The FDA Accepted Uva/Padova Type 1 Diabetes Simulator: Rationale, Methods and Clinical Applications

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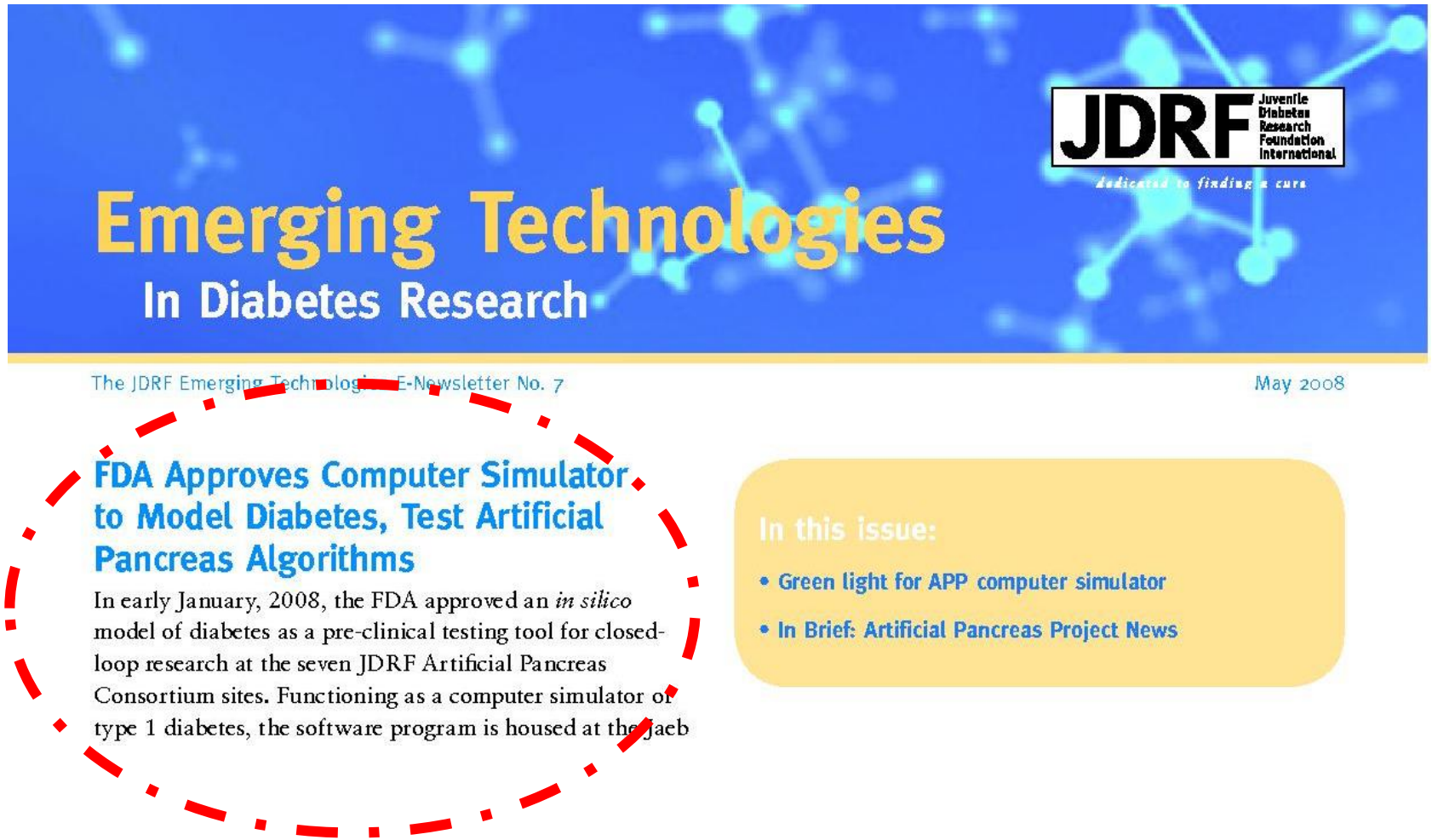
University of Padova, Italy

AIFA Workshop, Roma, May 26th, 2022

January 2008: FDA Accepts the UVA/Padova Type 1 Diabetes Simulator



Emerging Technologies
In Diabetes Research

JDRF Juvenile Diabetes Research Foundation International
Dedicated to finding a cure

The JDRF Emerging Technologies E-Newsletter No. 7 May 2008

FDA Approves Computer Simulator to Model Diabetes, Test Artificial Pancreas Algorithms

In early January, 2008, the FDA approved an *in silico* model of diabetes as a pre-clinical testing tool for closed-loop research at the seven JDRF Artificial Pancreas Consortium sites. Functioning as a computer simulator of type 1 diabetes, the software program is housed at the Jaeb

In this issue:

- Green light for APP computer simulator
- In Brief: Artificial Pancreas Project News

Closed-loop Glucose Control (Artificial Pancreas)

Insulin Pump

Glucose Sensor

Controller

- Dramatic improvment of subcutaneous glucose sensor accuracy
- Acceleration of artificial pancreas research

Before the Simulator: Animal Studies First, Then Humans

Original Article

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Original Article

Feasibility of Automating Insulin Delivery for the Treatment of Type 1 Diabetes

Garry M. Steil,[1] Kerstin Rebrin,[1] Christine Darwin,[2] Farzam Hariri,[2] and Mohammed F. Saad[3]

An automated closed-loop insulin delivery system based on subcutaneous glucose sensing and subcutaneous insulin delivery was evaluated in 10 subjects with type 1 diabetes (2 men, 8 women, mean [±SD] age 43.4 ± 11.4 years, duration of diabetes 18.2 ± 13.5 years). Closed-loop control was assessed over ~30 h and compared with open-loop control assessed over 3 days. Closed-loop insulin delivery was calculated using a model of the β-cell's multiphasic insulin response to glucose. Plasma glucose was 160 ± 66 mg/dl at the start of closed loop and was thereafter reduced to 71 ± 19 by 1:00 P.M. (preprandial lunch). Fasting glucose the subsequent morning on closed loop was not different from target (124 ± 25 vs. 120 mg/dl, respectively; $P > 0.05$). Mean glucose levels were not different between the open and closed loop (133 ± 63 vs. 133 ± 52 mg/dl, respectively; $P > 0.65$). However, glucose was within the range 70–180 mg/dl 75% of the time under closed loop versus 63% for open loop. Incidence of biochemical hypoglycemia (blood glucose <60 mg/dl) was similar under the two treatments. There were no episodes of severe hypoglycemia. The data provide proof of concept that glycemic control can be achieved by a completely automated external closed-loop insulin delivery system. *Diabetes* 55:3344–3350, 2006

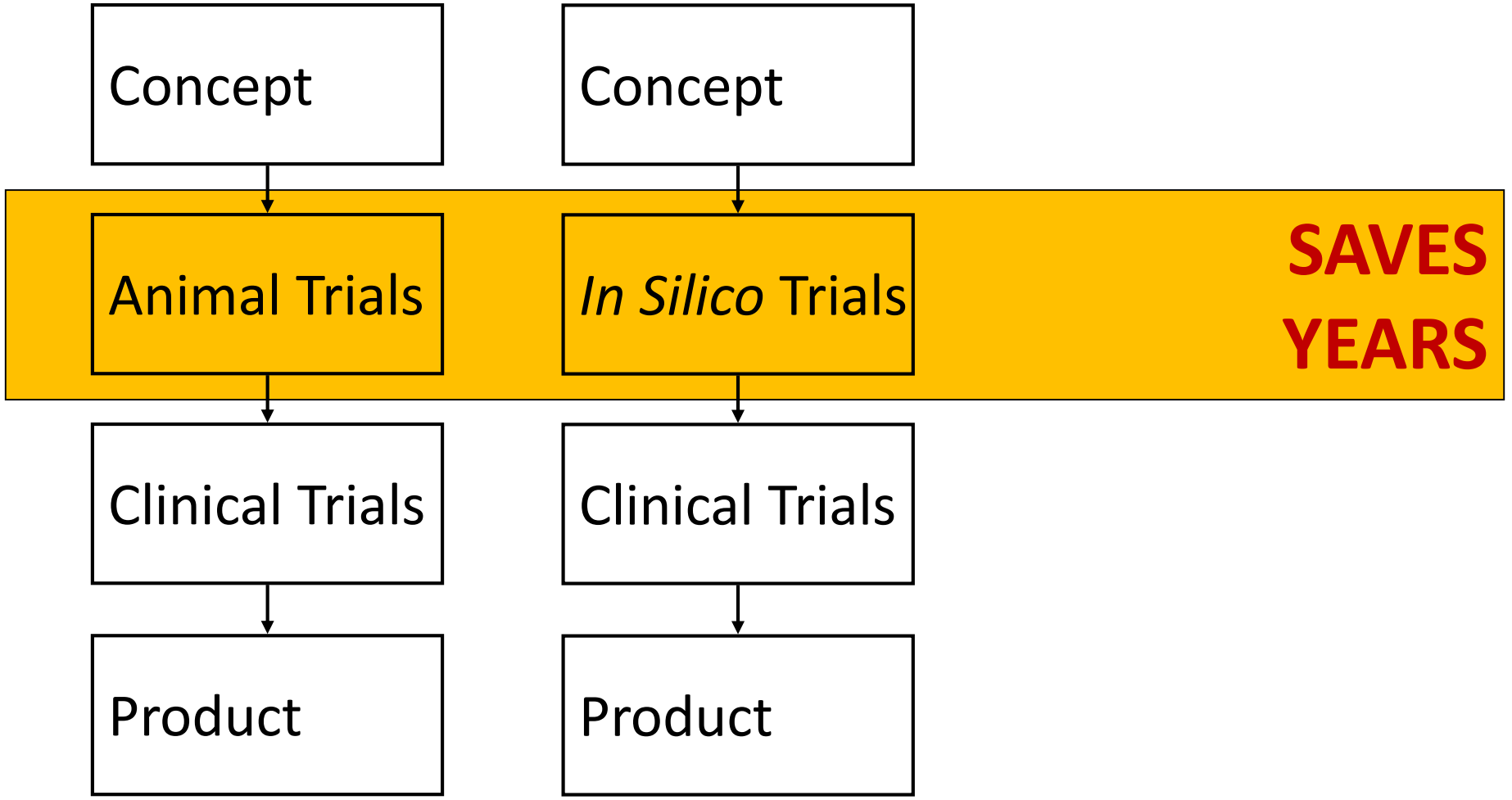
delivery. Technological and scientific advances have made sensors and pumps available, but linking the two as a "closed loop" has been challenging (2). Lingering questions remain regarding the suitability of different glucose-sensing sites (subcutaneous versus intravascular), insulin-delivery sites (subcutaneous versus intravascular versus intraperitoneal), and sensor reliability. In addition, no one algorithm has been universally accepted as optimal for insulin delivery (3).

Herein, we describe the feasibility of achieving glycemic control in patients with type 1 diabetes using a system comprised of a subcutaneous glucose sensor, an external insulin pump, and an algorithm emulating the β-cell's multiphasic glucose-induced insulin release (4–6).

RESEARCH DESIGN AND METHODS

Ten patients with previously diagnosed type 1 diabetes were studied (2 men, 8 women; mean [±SD] age 43.4 ± 11.4 years, BMI 26.5 ± 2.1 kg/m^2, diabetes duration 18.2 ± 13.5 years [range 4–48], HbA_{1c} 7.2 ± 0.8%, daily insulin requirement [DIR] 0.54 ± 0.08 units · kg^{-1} · day^{-1}). Subjects had been treated with continuous subcutaneous insulin infusion (CSII) using Lispro insulin (Lilly, Indianapolis, IN) for at least 6 months before study enrollment and were

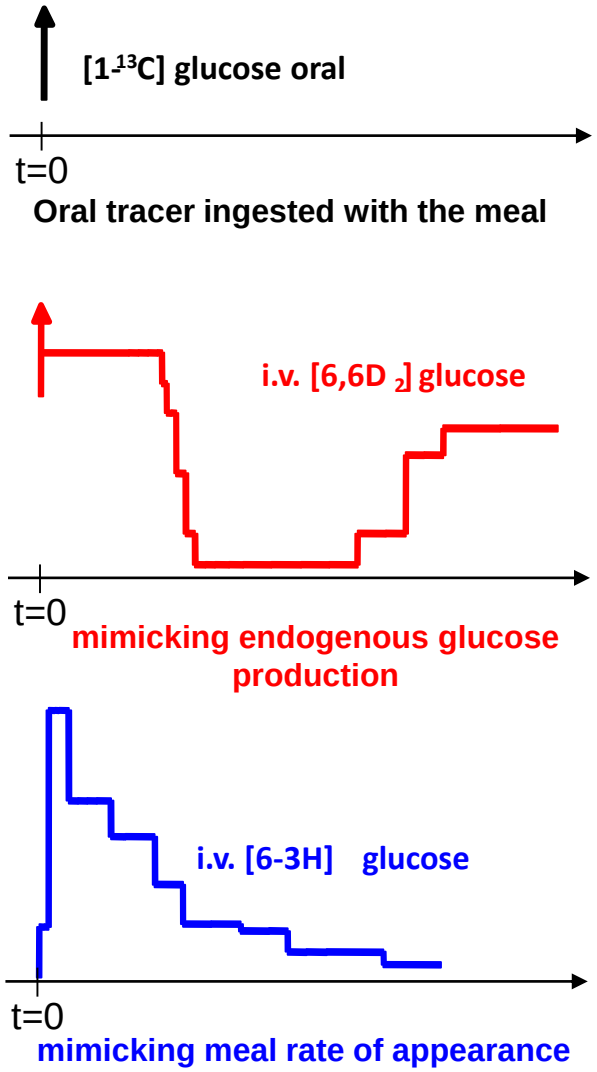
TRADITIONAL vs ACCELERATED DEVELOPMENT OF DRUGS & MEDICAL DEVICES



New Generation of Simulation Models

- Need to be **maximal** (large scale) not **minimal** (parsimonious)
- Need to describe **population variability**, i.e. average models are useless
- Are, generally, **nonlinear** dynamic models of **high order** with a **large** number of parameters

The Breakthrough: Triple Tracer Meal Studies at Mayo Clinic, Rochester, MN



Tracer-to-tracee clamp technique

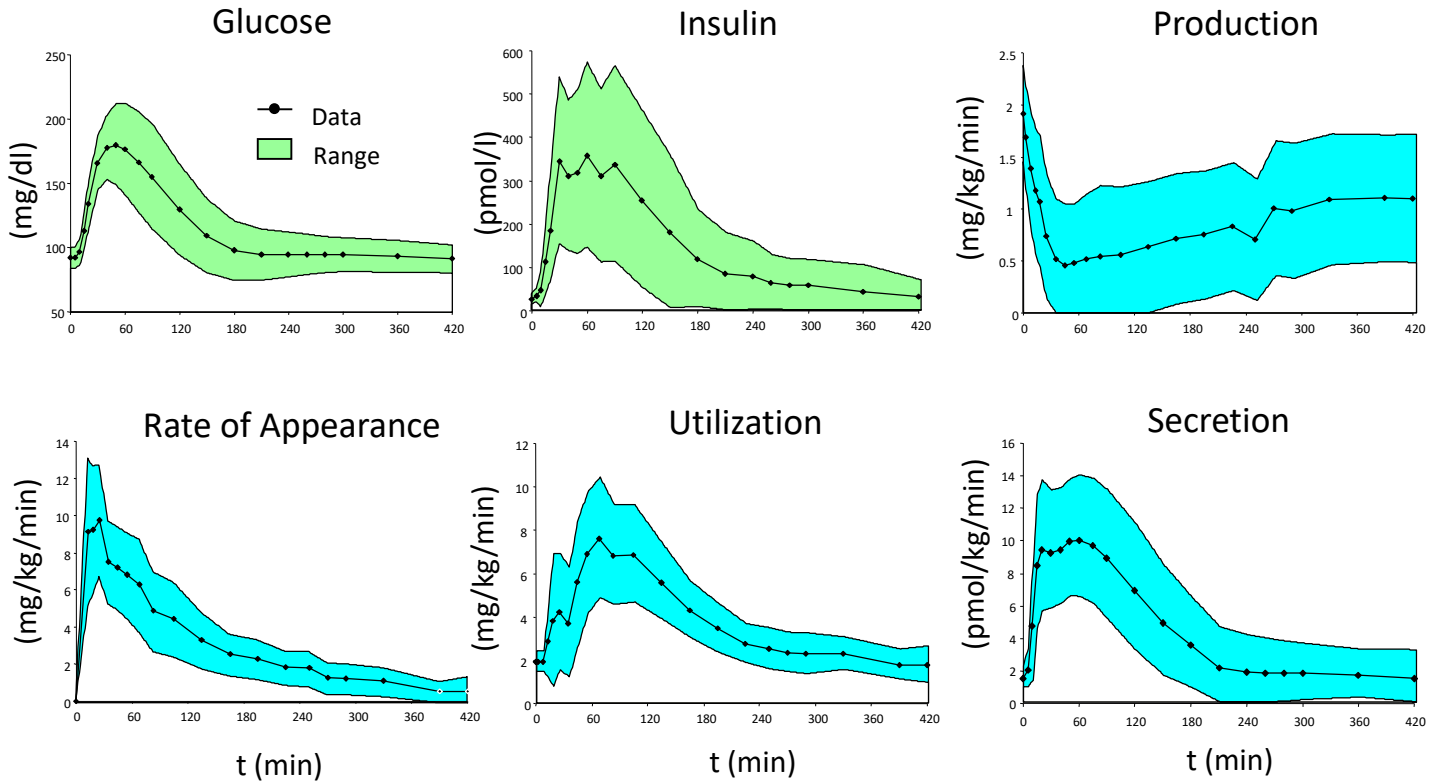
virtually model-independent:

- **Glucose Rate of Appearance**
- **Endogenous Glucose Production**
- **Glucose Utilization**
- **Insulin Secretion**

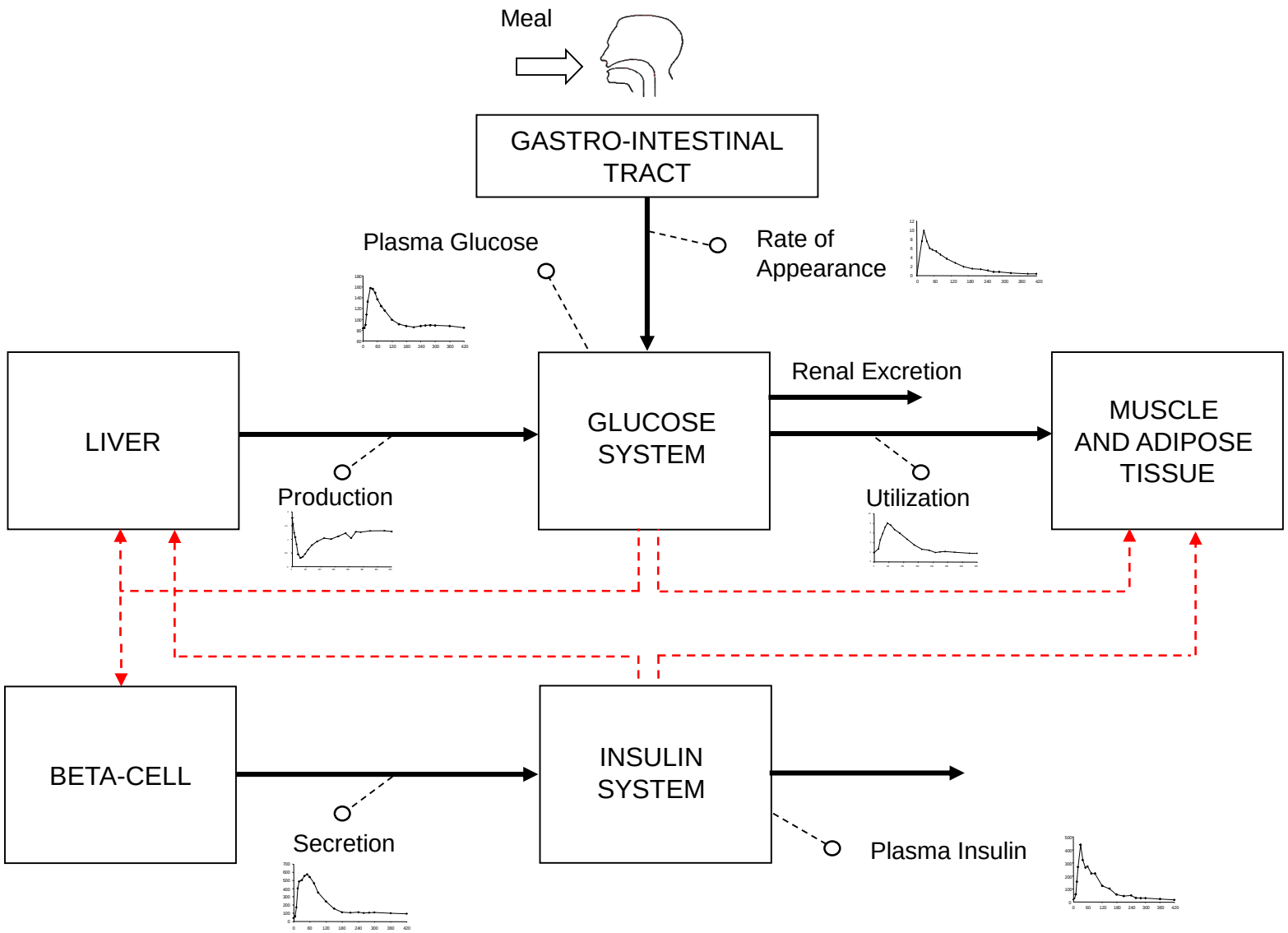
Fluxes, in addition to concentrations, measured in a quasi-model independent way in 244 healthy and Type 1 diabetes subjects

Basu et al., Diabetes 2006; Hinshaw et al., Diabetes 2013

Triple Tracer Meal Data in Healthy Individuals



The Simulator



Identification by system decomposition and bayesian forcing function strategy

The UVA/Padova Type 1 Diabetes Simulator

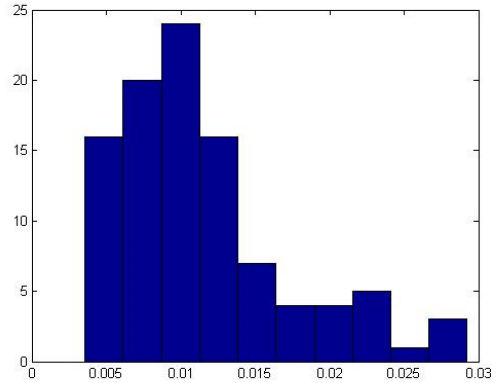
(Kovatchev et al., JSDT 2009; Visentin et al., JSDT 2018)

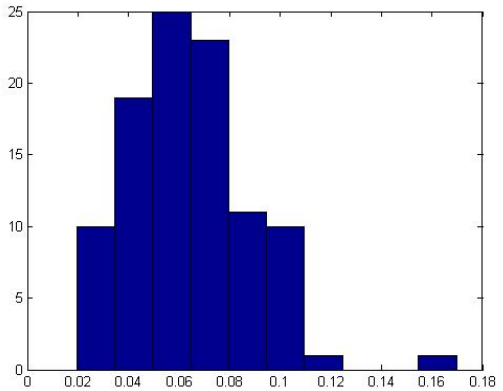
In Silico Subject

Key: Inter-Individual Variability

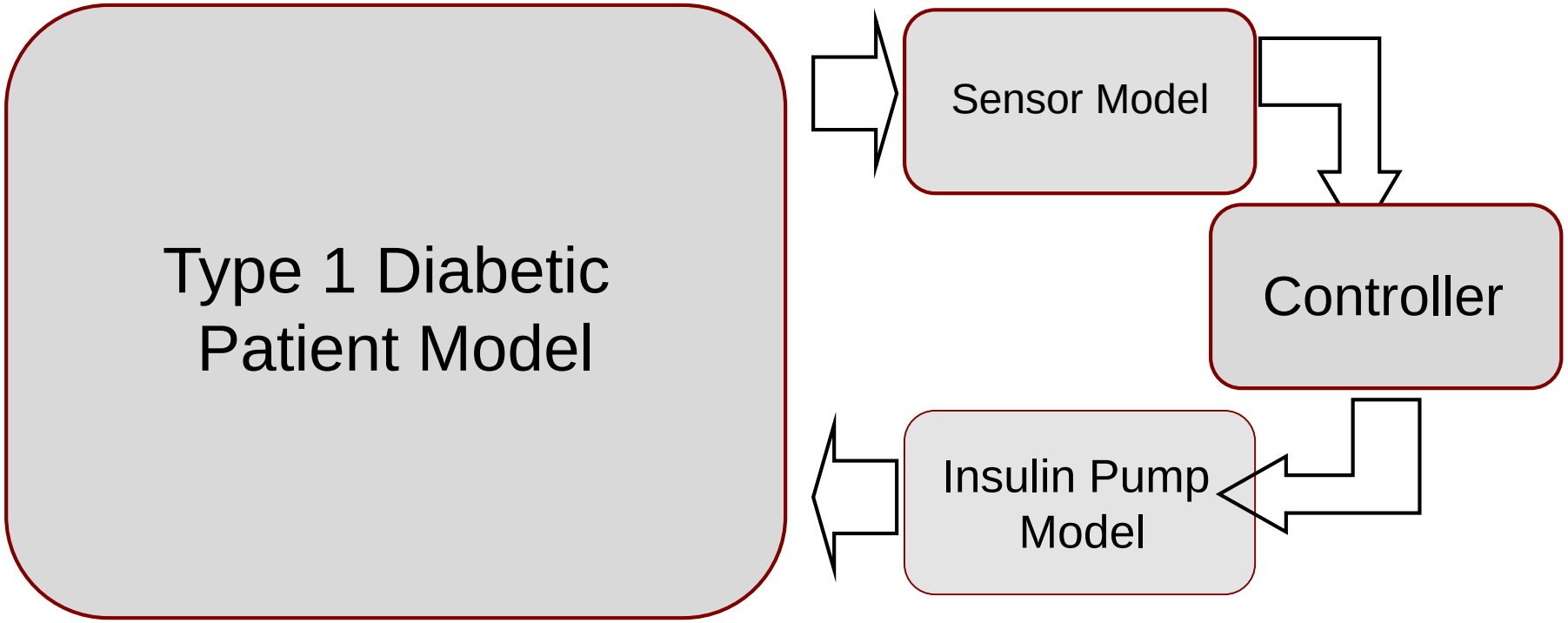
INSULIN ABSORPTION | **INSULIN ACTION**

Parameter	Adults (n=100)		Adolescents (n=100)		Children (n=100)	
					Min	Max
Weight (kg)		.7			27.6	60.7
Insulin (U/d		.4	5		17.6	56.1
Carb ratio (		.1			8.0	25.5



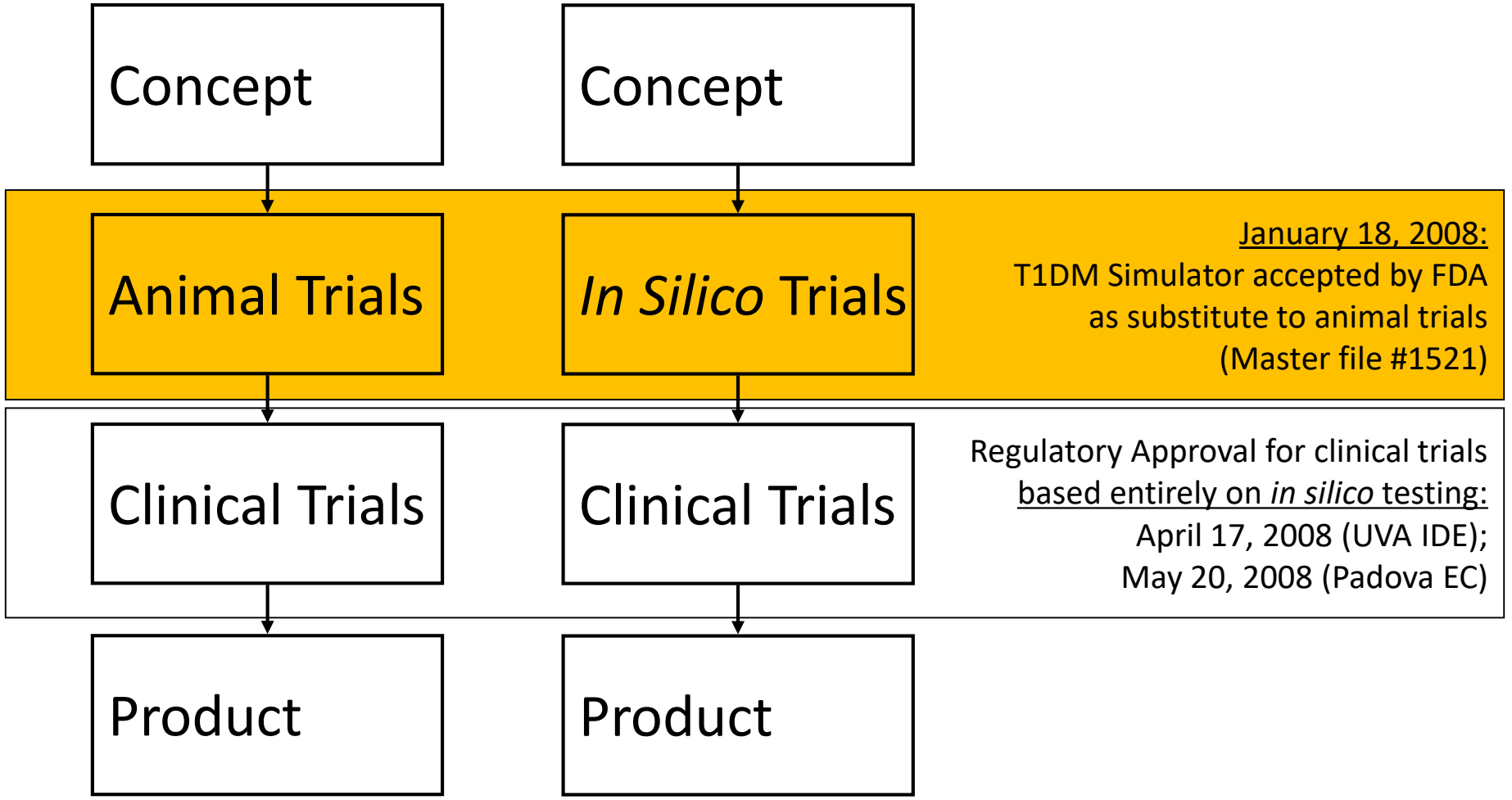


Type 1 Diabetes Simulator in AP Research

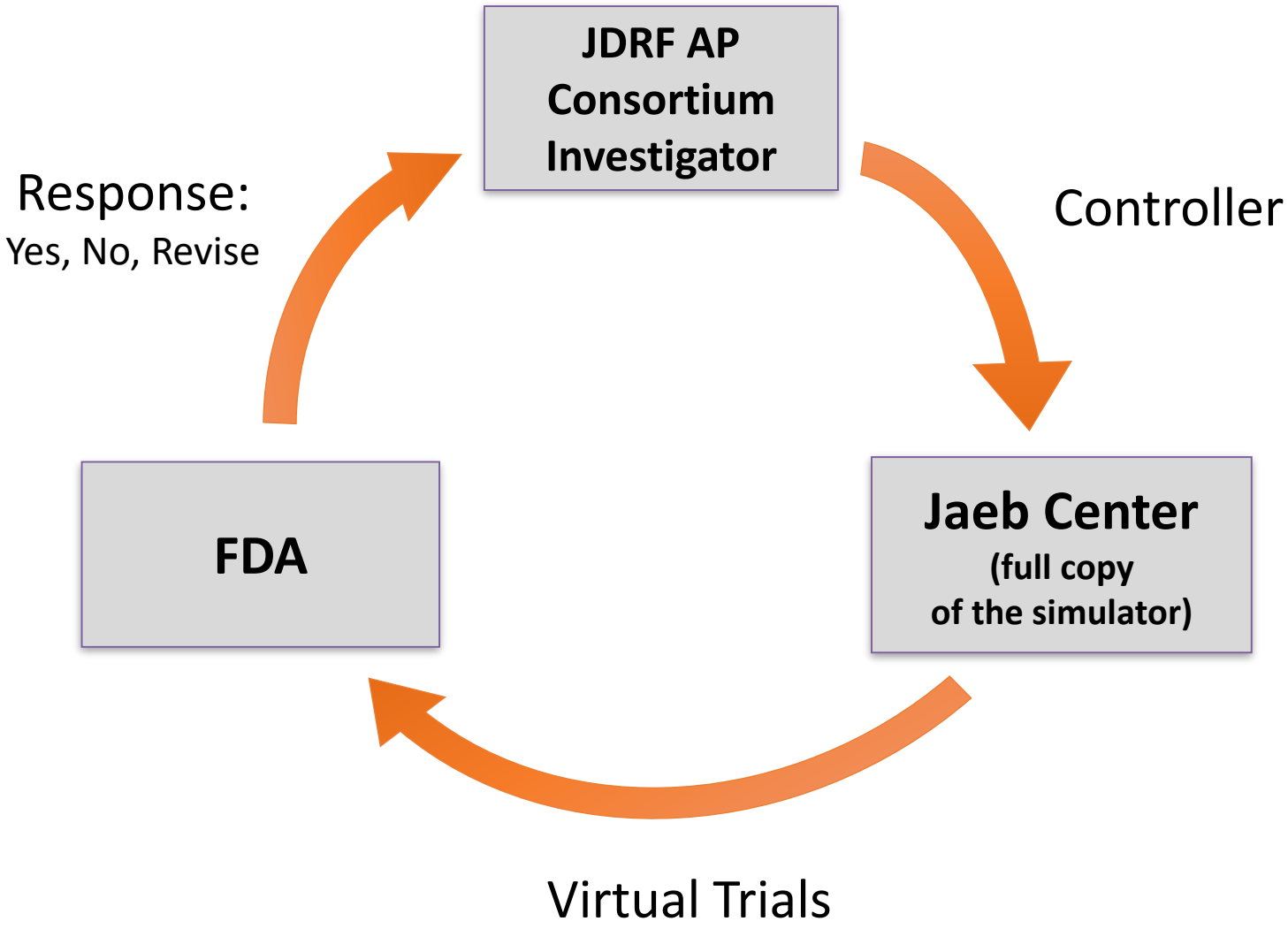


- Controller design, testing & validation
- In silico trials for regulatory purposes

Traditional vs. Accelerated Development of Drugs & Medical Devices



In Silico Procedure of Testing Controller



JDRF AP Consortium : Algorithm Verification for FDA Submissions

- A total of 140 candidate algorithm versions have been formally submitted to the Jaeb Center for validation

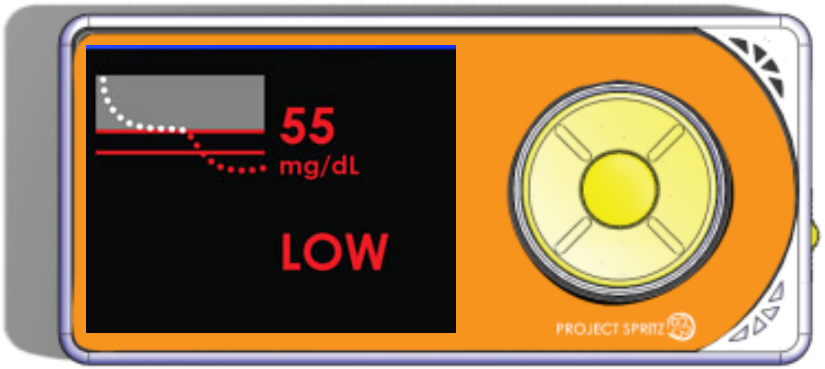
- The 140 submissions represent approximately 16 discrete projects for which one or more algorithm versions was submitted

- This resulted in an Investigational Device Exemption (IDE) being submitted to FDA after final validation

The FDA accepted T1D Simulator: Glucose Sensors , New Molecules & Insulin Delivery Modes

- SC glucose sensors: FDA Approval of Dexcom G5 Nonadjunctive Use, 2016
- Adjunctive T1D treatment (Pramlintide): Micheletto et al, DTT 2013; Riddle et al, DOM 2015
- Inhaled insulin (Afrezza): Visentin et al, DTT 2016
- Long-acting insulin: glargine & degludec: Schiavon et al, DTT 2020
- Intraperitoneal insulin delivery: the EU FET FORGETDIABETES project

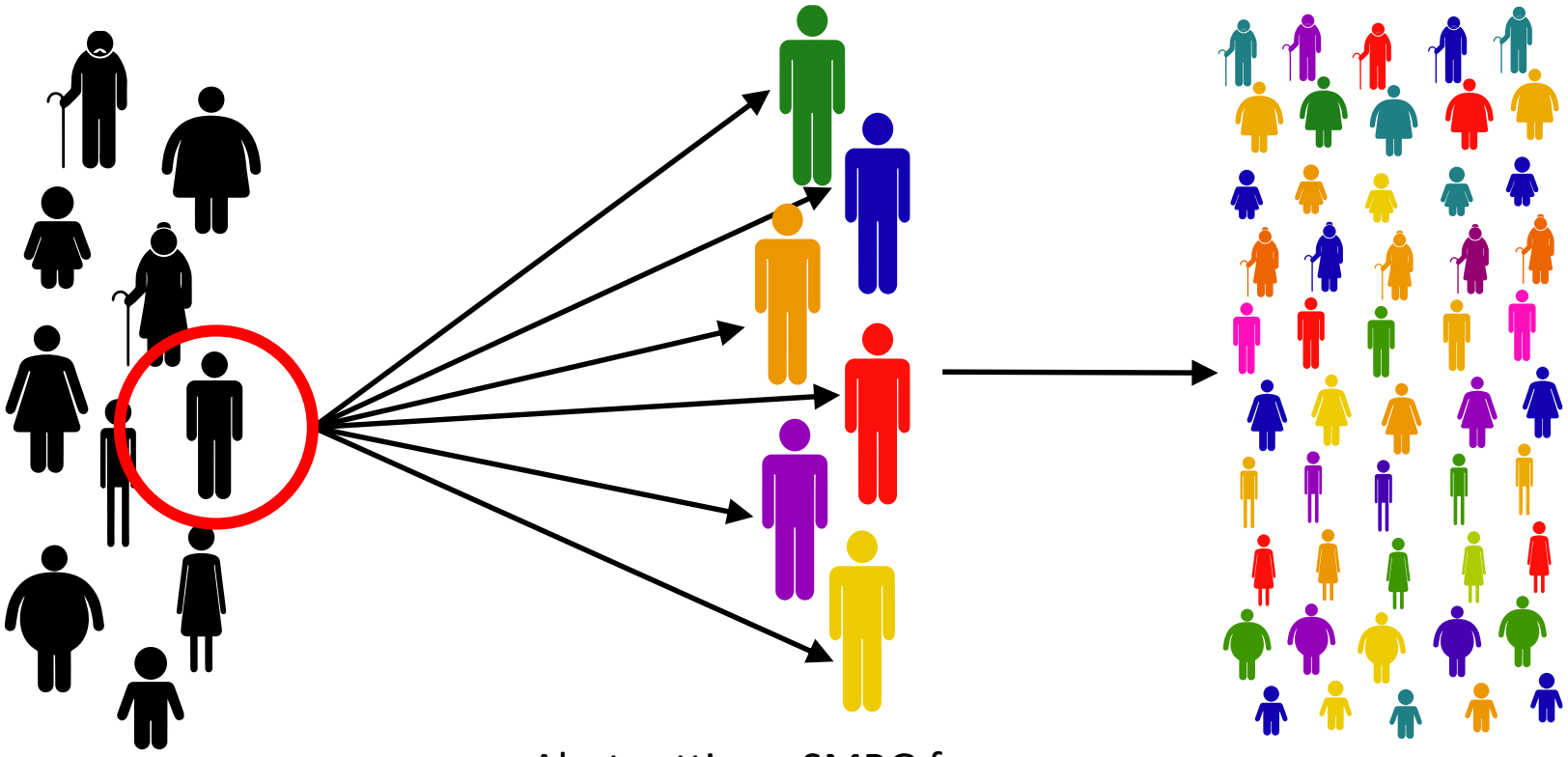
Dexcom G5 Mobile - Nonadjunctive Use



Nonadjunctive use: no need of self monitoring blood glucose to dose insulin

40,000 Unique Adult and Pediatric Combinations

200 Unique Physiologies **X** **100 Behaviors** **=** **20,000 Combinations**

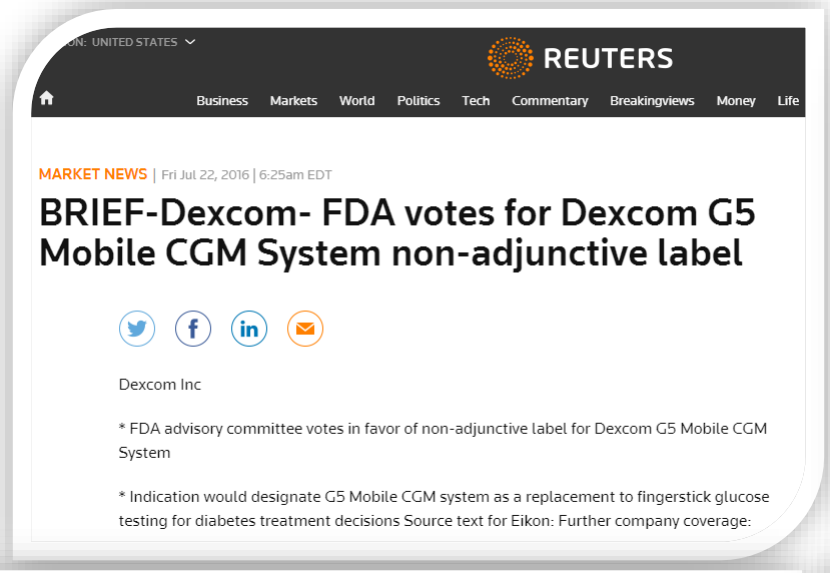


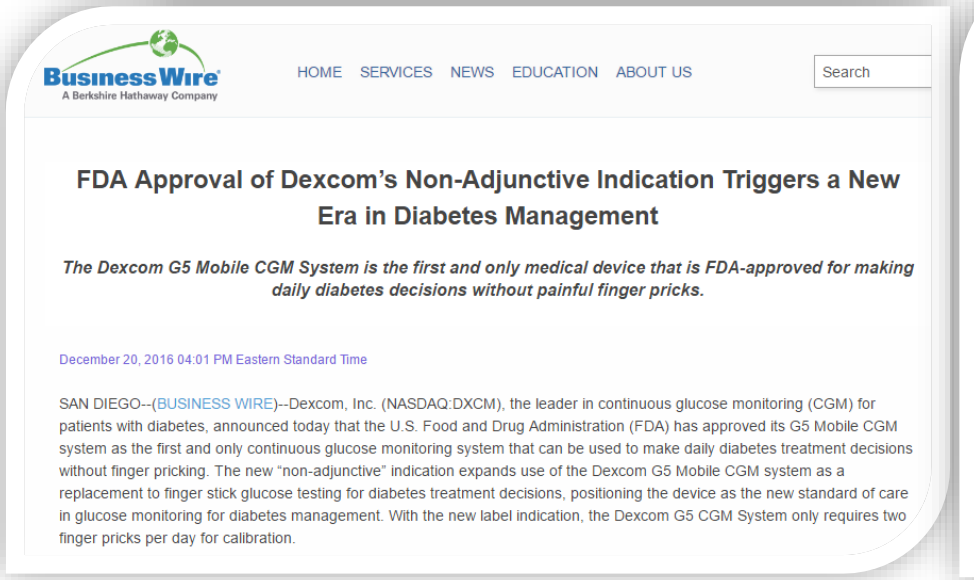
Insulin sensitivity, body weight,…

Alert settings, SMBG frequency, hypoglycemia awareness

Additional 20,000 for impaired hypoawareness

FDA Approves Dexcom G5 Nonadjunctive Use





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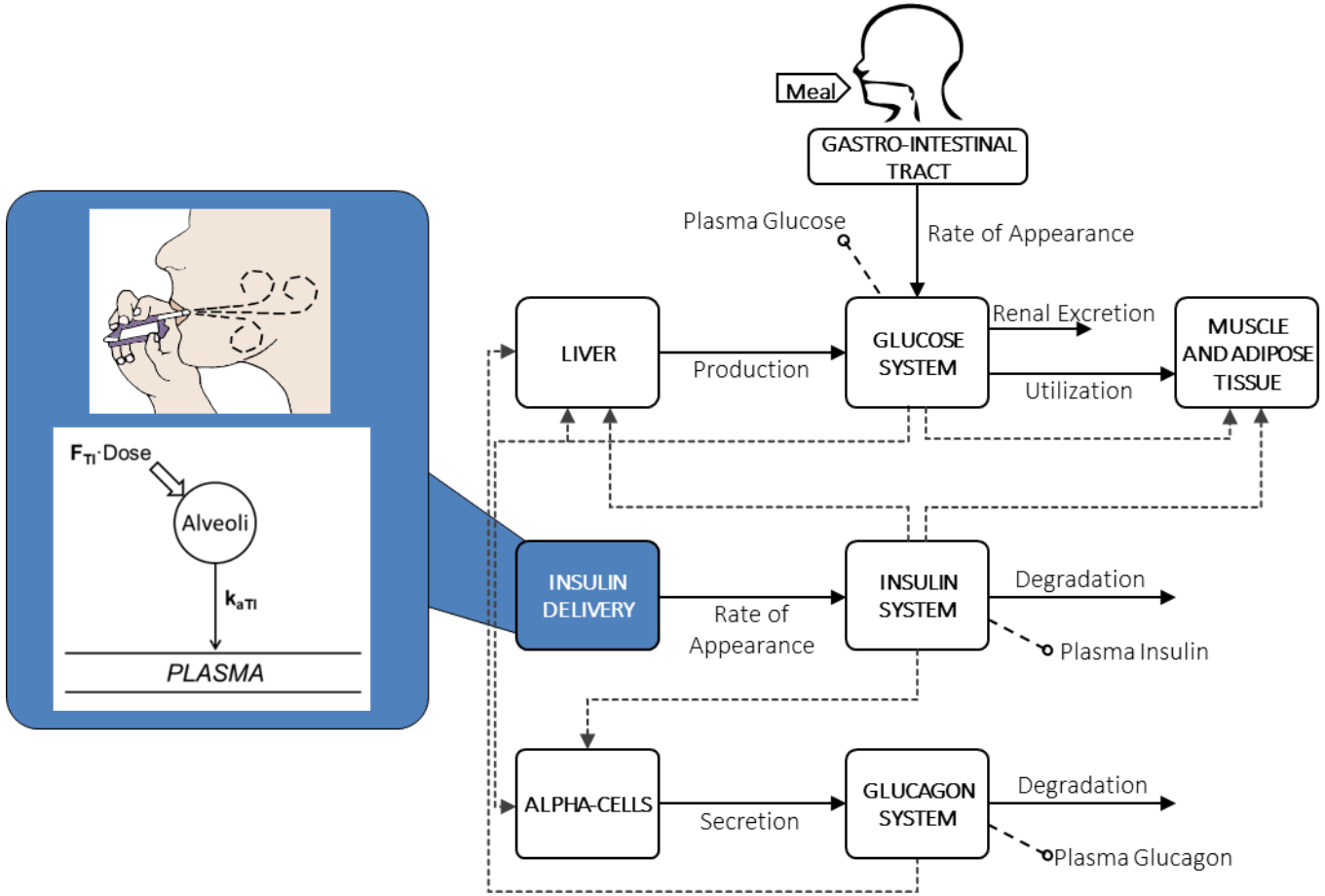
Incorporation into the UVA/Padova T1D Simulator

- The effect of inhaled insulin was then incorporated into the UVA/Padova T1D simulator



DIABETES TECHNOLOGY & THERAPEUTICS
Volume 18, Number 9, 2016
Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2016.0128

DTT

ORIGINAL ARTICLE

Improving Efficacy of Inhaled Technosphere Insulin (Afrezza) by Postmeal Dosing: In-silico Clinical Trial with the University of Virginia/Padova Type 1 Diabetes Simulator

Roberto Visentin, PhD,[1] Clemens Giegerich, MS,[2] Robert Jäger, PhD,[2]
Raphael Dahmen, MD,[2] Anders Boss, MD,[3] Marshall Grant, PhD,[4]
Chiara Dalla Man, PhD,[1] Claudio Cobelli, PhD,[1] and Thomas Klabunde, PhD[2]

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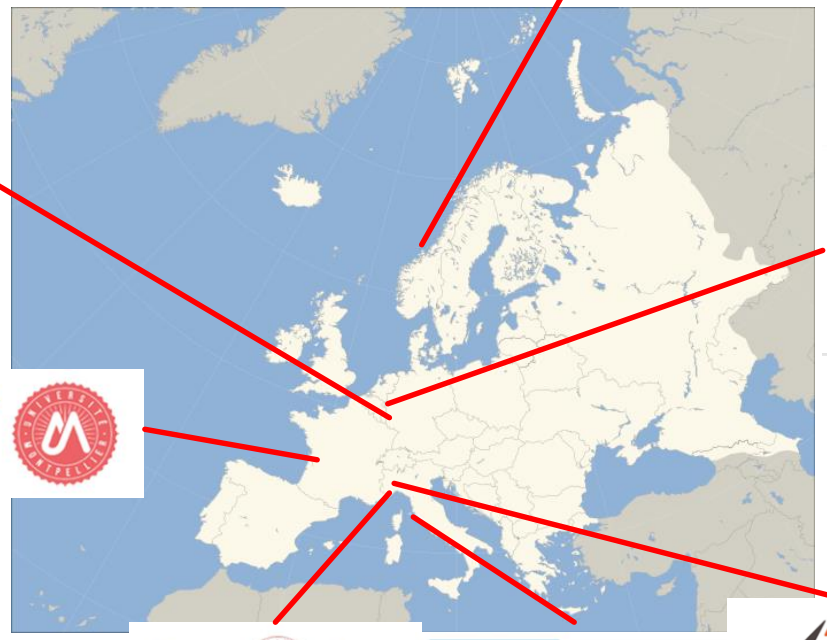
Future Emerging Technology (FET) call : high-risk high-gain breakthrough technology

Lifecare

Forschungsinstitut der Diabetes-Akademie Bad Mergentheim (FIDAM)



PFÜTZNER Science & Health Institute Diabeteszentrum & Praxis

CHU Montpellier

Université de Montpellier

800 1222-2022 Università degli Studi di Padova

THE BIOROBOTICS INSTITUTE

Scuola Superiore Sant'Anna

WAVECOMM electronic and wireless systems

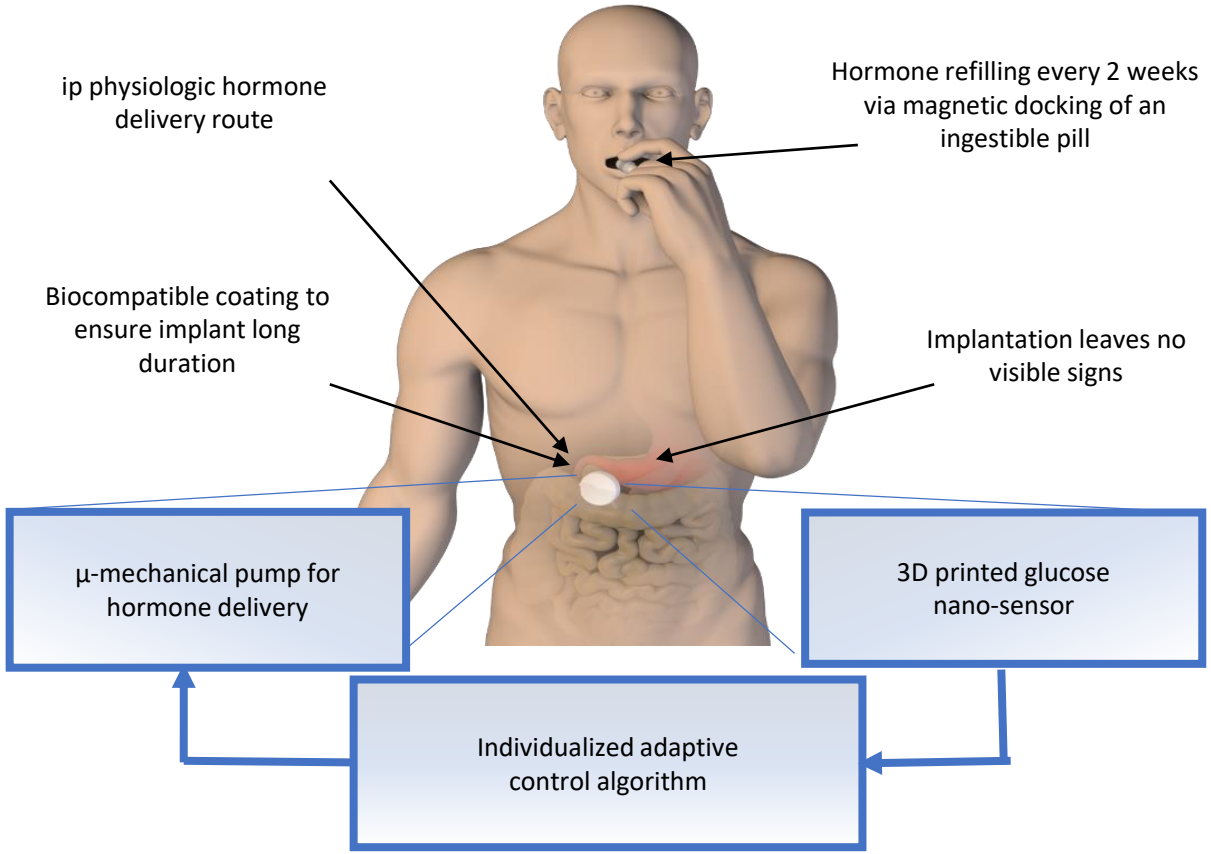
HORIZON 2020

Call: H2020-EIC-FETPROACT-2019
Type of Action: RIA
Acronym: FORGETDIABETES
Current Phase: Grant Management
Number: 951933
Duration: 54 months
GA based on the: H2020 General MGA — Multi - 5.null
Start Date: 01 Oct 2020
Estimated Project Cost: €3,901,014.75

Funded by European Union

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 951933

The bionic implantable pancreas :
a radically new intraperitoneal (ip) fully closed-loop technology



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ip fully automated CL

ORIGINAL ARTICLE

Intraperitoneal insulin delivery provides superior glycaemic regulation to subcutaneous insulin delivery in model predictive control-based fully-automated artificial pancreas in patients with type 1 diabetes: a pilot study

Eyal Dassau PhD[1,2] | Eric Renard MD, PhD[3,4] | Jérôme Place MS[4] | Anne Farret MD, PhD[3,4] | Marie-José Pelletier MD[3] | Justin Lee PhD[2] | Lauren M. Huyett PhD[2] | Ankush Chakrabarty PhD[1] | Francis J. Doyle III PhD[1,2] | Howard C. Zisser MD[2]

- *ip* Insulin delivery (Diaport)
- 1 day in hospital fully closed-loop ip vs sc with unannounced meal
- 10 individuals with type 1 diabetes
- ↑↑↑ TIR (80-140mg/dL)

Dassau et al, DOM 2017

*Bayesian in silico A*ugmentation of Clinical Trials

Artificial Pancreas: In Silico Study Shows No Need of Meal Announcement and Improved Time in Range of Glucose with Intraperitoneal vs Subcutaneous Insulin Delivery

Chiara Toffanin, Lalo Magni, and Claudio Cobelli, *Fellow, IEEE*

- 100 *in silico* subjects confirmed ip *in vivo 1-day* results of *Dassau et al* over a 4-weeks ip study with inter- and intra-day insulin sensitivity variability

Toffanin C, Cobelli C, IEEE 2022

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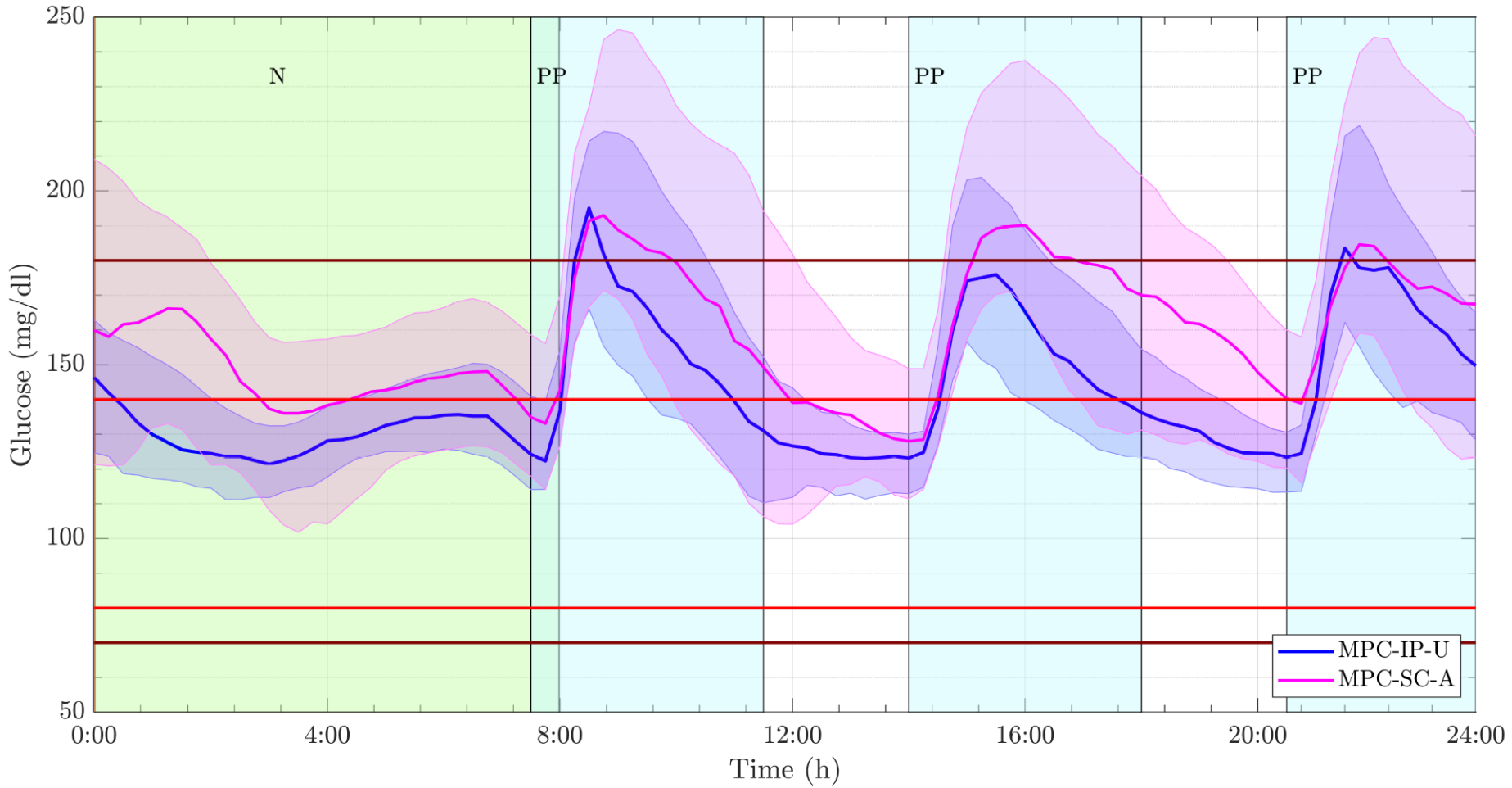

Fig. 3. Comparison of average glucose time courses with MPC-IP-U (blue) versus MPC-SC-A (magenta) on the 2-week scenario. Continuous lines are the median across patients, with [25th, 75th] percentiles as shading. Night (N) and Post-Prandial (PP) regions are highlighted in green and light blue, respectively.

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Glucose metrics

		Day & Night
A (mg/dl)	MPC-IP-U	**141.32 [126.73, 161.61]**
	MPC-SC-U	**169.74 [145.91, 209.55]**
SD (mg/dl)	MPC-IP-U	**28.72 [22.37, 36.02]**
	MPC-SC-U	**46.19 [33.38, 54.40]**
CV (mg/dl)	MPC-IP-U	**0.20 (± 0.06)**
	MPC-SC-U	**0.25 (± 0.09)**
Tr (%)	MPC-IP-U	**87.22 [72.37, 94.56]**
	MPC-SC-U	**59.52 [38.56, 72.10]**
Ttr (%)	MPC-IP-U	**56.67 [26.13, 69.21]**
	MPC-SC-U	**25.88 [2.65, 52.48]**
Ta (%)	MPC-IP-U	**9.15 [3.31, 26.06]**
	MPC-SC-U	**39.88 [26.07, 61.44]**
Tb (%)	MPC-IP-U	0.00 [0.00, 1.26]
	MPC-SC-U	0.00 [0.00, 0.99]

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CONCLUSIONS

- The FDA acceptance of the Type 1 Diabetes Simulator: an unprecedented event in the modeling community
- In silico trials have dramatically accelerated regulatory processes of artificial pancreas research
- The simulator is instrumental in diabetes technology research: glucose sensors, new molecules and insulin delivery modes
- In silico trials allow augmentation of small clinical trial by increasing numerosity and variability of the population
- Absence in Italy of the FDA Investigational Exemption Device penalizes research , and especially small innovative biotech companies or investigator initiated studies