MISSION-T2D

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

Work Package 1

Deliverable 1.3

Annual Activity Report – yr2

Document Information

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Abstract (for dissemination)	This deliverable provides an overview (per WPs) of the work performed by the consortium towards the objectives of the project, including achievements and attainment of milestones and deliverables. It also gives information about the project organisation and management procedures and mechanisms.
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1 Activity Report Summary

Participants

no.	Participant organization name	Acronym	Country	WP
1	Consiglio Nazionale delle Ricerche	CNR	IT	WP1, WP6
2	Università di Bologna	UniBO	IT	WP2
3	University of Cambridge	UniCAM	UK	WP3
4	Università degli Studi di Roma "Foro Italico"	UniRM	IT	WP5
5	Toegepast Natuurwetenschappelijk Onderzoek	TNO	NL	WP4,WP7
6	Medisana Space Technologies GMbH	MED	DE	WP8
7	University of Sheffield	USFD	UK	WP5

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2 Project objectives and achievements

In this section we give an overview of the project objectives for the reporting period in question, as included in Annex I to the Grant Agreement. These objectives are summarized herein in order to make this report consistent as a stand-alone document.

The overall progresses of the project’s work packages are now described per WP in the following sub-sections.

2.1 WP1 - Project Management

Detailed information on WP1 actions can be found in Deliverable 1.4. Annual Management & Dissemination Report. The Main Management actions in this first period were:

- Completion of the Reports rquired for the 1st Period.
- Organization of the First Review Meeting in Zeist (add date).
- Setup of the Executive Board and Advisory Board.
- Update of the project website, Intranet and project templates.
- Preparation of Project Brochure.
- Information on financial project reporting tp the Comission and Consortium.

- Preparation of the meeting minutes.
- Scientific reporting as usual:Within each WP and using the template for the annual report.
- Financial reporting: support to partners on admin/financial matters.

Changes to Original Plan:

- Delay in the closing of the 1st Reporting: Various corrections and modifications had to be made to the first submited report, and this ment a delay of a few months in obtaining approval and payment.
- Request of an amendment to the Annex-I that included (among other): Adjusted man months per deliverable, New deliverable in Dissemination, Updated Partner information, change of venues for annual meetings.

2.1.1 Deliverables

Deliverables: Project Deliverables have been prepared by the responsible partners, who have collected the needed information from the participating partners (if any). The Project Coordinator has reviewed them and sent them back to the author(s), who addressed the comments. The final version has been uploaded to the MISSION-T2D Intranet and sent via email to the Project Officer.

2.1.2 Project Networking in all WPs

Partners did attend the general project Meetings and participated in various intra and inter WP meetings. Please see Deliverable D1.4 Management report for the list of project and intra WP meetings.

2.1.3 Use of resources – New Personnel

No major deviation from the planned resources has been reported by any of the WPs. Please see 2nd Period Progress Report – Use of Rescources (due end of April) for detailed description of the personnel and dedication in each team.

2.2 WP2 - Clinical data provision (genetics and aging) and gut microbiota modelling

2.2.1 Scientific Activity

Project Objectives for the period

The work performed was related to Task 2.4 (Validation and refinement of the model in the overall workflow). Metanalysis of available datasets has been carried out.
The differences in gene expression between Healthy and Insulin Resistant or Type 2 Diabetes subjects in three tissues (skeletal muscle, adipose tissue and liver) have been studied.
Dataset of Gut Microbiota composition of old persons have been analysed and modeled according to different ecological models (Neutral model, Modified Chemostat 2D model .

Work Progress and Achievements

We computed a pathway describing metabolic flexibility in skeletal muscle.
We analyzed (ANOVA and pathway analysis) microarray data from public repository of Healthy, Insulin Resistant and Type 2 Diabetes patients, considering gene expression in 3 tissues: skeletal muscle, liver and adipose tissue.

We proposed a new ecological model for the Gut Microbiota Relative Species Abundance distribution, based on a 2D chemostat model, that relax the neutrality assumption of previous works (Volkov et al, 2007).

We computed the CME of the GM RSA model to take into account stochasticity. We obtained the analyticalstationary solution for the feasible cases and simulated the model numerically in the other cases.
We computed the GM RSA of 16S rRNA samples from human gut and assessed that the model works well and is discriminative.
We proposed a summary table describing the effects of diet on GM with specified the bacteria products that could participate to IR and T2D and affect metabolic flexibility.

2.2.2 Deliverables for the WP

UNIBO is involved in WP2 and during this reporting period has performed a series of studies leading to results that are detailed in D2.4: Report on the integration of clinical data modelling to the overall workflow. In particular, the main scientific results obtained in this deliverable are listed below:

- Gene expression data of Healthy, IR and T2D patients were obtained from the GEO database. These were analyzed with a one way ANOVA for the comparison between healthy and unhealthy, and with a 2 ways ANOVA with interaction to investigate metabolic flexibility. This last result was plotted on a metabolic flexibility pathway obtained integrating literature information and KEGG pathways.
- We found out two important genes that were significantly different in healthy and unhealthy: PIK3 in muscle (a key point in the metabolic flexibility pathway) and TCF7 in liver.
- Pathway analysis (Fisher's test) identified many differences between Healthy, IR and T2D, including different steps of the metabolic pathway.
- The GM RSA model was implemented in Python and simulated with the Gillespie algorithm.
- GM data from Claesson et al showed that the model works well and can be discriminative.
- We assessed the principal bacteria affected by diet and their main products, with particular attention to Short-Chain Fatty Acids, that notoriously have a great impact on the metabolic and immune systems, as well as on metabolic flexibility.

2.3 WP3 - Stress induced inflammation onset modeling

2.3.1 Scientific Activity

In this reporting period the activity in WP3 centered on task 3.2 to 3.3. Several deliverables due on month 18 show the progress in this WP.

WP3 has assisted WP6 in validating the integrated model workflow and took care of all aspects related to the stress-induced model developed in Task 3.2.

Main tasks developed in this WP:

Task 3.1 Data provision, statistical inference from nutrition, genetics, lifestyle, and environment

Task 3.2 Analysis of gene copy number, SNPs and other omics

Task 3.3 Inflammation onset modelling: developing multi-scale partially observed Markov process models

D3.2 Applying the approach to patient network at molecular and whole body levels (PM18)

D3.3 Applying the approach to adjust for parameter discrepancy at the interfaces between levels (PM18)

D3.4 Partially observed Markov process models of inflammation and nutritional and lifestyle aspect that have impact on T2D and inflammation (PM18)

D3.5 Report on the integration of stress induced inflammation modelling to the overall workflow (PM24)

2.4 WP4 - Metabolic data provision and modeling of aggregated metabolic and inflammatory processes

2.4.1 Scientific Activity

We participated to the writing of D6.2 (our deliverable), D5.3 through active discussion with TNO to define the model requirements, D7.2 through discussion on data acquisition.

Three milestones for this reporting period:

- MS3 Models (PM18) – all models (almost)ready for integration
- MS4 Integration first prototype (PM20) – first running prototype
- MS5 Integration (PM24) – full integration ready to run

Work Progress and Achievements-Task 4.3

Task 4.3 – The high-level aggregation model of the interaction between glucose metabolism and chronic inflammation, as well as other system health variables such as stress and gut health, has been further developed. To view the model and run simulations the Marvel Viewer tool has been made available to the Consortium as well.

This model was programmed in the TNO Marvel software, with all variables scaled between 0 and 1. The model was 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-type values. This allowed a first calibration of the model based on literature data which showed promising model simulation results.

To prepare for use of the model in P4 health applications, the model was connected with the Nutrition Researcher Cohort, an online resource that integrates personal health data derived from self monitoring devices as e.g. from partner Medisana.
This involved:

- 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 dashboard was created that allows the user to interactively see the predicted effects of lifestyle changes over a selected time period. Currently, the user can simulate the effects of calorie intake change and physical exercise change over time, taking his or her own weight, calorie intake and exercise levels as a starting point

Work Progress and Achievements-Task 4.4

Task 4.4 - Timescales and the operational interactions of the high- and lower aggregation models of MISSION-T2D were reassessed. As the models have very different time scales, they will run separately from a computational point of view but the metabolic-immune system simulator, once calibrated, can be used to generate appropriate subgroup-specific settings of the interaction speeds and –strengths in the MF-HOMA model.

In close cooperation of partners TNO and CNR, literature on gastric emptying and macronutrient absorption was studied and interpreted, and appropriate mathematical equations to model the intake and intestinal absorption of the three main macronutrients: carbohydrate, protein and fat were developed to be included in the detailed metabolic-immune system simulator (E-MF model) of MISSION-T2D.
The MISSION-T2D high level aggregation model was integrated into an existing Dutch eHealth coaching tool platform, PatientCoach. The MISSION-T2D predictive functionality added to PatientCoach allows the management of patient expectations by health care providers concerning dieting and exercising.

Understanding was gained on the extent to which the current high level aggregation model can be personalized to (pre)diabetes subtypes. Possibilities for the model run in isolation are limited, but will improve when the model is coupled to the lower aggregation model

Model simulations resulted in the proposal of 2 composite risk indicators that combine measures of insulin sensitivity, beta cell function and inflammation. One can provide an early sign of beta cell compensation, the other can indicate a failure of the pancreas to compensate for rising insulin resistance

There have been no major deviation from the planned resources, deliverables and milestones.

2.4.2 Deliverables and Milestones

Deliverable 4.2 “Report on MF-HOMA model (weeks-months’ time scale)” was submitted Aug 2014

Deliverable 4.3 “Report on Integration of Dynamic and High level aggregation models in overall workflow” is currently being finalized and will be submitted before end of February 2015.

Milestone M3 (Month 18): “ Models”: WP4 has contributed the Kim model which includes the interaction of metabolism and physical activity, and contributed knowledge of interaction networks between metabolism and inflammation to be considered for inclusion in the simulator.

Milestone M4 (Month 20):”Integration first prototype”. WP4 has made a first version of the high aggregation-level model available to the Consortium and assisted with the implementation of the Kim model

Milestone M5 (Month 24): ”Integration” WP4 has integrated the high aggregation-level model into an existing Dutch e-Health application, contributed to discussions on the operational interaction of the high- and low aggregation level models and assisted in integrating appropriate equations for macronutrient intake and absorption in the simulator.

2.5 WP5 - Modelling the effects of physical activity in T2D

2.5.1 Scientific Activity

Task 5.3: Integration with the overall workflow

This phase of the project aimed at providing model estimates of the effects of physical activity accounting for simulated periods ranging from days to years and at integrating them with the estimates coming from other WPs. In this phase the feedbacks from WP4/WP6 will be used for corrections and upgrades of the model in order to ameliorate models and parameters.

Work Progress and Achievements

- A multi-scale validated computational model of fuel-homeostasis during exercise (Kim et al. 2007) was assumed as a basis for the development of the MISSION-T2D overall model. For a complete description of the effects of physical activity on T2D, some new relationships were implemented and included in WP5 model.

There have been no major deviation from the planned resources, deliverables and milestones.

2.5.2 Deliverables and Milestones

D5.2 Report on the integration of the physical activity module in the overall workflow (PM18)

A description of the model proposed by Kim et al. (Kim et al. 2007), chosen as a starting point for the development of the overall MISSION-T2D model, is given. Since the Kim model is not straightaway suited for what concerns the development of the physical activity (WP5) part of the MISSION-T2D model, adequate modifications of the model equations parameters value have been hypothesized and new relationships have been added. As reported in D5.1, steps per day and heart rate were selected in Task 1 as input to the WP5 model. On this basis, for integration purpose, a correspondence between WP5 inputs (steps per day and heart rate) and the Kim model input (work rate) has been established.

D5.3 Report on validation and refinement of the physical activity module in the overall workflow (PM24)

This document is supposed to include the results of Task 5.4 (Validation and refinement of the model in the overall workflow). However, as reported in the DoW, Task 5.4 will start at PM 24 and will end at PM 36. Due to this error in reporting the date of delivery for the present document (PM24 in the DoW) with respect to the actual content of the deliverable, i.e., validation and refinement, we are unable to include the planned content of the deliverable. We have however decided to use this opportunity to present an update about the activities carried out in Task 5.3 (Integration in the overall workflow) and a description of the activities that will be carried out in Task 5.4, showing also an important aspect concerning the integration with another USFD project. The final version of this Deliverable 5.3 will be produced at the end of Task 5.4 (PM 36), as per intended original schedule.

Milestones

M3 Models (PM18): Models defined and available
M4 Integration first prototype (PM20) : Prototype of the overall integrated simulator available
M5 Integration (PM24): Overall integrated simulator available

2.6 WP6 - Immune system and inflammation modelling and workflow integration

2.6.1 Scientific Activity

Project Objectives for the period

Implementation of all sub-models provided by the project's partners in ANSI/C language (numerical integrator, debugging, parameter determination, etc.) . Update of the inflammation/immune agent-based model to account for a detailed description of T-helper differentiation (introducing Treg and Th17 phenotypes on top of Th1 / Th2). Assisting the definition and the development of the graphical user interface of the exploitation outcome (i.e., the mobile app) by partner MED

Work Progress and Achievements

- Update of the inflammation/immune agent-based model to account for a detailed description of T-helper differentiation (introducing Treg and Th17 phenotypes on top of Th1 / Th2)

- Implementation of the metabolic model in ANSI/C language using the CVODE numerical solver libraries
- Modification of the metabolic model to account for out-of-PA periods (the original model was hardcoded in terms of controls and parameters to work in regimens of physical activity for very short time horizons, i.e., an hour, whereas we need to follow the metabolism 24h/day): we removed few assumptions, modified the insulin-glucagon controller and re-tuned few parameters
- Integration of the metabolic model to the inflammation model in terms of computer code.
- Development of the C version of the Matlab code for food absorption developed by partner TNO in WP4
- Development of the C version of the beta-cell model originally developed in Matlab by partner UniCAM in WP3
- Development of the C version of the physical activity model originally developed in Matlab by partner USFD/UniRM in WP5
- Drive the development of the graphical user interface of the exploitation outcome (i.e., the mobile app) by partner MED: defining input and output, usability, etc.

There have been no major deviation from the planned resources, deliverables and milestones.

Deliverables and Milestones

We participated to the writing of D6.2 (our deliverable), D5.3 through active discussion with TNO to define the model requirements, D7.2 through discussion on data acquisition.

Three milestones for this reporting period:

MS3 Models (PM18) – all models (almost)ready for integration
MS4 Integration first prototype (PM20) – first running prototype
MS5 Integration (PM24) – full integration ready to run

2.7 WP7 - Clinical guidance, results analysis, T2D risk assessment and validation

2.7.1 Scientific Activity

Task 7.1: Provide experimental data from type 2 (pre)diabetes patient stress response curves relevant for model validation (Month 13 - 18)

Task 7.2: Provide experimental data from type 2 (pre)diabetes intervention studies with various sub phenotypes (Month 13 - 18)

Task 7.3: Provide experimental data from a series type 2 (pre)diabetes patient prior and after diagnosis and health care interventions based on the MISSION-T2D models (Month 13 - 24)

- Work Progress and Achievements

Tasks 7.1 : A total of 25 challenge response datasets were identified. Challenges are diverse and include OGTT, OLTT, MTT, exercise test, inflammatory stimulation, and mental stress. Subject groups include healthy, lean, metabolic syndrome, obese, cardiovascular disease, and various (pre) diabetic groups. Key characteristics of the datasets were described. It is expected that this data can provide a sufficiently diverse input to calibrate and validate especially the minute-to-day time scale MISSION-T2D models in various subgroups.

- Task 7.2: A total of 23 intervention study datasets were identified. Interventions are diverse and include high fat diets, low-calorie diets, diets with different fatty acid supplements (i.e. with different pro- or anti-inflammatory effects), different probiotic supplements, alcohol and lifestyle. Subject groups include healthy, lean, metabolic syndrome, obese, cardiovascular disease, and various (pre) diabetic groups. It is expected that this data can provide a sufficiently diverse input to calibrate and validate especially the high aggregation level MISSION-T2D models at the time scale of weeks to months (or longer), for various subgroups.

- Activities (contacting data owners, writing data application requests including data analysis project proposals to obtain access to data identified in Tasks 7.1 and 7.2 available for use by MISSION-T2D were launched

Task 7.3 :

Synopses of the TNO P4 healthcare innovation studies were supplied. Significant delays are experienced in establishing this P4 program. Alternative data sources for validation were considered and data application request were prepared and filed. Most importantly, data for 2 phases of the Whitehall II cohort was received in February 2015 for validation of the MISSION-T2D models.

Further external study data use requests thus far received very limited response.

The most relevant of the TNO datasets identified in Tasks 7.1 and 7.2 were selected and a pre-assessment of this data was performed.

Information on additional datasets from partners Univ Bologna, Univ Sheffield, Medisana and TNO was supplied.

A first pre-assessment of anonymized self-monitoring data by partner Medisana of their VitaDockOnline users was performed and revealed a rich data source that may have considerable potential, both for model validation and for user health support.

There have been no major deviation from the planned resources, deliverables and milestones.

2.7.2 Deliverables and Milestones

- Deliverable 7.1. “Report on data provision of the P4 dataset” was submitted in August 2014.
- Deliverable 7.2. “Report on data analysis” is currently being finalized and will be submitted end of February, 2015

2.8 WP8 Dissemination and Exploitation

Detailed information on dissemination actions can be found in Deliverable 1.4. Annual Management & Dissemination Report. The Main Management actions in this first period were:

2.8.1 Dissemination tasks

Main tasks in this period:

- Task 8.3 Specifications of exploitable results.
- Task 8.4 Specifications for the mobile apps

Dissemination activities in general, that to this stage focus on scientific publications and communication (oral, posters, etc.) at congresses. The web site and intranet have updated, and a project flyer has been prepared. Each Partner has distributed this in their local organised events, such as workshop, seminars, to visitors etc.

2.8.2 Deliverables and Milestones

The deliverables due in this 2nd period were:

- D8.3 Report on the specifications of the mobile apps (PM24)
- D8.4 Intermediate Exploitation Report (PM24)

This D8.4 is a new deliverable, part of the few amendment changes to the DoW requested after the first review meeting by the reviewer’s panel.

2.8.3 Project Dissemination Objectives during the period

Main objective of the period has been to produce the requested Deliverables, publish results and attend conferences in the field.

2.9 Deliverables and Milestones

Project Deliverables for the period

DD	Title	WP	Nature	Diss	Month
D2.3	Report on database processing	WP2	R	PU	15
D3.2	Applying the approach to patient network at molecular and whole body levels	WP3	R	PU	18
D3.3	Applying the approach to adjust for parameter discrepancy at the interfaces between levels	WP3	R	PU	18
D3.4	Partially observed Markov process models of inflammation and nutritional and lifestyle aspect that have impact on T2D and inflammation	WP3	R	PU	18
D4.2	Report on MF-HOMA model (weeks-months time scale)	WP4	R	PU	18
D5.2	Report on the integration of the physical activity module in the overall workflow	WP5	R	CO	18
D7.1	Report on data provision of the P4 dataset	WP7	R	RE	18
D1.3	Annual Activity Report – yr 2	WP1	R	PU	24
D1.4	Annual Management Report – yr 2	WP1	R	CO	24
D2.4	Report on the integration of clinical data model to the overall workflow	WP2	R	PU	24
D3.5	Report on the integration of stress induced inflammation model to the overall workflow	WP3	R	PU	24
D4.3	Report on the integration of metabolic and inflammatory processes model to the overall workflow	WP4	R	CO	24
D5.3	Report on validation and refinement of the physical activity module in the overall workflow	WP5	R	PU	24
D6.2	Report on the integration of the overall workflow	WP6	R, P	PU	24
D7.2	Report on data analysis	WP7	R	RE	24
D8.3	Report on the specifications of the mobile apps	WP8	R	CO	24
D8.4	Intermediate Exploitation report	WP8	R	CO	24

Project Milestones for the period

Milestone number	Milestone name	Work package(s) involved	Expected date	Means of verification
M3	Models	WP2, WP3, WP4, WP5, WP6	Month 18	Models defined and available
M4	Integration first prototype	WP2, WP3, WP4, WP5, WP6	Month 20	Prototype of the overall integrated simulator available
M5	Integration	WP2, WP3, WP4, WP5, WP6	Month 24	Overall integrated simulator available

MISSION-T2D

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

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