# MISSION-T2D

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

**Work Package 1**

**Deliverable 1.1**

**Annual Activity Report – yr1**

**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

In Europe, type 2 diabetes (T2D) is one of the most common age-related diseases and a major public health concern. Recent data show that T2D and its complications (heart, kidney, retina, diabetic foot) should be considered a systemic disease sustained by a pervasive, metabolically driven state of inflammation.

As we age, many people develop the metabolic syndrome, characterized by visceral obesity, insulin resistance, and possibly diabetes as well as the related complications. People usually develop type 2 diabetes after age 45 (even if recently a lower average age for the onset has been observed), probably because they tend to exercise less, lose muscle mass and gain weight as they age. Since life expectancy is observed to increase all over the world, the number of T2D cases is expected to grow accordingly. For this reason, there is an urgent need to understand the complex mechanisms underpinning the onset of T2D and to identify early diagnostic parameters and related inflammatory indicators, by following a personalized medicine approach.

A number of possible stress mechanisms (herein indicated as "stressors") leading to, and participating with insulin resistance and β-cell dysfunction, have been hypothesized to explain the complex T2D landscape, such as oxidative stress, endoplasmic reticulum stress, amyloid (i.e., insoluble fibrous proteins) deposition in the pancreas, ectopic lipid deposition in the muscle, liver and pancreas .

All of these stressors can be caused by over-nutrition although it has been difficult to determine which mechanism is the most important in each tissue or individual with T2D. However, it is noteworthy that each of these cellular stressors is thought to also either induce an *inflammatory response* by itself or to be exacerbated by or associated with inflammation. Inflammation is a complex, systemic, multi-scale physiological process necessary to cope with damaging agents and fundamental for survival, involving a variety of cells, organs and organ systems. The complexity of the inflammatory process escapes reductionist and linear approaches, since it is characterized, among other features, by non-proportional kinetics as well as numerous and nested feedback loops.

The ultimate conceptualization identifies the hallmark of T2D in a chronic inflammatory state initiated by an excess of nutrients and referred to as metabolic inflammation or metaflammation. Indeed, proof-of-concept clinical studies demonstrated the potential of use an anti-inflammatory molecule in T2D therapy.

The MISSION-T2D develops around this concepts. Its aim is to develop an integrated, multilevel patient-specific model for the simulation and prediction of metabolic and

inflammatory processes in the onset and progress of the type 2 diabetes. The ultimate goal is to provide a diagnostic tool, exploited through a mobile application, to estimate the risk of developing T2D and to predict its progression in response to lifestyle adjustments and possible therapies.

The multi-scale model will enable the study of the systemic interactions of the involved biological mechanisms (immunological/inflammatory processes, energy intake/expenditure ratio and cell cycle rate) in response to a variety of nutritional and metabolic stimuli/stressors.

The overall architecture will exploit an already established immune system simulator as well as several discrete and continuous mathematical methods for the modeling of the processes critically involved in the onset and progression of T2D. The crucial validation work will compare simulation predictions with actual biological and clinical data. MISSION-T2D aims at paving the way for translating validated multilevel immune-metabolic models into the clinical setting of T2D. Indeed, this approach will eventually generate predictive biomarkers from the integration of metabolic, nutritional, immune/inflammatory, genetic and gut microbiota profiles, as well as of clinical data, suitable to be translated into cost-effective mobile-based diagnostic tools.


The main goal of this first reporting period has been to identify, to modify or to develop from scratch, mathematical and/or computational models for the various layers and compartments that will eventually converge into a unified modeling framework.

Each WP is in charge for a different layer or compartment of the integrated architecture whereas WP6 is designated for the integration. The various WPs have developed their own models mainly independently from the other. Yet, a tight cooperation was demanded to have a unified view of both intent and final esplotable results. To this purpose the consortium has organized many meetings either face-to-face or on-line, to exchange ideas, share problems and suggest solutions. A number of questions have been raised and actions to overcome the problems have been implemented in concerts among the partners. The work of the WP pertaining model development was executed successfully and timely.

In particular WP2 has identified available (both in-house and open access) data to build a model accounting for the influence of gut microbiota to the emergence of a systemic inflammatory state. WP3 is (still) developing a model for diabetes linking inflammation and gut microbiota. WP4 has identified and is currently extending a model for the basic metabolism including insulin/glucose regulation under rest and stress conditions (e.g., physical exercise). WP5 has identified potential models to be connected to the metabolic

model in order to include the physical activity into account and is currently developing a second model describing inflammation parameters during moderate / intense physical exercise. WP6 has extended a general immune system simulation tool to model distinct anatomical compartments (e.g., adipose tissue, liver, muscle) for what concerns the emergence of an inflammatory pattern impinging upon pancreatic beta-cells producing insulin. In particular, a gene-level description has been added to detail the differentiation process of T helper lymphocytes into the Th1/2/17 and Treg phenotypes driving the immune reaction toward the pro- or anti-inflammatory state in normal conditions.

At the current stage the project consortium has developed a set of independent model each providing a description of a specific aspect indirectly or directly involved with the emergence of the disease. A crucial integration of these models will be the next step and is performed during the successive reporting period of the project.

The project's outcome, identifiable in a computer-simulation architecture and a mobile application potentially linkable to healthcare self-monitoring devices, will help understanding the complex mechanisms underpinning the onset of T2D. This will contribute to identify early diagnostic parameters and related inflammatory indicators, the latter being potential target of therapy. Indeed, this approach will eventually generate predictive biomarkers from the integration of metabolic, nutritional, immune/inflammatory, genetic and gut microbiota profiles, as well as of clinical data, suitable to be translated into cost-effective mobile-based diagnostic tools.

The project will improve the treatment of T2D by early diagnosis of T2D, followed by appropriate advice for changes to lifestyle like diet control, and exercise, continuous monitoring, all at a very personalized level with the assistance of self-monitoring devices.

For the dissemination purpose, the MISSION-T2D consortium has setup a public website where all relevant information about the project as well as news pertaining ongoing activities are presented to the community. The project website can be reached at the following address:

*http://www.mission-t2d.eu*

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

The first year of the project has been challenging and productive at the same time. The partners have met many times during this first year, starting with a pre-kickoff meeting before the project began, to consolidate relationships and mutual trust but also to plan the activity for the first reporting period.

The main goal for the first phase of the project has been to find useful data and to identify, modify or develop from scratch, mathematical and/or computational models for the various layers and compartments that will eventually (during yr2) converge into a unified modeling framework.

Each WP in charge for a different layer or compartment after a careful literature review, has identified and implemented one or more models. Figure 1 depicts the relationship among the WPs. In particular WP2, WP3, WP4, WP5 and WP6 have identified or developed model components to be finally integrated in the multi-scale MISSION-T2D architecture.
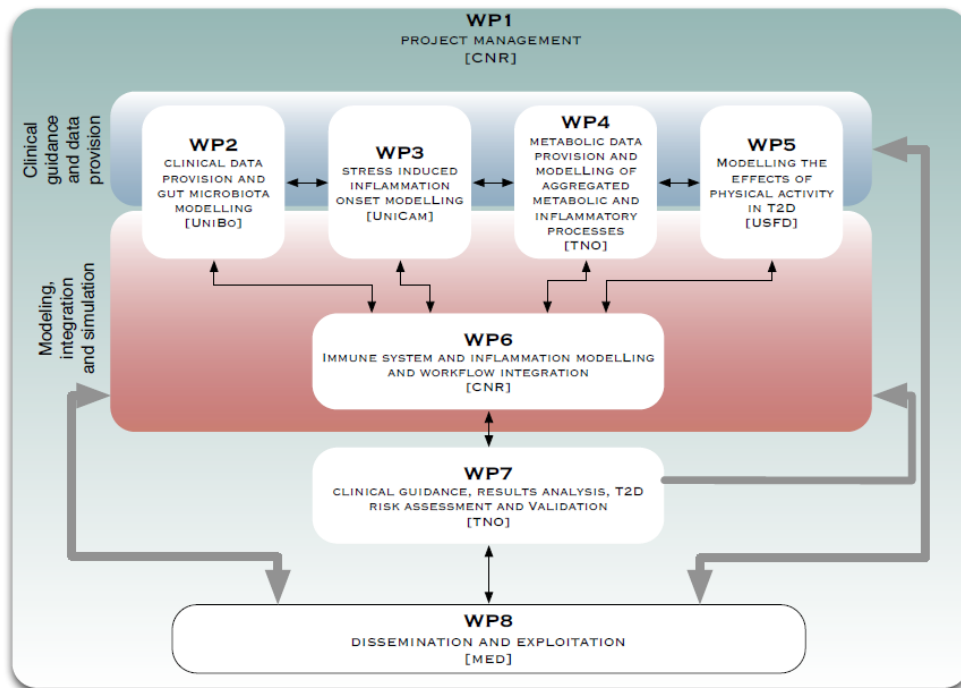
**Figure 1 This diagram shows the relationship between the various work packages.**

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 objectives for this reporting period have been:

- Identify in-house and literature data to be used to setup a model of the gut microbiota. WP2 has therefore retrieved datasets of genome wide surveys of genetic, epigenetic, transcriptomic and gut microbiota studies on Type 2 Diabetes and ageing process as described in deliverable D2.1.

- Developing a model that links the emergence of inflammatory signals in diabetes with gut microbiota profiles in order to incorporate nutritional habits. D3.1 describes the first implementation of the stochastic model.

- Identify in-house available at partner TNO that are suited to calibrate the integrated metabolism-inflammation model at the minute-to-day timescale (deliverable D4.1).

- Identify or develop a computational models of metabolism suitable to be incorporated / combined with the inflammation model developed in WP6. This model needed to account for metabolic regulations possibly linked with nutrition and gut profiles as in WP2 and WP3, ultimately controlling insulin, glucose, and other core metabolites in

diabetes.

- Identify or develop a model describing the influence of physical activity on metabolism (WP5).

- Develop the agent-based simulation of immune activation in inflammation of adipose tissues and other organs. Identify key metabolic players and immunological entities so to set up the relationship between metabolic disregulation and the emergence of tissue inflammation (WP6). Account for the direct influence on pro/anti-inflammatory cytokines by physical activity. Incorporate phenotype switch for macrophages and lymphocytes T helper in order to well characterize the emergence of inflammation.

- Start identifying the characteristics of the exploitable result (i.e., the mobile app) to be implemented in yr3. In particular define key input values characterizing the condition of the patient (of possible), accounting for his physical activity pattern and accounting for his nutrition habit. This was the objective of WP8 for this reporting period and is described in D8.2.

- The objective of WP1 – management was to guarantee a smooth take off of the procedures relative to reporting and communicating with the EC, provide all necessary information and generally guarantee a continuous support for any issue that might have arisen. Also, to provide templates for presentations, deliverables, acknowledgements, etc. Setup the boards of the project including the Advisory Board of eminent experts. Open a communication channel with them to be used in critical stages of the project evolution. Chairing inter-WP meetings either face-to-face or videoconferences and write the minutes of the meetings to disseminate among the partners.

- The dissemination objectives were, the set up of the project website, the setup of an intranet to allow data and documents exchange among the partners and the EC and the collection of all the dissemination activities performed by all partners (mostly scientific publications).

To address the above objectives of the MISSION-T2D project in this first phase a tight integration among the WPs has been realized through frequent on-line discussions and visits among the partners.

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

## 2.1  WP1 - Project Management

The First Period Management Review is based on the experience gathered along the 12 months corresponding to Work Packages WP1 Management and WP8 Dissemination in the first reporting period, and the information provided by the project partners.

More detailed information on WP1 is described in D1.2 Annual Management Report.

The tasks in this period have been the following. These tasks are reflected in deliverables D1.1 - 1.2.

Task 1.1 Project organization: Organization of consortium meetings: preparation of agendas, meeting chair, elaboration of meeting minutes; normally those meetings should take place every three months.

Task 1.2 Set up of the reporting procedures and mechanisms: Communication with the EU, setup of templates, of channels of information, of repositories of information, etc.

Task 1.3 Administrative and financial management: Elaboration and submission of periodic progress reports.

The Management actions to highlight in this first period are:

- Organization of the Kick off and First Technical meetings.
- Setup of the Executive Board.
- Setup of the Advisory Board.
- Preparation and launch of the project website and intranet.
- Follow-up of the recruitment of MISSION-T2D personnel by Partners.
- Setup of the reporting formats, preparation of deliverables, minutes and periodic report templates (all templates are available in the Intranet).
- Information on financial project reporting has been provided to the Consortium via email.
- Preparation of the meeting minutes, including the WP-meetings either online and face-to-face.
- Scientific and financial reporting as usual; support to partners on admin/financial matters ongoing; project repository (Intranet) in use; deliverables kept updated.
- Elaboration and submission of periodic progress reports including claiming of resources used and costs.
- Only 2 changes have been relevant: i) Address change of Partner MEDISANA; ii) Change of EU Officer.

### 2.1.1  Project Meetings

Project meetings dates are communicated well in advance and, whenever possible, feedback

on availability for different dates is collected from partners to set the most convenient date and schedule. Kick off Meeting and First technical Meeting have taken place as in Table 1.

| Project meetings | Date and place | Attendants |
|---|---|---|
| 1<sup>st</sup> KickOff meeting | March 2013<br>Rome (hosted by CNR) | Attendants: 6 partners<br>Online: 1 partner (UniCAM) |
| 1<sup>st</sup> Technical Meeting | February 2014<br>Cambridge (hosted by UniCAM) | Attendants: All 7 partners |

**Table 1  Kick off Meeting and First review Meeting have taken place up to date**

Meeting minutes containing the main points of discussion and decisions during the meeting are prepared by Project Management, and circulated to the rest of participants for comments, correction and validation. Minutes are considered accepted if no objections have been raised within 15 calendar days from sending. The latest updated version of the minutes is kept by the coordinator and made available upon request. WP leaders manage meetings/contact with WP partners with autonomy to decide frequency and means (live/online).

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.

The management activities are also described in the deliverable D1.1 Management Report

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

### 2.2.1  Scientific Activity

*Task 2.1 Data provision and preprocessing:* This task includes data provision of the available dataset from the Immunology lab of partner UniBO and from public data repositories. The data supplied will be used as input to the WP6 immune system and inflammation model are referred to different molecules (DNA variation, DNA methylation, RNA expression, Gut Microbiota (GM) phylotypes, metabolomic profiles) that exerts different effects on the observed phenotype and will provide the T2D molecular playground in which the ISS will work.

*Task 2.2 Deterministic and stochastic modeling:* This task includes the elaboration of a

mathematical model for the gut microbiota modeling by deterministic methods (systems of first order nonlinear differential equation) and stochastic methods such as Chemical Master Equation (CME). In particular, these last approaches will allow a direct linking with experimental data by probability distribution analysis.

Efficient modules for the integration of large systems of ODE will be shared with the other participants. Numerical solution of CME by Gillespie algorithm will be used for the exact stochastic Simulation.

We retrieved datasets of wide surveys of genetic, epigenetic, transcriptomic and gut macrobiota studies on Type 2 diabetes and ageing processes.

The datasets were obtained from two sources:  i) the proprietary datasets of the Laboratory of Immunology of the Dept. Of Experimental, Diagnostic and Specialist Medicine (UniBO); ii) public repositories

We implemented the gut microbiota mathematical model by adapting the model proposed by R. Stein et al., which includes parameters such as the species growth rate, the interaction between species and the effect of external factors (diet). We treated this model from a deterministic point of view (by Ordinary Differential Equations) and also stochastically (by Chemical Master Equations).


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


### 2.2.2   Deliverables for the WP

D2.1 Report on data gathering: Gene expression and methylation data were obtained from two sources: from Partner 3 and from GEO repository (Affymetrix Human Genome U133 Plus 2.0 oligonucleotide microarrays). Gut microbioma data were also retrieved from two sources: from Partner 3 (84 fecal samples from 4 classes of individuals: young, control, sons of centenarian and centenarians); from public repository (J. Qin et al. Nature 490, 55–60 and M. Claesson et al. Nature 488, 178-84).

D2.2 Report on deterministic and stochastic modelling: The gut microbiota mathematical model was derived by modification of the model developed by R. Stein et al. PLoS computational biology 9,e1003388. We implemented it in python and C++ both deterministically and stochastically.

For what concerns the milestone "M2 Model prototypes defined and available", a prototype for the gut microbiota model has been implemented and it will be soon available to other

partners.

### 2.2.3 Project Networking

MISSION-T2D project meeting, Cambridge (UK), 2014 - 02 - (20, 21, 22) - Attendants: Enrico Giampieri, travelled by airplane, guested by Prof. Lio; Claudia Sala, travelled by airplane, guested at the Moller Center

Meeting in Bologna, spring 2013 - Attendants: Liò, Tieri, Castiglione, Garagnani, Franceschi, Salvioli, Castellani, Sala

Internal meeting in Bologna, winter 2013/2014 - Attendants: Sala, Castellani, Fransceschi, Salvioli, Garagnani, Capri

Skype meeting January 2014 - Attendants Sala, Castellani, Castiglione, Tieri, Liò

### 2.2.4 New personnel for the WP

Postdoc Cristina Fabbri was hired in February 2014.

## 2.3 WP3 - Stress induced inflammation onset modeling

### 2.3.1 Scientific Activity

In this reporting period the activity in WP3 centered on task 3.1 (A probabilistic framework to account for the similarity/difference of the target patient to others in interfering variables related to the likelihood of T2D).

Task 3.1 consisted in particular, in developing a new ODE model for diabetes incorporating many aspects of published models and includes inflammation and (in a further extension) incorporates gut microbiota.

We have also completed a first implementation of a stochastic implementation based on Prism, probabilistic model checker (commonly used to calculate probability of events and verification of conditions; it can return either the exact solution if it operates directly on the structure of the Markov chains, or an approximated solution when it measures statistically the probability to satisfy a property for a set of samples, generated using a Monte Carlo simulation of the system model)..

We have also developed ComoR, a software in R that integrates clinical, gene ontology and molecular data and outputs comorbidity profiles. This software uses network regression and survival analysis data. Development of statistical (causality inference through decision trees) and mathematical models able to identify trajectories deviations from healthy aging as well

as disease progression. It is described in a paper accepted on Clinical Bioinformatics and in the software repository CranR.

A machine learning approach provide insights into disease –pathways  and drug-pathways relationships.

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

### 2.3.2 Deliverables for the WP

D3.1 has been delivered on time.

### 2.3.3 Project Networking

We have participated in various intra WP meetings, and organized the first annual meeting.

### 2.3.4 New personnel for the WP

Postdoc recruitment: Dr Gianluca Ascolani 15 July 2013. Mphil students involved in short projects.

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

### 2.4.1 Scientific Activity

Task 4.1 - Data provision for models of the interaction metabolism, inflammation and physical activity (Month 1-12 of 12)

The datasets available at partner TNO to calibrate the integrated metabolism-inflammation model at the minute-to-day timescale, for different subgroups and conditions, were identified. The datasets were extracted from the dbNP database, and the files were made available to the Consortium.  The dbNP database  (B. van Ommen et al., Genes & Nutrition, September 2010, Volume 5, Issue 3, pp 189-203, ) was created in the Nutritional Phenotype Database project, within the framework of NuGO (www.nugo.org/dbnp). NuGO evolved from a European-funded Network of Excellence, the full title of which was 'The European Nutrigenomics Organisation: linking genomics, nutrition and health research'. NuGO was funded by the European Commission's Research Directorate General under the Food Quality and Safety Priority of the Sixth Framework Programme for Research and Technological Development. The project began in January 2004 and was funded until June 2010.

Task 4.2 - Modeling of the dynamics of the interactions between metabolism, inflammation

and physical activity (Month 1-12 of 12)

The literature was searched for computational models of metabolism that can be interlinked with the agent-based inflammation model available at partner CNR. A best suited model was selected and the corresponding software code was implemented. This model is a physiologically based kinetic model that describes the influence of physical activity on energy metabolism. The model has been implemented at partner CNR and is currently being tested. Principles, and mathematical equations for model extension to include model input from nutrient absorption were formulated. The major points of interaction between metabolism and inflammation were identified from literature search. Generic mathematical equations for these interactions were developed.

Task 4.3 - Constructing a high-level aggregation model of the interaction between glucose metabolism and chronic inflammation (Month 1-12 of 18)

A descriptive model of diabetes development was developed based on causal loop diagrams at a very high aggregation level that from the beginning integrated mechanisms across all 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 was 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 tress-relieving lifestyles over a period of 3 years. The model has been made available to the Consortium members and can be downloaded from a server at partner TNO. A start is being made to pilot this model in a test environment called the Nutrition Researcher Cohort ([www.nugo.org/nrc](www.nugo.org/nrc)) (NRC)  that has been created also within the NuGO network of excellence. The NRC is a new generation open access cohort where each individual provides and owns her/his own health data that both provide an empowerment for individual health optimization and, brought together, a powerful open access cohort. NRC will make full use of data from self-monitoring devices including those developed by partner MEDISANA.

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

### 2.4.2   Deliverables and Milestones

Deliverable 4.1 "Report on Dynamic-E-MF model (minute-day time scale)" is currently being prepared and will be submitted before end of February.

Milestone 2: " Models Prototypes" : WP4 has contributed prototypes for the metabolic model at the minute-day timescale, and has made available a prototype integrated model at the month-years timescale.

### 2.4.3 Project Networking

May 29, 2013: Partner visit CNR at TNO, Zeist, The Netherlands, to discuss progress on WP4

Skype calls between TNO and CNR to discuss progress in WP4: Sept 11 and 25 and Nov 27, 2013, and Feb 5, 2014.

TNO-internal network meetings to discuss possible data sources and links of TNO-internal programs with MT2D project: Jun 4 and Nov 19, 2013, Zeist, The Netherlands. Attendants included P. van Dijken (Director of Biomedical Innovations), A. van Gool (Head of TNO Biomarker Development), Gerrit Beumer (Head of Biomedical Innovation business development).

### 2.4.4 Personnel and Planned Resources

Shaji Krishnan started work on the project Mar-1-2013 as a postdoc, partner TNO

## 2.5 WP5 - Modelling the effects of physical activity in T2D

### 2.5.1 Scientific Activity

With respect to the two tasks for the current period (Task 5.1: Definition of model input variables; Task 5.2: Definition and implementation of the relationships to be included in the model) a systematic review of the literature has been performed to identify the tools that are used to measure and monitor physical activity in patients with Type 2 Diabetes, with particular focus on daily life situations. Two main inputs fore the model have been identified: number of steps and heart rate.

An experimental comparison between different physical activity monitors has been performed to facilitate the interpretation of literature contradictory results.

The relationships linking the selected physical activity measurements and type 2 diabetes related outcomes have been reviewed and implemented in a first prototype of the model.

A model of IL-6 variation during exercise as a function of heart rate has been developed.

An adaptation of the model of fuel homeostasis during exercise proposed by Kim et al., which takes into account for different workloads has been performed. This adapted model is

based on the use of heart rate as measurable input.

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

### 2.5.2 Deliverables and Milestones

D5.1 (Project month 6): Report on the specifications of physical activity model input variables

M2 (Project month 12): Model prototypes

### 2.5.3 Project Networking

Intra workpackage meeting, USFD and UniRM

Regular Skype meeting every two weeks, normally involving all personnel

Physical meetings in Rome: May 5th, July 17th

Inter workpackage meeting

Kick Off Meeting, IASI, April 2014, all units

Skype meeting, September, 25th 2013. Attendants: Filippo Castiglione (CNR), Paolo Tieri (CNR), Teresa Colombo (CNR), Massimo Sacchetti (UniRM), Micaela Morettini (UniRM), Albert De Graaf (TNO), Ivana Bobeldijk (TNO), Claudia Mazzà (USFD), Mark Ernst (MED)

IASI, January, 14th 2014: Attendants: Filippo Castiglione (CNR), Paolo Tieri (CNR), Maria Concetta Palumbo (CNR), Micaela Morettini (UniRM)

IASI and Skype, Date: February, 3rd 2014: Attendants: Filippo Castiglione (CNR), Paolo Tieri (CNR), Maria Concetta Palumbo (CNR), Massimo Sacchetti (UniRM), Micaela Morettini (UniRM), Claudia Mazzà (USFD)

### 2.5.4 New personnel selected

Postdocs: Micaela Morettini, UniRM – Contract start date: June, 1st 2013

PhD: Fabio Storm, USFD– Contract start date: June, 1st 2013

## 2.6 WP6 - Immune system and inflammation modelling and workflow integration

### 2.6.1 Scientific Activity

In this reporting period the activity in WP6 centered around task 6.1 (Agent-based

customization for the inflammation) and task 6.2 (Define prerequisites for the integrated model).

CNR has contributed to the implementation of the metabolic model (Kim et al.) identified by TNO in WP4. In particular, the activity consisted in recode the model in C-language for optimal execution and integration with the overall simulation tool to be built in the second reporting period (i.e., year 2). A more detailed description of the metabolic model used can be found in D4.1.

We have implemented a number of modifications of the existing immune system model, in order to have a more refined immune cellular compartment such as M1/M2 (macrophages) in obesity-induced AT inflammation, differentiation of CD4 T cells in the Th1/2/17/reg phenotypes and to represent adipose tissue cells (i.e., adipocytes) as source of danger signals triggering inflammation. More details in deliverable D6.1

The simulation tool has been modified to account for different anatomical compartments (AT, Liver, Muscle, GI) each accounting for a different signaling background and each contribution to inflammation. More details in D6.1.

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

### 2.6.2 Deliverables and Milestones

In this reporting period WP6 was in charge of D6.1 "Report on agent-based customization for inflammation modeling" (delivered on-time, PM12).

The milestone M2 "Model prototypes" has been successfully reached as described in the deliverables related to the workpackages WP2 WP3, WP4, WP5 and WP6. In particular, for what concerns WP6, the prototype simulation tool has been setup and is in beta-testing phase (other minor features still need to be implemented and will be in due time).

### 2.6.3 Project Networking

CNR has organised and contributed to a number of virtual and face-to-face meeting. In particular WP6 has been present in all meetings (pre-kickoff, kickoff and first annual meeting). Moreover Paolo Tieri and Filippo Castiglione have visited UniBO five times, visited once UniRM, visited once TNO and visited once UniCAM. Details in Error! Reference source not found..

### 2.6.4 New personnel selected

Postdocs Vinca Prana and Teresa Colombo have been hired.

## 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 1-6 of 12)

An inventory was made of the projects in which TNO participates and in which Type 2 Diabetes patients with multiple sub-phenotypes have been subjected to nutritional as well as physical exercise challenge tests. The types of available data obtained during the 3-6 h time courses afer challenge tests have been recorded in a database. Blood clinical chemistry, metabolomics and proteomics data are available to use in the mesoscopic level (minute to day) model. Extraction of data for use in MISSION-T2D was begun. Datasets were preferred when they were also selected in Task 7.2.

Task 7.2: Provide experimental data from type 2 (pre)diabetes intervention studies with various subphenotypes (Month 1-6 of 12)

An inventory was made of datasets available at TNO, registered at www.clinicaltrials.gov, and in which human volunteers underwent a specific protocol of interventions of various nature, to give insight in the effect of treatment (both pharmaceutical and dietary / lifestyle). Datasets were selected based on relevance for validation of the models, specifically for the macroscopic level (month-year timescale), that will be performed in Task 7.4. Several datasets had been acquired in cooperation projects with third parties. Permission requests for use of this data in MISSION-T2D are currently being prepared.

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

### 2.7.2 Deliverables and Milestones

None for the current period.

### 2.7.3 Project Networking

Various internal meetings at TNO with local data managers and PI's were held to identify and select suitable datasets.

### 2.7.4 Personnel and Planned Resources

Shaji Krishnan started work on the project Mar-1-2013 as a postdoc, partner TNO

## 2.8 WP8 - Dissemination and Exploitation

### 2.8.1 Dissemination tasks

This section summarizes the activities carried in Tasks 8.1 Dissemination to target groups , 8.2 Project website and 8.3 Specifications of exploitable results.

Task 8.1 Dissemination

Dissemination activities in general,that to this stage focus on scientific publications and communication (oral, posters, etc) at congresses.

Task 8.2 Set up of the project web site. Task performed in first trimester of the project. The website is the Deliverable 8.1.

Task 8.3 Specifications of exploitable results. The Deliverable 8.2 contains the Specification of Exploitable Results to date.

There have been no major deviation from the planned dissemination activities in tthis period.

### 2.8.2 Deliverables and Milestones

Deliverable 8.1 Set up of the project web site.

The web site has been setup including an intranet containing useful documents for the projects partners and all deliverables sent to the EU.

Deliverable 8.2 Specification of Exploitable Results.

This deliverable describes the work performed in identifying and/or defining, all aspects relative to the modeling approach and results of the sub-modules that will be integrated in the MISSION-T2D model platform in terms of what can be exploited and how. This deliverable also drafts the specifications in the design of the mobile app including the graphical user interface, the user input fields, the graphical output, the possibility to upload data to the Medisana head quartier database for future reference or to implement a personal and local database to be stored on the mobile device.

### 2.8.3 Project Dissemination Objectives during the period

- Spread the aim, the structure and the results of the MISSION-T2D project to the

scientific and medical community.

This has been performed via scientific publications and presentation of the project to the scientific community in scientifi congresses and events.

- To exchange information with other initiatives and projects relevant for diabetes modelling.

This has been done mainly thanks to the activities in WP4. More work will be done in this line as we progress in the project.

- To promote the use of the models and applications created by the project partners .

**Project Website:**

Project website was setup on month 3. It contains relevant information concerning the project. Hereby a snapshot of the website available at:  http://www.mission-t2d.eu



**Figure 2 Snapshot of the welcome page of the MISSION-T2D project web site**

## 2.8.4 Dissemination activities

Scientific publications and dissemination activities to date:

- F. Castiglione, P. Tieri, A. De Graaf, C. Franceschi, P. Liò, B. Van Ommen, C. Mazzà, A. Tuchel, M. Bernaschi, C. Samson, T. Colombo, G. Castellani, M. Capri, P. Garagnani, S. Salvioli, V. Anh Nguyen, I. Bobeldijk-Pastorova, S. Krishnan, A. Cappozzo, M. Sacchetti, M. Morettini, M. Ernst. The Onset of Type 2 Diabetes: Proposal for a Multi-Scale Model. JMIR research protocols, 01/2013 2(2):e44 (2013) (doi: 10.2196/resprot.2854)(open access)

- F. Castiglione, P. Tieri, M. Bernaschi, C. Franceschi, G. Castellani, P. Garagnani, C. Sala, P. Liò, V. Nguyen, C. Mazzà, A. Cappozzo, M. Sacchetti, M. Morettini, A. De Graaf, B. van Ommen, S. Krishnan, A. Tuchel, M.Ernst. A multiscale immune system simulator for the onset of type 2 diabetes. Poster presented at V International Conference for Computational Bioengineering (ICCB2013).

- F. Castiglione, P. Tieri, M. Bernaschi, C. Franceschi, G. Castellani, P. Garagnani, C. Sala, P. Liò, V. Nguyen, C. Mazzà, A. Cappozzo, M. Sacchetti, M. Morettini, A. De Graaf, B. van Ommen, S. Krishnan, A. Tuchel, M.Ernst. A multiscale immune system simulator for the onset of type 2 diabetes. ScienceMED. 2014 (in press).

- L. De Oliveira, G. Castellani, G.Turchetti One parameters family of master equations for logistic growth and BCM theory. Accepted on Communications in Nonlinear Sciences and Numerical Simulation in February 2014

- Micaela Morettini, Fabio Storm, Massimo Sacchetti, Aurelio Cappozzo, Claudia Mazzà, "*The role of walking activity in preventing and managing low-grade inflammation in Type 2 Diabetes*" (Review Article), submitted to "Diabetes/Metabolism Research and Reviews"

- F. Castiglione, V. Diaz, A. Gaggioli, P. Liò, C. Mazzà, E. Merelli, C.G.M. Meskers, F. Pappalardo and R. von Ammon. Physio-environmental sensing and live modeling. Interact J Med Res. 2(1): e3 (2013) doi:10.2196/ijmr.2092 (open access)

- J. von Eichborn, A-L. Woelke, F. Castiglione, R. Preissner. VaccImm: Simulating peptide vaccination in cancer therapy. BMC Bioinformatics 14:127  (2013) doi:10.1186/1471-2105-14-127 (open access)

- Garagnani P, Giuliani C, Pirazzini C, Olivieri F, Bacalini MG, Ostan R, Mari D, Passarino G, Monti D, Bonfigli AR, Boemi M, Ceriello A, Genovese S, Sevini F, Luiselli D, Tieri P, Capri M, Salvioli S, Vijg J, Suh Y, Delledonne M, Testa R, Franceschi C. Centenarians as super-controls to assess the biological relevance of genetic risk factors for common age-related diseases: a proof of principle on type 2 diabetes. Aging (Albany NY). 2013 May;5(5):373-85.

- M. Moni and P. Lio' comoR: a software for disease comorbidity risk assessment. Journal of Clinical Bioinformatics (in press, ms 1638204891121462).

- Naruemon Pratanwanich and Pietro Lio' Pathway-based Q1 Q2 Bayesian inference of drug–disease interactions. Molecular Biosystems (in press Ms c4mb00014e)

Other Dissemination activities

The participants have presented the project and its progress at the following international conferences or workshops:

- Organisation of CIBB2014: Eleventh International Meeting on Computational Intelligence Methods for Bioinformatics and Biostatistics. 26-28 June 2014
- the INSIGNEO launch event, Sheffield, May 9th, 2014 (200 participants)
- the Symposium IL-1-mediated inflammation and diabetes: from basic science to clinical applications. NIJMEGEN, NL, October 10-11, 2013
- ISPGR 2014, Vancouver
- WCB 2014 Boston
- 3DAHM, Lausanne, 2014
- The 3rd International Conference, on Simulation and Modeling Methodologies, Technologies and Applications (SIMULTECH 2013), Reykjavik, Iceland, July 29 - 31, 2013.
- The 5th International Conference on Computational Bioengineering (ICCB2013), 11-13 September 2013, Leuven, Belgium

### 2.8.5 Exploitation

Deliverable 8.2 Specification of Exploitable Results contains all aspects relative to the modelling approach and results of the sub-modules that will be integrated in the integrated model platform in terms of what can be exploited and how.

During the First reporting period, there has been no application for patents or any other type of action for protection of Intellectual Property derived from this project.

## 2.9 Deliverables and Milestones

**Project Deliverables for the period**

| TABLE 3: DELIVERABLES | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Del. no. | Deliverable name | Version | WP no. | Lead beneficiary | Nature | Dissemination level[1] | Delivery date from Annex I (proj month) | Actual / Forecast delivery date Dd/mm/yyyy | Status Not yet submitted/ Submitted | Comments |
| D8.1 | MISSION-T2D web site | V1.0 | WP8 | CNR | 0 | PU | 31/05/2013 | 26/05/2013 | Online | |
| D2.1 | Report on data gathering | V1.3 | WP2 | UNIBO | R | CO | 31/08/2013 | 04/03/2014 | Submitted | These deliverables were uploaded to the intranet on-time, and information about their availability was sent by email to the EU Officer. |
| D5.1 | Report on the specifications of physical activity model input variables | V1.3 | WP5 | USFD | R | PU | 31/08/2013 | 23/09/2013 | Submitted | |
| D2.2 | Report on deterministic and stochastic modelling | V1.3 | WP2 | UNIBO | R | PU | 28/02/2014 | 13/03/2014 | Submitted | |
| D3.1 | A probabilistic framework to account for the similarity/difference of the target patient to others in | V1.3 | WP3 | UNICAM | R | PU | 28/02/2014 | 18/03/2014 | Submitted | |

[1] **PU** = Public **PP** = Restricted to other programme participants (including the Commission Services). **RE** = Restricted to a group specified by the consortium (including the Commission Services). **CO** = Confidential, only for members of the consortium (including the Commission Services). **Make sure that you are using the correct following label when your project has classified deliverables. EU restricted** = Classified with the mention of the classification level restricted "EU Restricted" **EU confidential** = Classified with the mention of the classification level confidential " EU Confidential " **EU secret** = Classified with the mention of the classification level secret "EU Secret "

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | interfering variables related to the likelihood of T2D | | | | | | | | | |
| D4.1 | Report on Dynamic-E-MF model (minute-day time scale) | V1.2 | WP4 | TNO | R | PU | 28/02/2014 | 17/03/2014 | Submitted | |
| D6.1 | Report on agent-based customization for inflammation modeling | V1.6 | WP4 | TNO | R | PU | 28/02/2014 | 04/03/2014 | Submitted | |
| D8.2 | Specifications of exploitable results | V1.6 | WP8 | MED | R | CO | 28/02/2014 | 04/03/2014 | Submitted | |
| D1.1 | Annual Activity Report - yr 1 | V2.0 | WP1 | CNR | R | CO | 28/02/2014 | 02/04/2014 | Submited | |
| D1.2 | Annual Management Report – yr 1 | | WP1 | CNR | R | CO | 28/02/2014 | | | To be submited before 30/04/2014 |

**Table 3 Project Deliverables for the period**

## Project Milestones for the period

| TABLE 4. MILESTONES | | | | | | | |
|---|---|---|---|---|---|---|---|
| Milestone no. | Milestone name | Work package no | Lead beneficiary | Delivery date from Annex I dd/mm/yyyy | Achieved Yes/No | Actual / Forecast achievement date        dd/mm/yyyy | Comments |
| M1 | MISSION-T2D web site | WP1, WP8 | CNR | 31/05/2013 | YES | 31.05.2013 / 31.05.2013 | |
| M2 | Models prototypes | WP2, WP3, WP4, WP5, WP6 | ALL PARTNERS | 28/02/2014 | YES | 28.02.2014 / 28.02.2014 | |

**Table 4 Project Milestones for the period**

# MISSION-T2D

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

Grant Agreement number: 600803

Funding Scheme: FP7-ICT-2011.5.2

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