Pre-empting Type 2 diabetes

Dr Filippo Castiglione and his colleagues discuss the 'Multi-scale Immune System Simulator for the Onset of Type 2 Diabetes' project and its potential to mitigate the explosive growth of this disease

What led you to launch the 'Multi-scale Immune System Simulator for the Onset of Type 2' (MISSION-T2D) project in March 2013?

Filippo Castiglione: MISSION-T2D came from a relatively recent hypothesis about the development of Type 2 diabetes (T2D), which is related to chronic inflammation mainly observed in obese individuals. Since inflammation is the result of an immune reaction, I thought I could use my group's competences to model the immune system and study T2D with a computer model that would encompass physical activity and metabolism.

Why did you choose to adopt a multi-scale approach when creating the MISSION-T2D model?

Shaji Krisnan: We chose a multi-scale approach to capture the interactions at the cellular level and aggregate the results to organ level, and then the whole body. This allows us to observe the metabolic and inflammatory changes at resolutions ranging from minutes to years.

Filippo Castiglione: T2D is a disease of metabolic dysregulation, characterised by a pervasive and multi-systemic state of inflammation. We therefore needed to develop a composite simulation system embracing four levels of description, from the intra-cellular metabolic and gene expression level, to the cellular level of the dynamics of the immune system cells, to the organ scale and, finally, to the whole body disease process. In MISSION-T2D, different mathematical and computational models map one or more aspects represented at these levels, with the outputs of a given model feeding directly into the variables and the parameters of the next, such that all models will merge into a single workflow, creating a multi-scale, integrated simulation.

Your project could have major implications for T2D patients. Will you be showcasing your research at any forthcoming events?

Paolo Tieri: Yes, we will attend some major events such as the International Conference on Systems Biology, the Virtual Physiological Human Conference and the International Conference on Computational Bioengineering, among others. We will also showcase our research and a prototype as soon as it is ready.

Albert De Graaf: In June 2014, we are attending the International Society for the Study of Fatty Acids and Lipids (ISSFAL) in Stockholm, Sweden.

The MISSION-T2D project is expected to be completed in February 2016. Do you have any preliminary results that you can share?

Albert De Graaf: We have an adipose tissue inflammation simulator, a simulator for metabolism in various organ tissues and a long-term diabetes development simulator. Each of them can be demonstrated separately; however, they will be integrated into a single system over the course of the project.

Filippo Castiglione: We already have different independent models working at different scales of description. One of the main challenges of the project lies in integrating these models into a unified simulation architecture.

What is the next step for the future of research surrounding T2D?

Albert De Graaf: The future lies in research that will deliver computer simulation models that can predict T2D on a personalised basis, and in the integration of such predictive models into both self-monitoring and clinical decision support systems. It can be thought of as a weather forecast for your health, describing the effectiveness of treatments that you take or for the effects of not adhering to a healthy lifestyle.

Paolo Tieri: Mounting evidence shows that abnormalities in the complex crosstalk between the immune system, gut microbiota and adipose tissue may be responsible for T2D, but further translational research and clinical studies focusing specifically on these issues are needed to validate hypotheses regarding the potential roles of these systems. Computational approaches should be used to discriminate potential disease-prone configurations and speed up this process. These investigations should complement epidemiological studies and augment the evidence for individual-based intervention recommendations.

Marc Ernst: I represent Medisana Space Technologies GmbH, Germany, which is a leader in home healthcare manufacturing and healthcare products for the end user. This project is innovative because it consists of the extrapolation of meaningful predictions and estimates from raw data collected by end users, in order to offer added value beyond visual representations of the results themselves. Medisana is hoping that the integration of key factors, such as user behaviour and eating habits, into the equation will enable end users to live a generally more healthy life. In the long run, we're curious whether similar models can be found for other conditions, such as cardiovascular diseases.

MISSION-T2D

Taking on Type 2 diabetes

An ambitious, international project that is integrating genetic, metabolic and nutritional data with computer modelling promises prediction and earlier diagnosis of Type 2 diabetes alongside personalised treatment options

TYPE 2 DIABETES mellitus (T2D) is a common age-related disease and a major health concern, particularly in developed countries. In 1985, around 30 million people worldwide were living with T2D, but today that figure has risen to some 285 million people, with 60 million of those living in Europe.

The sharp rise in T2D diagnoses in recent decades is not only due to the ageing populations of developed nations, but also to dietary differences and a largely sedentary lifestyle. These factors have combined to create an obesity epidemic, with as many as half of the people affected by T2D unaware of their condition. It is predominantly caused by pancreatic dysfunction and the body progressively losing its capability to respond to insulin, termed insulin resistance, and consequent increase in the blood sugar levels. As this resistance increases, β-cells in the pancreas grow in mass and produce greater

levels of insulin to compensate. Individuals whose β-cells are able to respond effectively to a greater demand for insulin do not become diabetic; however, in insulin-resistant people whose β-cells cannot keep up with demand, hyperglycaemia and T2D can result.

Although genetic and epigenetic factors can predispose someone toward developing T2D, obesity plays a primary role in its development and often characterises the disease, along with imbalance of metabolic pathways and immune dysfunction. It can result in various complications such as heart disease, stroke, glaucoma or kidney failure.

Scientists and healthcare professionals now believe that T2D should be considered a systemic disease, sustained by a pervasive, metabolically-driven state of inflammation. There is therefore a pressing need to better understand the relationships between the underlying mechanisms – intertwined in a complex manner at molecular, tissue and organ levels – which progress from obesity to insulin resistance to full-blown disease. It is also essential that this exploration take place within the context of personalised medicine, with earlier identification of patient-specific diagnostic parameters and related inflammatory indicators.

ADVANCED SIMULATION

'Multi-scale Immune System Simulator for the Onset of Type 2 Diabetes' (MISSION-T2D) is an EU-funded project that began in March 2013. It aims to develop and validate an integrated, multi-scale and patient-specific model comprising genetic, metabolic and nutritional data. Its goal is to simulate the metabolic and inflammatory processes involved in the onset and progression of T2D from those at the cellular level to whole-body functions across all of the major organs. The project consortium are working to make it an invaluable tool for clinical decision-makers in diagnosing T2D, predicting an individual's risk of developing the disease, and monitoring disease progression and response to potential therapies.

The project is based at the National Research Council's Institute for Applied Mathematics 'Mauro Picone' (IAC–CNR) in Rome, Italy, and Dr Filippo Castiglione – a computer scientist with an interest in simulating immune-related diseases – is the project coordinator. "MISSION-T2D will be able to calculate the consequences of adopting a certain lifestyle, in terms of nutritional habits and physical activity patterns, it will forecast the risk of developing the disease," he outlines. "The simulation will be dependent on user-specific parameters such as weight, gender and age, so it will be able to make personalised predictions."

SPECIALISED COMPETENCES

Multiple factors, including metabolism, inflammation, gut microbiota and mental stress, contribute to the development of T2D. Therefore, multidisciplinarity is vital to the success of MISSION-T2D, and it was essential for Castiglione to create a team that included expertise from across these domains. Castiglione's colleagues on the project are widespread, and the consortium includes four university partners, two research centres and one private sector business. Directly working on the project is physicist Dr Paolo Tieri, also at the IAC-CNR; Marc Ernst, a project manager at Medisana GmbH, in Neuss, Germany; Senior Scientist Dr Albert de Graaf at Netherlands Organisation for Applied Scientific Research (TNO); and the electronics engineer and scientist, Dr Shaji Krishnan, who is also at TNO. Though an all-star team of researchers, there was more expertise needed to ensure the project's success. "This project has not only required data from fundamental research projects, but from clinical studies, necessitating a good connection with the clinical domain," de Graaf explains. "Strong expertise in mathematical modelling is also vital in translating all of the complex interactions between factors into computer simulations."

To this point, the project team also comprises an array of biomathematicians, bioinformaticists, data analysers and computational modellers. Two of the partners – the Alma Mater Studiorum-University of Bologna (UniBO), Italy, and at TNO – have strong expertise in the biomedical field, while the CNR of Italy and Cambridge University, UK, bring experience in computing, modelling and the simulation of bio-related phenomena. Quantitative methods for assessing motor and postural abilities are contributed by the University of Rome 'Foro Italico', Italy, and the University of Sheffield, UK; and Medisana Space Technologies GmbH, based in Germany. Immunology, ageing and T2D metabolism knowledge and data will be provided by the two project's clinical partners UniBO and TNO.

COMPLEX SYSTEMS AND INFLAMMATORY RESPONSES

At the basis of MISSION-T2D is understanding the inner workings of several complex bodily systems such as cellular stress and inflammation. Cells are subject to a number of stress mechanisms that can lead to insulin resistance and β-cell dysfunction. These metabolic 'stressors' can be triggered by over-nutrition and are associated with immune system inflammatory responses, including the production and release of soluble mediators including several pro-inflammatory cytokines. The altered composition of these immune cells can lead to a pro-inflammatory tissue environment, which may last indefinitely. A second source of inflammation results from changes that occur in the overall composition of populations of intestinal microorganisms with age, with studies showing a correlation between these changes and increased levels of cytokines in blood plasma.

There are also differences in gut microbiota composition between obese individuals and those of average weight, which contributes to inflammation. These processes are not clearly understood; in fact, it seems that many are governed by non-linear kinetics and involve complex feedback loops. Additionally, the ageing process itself involves chronic, low-level inflammation (inflamm-aging) that, in concert with metabolically driven inflammation (metaflammation) and the inflammatory stimuli resulting from changes in gut microbiota, plays a central role in the pathogenesis of T2D.

The complexity of these systems and their interactions necessitates a comprehensive, multi-level approach to modelling them. MISSION-T2D does this by linking diabetes development in four levels: at a whole-body level; at a macroscopic level to address metaflammation-induced variation in insulin resistance; at mesoscopic level to include dynamic processes in inflammation and metabolism; and at the microscopic level to fill in molecular details. This hierarchy gives researchers unprecedented insight into the intricate interplay between all of these mechanisms.

PERSONALISING MEDICINE

Traditionally, medicine has taken a largely reactive approach to disease, with treatment taking place after the appearance of symptoms. However, modern advances in genetics are enabling a more comprehensive approach to human healthcare, heralding an age of personalised medicine where risk is quantified before the onset of disease, and managed proactively and preventatively. MISSION-T2D falls squarely within this new medical paradigm. While existing knowledge around the risks of developing T2D – age, weight, distribution of fat, race and family history – is already strong, as is our understanding of how to treat the condition, there remain limitations that the project will help to overcome. "Within the context of personalised medicine, existing knowledge is insufficient in helping us to predict the time from T2D onset to disease progression, and the result of therapeutic intervention," Krishnan explains. "Combining early warning inflammatory signals with knowledge of risks allows earlier diagnosis, augmenting our ability to predict the onset of disease."

Therapy regimes can be both personal and personally manageable with apps designed to help patients self-monitor

APPLYING THE RESEARCH

Earlier recognition of these signals and a more rapid diagnosis would bring significant benefits – particularly to insulin-resistant individuals at risk of developing T2D, as insulin resistance can be lowered, or even entirely reversed, if diagnosed early enough. β-cell function can also be improved significantly if appropriate lifestyle changes are adopted; moreover, these lifestyle changes such as diet control and exercise would not have to be as extreme. "By deepening our understanding of the complex mechanisms underpinning the onset of T2D, we hope to identify early diagnostic parameters and related inflammatory indicators, the latter being a therapeutic target," Castiglione asserts. "The integration of metabolic, nutritional, inflammatory, genetic and gut microbiota profiles with clinical data will eventually generate predictive biomarkers suitable for translation into cost-effective, mobile diagnostic tools."

Medisana will be at the heart of creating these mobile diagnostic tools in the form of an app. "Medisana has been working on medical and wellness products for the last 30 years, and in 2011 was one of the first companies to supply medical sensor devices that work with a smartphone," Ernst reveals. "In 2014, we introduced our online health platform, VitaDock Online, which will serve as the basis for MISSION-T2D."

The research team will expand the established VitaDock Online immune system simulator, adding various discrete and continuous mathematical methodologies in order to build in functionality around patient specificity, including data on metabolic flexibility, lifestyle parameters, nutritional habits and genetic signatures. This will enable researchers to not only model *in silico* the efficacy of a given treatment on various systemic features of the disease, but also to create an integrated modelling platform that will form the basis of a user-friendly diagnostic tool.

Ultimately, the international team will develop a cross-platform mobile app through Medisana that clinicians will be able to use for patient-specific interventions. It will also empower individual patients, allowing them to monitor their own metabolic health, assess the efficacy of various anti-inflammatory therapies and mitigate or lessen the complications associated with the disease. The research team intends for the app to encourage patients to pursue positive lifestyle changes such as the modification of dietary habits or changes in levels of physical activity through the creation of an emotional engagement with their real-time health data.

FROM T2D AND BEYOND

While there is still a year-and-a-half before MISSION-T2D is set to complete, the team is already looking to future applications. They want to apply the model to diseases that have similar underlying causes and habits to T2D. For example, other noncommunicable diseases such as cardiovascular disease might benefit from a similar model. "These simulation models include a more holistic view on health than only glucose and insulin metabolism. Even though there is still a long way to go before this project is finished, I believe it can be adapted to act as a preventative tool for other diseases," de Graaf states.

The MISSION-T2D project's partners.

INTELLIGENCE

MULTISCALE IMMUNE SYSTEM SIMULATOR FOR THE ONSET OF TYPE 2 DIABETES INTEGRATING GENETIC, METABOLIC AND NUTRITIONAL DATA

OBJECTIVES

To develop an integrated simulation architecture to estimate the risk of Type 2 diabetes on the basis of the metabolic and inflammatory status, and in response to a variety of nutritional and metabolic stimuli, as well as lifestyle habits such as physical activity.

KEY COLLABORATORS

Dr Paolo Tieri, Institute of Applied Mathematics, National Research Council of Italy (CNR), Italy • **Dr Albert de Graaf**; **Dr Shaji Krisnan**, Netherlands Organisation for Applied Scientific Research, The Netherlands • **Marc Ernst**, Medisana GmbH, Germany

PARTNERS

National Research Council of Italy • University of Sheffield • University of Rome 'Foro Italico' • The Chancellor, Masters and Scholars of the University of Cambridge • Alma Mater Studiorum-University of Bologna • Netherlands Organisation for Applied Scientific Research • Medisana Space Technologies GmbH

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FILIPPO CASTIGLIONE completed a degree in computer science from the University of Milan, Italy, and briefly visited the IBM Thomas J Watson Research Center, USA, and the Department of Molecular Biology at Princeton University, USA, in an academic capacity. After a year at ST Microelectronics in Italy, he started his scientific career, completing a doctorate in scientific computing at the University of Cologne in Germany. He continued his progression, becoming a four-month visiting scholar at Harvard Medical School, USA, and then completing a one-year postdoctoral study in Israel. Castiglione is now a Senior Researcher at CNR studying the modelling of complex biological systems with a particular interest in the immune system and related pathologies.