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PRIMARY PREVENTIVE CARE MODEL FOR TYPE 2 DIABETES: INPUT CALIBRATION WITH RESPONSE DATA

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) and its complications account for 11% of the global health expenditure (IDF 2012). Different primary, secondary, and tertiary preventive interventions promise better health outcomes and cost savings but are often studied separately. This paper proposes a simulation model for T2DM that comprehends the nonlinear interactions of multiple interventions for various stages of T2DM on population dynamics, health outcomes, and costs. We summarize the model, then demonstrate how we addressed the important challenge of fitting input parameters given that data needed to be combined from disparate sources of data sources in a way that calibrates input parameters to output metrics over a range of decision variables (a form of model calibration to achieve a response model match to clinical data). We present preliminary numerical results to inform policies for T2DM prevention and management.

1 TYPE 2 DIABETES MELLITUS AND DISEASE MANAGEMENT INTERVENTIONS

Type 2 Diabetes Mellitus (T2DM), or adult onset diabetes, is a metabolic disorder characterized by high blood glucose resulting from insulin resistance and relative insulin deficiency. The disease progresses slowly and T2DM is often diagnosed only after a hospitalization due to a major complication. Major complications of T2DM include coronary disease, kidney failure and retinopathy (IDF 2012).

The diabetes prevalence in the USA increased from 2.5% to 6.9% between 1980 and 2010 (CDC 2012). In the United Arab Emirates (UAE) more than 20% of the population has been diagnosed with diabetes and the fraction with prediabetes exceeds 15% (Hajat et al. 2012). Other Gulf Cooperation Council (GCC) countries also have a high prevalence. T2DM currently affects some 366 million people globally and is expected to affect 552 million people within the next 20 years (IDF 2012).

In contrast to people with Type 1 Diabetes, the majority of those with T2DM do not usually require daily insulin injections. Diabetics in the initial stages of T2DM are generally prescribed a healthy diet and increased physical activity, the combination of which can stop the disease from further progression (Williams 1994). The preventable nature of T2DM and its escalating societal burden strongly motivates the implementation of preventive policies. Health authorities in many countries are actively engaging in multiple levels of preventive actions including primary prevention (awareness programs for the general population), secondary and tertiary prevention (disease management programs) for people diagnosed with T2DM (Gillett et al. 2010, Lancet Editorial 2010, Hajat et al. 2012).

Waugh et al. (2010) note that early screening presents a chance to offer lifestyle suggestions and treatment to people with prediabetes who would otherwise develop diabetes. However, the benefits of primary prevention interventions have not yet been fully quantified. Given this observation, we develop a system dynamics model for optimizing a portfolio of preventive care interventions in a way that is not

directly amenable with typical Markov model or decision tree approaches to health economics (Brennan, Chick, and Davies 2006) because of relevant nonlinear dynamics described below.

A number of T2DM models have previously been developed at the population, cohort and intra-personal levels that account for a number of risk factors and outcomes. Many of these models are calibrated using results from the United Kingdom Prospective Diabetes Study Group (UKPDS), a group that has developed a comprehensive database of risk factors for T2DM (Stratton et al. 2000, Stevens et al. 2001).

This paper presents an overview of the system dynamics model we have used to assess the interactions of the preventive care interventions under consideration. In one way, our model is broader than the UKPDS work in the way that it simultaneously models several interventions and their interactions. In another way, the model is simpler than the UKPDS work in that fewer covariates are included: their effects are averaged for simplicity. This paper also describes how we fit the many parameters of our model to the situation in the UAE, a process which required nonstandard techniques because of the multiple sources of data for both system inputs and system outputs as measured at several values of decision variables. We also present preliminary results of our numerical analysis. Structural results and further policy questions are pursued in Aral, Chick, and Grabosch (2014).

2 MODEL FOR T2DM PREVENTION AND DISEASE MANAGEMENT INTERVENTIONS

We use a discrete-time deterministic system dynamics model to describe the dynamics of T2DM in a population and to optimize a portfolio of potential prevention and disease management interventions. §2.1 summarizes the system dynamics model for T2DM progression. §2.2 describes how interventions to influence T2DM progression are modeled. Financial and health objective functions are found in §2.3.

2.1 Disease Progression, Self-Management and Disease Control

The model is portrayed graphically in Figure 1. Stocks are referred to by their number (in parenthesis). Each stock corresponds to different combinations of disease progression, compliance with best-practice disease management recommendations, and levels of the clinical indicator $\mathrm{HbA_{1c}}$ (an important measure of good blood glucose management). Healthy individuals may be either at high or low risk for developing T2DM (stocks 1 and 2, respectively). Disease progression is modeled by states for impaired glucose tolerance (IGT), also called prediabetes; early stage diabetes (T2DM before any major complication); and late stage (presence of one or more major complication). The percentages give the estimated fraction of adult UAE nationals in each stock, as described in §3 below along with citations for data sources.

The presence of an arc indicates a potentially nonzero flow rate (other than birth and death flows, which are not shown). §2.2 describes these flows and §3 describes how we estimated their rates.

2.2 Interventions and System Dynamics

A number of activities may be undertaken in order to reduce the overall burden of T2DM by modifying the progression dynamics of the disease. Here we consider four levels of preventive interventions.

1. Primary Prevention: Awareness Programs for the general public to decrease diabetes incidence rate, also serves to increase the diagnosis rates for undiagnosed diabetes.
2. Secondary Prevention for diagnosed pre-diabetics: Disease management programs aimed at delaying or preventing the progression to early stage diabetes.
3. Secondary Prevention for diagnosed early stage diabetics: Disease management programs aimed at delaying or preventing major complications.
4. Tertiary Prevention for diagnosed late stage diabetics: Disease management programs aimed at delaying or preventing further major complications.

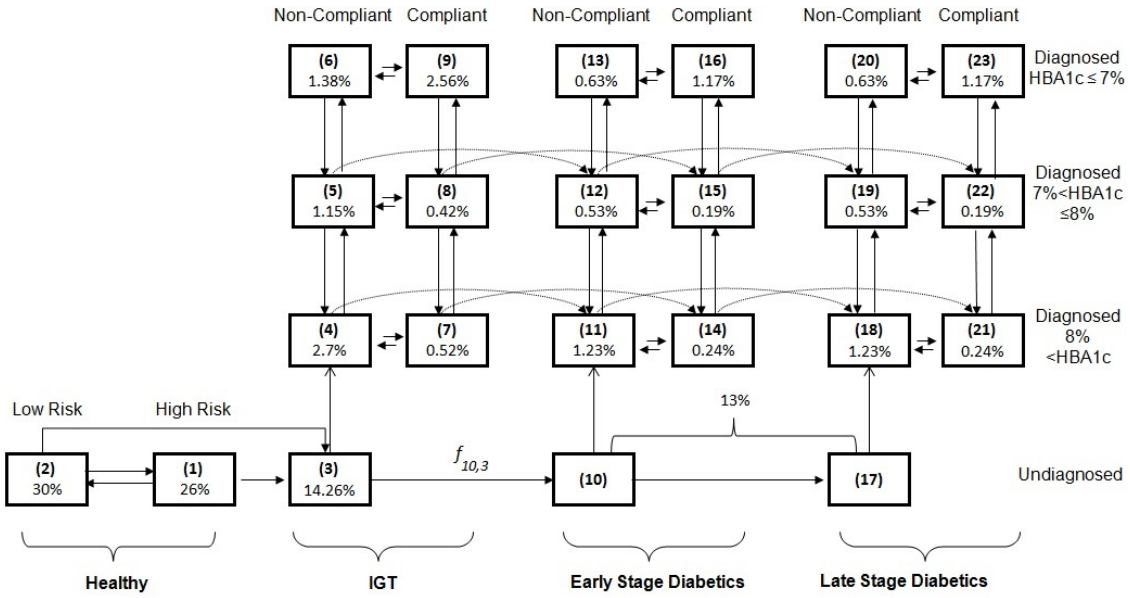

Figure 1: T2DM Progression from Left to Right, Levels of Behavioral Compliance, and Level of Glycemic Control Measured by $\mathrm{HbA_{1c}}$. Percentages reflect the population distribution in Abu Dhabi prior to the so-called Weqaya public health screening programme.

Typically, a primary prevention program (here, indexed by $k = 1$) takes the form of an awareness campaign that encourages both healthier lifestyles and screening. For example, a multi-channel media campaign communicating the risk factors for diabetes and promoting preventive actions in coordination with free-of-charge opportunistic screening would classify as a primary prevention program. Secondary prevention for people diagnosed with IGT/prediabetes ($k = 2$) or with diabetes ($k = 3$) and tertiary prevention for people with late stage diabetes ($k = 4$) are targeted disease management interventions designed for diagnosed patients at different stages of the disease.

At each time t, a decision is made to set the intensity of each type of intervention. To model this, we let $\mathbf{z}_t = (z_{1,t}, z_{2,t}, z_{3,t}, z_{4,t})$ denote the vector of the intensity of interventions ($k = 1,2,3,4$) at time t. We require each $z_{k,t}$ to be a nonnegative and real-valued rate of interventions/person/year. For example, $z_{2,t} = 4$ represents 4 interventions per year per person diagnosed with IGT. A planner who has a planning horizon of τ years is then interested in selecting a *policy* $\mathbf{z}_\bullet = (\mathbf{z}_0, \mathbf{z}_1, \ldots, \mathbf{z}_{\tau-1})$.

Let $\mathcal{F}_t$ be a disease progression matrix with flow rates $f_{i,j,t} = f_{i,j,t}(\mathbf{z}_t)$ from stock j into stock i at time period t. The $f_{i,j,t}$ are functions of the interventions $\mathbf{z}_t$ at time t. An increase in $z_{1,t}$ increases the flow rate into the healthy low risk stock and increases the flow rates from undiagnosed stocks into diagnosed stocks at time t. An increase in $z_{k,t}$ for $k = 2,3,4$ increases flows into compliant stocks at time t and thereby results in lower (improved) $\mathrm{HbA_{1c}}$ levels for the populations that they target. Thus, an increase in $z_{k,t}$ (for $k = 2$, 3) also decreases flows to more advanced stages of T2DM.

We describe the birth-death process with $b_{i,j}$, the rate of new entries to stock i per individual in stock j, and with d_i, the death rate for individuals in stock i. This determines the net birth/death rate $\mathcal{B}_{i,j,t} = b_{i,j}$ for $i \neq j$ and $\mathcal{B}_{i,i,t} = 1 + b_{i,i} - d_i$. Thus, birth-death rates can model risk factors for disease stage and disease management state, but are assumed to not depend on time and intervention intensity.

The counts of people in the $N_C = 23$ stocks in Figure 1 at time t are denoted with the column vector $\mathbf{x}_t$, for $t = 0, 1, \ldots$. The population dynamics are thus described by the flow equation

$$\mathbf{x}_{t+1} = \mathbf{P}_t \mathbf{x}_t,$$

where the flow rate matrix $\mathbf{P}_t = \mathcal{F}_t \mathcal{B}_t$ depends on both birth/death rates and flows between disease states.

2.3 Performance Objectives and Optimal Stationary Policies

Different objective functions to evaluate the performance of an intervention policy $\mathbf{z}_\bullet$ may include financial objectives (e.g., the NPV of intervention and treatment costs), health objectives and willingness to pay objectives which combine financial and health objectives. Both discounted and long-run average performance objectives might be considered. This section describes how we account for these objectives.

Expenditures due to T2DM include the cost of the interventions (as outlined in §2.2) and treatment costs (blood glucose measurement devices and consumable strips, regular primary care visits associated with full compliance, drugs, insulin, etc.). We include the average per capita costs attributable to T2DM-related complications in treatment costs.

The total cost of interventions in period t is modeled by $C(\mathbf{z}_t)G\mathbf{x}_t$, where $\mathbf{z}_t$ is a row vector of intervention decisions, $C(\mathbf{z}_t)$ the vector of per capita costs of interventions in period t and G is a matrix of zeros and ones such that G_{kj} is 1 if intervention k applies to subpopulation j and 0 otherwise. We denote the average annual cost of treatment and complications per person in stock i by c_i, and set $\mathbf{c}' = (c_1, c_2, \ldots, c_{N_C})$.

The *discounted* financial burden of prevention and treatment is an important economic measure of the burden of disease in a population. If the discount factor is $\beta \in [0,1)$ and the initial population is $\mathbf{x}_0$, then the total discounted cost over τ periods due to interventions and treatment is

$$J_{\$,\tau}(\mathbf{z}_\bullet) = \sum_{t=0}^{\tau-1} \beta^t \left(\mathbf{c}' + C(\mathbf{z}_t)G\right)\mathbf{x}_t.$$

The population $\mathbf{x}_t$ at time t depends upon the flow rate matrices $\mathbf{P}_{t-1}, \mathbf{P}_{t-2}, \ldots, \mathbf{P}_0$ and the initial population $\mathbf{x}_0$. Each $\mathbf{P}_t$ may depend on $\mathbf{z}_t$, $\mathbf{x}_t$ and t.

A commonly used measure of health is the quality adjusted life year, or QALY (Gold et al. 1996). We let q_i be the QALY per life year per person in stock i, and set $\mathbf{q}$ to be the vector of those values. The total discounted QALYs from a policy $\mathbf{z}_\bullet$ over τ time periods is

$$J_{QALY,\tau}(\mathbf{z}_\bullet) = \sum_{t=0}^{\tau-1} \beta^t \mathbf{q}'\mathbf{x}_t.$$

Financial outcomes and health outcomes can be combined with a willingness to pay (WTP) parameter λ. QALYs are monetized at the rate of λ dollars per QALY. This motivates a discounted WTP objective,

$$J_{\lambda,\tau}(\mathbf{z}_\bullet) = J_{\$,\tau}(\mathbf{z}_\bullet) - \lambda J_{QALY,\tau}(\mathbf{z}_\bullet).$$

An alternative to the discounted costs are *average* costs through time. Average costs are of particular interest for long-run sustainable performance goals. We denote the corresponding average performance objective function with a V. For example, the time average per capita cost of treatment and interventions is denoted by $V_{\$,\tau}(\mathbf{z}_\bullet) = \tau^{-1}\sum_{t=0}^{\tau-1}((\mathbf{c}' + C(\mathbf{z}_t)G)(\mathbf{x}_t/(\sum_{i=1}^{N_C} x_{i,t}))$ for finite τ. We define $V_{QALY,\tau}(\mathbf{z}_\bullet)$ and $V_{\lambda,\tau}(\mathbf{z}_\bullet)$ for average QALY and WTP objectives analogously.

Arbitrary feasible policies may be hard to implement. We therefore focus on *fixed* policies, whose values are constant through time, i.e., policies for which $\mathbf{z}_t = \mathbf{z}$ for some feasible, fixed $\mathbf{z}$.

In numerical experiments over a range of parameters (including many not reported here), we found long run convergence in both population growth rates and in the fraction of individuals in each stock for each given fixed policy. For a given fixed policy determined by $\mathbf{z}$, we describe the long-run limits by:

$$\begin{aligned} r_{0,\mathbf{z}} &= \text{growth factor, with long-run population growth of } 100(r_{0,\mathbf{z}} - 1)\% \\ \nu_{0,\mathbf{z}} &= \text{long run fraction of people in each stock, } \lim_{t\to\infty} \mathbf{x}_t / \textstyle\sum_{i=1}^{N_C} x_{i,t} \end{aligned}$$

The long-run average objective functions simplify with fixed policies. The long-run average annual per capita cost of disease maintenance, treatment and interventions for a fixed policy $\mathbf{z}$ is:

$$V_{\$,\infty}(\mathbf{z}) = (\mathbf{c}' + C(\mathbf{z})G)\nu_{0,\mathbf{z}}. \tag{1}$$

Similarly, the long-run average QALYs per capita per year for a fixed policy $\mathbf{z}$ simplifies to $V_{QALY,\infty}(\mathbf{z}) = \mathbf{q}'\nu_{0,\mathbf{z}}$ and the long-run average WTP per capita per year is $V_{\lambda,\infty}(\mathbf{z}) = (\mathbf{c}' + \mathbf{z}G - \lambda\mathbf{q}')\nu_{0,\mathbf{z}}$.

Optimality. A feasible fixed policy $\mathbf{z}$ which minimizes the objective function for figure of merit $\ell \in \{\$, QALY, \lambda\}$ and type $\eta \in \{J, V\}$ is denoted by $\mathbf{z}^{*,\eta_{\ell,\tau}}$ when it exists and is unique. For example, $\mathbf{z}^{*,V_{\$,\tau}}$ would be a policy that minimizes long-run average costs. We allow $\tau = \infty$ to denote the limiting case as $\tau \to \infty$, when the relevant limit exists.

We found a unique optimal policy within the class of fixed policies for each objective function in our numerical experiments. From (1) we see that an optimal policy for long-run average per capita costs, $\mathbf{z}^{*,V_{\$,\infty}}$, depends on the long-run population distribution but not on the initial population, $\mathbf{x}_0$. The optimal fixed policy for a discounted objective function, however, depends on $\mathbf{x}_0$.

3 PARAMETER ESTIMATION FOR THE T2DM MODEL

The structure of the model in Figure 1 is chosen to comprehend features of disease progression, the effect of interventions on compliance with self-management of T2DM, and their effects on the clinical indicator $\mathrm{HbA_{1c}}$ (which is measurable and has been associated with costs and risks of complications due to T2DM). There are no known studies which provide estimates for all parameters relevant to each of those features for the same population, and the fitting of input parameters to achieve an output response at each of several decision variables is a nonstandard estimation problem.

We therefore chose a hybrid approach to parameter estimation. When directly relevant medical, public health or financial data were available, we used standard estimation techniques as described in §3.1. Given the importance of the T2DM challenge in Abu Dhabi and the GCC more broadly, we tried to find the most relevant parameters for the adult Emirati nationals in Abu Dhabi. In cases where the data specific to that population were not available, we first searched for data from the UAE, then from the GCC, then globally. For parameters for which no data sources were available, we used a calibration process described in §3.2.

3.1 Parameters Estimated from Directly Relevant Sources of Data

This section describes the estimation of parameters which could be estimated from directly relevant data.

Initial Population Distribution: Table 1 summarizes the sources used to estimate the proportion of individuals in each stock just prior to a recent, large-scale public health screening programme called Weqaya. We thus describe an estimation process which may be relevant to other Emirates, other GCC countries, or other areas with high prevalence which have not yet had a full screening or which may be planning such a screening. The Weqaya Screening of the Health Authority-Abu Dhabi (HAAD) began in April 2008 and was in response to the increase in cardio-vascular problems in Abu Dhabi's Emirati population. To date, 96% of that population of 180,000 adults has been screened for risk factors related to cardio-vascular problems including diabetes and obesity. The International Diabetes Federation estimated that the undiagnosed diabetics constitute 62% of all cases (IDF 2006), and that half of the diagnosed diabetic population is in the late stage of diabetes having developed complications. To the best of our knowledge, the proportion of the undiagnosed population in early and late stage is not identified in prior studies. Hence, the proportion of the undiagnosed population in the late stage versus early stage is fit by the least-squares error minimization.

We use a conservative estimate for the proportion of healthy high risk (here, overweight to simplify): we assume that all diabetics and pre-diabetics were *de facto* at high risk so that the proportion of people at high risk of developing pre-diabetes is given by $70\% - 44\% = 26\%$. The compliance rate (under the base rate of intervention) of 40% among people with diabetes is based on a study of dietary habits in Saudi Arabia. We assume that the overall compliance rate including the drug refill and doctor visit rates is the same and is comparable between early and late stage diabetics. Harris et al. (1999) give the respective proportions of each glycemic control group both for diabetics under insulin and diet alone. We assume that insulin treatment is administered to those who do not comply with dietary modifications, and the patients

Table 1: Parameters For Estimating the Diabetic Population Distribution in the UAE.

Parameter	Value	Source(s)
Fraction diabetic	21%	HAAD (2011)
Fraction pre-diabetics+diabetics	44%	Khoja et al. (2010)
Fraction pre-diabetic	23%	(=44%-21%)
Fraction undiagnosed pre-Weqaya	62%	Lasry and Silva (2010)
Fraction overweight	70%	HAAD (2011)
Fraction healthy high risk	26%	(=70%-23%-21%)
Fraction healthy low risk	30%	(=100%-44%-26%)
Ratio of early/late stage	1	Lasry and Silva (2010)
Fraction late stage diabetics	10.5%	(=21%/2)
Fraction early stage diabetics	10.5%	(=21%/2)
Frac. compliant w/(good, fair, poor) glycemic control	(73.2%, 11.9%, 14.9%)	Harris et al. (1999)
Frac. non-compliant w/(good, fair, poor) glycemic control	(26.5%, 22.1%, 51.4%)	Harris et al. (1999)
Compliance rate	40%	Khattab et al. (1999)

treated with diet alone are considered to be compliant. Given these assumptions, algebra gives the HbA_{1c} distribution for compliant and non-compliant diabetics. These proportions are assumed to be the same for IGT, early and late stages.

The assumptions above result in the fraction of people in each stock that is given in Figure 1. These fractions are used for the initial population state vector $\mathbf{x}_0$ for the numerical analysis.

Birth and Death Rates: Average birth and death rate data are locally available (Table 2). Statistics Centre-Abu Dhabi (SCAD 2011) reports $d = 2.11 \times 10^{-3}$ as the death rate for Emirati nationals, and $b = 0.0311$ as the average birth rate. Death rates d_i for each stock are determined by using the relative risks factors for death by disease state (as computed using parameters in Table 2) and population distribution ($\mathbf{x}_0$ above) to result in the overall death rate, $\mathbf{d}$=[1.678 1.165 2.383 2.383 1.492 1.165 2.383 1.492 1.165 4.218 4.218 2.496 2.063 4.218 2.496 2.063 4.762 4.762 2.976 2.459 4.762 2.976 2.459] $\times 10^{-3}$.

The modeled population is insured adults aged 18 or older, so "births" may arrive to healthy stocks or those with T2DM. Christakisi and Fowler (2007) show that obesity (a prime risk factor for T2DM) "spreads" through networks of individuals (i.e., families). To model the "spread" of T2DM through "births" into unhealthy stocks, where a diabetic individual has a higher likelihood to give "birth" to a high risk or diabetic individual, we model the nonzero birthrates $b_{i,j}$ to stock i due to individuals in j as follows:

$$
\begin{aligned}
b_{i,j} &= bx_{i,0}/(x_{1,0}+x_{2,0}), \text{ for } i,j \in \{1,2\} \\
b_{i,j} &= bx_{i,0}/(x_{1,0}+x_{2,0}+x_{3,0}), \text{ for } i \in \{1,2,3\}, j \in \{3,4,\ldots,9\} \\
b_{i,j} &= bx_{i,0}/(x_{1,0}+x_{2,0}+x_{3,0}+x_{10,0}), \text{ for } i \in \{1,2,3,10\}, j \in \{10,11,\ldots,16\} \\
b_{i,j} &= bx_{i,0}/(x_{1,0}+x_{2,0}+x_{3,0}+x_{10,0}+x_{17,0}), \text{ for } i \in \{1,2,3,10,17\}, j \in \{17,18,\ldots,23\}
\end{aligned}
$$

Treatment and Intervention Costs: Treatment and intervention costs are largely available locally. Table 3 summarizes data and references that we use to fit the annual treatment costs, $\mathbf{c}$. Al-Maskari et al. (2010), whose data is from Al-Ain in the Emirate of Abu Dhabi, indicates that the average medical care cost for people with diabetes without complications is \$1,605 (in 2005 US\$), and gives the average cost for micro and macro complications. We estimate the cost of the first complication by a weighted sum of the corresponding costs of macro and micro complications. Gilmer et al. (1997) study the effect of glycemic control on medical costs and estimate that patients with HbA_{1c} levels of 7%, 8%, 9% and 10% have costs that are 4%, 10%, 20% and 30% higher than those with an HbA_{1c} of 6%. We assume these percent increases are valid for both early and late stage diabetics. We model variable costs but not fixed costs. These assumptions imply an estimated annual treatment cost (in US\$) per capita $\mathbf{c}$ = [497 497 497 497 497 497 497 497 497 497 1,824 1,537 1,465 1,738 1,537 1,465 6,185 7,701.3 6,488 6,185 7,337 6,488 6,185], including health costs not related to diabetes.

Table 2: Parameters for Estimating the Death and Birth Rates in the UAE for Various Stages of Diabetes.

Parameter	Value	Source(s)
Death Rate for nationals in Abu Dhabi (annual)	2.11/1000	SCAD (2011)
Increase in death rate in higher risk healthy group	0.44	Gonzalez and Hartge (2010)
Increase in death rate with IGT	0.42	Saydah et al. (1992)
Increase in death rate with diagnosed diabetes	1.11	Saydah et al. (1992)
Increase in death rate with undiagnosed diabetes	0.77	Saydah et al. (1992)
Increase in death rate with late stage diabetes over early stage	0.192	Saydah et al. (1992)
Increase in death rate per 1% increase in HbA_{1c} for nondiabetic	0.28	Khaw et al. (2001)
Increase in death rate per 1% increase in HbA_{1c} for diabetic	0.21	Stratton et al. (2000)
Average Birth Rate for nationals in Abu Dhabi	0.0331	SCAD (2011)

Based on reasonable but disguised data, the cost of primary prevention per person per contact is taken to be $C_1(1)$ = \$15. Based on the same source, the cost of disease management per person per intervention for people with IGT, Early, and Late Stage diabetes are taken to be $C_2(1)$ = US\$50, $C_3(1)$ = US\$81, and $C_4(1)$ = US\$100, respectively.

QALY: QALY data for health outcomes are not locally available. We assume that the QALYs per person per year for stocks without diabetes is 1. For the early stage we use a 0.78 QALY per year (Clarke et al. 2002). For late stages, we assume that a major complication results in a decrease of 0.1285 QALY on average (derived from results in Clarke et al. 2002, with an assumption that each major complication is equally likely), and that a 1 % increase in HbA_{1c} increases the probability of developing complications by 21% (Stratton et al. 2000), so $\mathbf{q}$ = [1 1 1 1 1 1 1 1 1 0.78 0.78 0.78 0.78 0.78 0.78 0.78 0.65 0.60 0.62 0.65 0.60 0.62 0.65].

3.2 Calibration of Flow Rate Parameters When No Directly Relevant Data Were Available

We use a calibration process for flow rate parameters for which no data is available. In summary, we posit logistic curves for the effects of interventions on flow rates and quantified the long-run fraction of people in each stock of the model for several relevant levels of intervention intensities. We compared population and clinical metrics which are implied by those long-run fractions with the values that would be implied by archival literature. We then fit the parameters of the logistic curves by finding the parameters of the logistic curves which minimized a sum of squared error terms for both the subpopulation (stock) sizes and for changes in the relevant clinical indicators as interventions vary.

Logistic curves for flow rates. For flow rates which may depend on intervention decisions (not births or deaths or progression rates), we assume that the effect of interventions on the flow rates $f_{i,j} = f_{i,j}(\mathbf{z})$ are logistic functions of the intervention intensities (we remove the subscript t from $\mathbf{z}_t$ and $f_{i,j,t}$ to reduce notational complexity and to focus on fixed policies). See Robins and Rotnitzky (2004) and Greenstein and Bonita (2000) on the use of logistic functions to model patient compliance behavior.

For example, consider interventions $i = 2,3,4$ (IGT, early, late). The flow rate from a non-compliant stock to a compliant stock is presumed to be of the form $1/(1+\exp[-a_{i,1} - a_{i,2}z_i])$, and flow rate from a

Table 3: Parameters Used in Estimating the Costs for Various Stages of Diabetes (in 2005 US\$).

Parameter	Value	Source(s)
Per capita expenditure on health care in Abu Dhabi	US\$497	Al-Maskari et al. (2010)
Annual average cost in early stage diabetes	US\$1,605	Al-Maskari et al. (2010)
Average cost of drug therapy	US\$2,000	Muslim, N. (2010)
Costs due to microvascular complications	US\$3,453	Al-Maskari et al. (2010)
Costs due to macrovascular complications	US\$10,300	Al-Maskari et al. (2010)
Ratio of prevalence of macro/micro complications	0.6635	Al-Maskari et al. (2010)
Weighted annual cost of the first complication	US\$6,185	Al-Maskari et al. (2010)
Increased risk of complications per 1% Increase in HbA_{1c}	0.21	Stratton et al. (2000)

compliant to non-compliant stock is of the form $1 - 1/(1 + \exp[-a_{i,3} - a_{i,4} z_i])$. The parameters $a_{i,j}$ were assumed to be constant across the three levels of $\mathrm{HbA_{1c}}$ benefitting from intervention i. The flow rate from the healthy high-risk to healthy low-risk is $1/(1 + \exp[-a_{1,5} - a_{1,6} z_1])$. The flow rate from healthy low-risk to healthy high risk is $1 - 1/(1 + \exp[-a_{1,7} - a_{1,8} z_1])$.

Summands of squared error terms to be minimized. There are two main categories of summands of squared error terms which we use for fitting the flow rate parameters $a_{i,j}$ above.

The first category is the relative squared error between the fraction of individuals in each stock at time 0 ($\mathbf{x}_0 / \sum_{i=1}^{N_C} x_{i,0}$) and the stationary distribution ($\nu_{0,\mathbf{z}^{base}}$) that results from employing a base level of interventions $\mathbf{z}^{base}$. These summands would be $\sum_{i=1}^{N_C} ((\nu_{0,\mathbf{z}^{base},i} - x_{i,0})/x_{i,0})^2$ if the number in each stock could be observed (relative squared errors are used in order to ensure proper fitting for the stocks with low population fractions). Because the number of undiagnosed cases of T2DM may not observable, we recall the estimated fraction of the population at time 0 in undiagnosed stocks 10 and 17 is 0.13, and replace the two summands for $i \in \{10, 17\}$ with $((\nu_{0,\mathbf{z}^{base},10} + \nu_{0,\mathbf{z}^{base},17} - 0.13)/0.13)^2$. We assume base intervention rates of $\mathbf{z}^{base} = (0.3, 0.3, 0.3, 0.3)$ as minimal intervention rates for the fitting process.

The second category is associated with calibrating the flow parameters so that reasonable values of clinical indicators are observed when the values of the decision variables $\mathbf{z}$ are changed. Those reasonable values are indirectly influenced by $\mathbf{z}$ through the logistic curves for the flows. We have two main terms in this category: one for $\mathrm{HbA_{1c}}$ and one for the compliance rate to primary prevention. To calibrate the effect of $\mathbf{z}$ on $\mathrm{HbA_{1c}}$, we assessed the average $\mathrm{HbA_{1c}}$ of individuals with diagnosed T2DM when targeted interventions were raised by one (i.e., $\mathbf{z}' = \mathbf{z}^{base} + [0, 1, 1, 1]'$) as predicted by the model compared with values reported in the literature (this term enables us to fit the parameters for modeling the effect of targeted interventions z_2, z_3, z_4). The model's results depend on the $a_{i,j}$. Literature (Rhee et al. 2005) shows empirically that each effective interaction with a qualified care provider has an effect of decreasing the average $\mathrm{HbA_{1c}}$ by 0.12% points. We assume that the same decrease in $\mathrm{HbA_{1c}}$ is achievable for IGT, early and late stage interventions in our context. For IGT interventions, we therefore include a squared error term $(\sum_{\ell=4}^{9} \mathrm{HbA_{1c},\ell}(x_{\ell,0} - x_{\ell,1}) - 0.12)^2$ in the sum of squared errors. Here, $\mathrm{HbA_{1c},\ell}$ is the average $\mathrm{HbA_{1c}}$ level for individuals in stock ℓ and the summand is the expected decrease in average $\mathrm{HbA_{1c}}$ in the next time period (starting from $t = 0$) when increasing intervention intensity of z_2 from 0.3 to 1.3. We included similar terms for early and late stage interventions in the sum of squared errors.

We now consider the calibration of the flow terms associated with primary prevention, z_1. Snyder et al. (2004) suggest an increase by 6% in compliant behavior per contact from a primary prevention intervention. Hence, we assume that the flow from the healthy high-risk stock to healthy low-risk increases by 6%, and the flow from the healthy low-risk to healthy high-risk decreases by 6% with the first primary prevention contact over the base rate. Primary prevention can also motivate people with undiagnosed IGT and early stage diabetes to get diagnosed. This 6% increase in diagnosis rate by the first primary prevention contact is used in fitting the logistic flow rates $f_{4,3} = 1/(1 + \exp[-a_{1,1} - a_{1,2} z_1])$ and $f_{11,10} = 1/(1 + \exp[-a_{1,3} - a_{1,4} z_1])$. For example, the contribution of $a_{1,3}$ and $a_{1,4}$ to the total squared error is $((1/(1 + \exp[-a_{1,1} - a_{1,2} \times 1.3])) - (1/(1 + \exp[-a_{1,1} - a_{1,2} \times 0.3])) - 0.06)^2$, the contribution of the remaining parameters to the total squared error are similarly defined.

Other constraints on flows. In order to respect risk ratios in the literature or to retain a level of consistency in parameter estimation where data are not available, we use a few additional assumptions. We constrain the ratio of flow rates from high risk and low risk to IGT to be 4.1 so as to match the risk ratio from Mohan et al. (2008). We assume that the sojourn time for undiagnosed complications is 1 (i.e., a treated complication was assumed to imply a diagnosis during treatment), so the diagnosis rate for late stage diabetics is $f_{18,17} = 1$. Non-compliant stocks with the highest $\mathrm{HbA_{1c}}$ levels are assumed to have the same disease progression rate as the undiagnosed cases ($f_{11,4} = f_{10,3}$ and $f_{18,11} = f_{17,10}$), because best practice disease management is not observed in those stocks.

For vertical flows within each of the three blocks of diagnosed stages (for each stage of disease) with six stocks each, we use assumptions about how the rates are linked. We assume that a given vertical flow

in one block of six equals the flow rate of the analogous vertical flow in the other blocks of six to simplify calculations and to avoid overfitting. This transforms the fitting of 24 vertical flow parameters to the fitting of 8 vertical flow parameters. These assumptions together with relative risk ratios of disease progression summarized in Table 4 are used to constrain the flow rates.

Calibration summary. In summary, we calibrate flows (flow rate parameters or the parameters $a_{i,j}$ of logistical models for flows which depends on an intervention) by choosing them to minimize the squared error terms (as explained above) to assure good fit for a reasonable range of decision parameters to some population and clinical metrics. We note that in general, such an optimization to calibrate parameters of a system dynamics model may lead to nonintuitive or counterintuitive parameter estimates for flow rates. In order to minimize such effects, we minimize the least squares while constraining flow rates to respect several known relative risk ratios or other criteria to retain face validity.

Table 4: Parameters used in indirect estimation of vertical flow rates and relative risks of disease progression.

Average HbA_{1c} for $\text{HbA}_{1c} > 8\%$	9.1%	Harris et al. (1999)
High and Low Risk population	26%, 30%	Table 1
Increase in Risk of comp. 1% HbA_{1c}	21%	Stratton et al. (2000)
Increase in Risk of comp. non-comp.	31%	Gleason et al. (2011)
RR with healthy High Risk	4.1	Mohan et al. (2008)

4 PRELIMINARY NUMERICAL EXPERIMENTS

This section presents some preliminary results and insights based on the conceptual model in §2 for T2DM progression as a function of a portfolio of primary and other disease management interventions, and on adaptation of that model to the data from the UAE (as fitted in §3). In what follows, we chose a discount factor $\beta = 0.95$ and a WTP parameter $\lambda = 50\text{K}$ US\$/QALY unless otherwise specified. Both of those choices are compatible with standard practice. We normalize the initial population size $\mathbf{x}_0$ to 1 so that objective function values reported for discounted figures of merit are per person at time 0.

Table 5 gives the optimal intervention intensity levels under several different objectives under the assumption that the disease status of all individuals is known. While this might not be true in general, the assumption is relatively reasonable for Abu Dhabi following the intensive Weqaya screening program (Hajat et al. 2012). On the one hand, we see that primary intervention is not cost saving from the discounted NPV perspective ($z_1^{*,J_{\$,\infty}} = 0$), but it is cost effective ($z_1^{*,J_{\lambda,\infty}} > 0$). On the other hand, if we take the long-run average per capita cost perspective, we see that primary prevention is both cost saving ($z_1^{*,V_{\$,\infty}} > 0$) and cost effective ($z_1^{*,V_{\lambda,\infty}} > 0$). Thus, a shift from a discounted NPV perspective to a long-run average per capita cost perspective shifts the optimal decision from not providing primary prevention services to providing primary prevention services. Table 5 also suggests that the discounted WTP perspective, which values health and discounts future costs, tends to provide more focus on treating patients throughout the later stages more so than the average cost WTP formulation.

We now explore what would happen if the number of individuals in each disease state were not as accurately known as in Abu Dhabi. We could ask the question: "How would optimal policies change if there was a way to immediately diagnose undiagnosed cases of IGT and T2DM?" Such an effect can be modeled by setting $f_{4,3} = f_{11,10} = 1$ and $f_{10,3} = f_{17,10} = 0$ (rather than using their calibrated values above).

Table 6 gives the optimal fixed policies under different objective functions with immediate diagnosis (no more than 1 time step undiagnosed). Differences in the optimal objective function values for the base model and the case of immediate diagnosis help determine the maximum reasonable cost of immediate diagnosis one might entertain. We therefore focus on differences in optimal policies as observed for the purely financial objectives, and first examine the discounted cost $J_{\$,\infty}$. The NPV per person for $\mathbf{z}^{*,J_{\$,\infty}}$ with immediate diagnosis (US\$41,181) is higher than without immediate diagnosis (US\$40,901). This is because more diagnosed individuals implies more treatment and intervention costs.

A greater practical difference is observed for the long-run average cost, $V_{\$,\infty}$. While primary prevention is an active part of the optimal portfolio when there is no immediate diagnosis, it is not an active part of the optimal portfolio when there is immediate diagnosis ($z_1^{*,V_{\$,\infty}} = 0$ in Table 6). Thus, the benefit of primary prevention for optimizing $V_{\$,\infty}$ seems to be in its role in identifying undetected cases more than in keeping healthy people to become or to remain at low risk. The reduction in primary prevention results in a lower per person cost ($598.5/person/year instead of $630/person/year) if immediate diagnosis were costless, but individuals would be at higher risk of IGT, and IGT prevalence would be higher.

The optimal policies for the two WTP objectives, ($\mathbf{z}^{*,J_{\lambda,\infty}}$ and $\mathbf{z}^{*,V_{\lambda,\infty}}$), are almost identical whether immediate diagnosis is available or not. Thus, a WTP decision maker's optimal policies do not strongly depend on immediate diagnosis – the high rates of general awareness associated with those policies (as expected from the monetizing of health) are sufficient for detecting new cases. Another interesting observation is that under the immediate diagnosis scenario, optimal policies for $J_{\$,\infty}$ and $V_{\$,\infty}$ objectives are aligned.

Table 5: Optimal Fixed Policies.

	$\mathbf{z}^{*,J_{\$,\infty}}$	$\mathbf{z}^{*,J_{\lambda,\infty}}$	$\mathbf{z}^{*,V_{\$,\infty}}$	$\mathbf{z}^{*,V_{\lambda,\infty}}$
z_1	0.0000	14.8471	3.8962	13.9260
z_2	0.7086	0.9396	0.7475	0.9933
z_3	0.6736	0.8722	0.7000	0.7458
z_4	0.6829	0.8538	0.6003	0.7480

Table 6: Opt. Fixed Policies w/ Immediate Diagnosis.

	$\mathbf{z}^{*,J_{\$,\infty}}$	$\mathbf{z}^{*,J_{\lambda,\infty}}$	$\mathbf{z}^{*,V_{\$,\infty}}$	$\mathbf{z}^{*,V_{\lambda,\infty}}$
z_1	0.0000	14.8471	0.0000	13.9255
z_2	0.7243	0.9396	0.7479	0.9935
z_3	0.6977	0.8722	0.6958	0.7457
z_4	0.6779	0.8538	0.5978	0.7072

5 DISCUSSION AND CONCLUSIONS

We develop a system dynamics model of the population level dynamics of T2DM progression which accounts for healthy individuals with high or low risk, disease progression, and the influence that primary prevention and disease management programs may have on disease progression. Although the dynamics might reasonably be described by linear and Markovian dynamics, the transition rates themselves are nonlinear in the intensity of disease management efforts. Furthermore, the data sources for informing the model require nonstandard techniques. There is no single study which estimates all the relevant parameters for a given population: some but not all parameters must be estimated indirectly.

We use an interesting combination of standard parameter modeling (e.g., for birth and death rates, marginal costs, QALYs) and some least squared error estimation to calibrate parameters to match output responses and the change in output responses as design parameters change. Such techniques might be useful in other contexts where parameter estimation is used to calibrate input parameters when the output must not only be calibrated for one set of values of decision variables, but also when the output response must be matched for a range of decision variables.

Future work includes the derivation of mathematical properties for the optimal solutions, as well as a deeper exploration of policy implications of the model. Relevant questions may include where to best allocate additional funds if they become available, and a more thorough understanding of the implications of choosing a discounted NPV or WTP perspective, which is common in health technology assessment, as compared to a long-run average cost per capita perspective (Aral, Chick, and Grabosch 2014).

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