_M^{AE}+C_M^{AE}+S_M^A+C_M^A)}{N^A} - d_F S_F^A$$

$$\frac{dS_F^{AE}}{dt} = \alpha_S^F S_F^E - \alpha_F S_F^{AE} \frac{(S_M^{AE}+C_M^{AE}+S_M^A+C_M^A)}{N^A} - d_F S_F^{AE}$$

$$\frac{dC_F^A}{dt} = \alpha_S^F C_F - \alpha_F C_F^A \frac{(S_M^{AE}+C_M^{AE}+S_M^A+C_M^A)}{N^A}$$

$$+\nu_F\alpha_F C_F^A \frac{(C_M^A+C_M^{AE})}{N^A} - d_F C_F^A$$

$$\frac{dC_F^{AE}}{dt} = \alpha_S^F C_F^E - \alpha_F C_F^{AE} \frac{(S_M^{AE}+C_M^{AE}+S_M^A+C_M^A)}{N^A}$$

$$+\tilde{\nu}_F\alpha_F C_F^{AE} \frac{(C_M^A+C_M^{AE})}{N^A} - d_F C_F^{AE}$$

Married Class:

$$\frac{dU}{dt} = \alpha_M(S_M^{AE}+C_M^{AE}+S_M^A+C_M^A) \times \frac{(S_F^{AE}+C_F^{AE}+S_F^A+C_F^A)}{N^A}$$

$$+\alpha_F(S_F^{AE}+C_F^{AE}+S_F^A+C_F^A) \times \frac{(S_M^{AE}+C_M^{AE}+S_M^A+C_M^A)}{N^A}$$

$$-\tilde{\nu}_M\alpha_M C_M^{AE} \frac{(C_F^A+C_F^{AE})}{N^A} - \nu_M\alpha_M C_M^A \frac{(C_F^A+C_F^{AE})}{N^A}$$

$$-\tilde{\nu_F}\alpha_F C_F^{AE} \frac{(C_M^A+C_M^{AE})}{N^A} - \nu_F\alpha_F C_F^A \frac{(C_M^A+C_M^{AE})}{N^A}$$

$$-\tfrac{1}{2}(d_M+d_F)U,$$

where

$$\zeta = \frac{1}{U}(\alpha_M(1-\tilde{\nu_M})C_M^{AE}\frac{(C_F^{AE}+C_F^A)}{N^A} + \alpha_M(1-\nu_M)C_M^A\frac{(C_F^{AE}+C_F^A)}{N^A} + \alpha_F(1-\tilde{\nu_F})C_F^{AE}\frac{(C_M^{AE}+C_M^A)}{N^A} + \alpha_F(1-\nu_F)C_F^A\frac{(C_M^{AE}+C_M^A)}{N^A})$$

is a proportion of marriages carrier-carrier marriage without marriage reconsideration. The parameters are defined as follows:

P1. b_M and b_F are the birth rates of boys and girls, respectively;
P2. d_M and d_F are the natural death rates of male and female, and d_T is thalassemia induced death rate;
P3. γ_M and γ_F are the proportions of children becoming young adults;

P4. η_{CG}^M and η_{CG}^F are the proportion of being identified as carrier babies from the newborn screening;
P5. β_s^M and β_s^F are the newborn baby screening rates for both male and female;
P6. α_s^M and α_s^F are the premarital screening rates of single male and female;
P7. η_T^M and η_T^F are the rates of being diagnosed as thalassemia major of male and female, respectively;
P8. α_M and α_F are the marriage rates of male and female;
P9. ν_M and ν_F are the marriage reconsideration rates of uneducated male and female carrier populations;
P10. ε is a proportion of educating marriageable single populations;
P11. ρ is a proportion of babies with concerned parents;
P12. $\tilde{\nu}_M$ and $\tilde{\nu}_F$ are marriage reconsideration rates of educated male and female carrier populations;
P13. d_M^G and d_F^G are child mortality rates;
P14. $\kappa = \min\{\varepsilon, \tilde{\varepsilon}, \rho\}$ represents a minimum proportion of educated normal and carrier young adult populations.

Note that all variables remain nonnegative, i.e. $\dfrac{dY}{dt} > 0$ if $Y = 0$, where $Y = \{G_M, G_F, G_M^C, G_F^C, T_M, T_F, S_M, S_M^E, C_M, C_M^E, S_M^A, S_M^{AE}, C_M^A, C_M^{AE}, S_F, S_F^E, C_F, C_F^E, S_F^A, S_F^{AE}, C_F^A, C_F^{AE}, U\}$. Also,

$$\frac{dN}{dt} \le (b_M + b_F)U - \bar{d}N \Rightarrow N(t) \le \frac{b_M + b_F}{\bar{d}}\bar{U},$$

where $N = \sum_{K=M,F}(G_K + S_K^E + S_K^{AE} + C_K^{AE} + S_K^A + C_K^A) + U$, $\bar{U}$ is the maximum number of married couples over a considered time span, and $\bar{d}$ is the minimum of all death rates.

III. Stability Analysis

A. Preliminaries

Consider an autonomous system given by

$$\dot{x} = f(x), \tag{1}$$

where $x = (x_1, \cdots, x_n) \in \mathbb{R}^n$ and $f = (f_1, \cdots, f_n)$. Let x^* be an equilibrium point of the system in (1) such that $f(x^*) = 0$.

Definition An equilibrium x^* is said to be *stable* if there exists $\delta(\epsilon) > 0$ such that

$$\|x(t) - x^*\| < \epsilon \text{ if } \|x(0)\| < \delta(\epsilon).$$

Moreover, x^* is said to be *asymptotically* stable if x^* is stable and satisfies that

$$\|x(t) - x^*\| \to 0 \text{ as } t \to \infty.$$

Definition A *Jacobian* J of f in (1) is given by

$$J = \begin{pmatrix} \frac{\partial f}{\partial x_1} & \cdots & \frac{\partial f}{\partial x_n} \end{pmatrix} = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial f_m}{\partial x_1} & \cdots & \frac{\partial f_m}{\partial x_n} \end{pmatrix} \tag{2}$$

composed of partial derivatives of f_i with respect to $x_1, \cdots x_n$ for $i = 1, \cdots, n$ in f.

Proposition 1: [23] An equilibrium point x^* is (asymptotically) stable if all the eigenvalues of J^*, the evaluated Jacobian at x^* in (2), have negative real parts. The equilibrium point is unstable if at least one of the eigenvalues of J^* has a positive real part.

B. Stability results

In order to see the effectiveness of Thalassemia management measures such as newborn screening, premarital screening and education factor, we will study the stability of two ideal situations that are represented by two equilibrium points, namely,

(i) Type I: Thalassemia free equilibrium point, i.e., $T_M = T_F = 0$, $G_M^C = G_F^C = 0$, $C_M = C_M^A = C_M^E = C_M^{AE} = 0$, and $C_F = C_F^A = C_F^E = C_F^{AE} = 0$;
(ii) Type II: Thalassemia major only free equilibirium point, i.e., $T_M = T_F = 0$ only and G_M^C, G_F^C, C_M, C_M^E, C_M^A, C_M^{AE}, C_F, C_F^A, C_F^E, C_F^{AE} are not necessarily zero

as time evolves in a long term. Type I equilibrium point means a complete eradication of Thalassemia disease including Thalassemia carriers from a given population under the three types of Thalassemai managements. On the other hand, Type II equilibrium point implies a situation that there is no Thalassemia major population but Thalassemia carrier population can exist under the three types of Thalassemia managements.

To investigate if (i) and (ii) are achievable via newborn baby screening, premarital screening and education factor, we will calculate two jacobian matrices which are obtained by differentiating each equation presented in Sec. II with twenty three variables in order $(G_M, G_F, G_M^C, G_F^C, T_M, T_F, S_M, S_M^E, C_M, C_M^E, S_M^A, S_M^{AE}, C_M^A, C_M^{AE}, S_F, S_F^E, C_F, C_F^E, S_F^A, S_F^{AE}, C_F^A, C_F^{AE}, U)$ and substituting the two equilibrium points in them.

Definition *Type I equilibrium point* is said to be Thalassemia free equilibrium point given by

$$(G_M^*, G_F^*, 0, 0, 0, 0, S_M^*, {S_M^E}^*, 0, 0, {S_M^A}^*, {S_M^{AE}}^*, 0, 0, S_F^*, {S_F^E}^*, 0, 0, {S_F^A}^*, {S_F^{AE}}^*, 0, 0, U^*),$$

where $T_M^* = T_F^* = 0$, ${G_M^C}^* = {G_M^C}^* = 0$, $C_M^* = C_F^* = 0$, ${C_M^A}^* = {C_F^A}^* = 0$ and ${C_M^{AE}}^* = {C_F^{AE}}^* = 0$.

We linearize our mathematical model about Type I equilibrium point, then obtain the following Jacobian matrix $L \in \mathbb{R}^{23\times 23}$ composed of 30 block matrices as follows:

$$L = \begin{bmatrix} L_{11} & L_{12} & L_{13} & L_{14} & L_{15} & L_{16} \\ L_{21} & L_{22} & L_{23} & L_{24} & L_{25} & L_{26} \\ L_{31} & L_{32} & L_{33} & L_{34} & L_{35} & L_{36} \\ L_{41} & L_{42} & L_{43} & L_{44} & L_{45} & L_{46} \\ L_{51} & L_{52} & L_{53} & L_{54} & L_{55} & L_{56} \end{bmatrix}, \tag{3}$$

where $0_{k\times l} \in \mathbb{R}^{k\times l}$ is a zero matrix whose entries are all zero, $N_A^* = S_F^{AE^*} + S_F^{A^*} + S_M^{AE^*} + S_M^{A^*}$, $N_{AF}^* = S_F^{AE^*} + S_F^{A^*}$, $N_{AM}^* = S_M^{AE^*} + S_M^{A^*}$, and

$$L_{11} = \begin{bmatrix} -a_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & -b_1 & 0 & 0 & 0 & 0 \\ c_1 & 0 & -c_2 & 0 & 0 & 0 \\ 0 & d_1 & 0 & -d_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & -e_1 & 0 \\ 0 & 0 & 0 & 0 & 0 & -f_1 \end{bmatrix}, \text{ where}$$

- $a_1 = \gamma_M + d_M^G$, $b_1 = \gamma_F + d_F^G, b_2 = b_F$
- $c_1 = d_M^G$, $c_2 = -\gamma_M$, $d_1 = d_F^G$, $d_2 = -\gamma_F$
- $e_1 = \left(\frac{k\gamma_M G_M^*}{\gamma_M G_M^* + \gamma_F G_F^*}\right) + d_T$
- $f_1 = \left(\frac{k\gamma_F G_F^*}{\gamma_M G_M^* + \gamma_F G_F^*}\right) + d_T$,

$L_{12} = L_{13} = L_{14} = L_{15} = 0_{6\times 4}$,

$L_{16} = \begin{bmatrix} b_M & b_F & 0 & 0 & 0 & 0 \end{bmatrix}^T \in \mathbb{R}^{6\times 1}$, where T indicates a transpose of a matrix,

$$L_{21} = \begin{bmatrix} (1-\varepsilon)\gamma_M & 0 & 0 & 0 & 0 & 0 \\ \varepsilon\gamma_M & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & (1-\rho)\gamma_M & 0 & 0 & 0 \\ 0 & \rho\gamma_M & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$L_{22} = \begin{bmatrix} -g_2 & 0 & 0 & 0 \\ 0 & -h_2 & 0 & 0 \\ 0 & 0 & -i_2 & 0 \\ 0 & 0 & j_2 & -j_3 \end{bmatrix}, \text{ where}$$

- $g_2 = h_2 = j_3 = \alpha_S^M + d_M$
- $i_2 = \tilde{\varepsilon} + \alpha_S^M + d_M$, $j_2 = \tilde{\varepsilon}$,

$L_{23} = L_{24} = L_{25} = 0_{4\times 4}$ and $L_{26} = 0_{4\times 1}$,

$L_{31} = 0_{4\times 6}$, $L_{34} = 0_{4\times 4}$, and $L_{36} = 0_{4\times 1}$,

$$L_{32} = \begin{bmatrix} \alpha_S^M & 0 & 0 & 0 \\ 0 & \alpha_S^M & 0 & 0 \\ 0 & 0 & \alpha_S^M & 0 \\ 0 & 0 & 0 & \alpha_S^M \end{bmatrix},$$

$$L_{33} = \begin{bmatrix} -k_2 & A & A & A \\ C & -l_2 & C & C \\ 0 & 0 & -m_2 & 0 \\ 0 & 0 & 0 & -n_2 \end{bmatrix}, \text{ where}$$

- $k_2 = \alpha_M\left(\frac{N_{AF}^*}{N_A^*}\right) - \alpha_M S_M^{A\,*}\left(\frac{N_{AF}^*}{N_A^{*\,2}}\right) + d_M$
- $A = \alpha_M S_M^{A\,*}\left(\frac{N_{AF}^*}{N_A^{*\,2}}\right)$, $C = \alpha_M S_M^{AE^*}\left(\frac{N_{AF}^*}{N_A^{*\,2}}\right)$
- $l_2 = \alpha_M\left(\frac{N_{AF}^*}{N_A^*}\right) - \alpha_M S_M^{AE^*}\left(\frac{N_{AF}^*}{N_A^{*\,2}}\right) + d_M$
- $m_2 = n_2 = \alpha_M\left(\frac{N_{AF}^*}{N_A^*}\right) + d_M$,

$$L_{35} = \begin{bmatrix} -B & -B & -B & -B \\ -D & -D & -D & -D \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \text{ where}$$

- $B = \alpha_M S_M^{A\,*}\left(\frac{N_{AM}^*}{N_A^{*\,2}}\right)$, $D = \alpha_M S_M^{AE^*}\left(\frac{N_{AM}^*}{N_A^{*\,2}}\right)$,

$$L_{41} = \begin{bmatrix} 0 & (1-\varepsilon)\gamma_F & 0 & 0 & 0 & 0 \\ 0 & \varepsilon\gamma_F & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & (1-\rho)\gamma_F & 0 & 0 \\ 0 & 0 & 0 & \rho\gamma_F & 0 & 0 \end{bmatrix},$$

$L_{42} = L_{43} = L_{45} = 0_{4\times 4}$ and $L_{46} = 0_{4\times 1}$,

$$L_{44} = \begin{bmatrix} -o_2 & 0 & 0 & 0 \\ 0 & -p_2 & 0 & 0 \\ 0 & 0 & -q_2 & 0 \\ 0 & 0 & r_2 & -r_3 \end{bmatrix}, \text{ where}$$

- $o_2 = \alpha_S^F + d_F$, $p_2 = \alpha_S^F + d_F$, $q_2 = \tilde{\varepsilon} + \alpha_S^F + d_F$
- $r_2 = \tilde{\varepsilon}$, $r_3 = \alpha_S^F + d_F$,

$L_{51} = 0_{5\times 6}$ and $L_{52} = 0_{5\times 4}$,

$$L_{53} = \begin{bmatrix} -E & -E & -E & -E \\ -G & -G & -G & -G \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ I & I & I & I \end{bmatrix}, \text{ where}$$

- $E = \alpha_F S_F^{A^*}\left(\frac{N_{AF}^*}{N_A^{*\,2}}\right)$, $G = \alpha_F S_F^{AE^*}\left(\frac{N_{AF}^*}{N_A^{*\,2}}\right)$
- $I = \alpha_M\left(\frac{N_{AF}^*}{N_A^*}\right) - \alpha_M\left(\frac{N_{AM}^* N_{AF}^*}{N_A^{*\,2}}\right) + \alpha_F\left(\frac{{N_{AF}^*}^2}{N_A^{*\,2}}\right)$,

$$L_{54} = \begin{bmatrix} \alpha_S^F & 0 & 0 & 0 \\ 0 & \alpha_S^F & 0 & 0 \\ 0 & 0 & \alpha_S^F & 0 \\ 0 & 0 & 0 & \alpha_S^F \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

$$L_{55} = \begin{bmatrix} -s_2 & F & F & F \\ H & -t_2 & H & H \\ 0 & 0 & -u_2 & 0 \\ 0 & 0 & 0 & -v_2 \\ J & J & J & J \end{bmatrix}, \text{ where}$$

- $s_2 = \alpha_M\left(\frac{N_{AM}^*}{N_A^*}\right) - \alpha_M S_F^{A^*}\left(\frac{N_{AM}^*}{N_A^{*\,2}}\right) + d_F$
- $t_2 = \alpha_F\left(\frac{N_{AM}^*}{N_A^*}\right) - \alpha_F S_F^{AE^*}\left(\frac{N_{AM}^*}{N_A^{*\,2}}\right) + d_F$
- $F = \alpha_F S_F^{A^*}\left(\frac{N_{AM}^*}{N_A^{*\,2}}\right)$, $H = \alpha_F S_F^{AE^*}\left(\frac{N_{AM}^*}{N_A^{*\,2}}\right)$
- $u_2 = v_2 = \alpha_F\left(\frac{N_{AM}^*}{N_A^*}\right) + d_F$
- $J = \alpha_F\left(\frac{N_{AM}^*}{N_A^*}\right) - \alpha_F\left(\frac{N_{AM}^* N_{AF}^*}{N_A^{*\,2}}\right) + \alpha_M\left(\frac{{N_{AM}^*}^2}{N_A^{*\,2}}\right)$,

$L_{56} = \begin{bmatrix} 0 & 0 & 0 & 0 & -\frac{1}{2}(d_M + d_F) \end{bmatrix}^T$.

Definition *Type II equilibrium point* is said to be Thalassemia major free only equilibrium point given by

$$(G_M^*, G_F^*, G_M^{C^*}, G_F^{C^*}, 0, 0, S_M^*, C_M^*, C_M^{E^*}, S_M^{A^*}, S_M^{AE^*}, C_M^{A^*}, C_M^{AE^*}, S_F^*, S_F^{E^*}, C_F^*, C_F^{E^*}, S_F^{A^*}, S_F^{AE^*}, C_F^{A^*}, C_F^{AE^*}, U^*),$$

where $T_M^* = T_F^* = 0$, but $G_M^{C^*}, G_M^{C^*}$, C_M^*, C_F^*, $C_M^{A^*}, C_F^{A^*}$ $C_M^{AE^*}, C_F^{AE^*}$ are not necessarily zero.

As Type I equilibrium case, we linearize our mathematical model about Type II equilibrium point, then obtain the following Jacobian matrix $\tilde{L} \in \mathbb{R}^{23\times 23}$ composed of 30 block matrices as follows:

$$\tilde{L} = \begin{bmatrix} \tilde{L}_{11} & \tilde{L}_{12} & \tilde{L}_{13} & \tilde{L}_{14} & \tilde{L}_{15} & \tilde{L}_{16} \\ \tilde{L}_{21} & \tilde{L}_{22} & \tilde{L}_{23} & \tilde{L}_{24} & \tilde{L}_{25} & \tilde{L}_{26} \\ \tilde{L}_{31} & \tilde{L}_{32} & \tilde{L}_{33} & \tilde{L}_{34} & \tilde{L}_{35} & \tilde{L}_{36} \\ \tilde{L}_{41} & \tilde{L}_{42} & \tilde{L}_{43} & \tilde{L}_{44} & \tilde{L}_{45} & \tilde{L}_{46} \\ \tilde{L}_{51} & \tilde{L}_{52} & \tilde{L}_{53} & \tilde{L}_{54} & \tilde{L}_{55} & \tilde{L}_{56} \end{bmatrix}, \quad (4)$$

where

(i) $0_{k\times l} \in \mathbb{R}^{k\times l}$ is a zero matrix whose entries are all zero,
$N_{AM}^* = S_M^{AE^*} + S_M^{A^*} + C_M^{AE^*} + C_M^{A^*}$,
$N_{AF}^* = S_F^{AE^*} + S_F^{A^*} + C_F^{AE^*} + C_F^{A^*}$,
$N_A^* = N_{AM}^* + N_{AF}^*$,

(ii) $C_{FM\zeta} = \alpha_M(C_F^{A^*} + C_F^{AE^*})\{(1-\nu_{\tilde{M}})C_M^{AE^*} + (1-\nu_M)C_M^{A^*}\}$,

$C_{MF\zeta} = \alpha_F(C_M^{A^*} + C_M^{AE^*})\{(1-\nu_{\tilde{F}})C_F^{AE^*} + (1-\nu_F)C_F^{A^*}\}$,

(iii) $Z_1 = \frac{C_{FM\zeta} + C_{MF\zeta}}{N_A^*}$,

(iv) $Z_2 = \frac{\alpha_F((1-\nu_F)C_F^{A^*} + (1-\tilde{\nu}_F)C_F^{AE^*})}{N_A^*} + \frac{\alpha_M(1-\nu_M)(C_F^{A^*} + C_F^{AE^*})}{N_A^*}$

(v) $\tilde{Z}_2 = \frac{\alpha_F((1-\nu_F)C_F^{A^*} + (1-\tilde{\nu}_F)C_F^{AE^*})}{N_A^*} + \frac{\alpha_M(1-\tilde{\nu}_M)(C_F^{A^*} + C_F^{AE^*})}{N_A^*}$

(vi) $Z_3 = \frac{\alpha_M((1-\nu_M)C_M^{A^*} + (1-\tilde{\nu}_M)C_M^{AE^*})}{N_A^*} + \frac{\alpha_F(1-\nu_F)(C_M^{AE^*} + C_M^{A^*})}{N_A^*}$

(vii) $\tilde{Z}_3 = \frac{\alpha_M((1-\nu_M)C_M^{A^*} + (1-\tilde{\nu}_M)C_M^{AE^*})}{N_A^*} + \frac{\alpha_F(1-\tilde{\nu}_F)(C_M^{AE^*} + C_M^{A^*})}{N_A^*}$,

and

$$\tilde{L}_{11} = \begin{bmatrix} -a_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & -b_1 & 0 & 0 & 0 & 0 \\ c_1 & 0 & -c_2 & 0 & 0 & 0 \\ 0 & d_1 & 0 & -d_2 & 0 & 0 \\ e_1 & 0 & 0 & 0 & -e_2 & 0 \\ f_1 & 0 & 0 & 0 & 0 & -f_2 \end{bmatrix}, \text{ where}$$

- $a_1 = \gamma_M + d_M^G + \dfrac{\beta_S^M(\eta_T^M + \eta_{CG}^M)Z_1}{U^*}$,
  $b_1 = \gamma_F + d_F^G + \dfrac{\beta_S^F(\eta_T^F + \eta_{CG}^F)Z_1}{U^*}$,
- $c_1 = \dfrac{\eta_{CG}^M \beta_S^M Z_1}{U^*} - d_M^G$,
  $c_2 = \gamma_M$, $d_1 = \dfrac{\eta_{CG}^F \beta_S^F Z_1}{U^*} - d_F^G$, $d_2 = \gamma_F$
- $e_1 = \dfrac{\eta_T^M \beta_S^M Z_1}{U^*}$,
  $e_2 = \dfrac{k\gamma_M(1-\eta_M^T)(G_M^* + G_M^{C^*})Z_1}{[(\gamma_M(G_M^* + G_M^{C^*}) + \gamma_F(G_F^* + G_F^{C^*})]U^*} + d_T$
- $f_1 = \dfrac{\eta_T^F \beta_S^F Z_1}{U^*}$,
  $f_2 = \dfrac{k\gamma_F(1-\eta_F^T)(G_F^* + G_F^{C^*})Z_1}{[(\gamma_M(G_M^* + G_M^{C^*}) + \gamma_F(G_F^* + G_F^{C^*})]U^*} + d_T$

$\tilde{L}_{12} = \tilde{L}_{14} = 0_{6\times 4}$,

$$\tilde{L}_{13} = \begin{bmatrix} A & A & B_t & A_t \\ \tilde{A} & \tilde{A} & \tilde{B}_t & \tilde{A}_t \\ C & C & D_t & C_t \\ \tilde{C} & \tilde{C} & \tilde{D}_t & \tilde{C}_t \\ C & C & D_t & C_t \\ \tilde{C} & \tilde{C} & \tilde{D}_t & \tilde{C}_t \end{bmatrix}, \text{ where}$$

- $A = \dfrac{\beta_S^M(\eta_T^M + \eta_{CG}^M)G_M^* Z_1}{N_A^* U^*}$ and
  $\tilde{A} = \dfrac{\beta_S^F(\eta_T^F + \eta_{CG}^F)G_F^* Z_1}{N_A^* U^*}$,
- $B_t = \dfrac{\beta_S^M(\eta_T^M + \eta_{CG}^M)G_M^*}{N_A^* U^*}(Z_1 - Z_2)$ and
  $\tilde{B}_t = \dfrac{\beta_S^F(\eta_T^F + \eta_{CG}^F)G_F^*}{N_A^* U^*}(Z_1 - Z_2)$,
- $A_t = \dfrac{\beta_S^M(\eta_T^M + \eta_{CG}^M)G_M^*}{N_A^* U^*}(Z_1 - \tilde{Z}_2)$ and
  $\tilde{A}_t = \dfrac{\beta_S^F(\eta_T^F + \eta_{CG}^F)G_F^*}{N_A^* U^*}(Z_1 - \tilde{Z}_2)$,
- $C = \dfrac{\eta_{CG}^M \beta_S^M G_M^* Z_1}{N_A^* U^*}$ and
  $\tilde{C} = \dfrac{\eta_{CG}^F \beta_S^F G_F^* Z_1}{N_A^* U^*}$,
- $D_t = \dfrac{\eta_{CG}^M \beta_S^M G_M^*}{N_A^* U^*}(Z_1 - Z_2)$ and
  $\tilde{D}_t = \dfrac{\eta_{CG}^F \beta_S^F G_F^*}{N_A^* U^*}(Z_1 - Z_2)$,
- $C_t = \dfrac{\eta_{CG}^M \beta_S^M G_M^*}{N_A^* U^*}(Z_1 - \tilde{Z}_2)$ and
  $\tilde{C}_t = \dfrac{\eta_{CG}^F \beta_S^F G_F^*}{N_A^* U^*}(Z_1 - \tilde{Z}_2)$,

$$\tilde{L}_{15} = \begin{bmatrix} A & A & B_t' & A_t' \\ \tilde{A} & \tilde{A} & \tilde{B}_t' & \tilde{A}_t' \\ C & C & D_t' & C_t' \\ \tilde{C} & \tilde{C} & \tilde{D}_t' & \tilde{C}_t' \\ C & C & D_t' & C_t' \\ \tilde{C} & \tilde{C} & \tilde{D}_t' & \tilde{C}_t' \end{bmatrix}, \text{ where}$$

- $A_t' = \dfrac{\beta_S^M(\eta_T^M + \eta_{CG}^M)G_M^*}{N_A^* U^*}(Z_1 - \tilde{Z}_3)$ and
  $\tilde{A}_t' = \dfrac{\beta_S^F(\eta_T^F + \eta_{CG}^F)G_F^*}{N_A^* U^*}(Z_1 - \tilde{Z}_3)$,
- $B_t' = \dfrac{\beta_S^M(\eta_T^M + \eta_{CG}^M)G_M^*}{N_A^* U^*}(Z_1 - Z_3)$ and
  $\tilde{B}_t' = \dfrac{\beta_S^F(\eta_T^F + \eta_{CG}^F)G_F^*}{N_A^* U^*}(Z_1 - Z_3)$,
- $C_t' = \dfrac{\eta_{CG}^M \beta_S^M G_M^*}{N_A^* U^*}(Z_1 - \tilde{Z}_3)$ and
  $\tilde{C}_t' = \dfrac{\eta_{CG}^F \beta_S^F G_F^*}{N_A^* U^*}(Z_1 - \tilde{Z}_3)$,
- $D_t' = \dfrac{\eta_{CG}^M \beta_S^M G_M^*}{N_A^* U^*}(Z_1 - Z_3)$ and
  $\tilde{D}_t' = \dfrac{\eta_{CG}^F \beta_S^F G_F^*}{N_A^* U^*}(Z_1 - Z_3)$,

$\tilde{L}_{16} = \begin{bmatrix} a_2 & b_2 & c_3 & d_3 & e_3 & f_3 \end{bmatrix}^T \in \mathbb{R}^{6\times 1}$, where T indicates a transpose of a matrix, and

- $a_2 = b_M - \dfrac{\beta_S^M(\eta_T^M + \eta_{CG}^M)G_M^* Z_1}{(U^*)^2}$,
- $b_2 = b_F - \dfrac{\beta_S^F(\eta_T^F + \eta_{CG}^F)G_F^* Z_1}{(U^*)^2}$,
- $c_3 = \dfrac{\eta_{CG}^M \beta_S^M G_M^* Z_1}{(U^*)^2}$,
- $d_3 = \dfrac{\eta_{CG}^F \beta_S^F G_F^* Z_1}{(U^*)^2}$,
- $e_3 = \dfrac{\eta_T^M \beta_S^M G_M^* Z_1}{(U^*)^2}$,
- $f_3 = \dfrac{\eta_T^F \beta_S^F G_F^* Z_1}{(U^*)^2}$,

$$\tilde{L}_{21} = \begin{bmatrix} (1-\varepsilon)\gamma_M & 0 & 0 & 0 & 0 & 0 \\ \varepsilon\gamma_M & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & (1-\rho)\gamma_M & 0 & 0 & 0 \\ 0 & 0 & \rho\gamma_M & 0 & 0 & 0 \end{bmatrix},$$

$$\tilde{L}_{22} = \begin{bmatrix} -g_2 & 0 & 0 & 0 \\ 0 & -h_2 & 0 & 0 \\ 0 & 0 & -i_2 & 0 \\ 0 & 0 & j_2 & -j_3 \end{bmatrix}, \text{ where}$$

- $g_2 = h_2 = j_3 = \alpha_S^M + d_M$
- $i_2 = \tilde{\varepsilon} + \alpha_S^M + d_M$, $j_2 = \tilde{\varepsilon}$,

$\tilde{L}_{23} = 0 = \tilde{L}_{24} = 0 = \tilde{L}_{25} = 0_{4\times4}$ and $\tilde{L}_{26} = 0_{4\times1}$,

$\tilde{L}_{31} = 0_{4\times6}$, $\tilde{L}_{34} = 0_{4\times4}$, and $\tilde{L}_{36} = 0_{4\times1}$,

$$\tilde{L}_{32} = \begin{bmatrix} \alpha_S^M & 0 & 0 & 0 \\ 0 & \alpha_S^M & 0 & 0 \\ 0 & 0 & \alpha_S^M & 0 \\ 0 & 0 & 0 & \alpha_S^M \end{bmatrix},$$

$$\tilde{L}_{33} = \begin{bmatrix} -k_2 & E & E & E \\ F & -l_2 & F & F \\ G & G & -m_2 & G \\ H & H & H & -n_2 \end{bmatrix}, \text{ where}$$

- $k_2 = \dfrac{\alpha_M {N_{AF}}^* (N_A^* - {S_M^A}^*)}{(N_A^*)^2} + d_M$,
- $E = \dfrac{\alpha_M {S_M^A}^* {N_{AF}}^*}{(N_A^*)^2}$,
- $l_2 = \dfrac{\alpha_M {N_{AF}}^* (N_A^* - {S_M^{AE}}^*)}{(N_A^*)^2} + d_M$,
- $F = \dfrac{\alpha_M {S_M^{AE}}^* {N_{AF}}^*}{(N_A^*)^2}$,
- $m_2 = \dfrac{\alpha_M (N_A^* - {C_M^A}^*)({N_{AF}}^* - \nu_M({C_F^A}^* + {C_F^{AE}}^*))}{(N_A^*)^2} + d_M$,
- $G = \dfrac{\alpha_M {C_M^A}^* ({N_{AF}}^* - \nu_M({C_F^A}^* + {C_F^{AE}}^*))}{(N_A^*)^2}$,
- $n_2 = \dfrac{\alpha_M (N_A^* - {C_M^{AE}}^*)({N_{AF}}^* - \tilde{\nu_M}({C_F^A}^* + {C_F^{AE}}^*))}{(N_A^*)^2} + d_M$,
- $H = \dfrac{\alpha_M {C_M^{AE}}^* ({N_{AF}}^* - \tilde{\nu_M}({C_F^A}^* + {C_F^{AE}}^*))}{(N_A^*)^2}$,

$$\tilde{L}_{35} = \begin{bmatrix} -\tilde{I} & -\tilde{I} & -\tilde{I} & -\tilde{I} \\ -\tilde{J} & -\tilde{J} & -\tilde{J} & -\tilde{J} \\ -\tilde{K} & -\tilde{K} & -\tilde{L} & -\tilde{L} \\ -\tilde{M} & -\tilde{M} & -\tilde{N} & -\tilde{N} \end{bmatrix}, \text{ where}$$

- $\tilde{I} = \dfrac{\alpha_M {S_M^A}^* {N_{AM}}^*}{(N_A^*)^2}$,
- $\tilde{J} = \dfrac{\alpha_M {S_M^{AE}}^* {N_{AM}}^*}{(N_A^*)^2}$,
- $\tilde{K} = \dfrac{\alpha_M {C_M^A}^* ({N_{AM}}^* + \nu_M({C_F^A}^* + {C_F^{AE}}^*))}{(N_A^*)^2}$,
- $\tilde{L} = \dfrac{\alpha_M {C_M^A}^* ({N_{AM}}^* - \nu_M((N_A^* - ({C_F^A}^* + {C_F^{AE}}^*)))}{(N_A^*)^2}$,
- $\tilde{M} = \dfrac{\alpha_M {C_M^{AE}}^* ({N_{AM}}^* + \tilde{\nu_M}({C_F^A}^* + {C_F^{AE}}^*))}{(N_A^*)^2}$,
- $\tilde{N} = \dfrac{\alpha_M {C_M^{AE}}^* ({N_{AM}}^* - \tilde{\nu_M}((N_A^* - ({C_F^A}^* + {C_F^{AE}}^*)))}{(N_A^*)^2}$,

$$\tilde{L}_{41} = \begin{bmatrix} 0 & (1-\varepsilon)\gamma_F & 0 & 0 & 0 & 0 \\ 0 & \varepsilon\gamma_F & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & (1-\rho)\gamma_F & 0 & 0 \\ 0 & 0 & 0 & \rho\gamma_F & 0 & 0 \end{bmatrix},$$

$\tilde{L}_{42} = \tilde{L}_{43} = \tilde{L}_{45} = 0_{4\times4}$ and $\tilde{L}_{46} = 0_{4\times1}$,

$$\tilde{L}_{44} = \begin{bmatrix} -o_2 & 0 & 0 & 0 \\ 0 & -p_2 & 0 & 0 \\ 0 & 0 & -q_2 & 0 \\ 0 & 0 & r_2 & -r_3 \end{bmatrix}, \text{ where}$$

- $o_2 = p_2 = \alpha_S^F + d_F$, $q_2 = \tilde{\varepsilon} + \alpha_S^F + d_F$
- $r_2 = \tilde{\varepsilon}$, $r_3 = \alpha_S^F + d_F$,

$\tilde{L}_{51} = 0_{5\times6}$ and $\tilde{L}_{52} = 0_{5\times4}$,

$$\tilde{L}_{53} = \begin{bmatrix} -I & -I & -I & -I \\ -J & -J & -J & -J \\ -K & -K & -L & -L \\ -M & -M & -N & -N \\ O & O & P & P \end{bmatrix}, \text{ where}$$

- $I = \dfrac{\alpha_F S_F^{A^*} N_{AF}^*}{(N_A^*)^2}$,
- $J = \dfrac{\alpha_F S_F^{AE^*} N_{AF}^*}{(N_A^*)^2}$,
- $K = \dfrac{\alpha_F C_F^{A^*}(N_{AF}^* + \nu_F(C_M^{A^*} + C_M^{AE^*}))}{(N_A^*)^2}$,
- $L = \dfrac{\alpha_F C_F^{A^*}(N_{AF}^* - \nu_F((N_A^* - (C_M^{A^*} + C_M^{AE^*})))}{(N_A^*)^2}$,
- $M = \dfrac{\alpha_F C_F^{AE^*}(N_{AF}^* + \tilde{\nu_F}(C_M^{A^*} + C_M^{AE^*}))}{(N_A^*)^2}$,
- $N = \dfrac{\alpha_F C_F^{AE^*}(N_{AF}^* - \tilde{\nu_F}((N_A^* - (C_M^{A^*} + C_M^{AE^*})))}{(N_A^*)^2}$,
- $O = \dfrac{(\alpha_M + \alpha_F)(N_{AF}^*)^2}{(N_A^*)^2} + \dfrac{\alpha_F(C_M^{A^*} + C_M^{AE^*})(\nu_F C_F^{A^*} + \tilde{\nu}_F C_F^{AE^*})}{(N_A^*)^2} + \dfrac{\alpha_M(C_F^{A^*} + C_F^{AE^*})(\nu_M C_M^{A^*} + \tilde{\nu}_M C_M^{AE^*})}{(N_A^*)^2}$,

$P = O - \dfrac{\alpha_F(\nu_F C_F^{A^*} + \tilde{\nu}_F C_F^{AE^*})}{N_A^*} + \dfrac{\alpha_M \tilde{\nu}_M(C_F^{A^*} + C_F^{AE^*})}{N_A^*}$,

$$\tilde{L}_{54} = \begin{bmatrix} \alpha_S^F & 0 & 0 & 0 \\ 0 & \alpha_S^F & 0 & 0 \\ 0 & 0 & \alpha_S^F & 0 \\ 0 & 0 & 0 & \alpha_S^F \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

$$\tilde{L}_{55} = \begin{bmatrix} -s_2 & \tilde{E} & \tilde{E} & \tilde{E} \\ \tilde{F} & -t_2 & \tilde{F} & \tilde{F} \\ \tilde{G} & \tilde{G} & -u_2 & \tilde{G} \\ \tilde{H} & \tilde{H} & \tilde{H} & -v_2 \\ O & O & \tilde{P} & \tilde{P} \end{bmatrix}, \text{ where}$$

- $s_2 = \dfrac{\alpha_F N_{AM}^*(N_A^* - S_F^{A^*})}{(N_A^*)^2} + d_F$
- $E = \dfrac{\alpha_F S_F^{A^*} N_{AM}^*}{(N_A^*)^2}$,
- $t_2 = \dfrac{\alpha_F N_{AM}^*(N_A^* - S_F^{AE^*})}{(N_A^*)^2} + d_F$
- $\tilde{F} = \dfrac{\alpha_F S_F^{AE^*} N_{AM}^*}{(N_A^*)^2}$,
- $\tilde{G} = \dfrac{\alpha_F C_F^{A^*}(N_{AM}^* - \nu_F(C_M^{A^*} + C_M^{AE^*}))}{(N_A^*)^2}$,
- $u_2 = \dfrac{\alpha_F N_{AM}^*(N_A^* - S_F^{AE^*})}{(N_A^*)^2} + d_F$
- $\tilde{H} = \dfrac{\alpha_F C_F^{AE^*}(N_{AM}^* - \tilde{\nu_F}(C_M^{A^*} + C_M^{AE^*}))}{(N_A^*)^2}$,
- $v_2 = \alpha_F\left(\dfrac{N_{AM}^*}{N_A^*}\right) + \tilde{\nu_F}\alpha_F C_F^{AE^*}\left(\dfrac{C_M^{AE^*} + C_M^{A^*}}{N_A^*}\right) + d_F$
- $O = \dfrac{(\alpha_M + \alpha_F)(N_{AF}^*)^2}{(N_A^*)^2} + \dfrac{\alpha_F(C_M^{A^*} + C_M^{AE^*})(\nu_F C_F^{A^*} + \tilde{\nu}_F C_F^{AE^*})}{(N_A^*)^2} + \dfrac{\alpha_M(C_F^{A^*} + C_F^{AE^*})(\nu_M C_M^{A^*} + \tilde{\nu}_M C_M^{AE^*})}{(N_A^*)^2}$,
- $\tilde{P} = O - \dfrac{\alpha_M(\nu_M C_M^{A^*} + \tilde{\nu}_M C_M^{AE^*})}{N_A^*} + \dfrac{\alpha_F \tilde{\nu}_F(C_M^{A^*} + C_M^{AE^*})}{N_A^*}$,

$$\tilde{L}_{56} = \begin{bmatrix} 0 & 0 & 0 & 0 & -\dfrac{1}{2}(d_M + d_F) \end{bmatrix}^T.$$

Then, we need the following proposition known as *Geršgorin disc theorem* before we present our main result.

Proposition 2: [24] [Chapter 6 Corollary 6.1.3] The eigenvalues of $A = [m_{ij}]_{n\times n}$, an n by n matrix, are in the union of n discs

$$\bigcup_{j=1}^{n}\{z \in \mathbb{C} : |z - a_{jj}| \leq C_j'(A)\},$$

where $\mathbb{C}$ is the set of complex numbers, a_{jj} are the diagonal entries in A, $\{z \in \mathbb{C} : |z - a_{jj}| \leq C_j'(A)\}$, is a disc in $\mathbb{C}$ centered at a_{jj} with the radius $C_j'(A)$, and

$$C_j'(A) = \sum_{i\neq j} |a_{ij}|,\ j = 1, \cdots, n,$$

which is the absolute column sum without the the diagonal entry in the j^{th} column.

Theorem 3: Type I equilibrium point, the thalassemia free equilibrium point and Type II equilibrium point, the thalassemia major free only equilibrium point are unstable.

Proof: From the jacobian matrices L and $\tilde{L}$ we can calculate $C_j'(L) = \sum_{i\neq j} |a_{ij}|$ and $C_j'(\tilde{L}) = \sum_{i\neq j} |\tilde{a}_{ij}|,\ j = 1, \cdots, n$ for both equilibrium points, respectively. Then, we have

$$\bigcup_{j=1}^{23}\{z \in \mathbb{C} : |z - a_{jj}| \leq C_j'(L)\}, \tag{5}$$

and

$$\bigcup_{j=1}^{23}\{z \in \mathbb{C} : |z - \tilde{a}_{jj}| \leq C_j'(\tilde{L})\}, \tag{6}$$

where a_{jj} and $\tilde{a}_{jj}$ are the diagonal entries in L and $\tilde{L}$, respectively. Note that in (5) the discs for $j = 2, 5, \cdots, 16$, and $j = 18, \cdots, 22$, locate in the left half plane of $\mathbb{C}$ since $|a_{jj}| > C'_j(L)$. However, the rest of discs may cross the origin and the right half plane of $\mathbb{C}$. In particular, consider the 23^{rd} disc in (5) given by

$$\left\{ z \in \mathbb{C} : \left| z - \left(-\frac{d_M + d_F}{2} \right) \right| \leq b_M + b_F \right\},$$

where the disc centered at $-\frac{d_M + d_F}{2}$ with the radius $C'_{23}(L) = b_M + b_F$. Note that the population of the UAE is increasing. Hence, the birth rates b_M and b_F must be greater than the death rates d_M and d_F. Thus, we conclude

$$\frac{d_M + d_F}{2} < b_M + b_F.$$

Therefore, the 23^{rd} disc in (5) crosses the origin and the right half plane of $\mathbb{C}$, which means that some eigenvalues will have positive real parts. Therefore, by Proposition 1 Type I equilibrium point is unstable.

Then, for Type II equilibrium point, consider (6). In (6) the discs for $j = 2, 5, \cdots, 10$, and $j = 15, \cdots, 18$, locate in the left half plane of $\mathbb{C}$ since $|\tilde{a}_{jj}| > C'_j(\tilde{L})$. In particular, consider the 23^{rd} disc in (6) given by

$$\left\{ z \in \mathbb{C} : \left| z - \left(-\frac{d_M + d_F}{2} \right) \right| \leq C'_{23}(\tilde{L}) \right\}, \tag{7}$$

where $C'_{23}(\tilde{L})$ is the radius of the 23^{rd} disc in (6) given by

$$\begin{aligned}
C'_{23}(\tilde{L}) &= |a_2| + |b_2| + |c_3| + |d_3| + |e_3| + |f_3| \\
&= \left| b_M - \frac{\beta_S^M (\eta_T^M + \eta_{CG}^M) G_M^* Z_1}{(U^*)^2} \right| \\
&\quad + \left| b_F - \frac{\beta_S^F (\eta_T^F + \eta_{CG}^F) G_F^* Z_1}{(U^*)^2} \right| \\
&\quad + \frac{\eta_{CG}^M \beta_S^M G_M^* Z_1}{(U^*)^2} + \frac{\eta_{CG}^F \beta_S^F G_F^* Z_1}{(U^*)^2} \\
&\quad + \frac{\eta_T^M \beta_S^M G_M^* Z_1}{(U^*)^2} + \frac{\eta_T^F \beta_S^F G_F^* Z_1}{(U^*)^2} \qquad (8) \\
&\geq b_M - \frac{\beta_S^M (\eta_T^M + \eta_{CG}^M) G_M^* Z_1}{(U^*)^2} \\
&\quad b_F - \frac{\beta_S^F (\eta_T^F + \eta_{CG}^F) G_F^* Z_1}{(U^*)^2} \\
&\quad + \frac{\eta_{CG}^M \beta_S^M G_M^* Z_1}{(U^*)^2} + \frac{\eta_{CG}^F \beta_S^F G_F^* Z_1}{(U^*)^2} \\
&\quad + \frac{\eta_T^M \beta_S^M G_M^* Z_1}{(U^*)^2} + \frac{\eta_T^F \beta_S^F G_F^* Z_1}{(U^*)^2} \\
&= b_M + b_F,
\end{aligned}$$

and $a_2 = b_M - \frac{\beta_S^M (\eta_T^M + \eta_{CG}^M) G_M^* Z_1}{(U^*)^2}$,
$b_2 = b_F - \frac{\beta_S^F (\eta_T^F + \eta_{CG}^F) G_F^* Z_1}{(U^*)^2}$, $c_3 = \frac{\eta_{CG}^M \beta_S^M G_M^* Z_1}{(U^*)^2} > 0$, $d_3 \frac{\eta_{CG}^F \beta_S^F G_F^* Z_1}{(U^*)^2} > 0$, $e_3 = \frac{\eta_T^M \beta_S^M G_M^* Z_1}{(U^*)^2} > 0$, and $f_3 = \frac{\eta_T^F \beta_S^F G_F^* Z_1}{(U^*)^2} > 0$. Note that a_2, b_2, c_3, d_3, e_3, and f_3 are from $\tilde{L}_{16}$ in the jacobian matrix $\tilde{L}$ in (4). Thus, the 23^{rd} disc in (6) is centered at $-\frac{d_M + d_F}{2}$ with the radius $C'_{23}(\tilde{L}) \geq b_M + b_F$. Since the UAE population is increasing, the birth rates b_M and b_F must be greater than the death rates d_M and d_F. Hence, the 23^{rd} disc in (7) crosses the origin and the right half plane of $\mathbb{C}$, which means that some eigenvalues will have positive real parts. Therefore, by Proposition 1 Type II equilibrium point is unstable. This completes the proof. ■

Remark In the result of Theorem 3 we observed the 23^{rd} disc crosses through the origin from the left half plane to the right half plane of $\mathbb{C}$ from the relation between the birth and death rates of the whole population. Thus, Types I and II equilibrium points are unstable regardless of the newborn baby screening, premarital screening and education factor. Hence, Types I and II equilibrium points that are our current goal in thalassemia management will not be achievable with the control measures considered above in the long term.

IV. Thalassemia Dynamics of the UAE

Through the analysis of the mathematical model, we verified that Types I and II equilibrium points are both *unstable* under thalassemia control measures such as newborn baby screening, premarital screening and the education factor. In fact, Type I equilibrium point, the thalassemia free equilibrium point and Type II equilibrium point, the thalassemia major only free equilibrium point, reflect the status of thalassemia in the UAE, these days. However, according to our stability analysis, although we may be able to push a given thalassemia status in the UAE toward Type I or Type II equilibrium points by the two screening methods and education factor, we will never achieve thalassemia free or thalassemia major only free status in the long term. The analysis result is coincident with the fact that thalassemia can be resurgent any time due to the carrier-carrier marriages that can produce thalassemia babies with a 25% chance. Thus, thalassemia prevention via two screening methods and education can lower the occurrence rate but not effective enough to achieve thalassemia free status as long as carrier-carrier marriages are performed. We will show how the carrier-carrier marriage affect the state of the thalassemia in the UAE via simulations of our mathematical model with the UAE demographic data. The necessary parameter values are shown in Table I.

In particular, the newborn baby screening rate (β_S^M and β_S^F) is chosen to be 95% since it has been increased close to 95% since 1995 [27]. The thalassemia detection adjusting rates (η_T^M and η_T^F) and thalassemia carrier detection adjusting rates (η_{CG}^M and η_{CG}^F) are selected to reflect the proportion of thalassemia major [17] and carrier populations in the UAE [6]. The rest of parameter values are estimated from various references as shown in Table I except a few. For example, since marriage reconsideration rate, education rate or proportion of concerned

TABLE I
LITERATURE BASED AND ESTIMATED PARAMETER VALUES

Parameter	Male	Female	Ref
Birth rates†	$b_M = 0.0363$	$b_F = 0.0352$	[25]
Child mortality rates†	$d_M^G = 0.014$	$d_F^G = 0.008$	[26]
Adult death rates†	$d_M = 0.003$	$d_F = 0.0019$	[25]
Thalassemia induced death rate†	$d_T = 0.016$	$d_T = 0.016$	[1]
Proportion of young adults†	$\gamma_M = 0.0363$	$\gamma_F = 0.0352$	[21]
Newborn baby screening rate	$\beta_S^M = \beta_S^F = 95\%$		[6]
Thalassemia detection adjusting rates	$\eta_T^M = 0.025$	$\eta_T^F = 0.015$	[6]
Thalassemia carrier detection adjusting rates	$\eta_{CG}^M = 40.21$	$\eta_{CG}^F = 39.6$	[18]
Marriage rates†	$\alpha_M = 0.014$	$\alpha_F = 0.008$	[25]
Premarital screening rates†	$\alpha_S^M = 0.0413$	$\alpha_S^F = 0.0335$	[25]
Marriage reconsideration rates (MRR)	$\nu_M = 30\%$	$\nu_F = 30\%$	
MRR of educated singles	$\tilde{\nu}_M = 50\%$	$\tilde{\nu}_F = 50\%$	
Education rates of marriageable singles	$\varepsilon = \tilde{\varepsilon} = \kappa = 20\%$		
Proportion of concerned parents	$\rho = 30\%$		

†The unit of the parameter values is per person.

parents has not been found, we assign values for simulation purpose in our study.

With the initial data $G_M^o = 160,400$, $G_F^o = 153,500$, $G_M^{C^o} = 16,040$, $G_F^{C^o} = 15,350$, $T_M^o = 120$, $T_F^o = 100$, $S_M^o = 100,000$, $S_M^{E^o} = 20,000$, $C_M^o = 85,000$, $C_M^{E^o} = 14,000$, $S_M^{A^o} = 65,000$, $S_M^{AE^o} = 4,500$, $C_M^{A^o} = 1,500$, $C_M^{AE^o} = 4,500$, $S_{F^o} = 100,000$, $S_F^{E^o} = 20,000$, $C_F^o = 20,000$, $C_F^{E^o} = 15,000$, $S_F^{A^o} = 55,000$, $S_F^{AE^o} = 4,400$, $C_F^{A^o} = 1,400$, $C_F^{AE^o} = 3,600$, and $U^o = 15,000$, we vary newborn baby screening rates, premarital screening rates and education rates in order to examine the effectiveness of these control measures. In Figs. 1 and 2, as the newborn baby screening rate increases more thalassemia populations are detected.

Also, in Figs. 3 and 4, as the premarital screening rate increases more marriageable carrier populations are screened. Thus, the higher the screening rates of either the newborn baby screening or the premarital screening are, the more thalassemia or carrier populations are recognized. As for the effectiveness of the education factor, we notice that the growth of the thalassemia population with the highest education rate is less rapid than the rest in Figs. 5 and 6. We can conclude that the two control measures are appropriate for thalassemia or carrier population detection. However, the education factor does not seem to be effective enough in reducing the thalassemia population to a thalassemia free level although a higher education rate tends to slow down the growth of the thalassemia population.

Then, we vary the marriage reconsideration rates of carrier populations from 0% to 100% with the given initial data. Figs. 7 and 8 show that as the marriage reconsideration rates of carrier populations increase, the number of thalassemia major population in both sexes decreases over time. However, this cannot be sustained unless the marriage reconsideration rate of carrier-carrier couples is 100%. Otherwise, the number of thalassemia major cases will increase eventually.

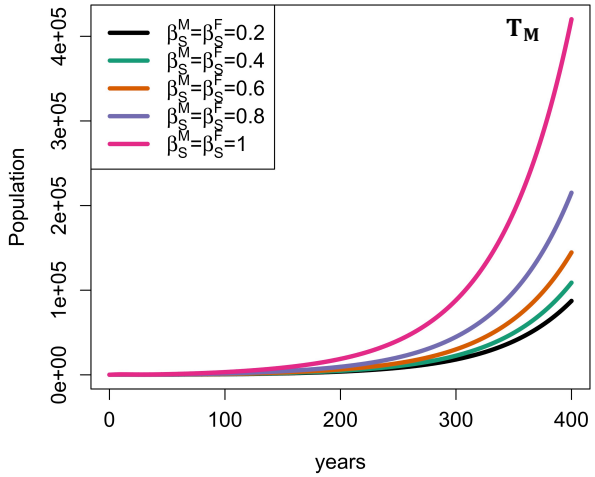

Fig. 1. Numerical simulation results of male thalassemia major population (T_M) with different level of newborn baby screening rates. β_S^M and β_S^F are the male and female newborn baby screening rates. $\beta_S^M = \beta_S^F = 0.1$ means 10% of newborn babies in both sexes receive newborn baby screening, whereas $\beta_S^M = \beta_S^F = 1$ means all of newborn babies in both sexes go through newborn baby screening. The rest of parameter values are as in Table I.

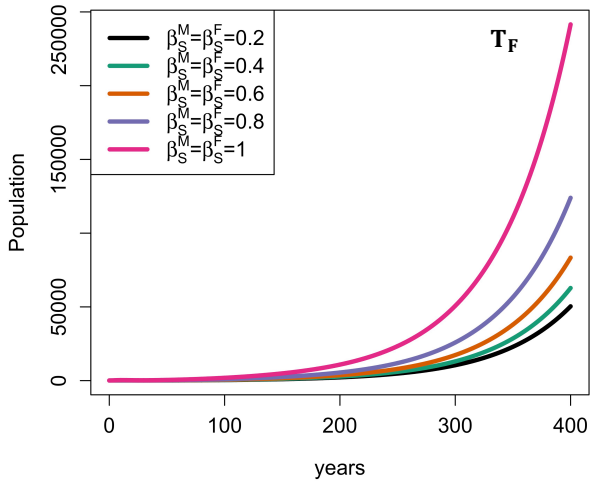

Fig. 2. Numerical simulation results of female thalassemia major population (T_F) with different level of newborn baby screening rates. β_S^M and β_S^F are the male and female newborn baby screening rates. $\beta_S^M = \beta_S^F = 0.1$ means 10% of newborn babies in both sexes receive newborn baby screening, whereas $\beta_S^M = \beta_S^F = 1$ means all of newborn babies in both sexes go through newborn baby screening. The rest of parameter values are as in Table I.

V. DISCUSSION

Thalassemia is a genetic disease and hence inherited via marriage to next generation. Since there is no cure for thalassemia but a life-long management through regular blood

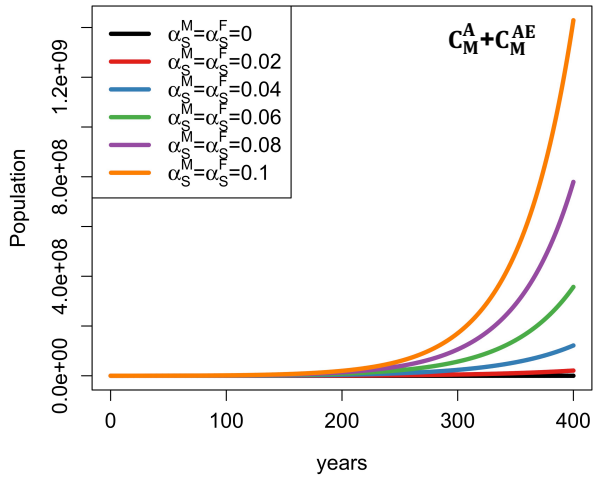

Fig. 3. Numerical simulation results of marriageable carrier male population (C_M^A and C_M^{AE}) with different levels of premarital screening rates. α_S^M and α_S^F are the male and female premarital screening rates. $\alpha_S^M = \alpha_S^F = 0.01$ means 10 out of 1000 carrier populations in both sexes go through premarital screening, whereas $\alpha_S^M = \alpha_S^F = 0.1$ means 100 out of 1000 carrier populations in both sexes go through premarital screening. The rest of parameter values are as in Table I.

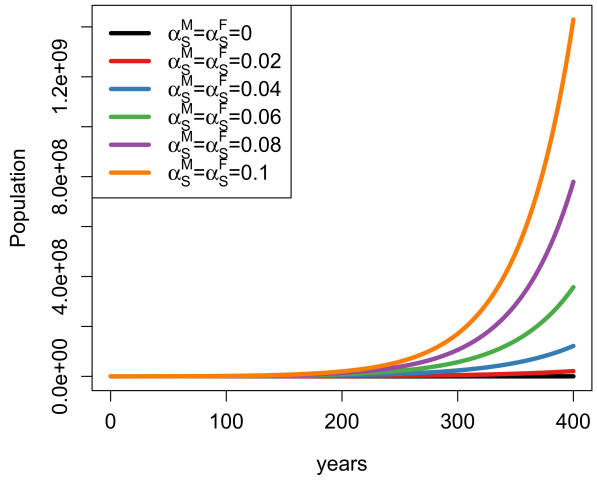

Fig. 4. Numerical simulation results of marriageable carrier female population (C_F^A and C_F^{AE}) with different levels of premarital screening rates. α_S^M and α_S^F are the male and female premarital screening rates. $\alpha_S^M = \alpha_S^F = 0.01$ means 10 out of 1000 carrier populations in both sexes go through premarital screening, whereas $\alpha_S^M = \alpha_S^F = 0.1$ means 100 out of 1000 carrier populations in both sexes go through premarital screening. The rest of parameter values are as in Table I.

transfusion and iron overload monitoring, once a thalassemia patient presents in a family, this will be a social, financial, emotional and personal burden not only in the family but also the society. In fact, UAE has a 50% consanguineous marriage rate [14], [17]–[19] and hence has a substantial prevalence of thalassemia carrier as well. Unfortunately, the rates has been increasing. The high prevalence of a thalassemia carrier population is a public health concern since there will be a 25% chance of having a thalassemia major child if a carrier-

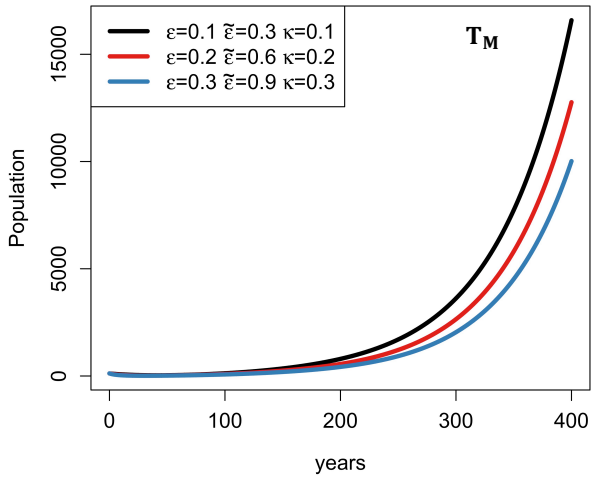

Fig. 5. Numerical simulation results of male thalassemia major population (T_M) with different levels of education rates. ϵ and $\tilde{\epsilon}$ are the education rates of young adult normal and carrier singles in both sexes, respectively. $\epsilon = 0.1$ means 10% of normal young adults in both sexes receive education about thalassemia, and $\tilde{\epsilon} = 0.3$ implies 30% of carrier young adults in both sexes are educated about thalassemia. κ is the minimum between ϵ and $\tilde{\epsilon}$. Higher number indicates more young adults being educated. The rest of parameter values are as in Table I.

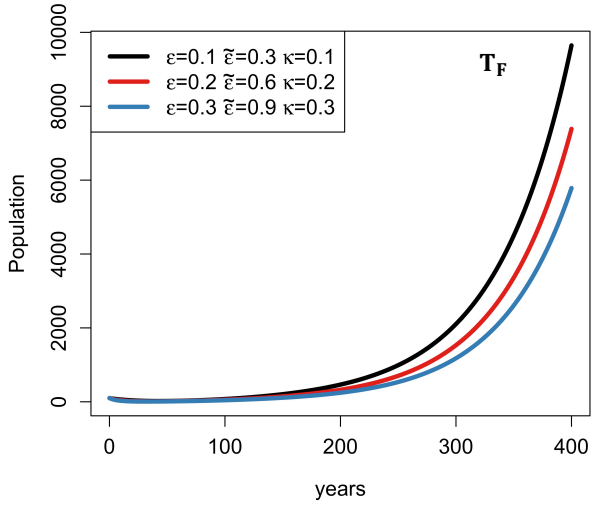

Fig. 6. Numerical simulation results of female thalassemia major population (T_F) with different levels of education rates. ϵ and $\tilde{\epsilon}$ are the education rates of young adult normal and carrier singles in both sexes, respectively. $\epsilon = 0.1$ means 10% of normal young adults in both sexes receive education about thalassemia, and $\tilde{\epsilon} = 0.3$ implies 30% of carrier young adults in both sexes are educated about thalassemia. κ is the minimum between ϵ and $\tilde{\epsilon}$. Higher number indicates more young adults being educated. The rest of parameter values are as in Table I.

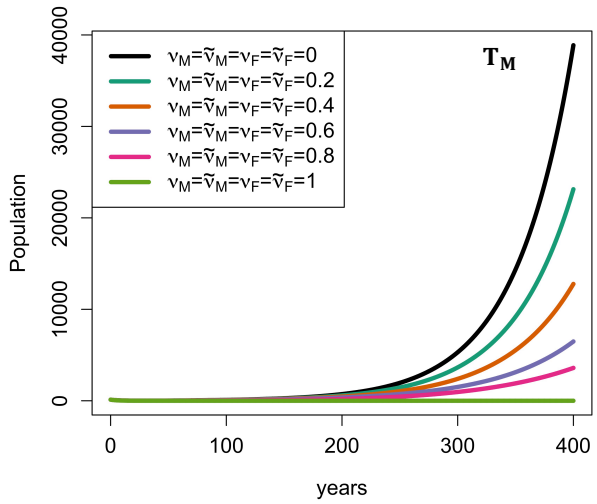

Fig. 7. Numerical simulation results of male thalassemia major population (T_M) with different levels of marriage reconsideration rates. ν_M and $\tilde{\nu}_M$ are the marriage reconsideration rates of educated and uneducated carrier male populations. $\nu_M = 0$ ($\tilde{\nu}_M = 0$) means all of uneducated (educated) carrier males do not give up their marriage decision, whereas $\nu_M = 1$ ($\tilde{\nu}_M = 1$) means all of uneducated (educated) carrier males do give up their marriage decision due to screening and education. The education and premarital screening rates are as in Table I.

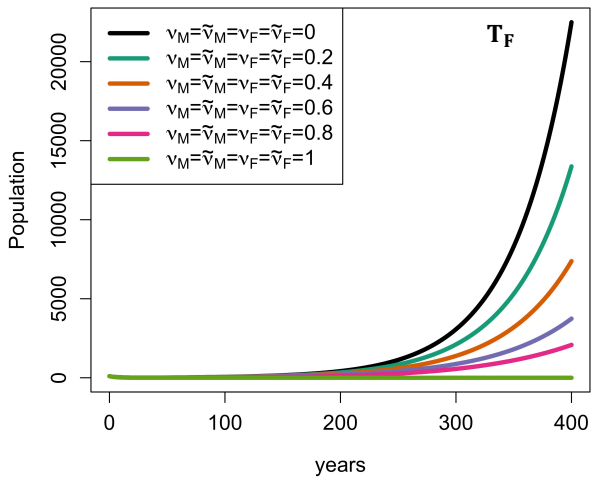

Fig. 8. Numerical simulation results of female thalassemia major population (T_F) with different levels of marriage reconsideration rates. ν_F and $\tilde{\nu}_F$ are the marriage reconsideration rates of educated and uneducated carrier female populations. $\nu_F = 0$ ($\tilde{\nu}_F = 0$) means all of uneducated (educated) carrier females do not give up their marriage decision, whereas $\nu_F = 1$ ($\tilde{\nu}_F = 1$) means all of uneducated (educated) carrier females do give up their marriage decision due to screening and education. The education and premarital screening rates are as in Table I.

carrier marriage occurs, leading to a potential increase in the thalassemia major population. Therefore, the prevention of thalassemia has been one of the major public health interests in the United Arab Emirates (UAE).

Thus, we developed a mathematical model for the thalassemia dynamics under three control measures to investigate whether the control measures can put an impact on eradication of thalassemia in the UAE in the long term. Our model is a compartment model that considered three different age groups such as children, young-adults, and adults, and imposed three thalassemia control measures such as newborn baby screening, premarital screening and education about thalassemia for school children to see the effect on the reduction of the marriage among carrier populations.

We showed in Theorem 3 that Types I and II equilibrium points, thalassemia free and thalassemia major only free equailibrium points, are unstable under the three control measures. In the public health sense, our result implies that although we may be able to push a given thalassemia status in the UAE toward Type I or Type II equilibrium point by two screening methods and education factor, we will never achieve thalassemia free or thalassemia major only free status in the long term. Thus, thalassemia prevention via newborn baby screening, premarital screening, and education can play a role in thalassemia population reduction but not effective enough to achieve thalassemia free status.

We illustrated the theoretical results via computer simulations with the UAE demographic data. The effectiveness of two screening measures and education was demonstrated in Figs. 1 to 6. These measures showed some degree of contribution in detection of thalassemia or carrier populations, or reduction of the growth rate of the thalassemia population. However, they were not enough to achieve the thalassemia eradication in the long term. In fact, As the marriage reconsideration rates of carrier-carrier couples increased, thalassemia major population substantially decreased. The impact of marriage reconsideration of carrier-carrier couples were shown in Figs. 7 and 8. The simulation results implied that the eradication of thalassemia will be achieved only when all carrier-carrier marriages are dropped regardless of the use of thalassemia control measures. However, this result does not mean that the education and two screening methods are not effective at all. Since these two prevention measures could send a warning on the risk of carrier-carrier marriage, i.e. 25% chance of having thalassemia major children, the influence of the three prevention measures should be considered in the marriage decision of carrier-carrier couples.

Although we focused on the thalassemia dynamics of the UAE in this paper, our mathematical model can be easily extended to other countries where thalassemia exists [7], [8]. With given demographic data specific to a country of interest, the similar way of stability analysis and computer simulations is possible. Thus, for the avenues of future work, we would like to build a bridge among multisectors including mathematics, public health and education by the comparison of the long-term impacts of different thalassemia control

measures in various countries.

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