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SYSTEMS AT THE CROSSROADS
17 - 20 October 2018 | Indianapolis, Indiana

A Multi-Domain, Patient-Specific Model of an Insulin Pump

Marc Horner, Technical Lead, Healthcare, ANSYS, Inc.

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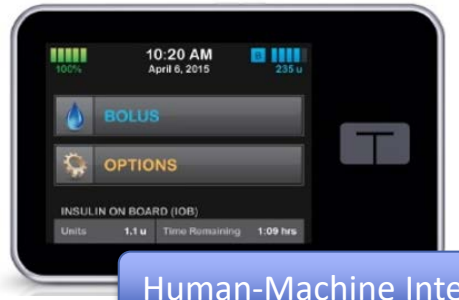
Components…through the Eyes of Designers

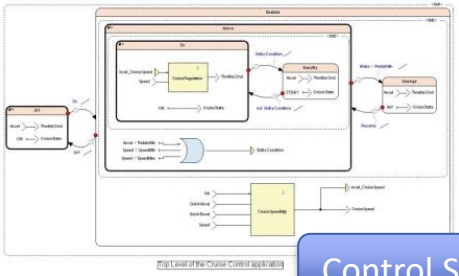
Actuators

Electronic Control



Human-Machine Interface

Sensors



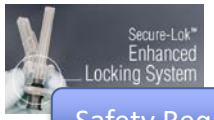
Control Software

Domain-specific

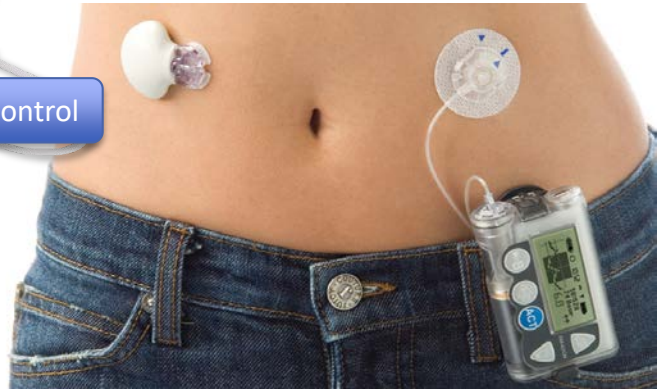
Component-centric

Are Ultimately Part of a System…

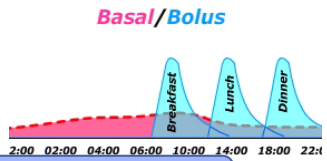
Electronic Control



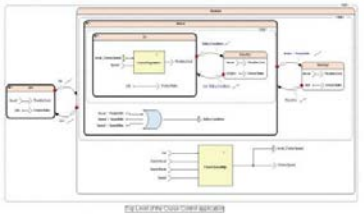
Safety Requirements



Actuators

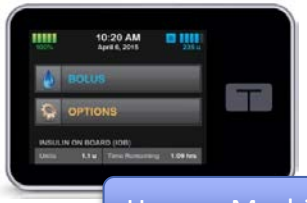


Operational Profiles



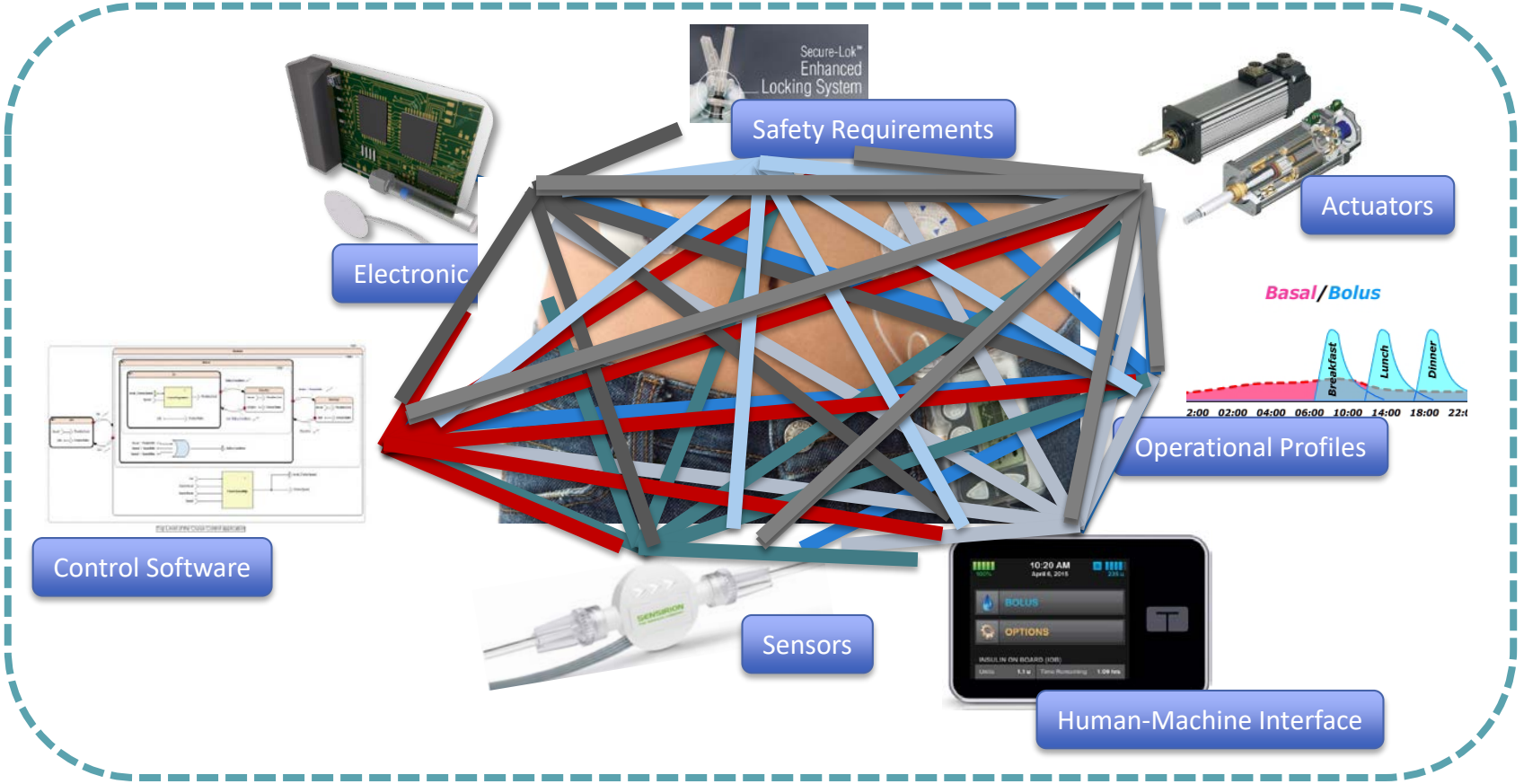
Control Software

Sensors



Human-Machine Interface

With Complex Interactions
…How Does the System Perform?



Outline

A. Healthcare Industry Overview
   - Industry Trends
   - Digital Systems Prototyping
   - Regulatory Update

B. Insulin Pump Example
   - Background
   - Drug Delivery Sub-system Model
     - Kink Detection Modeling
     - Virtual Patient Modeling

C. Conclude

Healthcare Industry Overview

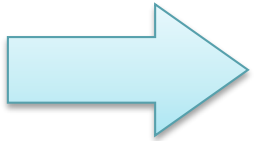
Today's Medical Devices are Increasingly

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

* Cognizant, How the IOT is Transforming Medical Devices, May 2016

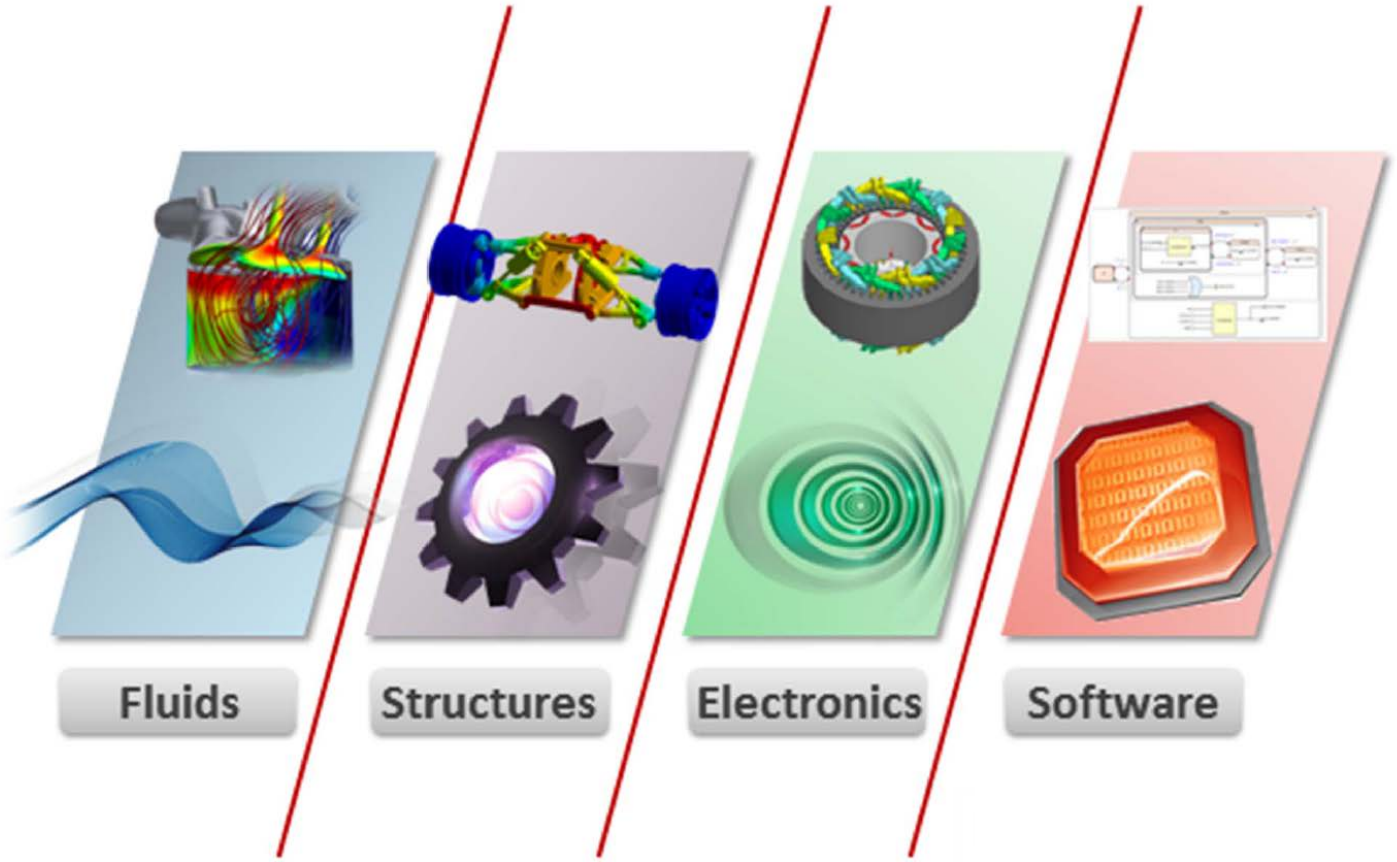
Challenge: System Complexity

- 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

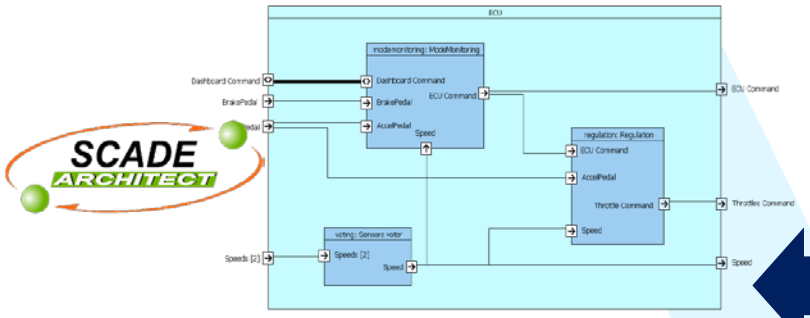


Each discipline has its' own set of tools, processes, and expertise.

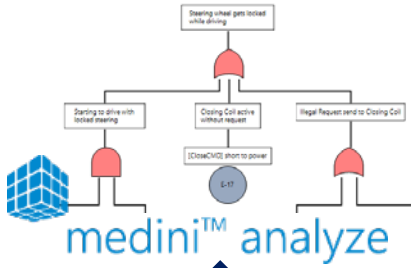
Systems Engineering: A Unifying Approach

The ANSYS Portfolio

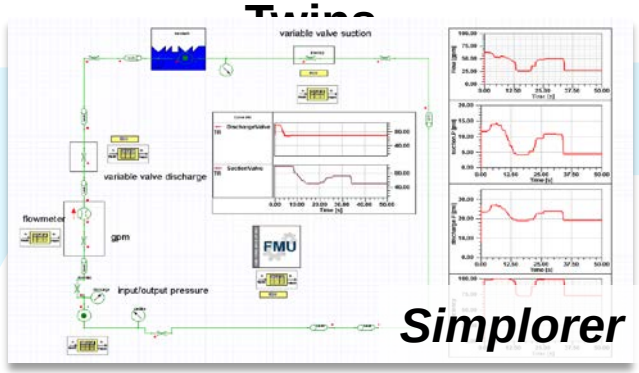
Model-Based Systems Engineering



System Safety



System Simulation & Digital Twins

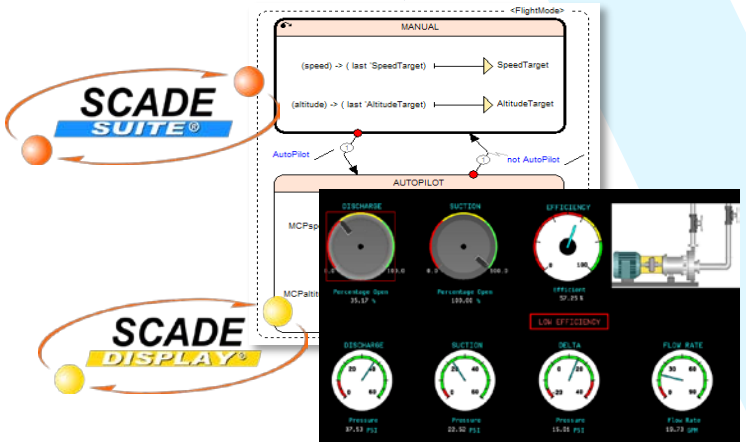


System Architecture

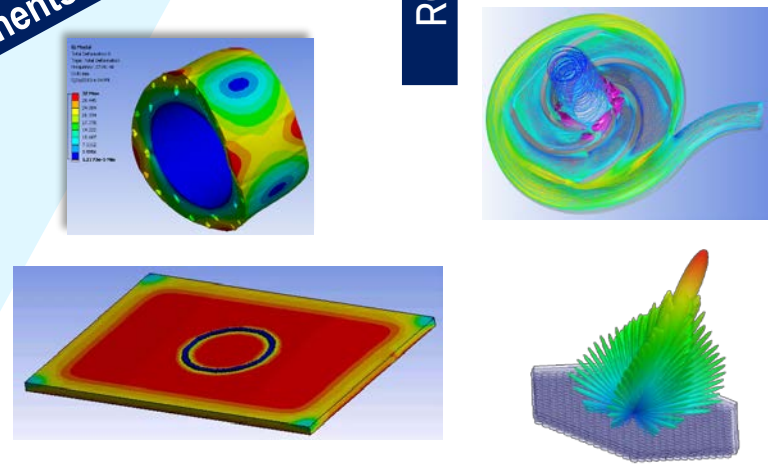
System/SW Architecture

SW Components (FMI)

ROM

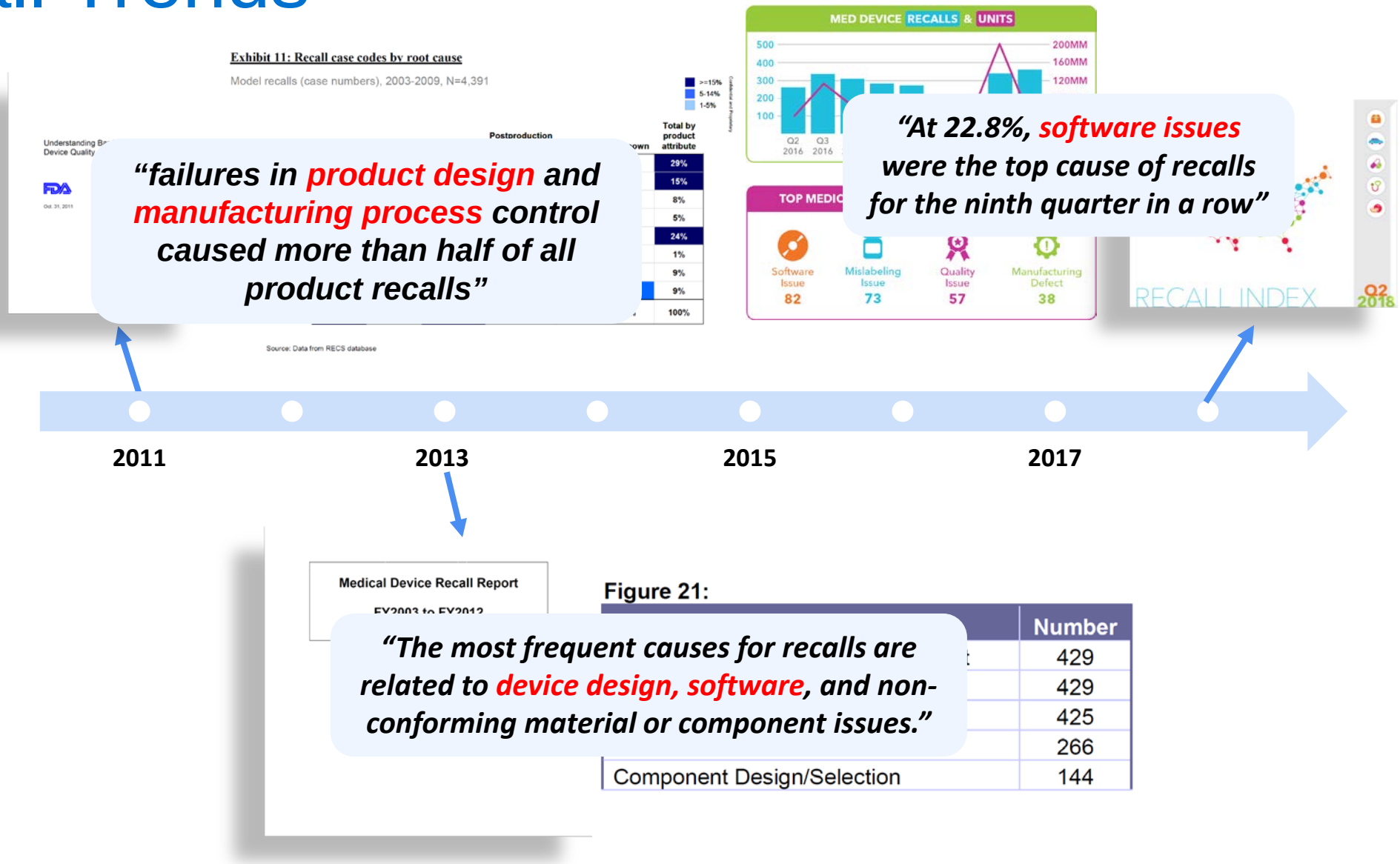


Model-Based Software Engineering



3D Physics Simulation

Recall Trends

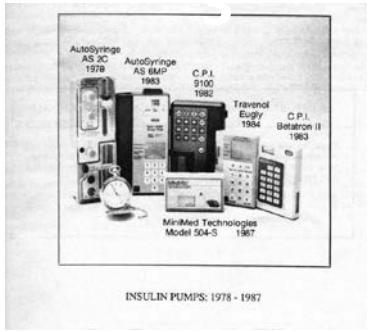


Infusion Pump Safety

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

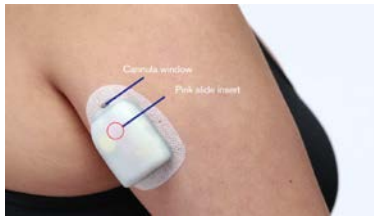
FDA Launches Initiative to Reduce Infusion Pump Risks
Agency calls for improvements in device design



…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"

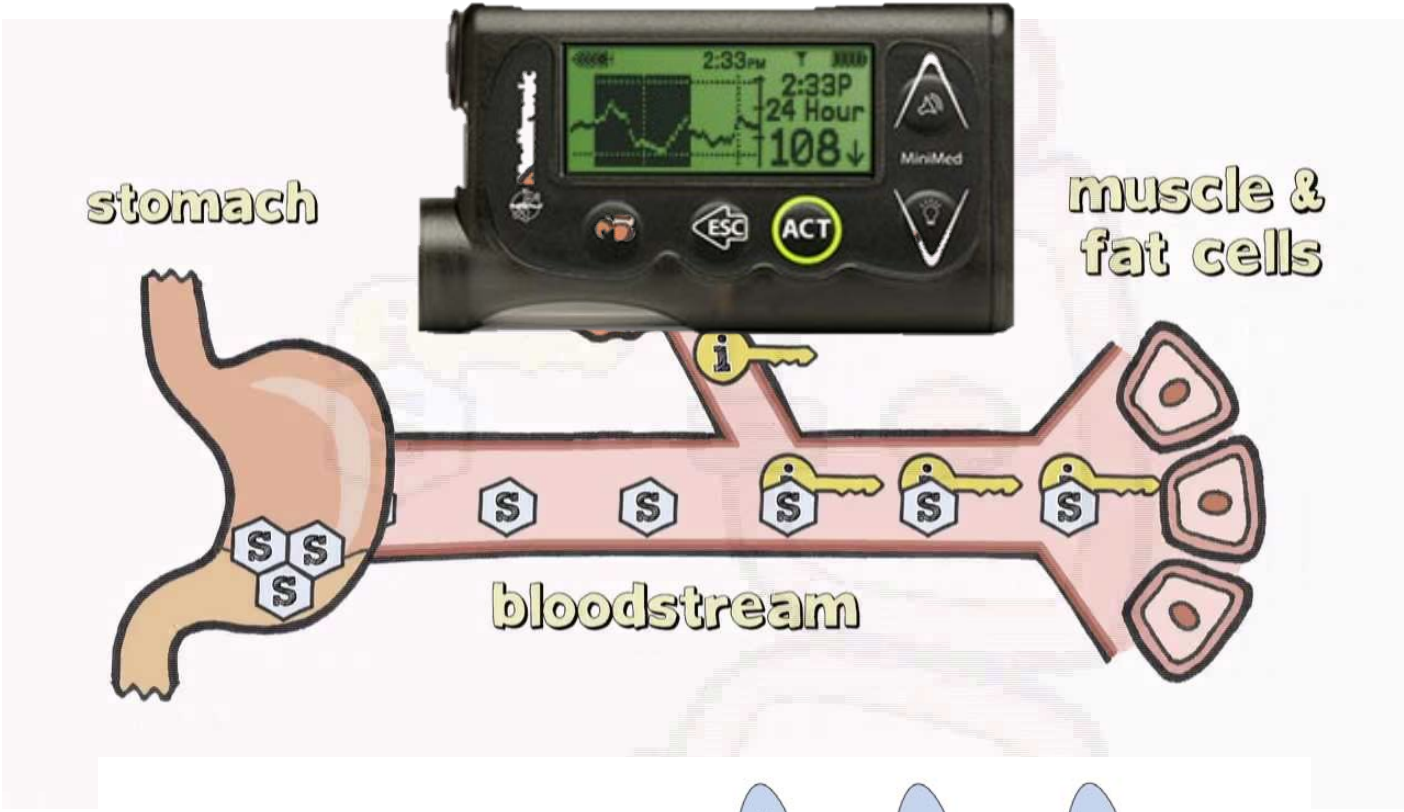
http://diyabetimben.com/diyabet-muzesi/

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

Insulin Pump Model

What is Diabetes?

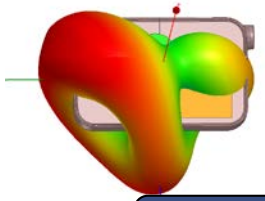
- Insulin is a hormone created by the pancreas. It is required for sugar molecules (from the food you eat) to move inside cells. Patients with diabetes either do not produce insulin (Type 1) or do not use insulin the right way (Type 2).
- Insulin pumps replace the function of the pancreas by injecting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



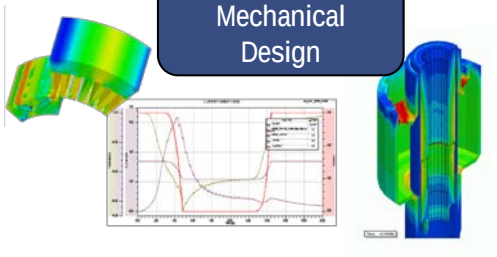
diabetes image from https://i.ytimg.com/vi/SCCb5GqhnrI/maxresdefault.jpg
Pump image from http://www.medtronicdiabetes.com/products/minimed-530g-diabetes-system-with-er

Components, Components, Components

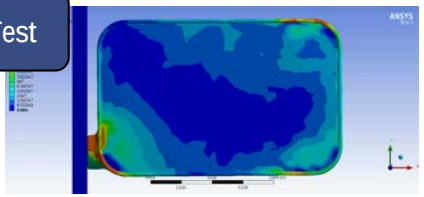
HBM EM



Antenna Design/Optimization

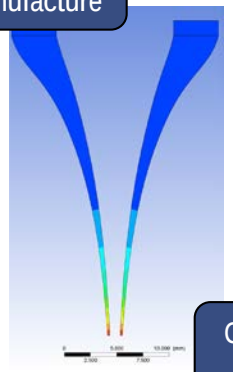


Electro-Mechanical Design



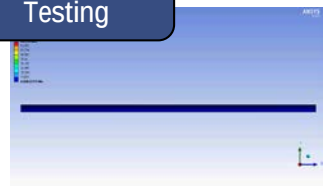
Drop Test

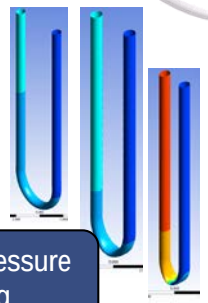
Catheter Manufacture



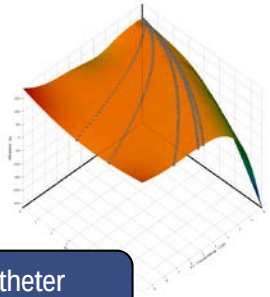
Embedded Software - Display

Catheter Kink Testing

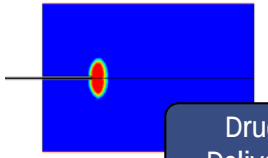




Catheter Pressure Testing

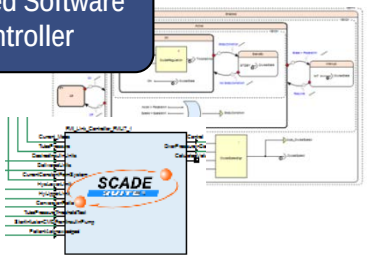


Catheter Occlusion ROM

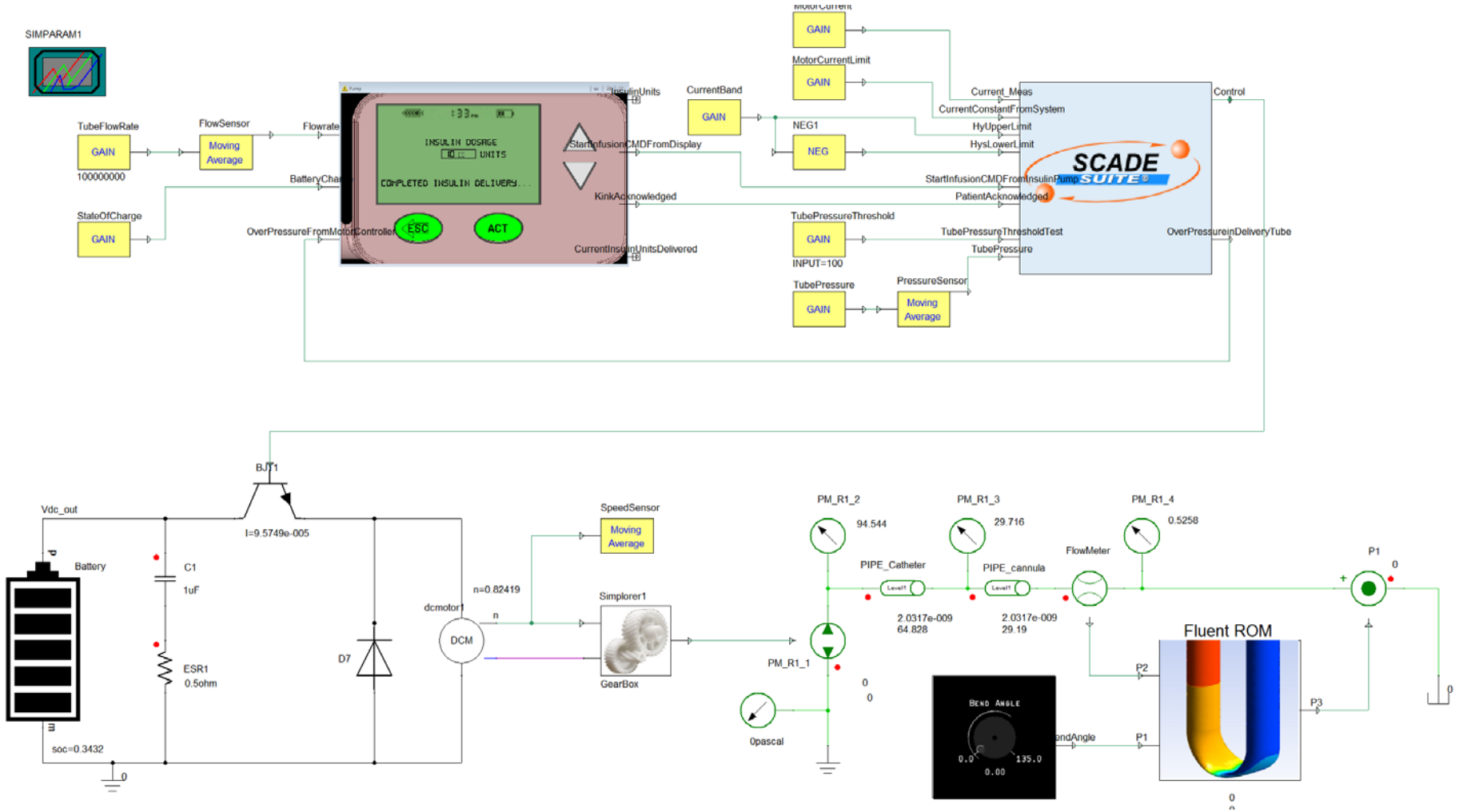


Drug Delivery

Embedded Software - Controller

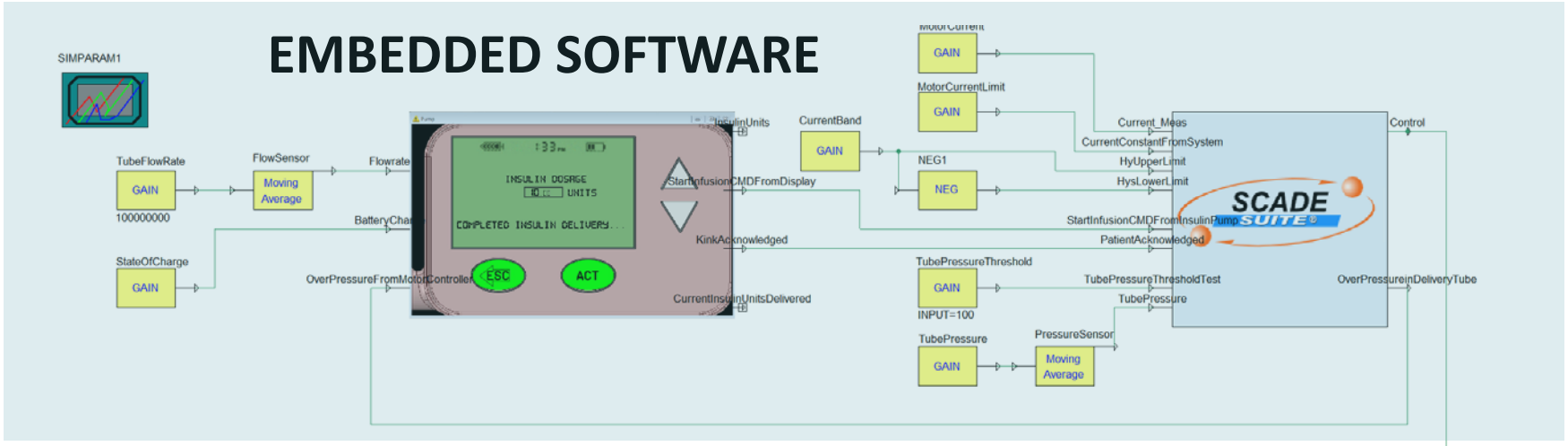


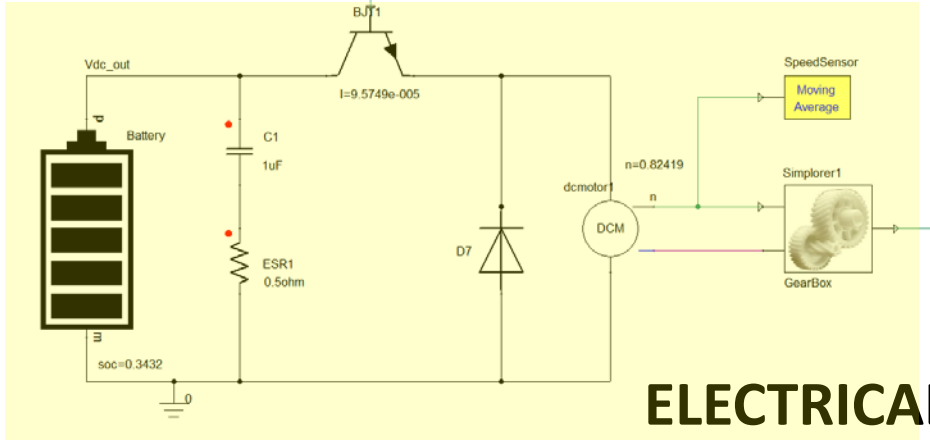
Drug Delivery Sub-System

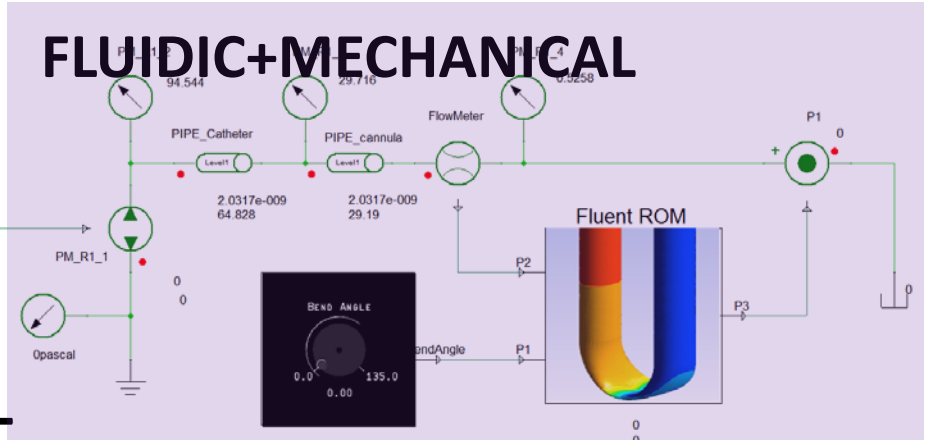


Drug Delivery Sub-System

MODEL DOMAINS

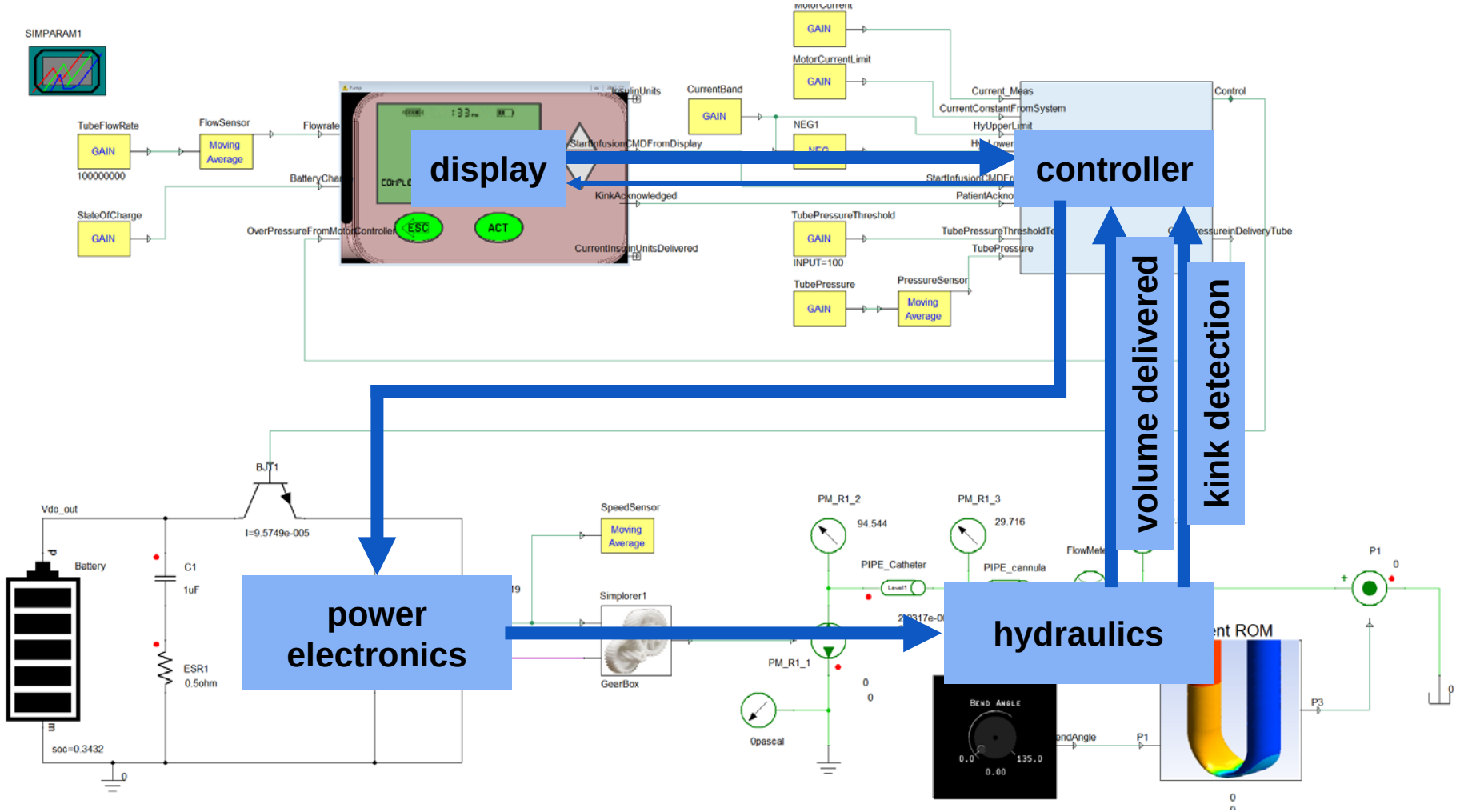




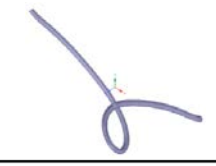
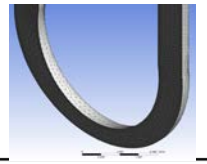
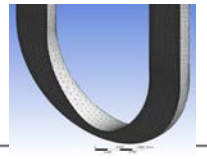
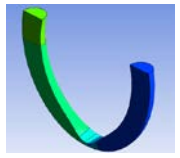
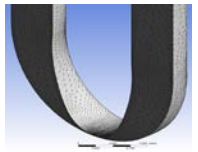
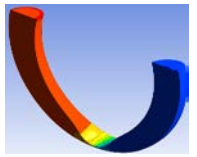


Drug Delivery Sub-System

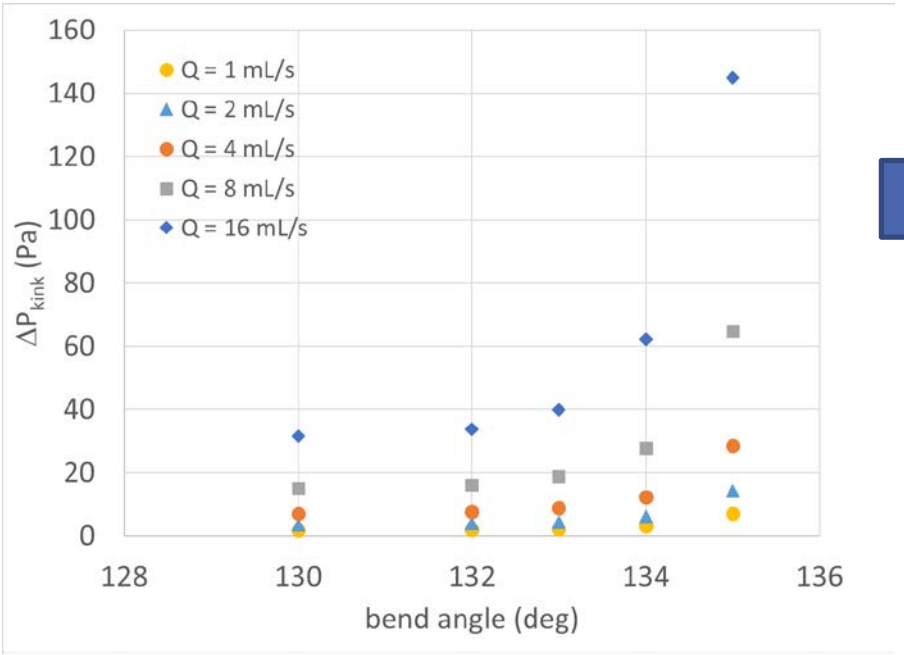
INFORMATION FLOW



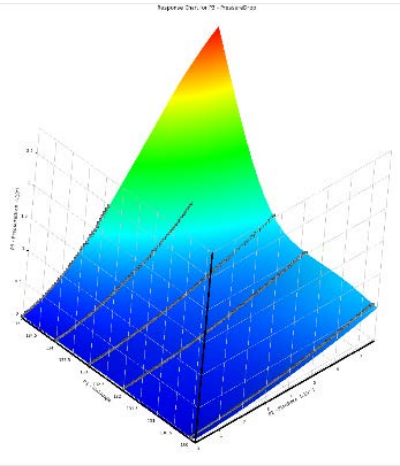
Pressure-Flow Analysis of Tube Bending

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



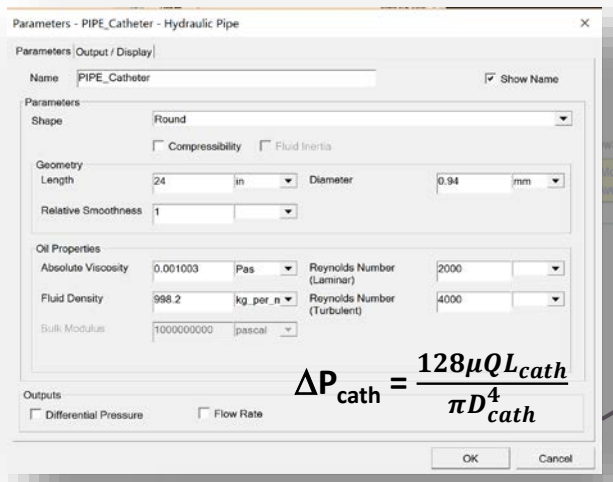
ROM



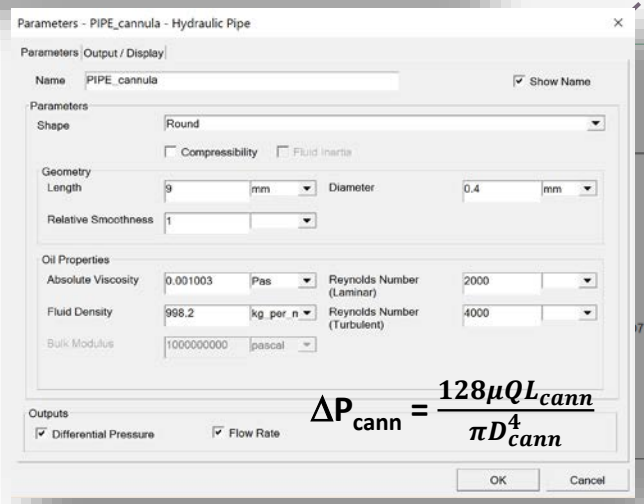
Insulin Pump – ROM Behavior

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

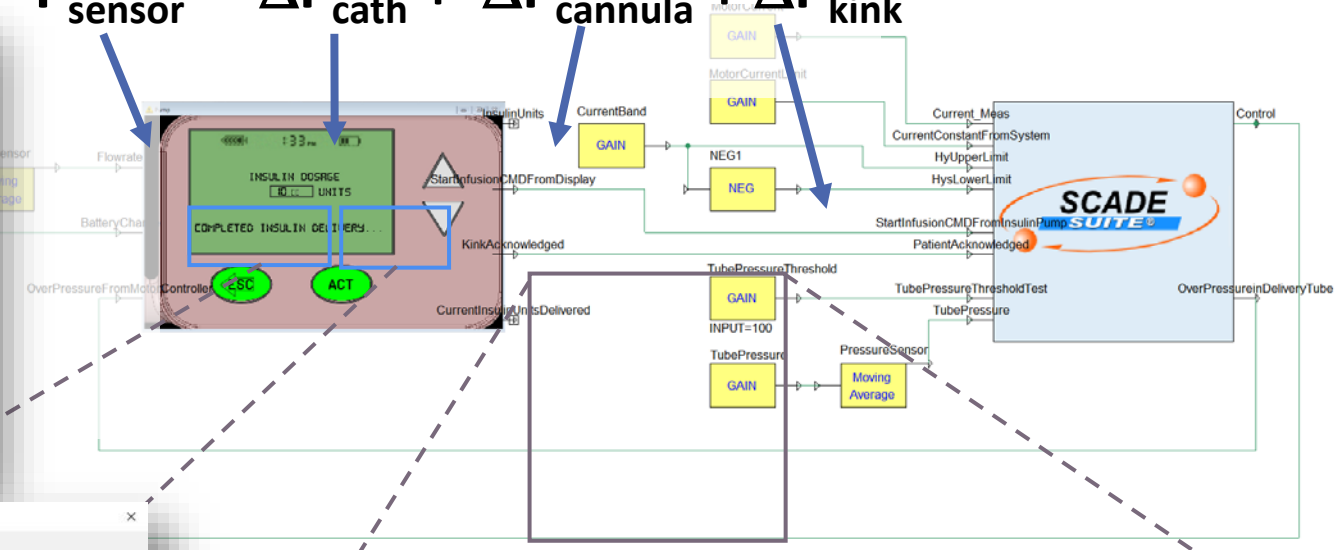
$$P_{sensor} = \Delta P_{cath} + \Delta P_{cannula} + \Delta P_{kink}$$

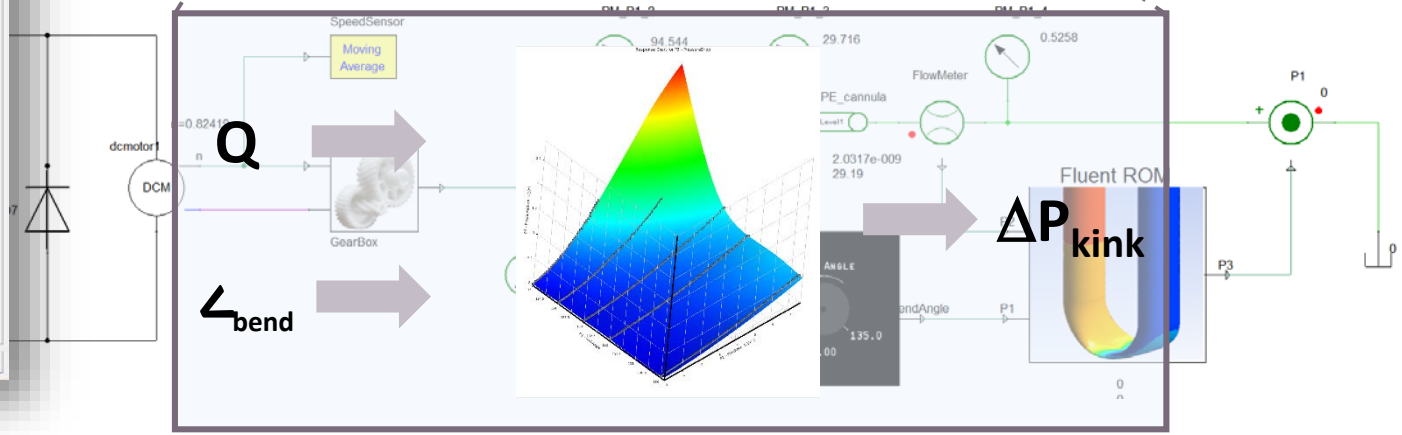


$$\Delta P_{cath} = \frac{128\mu Q L_{cath}}{\pi D_{cath}^4}$$



$$\Delta P_{cann} = \frac{128\mu Q L_{cann}}{\pi D_{cann}^4}$$

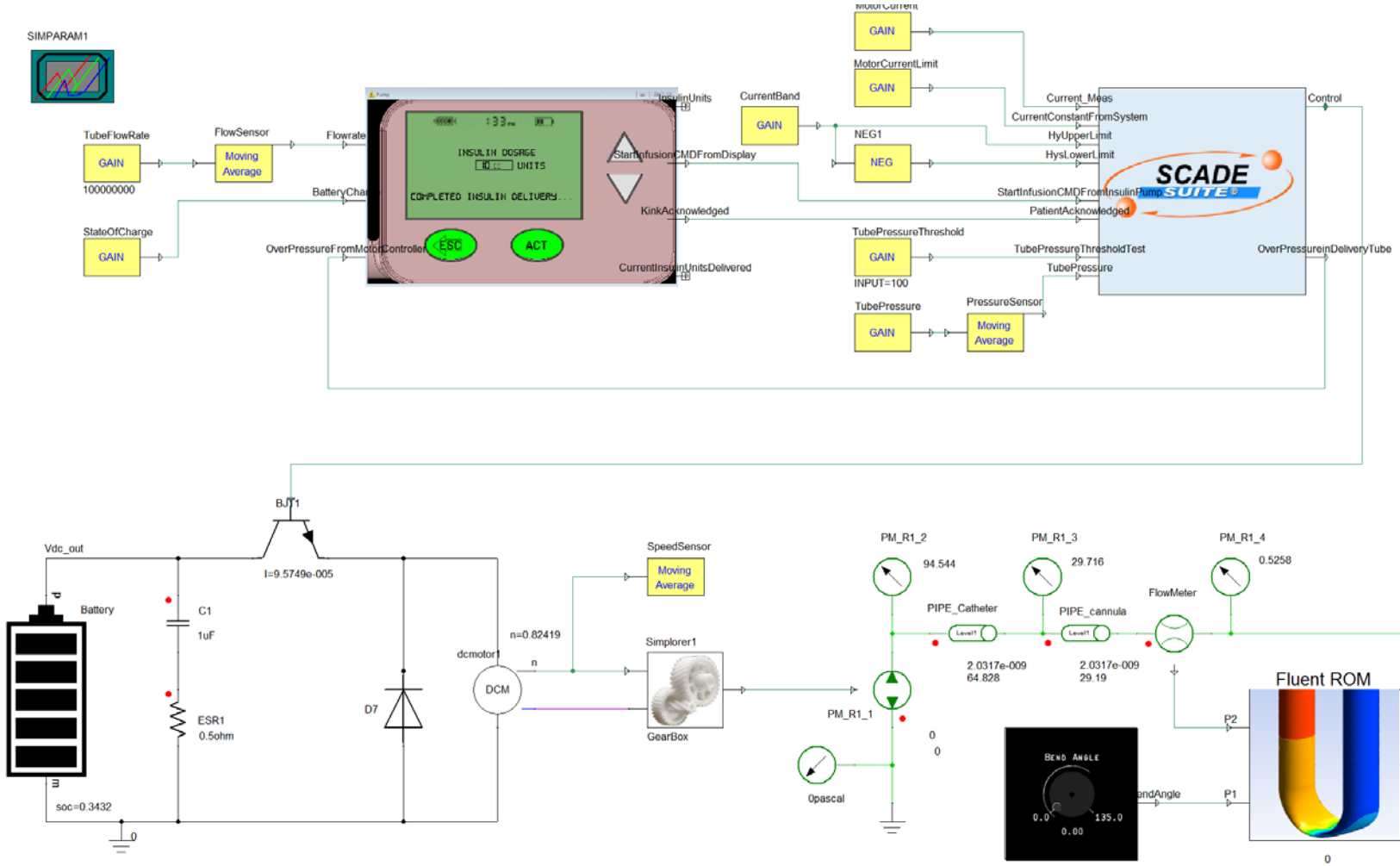




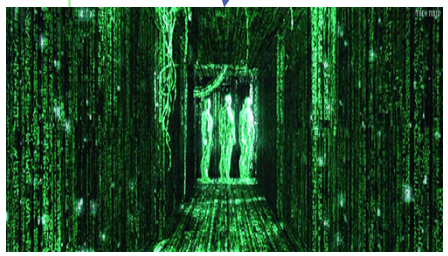
ΔP_{kink}

Drug Delivery Sub-System

VIRTUAL PATIENT

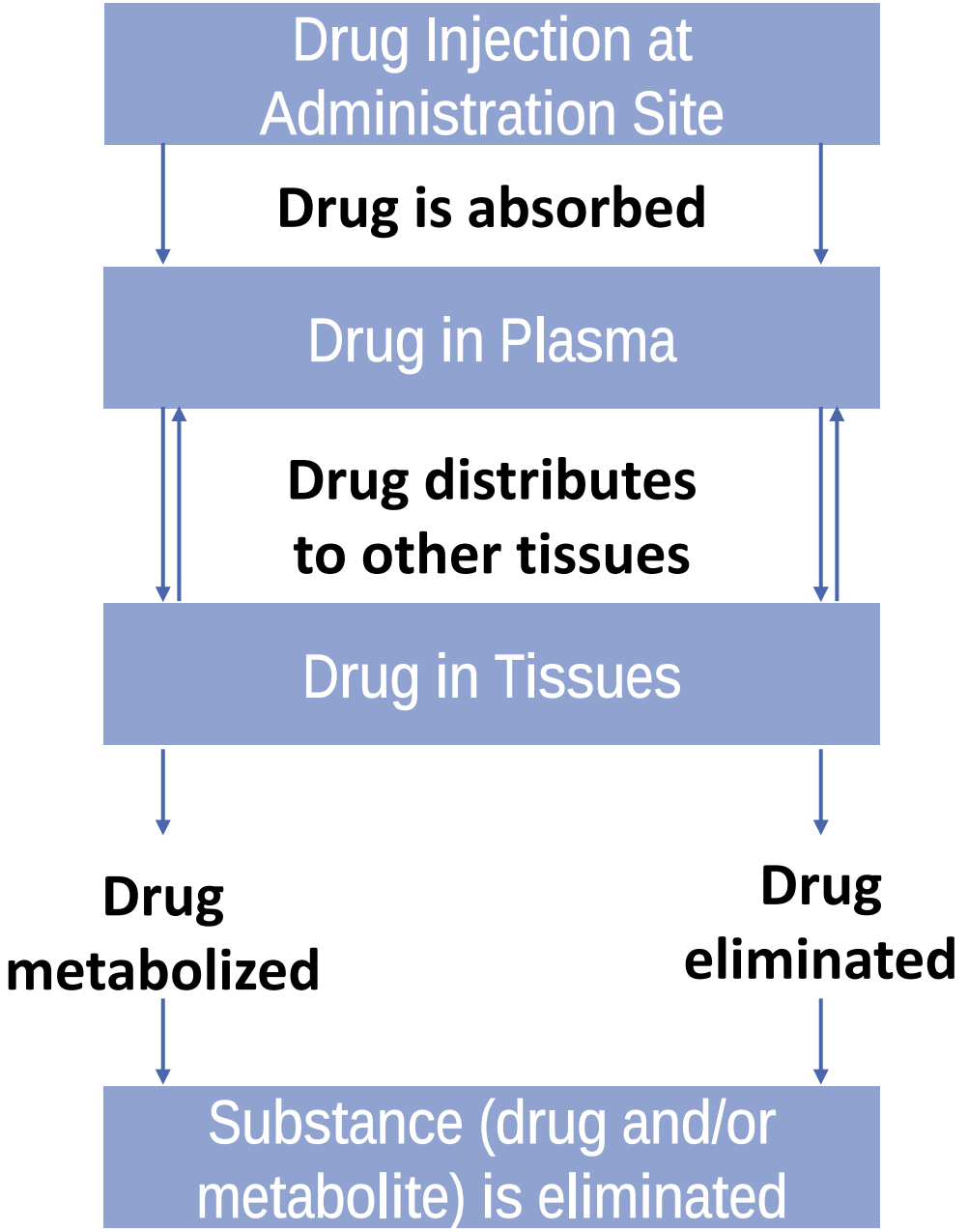


Couple the device model to a patient predictive model of glucose metabolism.



Pharmacokinetics (PK)

- PK refers to absorption, distribution, metabolism, and elimination (ADME) of a substance.
- The PK process involves the following steps:
  - Drug is introduced at the injection site
  - Drug is absorbed into the plasma
  - Drug is in equilibrium with other tissues
  - Either drug or metabolite are eliminated from tissues
- Each of these can be modeled using ODE's, with constants determined from clinical data.



Journal of Diabetes Science and Technology
Volume 3, Issue 5, September 2009
© Diabetes Technology Society
SYMPOSIUM

Virtual Patient Model

Identification of Intraday Metabolic Profiles during Closed-Loop Glucose Control in Individuals with Type 1 Diabetes

Sami S. Kanderian, M.S.,[1] Stu Weinzimer, M.D.,[2] Gayane Voskanyan, Ph.D.,[1] and Garry M. Steil, Ph.D.[3,4]

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

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

Two-compartment glucose model

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

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

- 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.

Unknowns: τ_1, τ_2, C_I, p_2, S_I, GEZI, EGP, V_G, τ_M

Virtual Patient Model

- *Model Training*

Two-compartment insulin model

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

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

Insulin effectiveness

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

Two-compartment glucose model

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

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

CLINICAL DATA

establish patient parameters

Journal of Diabetes Science and Technology
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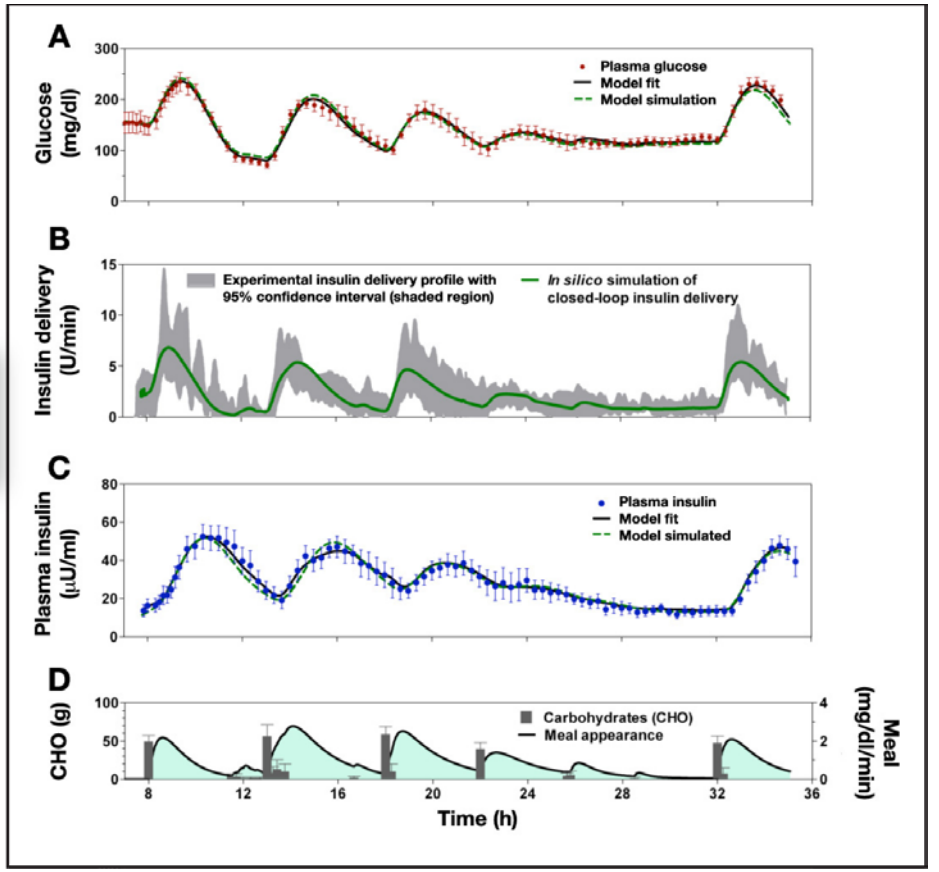
SYMPOSIUM

Identification of Intraday Metabolic Profiles during Closed-Loop Glucose Control in Individuals with Type 1 Diabetes

Sami S. Kanderian, M.S.,[1] Stu Weinzimer, M.D.,[2] Gayane Voskanyan, Ph.D.,[1] and Garry M. Steil, Ph.D.[3,4]



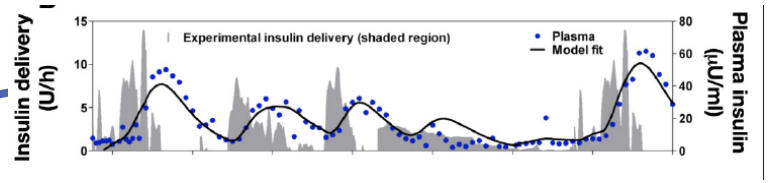
Virtual Patient Model

- Prediction

Two-compartment insulin model

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

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



Insulin effectiveness

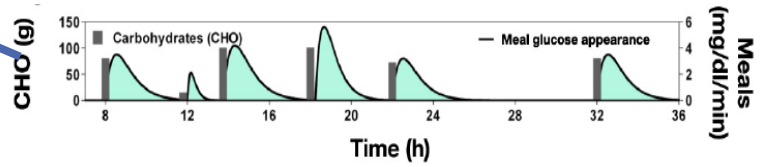
$$\frac{dI_{EFF}(t)}{dt} = -p_2\cdot I_{EFF}(t) +$$

DIGITAL *PHYSIOLOGICAL* TWIN

Two-compartment glucose model

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

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



KNOWN patient parameters

Digital Twin Predictive Platform

Monitor & Visualization

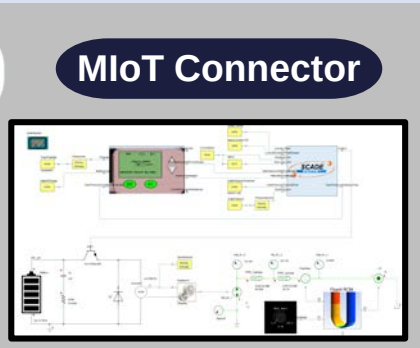
Execution Layer

thingworx

PREDIX

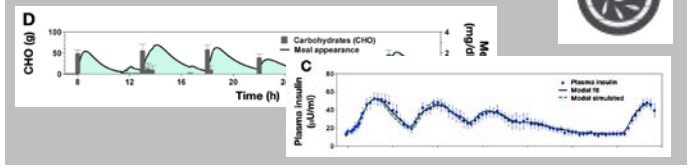
API

MIoT Connector



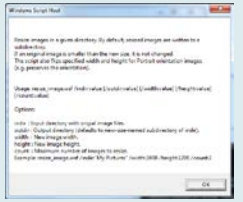
Digital Twin

Physical Asset



Data Layer - Device

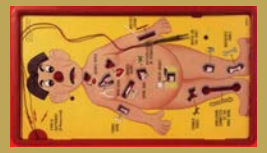
Data Layer - Patient



ROM Builder

P

Patient Physiology

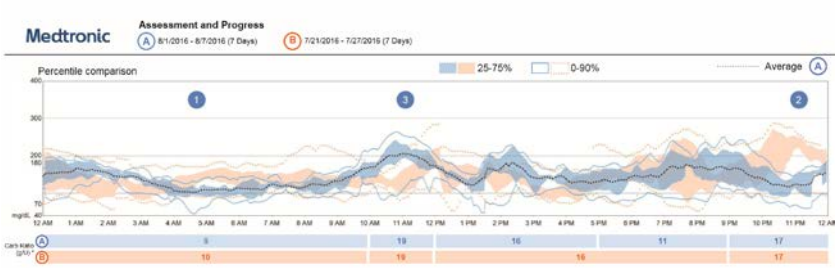


Electronic Medical Record

Simulation Data

Connected Care Platforms

- Companies are providing web-based platforms for patients and clinicians to view carbohydrate intake, blood glucose levels, and pump data.
- The intent is to help patients make more informed decisions about their disease management.

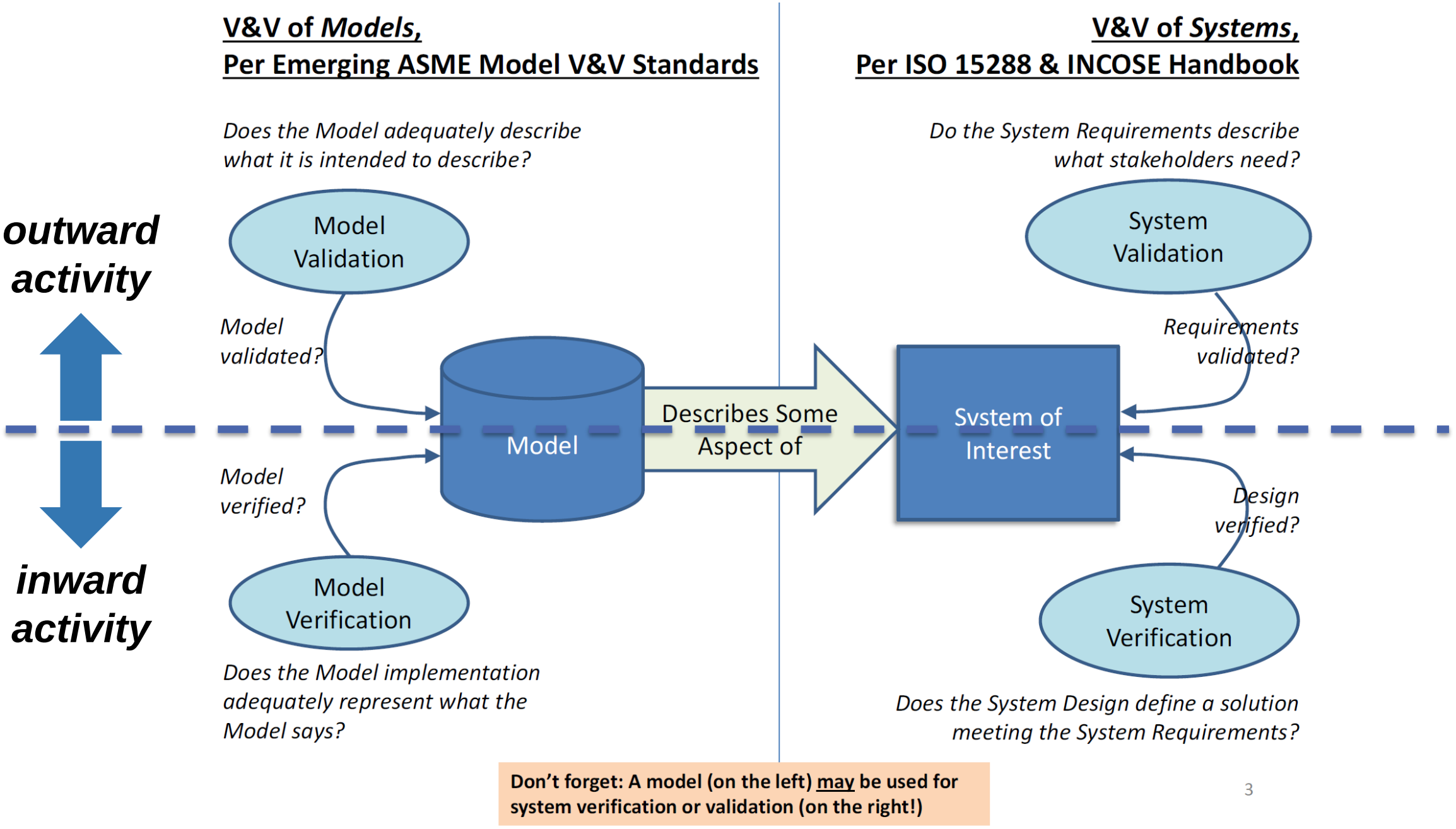


Statistics	A	B
Auto Mode (per week)	98% (6d 20hrs)	14% (1d 00hrs)
Manual Mode (per week)	2% (3hrs)	86% (6d 00hrs)
Sensor Wear (per week)	96% (6d 18hrs)	97% (6d 19hrs)
Average SG ± SD	143 ± 43 mg/dL	150 ± 56 mg/dL
Estimated A1C	6.6%	6.9%
Average BG	144 ± 34 mg/dL	174 ± 65 mg/dL
BG / Calibration (per day)	8.5 / 5.6	7.8 / 5.0
Total daily dose (per day)	29 units	24 units
Bolus amount (per day)	14U (48%)	12U (49%)
Auto Basal / Basal amount (per day)	15U (52%)	12U (51%)
Set Change	Every 3.0 days	Every 3.0 days
Reservoir Change	Every 3.0 days	Every 3.0 days
Meal (per day)	5.8	4.8
Carbs entered (per day)	176 ± 13g	170 ± 24g
Active Insulin time	3:00 hrs	3:00 hrs

https://www.medtronicdiabetes.com/products/carelink-personal-diabetes-software

Conclusions

- Chronic diseases and the aging population are placing significant strain on healthcare systems, motivating the need for more effective medical technologies.
- The risk (and failure) of medical devices has increased since incorporating new technologies and functionality, much of which is related to embedded software.
- Systems modeling can improve the robustness and safety of today’s medical devices.
- Digital twins for implanted devices that include models of human physiology (enabled by computer modeling) can improve treatment outcomes.



slide courtesy B. Schindel, V4I Workshop. 17OCT2018

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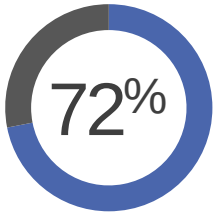

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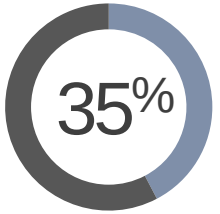

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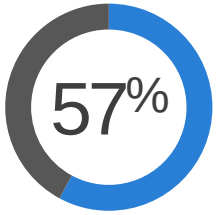

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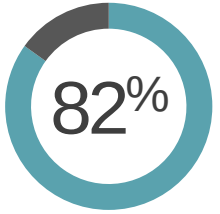

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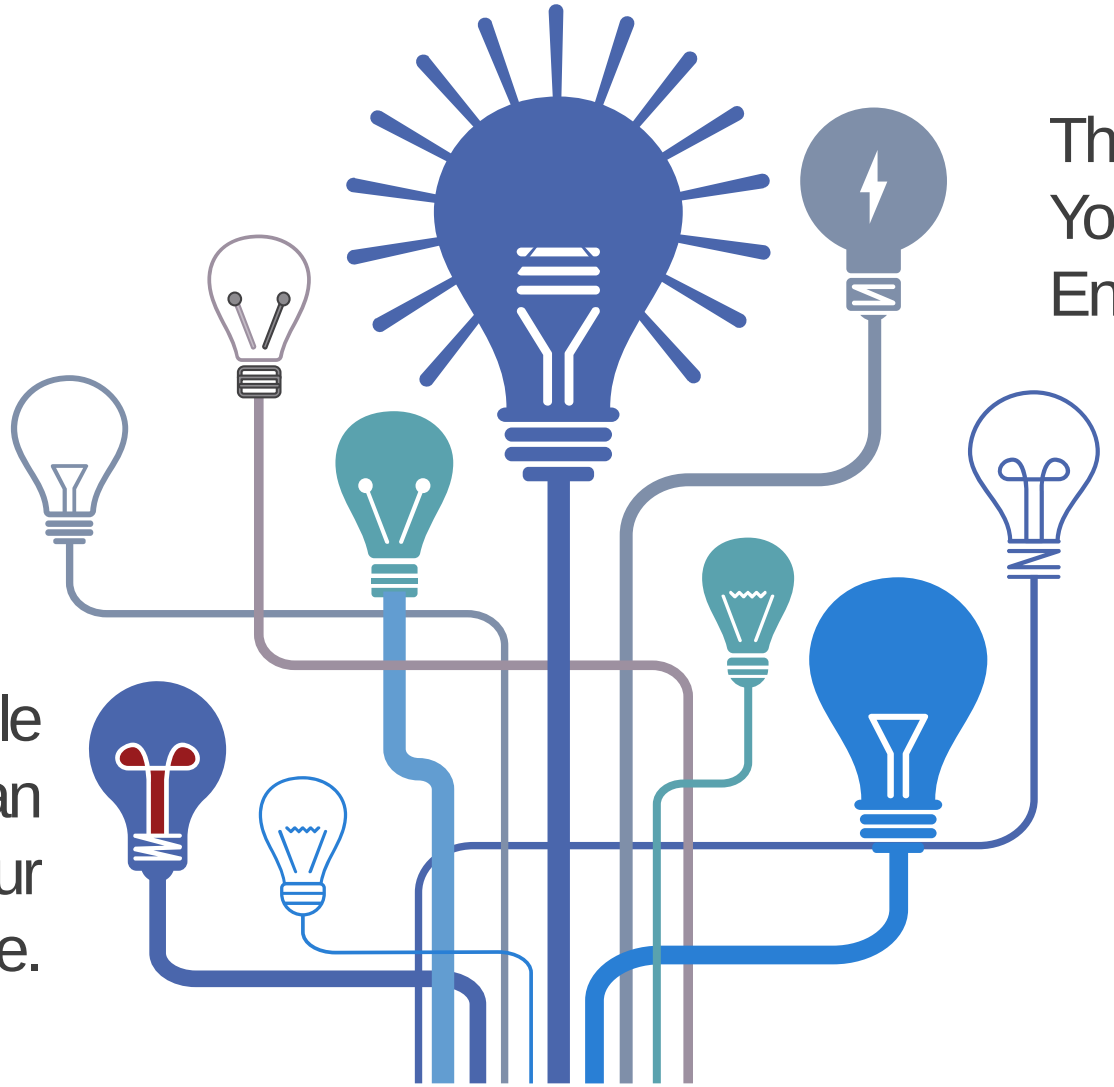

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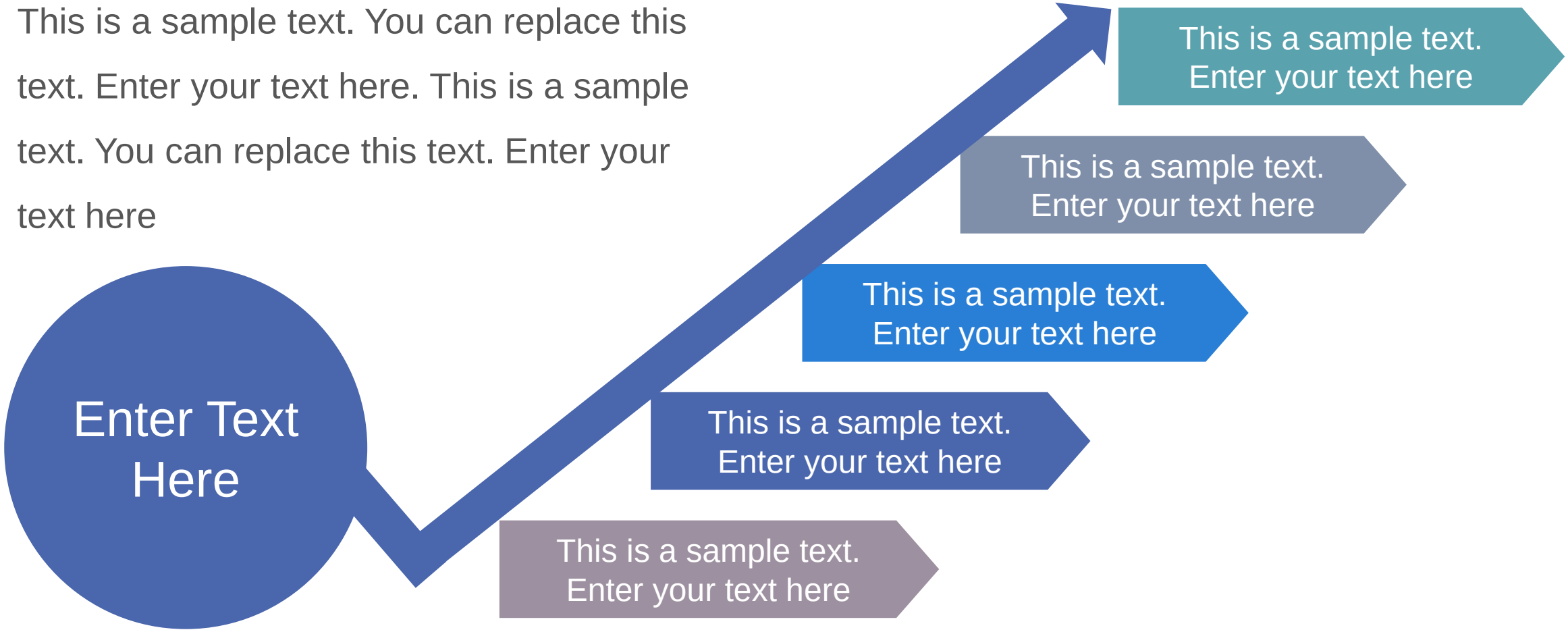

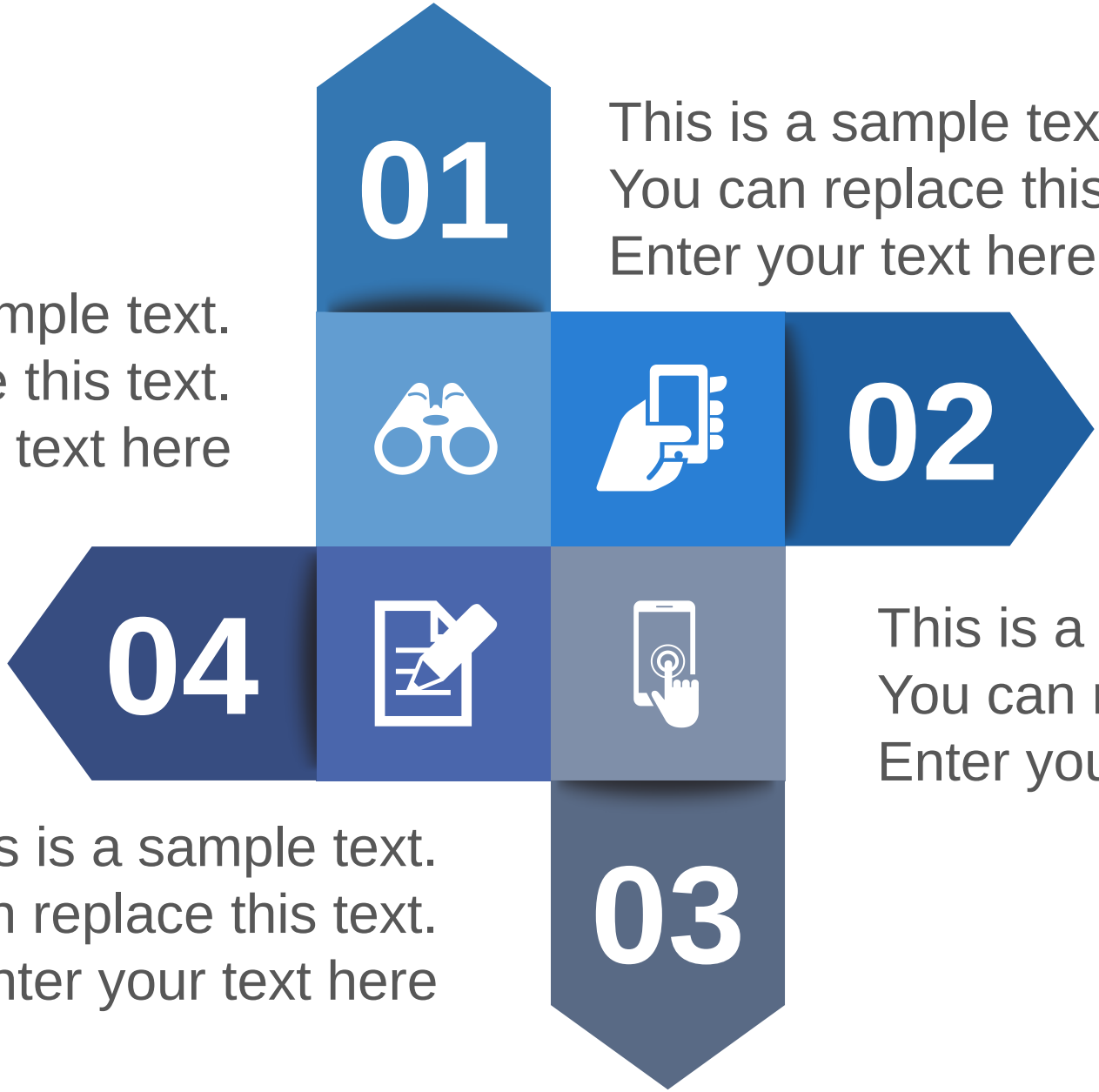

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Section 02

Section 03

Section 04

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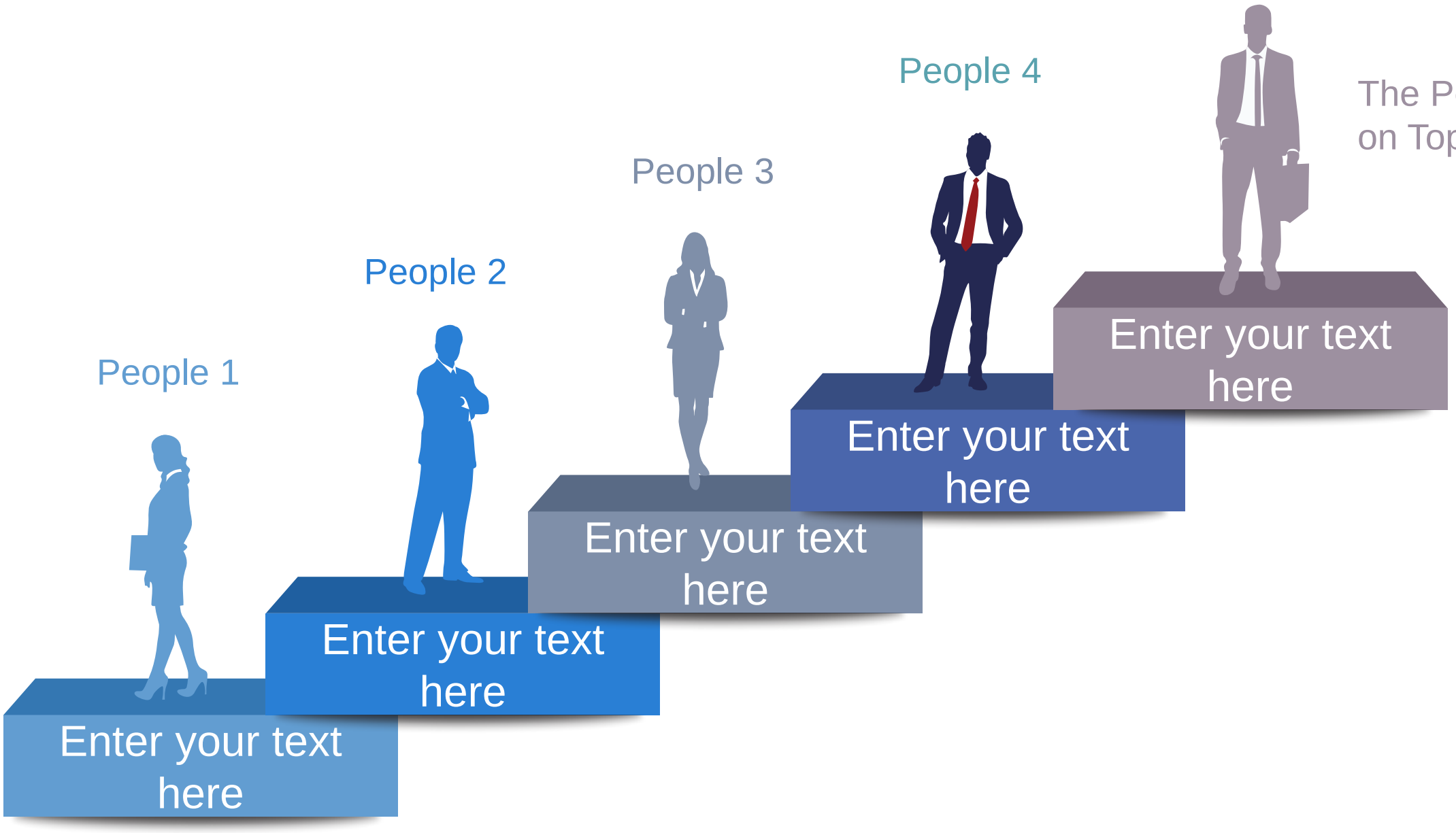
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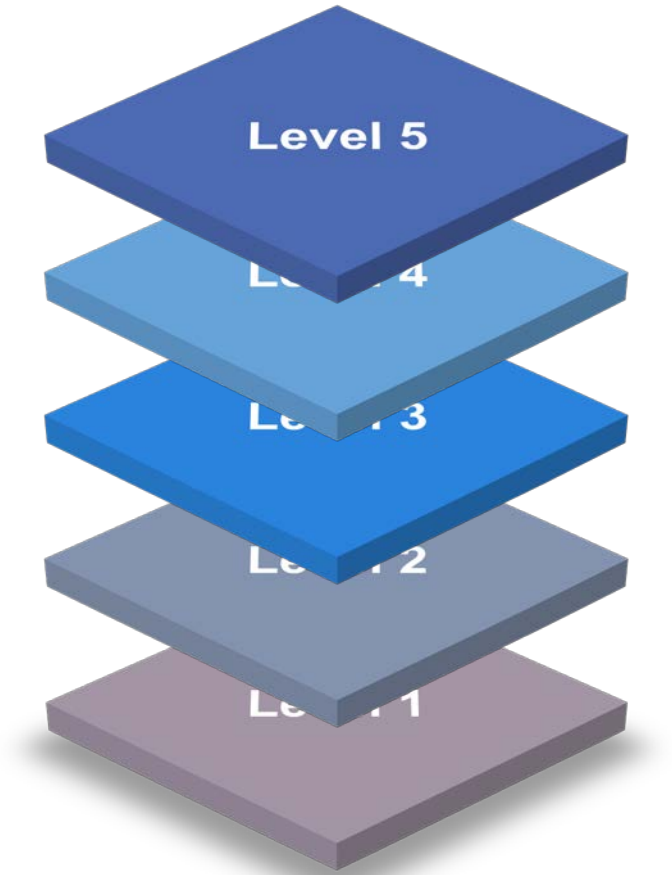

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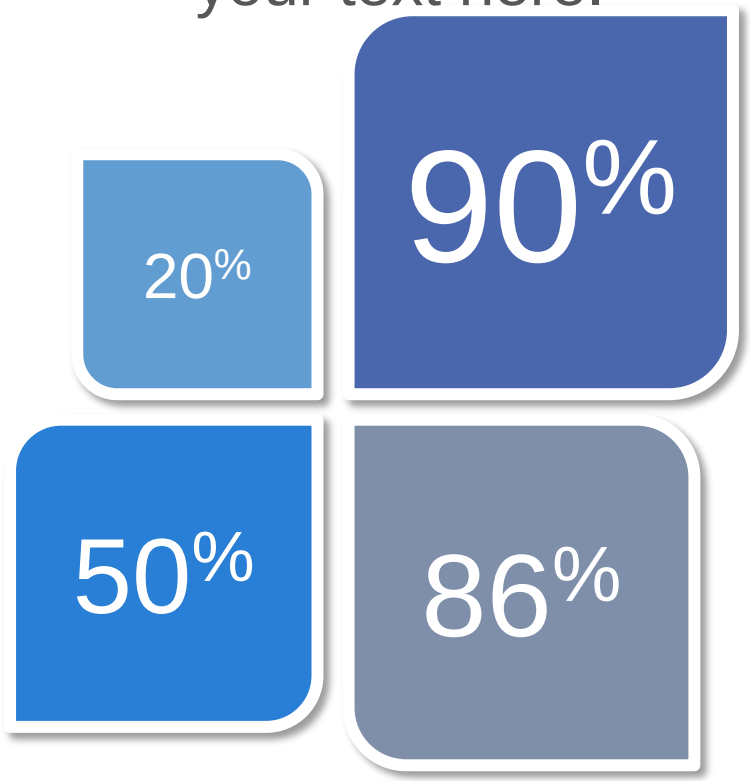

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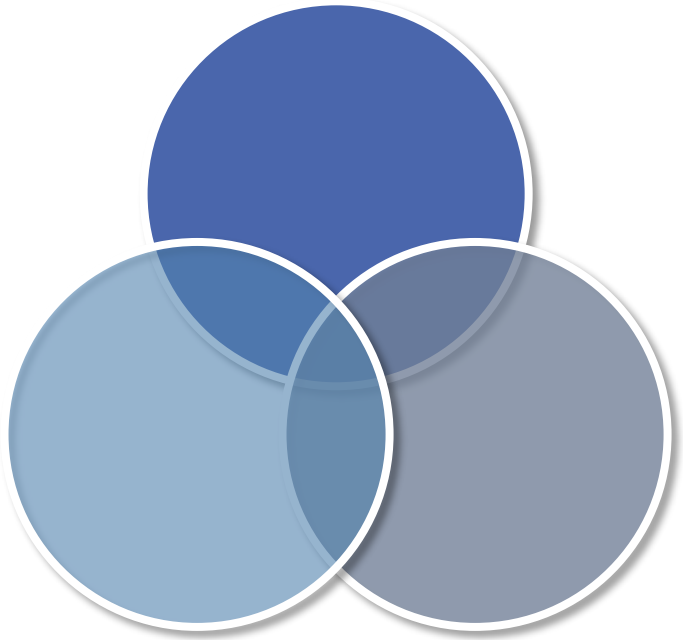

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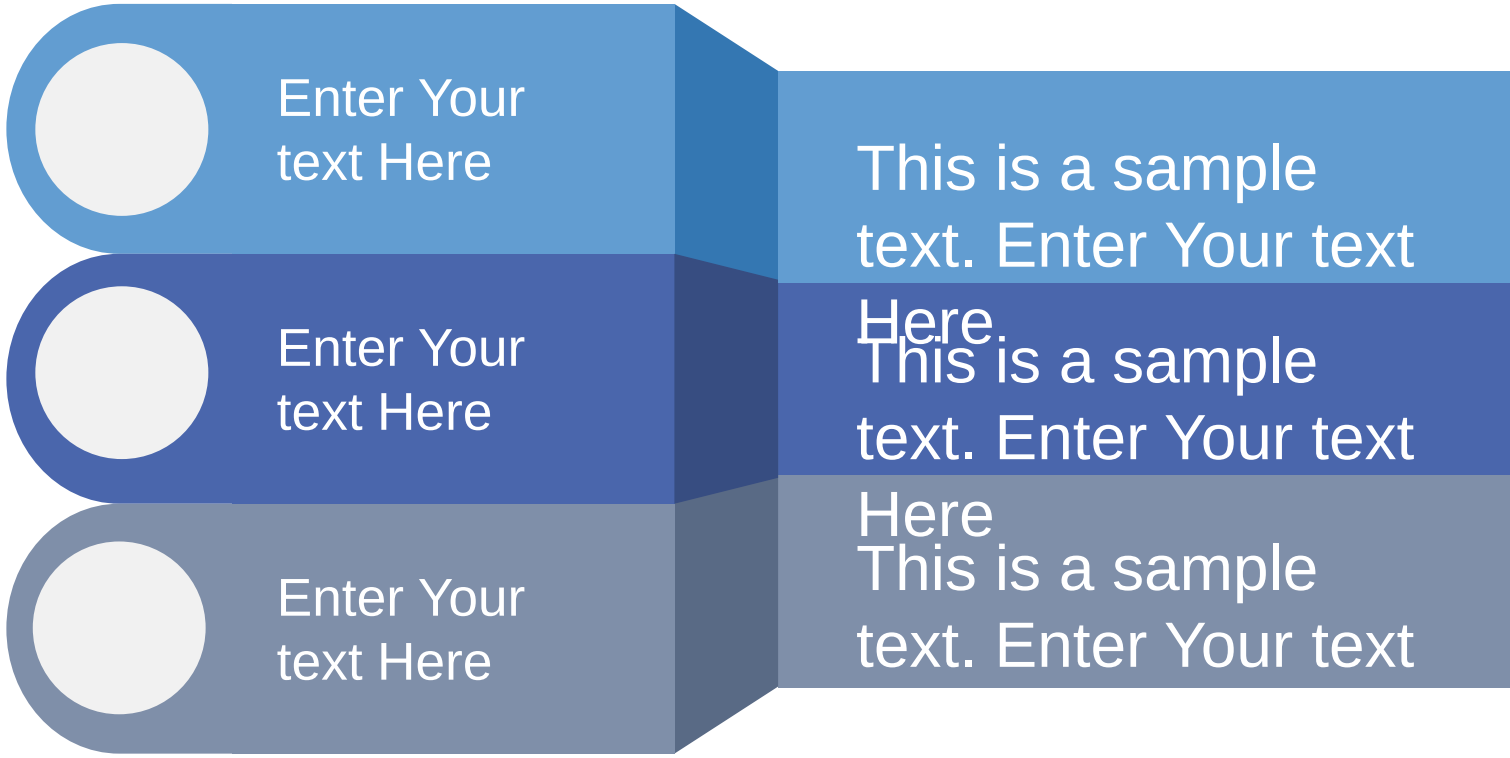

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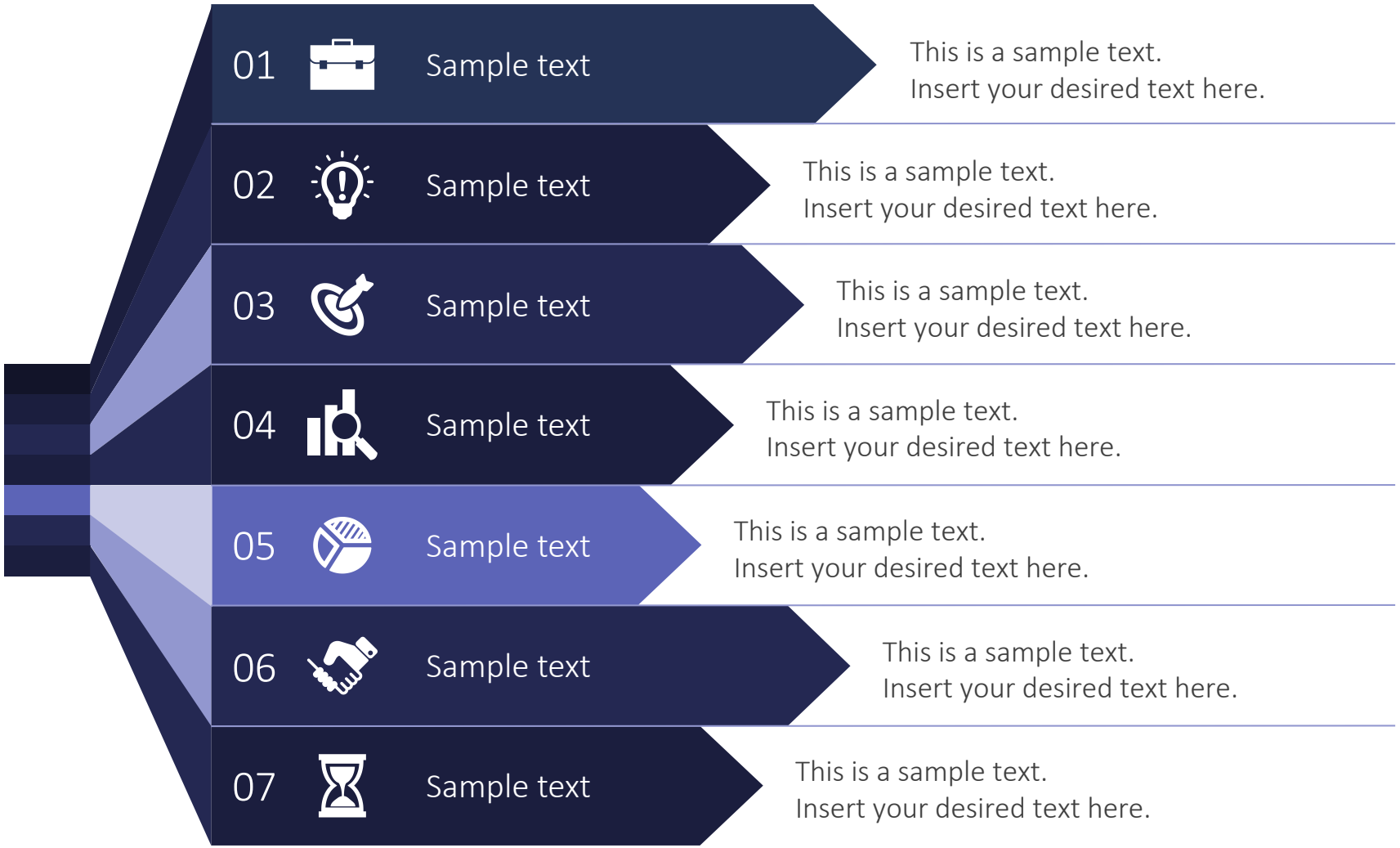

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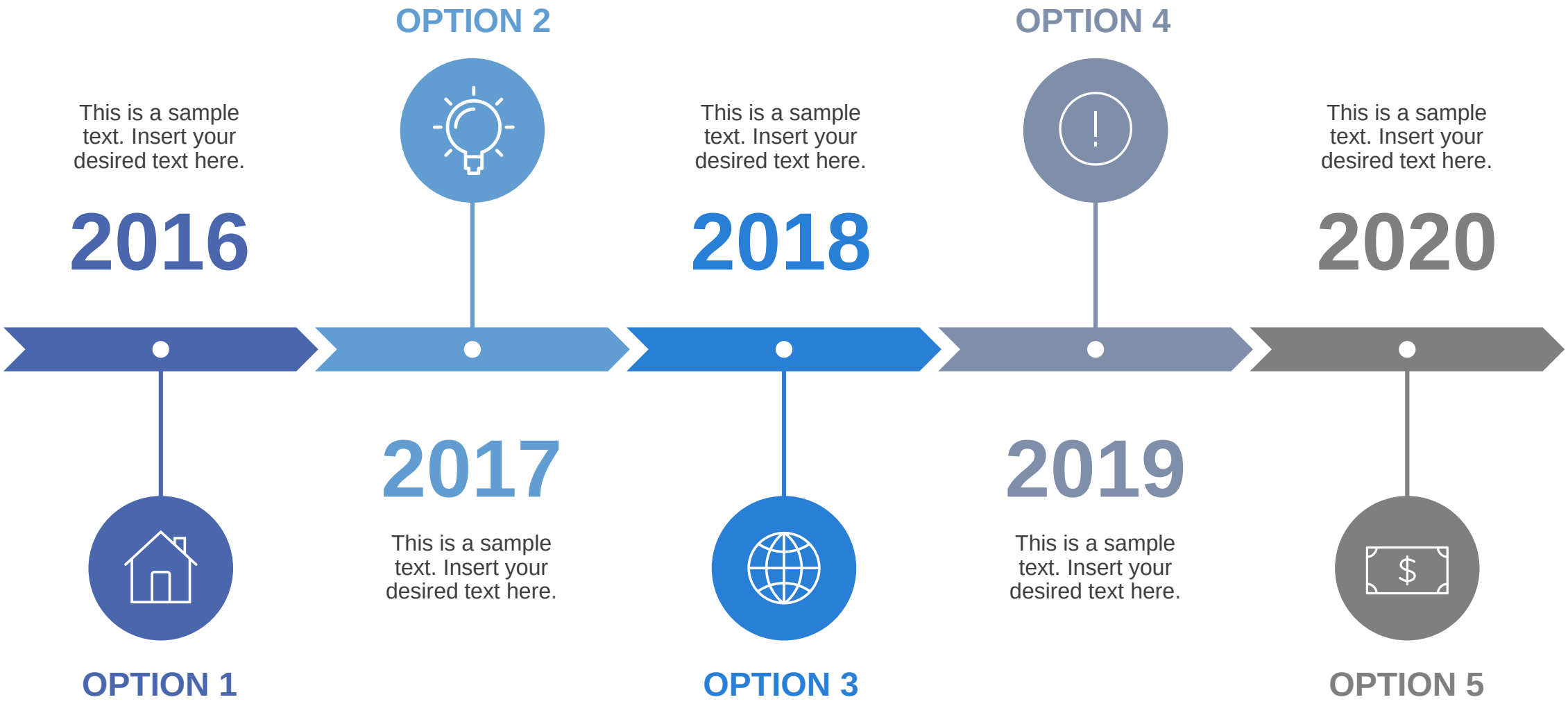
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2019
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OPTION 1
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