

Principal Investigator/Program Director (Last, First, Middle):

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
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NAME Cobelli, Claudio	POSITION TITLE Full Professor of Bioengineering		
eRA COMMONS USER NAME			
EDUCATION/TRAINING ( <i>Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.</i> )			
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 on mathematical modeling of the glucose system 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, more recently, on large scale (maximal) models of human metabolism, allowing for instance clinical trials to be made in silico.

### 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

Principal Investigator/Program Director (Last, First, Middle):

2003-present 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-present 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 Member Scientific Committee Tecnomed, University of Milan Bicocca  
2009-present Member Scientific Committee Consorzio Veneto di Ricerca

### **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. Selected peer-reviewed publications (from 1979-present)**

(54 from 350 peer-reviewed publications – as per June 21,2011, Scopus reports 394 papers in the period 1972-2011 quoted 6673 times (without autoquotations) with an Hirsch (h-index) of 42, while Google Scholar reports 346 papers quoted 8956 times with an Hirsch (h-index) of 49)

1. Bergman RN, Ider YZ, Bowden CR, Cobelli C: Quantitative estimation of insulin sensitivity. *Am. J. Physiol.* 236: E667-E677, 1979. PMID: 443421
2. Butler P., Caumo A., Zerman A., O'Brien P., Cobelli C., Rizza R.: Methods for assessment of the rate of onset and offset of insulin action during nonsteady state in humans. *Am. J. Physiol.* 264: E548-560, 1993. PMID: 8476033
3. Katz H., Butler P., Homan M., Zerman A., Caumo A., Cobelli C., Rizza R.: Hepatic and extrahepatic insulin action in humans: measurement in the absence of non-steady-state error. *Am. J. Physiol.* 264: E561-E566, 1993. PMID: 8476034
4. Alzaid A., Dinneen S., Turk D., Caumo A., Cobelli C., Rizza R.: Assessment of insulin action and glucose effectiveness in diabetic and nondiabetic humans. *J. Clin. Invest.* 94: 2341-2348, 1994. PMID: 7989590. PMCID: PMC330063
5. Caumo A., Homan M., Katz H.K., Cobelli C., Rizza R.: Measurement of glucose appearance and disappearance in the presence of changing glucose concentrations in humans. *Am. J. Physiol.* 269: E557-E567, 1995.
6. Toffolo G, De Grandi F, 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. PMID: 7789653
7. Basu A., Alzaid A., Dinneen S., Caumo A., Cobelli C., Rizza R.: Effects of a change in the pattern of insulin delivery on carbohydrate tolerance in diabetic and nondiabetic humans in the presence of differing degrees of insulin resistance. *J. Clin. Invest.* 97:2351-2361, 1996. PMID: 8636416. PMCID: PMC507316
8. Bonadonna RC, Del Prato S, Bonora E, Saccomani MP, Gulli G, Natali A, Frascerra S, Pecori N, Ferrannini E, Bier D, Cobelli C, DeFronzo RA: Roles of glucose transport and glucose phosphorylation in muscle insulin resistance of NIDDM. *Diabetes* 45: 915-925, 1996. PMID: 8666143
9. Basu A., Caumo A., Bettini F., Gelisio A., Alzaid A., Cobelli C., Rizza R.: Impaired basal glucose effectiveness in NIDDM-Contribution of defects in glucose disappearance and production, measured using an optimized minimal model independent protocol. *Diabetes* 46: 421-432, 1997. PMID: 9032098
10. Vicini P, Caumo A, Cobelli C: The hot IVGTT two compartment minimal model: indices of glucose effectiveness and insulin sensitivity. *Am. J. Physiol.* 273: E1024-E1031, 1997. PMID: 9374690

11. Cobelli C, Caumo A, Omenetto M: Minimal model SG overestimation and SI underestimation: improved accuracy by a Bayesian two-compartment model. *Am. J. Physiol.* 277: E481-E488, 1999. PMID: 10484360
12. Caumo A, Bergman RN, Cobelli C: Insulin sensitivity from meal tolerance tests in normal subjects: a minimal model index. *J Clin Endocrinol Metab*, 85: 4396-4402, 2000. PMID: 11095485
13. Audoly S, Bellu G, D'Angio L, Saccomani MP, Cobelli C: Global identifiability of nonlinear models of biological systems. *IEEE Trans Biomed Eng.* 48: 55-65, 2001. PMID: 11235592
14. Breda E, Cavaghan MK, Toffolo G, Polonsky KS, Cobelli C: Oral glucose tolerance test minimal model indexes of beta-cell function and insulin sensitivity. *Diabetes* 50: 150-158, 2001. PMID: 11147781
15. Dalla Man C, Caumo A, Cobelli C: The oral glucose minimal model: estimation of insulin sensitivity from a meal test. *IEEE Trans Biomed Eng.* 49: 419-429, 2002. PMID: 12002173
16. Pillonetto G, Sparacino G, Magni P, Bellazzi R, Cobelli C: Minimal model  $S(l)=0$  problem in NIDDM subjects: nonzero Bayesian estimates with credible confidence intervals. *Am J Physiol.* 282: E564-E573, 2002. PMID: 11832358
17. 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.* 284: E55-E69, 2003. PMID: 12485809
18. Dalla Man C, Caumo A, Basu R, Rizza R, Toffolo G, Cobelli C: Minimal model estimation of glucose absorption and insulin sensitivity from oral test: validation with a tracer method. *Am J Physiol* 287:E637-E643, 2004. PMID: 15138152
19. Bertoldo A., Price J., Mathis C., Mason S., Holt D., Kelley C., Cobelli C., Kelley D.E.: Quantitative assessment of glucose transport in human skeletal muscle: dynamic positron emission tomography imaging of [O-methyl-11C]3-O-methyl-D-glucose. *J Clin Endocrinol Metab* 90:1752-9, 2005. PMID: 15613423
20. Dalla Man C., Campioni M., Polonsky K.S., Basu R., Rizza R.A., Toffolo G., Cobelli C.: Two-hour seven-sample oral glucose tolerance test and meal protocol: minimal model assessment of beta-cell responsiveness and insulin sensitivity in nondiabetic individuals. *Diabetes* 54:3265-3273, 2005. PMID: 16249454
21. Dalla Man C., Caumo A., Basu R., Rizza R., Toffolo G., Cobelli C.: Measurement of selective effect of insulin on glucose disposal from labeled glucose oral test minimal model. *Am J Physiol Endocrinol Metab* 289:E909-914, 2005. PMID: 15972269
22. Dalla Man C., Yarasheski K.E., Caumo A., Robertson H., Toffolo G., Polonsky K.S., Cobelli C.: Insulin sensitivity by oral glucose minimal models: validation against clamp. *Am J Physiol Endocrinol Metab* 289:E954-959, 2005. PMID: 16014353
23. Toffolo G, Campioni M, Basu R, Rizza RA, Cobelli C: A minimal model of insulin secretion and kinetics to assess hepatic insulin extraction. *Am J Physiol Endocrinol Metab.* 290:E169-E176, 2006. PMID: 16144811
24. Basu R, Dalla Man C, Campioni M, Basu A, Klee G, Toffolo G, Cobelli C, Rizza RA: Effects of age and sex on postprandial glucose metabolism: differences in glucose turnover, insulin secretion, insulin action, and hepatic insulin extraction. *Diabetes* 55:2001-2014, 2006. PMID: 16804069
25. Bertoldo A., Pencek R.R., Azuma K., Price J.C., Kelley C., Cobelli C., Kelley D.E. Interactions between delivery, transport, and phosphorylation of glucose in governing uptake into human skeletal muscle. *Diabetes* 55:3028-37, 2006. PMID: 17065339
26. Bock G., Dalla Man C., Campioni M., Chittilapilly E., Basu R., Toffolo G., Cobelli C., Rizza R.A.: Pathogenesis of prediabetes: mechanisms of fasting and postprandial hyperglycemia in people with impaired fasting glucose and/or impaired glucose tolerance. *Diabetes* 55:3536-49, 2006. PMID: 17130502
27. Dalla Man C., Camilleri M., Cobelli C.: A system model of oral glucose absorption: validation on gold standard data. *IEEE Trans Biomed Eng.* 53:2472-8, 2006. PMID: 17153204
28. Nair K.S., Rizza R.A, O'Brein P., Short K.R., Nehra A, Vittone J.L., Klee G.G, Basu A., Basu R., Cobelli C., Toffolo G., Dalla Man C., Tindall D.J., Melton L.J., Smith G.E., Khosla S., Jensen M.D.: Effect of two years dehydroepiandrosterone in elderly men and women and testosterone in elderly men on physiological performance, body composition and bone density. *New England Journal of Medicine* 355:1647-1659, 2006. PMID: 17050889
29. Petersen K.F., Dufour S., Feng J., Befroy D., Dzuira J., Dalla Man C., Cobelli C., Shulman G.: Increased prevalence of insulin resistance and non-alcoholic fatty liver disease in asian indian men. *PNAS* 103:18273-7, 2006. PMID: 17114290. PMCID: PMC1693873. doi: 10.1073/pnas.0608537103

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30. Toffolo G., Basu R., Dalla Man C., Rizza R.A., Cobelli C.: Assessment of postprandial glucose metabolism: conventional dual versus triple tracer method. *Am J Physiol Endocrinol Metab* 291:E800-E806, 2006. PMID: 16720627 . doi: 10.1152/ajpendo.00461.2005
31. Toffolo G., Campioni M., Basu R., Rizza R.A., Cobelli C.: A minimal model of insulin secretion and kinetics to assess hepatic insulin extraction. *Am J Physiol Endocrinol Metab* 290:E169-E176, 2006. PMID: 16144811
32. Campioni M., Toffolo G., Shuster L.T., Service F.J., Rizza R.A., Cobelli C.: Incretin effect potentiates beta-cell responsiveness to glucose as well as to its rate of change: OGTT and matched intravenous study. *Am J Physiol Endocrinol Metab* 292:E54-60, 2007. PMID: 16868229
33. Bock G., Chittilapilly E., Basu R., Toffolo G., Cobelli C., Chandramouli V., Landau B.R., Rizza R.A.: Contribution of hepatic and extrahepatic insulin resistance to the pathogenesis of impaired fasting glucose: role of increased rates of gluconeogenesis. *Diabetes* 56:1703-1711, 2007. PMID: 17384334
34. Bock G., Dalla Man C., Campioni M., Chittilapilly E., Basu R., Toffolo G., Cobelli C., Rizza R.A.: Effects of nonglucose nutrients on insulin secretion and action in people with pre-diabetes. *Diabetes* 56:1113-1119, 2007. PMID: 17395750
35. Cobelli C., Toffolo G.M., Dalla Man C., Campioni M., Denti P., Caumo A., Butler P., Rizza R.A.: 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* 293:E1-E15, 2007. PMID: 17341552
36. Dalla Man C., Rizza R.A., Cobelli C.: Meal simulation model of the glucose-insulin system. *IEEE Trans Biomed Eng* 54:1740-1749, 2007. PMID: 17926672
37. Ravikumar B., Gerrard J., Dalla Man C., Firbank M.J., Lane A., English P.T., Cobelli C., Taylor R.: Pioglitazone decreases fasting and postprandial endogenous glucose production in proportion to decrease in hepatic triglyceride content. *Diabetes* 57:2288-95, 2008. PMID: 18535187
38. Dalla Man C., Toffolo G., Basu R., Rizza R.A., Cobelli C.: Use of Labeled Oral Minimal Model to Measure Hepatic Insulin Sensitivity. *Am J Physiol Endocrinol Metab* 295:E1152-9, 2008. PMID: 18765681
39. Dalla Man C., Bock G., Toffolo G., Basu R., Rizza R.A., Cobelli C.: Hepatic insulin sensitivity from labelled meal: Validation against euglycemic-hyperinsulinemic clamp. *Diabetes* 57:A367, 2008.
40. Pedersen M.G., Corradin A., Toffolo G., Cobelli C.: Subcellular model of glucose-stimulated pancreatic insulin secretion. *Philosophical Transactions of the Royal Society of London Series A: Mathematical Physical and Engineering Sciences* 366:3525-3543, 2008. PMID: 18653438
41. Dalla Man C., Bock G., Giesler P.D., Serra D.B., Ligueros Saylan M., Foley J.E., Camilleri M., Toffolo G., Cobelli C., Rizza R.A., Vella A.: Dipeptidyl peptidase 4 inhibition by Vildagliptin and the effect on insulin secretion and action in response to meal ingestion in type 2 diabetes. *Diabetes Care* 32:14-18, 2009. PMID: 18931099
42. Sunehag A.L., Dalla Man C., Toffolo G., Haymond M.W., Bier D.M., Cobelli C.: Beta-cell function and insulin sensitivity in adolescents from an OGTT. *Obesity* 17:233-239, 2009. PMID: 19057529
43. Dalla Man C., Bock G., Giesler P.D., Serra D.B., Ligueros Saylan M., Foley J.E., Camilleri M., Toffolo G., Cobelli C., Rizza R.A., Vella A.: Dipeptidyl Peptidase 4 inhibition by Vildagliptin and the effect on insulin secretion and action in response to meal ingestion in type 2 diabetes. *Diabetes Care* 32:14-8, 2009. PMID: 18931099
44. Kovatchev B.P., Breton M.D., 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. PMID: 19444330
45. Dalla Man C., Breton M.D., Cobelli C.: Physical Activity into the Meal Glucose-Insulin Model of Type 1 Diabetes: In Silico Studies. *J. Diabetes Sci. Technol.* 3:56-67, 2009. PMID: 20046650
46. Cali A.M., Dalla Man C., Cobelli C., Dziura J., Seyal A., Shaw M., Allen K., Chen S., Caprio S.: Primary Defects in Beta-Cell Function Further Exacerbated by Worsening of Insulin Resistance Mark the Development of Impaired Glucose Tolerance in Obese Adolescents. *Diabetes Care* 32:456-61, 2009. PMID: 19106382
47. Basu A., Dalla Man C., Basu R., Toffolo G., Cobelli C., Rizza R.A., Effects of Type 2 Diabetes on Insulin Secretion, Insulin Action, Glucose Effectiveness and Postprandial Glucose Metabolism. *Diabetes Care* 32:866-72, 2009.
48. Magni L., Forgiione M., Toffanin C., Dalla Man C., Kovatchev B.P., De Nicolao G., Cobelli C.: Run-to-Run Tuning of Model Predictive Control for Type 1 Diabetes Subjects: In Silico Trial. *J. Diabetes Sci. technol.* 3:1091-1098, 2009. PMID: 20144422

Principal Investigator/Program Director (Last, First, Middle):

49. Cobelli C., Dalla Man C., Sparacino G., Magni L., De Nicolao G., Kovatchev B.P.: Diabetes: Models, Signals, and Control. *IEEE Rev. Biomed. Eng.* 2: 54-96, 2009. PMID: 20936056
50. Campioni M., Toffolo G.M., Basu R., Rizza R.A., Cobelli C.: Minimal model assessment of hepatic insulin extraction during an oral test from standard insulin kinetic parameters. *Am. J. Physiol. Endocrinol. Metab.*, 2009 August 11 [Epub ahead of print]. PMID: 19671837
51. Denti P., Bertoldo A., Vicini P., Cobelli, C.: Nonlinear mixed effects to improve glucose minimal model parameter estimation: a simulation study in intensive and sparse sampling. *IEEE Trans. Biomed. Eng. BME* 56:2156-66, 2009. PMID: 19380266
52. Manesso E., Toffolo G.M., Saisho Y., Butler A.E., Matveyenko A.V., Cobelli C., Butler P.C.: Dynamics of Beta-cell turnover; evidence for Beta-cell turnover and regeneration from sources of Beta-cells other than Beta-cell replication in the HIP rat. *Am. J. Physiol. Endocrinol. Metab.* 297:E323-30, 2009. PMID: 19470833
53. Pillonetto G., De Nicolao G., Chierici M., Cobelli C.: Fast algorithms for nonparametric population modeling of large data sets. *Automatica* 45:173-179, 2009.
54. Zanderigo F., Bertoldo A., Pillonetto G., Cobelli C.: Nonlinear stochastic regularization to characterize tissue residue function in bolus-tracking MRI: assessment and comparison with SVD, block-circulant SVD and Tikhonov. *IEEE Trans. Biomed. Eng.* 56:1287-1297, 2009. PMID: 19188118

#### D. Research Support

RO1 DK061539 Butler (PI)

06/01/09 - 05/31/13 1.20 calendar

NIH/NIDDK \$45,000

Role of Pulsatile Insulin Secretion

The overall goals of the program grant are to address (1) the impact of a beta cell mass deficit in humans on insulin secretion and action, (2) to address the role of pulsatile insulin secretion on insulin action on hepatic and extra-hepatic issues, (3) the role of pulsatile insulin secretion on hepatic and extra-hepatic insulin signaling.

Role: Co-Investigator

ROI DK029953-27 (Rizza & R. Basu, CoPI)

08/01/09-07/31/13 1.00 calendar

NIH/NIDDK \$30,160

Mechanisms of Insulin Resistance in Man

The major goals of this study are understand the factors that regulate postabsorptive and postprandial glucose metabolism in diabetic and non-diabetic humans

Principal Investigator/Program Director (Last, First, Middle):

Role: Co-Investigator

R01 DK 76486 Vella (PI)

06/01/09-05/31/13

1.20 calendar

NIH/NIDDK \$25,693

The Effects of TCF7L2 on Glucose Metabolism

The aim is to determine the mechanism(s) by which common genetic variations in TCF7L2, recently associated with type 2 diabetes, alters glucose metabolism

Role: Co-Investigator

RO1 DK 085623 Kovatchev (PI)

09/01/09-08/31/12

1.20 calendar

NIH/NIDDK \$92,695

Modular Bio-Behavioral Closed-Loop Control of T1 DM

This project proposes to lay the foundation for bio-behavioral control strategies in type 1 diabetes including open-loop patient initiated control and closed-loop control informed by stochastic analysis of patients' behavioral profiles.

Role: Co-Investigator

22-2006-1116 Kovatchev (PI)

09/01/06-12/31/2011

1.20 calendar

Juvenile Diabetes Research Foundation – JDRF \$101,700

The Artificial Pancreas Project at the University of Virginia

This study is a part of the JDRF Artificial Pancreas Project, which aims the industrial implementation of automated systems for insulin pump control based on continuous glucose monitoring.

Role: Co-Investigator

R01 DK 085516-01 (A Basu & Kudva, CoPI)

09/01/09-

08/31/12

1.80 calendar

Principal Investigator/Program Director (Last, First, Middle):

NIH/NIDDK

\$ 81,071

Integrated approaches to close the loop in Type 1 diabetes

This grant will improve the algorithm used for an Artificial Endocrine pancreas consisting of continuous interstitial fluid glucose sensing and continuous subcutaneous insulin delivery. Experiments will examine circadian variability in insulin action, the contribution of different grades of physical activity on glucose variability and the contribution of variability in gastric emptying to glycemic variability. During the grant, we will use highly accurate accelerometers to capture physical activity so that the next generation of artificial endocrine includes physical activity capture in real time.

Role: Co-Investigator

R01DK082396-01A2 (Vella, PI)

04/01/2010 – 03/31/2015 1.20 calendar

NIH

\$ 48,600

The effect of bariatric surgery on carbohydrate metabolism

Examine the changes in insulin secretion and action, glucose metabolism, gastric emptying and enteroendocrine secretion.

Role: Co-Investigator

European Projects 7th Framework

EU 216592 DIAdvisor (Poulsen ,PI)  
03/01/08-02/28/12

EU-IMI 115006 Summit (Groop ,PI)  
11/01/09-10/31/14

EU 247138 AP@home (DeVries ,PI)  
02/01/10-01/31/14

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