CURRICULUM VITAE CLAUDIO COBELLI

PERSONAL INFORMATION

Family name, First name: Cobelli Claudio
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EDUCATION

1970	Laurea Electronic Engineering, Faculty of Engineering, University of Padova, Italy

CURRENT POSITION

1981-2018	Full Professor of Bioengineering, University of Padova, Italy; Senior Teaching Scholar since 2017

PREVIOUS POSITIONS

1970-1973	Research Scientist, Institute of System Science and Bioengineering, National Research Council, Padova, Italy
1973-1975	Associate Professor of Biological Systems, University of Firenze, Italy
1975-1981	Associate Professor of Biomedical Engineering, University of Padova, Italy
1978	Visiting Professor, Northwestern University, Evanston, IL
1980	Visiting Professor, The City University, London, UK
2000-2006	Affiliate Professor with Bioengineering, University of Washington, Seattle, WA

FELLOWSHIPS AND AWARDS

1976-1977	NATO Fellowship, Laboratory of Theoretical Biology, NCI, NIH, Bethesda, MD
2003	Fellow Institute of Electrical and Electronic Engineers (IEEE),1997-2002 Senior Member
2003	Fellow Member Galileian Academy of Science, Literature and Arts, University of Padova
2005	Fellow Biomedical Engineering Society (BMES), 1990-2005 Senior Member
2010	Fellow American Institute for Medical and Biological Engineering (AIMBE)
2010	Artificial Pancreas Award, Diabetes Technology Society (DTS)
2012	European Alliance for Medical and Biological Engineering & Science (EAMBES)

INSTITUTIONAL RESPONSIBILITIES

1982-1999	Member, Ph.D. Program on Bioengineering, Polytechnic of Milano, Italy
1986-1994	Member, International Measurement Confederation (IMEKO) Technical Committee on Measurement in Biology and Medicine
1990-1996	Chairman, International Federation of Automatic Control (IFAC), Technical Committee on Modelling and Control Biomedical Systems
1997-2003	Chairman, Italian Bioengineering Group
2000-2009	Chairman, Graduate Programs on Bioengineering, University of Padova, Italy
2000-2011	Chairman, Ph.D. Program on Bioengineering, University of Padova, Italy
2002-2004	Co-Chairman Joint Ph.D. Program University of Padova & City University, London,UK

2003-present	Steering Committee Member of the Italian Bioengineeering Group
2007-2008	Amministrative Committee, IEEE Engineering in Medicine and Biology Society (EMBS)
2007-2010	Member Steering Committee Galileian School of Higher Education, University of Padova, Italy
2011-2015	Chairman, Steering Committee of the Trieste University Hospital, Trieste, Italy
2012-2015	Member of the Evaluation Group for Assessment of Research of Italian Ministery of University and Research 2004-2010
2019-2022	Member of Consiglio Superiore di Sanita', Italian Ministry of Health

ADVISORY & EDITORIAL BOARD RESPONSABILITIES

1993-1999	Advisory Board Children Nutrition Research Center, Baylor College of Medicine, Houston, US
1995-1997	Evaluator of PhDs at City University, London, and University of Turku, Turku and Reader Professorship, City University, London
2003-2008	Member of IEEE Award Committee
2005-2011	Panel member of Italian Strategic Program on New Developments of Biomedical Industries of the Ministery of University and Research
1983-2008	Mathematical Biosciences, Q1 (**Associate Editor**)
1984-1997	American Journal of Physiology, Modelling in Physiology, Q1 (**Editorial Board**)
1990-1996	Control Engineering Practice, Q1 (**Editorial Board**)
1991-2009	American Journal of Physiology, Endocrinology and Metabolism, Q1 (**Editorial Board**)
1993-1996	Diabetologia, Q1 (**Associate Editor**)
2003-present	IEEE Transactions on Biomedical Engineering, Q1 (**Associate Editor**)
2006-2013	J. Diabetes Science & Technology, Q1 (**Editorial Board**)
2013-present	J. Diabetes Science & Technology, Q1 (**Associate Editor**)
2007-present	Member Steering Committee of IEEE Trans on NanoBiosciences
2008-2015	Representative of IEEE EMBS to IEEE Trans on Comp Biol & Bioinf
2009-present	Member Scientific Committee Tecnomed, University of Milan Bicocca
2009-present	Member Scientific Committee Consorzio Veneto di Ricerca

SUPERVISION OF GRADUATE STUDENTS AND POSTDOCTORAL FELLOWS

I was among the founders of bioengineering in Italy, the 1st President of the Italian Bioengineering Group, and the initiator of bioengineering at the Department of Information Engineering, University of Padova, which, today consists of more than 40 people, among professors, researchers, graduate and postdoc fellows

1980 – 2011 23 Postdocs/ 42 PhD/ more than 400 Master Students

Several fellows went to prestigious US and EU universities, other fellows moved to research and to biomedical/biotech companies.

TEACHING ACTIVITIES

1973-1975	Biological Systems, Department of Electronics, University of Firenze, Italy
1975-2005	Bioengineering, Department of Information Engineering, University of Padova, Italy
2006-2018	Modelling & Control of Biological Systems, Department of Information Engineering, University of Padova, Italy (taught in English since 2015)

ORGANISATION OF SCIENTIFIC MEETINGS

I organized and chaired:

1981 - Carbohydrate Metabolism. Quantitative Physiology and Mathematical Modelling, Padova, Italy

1988 - Modelling and Control in Biomedical Systems, International Federation of Automatic Control (IFAC) 1st Congress, Venice, Italy.

In addition, I was member of the Steering Committee of the IFAC Modelling and Control Conferences 1991,1994,1997, 2000, 2003, 2006, 2008, 2010 and of the IEEE EMBS conferences 2001, 2003, 2005, 2008, 2010, 2012 and 2015.

MEMBERSHIPS OF SCIENTIFIC SOCIETIES

1985-present Member, American Diabetes Association (ADA);1985-present Member, European Association for the Study of Diabetes (EASD);1985-1996 Member, IEEE; 1997-2002 Senior Member IEEE; 1990-2005 Senior Member; Biomedical Engineering Society (BMES)

MAJOR RESEARCH GRANT

NIH PI: Deconvolution of Physiological Systems,2003-2006; Role of Pulsatile Insulin Secretion,2009-2013; Mechanisms of Insulin Resistance in Man,2009-2013; Integrated Approaches to Close the Loop in Type 1 Diabetes,2009-2014; Modular Bio-Behavioral Closed-Loop Control of T1D,2009-2014; Integrated Approaches to Close the Loop in Type 1 Diabetes,2009-2014; The Effects of TCF7L2 on Glucose Metabolism,2009-2017; The Effect of Bariatric Surgery on Glucose Metabolism,2010-2015; Ambulatory Artificial Pancreas: Merging Physiology, Behavior & Control,2011-2016.

Foundations PI: *Juvenile Diabetes Research Foundation*, The Artificial Pancreas Project,2006-2011; *Leona M and Harry B Helmsley Charitable Trust*, Novel Method to Measure Subcutaneous Glucose Transport in Humans,2012-2015.

EU PI: *FP6*: Fighting cardio-vascular diseases by preventive lifestyle & early diagnosis, 2003-2009; Biosimulation-A New Tool in Drug Development, 2004-2010; FP7 : Diabetes Advisor 2008-2012;IMI-Surrogate Markers for Micro- and Macrovascular Hard Endpoints for Innovative Diabetes Tools, 2009-2014; Artificial Pancreas at Home 2010-2014.

***Italian Ministry of Research & University Projects: National Scientific Coordinator*:** five 3-year projects 2000-2002; 2001-2003; 2004-2006; 2008-2010; 2017-2020.

Industry Projects PI : Sanofi Aventi Deutschland GmbH 2012-2014; Dexcom Inc. 2011-2018.

PUBLICATIONS, H-INDEX and PATENTS

I published **564 papers** in internationally refereed journals, co-author of **8 books** and holds **10 patents** with an **h-index of 83, citations 27951 (Scopus) and 104, citations 46154 (Google).** All the details are reported separately in the Publications and Patents document.

CONTRIBUTION TO SCIENCE

I pioneered the use of mathematical models to describe glucose homeostasis in humans. My research activity has largely focused on developing *glucose minimal (parsimonious) models* of healthy, prediabetes and Type 2 diabetes pathophysiology to measure crucial parameters otherwise not accessible to direct measurement from *in vivo* clinical tests, also using tracers. These models are now used world-wide to determine the cause of hyperglycemia in people with diabetes of diverse backgrounds and to target and assess the effectiveness of novel therapies.

In the last 10 years I also worked on Type 1 diabetes by developing the *glucose maximal (large-scale) model* of Type 1 diabetes to perform *in silico* clinical trials which has been accepted in 2008 by FDA as a substitute to animal trials for the preclinical testing of certain insulin treatments, an unprecedented event.

Also central in the last years is the research on *closed-loop control of glucose in Type 1 diabetes* (*artificial pancreas*) with a focus on *glucose sensors, control algorithms and clinical trials*. I created an *algorithmically "smart" continous glucose monitoring (CGM) sensor,* which on December 2017 FDA approved for non-adjunctive use , and subsequently, in March 2018, Medicare announced criteria for

system reimbursement to all Type 1 and Type 2 people on intensive insulin therapy. Artificial pancreas research was accelerated thanks to the FDA accepted Type 1 diabetes glucose maximal model: I was able to do the first artificial pancreas trial in humans in 2008 in the hospital after 3 months of the IDE granted by FDA solely on the basis of *in silico* testing of the safety and efficacy of the designed system. My group was also the first to demonstrate the feasibility of outpatient ambulatory closed-loop for 48 hrs. employing a "wearable" smartphone-based artificial pancreas prototypes. Outpatient trials have now month duration and I contributed to improve the *control algorithms* to render them person-specific, adaptive and fault tolerant which is critical, given the large inter-individual variability, for patient safety and treatment effectiveness in long-lasting free-living condition
In essence my seminal work has resulted in the convergence of discovery science, in depth clinical assessment, and use sophisticated *in silico* models to improve the life the millions of people through the world who have diabetes.

1. **Measurement of insulin action and secretion from an intravenous glucose tolerance test (IVGTT)**.

I pioneered the use of mathematical models to assess ***insulin action*** in humans by developing with Dr. Bergman in 1979 the IVGTT glucose minimal model that enabled to arrive at an index of insulin action, called insulin sensitivity. The model was derived first in dogs [1] and two years later in humans [2]. The idea was that minimal models must be parsimonious, i.e., they only describe the key components of the system. Desirable features of a minimal model include i) physiology based; ii) parameters estimated with reasonable precision; iii) parameter values within physiologically plausible ranges; and iv) system dynamics described with the smallest number of identifiable parameters. One generally proceeds by proposing a series of system models, beginning with the simplest and systematically increasing the complexity by including more known physiological details. Each model is first tested for a priori identifiability, subsequently numerically identified from the data, and finally the most parsimonious model is selected by using the identification/validation criteria described before. To facilitate the model selection process, system partition was introduced. In fact, to describe plasma glucose and insulin data it is necessary to simultaneously model not only the glucose, but also the insulin system and their interactions. This means that, in addition to modeling insulin action, one has also to model glucose-stimulated insulin secretion. Since models are, by definition, wrong, an error in the insulin model would be compensated by an error in the glucose model, thus introducing a bias in insulin sensitivity. To avoid this interference, the dynamic contribution of a subsystem should be eliminated. The authors developed a conceptual "loop cut" [3]: the system is partitioned in two subsystems which are linked together by measured variables, the insulin and the glucose subsystems. When the system is perturbed, e.g., by a glucose injection, and the time courses of plasma glucose and insulin are measured, then their time course can be considered as "input" (assumed known) and "output" (to be fitted) of the insulin and glucose subsystems, respectively. Models are then proposed not for the whole system but for each of the two subsystems, independently, thus considerably reducing the difficulties of modeling. Seven models of increasing complexity were proposed to explain plasma glucose concentration by using plasma insulin as the known input. The chosen minimal model was a nonlinear model: it assumes that glucose kinetics can be described with one compartment and that remote (with respect to plasma) insulin controls both net hepatic glucose balance and peripheral glucose disposal. The remote insulin finding was later experimentally proven to be the interstitial fluid [4]. The model provides an index of insulin sensitivity, which has been validated in numerous studies against the independent glucose clamp technique and has been widely employed in more than 1000 papers [4].
This index is essentially a steady-state measure, i.e., it provides the magnitude of insulin sensitivity but does not account for how fast or slow insulin action takes place. A new index, called dynamic insulin sensitivity, has been introduced to incorporate also the timing of insulin action [5].

The IVGTT glucose minimal model was later complemented by the IVGTT C-peptide minimal model to measure ***beta-cell function*** [6]. C-peptide is the correct signal to assess beta-cell responsivity since it is

secreted equimolarly with insulin but it is not degraded by the liver. The model integrates a secretion model into the two compartment model of C-peptide kinetics. Insulin secretion is modeled with two components: first-phase secretion, likely representing exocytosis of previously primed insulin secretory granules, is portrayed as the release of insulin from a rapidly turning over compartment. Glucose exerts a derivative control, since first-phase secretion is assumed to be proportional to the increase of glucose from basal up to the maximum, through a parameter that defines the first-phase responsivity. Second-phase insulin secretion is believed to be derived from the provision and/or docking of new insulin secretory granules, and is assumed to be proportional to glucose concentration through a parameter that defines the second-phase responsivity. The second-phase secretion term includes a delay, presumably representing the time required for new granules to dock, be primed and then exocytosed.

Since the glucose–insulin system is a negative feedback control system, beta-cell function needs to be interpreted in light of the prevailing insulin sensitivity. One possibility is to resort to a normalization of beta-cell function based on the ***disposition index paradigm***, first introduced in [2], where the disposition index DI is given by beta-cell function multiplied by insulin sensitivity. While regulation of carbohydrate tolerance is undoubtedly more complex, the paradigm proposed that beta-cells' ability to respond to a decrease in insulin sensitivity by adequately increasing insulin secretion can be assessed by measuring the product of beta-cell function and insulin sensitivity. DI allows to assess if the beta-cell function is appropriate in light of the prevailing insulin sensitivity, to monitor their variations in time, and to quantify the effect of different treatment strategies, However, the glucose–insulin feedback system is in all likelihood more complex than a rectangular hyperbola, i.e., a power function DI = beta-cell function x (insulin sensitivity)^{alfa} = constant. This issue, as well as several methodological issues which, unlessfully appreciated, could lead to errors in interpretation, have been thoroughly addressed in [7].

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2. Bergman RN, Phillips LS, Cobelli C, "Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose". J Clin Invest 68:1456-1467,1981.
3. Bergman RN, Cobelli C, "Minimal modeling, partition analysis, and the estimation of insulin sensitivity". Fed Proc 39: 110-115, 1980.
4. Bergman RN, "Lilly lecture 1989. Toward physiological understanding of glucose tolerance. Minimal-model approach," Diabetes, 38: 1512–1527, 1989.
5. G. Pillonetto, A. Caumo, G. Sparacino, and C. Cobelli, "A new dynamic index of insulin sensitivity". IEEE Trans.Biomed Eng 53: 369–379, 2006.
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2. **Measurement of insulin action and secretion from an oral test (Mixed Meal Tolerance Test, MMTT/ Oral Glucose Tolerance Test, OGTT)**

The IVGTT establishes glucose and insulin concentrations that are not seen in the normal life, and it would be desirable to measure ***insulin sensitivity*** in the presence of physiological conditions, e.g., during a meal MMTT or OGTT. In addition the IVGTT does not provide a measure of the incretin effect on insulin secretion. By sitting on the giant shoulders of the IVGTT minimal model method, the oral glucose minimal model has been developed. It has a similar structure to the IVGTT model apart from the input: the known

injected glucose dose is substituted by the rate of appearance of glucose in plasma described by a parametric function [1]. The availability of a model-independent, tracer-based measure of the systemic appearance of ingested glucose (see Section 3) enabled the development and validation of a model to describe glucose appearance after ingestion of oral glucose alone or as part of a mixed meal.
The model provides an index of insulin sensitivity, which has been validated against independent techniques [2,3]. Also for MMTT/OGTT, the dynamic insulin sensitivity index can be calculated [4].

Also beta-cell function has been assessed from MTT/OGTT [5], by properly adapting the IVGTT minimal model to the more gradual changes in glucose, insulin, and C-peptide concentrations. From the oral model, two ***beta-cell responsivity*** indices can be derived as well, related to the dynamic (i.e., proportional to the rate of change) and the static (i.e., proportional to) glucose control. Of note, the oral beta-cell function model has allowed to quantitate the incretin effect [6].

By using the C-peptide oral minimal model in conjunction with a an insulin (post-hepatic) minimal model it has been possible to also quantitate ***hepatic insulin extraction*** [7], an important parameter to enrich the metabolic parametric portrait of an individual.

More recently a ***glucagon-like-peptide 1 (GLP-1) minimal model*** has been developed [8] by describing the action of gut hormones on insulin secretion. This new model completes the metabolic indices portrait one can obtain from an OGTT/MMTT.

The ***Disposition Index***, like in the IVGTT, can be calculated in order to express the insulin secretory response as a function of the prevailing insulin action.

The two glucose and C-peptide oral minimal models constitute the ***Oral Minimal Method*** which has been recently presented in a Perspective paper in Diabetes [9] and has been used in a number of pathophysiological studies, including:

- Role of age and gender (Basu et al., Diabetes 2006)
- Reduced OGTT & meal Protocols (Dalla Man et al., Diabetes 2006)
- Pathogenesis of prediabetes (Bock et al., Diabetes 2006)
- Role of race (Petersen et al., Proceedings of the National Academy of Science 2006)
- Efficiency of anti-aging drugs (Nair et al., New England Journal of Medicine 2006)
- Type 2 diabetes (Basu et al., Diabetes Care 2009)
- Effect of DPP-4 inhibitors (Bock et al., Diabetes Care 2009)
- Children and adolescents (Cali et al., Diabetes Care 2009; Sunehag et al., Obesity 2009)
- Effect of PPAR alpha and gamma agonists (Balasubramanian et al., Diabetic Medicine 2010)
- Model of GLP-1 action on insulin secretion (Dalla Man et al., Am J Physiol Endocrinol Metab 2010; Dalla Man et al., Diabetes Technol Ther. 2016)
- Insulin secretion and action across the spectrum of prediabetes (Bock et al., Clin Endocrinol 2012)
- Effect of common genetic variation on insulin secretion and action (Sathananthan et al., Diabetes 2012)
- Pregnancy (Hodson et al., Hormone Metab Res 2013)
- Type 1 diabetes (Hinshaw et al., Diabetes 2013)
- Effect of colesevelam on type 2 diabetes (Smushkin et al., Diabetes 2013)
- Effect of pramlintide administration in healthy (Hinshaw et al., Am J Physiol EM 2014) and type 1 diabetes (Hinshaw et al., J Clin Endocrinol Metab 2016)
- Effects of GLP-1 receptor blockade in health and after bariatric surgery (Sathananthan et al., Diabetes Metab Syndr Obes 2014; Shah et al., Diabetes 2014)
- Effect of caloric restriction (Sathananthan et al., J. Nutr 2015)
- Role of a common variant in the MTNR1b gene (Zheng et al., Obesity 2015)

- Association between thyrotropin levels & insulin sensitivity in euthyroid obese adolescents (Javed et al., Thyroid 2015)
- Effect of Cholecalciferol supplementation (Javed et al., J Nutr. 2015)
- Defects in mitochondrial efficiency and H2O emissions in obese women (Konopka et al., Diabetes 2015)
- Effects of biliopancreatic diversion (Vasques et al., Obes Surg. 2015; Vasques et al., Obes Surg. 2016)
- Effect of metformin in prediabetes (Konopka et al., Cell Rep 2016)
- Effect of slow-wave disruption in adolescents (Shaw et al., Sleep 2016)
- TCF7L2 Genotype and α-cell Function in Humans Without Diabetes (Shah et al., Diabetes 2016)
- Effects of the BET-inhibitor, RVX-208 on the HDL lipidome and glucose metabolism in individuals with prediabetes (Siebel et al., Metabolism 2016)
- Effects of the BET-inhibitor, RVX-208 on the HDL lipidome and glucose metabolism in individuals with prediabetes (Siebel et al., Metabolism 2016)
- Effects of dual GLP1/GCG agonist on postprandial glucose metabolism (Goebel et al., ADA 2018)

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3. C. Dalla Man, K. E. Yarasheski, A. Caumo, H. Robertson, G. Toffolo, K. S. Polonsky, and C. Cobelli, Insulin sensitivity by oral glucose minimal models: Validation against clamp. Amer J Physiol Endocrinol Metab 289: E954–E959, 2005.
4. G. Pillonetto, A. Caumo, G. Sparacino, and C. Cobelli, "A new dynamic index of insulin sensitivity". IEEE Trans. Biomed Eng 53: 369–379, 2006.
5. E. Breda, M. K. Cavaghan, G. Toffolo, K. S. Polonsky, and C. Cobelli, "Oral glucose tolerance test minimal model indexes of β-cell function and insulin sensitivity". Diabetes 50: 150–158, 2001.
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3. **Tracer-based measurement of glucose metabolism**

Measurement of disposal and liver insulin sensitivity from an oral test

Both the IVGTT and MTT/OGTT minimal models provide a composite measure of insulin action, i.e., the net effect of insulin to inhibit glucose production and stimulate glucose utilization. It is possible to dissect insulin action into its two individual components by adding a glucose tracer to the IVGTT or MTT/OGTT, thanks to the tracer's ability to separate glucose utilization from production. The labeled IVGTT single

compartment model came first [1,2], later improved by a two-compartment version [3]. More recently, a stable labeled MTT/OGTT model was proposed in [4] and subsequently refined in [5]. The indices of disposal and liver insulin sensitivity have been validated against the independent euglycemic hyperinsulinemic clamp technique, e.g., for the MTT/OGTT in [6,7]. Of note is that the combined use of the tracer and tracee models can also provide glucose fluxes, i.e., one can arrive at the flux portrait by using a different experimental/modeling strategy than that described in the Section below belo. For instance during MTT, they provide the rate of appearance of glucose, its rate of disappearance and hepatic glucose production, a flux portrait [5] which has been validated against that provided by the tracer clamp technique [8,9,10].

Postprandial Glucose Fluxes.

Glucose production and utilization vary as an effect of a perturbation, e.g., a meal, due to endocrine and nervous control mechanisms. To circumvent the need of explicitly describing these controls, Steele [11] proposed to use a glucose tracer and interpret the data with a single compartment model with a time-varying parameter. The model allowed calculating the rate of appearance Ra, and disappearance Rd, of glucose from the mass balance equation. An important contribution was provided by Norwich and Radziuk [12] they proposed an ingenious tracer clamp infusion protocol, which renders the estimation of Ra less model-dependent, i.e., with a perfect clamp, the Ra can be calculated from the tracer infusion rate with an algebraic equation. This new approach was validated in dogs [13], and later put on more solid theoretical grounds by us [14]. The increased availability and use of stable glucose isotopes has stimulated the generalization to the tracer-to-tracee clamp technique [15,16,17]. Today the clamp technique has become a standard to measure glucose fluxes. Depending on the question being asked, both dual or triple tracer protocols are implemented, the rule being that if one is interested in n fluxes it is necessary to use n + 1 tracers, e.g., to estimate glucose production and Ra after a meal one has to use three tracers. The tracer techniques to assess postprandial glucose metabolism have been recently the object of a Perspective paper in Diabetes [18] where guidelines and operational formulas have been presented to make the technique easy to implement to assess postprandial glucose metabolism in prediabetes and type 2 diabetes.

Cellular Portrait of Insulin Sensitivity in Muscle by Positron Emission Tomography (PET).

While whole-body models can provide an overall measure of insulin action, it is important to measure insulin action at the organ/tissue level, e.g., the skeletal muscle, by quantitating the effect of insulin on the individual steps of glucose metabolism, i.e., transport from plasma to interstitium, transport from interstitium to cell, and phosphorylation. Understanding which metabolic step is impaired, e.g., in prediabetes or type 2 diabetes, can guide a targeted therapeutic strategy. Direct measurement *in vivo* of these individual steps is not possible, and two model-based approaches are available both employing tracers with glucose at steady state: the classical multiple tracer dilution technique and the more recent PET technique. The multitracer dilution technique consists of the simultaneous injection, upstream of the organ, of more than one tracer, which allows separate monitoring of the individual steps of glucose metabolism. Compartmental models have been intensively applied to interpret multiple tracer dilution data in the human forearm skeletal muscle. First a two-tracer compartmental model was developed to measure transmembrane glucose transport [19], subsequently extended to a three-tracer model to also measure glucose phosphorylation [20]. These models allowed important pathophysiological findings in diabetes, e.g., they enabled demonstrating that cellular transport plays a very important role in the defective insulin action in diabetes [21].
PET is an imaging technique that allows deriving highly specific and rich biochemical information if applied in dynamic mode, i.e., sequential tissue images acquired following a bolus injection of radiotracer so that the time course of the tissue behavior is monitored. Quantitative PET information can be extracted at whole-organ level (i.e., comparable with the triple tracer technique) as well as at region of interest (i.e., a specific area/volume of the organ) or voxel level. The three-rate constant glucose model of the brain by Sokoloff et al. [22] has been a landmark for quantitative PET metabolic studies. The model, originally proposed for 2-deoxy-D-[^{14}C]glucose ([^{14}C]DG), a glucose analog, and quantified in the rat from autoradiography data, was immediately extended to the PET tracer [^{18}F]fluorodeoxyglucose ([^{18}F]FDG), another glucose analog. The advantage of using an analog, instead of the ideal [^{11}C]glucose tracer, is that the end-product of

phosphorylation is trapped in the tissue, thus reducing significantly the model complexity; the disadvantage is the necessity to correct for the differences in transport and phosphorylation between the analog and glucose with a correction factor, called lumped constant (LC). We developed a new model for studying glucose metabolism in the skeletal muscle: the model needed to be more complex to account for the PET data, and it is a five-rate constant model [23]. In fact, an additional compartment is needed to account for the difference between arterial and interstitial concentrations, thus introducing the two new rate constants of [^{18}F]FDG exchange between plasma and extracellular space. Also with this model, by using the skeletal muscle LC, one can derive the glucose fractional uptake. The model has revealed inefficient transport and phosphorylation [^{18}F]FDG rate constants in obesity and type 2 diabetes, but also the plasticity of the system, i.e., defects can be substantially reversed with weight loss [24]. The LC allows moving from [^{18}F]FDG to glucose fractional uptake but not to the glucose transport and phosphorylation rate constants. To this end, a multiple tracer approach was needed with three different PET tracers injected sequentially [25]. This multi-tracer PET imaging method allows quantification of blood flow from [^{15}O]H2O images with a one compartment two-rate constant model; glucose transport from [^{11}C]3-OMG images with a three-compartment four-rate-constant model, and, finally, glucose phosphorylation by combining [^{18}F]FDG fractional uptake with [^{11}C]3-OMG rate constants. This method has shown that glucose transport from plasma into interstitial space is not affected by insulin, while insulin increases both glucose transport and phosphorylation. In addition, the study has elucidated that predominately oxidative muscles (soleus) have higher perfusion and higher capacity for glucose phosphorylation than less oxidative muscles (tibialis).

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4. *Maximal Models of Glucose Metabolism for In Silico Trials*

All the modeling work done in the last 20 years, has opened the path to a complex *glucose “maximal” model* to perform *in silico clinical trials*, which are defined as the use of individualized computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention, and have been proposed as a possible strategy to reduce the regulatory costs of innovation and the time to market for biomedical products. In fact it is often not possible, appropriate, convenient, or desirable to perform an experiment on human subjects because it cannot be done at all, or it is too difficult, too dangerous, or unethical. In such cases, simulation offers an alternative way of experimenting *in silico* with the system. They also allow to solve subject numerosity in trials where recruitment is impossible, or to explore patients’ phenotypes that are unlikely to appear in the trial cohort, but are still frequent enough to be of concern.
A number of simulation models have been published in the last four decades and used in particular to examine the performance of control algorithms and insulin infusion routes for the therapy of Type 1 diabetes but their impact has been very modest [1]. The reason is that all these models are “average,” meaning that they are only able to simulate average population dynamics, but not the inter-individual variability. The average-model approach is not sufficient for realistic *in silico* experimentation with control scenarios, where facing with inter-subject variability is particularly challenging. A good simulator should be equipped with a cohort of in silico subjects that spans sufficiently well the observed inter-person variability of key metabolic parameters, thus providing better information about controller safety and limitations than small-size animal trials. Building on the large-scale model developed in the healthy state from a rich triple tracer meal data set [2], a Type 1 diabetes simulator has been developed, able to realistically describe inter-subject variability.

This was a paradigm change in the field of Type 1 diabetes: for the first time a computer model has been accepted by a regulatory agency as a substitute of animal trials for certain insulin treatments [3].
In this simulator, a virtual "human" is described as a combination of several glucose and insulin subsystems. In summary, the model consists of 13 differential equations and 35 parameters for each subject. The simulator is equipped with 100 virtual adults, 100 adolescents, and 100 children, spanning the variability of Type 1 diabetes population observed *in vivo*. Type 1 diabetes simulator equipped with glucose sensor and insulin pump models allows testing of closed-loop control algorithm for insulin infusion [3].Each virtual subject is represented by a model parameter vector, which is randomly extracted from an appropriate joint parameter distribution. With this technology, any meal and insulin delivery scenario can be pilot-tested very efficiently in silico, prior to its clinical application. This simulator has been adopted by the JDRF Artificial Pancreas Consortium and has allowed an important acceleration of closed-loop studies with a number of regulatory approvals obtained based on simulation only. The simulator has been used by 32 research groups in academia, by five companies active in the field of diabetes and has led to 63 publications in peer reviewed journals.
Recently new data and models have become available, in particular on hypoglycemia and counterregulation, [4] and on intra-day variability of key signals, e.g., insulin sensitivity: 19 Type 1 diabetic underwent a triple-tracer study [5] which allowed the incorporation of a circadian time-varying insulin sensitivity into the simulator, thus making this technology suitable for running multiple–meal scenarios and enabling a more robust design of artificial pancreas control algorithms [6,7].
In January 2008, my "maximal" model of Type 1 diabetes was accepted by the U.S. Food and Drug Administration (FDA) as a substitute to animal trials for the preclinical testing of certain insulin treatments, including the artificial pancreas. The simulator was immediately put to its intended use with the in silico testing of a control algorithm, and in April 2008 an investigational device exemption (IDE) was granted by the FDA for a closed-loop control clinical trial. This IDE was issued solely on the basis of *in silico* testing of the safety and efficacy of AP control algorithm, an event that set a precedent for future preclinical studies. Thus, the following paradigm has emerged: in silico modeling can produce credible preclinical results that could substitute certain animal trials and these results are obtained in a fraction of the time and the cost required for animal trials. This was a landmark change in the field of Type 1 diabetes research: for the first time a computer model has been accepted by a regulatory agency as a substitute of animal trials in the testing of insulin treatments. Since its introduction, this simulator enabled an important acceleration of artificial pancreas studies, with a number of regulatory approvals obtained using in silico testing. A total of 140 candidate control algorithms have been formally evaluated by FDA resulting in 16 IDEs. In addition, he simulator has been used in a variety of contexts by 32 research groups in academia, by companies active in the field of diabetes pharma and technology and has led to more than 100 publications in peer reviewed journals.
The simulator has also been used in context different from the artificial pancreas, in particular for testing new insulin molecules, in particular inhaled insulin [9] and long-acting glargine (ms under review) and interesting molecules for diabetes therapy, like pramlintide [10]. The use of the simulator in the context of subcutaneous glucose sensors is examined separately below given the important results achieved.

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5. ***Glucose Sensors***

I have used my modeling insights to create an *algorithmically “smart” continuous glucose monitoring (CGM) sensor*, which consists of placing, in a cascade of the output of a commercial CGM sensor, three software modules for (i) denoising; (ii) enhancement; and (iii) prediction [1].The signal processing code was released by Dexcom Inc. in its G5 sensor, which allowed by itself to optimize its accuracy from 13% to 9%, making this device, in 2014, the first CGM sensor reaching one-digit accuracy. This now allows real-time algorithms for CGM data calibration, prediction of CGM data for the early detection of hypo- and hyperglycaemia, real-time detection of insulin pump data faults. The sensor has been further improved by reducing the number of calibrations [2].

The burning question was “Does this improved accuracy make subcutaneous glucose sensors reliable for insulin treatment decisions?” As of today, FDA has still not approved non-adjunctive use of CGS and self-monitoring of blood glucose is still the only admissible insulin dosing strategy. A clinical trial addressing this question would be almost impossible since the required number of patients to ensure exploration of the tail of the sensor MARD distribution would be huge. Also retrospective data are not too useful because it is impossible to see what would have happened of the insulin dosing was based on CGS rather than self-monitored blood glucose. Can modelling and simulation be of help in this respect? A further contribution was based on using the simulator by in the context of a patient decision-making model [3]. By defining *in silico* scenarios to recreate real-life conditions, e.g. 100 adults and 100 pediatric patients, 3 meals per day with variability in time & amount and meal bolus behavior, we evaluated standard outcome metrics, e.g. time in severe hypo, time in hypo, time in target, hypo- or hyperglycemic events, for both CGS and self-monitored blood glucose scenarios. Ou results in adults support the non-inferiority of CGS vs. self-monitored blood glucose; moreover, time below 50 mg/dl and time below 70 mg/dl are significantly improved, time between 70 and 180 mg/dl and time above 180 mg/dl are slightly improved, and the number, extent, and duration of hypoglycemic events are significantly reduced.

It is remarkable, in my view, that proof of the safety and effectiveness of the non-adjunctive use of CGM sensors has been so compelling that on December 20, 2017 the FDA approved it for non-adjunctive use , and subsequently, in March 2018, Medicare announced criteria for system reimbursement to all T1D and T2D people on intensive insulin therapy. In essence, his seminal work has resulted in the convergence of discovery science, in depth clinical assessment, and use sophisticated in silico models to improve the life the millions of people through the world who have diabetes.

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6. ***Artificial Pancreas***

We have pioneered development of the artificial pancreas as part of a JDRF international consortium to which we have lent our expertise in *in silico* and *in vivo* modeling with the goal of developing an artificial pancreas which can autonomously regulate glucose concentrations in people with Type 1 diabetes. The FDA accepted maximal model of Type 1 diabetes glucose metabolism and the improvement in accuracy of glucose sensors have allowed an incredible acceleration in the artificial pancreas research aimed at optimizing insulin therapy in Type 1 diabetic subjects. Targeting nearly normal glucose with insulin therapy in Type 1 diabetes to prevent long-term hyperglycemia diabetic complications and to reduce hypoglycemia occurrence remains a daily challenge for the subject. An artificial pancreas is a device composed by a glucose sensor, a wearable insulin pump and a control unit embedded in a smartphone/small tablet wirelessly linked to the two other devices: it aims to automate insulin infusion to achieve more time in target range, while reducing both time spent in hypo- and hyperglycemia and decreasing the disease burden. Thanks to the FDA accepted maximal model we were able to do the first artificial pancreas trial in humans in 2008 in the hospital after 3 months of the investigational device exemption granted by FDA issued solely on the basis of *in silico* testing of the safety and efficacy of the designed system [1]. In 2007 we developed a Modular Model Predictive Control (MMPC) algorithm for blood glucose regulation and a novel model-predictive control algorithm has been developed which uses a glucose model of the subject. In simple words, the algorithm works as a chess strategy, i.e. on the basis of past game (glucose) history, a several-moves-ahead strategy (insulin infusion) is planned, but only the first move (e.g., the next 15-min insulin infusion) is implemented; after the response of the opponent, the strategy is reassessed, but only the second move (the 30-min insulin infusion rate) is implemented, and so on. In reality glucose prediction may be different from the actual glucose measurement or an unexpected event may happen; with this strategy these events are taken into account in the next plan [2-4]. From 2007 to 2012, our MMPC algorithm was tested in 3 international studies in hospitalized patients, where 127 adult patients were recruited in 11 centers of 7 different countries [5-7]. We collected solid evidences on superior safety and efficacy of closed-loop control with respect to standard therapy in this controlled set-up. From 2012 to 2014 we moved outside the hospital for experiments lasting 2-5 days that were performed in environments more closely resembling daily life and free from strict protocol prescriptions: my group was the first to demonstrate the feasibility of outpatient ambulatory closed-loop for 48 hrs employing a "wearable" smartphone-based AP prototype [8]. We conduct 4 studies, recruiting a total of 85 adult patients in 5 centers of 4 countries [9-12]. Given the encouraging results in hotel, in 2014-2015 we run a 4 month long trial, where 32 adult patients, recruited in 3 countries, used our AP system during their daily life. The system tightened patients' blood glucose control by reducing simultaneously hypoglycemia and hyperglycemia. In 2015 we felt that this technology was robust and mature enough to be tested on the most delicate population of type one diabetic patients: kids. We conducted the first clinical trial outside the hospital testing the a single hormone artificial pancreas in scholar children. 30 children, 5-9 years old, recruited in 5 Italian center were studied for 3 days during a summer camp. We prove the ability of the AP to reduce the incidence of hypoglycemia, an especially dangerous event in the especially fragile population [13].
In a 2016 trial we moved to a next generation of artificial pancreas devices capable of learning and constantly updating a model describing the inter- and intra-individual variability of the subject-specific response to insulin, thus realizing an individualized, adaptive and fault tolerant (prompt detection of failures in system components, e.g. insulin pump occlusion or detachment) which is critical for patient

safety and treatment effectiveness in long-lasting free-living conditions. The results were first proven *in silico* [14] and subsequently confirmed in a successful outpatient trial [15,16]

In summary, our artificial pancreas venture has involved a large international team and 127 Type 1 diabetic subjects participating to in-patient testing (11 centers of 7 different countries), 85 patients participating to the transitional studies held in a hotel (involving 5 centers of 4 countries) and 32 patients participating to real-life testing (3 centers of 3 countries) with more than 300.000 hours of closed-loop data.

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