BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Cobelli, Claudio	Full Professor of Bioengineering
eRA COMMONS USER NAME	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Padova, Italy	Laurea	1970	Electronic Engineering

A. Personal Statement

My research activity has largely focused on developing parsimonious (minimal) models to measure crucial parameters otherwise not accessible to direct measurement like insulin action and secretion from *in vivo* clinical tests (also using tracers) and on large scale (maximal) models of human metabolism. This has enabled the completion of *in silico* clinical trials. Also central in these last years is the research on closed-loop control of glucose in type 1 diabetes (artificial pancreas) with a focus on the use of glucose sensors, control algorithms and clinical trials.

B. Positions and Honors.

Positions and Employment

1970-1973 Research Scientist, Institute of System Science and Bioengineering, CNR, Padova, Italy
1973-1975 Associate Professor of Biological Systems, University of Firenze, Firenze, Italy
1975-1981 Associate Professor of Biomedical Engineering, University of Padova, Padova, Italy
1976-1977 NATO Fellow, Laboratory of Theoretical Biology, NCI, NIH, Bethesda, MD
1978 Visiting Professor, Northwestern University, Evanston, IL
1980 Visiting Professor, The City University, London, UK.
1981-present Full Professor of Bioengineering, University of Padova, Padova, Italy
2000-present Affiliate Professor with Bioengineering, University of Washington, Seattle, WA, USA

Other Experience and Professional Memberships

1982-1999 Member, Ph.D. Program on Bioengineering, Polytechnic of Milano, Milano, Italy
1983-2008 Mathematical Biosciences (Ass Editor)
1984-1997 American Journal of Physiology, Modeling in Physiology (Ed. Board)
1985-present Member, American Diabetes Association (ADA)
1985-present Member, European Association for the Study of Diabetes (EASD)
1985-present Member, Institute of Electrical and Electronics Engineering (IEEE)
1986-1994 Member, IMEKO Technical Committee on Measurement in Biology and Medicine
1988-1995 Diabetes, Nutrition and Metabolism (Ed. Board)
1990-1996 Control Engineering Practice (Ed. Board)
1990-1996 Chairman, IFAC Technical Committee on Modeling and Control Biomedical Systems
1990-2005 Senior Member, Biomedical Engineering Society (BMES)
1991-2009 American Journal of Physiology, Endocrinology and Metabolism (Ed. Board)
1993-1996 Diabetologia (Ass Editor);
1993-1999 Advisory Board Children Nutrition Research Center, Baylor College of Medicine, Houston, TX
1997-2002 Senior Member IEEE
1997-2003 Chairman, Italian Biomedical Engineering Group (GNB)
2000-2009 Chairman, Graduate Programs on Biomedical Engineering, University of Padova, Padova, Italy
2000-2011 Chairman, Ph.D. Program on Bioengineering, University of Padova, Padova, Italy
2003-present Steering Committee Member of GNB

2003-2009 IEEE Transactions on Biomedical Engineering (Ass Editor)
2003-2008 Member of IEEE Award Committee
2005-2011 Reviewer Strategic Program Nuovi Sviluppi dell' Industria Biomedicale, PNR,MIUR
2006-2013 J. Diabetes Science & Technology (Ed. Board)
2007-2008 IEEE EMBS AdCom Member
2007-2010 Member Steering Committee Scuola Galileiana di Studi Superiori
2007-present Member Steering Committee of IEEE Trans on NanoBiosciences
2008-present Representative of IEEE EMBS to IEEE Trans on Comp Biol & Bioinf
2009-present Journal of Healthcare Engineering (Ass. Editor)
2009-present Member Scientific Committee Tecnomed, University of Milan Bicocca
2009-present Member Scientific Committee Consorzio Veneto di Ricerca
2011-present Chairman of the Steering Committee of the Trieste Univerity Hospital, Trieste, Italy
2012-present Member of the Evaluation Group GEV 09 for assesment of MIUR Research 2004-10
2013-present Medical & Biological Engineering and Computing (Ed. Board)
2014-present J. Diabetes Science & Technology (Ass. Editor)
2014-present Diabetes Technology & Therapeutics (Ed.Board)
2015-present IEEE Transactions on Biomedical Engineering (Ass Editor)

Honors

2003 Fellow Institute of Electrical and Electronic Engineers (IEEE)
2003 Correspondent Member Accademia Galileiana di Scienze, Lettere e Arti
2005 Fellow Biomedical Engineering Society (BMES)
2010 Fellow American Institute for Medical and Biological Engineering (AIMBE)
2010 Artificial Pancreas Award, Diabetes Technology Society

C. Contribution to Science

1. Measurement of insulin secretion and action *in vivo*. We developed the frequently-Sampled Intravenous Glucose Tolerance Test (FSIGT) with Dr. Bergman to assess metabolic function through an intravenous protocol, leveraging a modeling approach - the minimal model. The minimal model is a mathematical construct, which uses the time course of insulin and glucose during the FSIGT to yield important metabolic parameters including insulin sensitivity, beta cell responsivity, insulin clearance, and glucose effectiveness. The insulin sensitivity index correlates with that calculated from the euglycemic clamp method. Since its development, the test has been utilized in a large number of clinical, epidemiological and genetic studies.

1. Alzaid AA, Dinneen SF, Turk DJ, Caumo A, **Cobelli C**, Rizza RA: Assessment of insulin action and glucose effectiveness in diabetic and nondiabetic humans. J Clin Invest 1994;94:2341-2348
2. Avogaro A, Vicini P, Valerio A, Caumo A, **Cobelli C**: The hot but not the cold minimal model allows precise assessment of insulin sensitivity in NIDDM subjects. Am J Physiol 1996;270:E532-540
3. Bergman RN, **Cobelli C**: Minimal modeling, partition analysis, and the estimation of insulin sensitivity. Fed Proc 1980;39:110-115
4. Bergman RN, Ider YZ, Bowden CR, **Cobelli C**: Quantitative estimation of insulin sensitivity. Am J Physiol 1979;236:E667-677
5. 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 1981;68:1456-1467

2. Use of an oral test to measure insulin secretion and action. The mixed meal test better captures normal physiology compared to the FSIGT and provides a measure of the incretin effect on insulin secretion. However, a potential problem with modelling an oral challenge is uncertainty around the rate of glucose appearance in plasma requiring assumptions to be made about the fraction of ingested glucose reaching the circulation. In contrast, the FSIGT can be simpler to model because the exact nature of the stimulus (i.e., the glucose injected intravenously) is known. The availability of a model-independent, tracer-based measure of the systemic appearance of ingested glucose enabled the development of a model to describe glucose appearance after ingestion of oral glucose alone or as part of a mixed meal. The model that best fits available data describes a nonlinear relationship between glucose ingested and its systemic

appearance, accounting for total amount of glucose in the stomach, the composition and physical nature of the meal which alters the linearity or otherwise of gastric emptying. Subsequent reconstruction of systemic glucose appearance provides the glucose input necessary to model the relationship between insulin and glucose concentrations (insulin sensitivity – Si) and between C-peptide and glucose concentrations (beta cell responsivity – Φ). The ensuing Disposition Index (DI) – as in the IVGTT – expresses the insulin secretory response as a function of the prevailing insulin action. (1)

1. 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 2003;284:E55-69
2. Campioni M, Toffolo G, Basu R, Rizza RA, **Cobelli C**: Minimal model assessment of hepatic insulin extraction during an oral test from standard insulin kinetic parameters. Am J Physiol Endocrinol Metab 2009;297:E941-948
3. 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
4. **Cobelli C**, Dalla Man C, Toffolo G, Basu R, Vella A, Rizza R: The oral minimal model method. Diabetes 2014;63:1203-1213
5. Cobelli C, Toffolo GM, Dalla Man C, Campioni M, Denti P, Caumo A, Butler P, Rizza R: Assessment of beta-cell function in humans, simultaneously with insulin sensitivity and hepatic extraction, from intravenous and oral glucose tests. Am J Physiol Endocrinol Metab 2007;293:E1-E15

3. Application of tracer-based measures to the measurement of glucose metabolism. We have utilized our expertise in mathematical modelling to apply the indices of insulin secretion and action to partitioning the effects of insulin action and glucose effectiveness on the suppression of endogenous glucose production by glucose and insulin. Similar indices for peripheral glucose disposal have also been developed. The triple-tracer mixed meal was similarly developed to maintain relatively constant steady-state of tracer / tracee concentrations allowing accurate measurements of glucose turnover in the postprandial state.

1. Basu R, Breda E, Oberg AL, Powell CC, Dalla Man C, Basu A, Vittone JL, Klee GG, Arora P, Jensen MD, Toffolo G, **Cobelli C**, Rizza RA: Mechanisms of the age-associated deterioration in glucose tolerance: contribution of alterations in insulin secretion, action, and clearance. Diabetes 2003;52:1738-1748
2. 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 2014;63:1058-1068
3. Bock G, Dalla Man C, Campioni M, Chittilapilly E, Basu R, Toffolo G, **Cobelli C**, Rizza R: Pathogenesis of pre-diabetes: mechanisms of fasting and postprandial hyperglycemia in people with impaired fasting glucose and/or impaired glucose tolerance. Diabetes 2006;55:3536-3549
4. Campioni M, Toffolo G, Basu R, Rizza RA, **Cobelli C**: Minimal model assessment of hepatic insulin extraction during an oral test from standard insulin kinetic parameters. Am J Physiol Endocrinol Metab 2009;297:E941-948
5. Toffolo G, Basu R, Dalla Man C, Rizza R, **Cobelli C**: Assessment of postprandial glucose metabolism: conventional dual- vs. triple-tracer method. Am J Physiol Endocrinol Metab 2006;291:E800-806

4. Development of the artificial pancreas. We have pioneered development of the artificial pancreas as part of an international consortium to which we have lent our expertise in *in silico* and *in vivo* modelling with the goal of developing an artificial pancreas which can autonomously regulate glucose concentrations in people with type 1 diabetes. Of note was the development of the Type 1 diabetes simulator which was accepted by FDA as a substitute of preclinical trials for certain insulin treatments, including the artificial pancreas. This simulator has allowed an important acceleration towards a wearable artificial pancreas for Type 1 diabetic subjects.

1. **Cobelli C**, Renard E, Kovatchev BP, Keith-Hynes P, Ben Brahim N, Place J, Del Favero S, Breton MD, Farret A, Bruttomesso D, Dassau E, Zisser H, Doyle FJ III, Patek S, Avogaro A. Pilot Studies of Wearable Artificial Pancreas in Type 1 Diabetes. Diabetes Care, 35: e65-67, 2012. PMID: 22923687 PMCID: PMC3424989
2. Cobelli C, Renard E, Kovatchev B: Artificial pancreas: past, present, future. Diabetes 2011;60:2672-2682

3. Kovatchev B.P., Renard E., **Cobelli C.** , Zisser H.C., Keith-Hynes P., Anderson S.M. , Brown S.A., Chernavvsky D.R., Breton M.D., Farret A., Pelletier M.J.,Place J. , Bruttomesso D. , Del Favero S., Visentin R., Filippi A., Scotton R., Avogaro A., Doyle F.J. 3rd: Feasibility of outpatient fully integrated closed-loop control: first studies of wearable artificial pancreas. Diabetes Care 36(7):1851-8, 2013. PMID: 23801798 PMCID: PMC3687268
4. Kovatchev BP, Renard E, **Cobelli C**, Zisser H, et al. Feasibility of Outpatient Fully Integrated Closed-Loop Control: First Studies of Wearable Artificial Pancreas. Diabetes Care, 36:1851-1858, 2013 PMID:23801798 PMCID: PMC3687268
5. Dalla Man C., Micheletto F., Lv D., Breton M., Kovatchev B., **Cobelli C.**: The UVA/PADOVA Type 1 Diabetes Simulator: New Features. J Diabetes Sci Technol. 8(1):26-34, 2014. PMID: 24876534