Multi-Physics, Multi-Scale, Systems-Level Modeling w/ANSYS Software

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Today’s medical devices are increasingly:

Electric → **Smarter** → **Connected**

IVD devices	Physiological Monitors	Mobile Medical Apps	Wearables	Capital Intensive Devices
Blood Analyzers Immuno-assays Breast Biopsy Equipment HIV Detection Systems	Weighing scales Pulse Oximeter BP Meter ECG Ventilators Blood Glucose Meters Heart Rate Monitors	Medication Adherence Systems Dosage Calculation Systems	Activity Tracker Pedometer Sleep Apnea Detector	Implants Prostheses MRI/CT/ Ultrasound Scanners

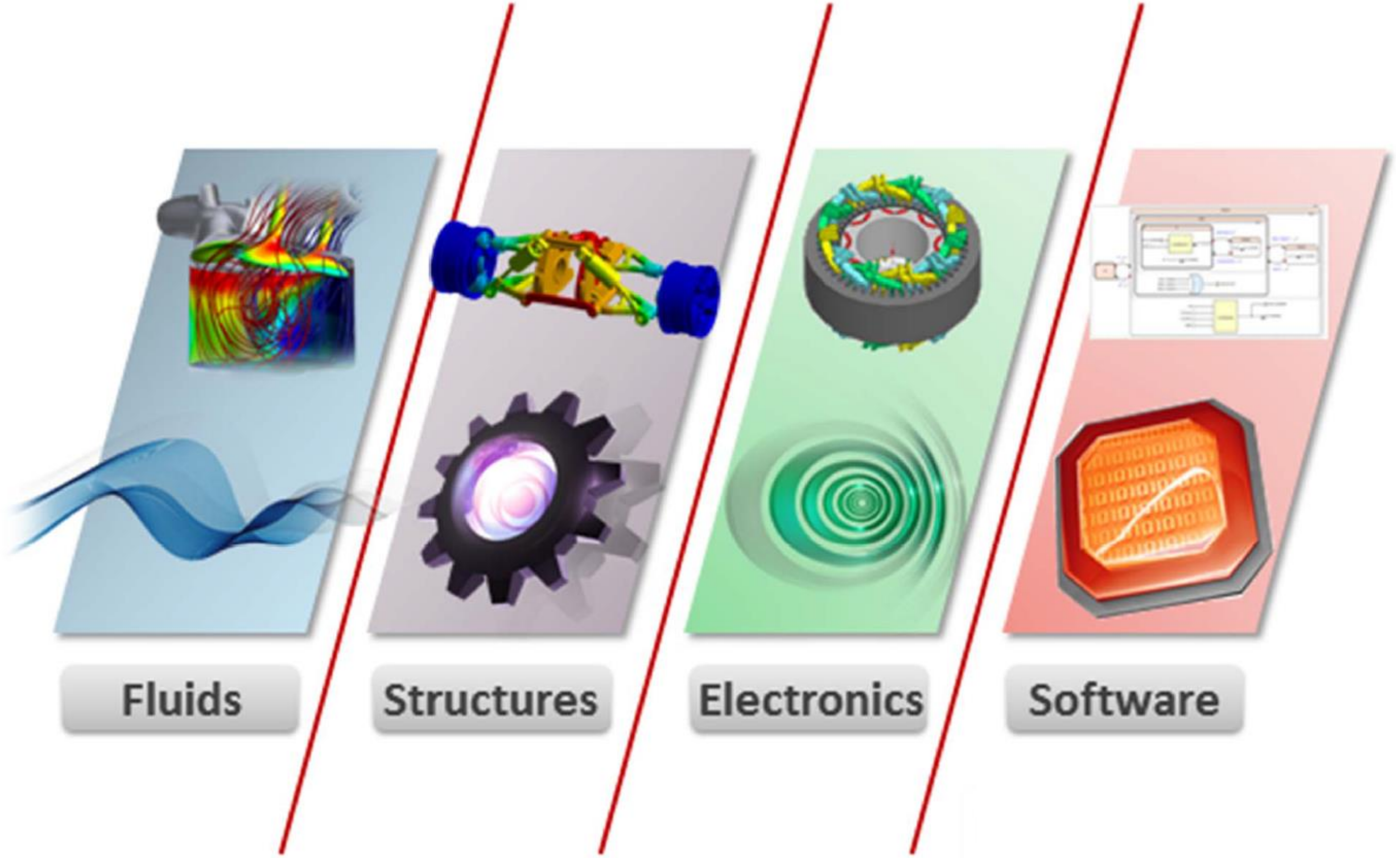
* Cogizant, How the IOT is Transformng Medical Devices, May 2016

Challenge: System Complexity

- Understand and optimize performance
- Eliminate late-stage integration failures
- Improve collaboration among design disciplines
- Enhance or reduce physical testing
- Accelerate innovation

→ **Digital System Prototyping**

Design Still Happens in Silos



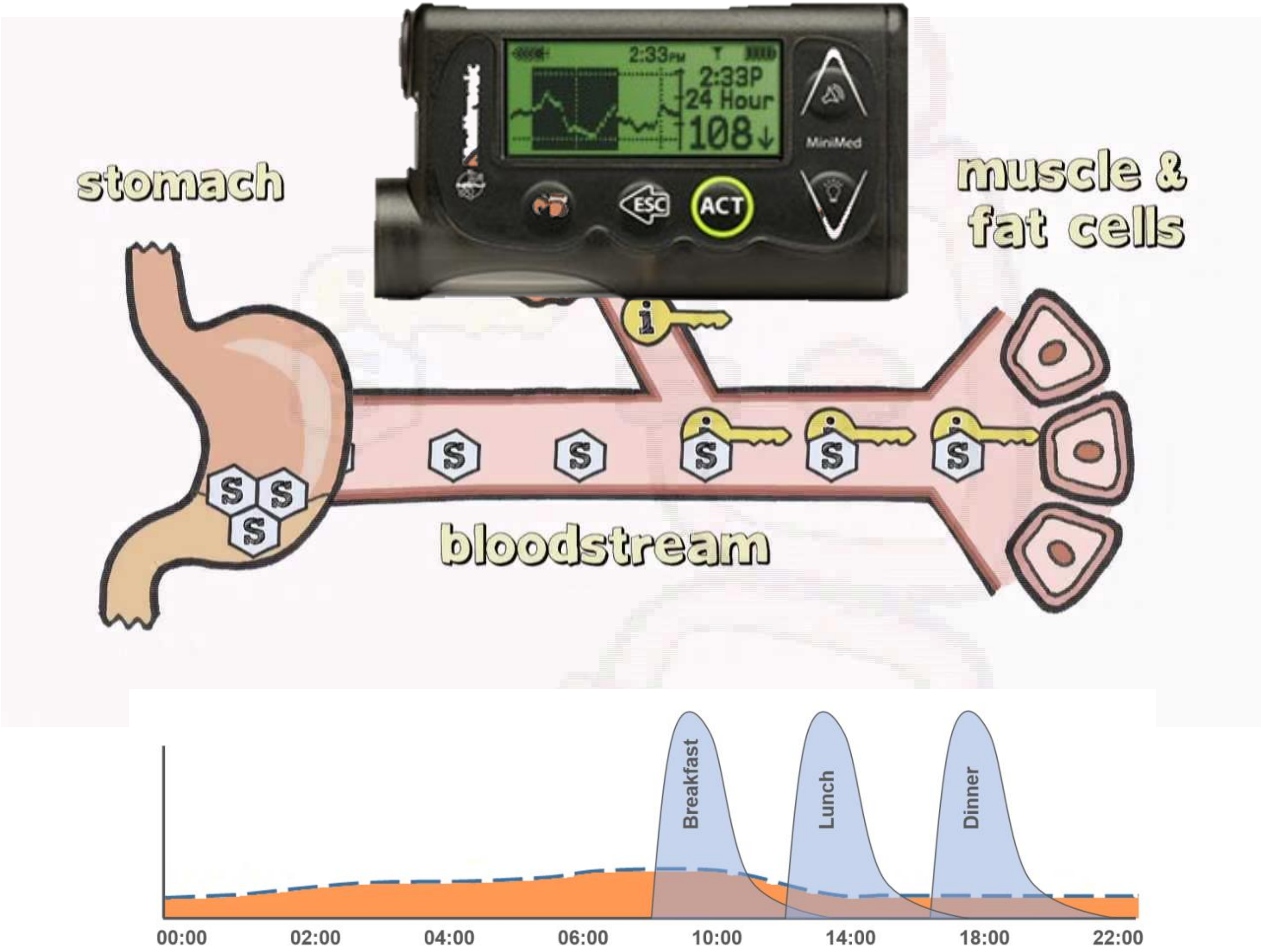
Each discipline has its' own set of tools, processes, and expertise.

Systems Engineering: A Unifying Approach

Insulin Pump Model Overview

What is Diabetes?

- Insulin is a hormone created by the pancreas. It is required for sugar molecules (from the food you eat) to move inside cells. Patients with diabetes either do not produce insulin (Type 1) or do not use insulin the right way (Type 2).
- Insulin pumps replace the function of the pancreas by injecting insulin under the skin throughout the day.



Diabetes image from https://i.ytimg.com/vi/SCCb5GqhnrI/maxresdefault.jpg
Pump image from http://www.medtronicdiabetes.com/products/minimed-530g-diabetes-system-with-enlite

Regulatory Perspective

FDA NEWS RELEASE

For Immediate Release: April 23, 2010
Media Inquiries: Dick Thompson, 301 796 7566; dick.thompson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA Launches Initiative to Reduce Infusion Pump Risks
Agency calls for improvements in device design

…infusion pumps also have been the source of persistent safety problems. In the past five years, the FDA has received more than 56,000 reports of adverse events associated with the use of infusion pumps. Those events have included serious injuries and more than 500 deaths. Between 2005 and 2009, 87 infusion pump recalls were conducted to address identified safety concerns, according to FDA data.

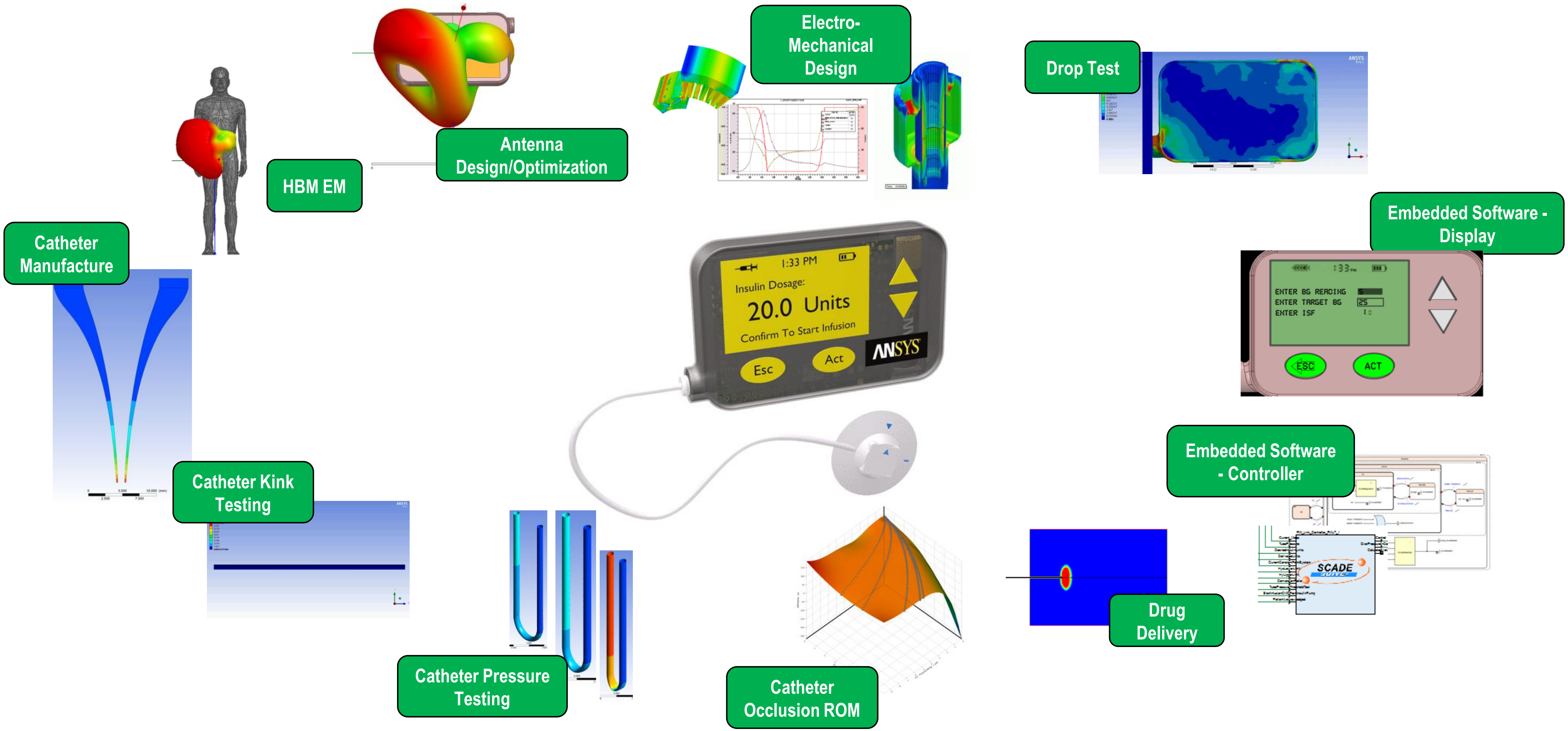
The most common types of reported problems have been related to:

- software defects, including failures of built-in safety alarms;
- user interface issues, such as ambiguous on-screen instructions that lead to dosing errors; and
- mechanical or electrical failures, including components that break under routine use, premature battery failures, and sparks or pump fires.

"many of the reported problems appear to be related to deficiencies in device design and engineering"

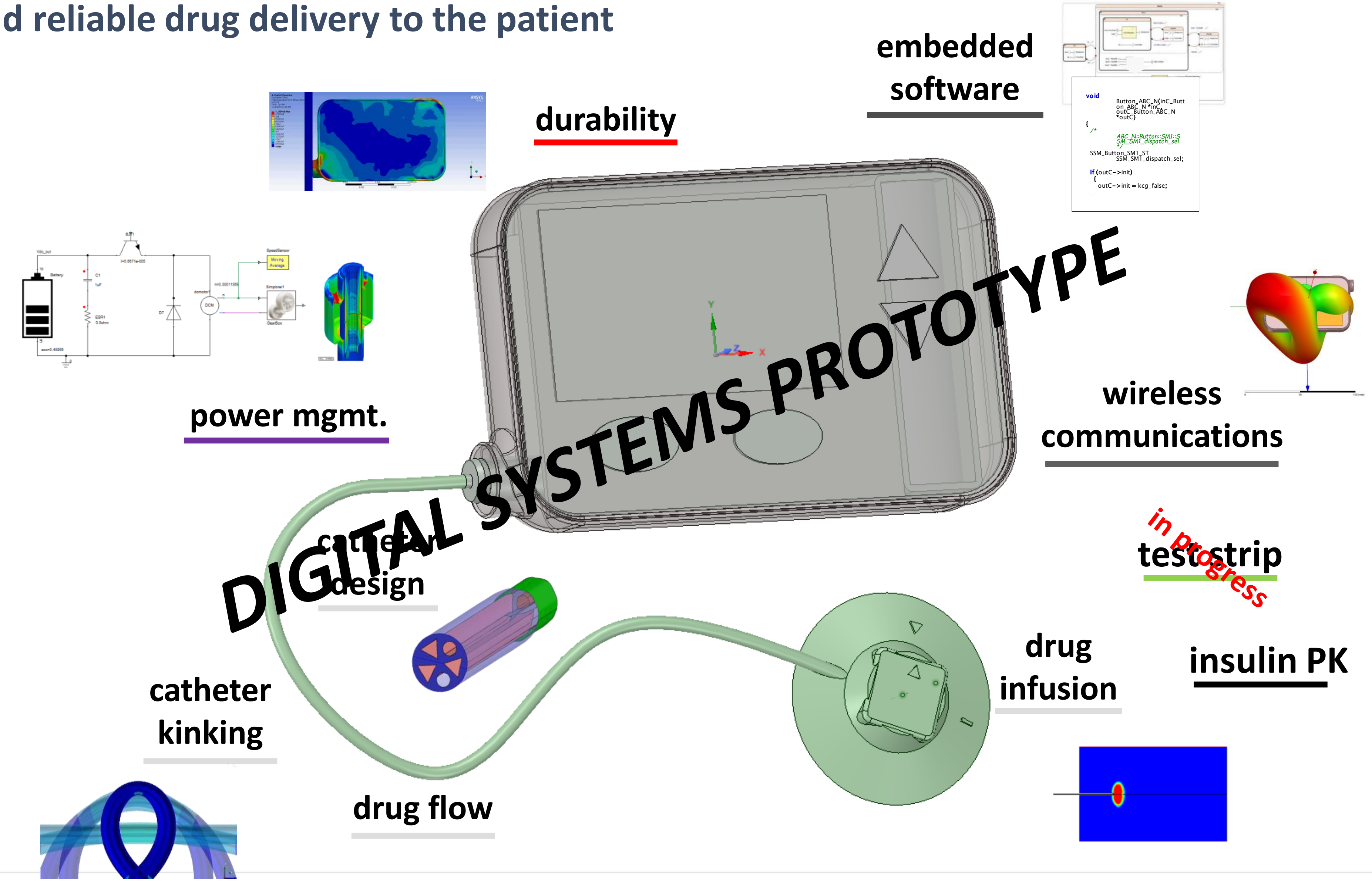
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm209042.htm

Digital Prototype of an Insulin Pump

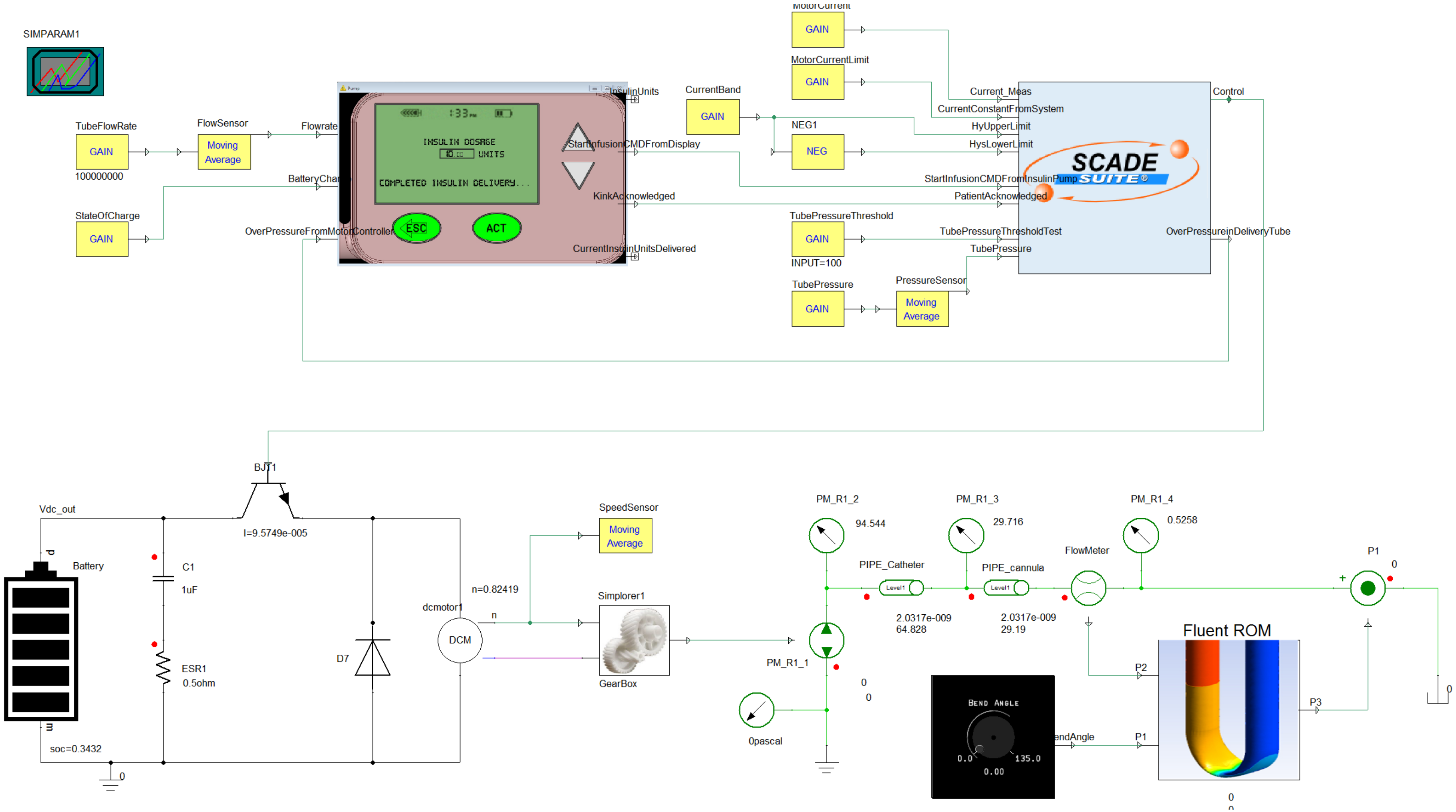


Engineering Challenge

→ accurate and reliable drug delivery to the patient

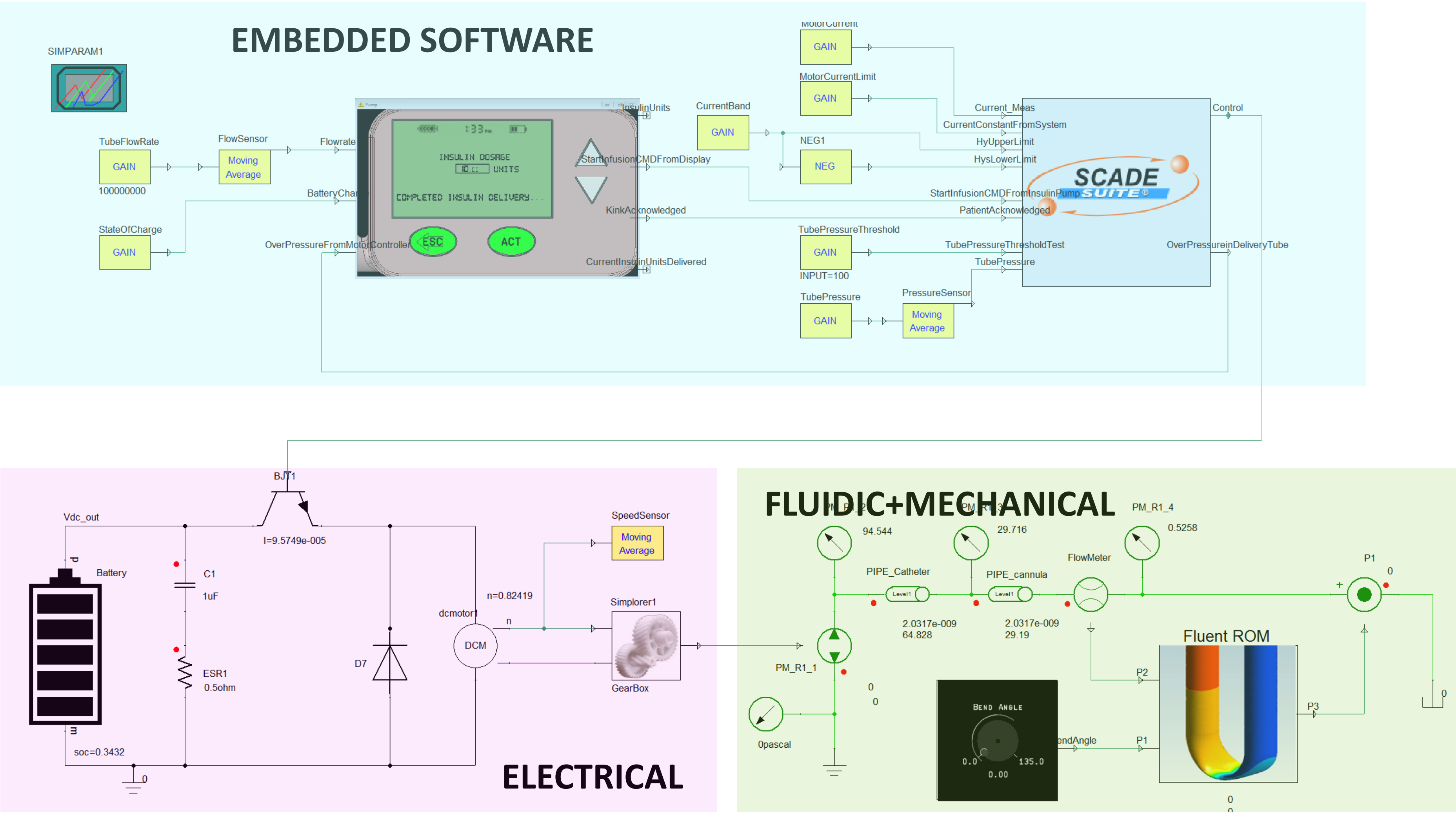


Insulin Pump – Drug Delivery Sub-System View



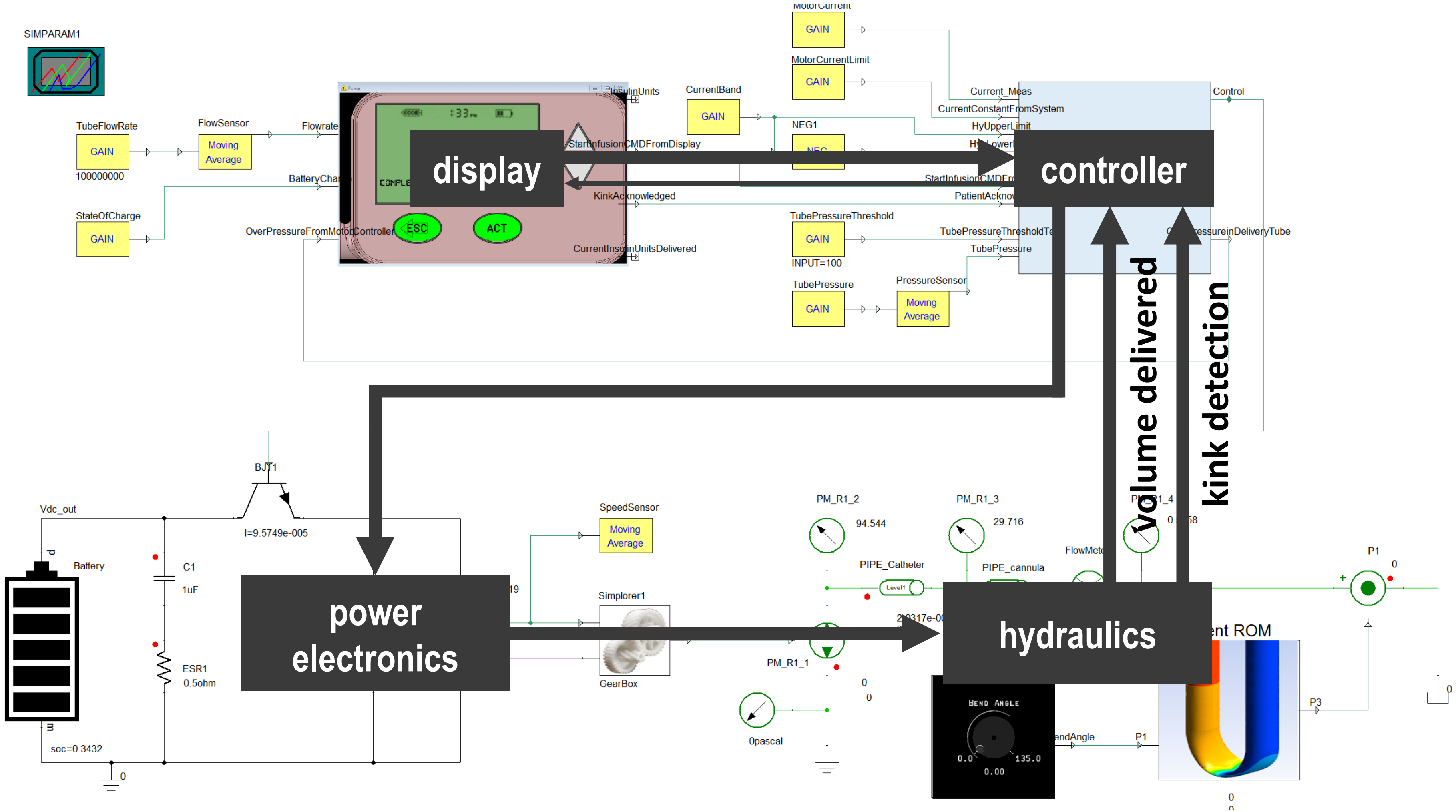
Insulin Pump – Drug Delivery Sub-System View

MODEL DOMAINS

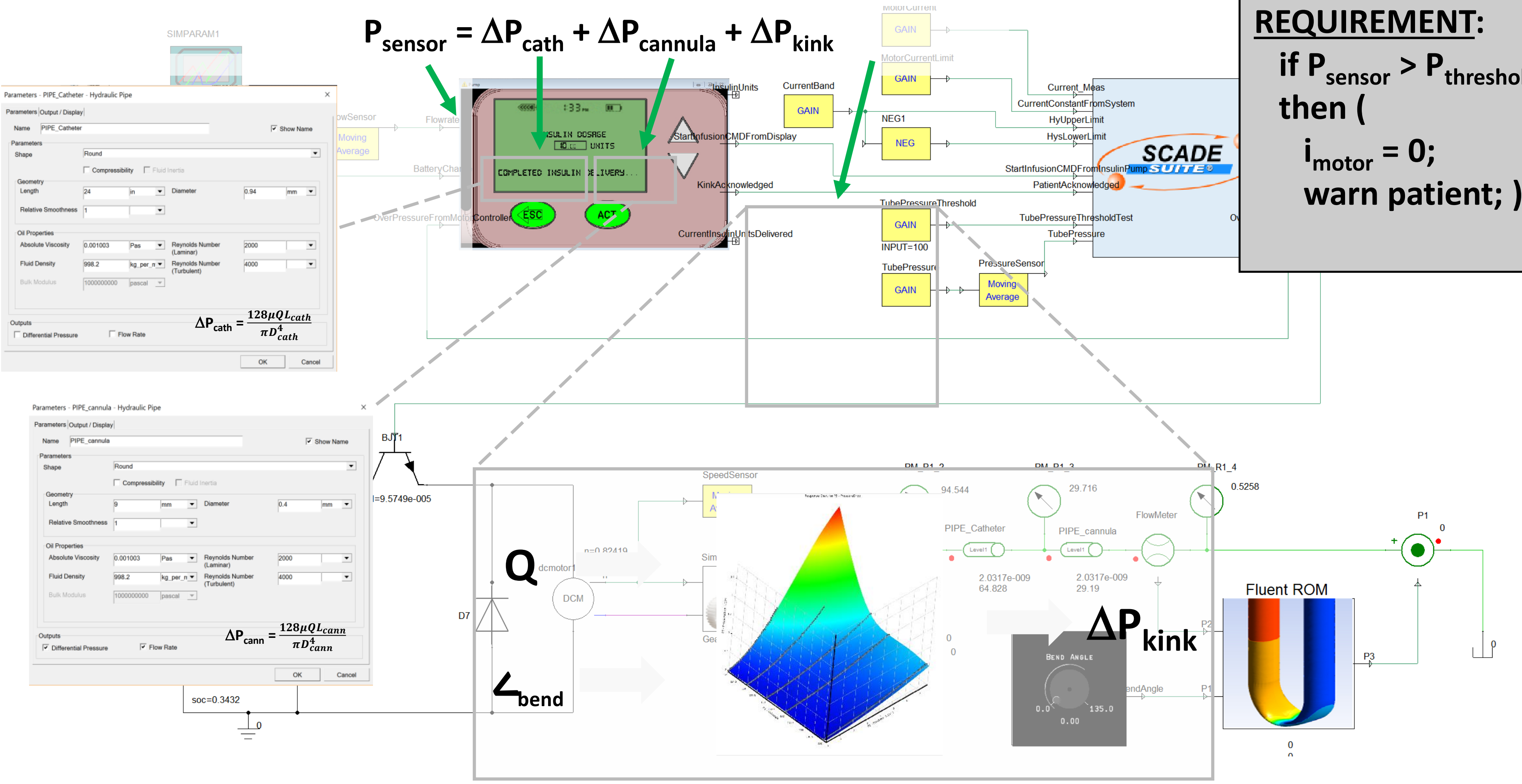


Insulin Pump – Drug Delivery Sub-System View

INFORMATION FLOW



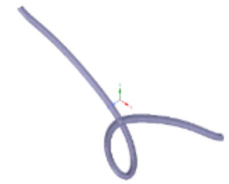
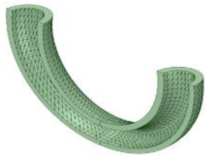
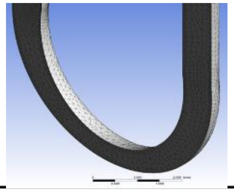
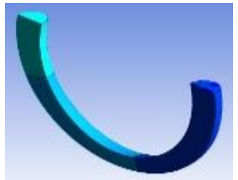
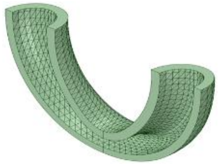
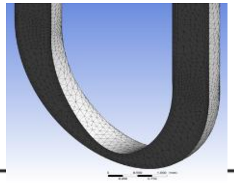
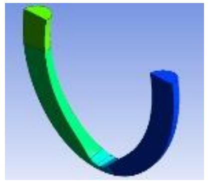
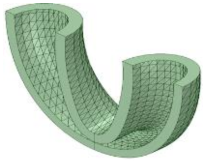
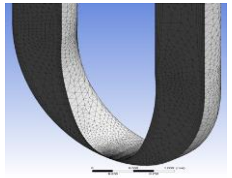
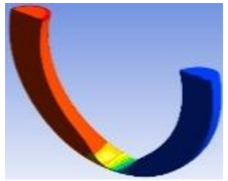
Insulin Pump – Drug Delivery Sub-System View - Kink Detection



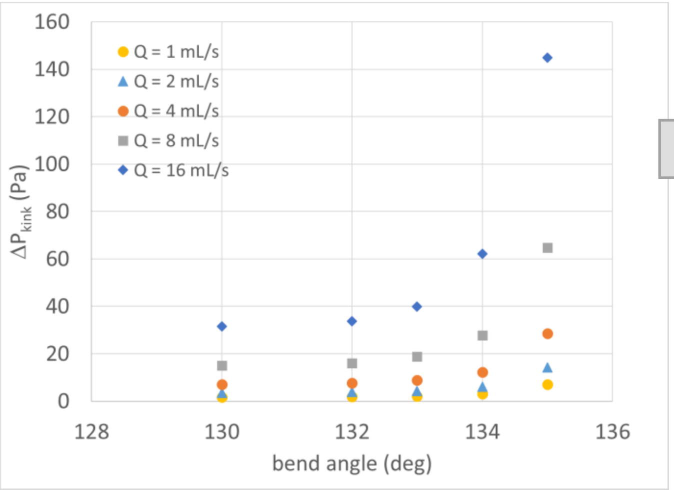
REQUIREMENT:

if $P_{sensor} > P_{threshold}$
then (
$i_{motor} = 0$;
warn patient;)

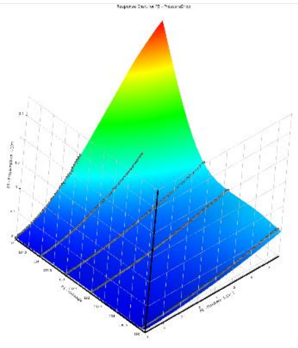
Pressure-Flow Analysis of Tube Bending

Non Linear Kink Prediction *__3D FEA__*	Deformed Geometry Export *__3D FEA → CAD__*	Fluid volume extraction of kinked model *__CAD → 3D CFD__*	Detailed Flow Simulation (kink angles & flow rates → pressure drop) *__3D CFD__*
			
			
			

Family of Structural Fluid Simulations

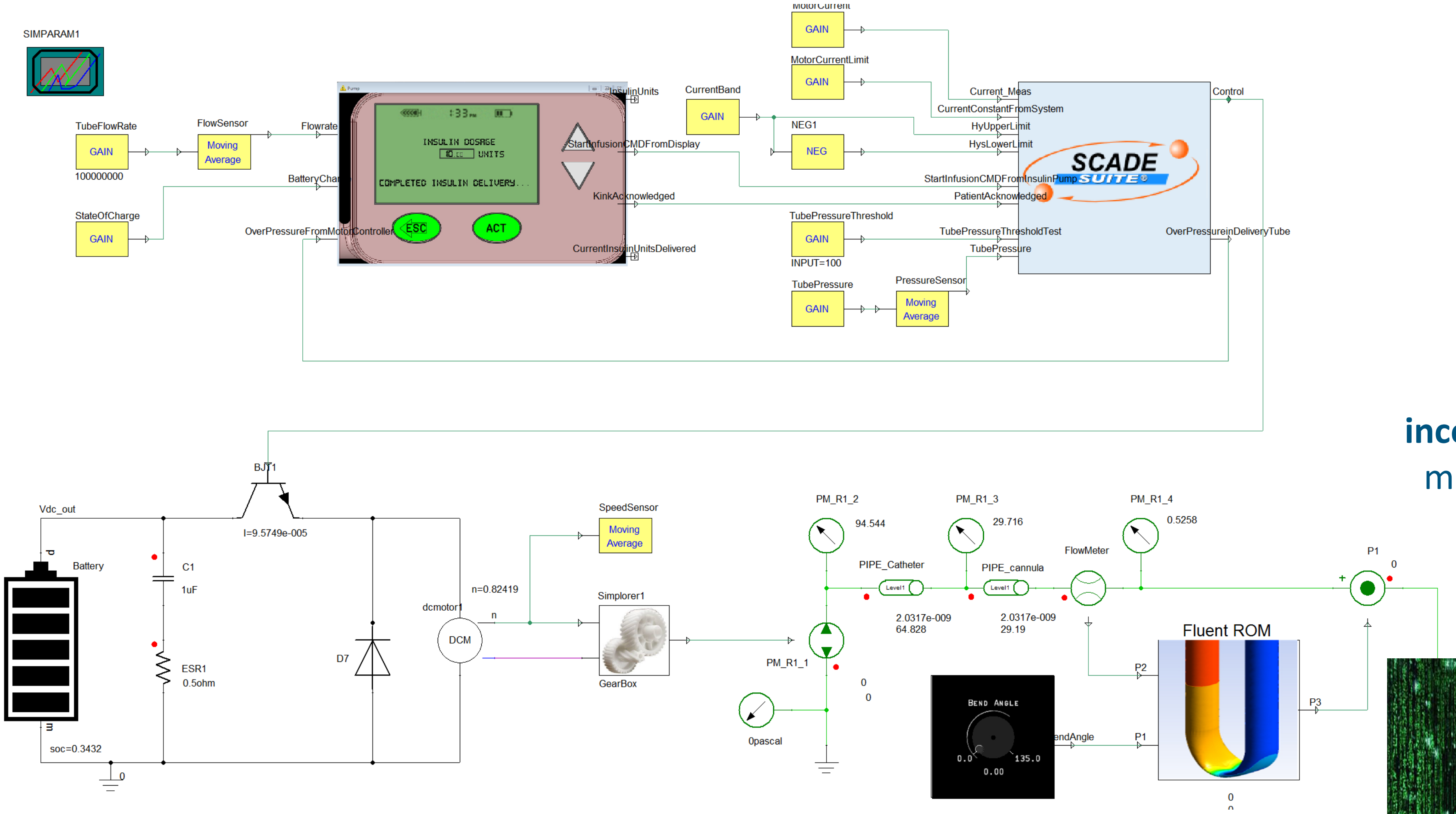


ROM



Insulin Pump – Drug Delivery Sub-System View

VIRTUAL PATIENT



!! Need to **incorporate** patient models to have a digital twin

Virtual Patient Model - Overview

Two-compartment insulin model

$$\frac{dI_{SC}(t)}{dt} = -\frac{1}{\tau_1}\cdot I_{SC}(t) + \frac{1}{\tau_1}\frac{ID(t)}{C_I} \quad (1)$$

$$\frac{dI_P(t)}{dt} = -\frac{1}{\tau_2}\cdot I_P(t) + \frac{1}{\tau_2}\cdot I_{SC}(t) \quad (2)$$

Insulin effectiveness

$$\frac{dI_{EFF}(t)}{dt} = -p_2\cdot I_{EFF}(t) + p_2 S_I\cdot I_P(t) \quad (3)$$

Two-compartment glucose model

$$\frac{dG(t)}{dt} = -(GEZI + I_{EFF})\cdot G(t) + EGP + R_A(t) \quad (4)$$

$$R_A(t) = \frac{C_H(t)}{V_G\cdot\tau_m^2}\cdot t\cdot e^{-\frac{t}{\tau_m}} \quad (5)$$

PK-related unknowns: τ_1, τ_2, C_I, p_2, S_I, GEZI, EGP, V_G, τ_M
Other model inputs: $R_A(t)$, ID(t)

- The patient model requires a **mathematical** representation of the relevant physics.
- The model should capture insulin metabolism as well as the ability of insulin to effect glucose uptake into cells.
- Researchers and industry typically rely on pharmacokinetic/pharmacodynamics (PK/PD) modeling to represent these processes.

*Kanderian et al., Identification of Intraday Metabolic Profiles during Closed-Loop Glucose Control in Individuals with Type 1 Diabetes, J Diabetes Sci and Tech , Vol. 3 (2009).

Virtual Patient Model
- Model Training

Two-compartment insulin model

$$\frac{dI_{SC}(t)}{dt} = -\frac{1}{\tau_1}\cdot I_{SC}(t) + \frac{1}{\tau_1}\frac{ID(t)}{C_I} \quad (1)$$

$$\frac{dI_P(t)}{dt} = -\frac{1}{\tau_2}\cdot I_P(t) + \frac{1}{\tau_2}\cdot I_{SC}(t) \quad (2)$$

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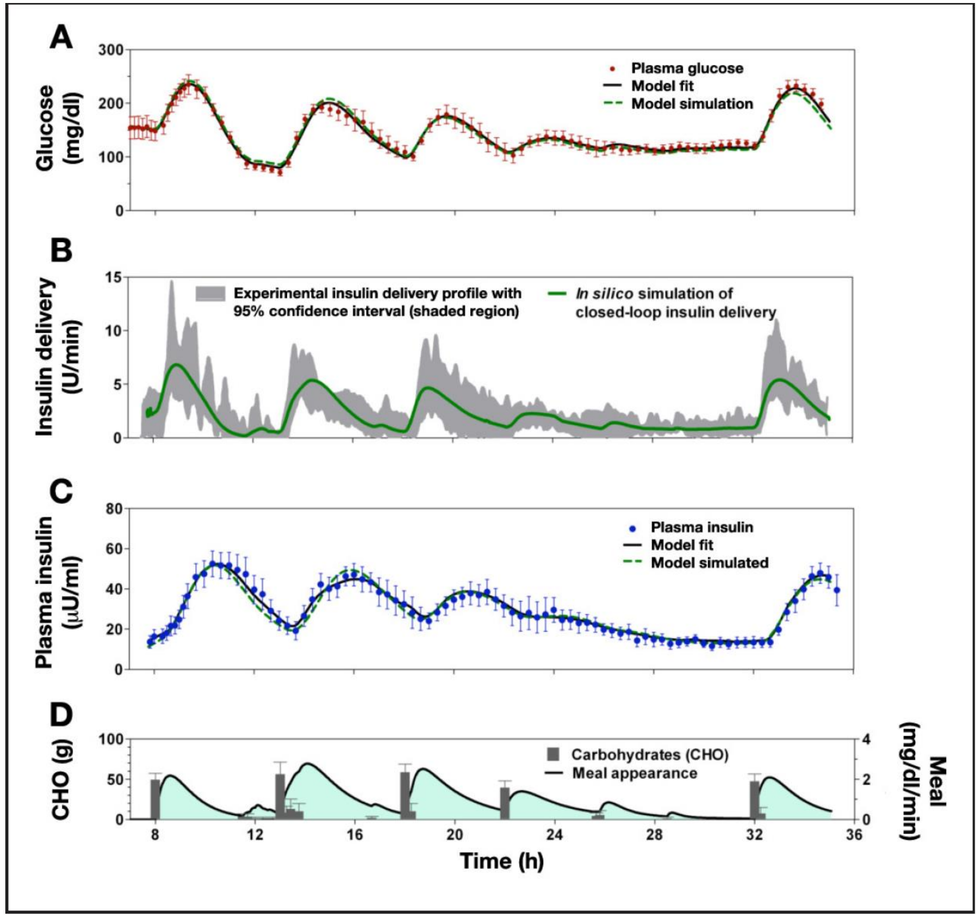
PK-related unknowns: τ_1, τ_2, C_I, p_2, S_I, GEZI, EGP, V_G, τ_M

Other model inputs: $R_A(t)$, ID(t)

CLINICAL DATA

establish patient-specific parameters



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Virtual Patient Model - Prediction

Two-compartment insulin model

$$\frac{dI_{SC}(t)}{dt} = -\frac{1}{\tau_1} \cdot I_{SC}(t) + \frac{1}{\tau_1}\frac{ID(t)}{C_I} \qquad (1)$$

$$\frac{dI_P(t)}{dt} = -\frac{1}{\tau_2} \cdot I_P(t) + \frac{1}{\tau_2} \cdot I_{SC}(t) \qquad (2)$$

Insulin effectiveness

$$\frac{dI_{EFF}(t)}{dt} = -p_2 \cdot I_{EFF}(t$$

Two-compartment glucose model

$$\frac{dG(t)}{dt} = -(GEZI + I_{EFF}) \cdot G(t) + EGP + R_A(t) \qquad (4)$$

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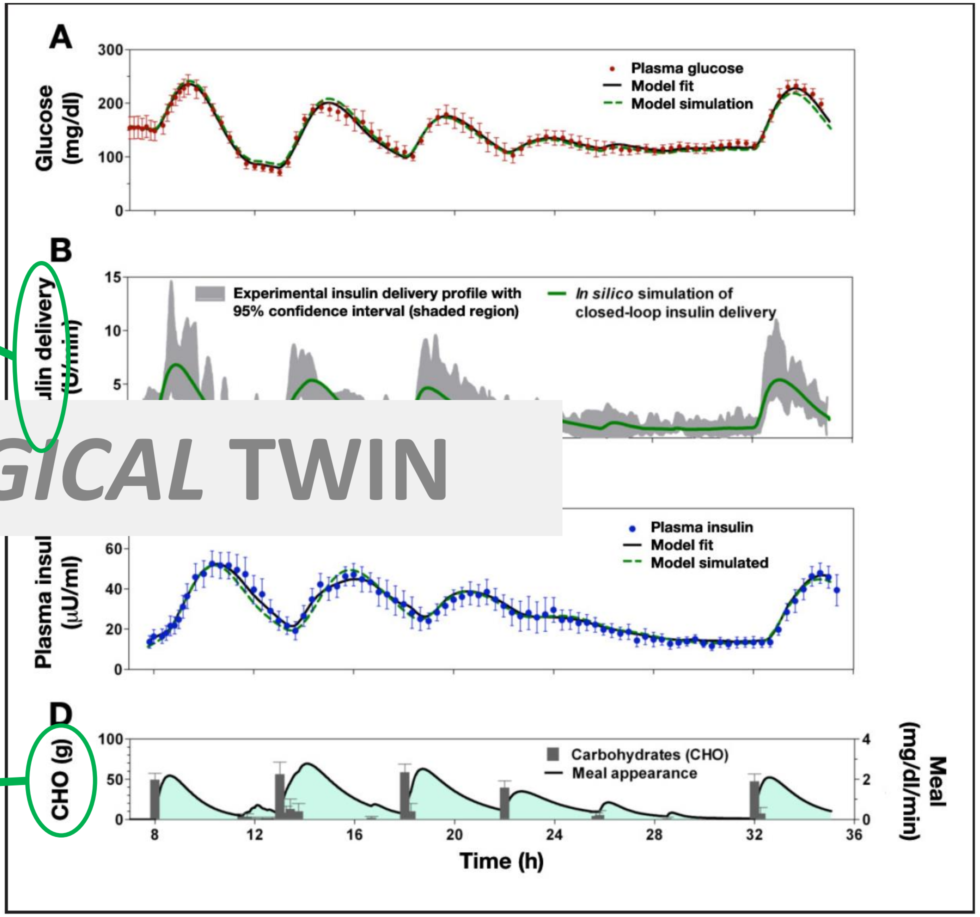
therapy optimization

PATIENT STATUS

DIGITAL *PHYSIOLOGICAL* TWIN

CLINICAL DATA

continuous learning



PK-related unknowns: τ_1, τ_2, C_I, p_2, S_I, GEZI, EGP, V_G, τ_M ✓
Other model inputs: R_A(t), ID(t)

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Conclusions

- Chronic diseases and the aging population are placing significant strain on healthcare systems, motivating the need for more effective medical technologies.
- A digital twin is a multiphysics, multiscale, probabilistic simulation of an as-built system that combines models, sensor information, and input data to mirror and predict activities/performance over the life of its corresponding physical twin.
- Computer modeling & simulation is a key enabling technology of the digital twin.
- Digital twin for implanted devices that include models of human physiology can improve device design and treatment outcomes.

Link to youtube video of the insulin pump model: https://youtu.be/fuTQyZ0KDww

THANK YOU