BIOGRAPHICAL SKETCH

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NAME: Cobelli, Claudio

eRA COMMONS USER NAME (credential, e.g., agency login): COBELLI_PI

POSITION TITLE: Full Professor of Bioengineering

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Padova, Padova, Italy	Laurea	1970	Electronic Engineering

A. Personal Statement

I pioneered the use of 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 to measure crucial parameters, like insulin action and secretion otherwise not accessible to direct measurement from *in vivo* clinical tests, also using tracers..Of particular relevance for the present application is the Oral Minimal Model method which I developed for an oral glucose tolerance test (either a mixed meal or an OGTT). The method allows to measure, e.g. from an 8-sample OGTT, insulin sensitvity and beta-cell function. The method has been validated against gold-standard model-independent more invasive measurements. The method is 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 ten 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 my research on *closed-loop control of glucose in Type 1 diabetes* (*artificial pancreas*) with focus on *glucose sensors, control algorithms and clinical trials*.

Relevant active grants:

R01 DK078646-14 Vella (PI) 06/05/2019 - 05/31/2024, $24,861
The effect of fasting milieu on beta-cell function in vivo
Goals: Understand how fasting FFA and glucose alter β-cell function and proinsulin secretion
Role: Co-Investigator

R01 R01HL153969 Scheer (PI) 07/012021 – 06/30/2026, $32,400
Food timing to mitigate adverse consequences of night work
Goals: Determine whether restricting meal timing to the biological day shows beneficial effects on metabolic markers of health, which holds great translational value for vulnerable populations such as night shift workers.
Role: Co-Investigator

H2020: PI FET Proactive Consortium FORGETDIABETES, 2020-2025, 4.0 MEuro
Goals: Develop an innovative technology based on intraperitoneal insulin delivery and glucose sensing to allow people with type1 diabetes to forget their disease.
Role: Coordinator

Relevant papers:
1.Bergman RN, Ider YZ, Bowden CR, **Cobelli C**: Quantitative estimation of insulin sensitivity. Am J Physiol 236: E667-67t7, 1979.
2. **Cobelli C**, Dalla Man C, Toffolo G, Basu R, Vella A, Rizza R: The oral minimal model method. Diabetes ;63:1203-1213, 2014.
3. Rizza R, Toffolo G, **Cobelli C**: Accurate measurement of postprandial glucose turnover: why is it difficult and how can it be done (relatively) simply. Diabetes 2016; 65:1133-1145.
4. **Cobelli C**, Dalla Man: Minimal and maximal models to quantitate glucose metabolism: tools to measure, to simulate and to run in silico trial. J Sc Diab Sci &Technol, 2021, 1-29.

B. Positions and Honors

CURRENT POSITION
2018- present Emeritus Professor of Bioengineering, University of Padova, Italy
1981-2018 Full Professor of Bioengineering, University of Padova, Italy

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

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

INSTITUTIONAL RESPONSIBILITIES
2012-2015 Member of the Evaluation Group for Assessment of Research of Italian Ministry of University and Research 2004-2010
2011-2015 Chairman, Steering Committee of the Trieste University Hospital, Trieste, Italy
2007-2010 Member Steering Committee Galileian School, University of Padova, Italy
12007-2008 Administrative Committee, IEEE Engineering in Medicine and Biology Society
2003-present Steering Committee Member of the Italian Bioengineeering Group
2002-2004 Co-Chairman Joint Ph.D. Program Padova & City University, London,UK
2000-2011 Chairman, Ph.D. Program on Bioengineering, University of Padova, Italy
2000-2009 Chairman, Graduate Programs on Bioengineering, University of Padova, Italy
1997-2003 Chairman, Italian Bioengineering Group
1990-1996 Chairman, International Federation of Automatic Control (IFAC), Technical Committee on Modelling and Control Biomedical Systems

1990-1996 Chairman, International Federation of Automatic Control (IFAC), Technical Committee on Modelling and Control Biomedical Systems
1982-1999 Member, Ph.D. Program on Bioengineering, Polytechnic of Milano, Italy

ADVISORY & EDITORIAL BOARD RESPONSABILITIES
2009-present Member Scientific Committee Tecnomed, University of Milano Bicocca, Italy
2013-present J. Diabetes Science & Technology, Q1 (**Associate Editor**)
2006-2013 J. Diabetes Science & Technology, Q1 (**Editorial Board**)
2003-present IEEE Transactions on Biomedical Engineering, Q1 (**Associate Editor**)
1993-1996 Diabetologia, Q1 (**Associate Editor**)
1990-1996 Control Engineering Practice, Q1 (**Editorial Board**)
1984-1997 American Journal of Physiology, Modeling in Physiology, Q1 (**Editorial Board**)
1983-2008 Mathematical Biosciences, Q1 (**Associate Editor**)
2003-2008 Member of IEEE Award Committee
1995-1997 Evaluator of PhDs at City University, London, and University of Turku, Turku and Reader Professorship, City University, London
1993-1999 Advisory Board Children Nutrition Research Center, Baylor College of Medicine, Houston, TX

PUBLICATIONS, H-INDEX and PATENTS
I published 752 papers in internationally refereed journals
http://www.ncbi.nlm.nih.gov/pubmed/?term=cobelli%20c (co-author of 8 books and I hold 10 patents with an h-index of 93, citations 36937 (Scopus).

C. Contribution to Science

1. *Measurement of insulin action and secretion from an intravenous glucose tolerance test (IVGTT)*: I developed with Dr. Bergman the IVGTT minimal model to measure insulin sensitivity. Later, a C-peptide minimal model was developed to assess beta-cell function and the disposition index paradigm was introduced. Since its development, the test has been utilized in a large number of clinical, epidemiological and genetic studies.

a. Bergman RN, Ider YZ, Bowden CR, **Cobelli C**: Quantitative estimation of insulin sensitivity. Am J Physiol 236: E667-67t7, 1979.
b. 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.
c. Toffolo G, De Grandi F, and **Cobelli C**: Estimation of beta-cell sensitivity from intravenous glucose tolerance test C-peptide data. Knowledge of the kinetics avoids errors in modeling the secretion. Diabetes 44: 845–854, 1995.
d. Denti P, Toffolo G, and **Cobelli C:** The disposition index: From individual to population approach. Amer J Physiol Endocrinol Metab 303: E576–E586, 2012.

2. *Measurement of insulin action and secretion from an oral test (Mixed Meal Tolerance Test, MMTT/ Oral Glucose Tolerance Test, OGTT)*: More physiological minimal models were developed to assess insulin sensitivity, beta-cell function and hepatic extraction from an MMTT/OGTT. These models have been used in numerous pathophysiological studies.

a. Dalla Man C, Caumo A, Basu R, Rizza R A, Toffolo G, **Cobelli C**: Minimal model estimation of glucose absorption and insulin sensitivity from oral test: Validation with a tracer method. Amer J Physiol Endocrinol. Metab 287: E637–E343, 2004.
b. Breda E, Cavaghan M KToffolo G, Polonsky K S, **Cobelli C**: Oral glucose tolerance test minimal model indexes of β-cell function and insulin sensitivity". Diabetes 50: 150–158, 2001.

c. Campioni M, Toffolo G, Shuster LT, Service FJ, Rizza RA, **Cobelli C**: Incretin effect potentiates beta-cell responsivity to glucose as well as to its rate of change: OGTT and matched intravenous study. Am J Physiol Endocrinol Metab 2007;292:E54-E60, 2007.
d. **Cobelli C**, Dalla Man C, Toffolo G, Basu R, Vella A, Rizza R: The oral minimal model method. Diabetes ;63:1203-1213, 2014.

3. ***Tracer-based measurement of whole-body and regional glucose metabolism***: Tracers provide a unique rich information to enhance our understanding of diabetes pathophysiology. We have been able to measure glucose disposal and liver insulin sensitivity from an MMTT/OGTT test, developed the triple-racer MMTT technique to accurately measure glucose turnover in the postprandial state, and provided a cellular portrait of insulin sensitivity in muscle by Positron Emission Tomography.

a. Dalla Man C, Caumo A, Basu R, Rizza R A, Toffolo G, **Cobelli C**: Measurement of selective effect of insulin on glucose disposal from labeled glucose oral test minimal model". Amer J Physiol Endocrinol Metab 289: E909–E914, 2005.
b. Basu R, Di Camillo B, Toffolo G, Basu A, Shah P, Vella A, Rizza R, **Cobelli C**: Use of a novel triple-tracer approach to assess postprandial glucose metabolism". Am J Physiol Endocrinol Metab 284:E55-69, 2003.
c. Rizza R, Toffolo G, **Cobelli C**: Accurate measurement of postprandial glucose turnover: why is it difficult and how can it be done (relatively) simply. Diabetes 2016; 65:1133-1145.
d. Bertoldo A, Ng JM, Azuma K, Pencek RR, Kelley C, Price JC, **Cobelli C**, Kelley DE: Interactions among glucose delivery, transport, and phosphorylation that underlie skeletal muscle insulin resistance in obesity and type 2 diabetes: studies with dynamic PET imaging. Diabetes 63:1058-1068, 2014

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. 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 FDA as a substitute of animal trials for certain insulin treatments. The current simulator has a circadian time-varying insulin, thus making this technology suitable for running multiple–meal scenarios and enabling a more robust design of artificial pancreas control algorithms. The simulator has also been used for testing inhaled insulin and pramlintide.

a. Kovatchev BP, Breton M, Dalla Man C, **Cobelli C**:In silico preclinical trials: A proof of concept in closed-loop control of type 1 diabetes. J Diabetes Sci Technol 3: 44–55, 2009.
b. Toffanin C, Visentin R, Messori M, Palma FD, Magni L, **Cobelli C**: Toward a Run-to-Run Adaptive Artificial Pancreas: In Silico Results". IEEE Trans Biomed Eng 65:479-488, 2018.
c. Visentin R, Campos-Nanez E, Schiavon M, Lv D, Vettoreti M, Breton M, Kovatchev B P, Dalla Man C, **Cobelli C**: The UVA/Padova Type 1 Diabetes Simulator Goes from Single Meal to Single Day. J Diabetes Sci Technol 12:273-281, 2018.
d. Micheletto F, Dalla Man C, Kolterman O, Chiquette E, Herrmann K, Schirra J, Kovatchev B, **Cobelli C**: In silico design of optimal ratio for co-administration of pramlintide and insulin in type 1 diabetes. Diabetes Technol Ther. 15: 802- 809, 2013.

5. ***Artificial Pancreas (AP)***: Thanks to the FDA accepted maximal model of Type 1 diabetes we were able to do the first AP trial in humans in 2008 in the hospital after 3 months of the IDE granted by FDA issued solely on the basis of *in silico* testing of the safety and efficacy of the system. Later we developed a Modular Model Predictive Control (MMPC) algorithm for blood glucose regulation and a novel model-predictive control algorithm. 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. 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. We conducted 4 studies, recruiting a total of 85 adult patients in 5 centers of 4 countries. 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. In 2015, we felt that this technology was robust and mature enough to be tested in kids. We tested the system in 30 children, 5-9 years old, recruited in 5 Italian

centers for 3 days during a summer camp. In a 2016 trial we moved to a next generation of Ap devices with an individualized, adaptive and fault tolerant. The results were first proven *in silico* and subsequently confirmed in an outpatient trial. In summary, our AP 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.

a. **Cobelli C**, Renard E, Kovatchev B P, Keith-Hynes P, Ben Brahim N, Place J, Del Favero S, Breton M, Farret A, Bruttomesso D, Dassau E, Zisser HDoyle III F J, Patek, S D, Avogaro A: Pilot studies of wearable outpatient artificial pancreas in Type 1 diabetes. Diabetes Care 35: e65-e67, 2012.
b. Kropff* J, Del Favero* S, Place* J,Toffanin* C, Visentin R, Monaro M, Messori, M, Di Palma F, Lanzola G, Farret A, Boscari F, Galasso S, Magni P, Avogaro A, Keith-Hynes P, Kovatchev, B P, Bruttomesso D, **Cobelli* C**, DeVries* J H, Renard* E, Magni*: 2 month evening and night closed-loop glucose control in patients with Type 1 diabetes under free-living conditions: a randomised crossover trial". Lancet Diabetes Endocrinol. 3:939-47, 2015.
c. Messori* M, Kropff* J, Del Favero* S, Place* J, Visentin R, Calore R, Toffanin C, Di Palma F, Lanzola G, Farret A, Boscari F, Galasso S, Avogaro A, Keith-Hynes Kovatchev B P, Bruttomesso D, Magni L, DeVries J H, Renard E, **Cobelli C**: Individually adaptive artificial pancreas in subjects with Type 1 diabetes: a one-month proof-of-concept trial in free-living conditions. Diabetes Technology and Therapeutics 19:560-571, 2017.
d. Del Favero S, Boscari F, Messori M, Rabbone I, Bonfant Ri, Sabbion A, Iafusco D, Schiaffini R, Visentin R, Calore R, Leal Y, Galasso S, Galderisi A, Vallone A, Di Palma F, Losiouk E, Lanzola G, Tinti D, Rigamonti A, Marigliano M, Zanfardino A, Rapini N, Avogaro A, Chernavvsky D, Magni L**, Cobelli C,** Bruttomesso D: Randomized summer camp crossover trial in 5- to 9-year-old children: outpatient wearable artificial pancreas is feasible and safe. Diabetes Care 39:1180-5, 2016.