MISSION-T2D

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

Work Package 8

Deliverable 8.4

Intermediate Exploitation Report

Document Information

Grant Agreement	**Nº**	600803	**Acronym**	MISSION-T2D
Full Title	Multiscale Immune System SImulator for the Onset of Type 2 Diabetes integrating genetic, metabolic and nutritional data			
Project URL	http://www.mission-t2d.eu			
EU Project Officer	**Name**	Dr. Adina Ratoi		

Deliverable	**No**	8.4	**Title**	Intermediate Exploitation Report
Work package	**No**	8	**Title**	Dissemination and Exploitation

Date of delivery	**Contractual**		**28.02.2015**		**Actual**	**13.03.2015**		
Status	**Version 1.3**				**Final**	**1.3**		
Nature	**Prototype**		**Report**	X	**Dissemination**		**Other**	

Dissemination level	Consortium+EU	X
	Public	

Target Group (If Public)		Society (in general)	
Specialized research communities		Health care enterprises	
Health care professionals		Citizens and Public Authorities	

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Version Log

Issue Date	Version	Author (Name)	Partner
05.03.2015	1.0	Marc Ernst / L.Piechulek	MED
13.03.2015	1.3	Marc Ernst / L.Piechulek / Filippo Castiglione	MED, CNR

Executive Summary	In this deliverable we describe the intermediate exploitation of T2D Mission results, in particular the state of the mobile application as the main means of exploitation. But the document also intends to provide an outlook beyond the initial project duration and the integration of results into products like health management platforms and third party applications.
Keywords	Model, Mobile Application, Exploitation, Results

Contents

1 Introduction

Over the duration of the MISSION-T2D project, the project partners identified and/or developed several models describing different areas covering aspects of the human physiology related to the metabolic instabilities leading to type 2 diabetes. These models include one describing the immune activation and inflammation, integrating and extending an agent-based model of the immune system (CNR, M1), a model for metabolism, including multiple tissue compartments (TNO, M2), a model for mTOR signalling inside immune cells (UniCAM, M3) and a model to account for the effects of physical activity on the inflammatory state of the individual as well as its energy intake-expenditure balance (USFD, UniRM, M4) with the purpose of providing a diagnostic tool to estimate the risk of developing Type 2 Diabetes and predict its progression over time.

1.1 Use of MISSION-T2D findings in mobile applications

These models and the extensive simulations' loads of these models exceed the capabilities of modern day smartphones by far. On the other hand, the resulting data is of such detail that it is not feasible to be displayed on the limited space for visualization of today's mobile devices. A fairly average personal computing device (e.g., PC) currently requires up to about a week to compute the data produced by such an extensive simulation for a time period of one year at a resolution of one minute. As a consequence the computations required to determine an individual's risk of developing Type 2 Diabetes cannot be run on a mobile device at present time. The computational time required to run a single simulation corresponding to a query for forecast issued by the user is "to date" very demanding, notwithstanding the effort of partner CNR to speed-up computation. Even if the six-days time required will be reduced by an order of magnitude, it is unrealistic to hope for a real-time execution of the model on a limited capacity hardware as a mobile device. This was already foreseen at the beginning of the project and a solution to this problem has been long identified as discussed below.

With mobile phones and especially smartphones, devices with advanced operating systems, capable of internet access and running third party applications and interfaces for internal and external sensors, having spread into almost every household in society, they are an ideal tool for self-monitoring health and lifestyle aspects, and, in particular, for the findings of the project MISSION-T2D.

The solution to bypass the computational capacity deficit in current day smartphones and tablets and to work around the extended simulation time even on much faster and more capable platforms, is to run and record an extensive amount of simulations on appropriate hardware, like university computing centers or cloud computing facilities, to create a vast number of results for a wide spectrum of physiological parameters. The resulting data is then broken down into one or multiple lookup tables, which summarize results for specific configurations (or set of configurations clumped together) and subsequently enabling estimations to be made on mobile devices. Partner CNR in charge for the development of the final simulation engine (WP6) will be conducting the required extensive scan of the parameter space and clusterize the results on the basis of carefully chosen identifiable outputs. The resulting parameter & initial condition / forecasted values will constitute the lookup tables that will eventually be imported into the mobile app and consulted upon the user request.

2 The MISSION-T2D Integrated Model

The development of the integrated model is due to partner CNR as described in deliverable D6.2. To the purpose of the present exploitation report we now give a brief overview of the main idea and functions. The following figure evidences the kind of input/outputs taken/given by the MISSION-T2D integrated model. The input includes a parameterised version of the physical activity pattern of the user, e.g., total number of hours of PA per week and the average intensity or a more detailed weekly schedule or - if a measurement device is available - the weekly pattern of activity as measured which is then assumed to repeat unchanged for each week. Another input is the nutritional habit of the user on a daily or weekly basis. The cumulative daily meal will be broken down in the macronutrients, meaning, proteins, fat, fibres and carbohydrates. A finer grain classification of nutrients is actually used at this stage as the model developed by UniBO in WP2 accounts for these to determine the level of butyrate and propionate directly influencing the tendency of the immune system to drift toward the inflammatory state.

Other general parameters characterising the user include the age, gender, weight, etc.

All these constitute the boundary condition of the model execution which will then forecast the metaflammation state at the “forecasting horizon time T”. The simulation runs and returns the detailed dynamics of dozens of variables. These are ultimately used to calculate a unique value identifying the risk of T2D at time T (as indicated in the figure). The “risk of T2D” will therefore be a complex function accounting for the level of insulin resistance (e.g., efficiency of beta-cells) and the level of inflammatory cytokines and pro-inflammatory cell counts.

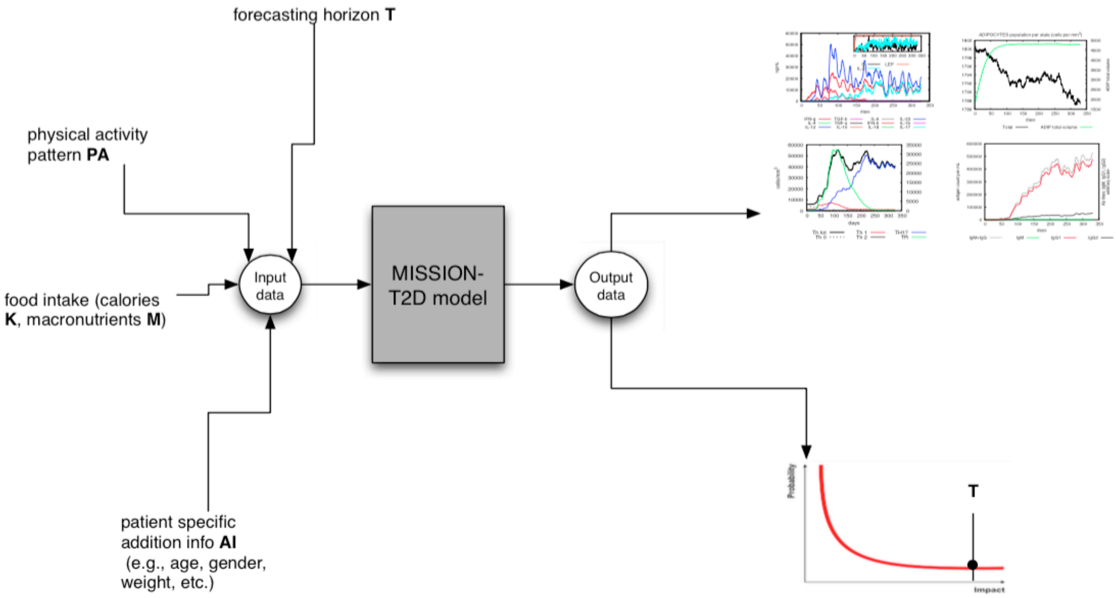

Image 2.1: The MISSION-T2D Integrated Model

As mentioned, the mobile app will not run the simulation for computational reasons, therefore we will precompute a number (large) of input/output relationships, and fill a multidimensional table that will represent a sampling of the function realised by the model. This table will then be plugged into the mobile app.

3 Specification of the MISSION-T2D mobile application

The mobile application as MISSION-T2D’s primary means of exploitation is specified to provide users with a powerful tool to self-monitor health and lifestyle aspects and employ these to receive an estimate on the risk of developing Type 2 Diabetes.

3.1 User Profile

By querying the current user for some initial personal information, such as the birthdate, the body height and initial weight, as well as the user’s gender upon first start of the application, the mobile application is able to create an individual user profile. Additional information, specifically requested for the purpose of determining the Type 2

Diabetes risk (such as the Enterotype levels, Butyrate, Pyruvate, if available, or an estimation of proportion of macronutrients in her/his diet; the level of physical activity exercise per week) but also data to specify individual goals and target range values for measurement results can be entered in corresponding sections in the application's settings.

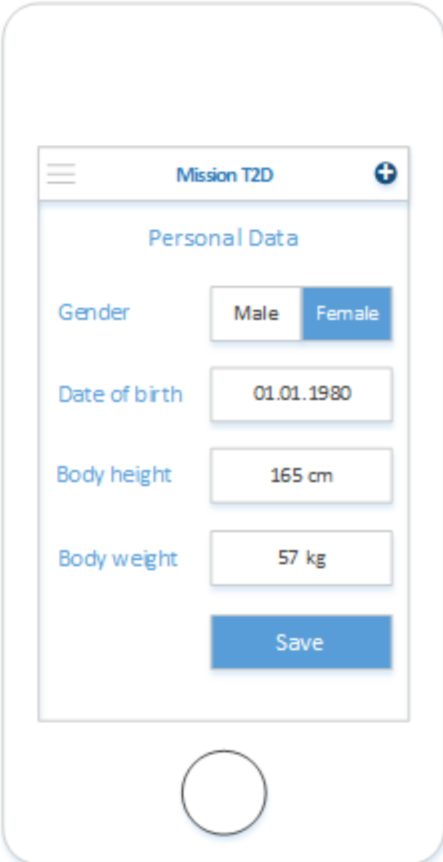

Image 3.1.1: Personal Data in Mission T2D mobile application

Already from this information, assuming average levels for all measurable inputs to be covered by the mobile application, the software should be able to derive a basic estimate of the risk of developing Type 2 Diabetes in the context of the current user.

3.2 External Sensors

With the increasing miniaturisation of digital sensors more and more mobile devices have been equipped with these sensors and they're applied to all kinds of scenarios. First mobile phones received sensors such as gyroscopes, magnetometers, accelerometers and barometers, only to name a few.

Then, as of late, many more sensor equipped devices, primarily from the sports and lifestyle sector have flooded the markets. These devices, mainly activity meters and heart rate monitors, some including GPS localization services, are commonly referred to as 'wearables' and can be employed to measure a user's physical activity, which is one of many important factors in determining the user's health. The sector of Wearables is thought to grow exponentially over the coming years, a trend that is underlined for example by numerous activity trackers and the rise of "smartwatches", which are usually equipped with multiple sensors.

In addition a broad range of medical sensors, such as glucose meters, blood pressure meters, pulse oximeters and others featuring wired or wireless data transfer mechanisms have become widely available. The combination of smartphones, external sensors and transmission through short range wireless technology such as Near Field Communication (NFC), Bluetooth or WiFi open up a broad range of applications and come in handy for MISSION-T2D in particular.

3.3 Self-monitoring in MISSION-T2D application

In order to improve the individual estimation of the Type 2 Diabetes risk the MISSION-T2D mobile application establishes a user journal of health and lifestyle parameters containing automatically measured or manually entered values. Within the duration of the project the inclusion of a minimum of two external sensors is anticipated to support users in self-monitoring and reduce uncertainties in the estimate of Type 2 Diabetes risk. Additional means of entering data manually will be supplied for users not making use of compatible sensor devices and where such sensors are not available.

3.3.1 Measuring Physical Activity

As a means of measuring physical activity a wrist or pocket worn pedometer is employed to provide an account of steps taken by the user of up to 96 intervals of 15 minutes each. Additionally the data contains the amount of actively burned calories and an estimation of crossed distance within the interval. The sensor supports wireless transmission of data through Bluetooth Low Energy technology and is compatible with most modern Bluetooth capable mobile devices. The sensor can store data of up to 15 days before the local memory is exceeded and old data is being overwritten.

Image 3.3.1.1: Wrist worn activity meter ViFit Connect

Also capable of measuring movements during sleep, the pedometer may, at a later point, be used to determine sleep quality data, if required.

3.3.2 Estimating Physical Activity

The application also permits the user to manually specify levels of activity on a per day basis, asking the user to describe his performance in terms of low, medium or high levels of activity, which, under consideration of the personal step goal specified by the user, will be used to estimate an absolute daily total amount of steps for the specified day.

While not exact and subject to misinterpretation by the user, a very basic account for the user's physical activity is favourable over not having any such data, of course.

Resembling the design of the weekly overview graph in the mobile application, in the manual entry section the user can quickly and easily provide an estimate without having to refer to complex mechanisms to describe individual sessions of physical activity. Such more advanced methods may be supplied at a later stage, should it become obvious that a greater level of detail in regards to individual sessions is required. Initial research into this area did not hint in this direction and make it likely that a daily performance summary may be sufficient for computing an estimation.

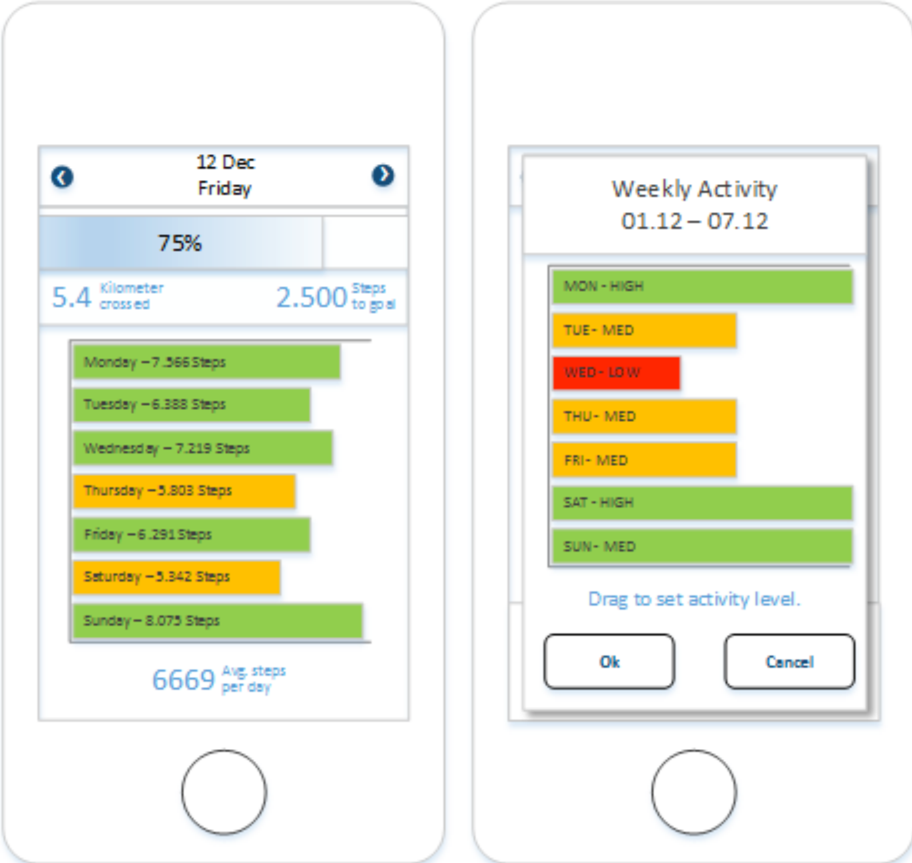

Image 3.3.2.1: Weekly Overview (left) and manually entering physical activity (right)

3.3.3 Measuring Blood Glucose

In order to measure the blood glucose levels a small teststrip based sensor is used. The sensor determines the concentration of glucose through enzymes on the teststrip, which is being inserted into the sensor device prior to the application of a small amount of blood. The device has a large display and a local memory has a capacity for up to 480 measurements before old results are being overwritten.

Image 3.3.3.1: Teststrip based glucose meter MediTouch 2 Connect

The device also enables the user to determine whether a measurement was performed prior or following a meal, as the time of measurement in respect to food intake can influence the measurement result.

3.3.4 Manually entering glucose data

As an optional means of adding glucose level results to the journal of health and lifestyle parameters, an interface is being provided through which the user can enter the results of glucose measurement and provide the date and time of such a measurement.

Additionally, it is intended to provide means of entering additional data determined through more sophisticated means of measurement, e.g., through a GP, covering inflammatory markers such as IL-6.

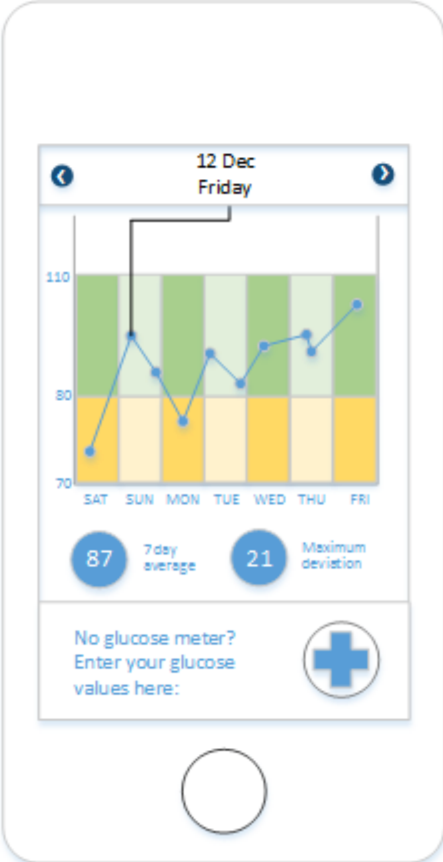

Image 3.3.4.1: Entering glucose data manually in MISSION-T2D mobile application

3.3.5 Monitoring nutritional habits

Another major factor in personal health, nutritional habits play an important role in the models employed by MISSION-T2D. Currently no sensors devices measuring the intake of (macronutrients) carbohydrates, proteins and fat are available, thus the mobile application's interface will provide the user with means of entering estimates of the percentage of each in relation to the weekly total meals.

3.3.6 Additional measurement data and sensor devices

While initially only two sensors will be included, many more such sensors are available and may be feasible to be included in the application. Additionally, with the use of the VitaDock Online platform, there exists the option to access measurement data gathered through the platform itself without having to implement the routines for data synchronization with an external measurement device in the MISSION-T2D software application itself. This, given sufficient time and resources, may allow to extend the mobile application to also include long term observations of a user's body weight, heart rate and blood pressure, for example.

Image 3.3.5.1: Bodyweight scale BS 440

3.4 Estimating the risk of Type 2 Diabetes

The goal of the journal, apart from providing the user with the opportunity to collect and review a history of health and lifestyle parameters, is to use these parameters as input for the estimate of the risk of developing Type 2 Diabetes through the lookup tables derived from the simulations. The additional input generated through the supported sensor devices and manual entries help reducing uncertainties in the estimation.

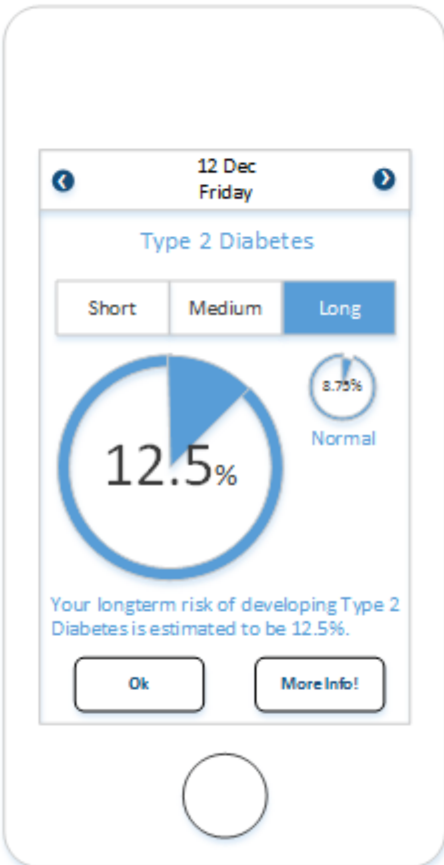

Image 3.4.1: Type 2 Diabetes risk estimation

Estimations are provided to the user in percentage values, representing the likelihood of developing Type 2 Diabetes over the given period of time.

4 Limitations

Despite the successful use of lookup tables in order to circumvent the limitations in computing power when it comes to the full-fledged simulations of physiological processes over a long time period, mobile applications face a range of other limitations imposing restrictions on the use of these devices on self-monitoring and self-diagnosis.

4.1 Capacity limitations

The mobile application itself only maintains records of the last 30 days, a step that ensures faster loading of the application and reduced data requirements when synchronizing with the VitaDock Online platform, as well, in general, a lesser risk of exposure, in case the device running the mobile application is subject to unauthorized access.

Already during the MISSION-T2D lifetime and the realization of the mobile application, it may become a requirement to include a mobile database engine to support more performant data management.

4.2 Risk factors

One risk standing out aside from normal considerations, such as using the software application in unintended ways or misinterpreting the application's output, is that any potential error made during the programming or even the preceding simulations and generation of the used lookup tables requires an update to the application, which also must be deployed on the affected devices.

While adoption rates of application updates are in good in general, it needs to be considered that the error analysis, planning, realization and verification of a bugfix as well as additional requirements for approval and distribution through the corresponding channels, Apple's App Store and the Google Play Store, delay the arrival of results at the end user and as such extend the time period during which the user is likely to be affected by the errors.

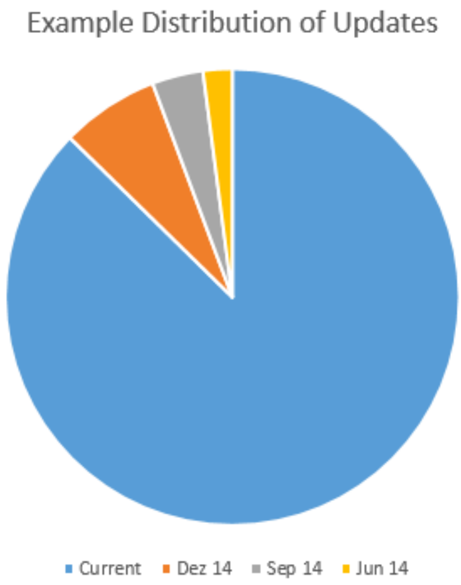

Image 4.2.1: Update adoption of a mobile application in March 2015 by partner MED, showing 13% of users running outdated software versions, some not having updated for over a year.

Also, facing the fact that giving an estimate on the development of type 2 diabetes effectively makes the MISSION-T2D mobile application a tool not only for self monitoring but diagnosis in a limited sense, it is desirable that not just the majority of users have access to the latest versions, but all users.

5 Further exploitation

Due to the focus on research and innovation, as well as the limited timeframe of the project, the MISSION-T2D mobile application is only the initial means of exploitation. In discussions among partners a number of ideas have been brought to the table, which may be realized by the end or after the completion of the project.

5.1 Integration in existing client solutions

Already near the end of the MISSION-T2D lifetime or shortly thereafter, the integration of the project's findings into existing, commercially available products can be considered likely. Partner MED does provide multiple mobile applications which may benefit greatly from the features similar to those implemented into the MISSION-T2D mobile application and can further improve the input parameters by including data from more sensor devices, too.

Such an integration, potentially also at first delivered as an optional, manually activated feature, would serve to carry the results of the project to audiences of several ten to hundred-thousand users, based upon the choice of the application.

5.2 Integration in existing online platforms

Aside from its mobile applications partner MED also maintains a commercially available web-based platform with more than 100.000 registered users at the end of 2014. This platform aggregated over 4 million individual measurement results gathered through over a dozen available sensor devices and multiple mobile and desktop applications and serves both as a means for data backup as well as device to device synchronization of measurements and user profiles.

Image 5.2.1: Weight section of VitaDock Online platform.

A publicly available API allows for reading and writing data, with a complex authentication system restricting access to only those applications approved by partner MED and only to those accounts and stored results where the explicit user's consent was given.

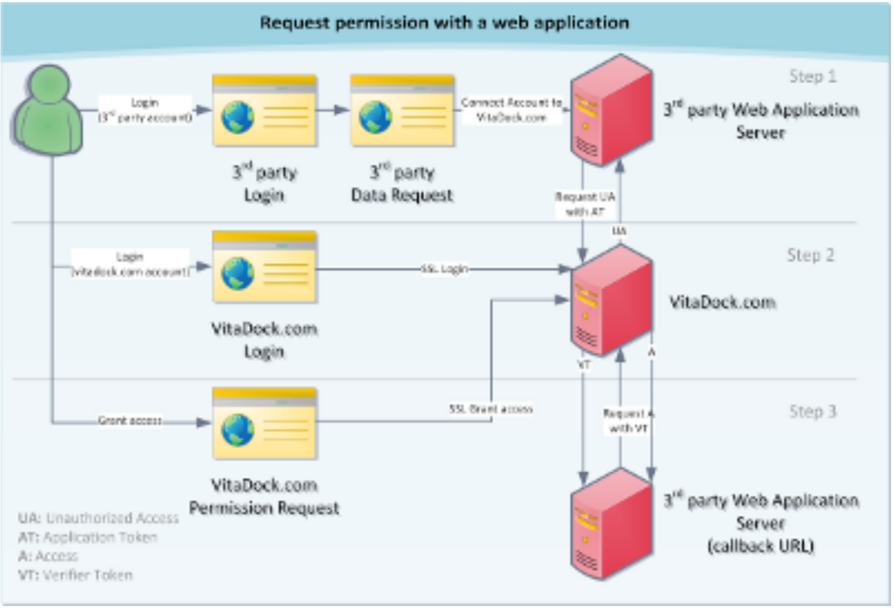

Image 5.2.2: VitaDock API Access.

One distinguishing aspect of integrating the MISSION-T2D findings into this or a comparable platform is the ability to not merely calculate an estimate for an individual person based upon the complete historical record of individual measurement results, but to also provide comparisons in regards to greater groups of users.

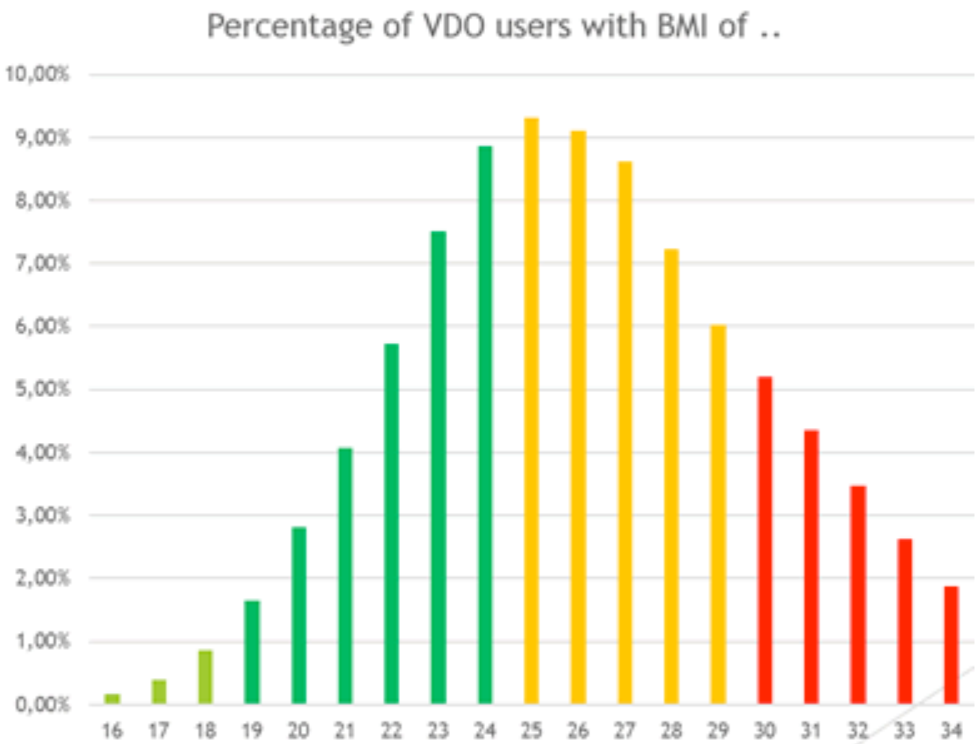

Image 5.2.3: Distribution of users with BMI on VitaDock Online Platform.

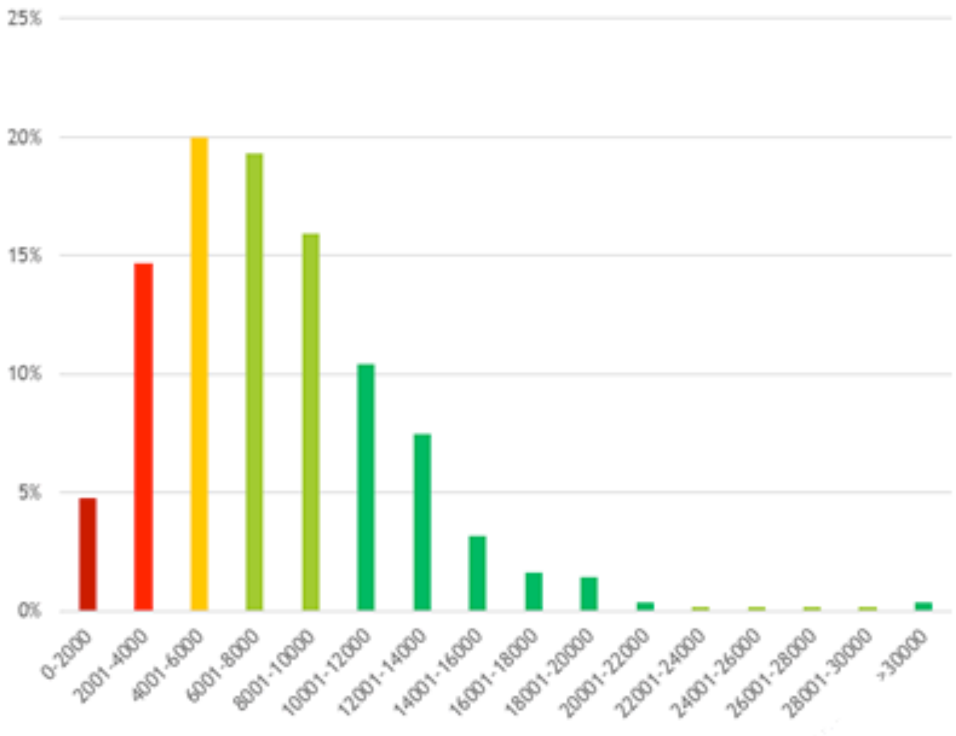

Image 5.2.4: Weekly averages of active ViFit users

In such a scenario an individual user would be enabled to compare his own estimation of the risk of developing type 2 diabetes against that of one of multiple virtual groups, say other VitaDock users of the same age, gender or BMI, further taking into account the measured health and lifestyle parameters of members of these groups.

5.3 Server based approach

The MISSION-T2D approach of implementing the lookup tables resulting from the extensive simulations inside a mobile device application may at some point need to be replaced by a server-based implementation, which, while not reducing the risk of errors in the implementation, dramatically reduces the response time to any such error and guarantees a 100% adoption rate of the affected areas, as only a single central instance of the approach requires maintenance in this special case.

Despite the greater computational capacity of server technology, it is however still not likely to perform a complete simulation for an individual user profile, but instead the concept of lookup tables may be exploited in increased resolution.

5.3.1 Exploitation as a service

Another positive aspect of a central interface accessible through mobile - or other - applications is that the coverage can be easily extended to inclusion in web-based services, which may be exploited internally by the project partners or even provided as a publicly accessible service, as far as offering means of integration into third party applications, by far extending the initial intended use.

This is likely to lead to inclusion in a greater number of projects and platforms, which may combine the results with other, similar estimation technologies for other areas of human physiology.

Partner MED already participates with 3rd parties, such as health insurers, in separate programs focused on coaching diabetes patients, as well as customers without imminent medical conditions, to promote the positive effects of physical activity and a healthy diet on personal health and mental wellbeing. These, as well as related programs are ideal to feature findings of the project.