MISSION-T2D

Multiscale Immune System SImulator for the Onset of Type 2 Diabetes integrating genetic, metabolic and nutritional data

Work Package 4

Deliverable 4.2

Report on MF-HOMA model (weeks-months' time scale)

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Executive Summary	This document describes the work done in Task 4.3. Task 4.3 – Constructing a high-level aggregation model of the interaction between glucose metabolism and chronic inflammation. The model has been constructed and has been made available to the Consortium. To view the model and run simulations the Marvel Viewer tool has been made available to the Consortium as well. To prepare for use of the model in P4 health applications, a start was made to connect the model with the Nutrition Researcher Cohort, an online resource that integrates personal health data.
Keywords	Semi-quantitative, model, metabolism, systems biology, inflammation, personal health data

Contents

1 Deliverable description

Deliverable 4.2 is the result of Task 4.3: Constructing a high-level aggregation model of the interaction between glucose metabolism and chronic inflammation (weeks-months' time scale).

The integrated metabolism-inflammation simulator developed in MISSION-T2D is constructed as a multilevel model, connecting and integrating descriptions at different space-time scales ranging from subcellular/molecular to whole body levels, and from (sub)seconds to years. The model developed in Task 4.3 is required to describe changes at the whole body, weeks-months' timescale. This aggregation level has been chosen since it allows for model calibration using data from controlled intervention studies, for which ample literature resources are available.

Also at such a high aggregation level, one could include biological processes known to be relevant for the development of T2D to a considerable level of detail. However, as an additional requirement the model should connect to parameters measured and reported by homecare devices. This will facilitate the actual use of the model in practice e.g. for personal lifestyle coaching in the prevention of T2D. Unfortunately, the choice of measured parameters by self-monitoring devices is currently still rather limited. Therefore, we decided to start the model from a very high level of aggregation, leaving out much detail but taking care to connect to readily available self-monitoring data as much as possible. Aspects relevant for Mission-T2D were included to one or more levels of detail so as to generate a well-balanced description. Care was taken to build the model with a systems view in mind, acknowledging the fact that many biological processes in different domains mutually interact to produce an integrated outcome (in this case, T2D). The model was therefore based on a system dynamics model previously developed by TNO that integrates energy intake, glucose/insulin metabolism, gut health, inflammation, mental stress and organ function.

A further objective is to make the model suitable for actual use in P4 Health applications. This requires that the model can run scenario simulations and generate predictions of lifestyle choices-dependent T2D development based on an individual's personal health data. We prepared for such use of the model by linking it to the Nutrition Researcher Cohort, an online resource that integrates personal health data.

2 Deliverable Results

2.1 Diabetes model v1.0

The model described in this report should be considered a prototype, representing a first step in the development of a holistic systemic health model that describes some major subsystems that determine human health status and their interactions. Primary subsystems of interest included are energy metabolism, glucose/insulin dynamics, inflammation, stress response systems and tissue damage. The model can use the following life style factors as inputs for simulations ("control variables"): dietary energy intake, exercise/physical activity, sleep/meditation/relaxation and food quality.

The model file together with the model viewer software and a guideline for using the software is made available to the consortium on the following ftp location:

ftp://tnopresenter.nl

Filename: Marvelousviewer.exe

2.1.1 Model properties

The model was created using a TNO proprietary interactive software (Marvel) as a set of variables characterized by starting values, interconnected by causal relations. For computational purposes, in the Marvel software all variables are scaled between 0 and 1. Thus, for all variables a scaling protocol is needed to translate the Marvel value into a "real world" value, The relations between variables are programmed as causal effects, as follows: every interaction is assigned a strength and a speed, each to be chosen from 5 predefined categories. A step change D in source variable S then causes the target variable T to change in a time-dependent manner according to:

$$T(t) = T(0) + D.B.(1-e^{-k.t}), \qquad \text{(Eq. 1)}$$

where B and k are the strength and speed of the interaction, and T(0) is the value of T at the time immediately before the change in S occurs. This type of kinetics ensures a very stable behaviour of the model as a whole. This was verified by Monte-Carlo simulations showing that the time trajectories of variables were influenced only to a limited extent by variation of the speed and strength values of the interactions (data not shown).

Causal interactions between variables were included in the model based on expert knowledge, i.e. mostly taken from review articles in highly cited literature. To perform simulations, a change in one or more control variables can be specified and the model

is run to calculate the effect in time of that change on all the non-control variables in the model. These effects are propagated throughout the model along the causal interactions specified.

To allow for the use of data obtained from individuals that were followed over multi-year periods such as in the Whitehall II cohort, it was decided to increase the time span covered by the model to years. While this choice necessarily will reduce the available time resolution for the description of intervention study data, we consider that this choice will add to the model's relevance for the description of T2D development as this is generally a multi-year process.

2.1.1.1 Time scale

The time scales of interest are in the range from weeks to years. Typically, variables in the model are derived from daily averages when using data from self-monitoring devices. This choice avoids further complication due to diurnal variations caused by circadian rhythms and acute responses to events.

The current version of the model describes a period of (roughly) six years (indicated by "Long Term (6 yrs)"). Also intermediate time points "Short term (2 yrs)" and "Midterm (4 yrs)" are defined.

2.1.1.2 Interaction specifications

Each interaction between two variables has three attributes, a direction, a speed and a strength. Interactions can be either positive (+) or negative (-). For Speed the following classes are used:

- Very slow: 1 (i.e. kinetic constant k in Eq. (1))
- Slow: 2 (i.e. kinetic constant k in Eq. (1))
- Average: 4
- Fast: 8
- Very fast: 20

The Strength of the relationship denotes the amount of change that is passed from the cause variable to the effect variable. For instance, a strength of 1 indicates that a change of 0.2 in the cause variable will eventually result in an identical change of 0.2 in the effect variable. Thus, 100% of the change is transmitted.. The following strength classes are used:

- Very weak: 0.3

- Weak: 0.6
- Equal: 1
- Strong: 1,2
- Very Strong: 2

2.1.2 Diabetes model v1.0 topology

Many details of the system of interest (i.e., the biological processes operative in the development of T2D in humans) are largely unknown. Many datasets are available, but most datasets give only limited information about certain details of the system. This, combined with the large number of interacting components, may give rise to an overwhelming complexity should one want to build the model from all available data. To avoid too much combinatorial complexity, the number of components in the model was limited to certain variables that represent key processes. We focused on variables for which values could be determined or estimated (either directly or indirectly). Latent variables were needed to (1) reduce complexity and inter-individual variation and (2) obtain a better representation in terms of physiological (dys-)functioning.

For some of the model components and their interactions quantitative data is available. However, for various components only an estimate of interactions could be made, based on qualitative knowledge from literature and expert opinions. An extended literature search has been performed to identify suitable components and obtain information about the form and strength of their interactions. Key findings of this literature study are summarized in Appendix 4.2.

Error! Reference source not found. shows the first version of the model. Three domains can be distinguished, depicted in different background colors: (1) energy balance, (2) glucose metabolism, (3) other systemic health variables. For each of these three parts, the variables and interactions are discussed below.

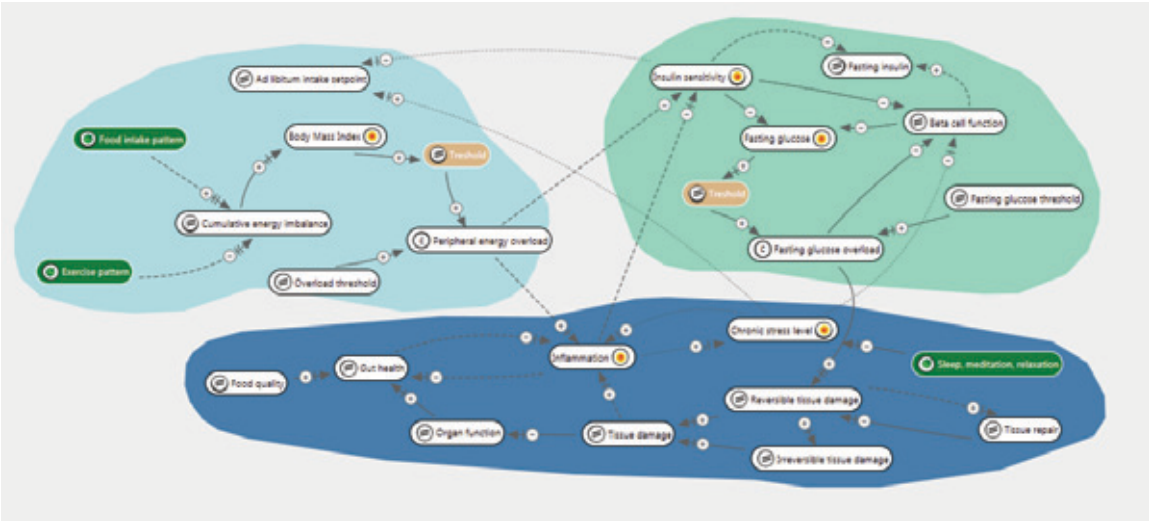


Figure 1. Topology of Diabetes model V1.0

2.1.3 Model components

The components that describe energy balance were kept relatively simple (Figure 2). The caloric balance was described with only two general variables, one related to calorie intake (“food intake pattern”) and one related to calorie expenditure (“exercise”). Calorie expenditure includes energy expenditure due to resting metabolism in addition to energy expenditure due to exercise. For applications in which a more detailed description of energy balance and effects of macronutrients (carbohydrates, fat and proteins) on body mass and body composition is required, a Vensim implementation of the body weight dynamics model of Hall (2010) is available within TNO that could be integrated in the model.

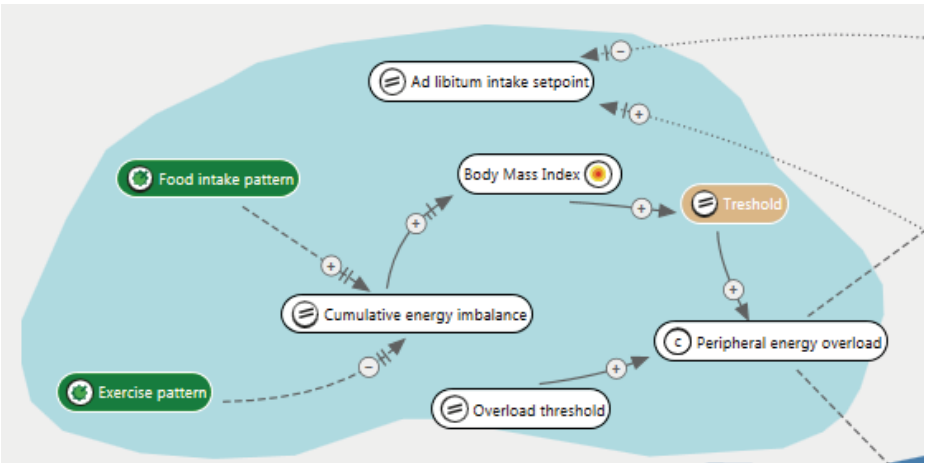


Figure 2. Model component: Energy metabolism

Note that also more subtle effects of exercise have not been taken into account.

Exercise may for instance cause changes in fat oxidative capacity of muscular tissue. Also possibly beneficial effects of exercise on stress levels have not been taken into account. These and other effects of exercise/physical activity may be interesting subjects for further refinement and improvement of the model.

In the model, difference between the food intake pattern and the exercise pattern leads to a "Cumulative energy imbalance", which affects the Body Mass Index over time. Note that Body Mass index, just like all other model variables, is described in the Marvel model on a 0-1 (or 0-100%) scale. The 0-1 range should cover more or less the whole range that the 'real world" variable can have in reality. Therefore, to scale to real values, we let 0 correspond to a BMI value of 15 kg/m^2 (BMI up to 18.5 kg/m^2 is considered underweight), while 1 corresponds to a BMI of 50 kg/m^2 (BMI above 30 kg/m^2 is considered obese and BMI above 40 kg/m^2 is considered morbidly obese).

The ad libitum intake setpoint describes alteration in hunger and satiety due to systemic health changes. Since the food intake itself is already prescribed as an input in the first version of the model, there is no further downstream effect of this variable. Depending on the exact application, possible future model extensions could include a direct alteration of food intake due to a changed setpoint or the calculation of the discrepancy between this setpoint and the actual intake. The latter may be useful for predicting problems of adherence to caloric restriction (i.e., dieting).

[illegible]

Due to the large diurnal variation and complex dynamics due to interactions with other physiological parameters, daily averages of plasma insulin and glucose concentrations were not directly used as model variables. Instead, the model uses fasting plasma levels of both insulin and glucose as well as insulin sensitivity and beta cell function as indicators (Figure 3).

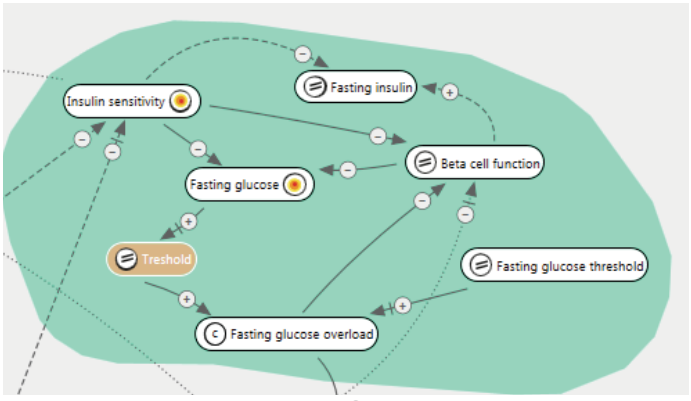


Figure 3. Model component: Glucose metabolism

This part of the model was inspired by the clinically established HOMA2 model (Wallace et al., 2004). The variables HOMA2-S and HOMA2-B in the HOMA2 model, are reliable indicators for the insulin sensitivity and beta cell function. Both variables are expressed as percentage of a standard healthy situation. A set of plasma concentrations of insulin and glucose under fasting conditions can be directly translated into the corresponding HOMA2-S and HOMA2-B values using the HOMA2 computer model (available from https://www.dtu.ox.ac.uk/homacalculator/).

The interactions between insulin sensitivity, beta cell function and insulin and glucose levels that were included in the Marvel model (**Error! Reference source not found.**) can be regarded as a linearization of the HOMA2 model as depicted in Figure and explained in Table 1. These interactions were all assumed to be very fast. This will be further optimized after comparing Whitehall II data with model simulation results.

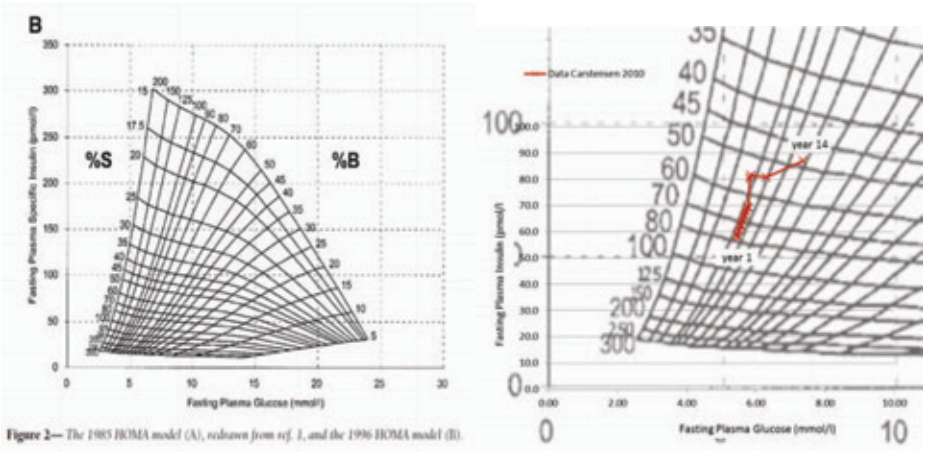


Figure 4: Left: HOMA2 model. relation between beta cell function, insulin sensitivity, plasma insulin and plasma glucose. Right: detail with estimated trajectory of onset of type 2 diabetes (model of Carstensen 2010)

Table 1. Glucose metabolism interactions

Arrow from	Arrow to	Description
Insulin sensitivity	Beta cell function	Under normal physiological conditions, beta cells can compensate for changes in insulin sensitivity such that normal glucose tolerance is maintained. Decreased insulin sensitivity leads to increased beta cell function (negative effect) Assumed to be a fast mechanism. See: Kahn et al. Nature 444, 840–6 (2006)
Beta cell function	Fasting insulin	Linearization of HOMA2 model. Beta cells produce insulin. Increased beta cell function combined with constant insulin sensitivity yields an increased fasting insulin concentration (positive effect).
Insulin sensitivity	Fasting insulin	Linearization of HOMA2 model. Increased insulin sensitivity combined with constant beta cell function yields a decreased insulin level (negative effect).

Beta cell function	Fasting glucose	Linearization of HOMA2 model. Increased beta cell function combined with constant insulin sensitivity yields an decreased fasting glucose concentration (negative effect).
Insulin sensitivity	Fasting glucose	Linearization of HOMA2 model. Increased insulin sensitivity combined with constant beta cell function yields an decreased fasting glucose concentration (negative effect).
Fasting glucose	Beta cell function	If prolonged high concentrations of glucose occur (hyperglycemia), this has detrimental effects on the functioning of the beta cell either due to tissue damage or 'stunning' of the beta cells (see Ferranni, Cell metabolism 11, 349–52 (2010)). This is implemented by a negative effect that only occurs once the fasting glucose level exceeds a threshold value of 0.3.

[illegible]

As discussed above, the dark blue part of **Error! Reference source not found.** contains various non-metabolic health variables (see also **Error! Reference source not found.**). In contrast to other parts of the system, there is less detailed knowledge of, and much less quantitative information for many interactions in this part of the model. The interactions (and their signs) included in this part of the model were chosen based on evidence from literature (see appendices 4.2 for key findings from evaluated literature). However, the strengths and speeds of those interactions are generally unknown. Hence, rough estimates were used. Calibration of the model using datasets provided in WP7 should provide means to improve these parts of the model. In the following section, we will sequentially discuss each variable and its outward interactions to other variables within the model component.

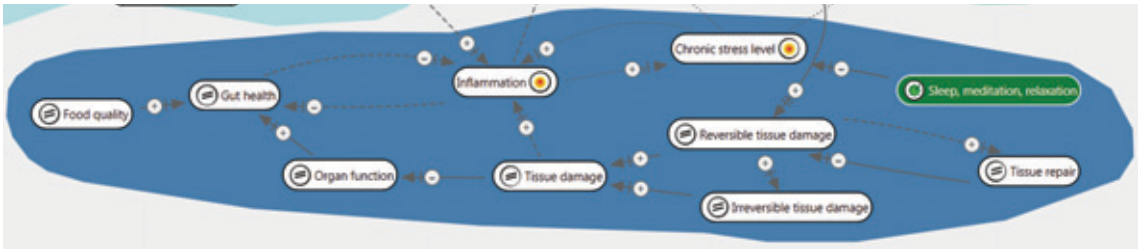


Figure 5. Model component: other systemic health variables

The (dys-)functioning of the brain regions and neuro-endocrine systems related to mental stress were described by a single variable 'chronic stress level'. This level can be roughly related to the activity of the hypothalamic-pituitary-adrenal axis (HPA)-axis and the resulting plasma levels of the 'stress hormone' cortisol. Chronic stress has been shown to reduce the protective effects of the immune systems (Dhabhar 2009). The pro-inflammatory cytokines produced induce low-grade inflammatory responses

resulting in a further increase in production of pro-inflammatory cytokines. These cytokines in turn induce an increase in CRP production, a well-established marker of inflammation (Black 2002, Gabay 1999). This effect of chronic stress on inflammation is defined as weak in the model.

The “Inflammation” variable in the model refers to systemic low-grade inflammation. It corresponds to metaflammation which in MISSION-T2D is considered a main driver of T2D development (Donath 2011, Stringhini 2013). This type of sterile inflammation is characterized by chronically increased levels of various inflammatory biomarkers including C-reactive protein (CRP). As briefly discussed above this type of inflammation is associated with metabolic dysfunction and diabetes, although the precise order of causes and effects are still debated. In the model component, inflammation influences gut health and chronic stress, The effects of inflammation on gut health are not well studied. An important role of the immune system is to minimalize direct contact between intestinal epithelial tissue and microbiota and compartmentalize microbiota to certain sites (Hooper 2012). Reasoning that a chronically elevated inflammatory state will somewhat impair the immune defensive functioning, a weak negative effect of inflammation on gut health was assumed. Cytokines, with IL-6 as the main driver, and humoral mediators of inflammation are potent activators of the stress response. In the case of metabolic syndrome this stress response will remain activated through the presence of macrophages and other immune cells in the adipose tissue (Kyrou 2009) i.e. a positive effect is included..

Gut health is defined as a combination of barrier integrity, microbiota composition and -function in this model. Relationships between gut microbiota function and the immune system are well known (Hooper 2012). For instance an increase in gram-negative microbiota by adopting a high fat diet increases the production of LPS, which induces low-grade chronic inflammation (Nicholson 2012). Evidence is accumulating that gut microbiome composition is related to metabolic syndrome and obesity (Le Chatelier 2013, Tilg 2011). In the model the (negative) effect of gut health state on inflammation was assumed to be slow and weak.

Type 2 diabetes is a complex, life-style related disease in which food consumption and exercise play a major role. Not only overeating has been shown to cause overweight, also the composition of food is essential for maintaining good health. Food quality has been shown to impact gut microbiota composition and -function (Ley 2006, Duncan 2007). For instance dietary fiber is a key component of a healthy diet and evidence of

the positive health effects on microbiota function are accumulating (Kaczmarczyk 2012). Another example is the increase in LPS production by gram-negative microbiota by a high fat diet (Nicholson 2012). It has recently become clear that even rapid changes in microbiota composition can occur by changing diet from animal based to plant based (David 2013). Therefore food quality was added as a variable to the model and in particular as a driver of gut health.

A dysfunctional metabolism can lead to the accumulation of tissue damage. This may sometimes be reversible, but eventually also irreversible tissue damage can occur. A dramatic example of the latter is the occurrence of a myocardial infarction after which the heart irreversibly loses a part of its pumping capability. Common complications of chronically elevated glucose levels in untreated diabetes mellitus are retinopathy (which ultimately can cause blindness) and kidney failure. Currently, the description of tissue damage does not distinguish between different tissues but does differentiate between reversible and irreversible tissue damage. The only exception are the beta cells in the pancreas, for which the damage is included in the decreased value of 'beta cell function' at elevated glucose levels. The tissue damage is assumed to accumulate once fasting glucose levels exceed the Fasting glucose threshold (which is also used for the effect on beta cells). The detrimental effects are countered by tissue repair mechanisms which are also present as a variable in the model.

Damaged tissue was assumed to contribute to the inflammatory tone, as implemented by a positive influence on the Inflammation variable. The decreased function of organs due to accumulation of tissue damage may have many systemic health effects. Currently, only the effect on gut health was included, but this can be extended in future.

2.1.3.4 Interactions between model components

Once the Body Mass Index in the model exceeds the threshold of 0.4 (corresponding to a BMI of 29), it starts suppressing insulin sensitivity and activating inflammation. Inflammation has a negative effect on insulin sensitivity. The arrows in this "triangle" are still subject of scientific debate. There is a clear association between overweight on one hand and systemic inflammation and insulin resistance on the other. However, the precise mechanisms are still debated as well as what is causing what downstream of the overweight.

In the first model version the links between glucose metabolism and tissue damage were highly simplified. Future model version may also take into account key aspects of

lipid and cholesterol metabolism and the deleterious effects of dyslipidemia. In addition, explicitly including atherosclerotic plaque formation into the model can lead to a more accurate description of the links between disturbed metabolism and cardiovascular disease.

The influence of the stress level on the metabolism was considered to be two-fold. Firstly, stress can lead to an increased food intake (Dallman 2003), which we implemented by a positive influence on 'Ad libitum intake setpoint'. As discussed above, this setpoint currently has no downstream influence, but may be connected in a future version of the model. Secondly, stress was assumed to lead to a decreased beta cell function (based on mouse data from Delauny 1997 and human associations discussed in Anagnostis 2009). The model does not include a direct effect of stress on insulin sensitivity. As there are indications that such a mechanism may occur as well (Anagnostis 2009), this mechanism should be considered for future version of the model.

2.1.3.5 Control variables

The model contains three control variables, i.e. variables that can be set before running model simulations.

Food intake pattern indicates the amount of calories that are consumed. Obviously this is an important factor for type 2 diabetes, both as a risk factor as well as an often-used intervention. This control variable can be used to simulate weight reduction interventions. Therefore this control variable is connected to the Cumulative energy imbalance variable.

Exercise pattern is a variable that represents calories burned, and includes basic metabolic rate in this version of the model. In future model versions this element could be modelled as a separate variable, leaving Exercise pattern as a variable exclusively for calories burned due to physical activity. This control variable is used to simulate the effects of increasing or decreasing exercise.

The third control variable is called 'Sleep, meditation, relaxation' and used to represent interventions for reducing or environmental factors that increase chronic stress levels. Sleep debt and sleep fragmentation are associated with increasing chronic stress levels. Patients with those particular problems might benefit strongly from interventions to improve sleep quality. Meditation and relaxation are interventions that are proven to reduce stress levels. This variable therefore also represents specific treatment options such as mindfulness-based stress reduction that can be useful for type 2 diabetes

patients (Merkes 2010).

2.1.4 Model simulation results

The model can be used to evaluate the effects of life style changes on various aspects of human health, especially T2D development. As an illustration, in this document three scenario simulation examples are shown. In all three simulations we assumed an apparently health, overweight individual (BMI ± 25).

In the first scenario, over the course of 6 years, we assumed this person would consume too much food (0.2 on the scale of 0 to 1 more on a daily basis than the energy requirements for basal metabolism and physical activity). **Error! Reference source not found.** shows the simulation result i.e. an increasing Body Mass Index, accompanied by a slight deteriorating of various other health indicators. Insulin sensitivity started to decrease slightly after 2 years and systemic inflammation slowly rose over the course of the six years. The fasting glucose levels remained stable because the reduction in insulin sensitivity was compensated by an increase in pancreas function.

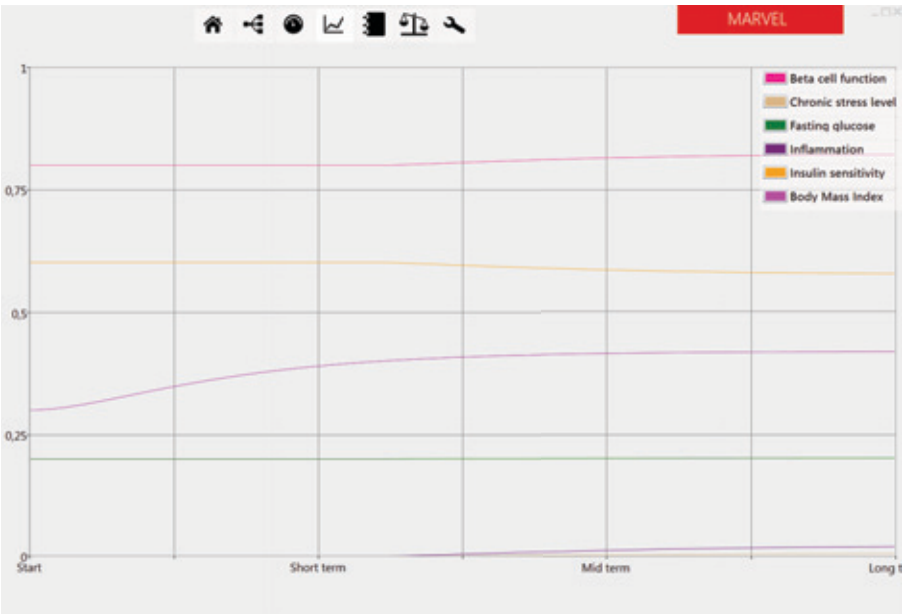


Figure 6. Simulation of 0.2 overeating per day.

The second scenario simulated the development of diabetes after sustaining an even larger energy imbalance (0.65). Figure 7 shows that fasting glucose levels did not remain stable but started to rise after the short term period. Around the mid term period, an acceleration of this rise in fasting glucose was seen. BMI kept increasing but levelled off at a maximum. The simulation also showed that the compensatory function

of the pancreas reached a maximum and then decreased. This represents the damage that the pancreas will eventually take if it is not able to compensate for the increased glucose levels anymore. The timing of this event corresponded to the start of the strong rise in fasting glucose levels. Inflammation was also rapidly increasing after pancreas failure.

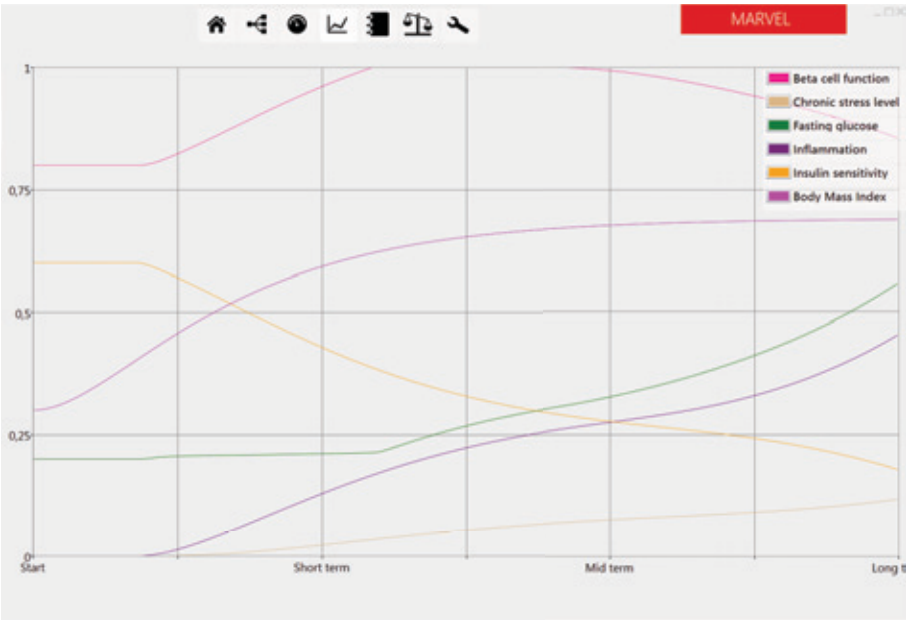


Figure 7. Simulation of the development of diabetes (0.65 overeating per day)

The third scenario (illustrated in Figure 8) shows a simulation of the effects of a life-style intervention on early stage Type 2 diabetes. First an overweight hypothetical subject was assumed to consume much more energy than expended (similar to scenario 2). After 4 years, at mid-term, this subject decided to change lifestyle in such a way that energy expenditure was larger than intake for the rest of the time. The simulation result shows that insulin sensitivity, BMI as well as inflammation all improved after this change. There still was a rise in fasting glucose levels at short term, but instead of an acceleration of the rise at mid term, fasting glucose started to normalize. Apparently, the pancreas was able to compensate for most of the decreased insulin sensitivity during the first stage of the scenario, and did not develop permanent damage thanks to the lifestyle change at mid term.

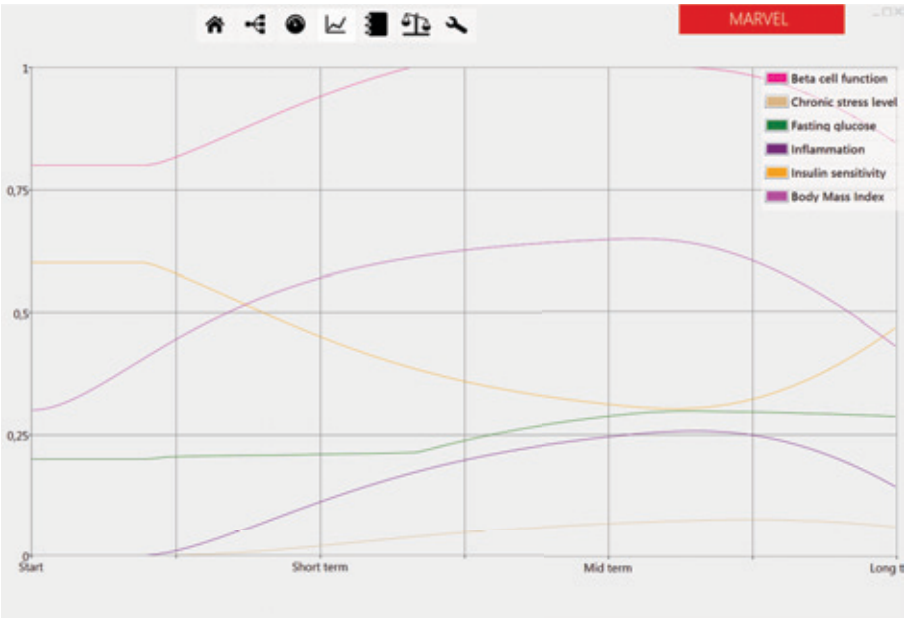


Figure 8. Simulation of 0.65 energy excess per day up to mid-term. After 4 years a lifestyle change was made towards more energy expenditure than intake (0.60 intake, 1.0 expenditure).

2.2 Diabetes model quantification

Although the modelling approach that was chosen for this project is semi-quantitative in nature, an attempt was made to relate the model variables, the strengths and speeds of the relationships to real data. The process of quantification consisted of the following steps:

- Selection of variables to quantify
- Selection of the variable ranges
- Selection of the transformations to map Marvel variables to true variable ranges

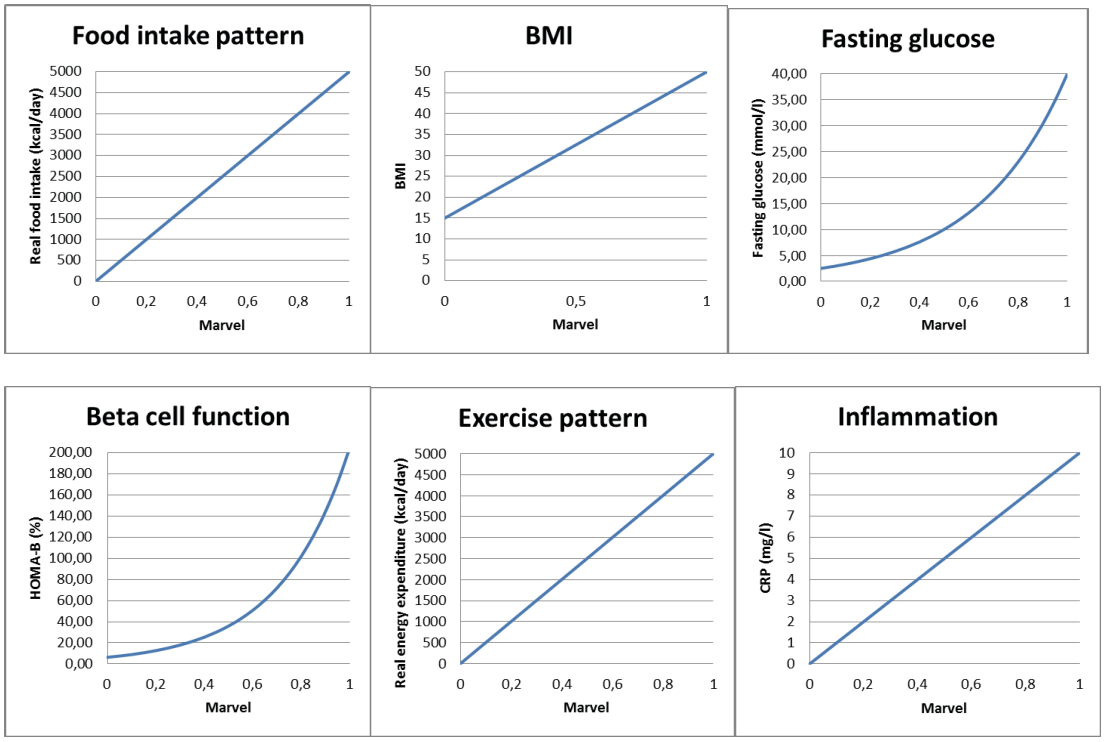
2.2.1 Selection of variables to quantify

Several variables were selected for quantification based on the relevance for diabetes patients as well as the availability of a real measure for the variable. BMI is a key variable that can be determined from body weight and length measurements. Fasting glucose and fasting insulin can be measured in blood samples. Beta cell function and insulin sensitivity can be calculated using the HOMA2 model, an algorithm described in Wallace 2004, based on measured fasting glucose and insulin. Calorie intake and expenditure must be quantified since they constitute the key control variable in the model. Calorie intake can be calculated based on food intake diaries, and obtained by using apps such as Fat Secret (http://www.fatsecret.com). Energy expenditure can be measured by several devices such as FitBit, ViaFit, Active8, and Basis. As also

concluded in WP5, and documented in Deliverable 5.1, although the reliability of such devices is still under debate, a rough estimate can still be given and individual changes over time can be monitored (Danecker 2013). Inflammation can be estimated by C-reactive protein measurements in blood samples. A reasonable estimate of chronic stress could be the measurement of hair cortisol levels. An acceptable proxy for Gut health could be serum LPS levels. A quantification of the gut health variable is not implemented in the model yet.

2.2.2 Selection of the variable ranges and Marvel value transformations.

The next step in the quantification of the selected variables was to determine physiological ranges of the variables and mapping those ranges on the Marvel range of 0 to 1. In Figure 9 below, the mapping of the variables is shown. The X-axis is always the Marvel range of 0 – 1, while the Y-axis represents the real measurable range of the respective variable.



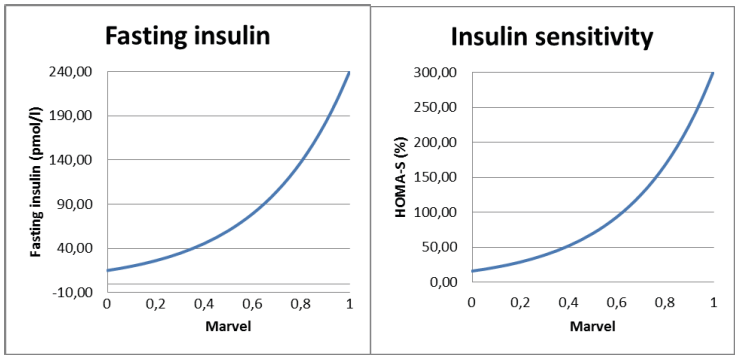


Figure 9. Variable mappings

Based on the physiological ranges of the variables and the mappings, formulas were constructed to convert real measured values into marvel ranges and back again. Table 2 shows the formula's for each of the variables. The table also indicates the starting values of the variables and the related real values. Currently the model is set for an overweight person (BMI is 25) with a fasting glucose level of 4,36 mmol/l, a properly functioning pancreas (beta-cell function is 100%), fasting insulin is also good (100 pmol/l), inflammation is assumed to be 0 (CRP is 0 mg/l), insulin sensitivity is good (HOMA-s is 100%). The quantification of the variables now allows setting the model for persons with a different set of starting values, for instance reflecting a pre-diabetic or diabetic state. Values for the variables can be gathered from medical records or measured using do-it-yourself technology to provide input for the model.

Table 2

Variable name	Type	Valid M range	Real range	M start Value	Real start value	Marvel -> Real	Real -> Marvel	Measure
Ad libitum intake setpoint		0-1		0,5				
Beta cell function	Goal	0-1	6,25 - 200 % (log)	0,8	100%	HB=10^((MHB*1,51)+0,8)	MHB=(Log10(HB-0,8)/1,51	HOMA2 %B
Chronic stress level		0-1		0,0				Hair cortisol levels
Cumulative energy imbalance		0-1		0,3				
Exercise pattern	Control	0-1	0 - 5000 kcal	0,0	0	EP=MEP*5000	MEP=EP/5000	Daily calories burned
Fasting glucose	Goal	0-1	2,5 - 40 mmol/l (log)	0,2	4,36 mmol/l	FG=10^((MFG*1,20)+0,4)	MFG=(Log10(FG)-0,4)/1,20	Fasting Glucose
Fasting glucose overload		0-1		0,3				
Fasting glucose threshold		0-1		0,3				
Fasting insulin		0-1	15 - 240 pmol/l (log)	0,7	100 pmol/l	FI=10^((MFI*1,20)+1,18)	MFI=(Log10(FI)-1,18)/1,20	Fasting Insulin

Food intake pattern	Control	0-1	0 - 5000 kcal	0,0	0	FI=MFI*5000	MFI=FI/5000	Calorie intake
Food quality		0-1		0,2				
Gut health		0-1		0,8				serum LPS
Inflammation	Goal	0-1	0-10 mg/l	0,0	0 mg/l	I=MI*10	MI=I/10	CRP
Insulin sensitivity	Goal	0-1	16,1 - 300 % (log)	0,6	100%	HS=10^((MHS*1,27)+1,21)	MHS=(log10(HS-1,21)/1,27	HOMA2 %S
Irreversible tissue damage		0-1		0,1				
Organ function		0-1		0,9				
Body Mass Index	Goal	0-1	15 - 50 kg/m²	0,3	25	BMI=MBMI*35+15	MBMI=(BMI-15)/35	0 = 15 kg/m², 1 = 50 kg/m²
Peripheral energy overload		0-1		0,4				
Reversible tissue damage		0-1		0,2				
Sleep, meditation, relaxation	Control	0-0.5		0,0				
Tissue damage	Goal	0-1		0,2				
Tissue repair		0-1		0,0				
Overload threshold		0-1		0,4				

2.2.3 Model calibration

After setting the ranges of the variables, the following model parameters were calibrated: starting values of the variables, strengths of the relationships and speeds of the relationships. The first estimation the these parameters was done based on the literature described in the previous section in addition to TNO expert judgement.

First of all effect of energy imbalance on BMI change was calibrated. We adopted the results of the Hall model (Wallace 2004) as a benchmark for the model performance. According to the Hall model a reduction in consumption of 100 kcal per day would lead to 1 kg of weight reduction in 3 years. The current model only gives BMI change. For this simulation we chose to calculate weight change from the BMI change for an average person height of 180 cm. The results from the Hall model are compared with the model simulation in Figure 10. It can be observed that the model performs very similar to the Hall model for the range of excess calorie consumption between 500 kcal and 1500 kcal over 3 years.

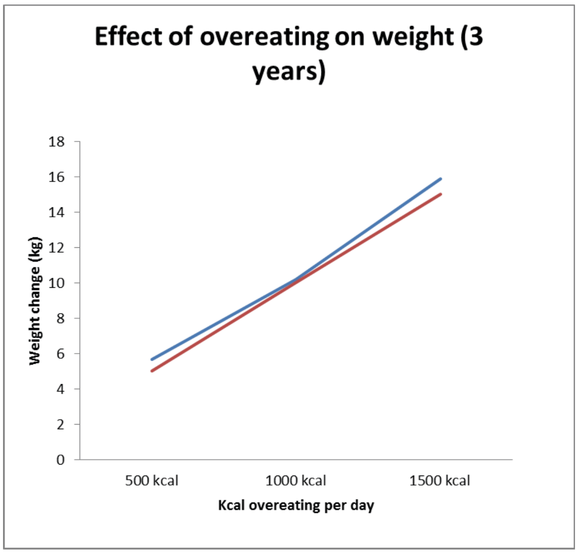


Figure 10. Comparison of the model with the Hall model (blue line represents the diabetes model simulation results and the red line the Hall model).

The next calibration action was based on four papers describing relationships between BMI changes and insulin, glucose, triglycerides, IL-6, TNF-[illegible], IL-18, adiponectin, leptin, CRP, HOMA2-B, HOMA2-S and HOMA2-IR (Esposito 2003, Goldberg 2009, Agueda 2012, Dvorakova 2006). The average change in the parameters was calculated per BMI point change measured in the subjects (Table 3).

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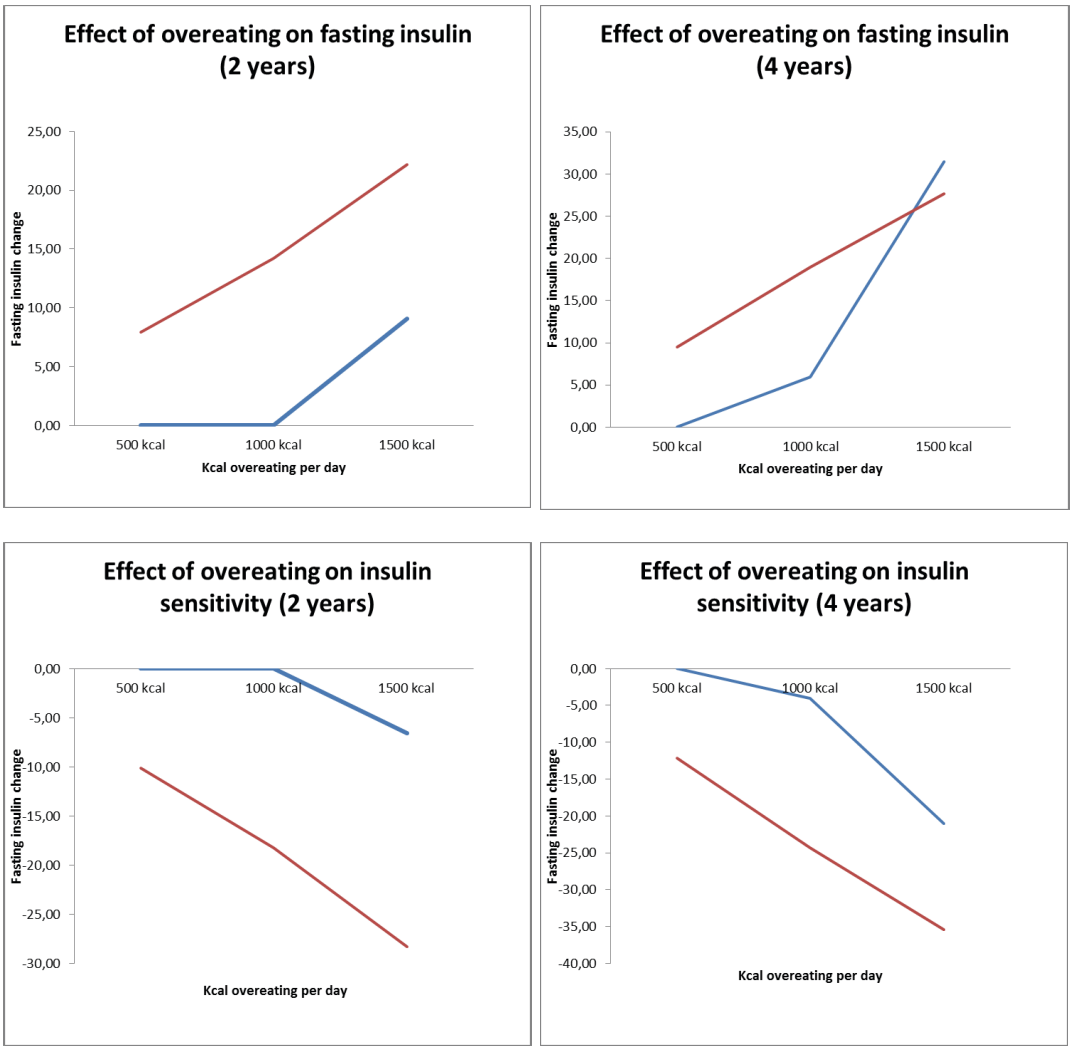
BMI change was then simulated using the model by increasing Food intake pattern to 0.1, 0.2 and 0.3. The effects on the fasting insulin, beta-cell function and insulin sensitivity after 2 and 4 years were extracted from the model simulations and compared to the calculated expected values based on the literature presented in Table 3. In Figure 11 the model results and the estimations from the literature were compared.



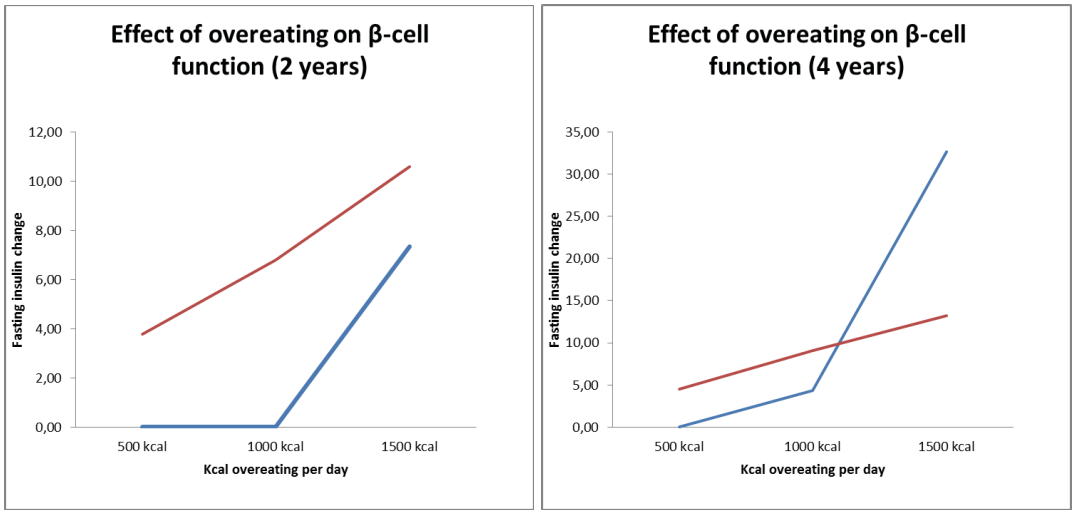


Figure 11. Comparison of model simulations with literature estimates (blue lines represent the model simulation results, the red lines represent the estimations from the literature).

The model simulations for fasting insulin, insulin sensitivity and beta-cell function show the same trends as the literature estimates. However, the effect size differs between the simulations and the literature. This indicates that the model settings for the strengths of some relationships will have to be adjusted. This will be done with the help of datasets collected in WP7. The same holds for the settings of the speeds of certain relationships in the model, since for instance the simulated rate of change in beta-cell function is different from literature findings. However, the literature findings show considerable variation, indicating that the results might be different in different populations. We conclude that for a first calibration, the model seems to perform reasonably well on these variables. After a proper calibration using the data from WP7, it is foreseen to validate the model using data from the Whitehall II cohort.

2.3 Connection between diabetes model and NRC database

The aim of the project is to produce tools that can be used in clinical practice to support patients in managing diabetes. An important step towards this aim is to connect the systems health model with a database containing real patient data. We choose to develop such a connection with the Nutritional Researcher Cohort (NRC) database that is currently running at TNO (http://www.nugo.org/nrc and http://ci.dbnp.org). This database contains data uploaded by hundreds of people mainly measured with Do-It-

Yourself techniques. Additionally, the database can be used to upload other medical data obtained from other sources.

Establishing the connection between the NRC and Marvel entailed the following steps:

- Establishing a web based service for the model
- Developing an API to access the web service
- Developing a user interface to interact with the model

A web service was developed that is able to run Marvel models. A number of functions were made available to upload new models, to set model variables and to receive simulation results. The API for accessing the service currently enables accessing the NRC database to extract calorie intake and calorie expenditure. These values are converted into Marvel variable ranges (between 0 and 1) using the conversion rules specified in Table 2. The values are sent to the model on the web service which returns model simulation results. In addition, a first version of a user interface is developed as shown in Figure 12. Currently this user interface shows 4 main objects of information. In the upper left part of the dashboard, information on population minimum, maximum and average values of weight, calorie intake and calories burned is given. This information is extracted from all the individual datasets in the NRC database. This data is mainly used for development purposes and will be removed from future user interfaces. A second box contains the personal status of the subject logged into the tool. Weight, calorie intake and burned calories averaged over a month is shown. Then to the right of this box are two slide bars that can be used to simulate the effects of changing eating (calorie intake) and exercise (calories burned) behaviour.

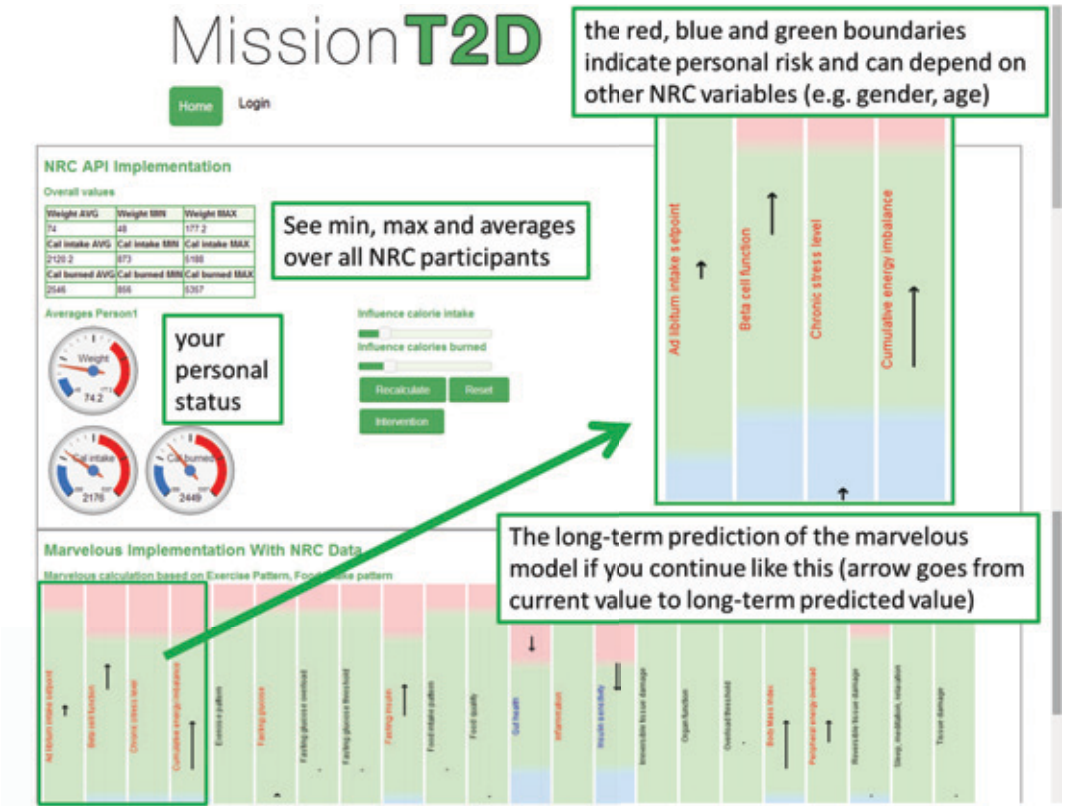


Figure 12. User interface of the MT2D simulation tool connected to the Nutrition Researcher Cohort and database.

The bottom part of the dashboard is used to present the current levels of all the variables present in the diabetes model v1.0 as well as the results of the simulation. Each variable is represented by an individual vertical bar graph. The black arrow represents the variable, the start point of the arrow is the current value while the end point of the arrow is the result of the simulation. The bars are furthermore colour-coded, green meaning good (healthy) while red and blue indicate impaired health zones, the marker being either too hogh or too low, respectively.. .An arrow pointing towards the center of the green zone generally indicates improvement and an arrow pointing away from the center of the green zone a worsening. The sizes of the arrows can be interpreted as relative strengths of the effects. In this way, the user can get immediate feedback on the expected result of a lifestyle change.

Currently, the user can simulate the effects of calorie intake change and calorie burned change over time, based on his or her own weight, calorie intake and consumption levels.

2.4 Future work

In the near future, measured values for fasting glucose, fasting insulin, insulin sensitivity, beta-cell function and inflammation will be implemented in the model. This means that measurements of those variables stored in the NRC database must be extracted from the database and loaded into the model. Then simulations can be performed with this more personalized model. The results can then be translated back into changes in real values of those variables over time. This allows a more personalized prediction of intervention effects and more detailed information about metabolic changes.

Additionally, the model will be calibrated by using data from several datasets collected in WP7.. The aim is to use such a combination of data sets that all the variables in the model are represented in at least one data set. After this extensive calibration step the model will be validated using Whitehall 2 data. The simulation model will then be able to also generate meaningful predictions for different time spans, allowing the user to see expected results of lifestyle changes on the short-, mid-, and long-term.

3 Deliverable Conclusions

A version 1.0 of a high-level aggregation model of diabetes was developed integrating energy metabolism, glucose metabolism, inflammation and other system health variables. This model was programmed in the TNO Marvel software, with all variables scaled between 0 and 1. The model was then quantified by defining ranges for variables and providing formulas to convert real values of BMI, fasting glucose, fasting insulin, insulin resistance, beta-cell function and inflammation to Marvel-values. This allowed a first calibration of the model based on literature data which showed promising model simulation results. Finally, a prototype user interface was developed as well as software (API) to connect the model with a database containing individual data derived from self monitoring devices (i.e., the NRC database). The prototype model can now be applied to simulate interventions based on personalized data collected from portable devices and stored in the NRC database. Future versions of the model and user interface will include the quantification of additional systems health variables, and allow for more accurate predictions after more extensive calibration and validation of the model is done based on data provided in WP7.

4 Appendices

4.1 List of abbreviations used

BMI	Body Mass Index
CRP	C-reactive protein
HOMA	Homeostatic Model Assessment
HPA	Hypothalamic Pituitary Adrenal axis
IL	Interleukin (signalling molecule)
LPS	Lipopolysaccharide (component of pathogen cell walls, signal of danger)
NRC	Nutrition Researcher Cohort
P4	Personalized, preventive, predictive, participatory
T2D	Type 2 Diabetes

4.2 Literature results related to the model

4.2.1 Gut health interactions (Gut health, inflammation and diet)

Key findings:

- LPS (endotoxin) concentration in blood plasma is a common marker for (impaired) gut barrier function.
- The most clear diet effects are those of a high (saturated) fat diet
- Short term effect: high fat meal yield an increase in plasma LPS (e.g. Ghanim et al. Diabetes care 2009 (32): 47% increase of LPS at 3 hours after high fat meal, compared to overnight fasting state). This also leads to some effects in inflammation markers: 57% increase in NF-κB binding, 7% increase in CRP (not significant)
- Short term effect of high-fat meal on inflammation markers stronger in diabetic subjects compared to healthy subjects
- Long term effect of high-fat and “healthy diet” compared to original diet of subjects: 4 weeks of high fat diet lead to a 71% increase of plasma LPS, 4 weeks of “healthy diet” leads to a 31% decreased in plasma LPS (Amar et al. Gastroenterolgy 142, 2012). However, no increase in inflammation observed! Thus, no clue provided that long-term high-fat diet alone can induce inflammation.
- Grouping of healthy men according to endotoxin levels, shows that increased endotoxin levels are associated with high fat in (long-term) diet (Amar et al. The American Journal of Clinical Nutrition 2008). However, no effect on IL-6.
- Mouse data (Cani 2008), shows significantly increased mRNA expression in tissues of some pro-inflammatory markers after either 4 weeks of high fat diet or 4 weeks subcutaneous LPS infusion
- Obese, diabetic and subjects with impaired glucose tolerance display a decreased barrier function (Harte al et al. Diabetes Care 2012 (35)). Note: no indication if obesity/diabetes has any influence on the barrier function.
- Link with stress systems unclear: Taudorf at al. (Clinical and Vaccine Immunology 2007 (14)) shows acute effect of LPS on TNF-alpha but not on plasma cortisol in human. According to Noti et al. (The Faseb Journal 2010 (24)), a single dose of LPS does stimulate glucocorticoids via TNF-alpha (mouse data).
- The complex mechanisms in linking LPS and inflammation are not fully understood. Mechanism such as endotoxin tolerance and endoxin priming (Fu 2012) may contribute to this complexity.
- In short, high fat diets increase fasting plasma LPS levels. There is no conclusive proof that this diet-induced low-grade-endotoxemia causes/increases low-grade inflammation in man. However, mouse data suggest such long-term effects. Note that the 4-weeks effect is different in mice and man. Although this may reflect differences in experimental

conditions (e.g. strengths of stimuli/dietary intervention), this also provides an indication that pro-inflammatory effects of high-fat diet and LPS are much slower in humans compared to mice.

4.2.2 Overweight, insulin sensitivity, inflammation

Key findings:

- Data sets available for
  - Comparisons between groups (e.g. morbidly obese vs healthy control)
  - Lifestyle interventions (change of dietary intake; 6 months - 2 years)
  - Drug effects (e.g. metformin)
- Focus on data from adults (weight 80-90 kg; BMI 30-35) and weight-loss due to lifestyle interventions
- For modeling purposes in this project, this data can be used to calculate change of HOMA2-indices (HOMA2-%S, HOMA2-%B) and inflammation (CRP) with change of body weight or BMI.
- CRP decreases with weight loss (0.09-0.54 mg/l per unit BMI)
- Beta cell function (HOMA2-%B) can either decrease or increase with weight loss (decrease of 5.6 percentage point per unit BMI and increase up to 1.3 percentage point per unit BMI have been reported)
- Insulin sensitivity (HOMA2-%S) increases with weight loss (2.4 – 10.7 percentage point per unit BMI)

4.2.3 Beta cell failure

Key findings:

- The precise mechanisms of beta cell dysfunction are still largely unknown; Individual trajectories for onset of beta cell dysfunction may differ (Kahn 2006, Gastaldelli 2011)
- Chain of events:
  - Decreased insulin sensitivity compensated by increased beta cell activity; this occurs in various cases, incl. obesity, puberty, pregnancy (Kahn et al., Nature 2006)
  - In some cases the demand for additional insulin production to compensate for increased insulin resistance is larger than the capabilities of the beta-cells (this threshold may be individually determined due to genetic predisposition etc.). This results in slightly increasing fasting glucose levels (which may pass the threshold levels for diagnosis of pre-diabetes or even diabetes).
  - Long-term increased (fasting) glucose levels may lead to loss of beta-cell functionality due to mechanisms such as glucose toxicity. This may include reversible “stunning” effects (Ferrannini Cell Metabolism 2010).
- The long-term change in (2-hr postprandial) glucose levels seems to develop in two phases: a slow approximately linear rise and a steeper rise during the period before the diagnosis of diabetes. This period is estimated to be much shorter than 4 years (Mason et al. Diabetes 2007)
- Ferrannini Diabetes 2004 estimate the rise in plasma glucose during the fast onset of diabetes 2-3 mmol/l per 3.25 years → 0.6-0.9 mmol/l/year
- Tabák (Lancet 2009) describes a fitted time course of HOMA2-indices and fasting glucose for a subgroup (“cases”) in the Whitehall II consortium over the 14 years before the diagnosis of type 2 diabetes. This is compared with estimates for another subgroup (“non-cases”) that does not develop diabetes.

4.2.4 Stress Systems

Key findings:

- Focus on increased HPA axis/cortisol levels (although endocrine dysregulation may also act in the opposite direction).
- Increased HPA axis activity leads to increased eating (Dallman 2003).
- Chronic stress has negative effect on immune function (Dhabdar 2009). However, it may still increase low grade inflammation due to suppression of immunoregulatory/inhibitory (anti-inflammatory) mechanisms
- Inflammation activates stress pathways (Kyrou and Tsigos 2009)
- Glucocorticoids in mice inhibited insulin release (Delaunay 1997). In human also associations between cortisol levels and both insulin secretion and insulin sensitivity (Anagnostis 2009 and references therein).

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