MISSION-T2D

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

Work Package 1

Deliverable 1.5

Annual Activity Report – yr3

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 during the 3rd period. 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 main activity of this period were

- Finalize the integrated model simulation tool
- Validate the integrated model simulation tool using TNO-provided data and other literature source data
- Produce the User Scenarios Database to be handled to partner MED for the Mobile App
- Devise and implement the Mobile App
- Release the App and collect user preferences and feedbacks.

These activities have been successfully achieved as planned in the Annex I and described in the various deliverables provided.

3 WP1 - Project Management

The activity reported in D1.6 (Annual Management Report) is based on the management work performed in months 24-36.

The tasks in this period have been the following:

- Task 1.3 Administrative and financial management.

The Project Management Team has chaired inter-WP meetings either face-to-face or videoconferences and for each meeting has created a document with the minutes and follow up the agreed decisions. Support by the project management was permanently available, searching to minimize the administrative burden and leaving a high degree of autonomy to each partner to perform his or her assigned tasks, under the coordination of the Scientific Coordinator.

The Main Management actions in this period were:

- ***Implementation of corrective actions following the Technical Review Report dated 20.07.2017***
- Organisation of the 2nd Project Meeting in Rome in June 2015
- Completion of the Reports of 3rd Period
- Request of Amendment to the Annex I – Nov. 2015
- Completion of the FormCs, including adjustments
- Reception and transfer of the 2nd payment by the EC
- Organization of the 2nd Review Meeting in Brussels
- Setup of the Executive Board and Advisory Board

- Update of the project website, Intranet and project templates
- Preparation of various dissemination activities
- Information on financial project reporting to the Consortium
- Preparation of the meeting minutes
- Scientific reporting using the template for the annual report
- Financial reporting: support to partners on admin/financial matters.

Changes to the original plan described in Annex I:

- Delay in the closing of the 2nd Financial Reporting: various corrections and modifications had to be made to a number of Form Cs, including adjustment to Form Cs as a consequence of audit results.
- The Commission requested again to delay the period payment. Once received the transfer of the corresponding amounts to each partner was done within the legal time. The distribution followed the proportions of the justified costs to the period.

3.1 Deliverables

The present Annual Activity Report D1.5 available as Periodic Report includes the information on 3rd project period. Its content will be significantly reduced compared to previous activity reports, as the consortium simultaneously generates the Project FINAL Report.

3.2 Project Networking in all WPs

Partners did attend the scientific and management project meetings (organised in June 2015 in Rome and in October 2015 in Cambridge) and participated to various intra and inter WP meetings. Please see Deliverable D1.6 Management report for the list of project and intra WP meetings.

3.3 Use of resources – New Personnel

No major deviation from the planned resources has been reported to date by any of the WPs. Please see Project Final Report for detailed description of the personnel and dedication for each team.

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

4.1 Scientific Activity

The work performed on the search of inflammatory cytokines capable to impact the balance of

metabolic flexibility has been described in Deliverable D2.5. Moreover, partner UniBO has provided expertise and consultancy to partner CNR for the whole model validation activity.

4.2 Deliverables and Milestones

D2.5 regards the activities of identification of the main inflammatory mediators and regulators that interact with metabolic flexibility and homeostasis to provide a detailed framework of the most relevant molecular players and cell/organs interactions that can help in interpreting and classifying the results of the simulations that are reported in D6.3.

5 WP3 - Stress induced inflammation onset modeling

5.1 Scientific Activity

UniCAM has performed research on: 1) development of multi omic metabolic models of gut microbiota bacteria. The work has considered beneficial and pathogenic bacteria (pre- and post-infection metabolism). This provides clues on the effects of the bacteria on gut environment and the interaction with the immune system in the gut. A multi omic metabolic model for pathogenic gut bacteria (clostridium difficile) has been developed. The methodology is novel as it integrates different information (metabolic map and transcriptome); 2) Machine learning methods of patients versus normal autoimmune, diabetes and arthritis-related diseases data has been employed to identify key biomarkers occurring during infectious diseases.

5.2 Deliverables and Milestones

The previous deliverable D3.5 describes the work done in the second period pertaining the ODE system model for diabetes incorporating inflammation. This model has been partly embedded into the overall MISSION-T2D workflow and therefore validated altogether as described in deliverable D6.3.

In deliverable D3.6 UniCAM presents a new methodology for the analysis of signaling factors in T2D and autoimmune diseases. The methodology integrates epigenetic and transcriptomic data and is able to identify new disease associated genes. For both aspects publications have been submitted.

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

6.1 Scientific Activity

In WP4 the aim was to integrate mechanisms involved in nutritional metabolic responses, with immune system response mechanisms studied in WP2 and WP3 into the multiscale immune system simulator, or overall MISSION-T2D simulation architecture. The objectives leading to this goal were:

- Data provision for a model of the dynamics of the interactions between metabolism, inflammation and physical activity;
- Derivation of markers for glucose/inflammation homeostatic capacity from this dynamic model that can be integrated in a diabetes prevention ands reduction lifestyle coaching program;
- Development of a high-level aggregation model of the interaction between glucose metabolism and chronic inflammation that can be used for metaflammation diagnostics and risk prediction;
- Integration of the dynamic and high-level aggregation models in the overall workflow;
- Validation and refinement of the models in the overall workflow.

In WP4, datasets suited to calibrate the MISSION-T2D simulator describing the minute-to-day dynamics of the interactions between metabolism, inflammation and physical activity, were identified and the data was made available to the consortium. This demonstrate the availability of appropriate data for model validation as requested in the 2nd Technical Review Report compiled by the Expert Panel of Reviewers in date 20.07.2015.

Originally it was planned to build a multiscale model by interlinking models at two different distinct timescales: minute-to-day and weeks-to-months. After initial developments, the operational interactions of the high and lower aggregation models of MISSION-T2D were reassessed. As the models have very different time scales, it was decided that they would run separately from a computational point of view but the metabolic-immune system simulator (the model describing minute-to-day dynamics), once calibrated, can be used to generate appropriate subgroup-specific settings of the interaction speeds and strengths in the high-level aggregation model. The latter is called the MT2D-Marvel model. This model is directly derived from a model developed in TNO's internal research program in the years prior to MISSION-T2D, i.e., representing TNO background.

The model of Kim et al. (Kim, J., G.M. Saidel, and M.E. Cabrera. Multi-scale computational model of fuel homeostasis during exercise: effect of hormonal control. Ann. Biomed. Eng. 35:69-90, 2007) was selected as the best suited computational model of metabolism to be interlinked with the agent-based inflammation model available at partner CNR (WP6) for integration in the metabolic-immune system simulator. The corresponding software code was implemented in close cooperation between TNO and CNR. The major points of interaction between metabolism and inflammation were identified for incorporation into the MISSION-T2D simulator. Since the Kim et al. model had been

developed to only describe the dynamics of metabolic changes following physical exercise, the model was extended and adapted by TNO and CNR to also include the metabolic dynamics associated with nutrient input following a meal. This required analysis of the literature on gastric emptying and macronutrient absorption as well as the formulation of appropriate mathematical equations and software code to model the intake and intestinal absorption of the three main macronutrients. Macronutrients accounted for are: carbohydrate, protein and fat. Using the data supplied in WP4 as well as in WP7 (see below), TNO and CNR jointly calibrated and validated the integrated model. As the main outcome, the metabolic model embedded in the metabolic-immune system simulator is capable to successfully simulate multi-organ metabolism dynamics that result from any arbitrary sequence of periods with arbitrary intensity and duration of food intake and exercise.

The MT2D-Marvel model of diabetes development is based on causal loop diagrams at a very high aggregation level and integrates mechanisms across relevant domains including body weight dynamics, glucose/insulin dynamics, inflammation, gut health, and mental stress. The model integrates qualitative and semi-quantitative information and expert knowledge. The model is able to simulate the development of type-2 diabetes following different food intake profiles, and the modulation of disease development induced by physical activity and mental stress-relieving lifestyles over a period of 3 years. In WP4, this model was calibrated based on literature data as well as on data from the Whitehall II cohort made available to the MISSION-T2D Consortium as result of work in WP7. The calibration indicated that the model can be personalized to (pre)diabetes subtypes mainly based on different levels of BMI and fasting glucose.

Validation of the MT2D-Marvel model based on the available Whitehall II cohort data is still ongoing. The validation required simplification of the model to fit the data availability. Initial model subdomain analyses gave satisfactory results but at the time of writing this report, challenges for overall validation remain.

MT2D-Marvel model simulations resulted in the proposal of 2 composite risk indicators that combine measures of insulin sensitivity, beta-cell function and inflammation. The first provides an early sign of beta-cell compensation; the second can indicate a failure of the pancreas to compensate for rising insulin resistance. Taken together these fundamental phenomena form the basis of the high-level aggregation model and are incorporated in the overall MISSION-T2D simulator. This latter answer the Expert Review request (Technical Review Report dated 20.07.2015) of providing evidence of cross-fertilization of the two models developed within the project period on different levels of details.

To prepare for use of the MT2D-Marvel model in personal healthcare 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 (MED).

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;
- Creating a dashboard 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.

Preparing also for use in medical care, the MT2D-Marvel 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.

6.2 Deliverables and Milestones

Deliverable D4.4 describes the work done in Task 4.5 Validation and refinement of the models in the overall workflow.

In close cooperation of partners TNO and CNR, the predictions of the lower aggregation metabolic model embedded in the overall workflow were assessed by comparing with datasets collected throughout the project in WP7. As a consequence, the low level metabolic model was refined especially to correctly model the action of insulin on metabolic pathway activities across different tissues so as to yield realistic simulated time profiles of extracellular metabolites during feeding.

The MT2D-Marvel model (low level of detail, month - 6 year time scale) was simplified and refined based on the available Whitehall II cohort data. Initial model subdomain analyses gave satisfactory results but challenges for overall validation remain.

Concluding, the metabolic model embedded in the MISSION-T2D simulator (high level of detail, 1 minute - 1 year time scale) was refined and partially validated and as a result can successfully simulate multi-organ metabolism dynamics for various lifestyle scenarios differing in food intake and exercise frequency and -intensity.

MS6 Validation has been achieved in strict collaboration with partner CNR and UniRM as described in D6.3 “Report on the validation of the computational model and refinement of the integrated model”.

7 WP5 - Modelling the effects of physical activity in T2D

7.1 Scientific Activity

Task 5.4 Validation and refinement of the model in the overall workflow: For the validation of physical activity effects on whole body metabolism we referred to three different studies. In these studies different exercise protocols in terms of duration and intensity were considered. Moreover, the considered subjects have different physical fitness status (e.g., trained or untrained). The validation of physical activity effects on fat mass increase/decrease and on variation of fasting glucose and insulin was also performed. Results suggested that the refined version of physical activity contribution to MISSION-T2D model is able to capture with good precision the metabolic changes occurring during and after exercise. Precision is higher when an untrained subject is simulated, with respect to a trained subject. Weight change in response to a physical activity protocol seems to be optimally described.

Task 5.5 implementation of the physical activity measurement in the Mobile App: Number of steps walked per day and heart rate were identified as the most appropriate inputs to monitor physical activity within WP5 of MISSION-T2D project. Moreover, algorithms and procedures specific for the monitoring of T2D patients have been defined as planned in Task 5.5 of MISSION-T2D project.

7.2 Deliverables and Milestones

D5.3 includes the results of Task 5.4 (Validation and refinement of the model in the overall workflow). Three different data sets were considered to validate the hormonal, metabolic and inflammatory response of the MISSION-T2D simulator to an exercise session. Moreover, the validation of the effect of lifestyle intervention including physical activity on the fat-mass, body weight reduction and fasting glucose change was performed.

D5.4 includes the results of Task 5.5 (Implementation of the physical activity measurement in the Mobile App). The use of smartphones or similar devices for the assessment of physical activity is one of the hot-topics in human movement analysis. Various apps are available that allow, e.g., to count the number of steps walked per day using inertial sensors and to register the heart rate. Interactive apps using pedometers and smart phones have also been proposed. However, since the computations required determining an individual's risk of developing T2D using MISSION-T2D model cannot be run in real time on a mobile device, the User Scenarios Database has been constructed. In other words, the implementation of the MISSION-T2D results in the mobile application has been performed by defining a limited number of input consisting of number and intensity of physical activity sessions. An extensive amount of simulations on appropriate hardware has been run by partner CNR. The resulting data has been collected in a lookup table, which will be

consulted upon the user request in the mobile app developed by partner MED (WP8). However, the ability of MISSION-T2D model to reproduce an output similar to that provided by a physical activity monitor was tested against data of hormonal and metabolic responses of trained and untrained subjects to an exercise in which the intensity is varied in a realistic manner. The results support the consideration that MISSION-T2D model is able to capture with good precision the time course of metabolites and hormones of a young untrained subject performing an intensity-varying exercise. According to these results, it can be concluded that the model is satisfactorily representing the effects of physical activity for the context at hand. In addition, it is ready to represent the physical activity input coming from a physical activity monitor, which might be useful for future applications.

8 WP6 - Immune system and inflammation modelling and workflow integration

8.1 Scientific Activity

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.

A parameter scanning procedure (sensitivity analysis) has been performed to understand the dependence of important output variables such as body mass index (BMI) and fasting glucose (or glucose base level, Gbl). This is described in D6.3.

Set the model parameters in a way to be able to reproduce (qualitatively but also quantitatively) real data coming from cohort studies. This data has been either identified and extracted from literature or provided by partner TNO. This phase constitute the validation phase described in D6.3. The whole validation work has been conducted by partner CNR (WP6), in close collaboration with the other partners responsible for the various components. In particular, partners CNR, UniRM and TNO have frequently interacted in this task.

Perform a large set of simulations in order to fill the User Scenarios Database as described in D6.4.

8.2 Deliverables and Milestones

Deliverable D6.3 describes the work performed to set the model parameters in a way to be able to reproduce (qualitatively but also quantitatively) real data coming from cohort studies. This data has been either identified and extracted from literature or provided by partner TNO as described in the

previous deliverable D7.1 and D7.2 of WP7.

A parameter scanning procedure (sensitivity analysis) has been performed to understand the dependence of important output variables such as body mass index (BMI) and fasting glucose (or glucose base level, Gbl).

D6.4 describes the overall model and the way it has been used to construct the User Scenarios Database that has been given to partner MED in order to assemble the mobile app.

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

9.1 Scientific Activity

In WP7 the aim was to provide experimental data from actual healthcare treatment of T2D patients based on systems biology analysis of their metabolic / inflammatory status related to the many processes involved in maintaining optimal “phenotypic flexibility”. It was expected that this data would become available from a program on health care innovation in metabolic diseases initiated by TNO that would apply a systems medicine approach to optimize “phenotypic flexibility” in (pre)diabetic patients.

The objectives of WP7 were:

- Provide experimental data from type 2 (pre)diabetes patient stress response curves relevant for model validation;
- Provide experimental data from type 2 (pre)diabetes intervention studies with various sub-phenotypes;
- Provide experimental data from a series of type 2 (pre)diabetes patients prior and after diagnosis and healthcare interventions based on the MISSION-T2D models;
- Assist the modeling WPs in preprocessing the experimental data to “model-ready” parameters.

In WP7, the observed behavior of the minute-to-day model dynamics was made available to the consortium and used during the validation phase in assessing the MISSION-T2D integrated model simulation correctness (as suggested by the Expert Panel of Reviewers in the 2nd Technical Review Report compiled dated 20.07.2015). Also, the validation phase has required the collaboration of partners CNR, TNO, UniRM/USFD, UniBO and UniCAM; this is demonstrated by the tight interaction pattern of communication among teams as reported in the Annual Management Report deliverable D1.6.

9.2 Deliverables and Milestones

Deliverable D7.3 reports on Task 7.4: Assist the modeling WPs in preprocessing the experimental data to “model-ready” parameters.

A status update on progress of the TNO P4 Health studies and on data availability from other studies identified in Tasks 7.1 - 7.3 is given. Data use requests for additional datasets for validation of the MISSION- T2D models were filed and access to several additional datasets was granted. Data were pre-processed and partially stored in the phenotype database dbNP (http://www.dbnp.org) for easy retrieval by partners. The procedure for dbNP access and data download is described. Data preparation of the Whitehall II cohort data transferred to MISSION-T2D partners was performed and is described.

The milestone for this reporting period:

- MS6 Validation (PM38)

10 WP8 - Dissemination and Exploitation

Detailed information on dissemination actions can be found in Deliverable 1.6. Annual Management Report.

10.1 Dissemination and exploitation activity

Main tasks in this period:

- Task 8.1 Dissemination
- Task 8.5 Implementation of the *physician assistant app*
- Task 8.6 Implementation of the *personal coach app*

Partners of the MISSION-T2D consortium, namely UniCAM and CNR, have organised the Workshop Modelling Metabolic Health (MMH16, http://www.mission-t2d.eu/MISSION-T2D/news/mmh15.html) in Cambridge, UK, gathering international experts on gut microbiome inflammation and type 2 diabetes. Two advisory committee members (Prof. Laubenbacher and Celada) have participated as invited speakers to the workshop. Besides that, they have actively participated to the project internal meeting, which took place in parallel during the workshop days. MISSION-T2D had a strong visibility among other projects in the field and was further divulged in an

article published on The Lancet journal.

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 locally organised events, such as workshop, seminars, to visitors, etc..

A preliminary summary of the users' responses regarding the MISSION-T2D feature in the mobile application released in May 2016 on Online App stores (Apple Store for iOS and Google Play for Android) reveals a significant interest in the effects of a healthy diet and physical activity on the risk of developing Type 2 Diabetes. This is described in D8.7. Note that as mentioned in D8.6 the two tasks Task 8.5 and Task 8.6 have been combined in one activity. Likewise, the mobile apps originally planned (the personal coach and the physician assistance) have been eventually united in one single software feature implemented into the Medisana's VitaDock+ app. This is described in D8.6.

As already mentioned, the exploitation activity consisted in

- The Mobile App itself
- A user survey.

In particular, the user survey, consisting in a series of questions asked upon completing the MISSION-T2D risk calculation in the VitaDock+ mobile app, was meant to gather feedback and to provide it to the project partners to improve the overall application quality and to offer a better experience to the users.

The resulting answers (D8.6), feedbacks and general usage statistics are provided *to project partners in an anonymised form* for further analysis and improvement of data as well as the overall quality of the service. A preliminary and partial analysis provide evidence of a positive impact at least among the VitaDock+ Medisana users and constitute a strong incentive to further develop the service as described in D8.6.

This addresses the Expert Panel of Reviewers request (see 2nd Technical Review Report dated 20.07.2015).

10.2 Deliverables and Milestones

Deliverable D8.6 reports the final version of the mobile app as the project's main exploitable results. The mobile application is meant to provide the end users with a mean to compute their risk of developing T2D on the basis of personal anthropometric data, nutritional habits and physical activity patterns. It is an update of D8.5 and expands its content by showing the latest graphical user interface and general user experience as well as other details about the disclaimer and user

questionnaire.

Deliverable D8.7 is the “final” exploitation report, following the intermediate exploitation report D8.4 (delivered on PM24). D8.7 accounts for the updated integration with the T2D-MISSION model results, and also with the state of the mobile application as the main means of exploitation of the project. It also provides an assessment of user feedback in terms of statistical measure of user answers to the survey created for the purpose and described in D8.6.

The milestone for this reporting period:

- MS7 Exploitation (PM38)

11 Deliverables and Milestones

Project Deliverables for the period

Del N.	Name	WP	Nature	Diss	Month
D8.4	Intermediate exploitation report	WP8	R	CO	24
D8.5	Implementation of the physician assistant app	WP8	P	CO	30
D1.5	Annual Activity Report – yr 3	WP1	R	PU	38
D1.6	Annual Management Report – yr 3	WP1	R	CO	38
D2.5	Report on the search of inflammatory cytokines capable to impact on the balance of metabolic flexibility	WP2	R	PU	36
D3.6	Report on validation and refinement of the stress induced inflammation model in the overall workflow	WP3	R	PU	36
D4.4	Report on validation and refinement of the metabolic and inflammatory processes model in the overall workflow	WP4	R	PU	36
D5.4	Report on the implementation of the physical activity measurement module in the mobile apps	WP5	R	CO	36
D6.3	Report on the validation of the computational model and refinement of the integrated model	WP6	R	PU	36
D6.4	Report on the implementation of the integrated model in the mobile apps	WP6	R	CO	38
D7.3	Report on the analysis and validation of the integrated model results	WP7	R	PU	38
D8.6	Implementation of the personal coach app	WP8	P	CO	38
D8.7	Exploitation report	WP8	R	PU	38

Project Milestones for the period

TABLE 4. MILESTONES

no.	Work package	Name	Lead beneficiary	Delivery date	Achieved Yes/No	Actual / Forecast achievement date	Comments
MS6	WP2, WP3, WP4, WP5, WP6, WP7, WP8	Validation	TNO	PM38	Yes	PM38	
MS7	WP2, WP3, WP4, WP5, WP6, WP7, WP8	Exploitation	MED	PM38	Yes	PM38	

MISSION-T2D

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