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Evolución del Páncreas Artificial

y áreas de investigación para el futuro

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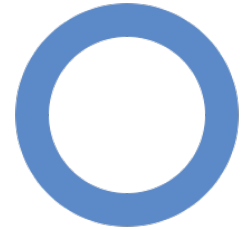

Agenda

1. Diabetes and its complications
2. Artificial pancreas technology
3. Insulin delivery technologies
4. Glucose measurement technologies
5. Alternative proposed solutions to diabetes
6. Conclusion

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Diabetes and its Complications

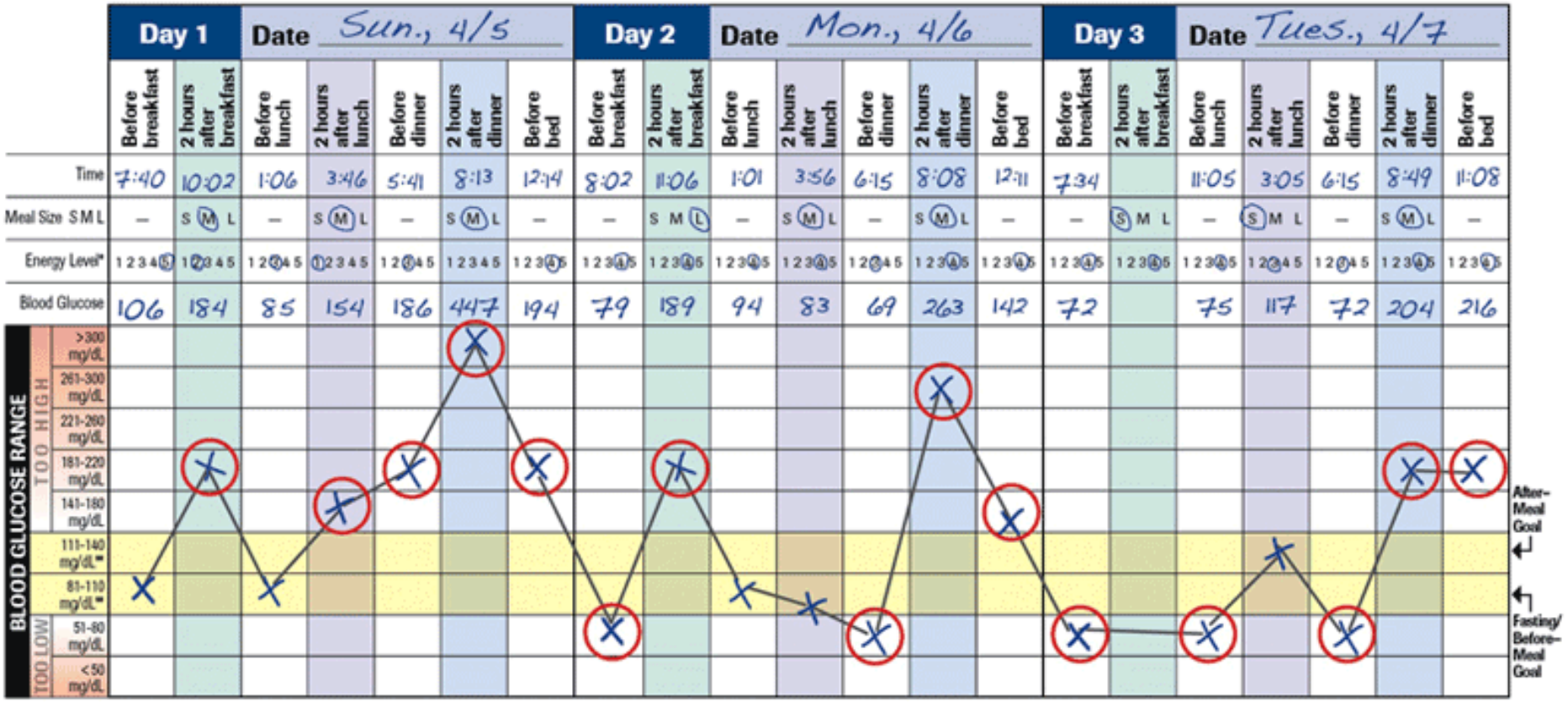
Diabetes Prevalence

Overall Numbers, Diabetes and Prediabetes

- **Prevalence:** In 2015, 30.3 million Americans, or 9.4% of the population, had diabetes. Approximately 1.25 million American children and adults have type 1 diabetes.
- **Undiagnosed:** Of the 30.3 million adults with diabetes, 23.1 million were diagnosed, and 7.2 million were undiagnosed.
- **Prevalence in Seniors:** The percentage of Americans age 65 and older remains high, at 25.2%, or 12.0 million seniors (diagnosed and undiagnosed).
- **New Cases:** 1.5 million Americans are diagnosed with diabetes every year.
- **Prediabetes:** In 2015, 84.1 million Americans age 18 and older had prediabetes. Deaths: Diabetes remains the 7th leading cause of death in the United States in 2015, with 79,535 death certificates listing it as the underlying cause of death, and a total of 252,806 death certificates listing diabetes as an underlying or contributing cause of death.

Reference: 2017 National Diabetes Statistics Report, National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation
http://www.diabetes.org/diabetes-basics/statistics/

Personal Glucose Chart



Diabetes Complications

- Diabetes produces devastating complications on patients with high HbA1C levels sustained over a long time, including:
- **Stroke and high blood pressure**
- **Heart disease** (infarction, heart failure)
- **Diabetic neuropathy** (resulting in amputations)
- **Kidney failure** (resulting in transplant or death)
- **Eye complications** (resulting in blindness)
- **Skin complications** (open sores, blisters, others)

Two Types of Diabetes

- **Type 1 Diabetes:**
  - Chronic autoimmune disorder
  - Immune system attacks insulin-producing β cells in the pancreas as if they were foreign bodies
  - Lack of insulin production
- **Type 2 Diabetes:**
  - Metabolic disease
  - Very often correlated with unhealthy lifestyle, including obesity and lack of exercise
  - Insulin resistance
- **Similar symptoms and complications:**
  - Hypoglycemia
  - Hyperglycemia
  - Diabetic Keto-Acidosis (DKA)

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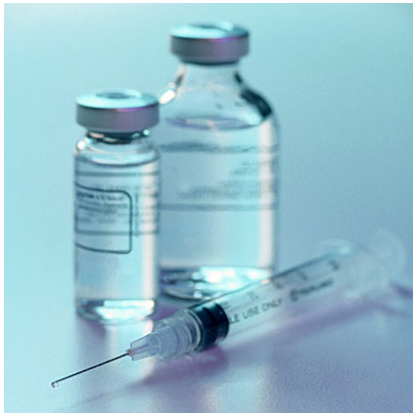
Artificial Pancreas Technology

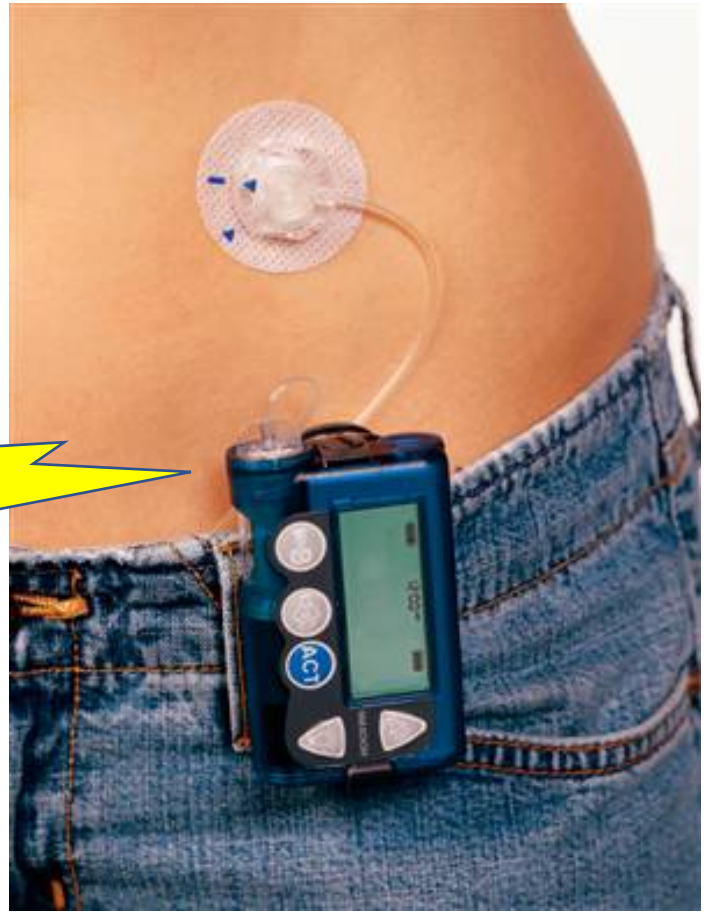
Therapies and Tools for Diabetes

- Insulin, GLP-1, Amylin
- Insulin pens
- Insulin pumps
- Orals (metformin and others)
- Glucagon injections (emergency only)
- Continuous glucose monitors
- Blood glucose meters

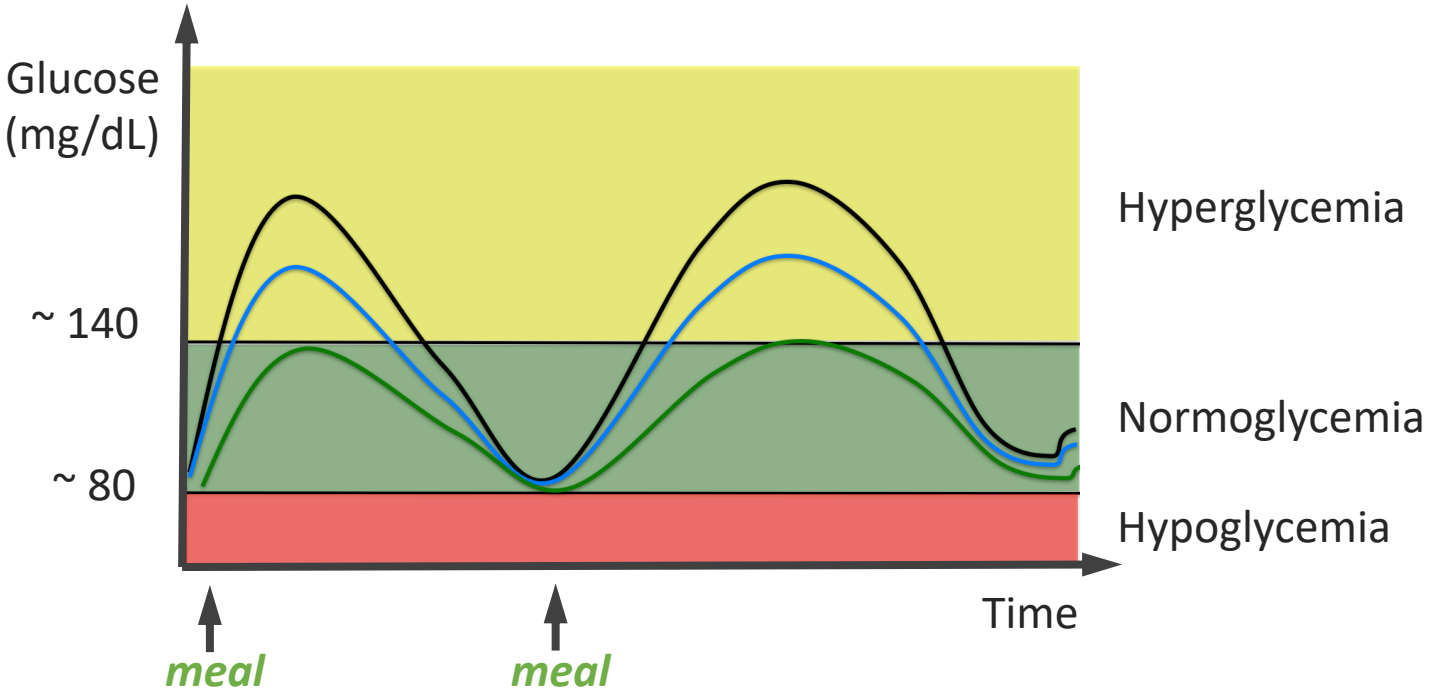


Closing the Loop (2009)

- Insulin pumps + CGM
- CGM data could be used as a negative feedback signal to implement a closed-loop controller for automated insulin delivery.



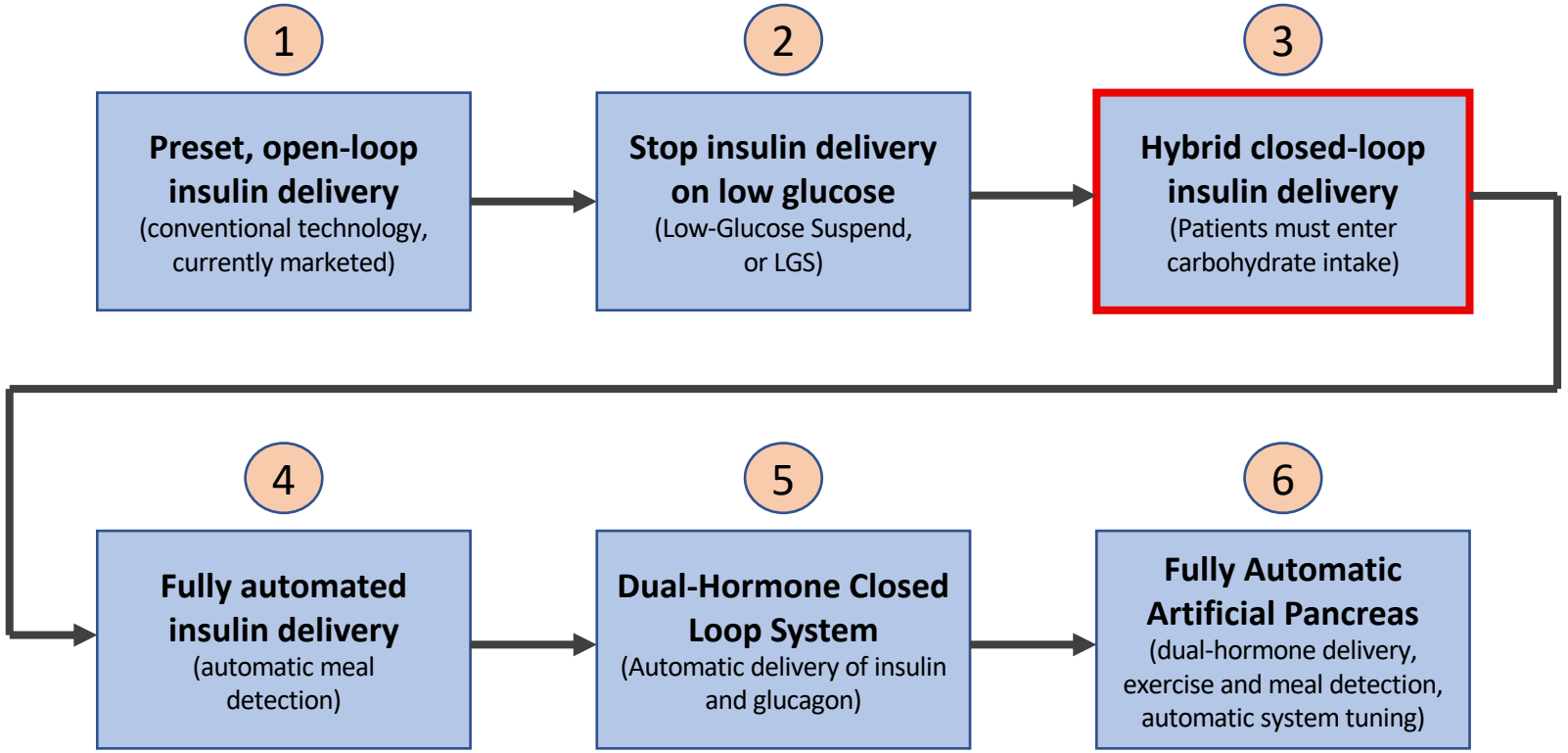
Automatic Control of Glucose Concentration



Variation of glucose concentration as a function of time and meal intake

Source: Based on Close, K. and Brown, A. "CGM and Time-in-Range: What Do Diabetes Experts Think About Goals?". Available online at https://diatribe.org/cgm-and-time-range-what-do-diabetes-experts-think-about-goals

Technology roadmap towards an Artificial Pancreas

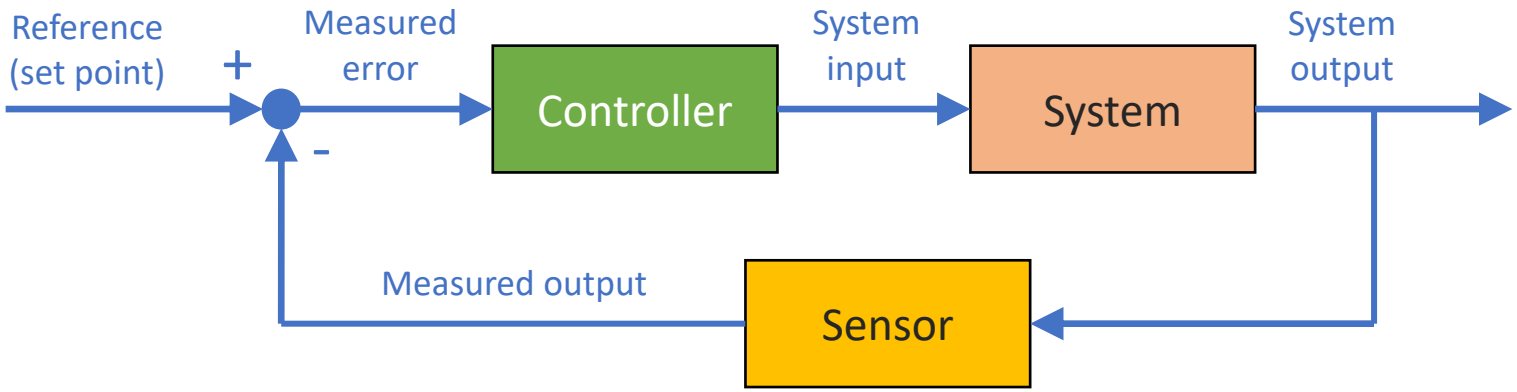


Source: Partially based on Kowalski, AJ, "Can We Really Close the Loop and How Soon? Accelerating the Availability of an Artificial Pancreas: A Roadmap to Better Diabetes Outcomes", Diabetes Technology & Therapeutics, Vol. 11, No. S1, 2009. https://doi.org/10.1089/dia.2009.0031

Artificial Pancreas Project Chronology

- **2009**: Artificial Pancreas (AP) Project established, a joint venture between JDRF and Johnson & Johnson.
- **2010**: First successful *in silico* clinical study.
- **2011**: First acute clinical study in humans (hospital).
- **2012**: First conference presentation on JDRF AP.
- **2013**: First technical journal publication.
- **2014**: First intermediate ambulatory study (hotel).
- **2015**: First ambulatory study (at home).
- **2016**: J&J decides to exit diabetes market and transfer assets to JDRF and patients to Medtronic.
- **2017**: First commercial AP product launched by Medtronic.

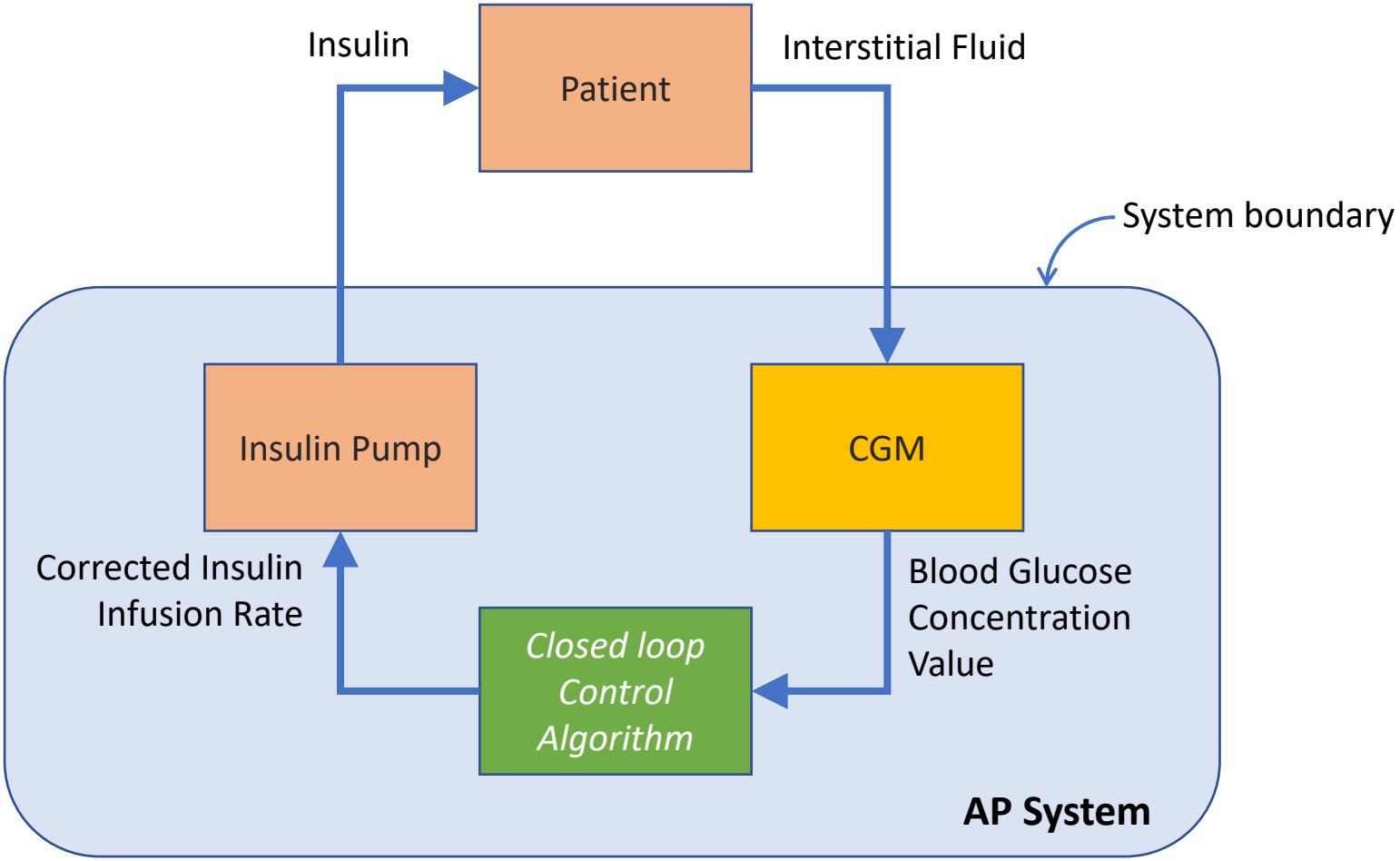
Fundamental Problem of an Artificial Pancreas System



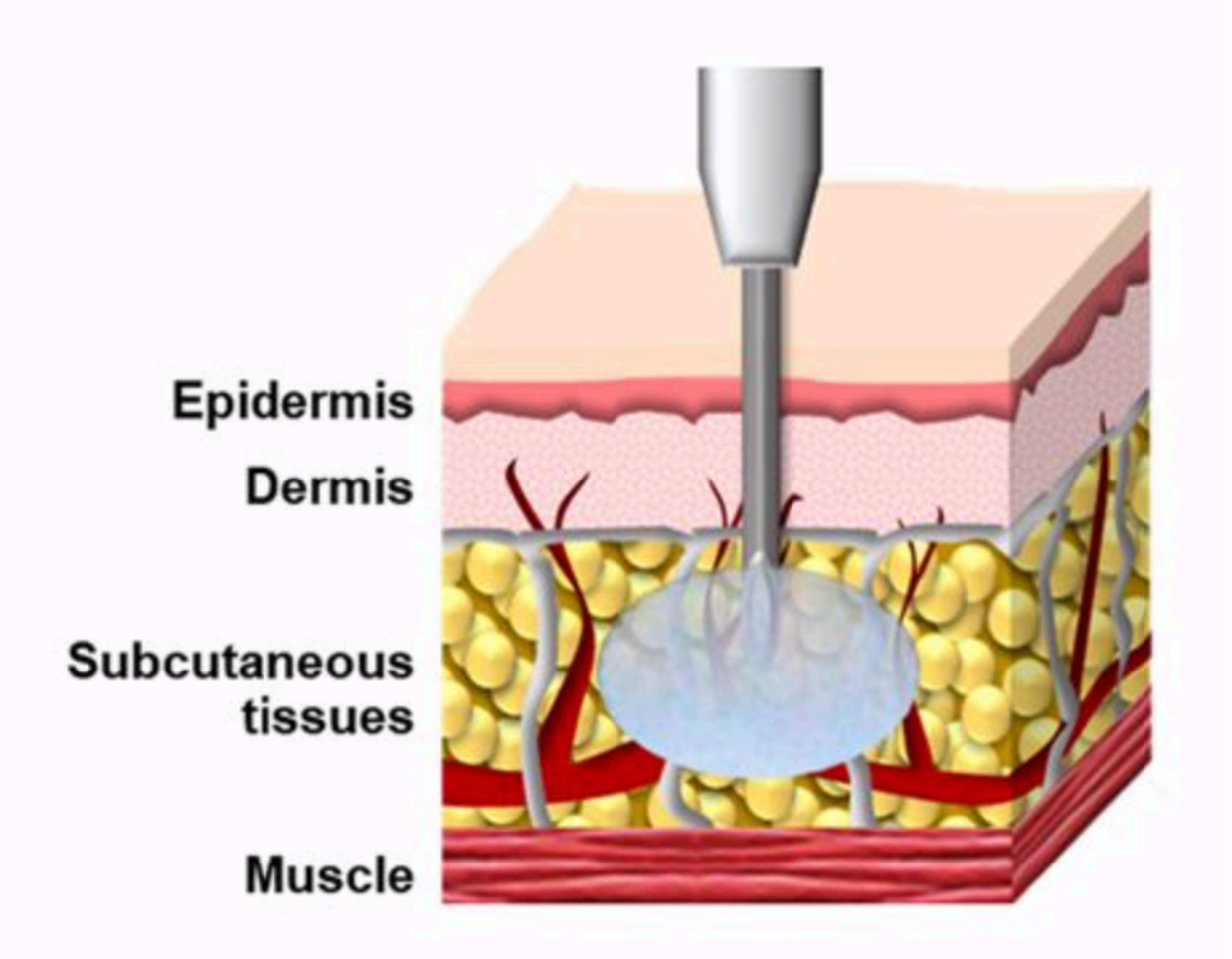
Control strategies:

- PID: Proportional-Integrative-Derivative
- Fuzzy Logic (rule-based)
- MPC: Model-Predictive Control

AP Context Diagram



Subcutaneous infusion and measurement



Source: Kim H, Park H, Lee S, "Effective method for drug injection into subcutaneous tissue", Nature Scientific Reports, volume 7, Article number: 9613 (2017). Available online: https://www.nature.com/articles/s41598-017-10110-w

The Challenge

Model-Predictive Control

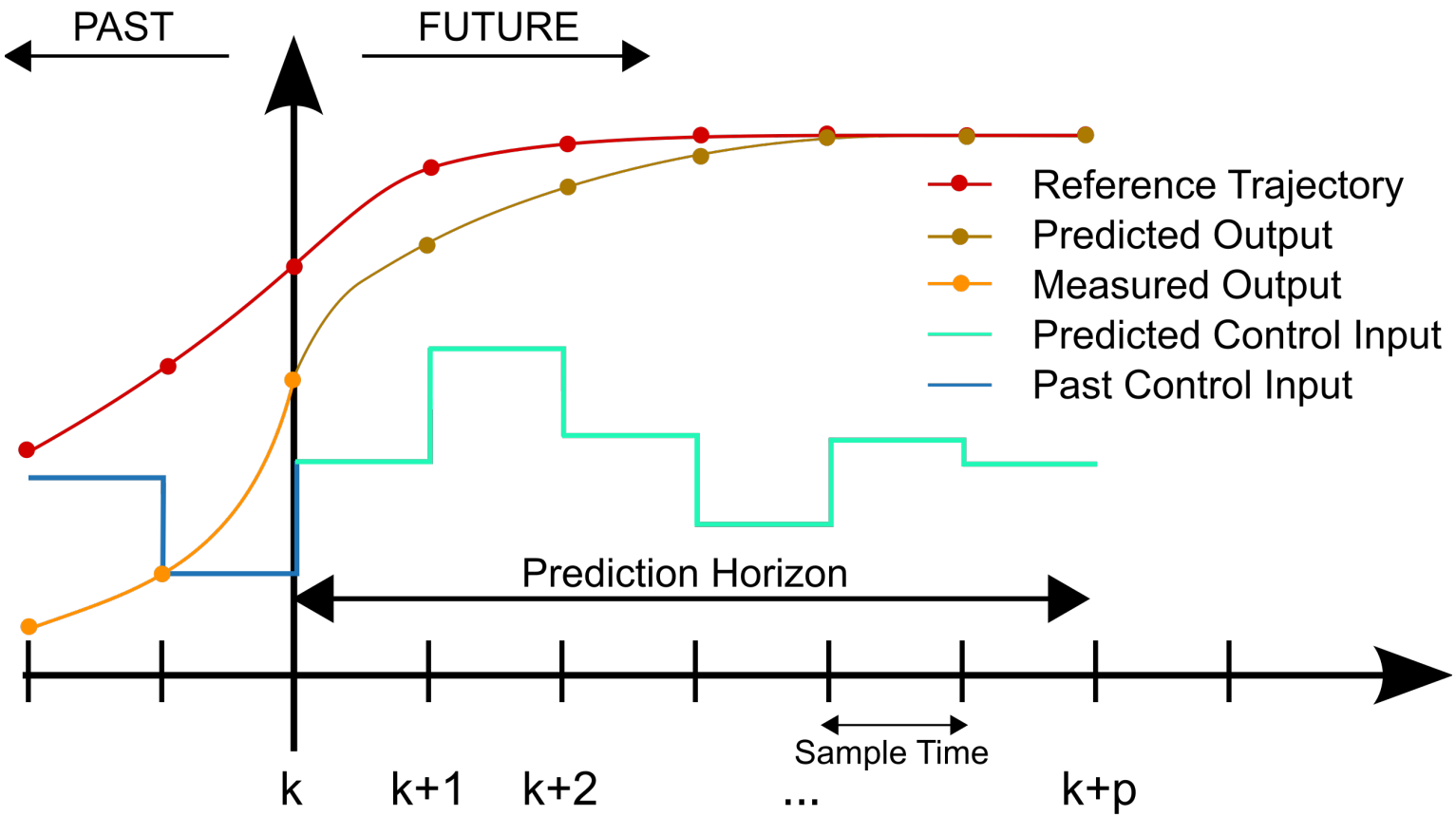
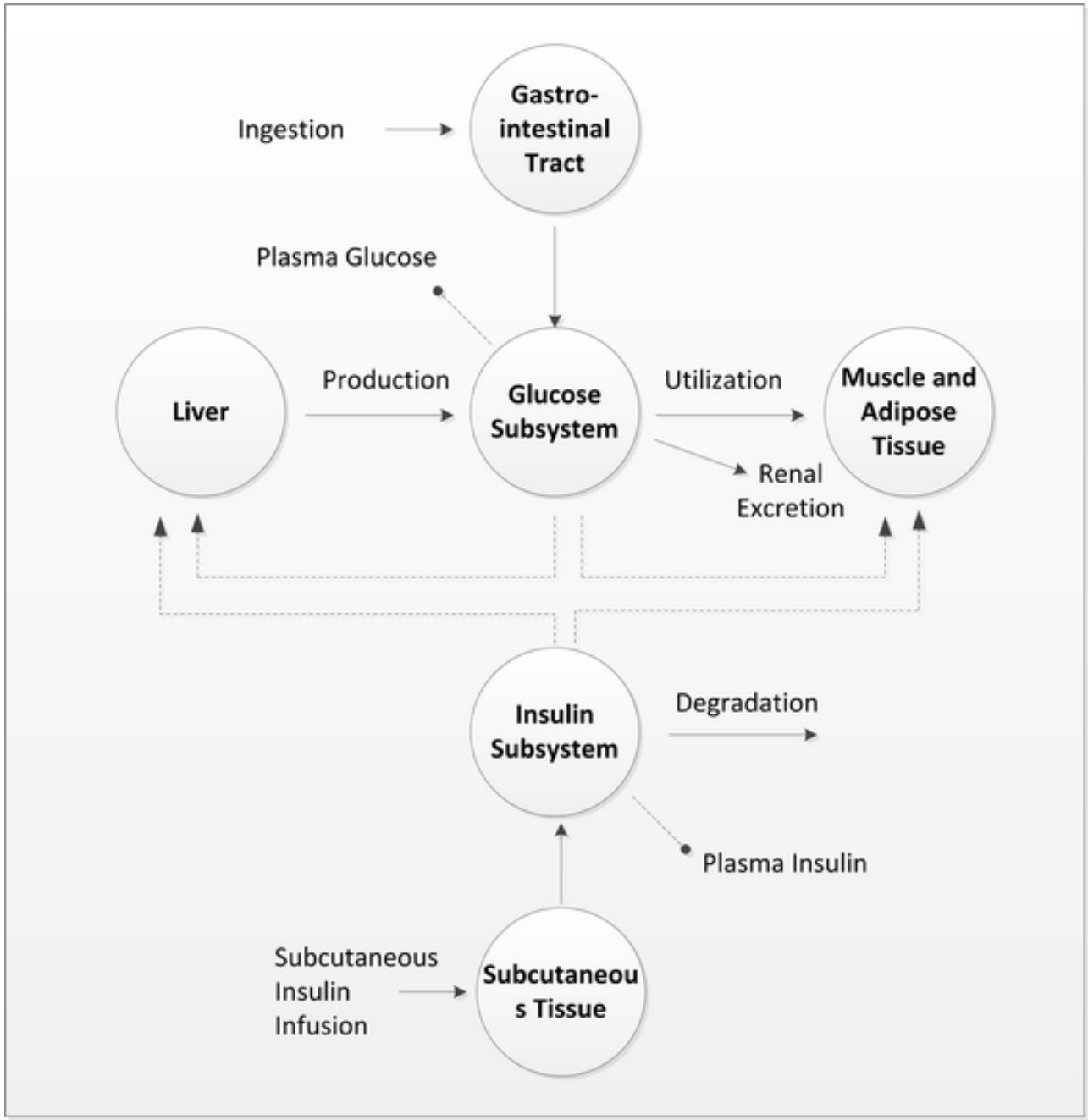


Image: Martin Behrendt (2009), Creative Commons, Wikimedia.

Reference: Michael Nikolaou, Model predictive controllers: A critical synthesis of theory and industrial needs, Advances in Chemical Engineering, Academic Press, 2001, Volume 26, Pages 131-204

Cobelli's glucose – insulin model



Source: Li, P., Yu, L., Fang, Q. et al. Med Biol Eng Comput (2016) 54: 1563. https://doi.org/10.1007/s11517-015-1436-y

Model Predictive Control

Principles of MPC

Model Predictive Control (MPC) is a multivariable control algorithm that uses:

- an internal dynamic model of the process
- a history of past control moves and
- an optimization cost function J over the receding prediction horizon,

to calculate the optimum control moves.

An example of a non-linear cost function for optimization is given by:

$$J = \sum_{i=1}^{N} w_{x_i} (r_i - x_i)^2 + \sum_{i=1}^{N} w_{u_i} \Delta u_i{}^2$$

without violating constraints (low/high limits) with

x_i: i^{th} controlled variable (e.g. measured temperature)

r_i: i^{th} reference variable (e.g. required temperature)

u_i: i^{th} manipulated variable (e.g. control valve)

w_{x_i}: weighting coefficient reflecting the relative importance of x_i

w_{u_i}: weighting coefficient penalizing relative big changes in u_i

Hypo-Hyper Minimizer MPC

$$G'(k)=a_1G'(k-1)+a_2G'(k-2)+a_3G'(k-3)+a_4G'(k-4)+ a_5G'(k-5)+bI_M(k-4)$$

$$I_M(k)=c_1I_M(k-1)+c_2I_M(k-2)+d_1I'_D(k-1)+d_2I'_D(k-2)$$

k is the discrete time interval index having a series of indexing counters where k=1, 2, 3 . . . .

G' is the measured glucose concentration

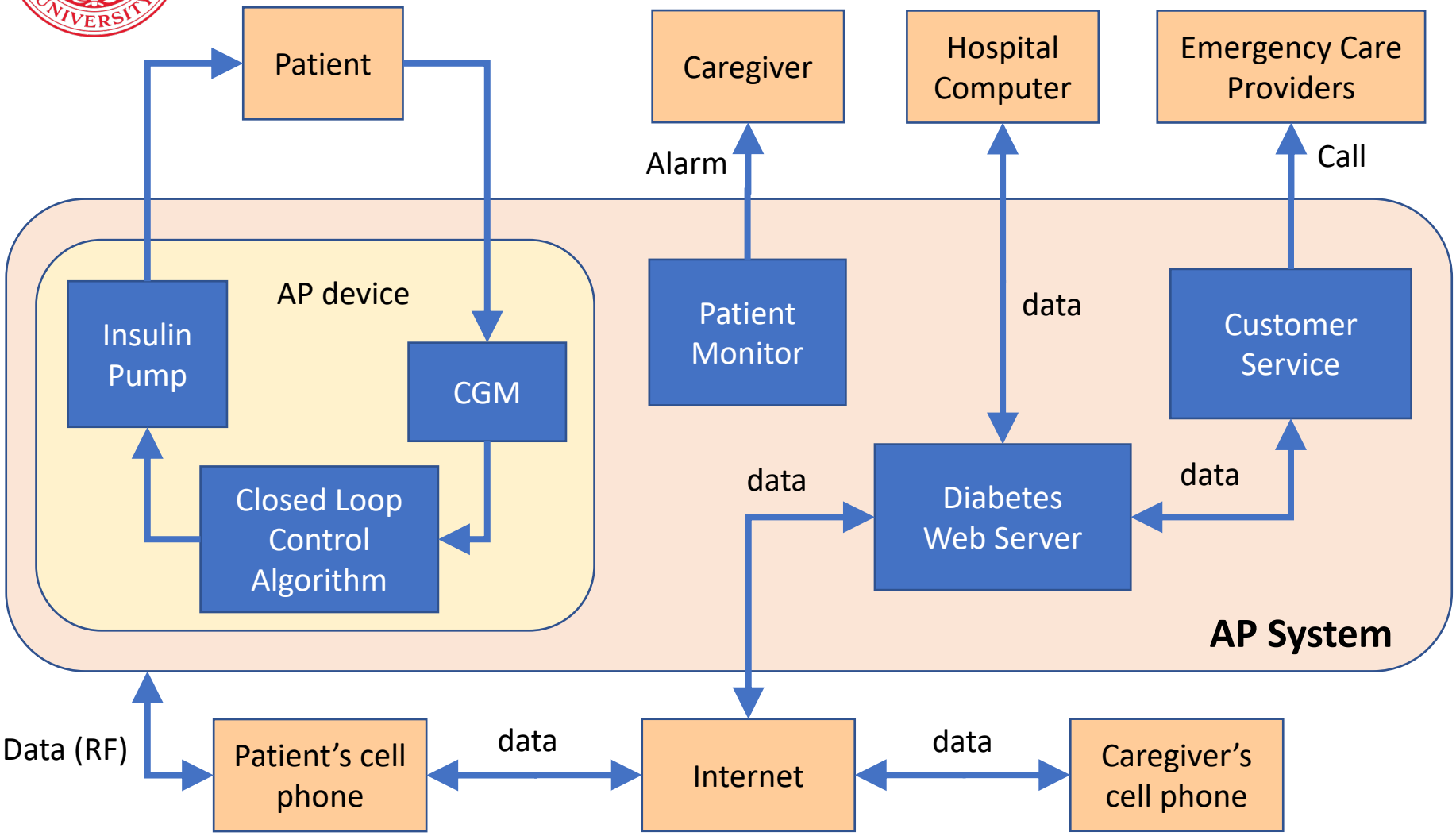
I_M is the "mapped insulin" which is not a measured quantity

I'_D is the delivered insulin or a manipulated variable

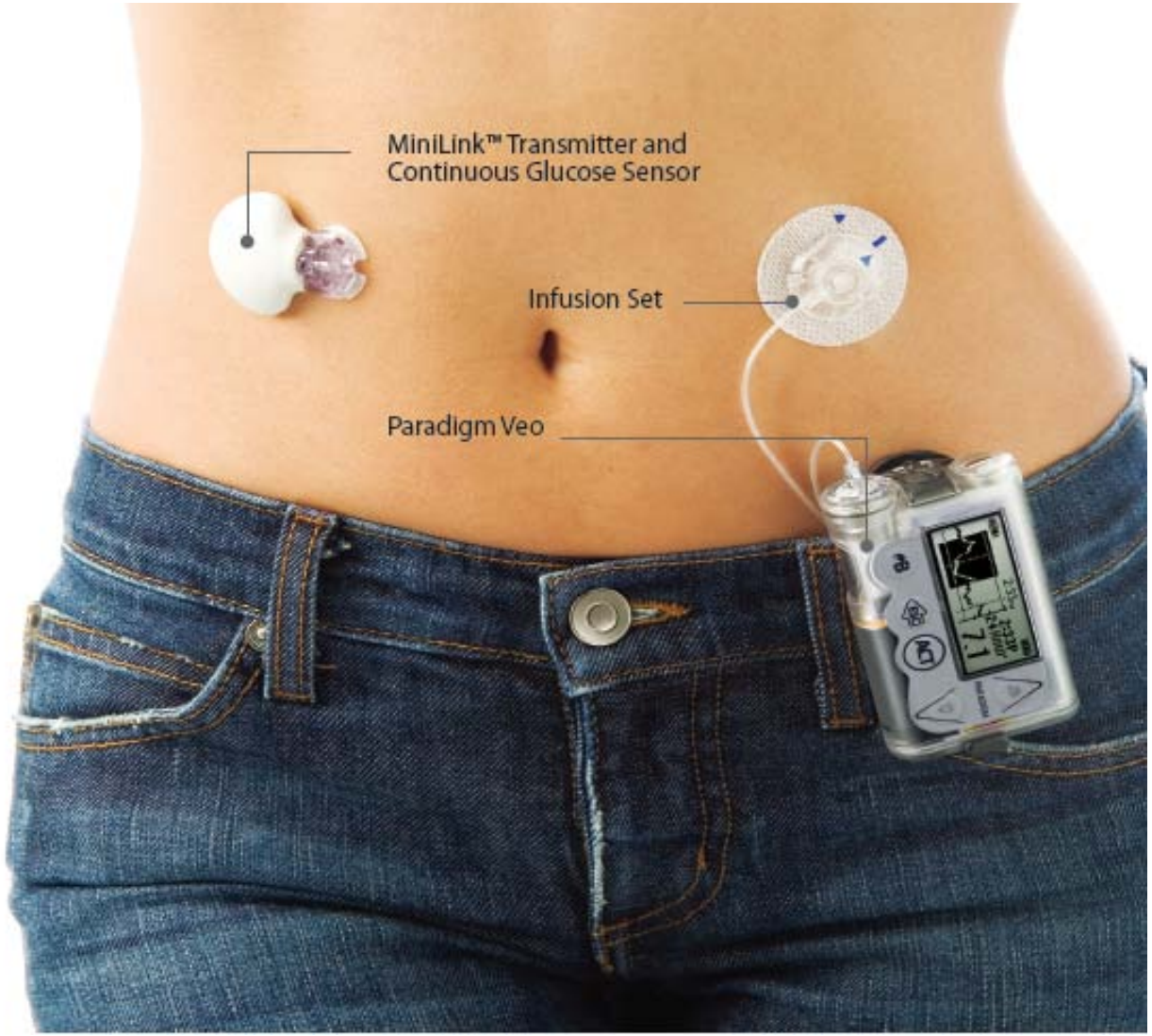
and coefficients a_1~2.993; a_2~(–3.775); a_3~2.568; a_4~(–0.886); a_5~0.09776; b~(–1.5); c_1~1.665; c_2~(–0.693); d_1~0.01476; d_2~0.01306.

Source: US Patent: 9517306, Morales, C.O., Dec. 13, 2016

AP System Context Diagram (Complete)



First AP System



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Insulin Delivery Technologies

Closed-Loop Systems Today

Medtronic 670G

Launch: 2017

Reference: https://www.medtronicdiabetes.com/products/minimed-670g-insulin-pump-system

Closed-Loop Systems Today

Tandem Basal-IQ

Launch: 2018

Low-Glucose Suspend

Reference: https://www.tandemdiabetes.com/products/t-slim-x2-insulin-pump

Closed-Loop Systems Today

omnipod® HORIZON®
AUTOMATED GLUCOSE CONTROL

Horizon
Launch: 2020 (expected)

Reference: https://www.myomnipod.com/healthcareproviders/about-omnipod/innovation

Closed-Loop Systems Today

Diabeloop DBLG1

Launch: 2019

Reference: https://www.diabeloop.com/products

Dual-Hormone Closed-Loop Systems

iLet Dual Pump

Expected Launch: Unknown

Beta Bionics

(Boston University)

Reference: https://www.betabionics.com

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Glucose Measurement Technologies

Blood Glucose Meters

Roche Accu-Chek

https://www.accu-chek.com

Glucose Oxidase enzyme:

This is the oldest technology in continued use to measure glucose concentration in whole blood. The glucose oxidase enzyme (GOx) also known as notatin is an oxido-reductase that catalyzes the oxidation of glucose to hydrogen peroxide and D-glucono-δ-lactone. This enzyme is produced by certain species of fungi and insects and displays antibacterial activity when oxygen and glucose are present [1].

Enzymatic glucose biosensors use an electrode instead of O2 to take up the electrons needed to oxidize glucose and produce an electronic current in proportion to glucose concentration [2].

References:
[1] Wong CM, Wong KH, Chen XD (Apr 2008). "Glucose oxidase: natural occurrence, function, properties and industrial applications". Applied Microbiology and Biotechnology. 78 (6). doi:10.1007/s00253-008-1407-4. PMID 18330562

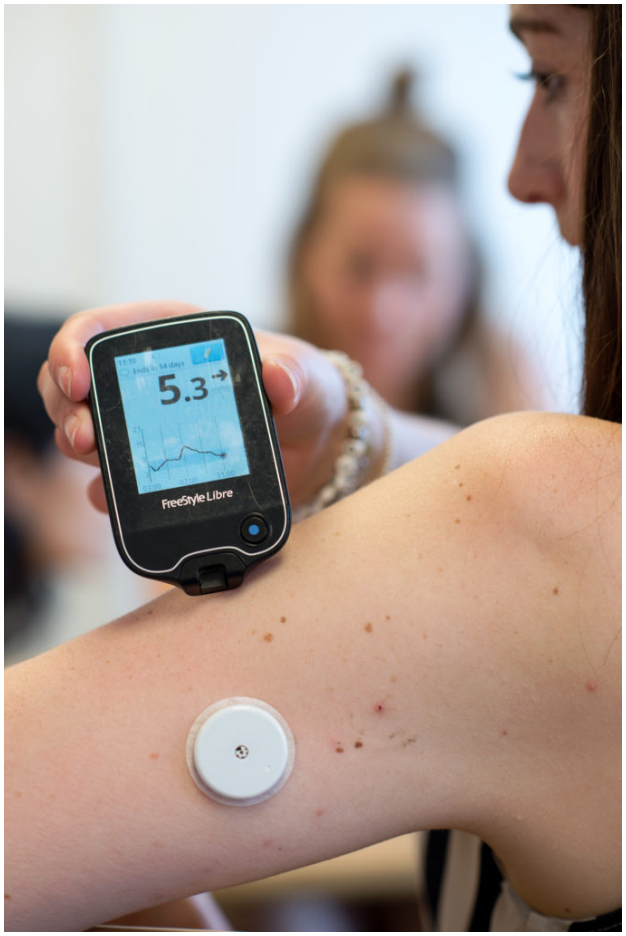
[2] Cass AE, Davis G, Francis GD, Hill HA, Aston WJ, Higgins IJ, Plotkin EV, Scott LD, Turner AP (Apr 1984). "Ferrocene-mediated enzyme electrode for amperometric determination of glucose". Analytical Chemistry. American Chemical Society. 56 (4): 667-671. doi:10.1021/ac00268a018. PMID 6721151

See also:
[3] Rodgers, Ritchie, Zvikhachevskaya, Nelson, and Morales, "Orientation Independent Meter", US Patent 9354194, May 31, 2016.

Continuous Glucose Monitors

Dexcom G5

https://www.dexcom.com



Abbott FreeStyle Libre

https://www.myfreestyle.com

Lipohypertrophy Nodules

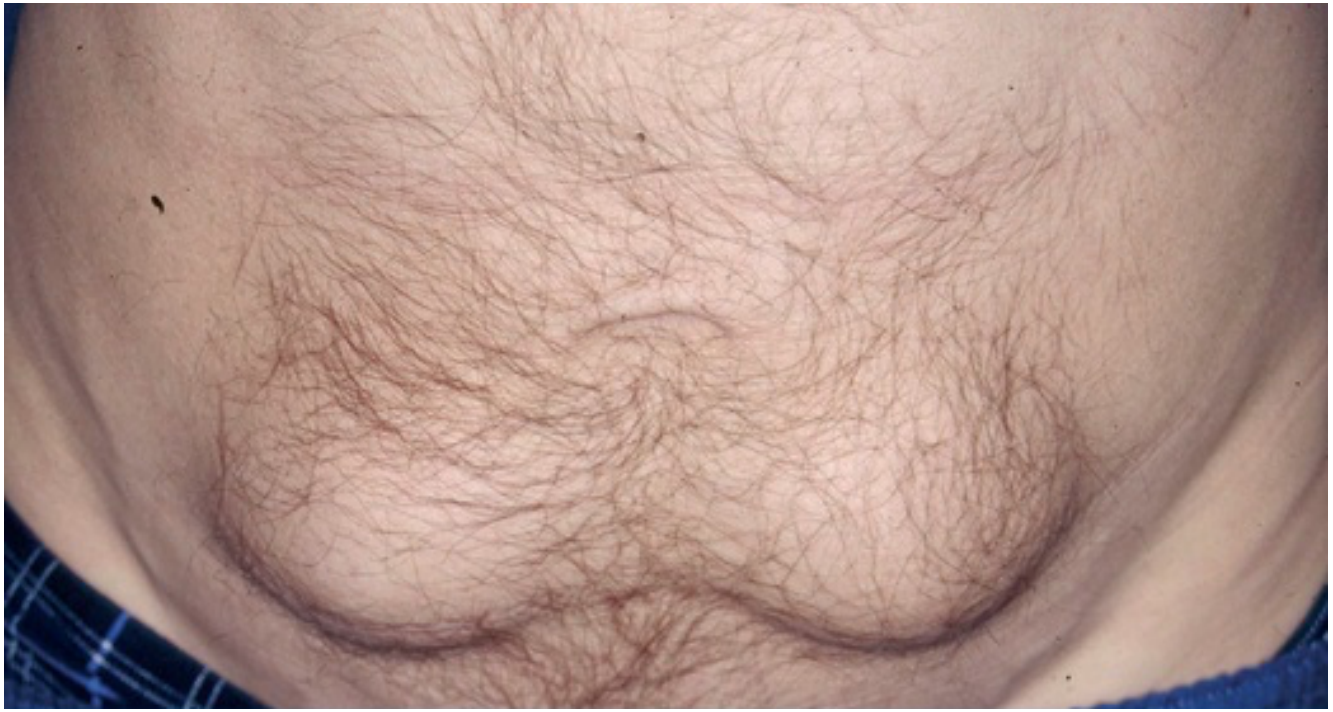
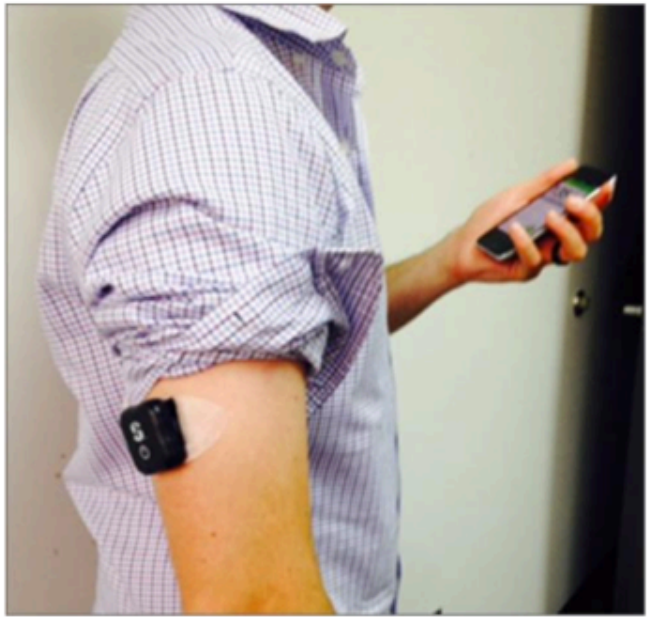


Photo credit: Maureen Wallymahmed, in "Insulin therapy in the management of type 1 and 2 diabetes"

Reference: M. Blanco, M.T. Hernández, K.W. Strauss, M. Amaya, "Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes", Diabetes & Metabolism, Volume 39, Issue 5, 2013, Pages 445-453, ISSN 1262-3636, https://doi.org/10.1016/j.diabet.2013.05.006.

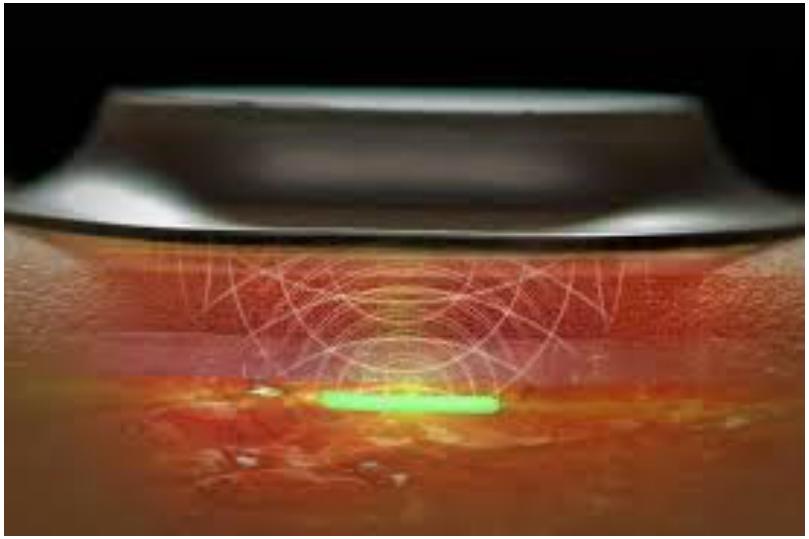
Continuous Glucose Monitors

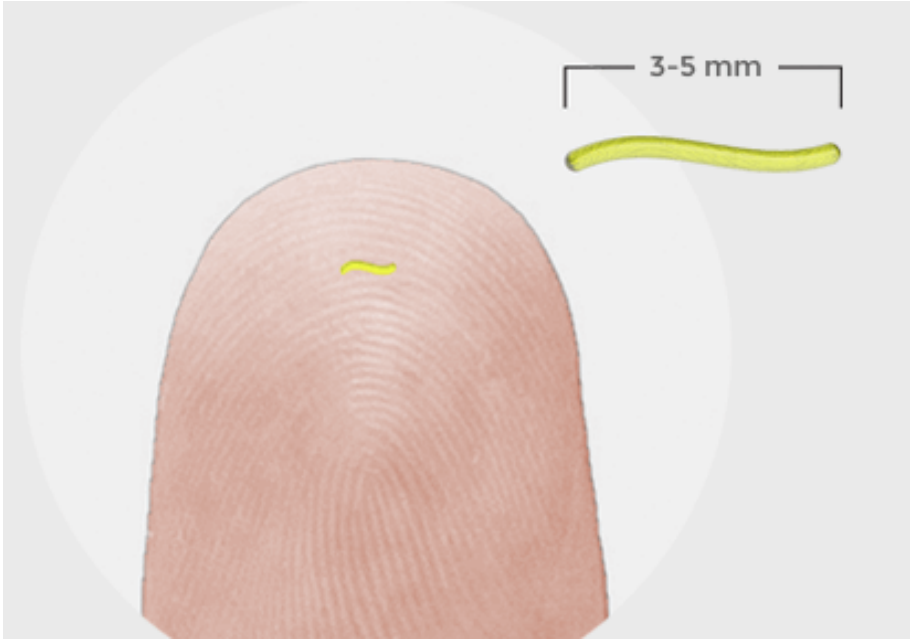


Senseonics 3-month implantable sensor

https://www.senseonics.com

Fluorescence-based glucose measurement





Profusa Lumee

www.profusa.com

Reference: Klonoff DC. Overview of fluorescence glucose sensing: a technology with a bright future. J Diabetes Sci Technol. 2012;6(6):1242–1250. Published 2012 Nov 1. doi:10.1177/193229681200600602

Fluorescence-based glucose measurement

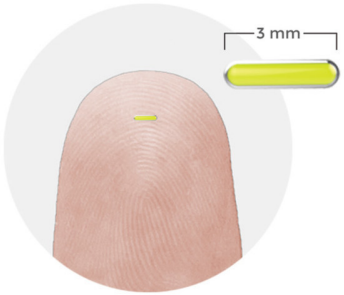
Profusa Lumee

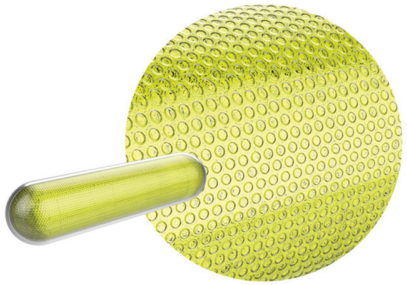
www.profusa.com

profusa

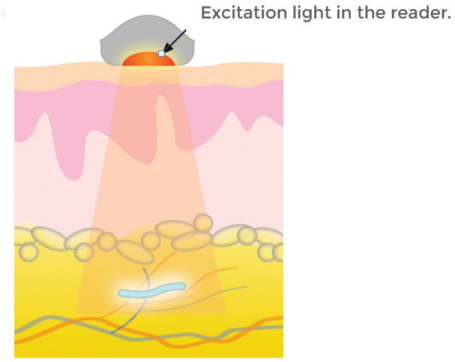
Biologically Integrated Sensors

Less than 3mm and 250 microns in diameter, each tiny biosensor is a soft, flexible fiber biocompatible with the body's tissues for long-term monitoring up to two years without local inflammation or rejection.

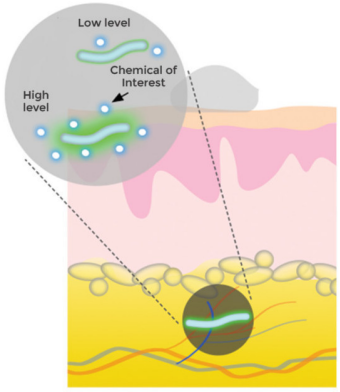




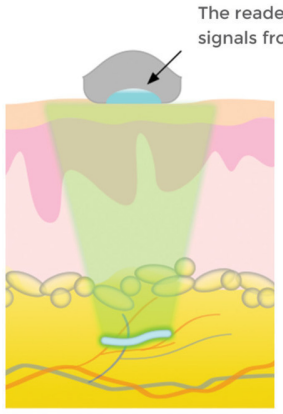
The biosensor is made of a porous "smart gel" that mimics the 3D environment of cells.



1. Excitation light is shined on the skin surface from the reader and reaches the biosensor under the skin.

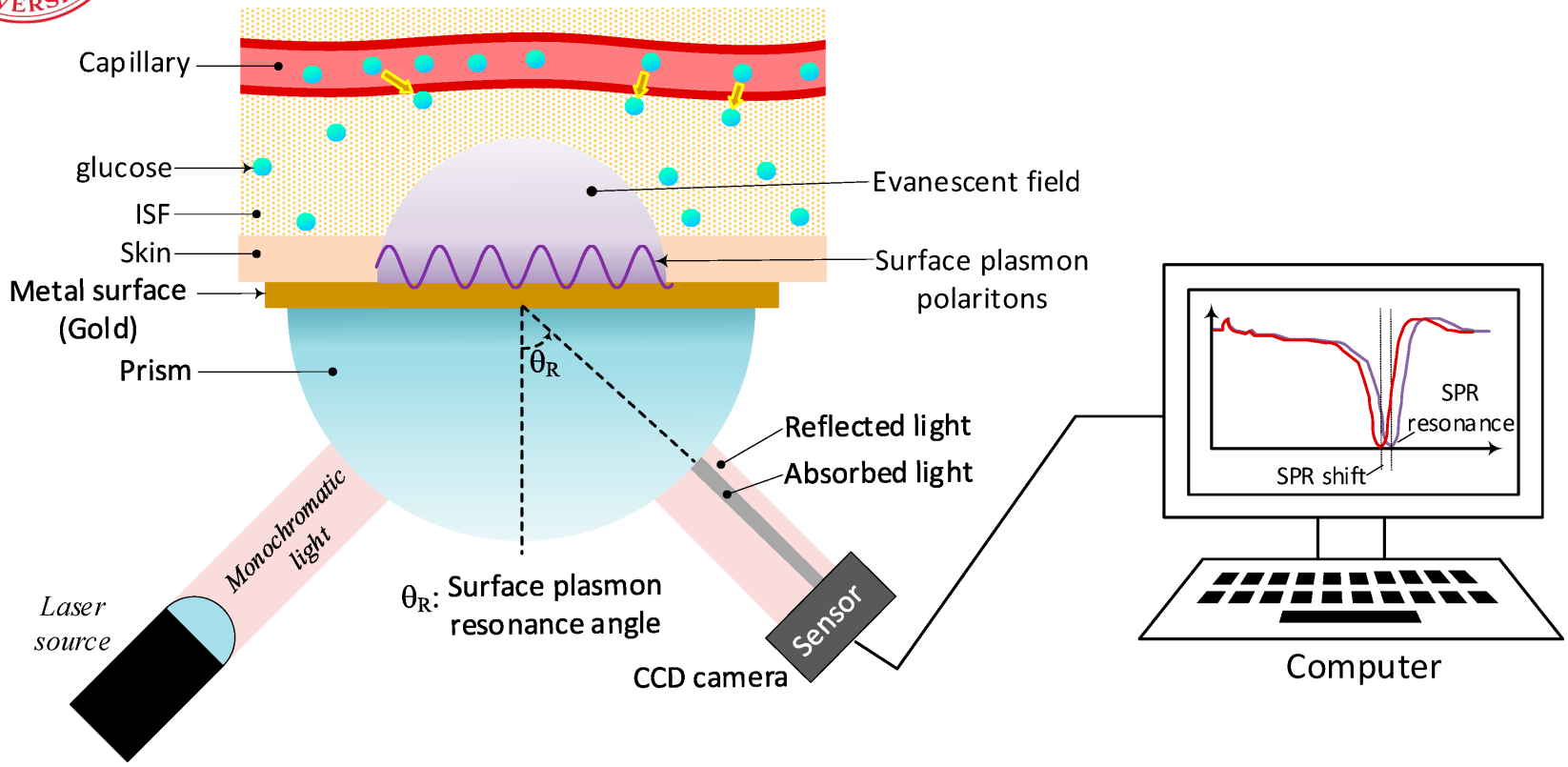


2. The biosensor is embedded with a biochemical that emits fluorescent light proportional to the chemical of interest in the tissue.



3. Fluorescent signals from the biosensor travel to the surface of the skin where they are captured by the reader. Results can be uploaded to a smart phone and the Internet for an encrypted personal record and historical tracking.

Non-invasive glucose measurement



Surface plasmon resonance for glucose monitoring

Reference: Villena Gonzales, W.; Mobashsher, A.T.; Abbosh, A. The Progress of Glucose Monitoring—A Review of Invasive to Minimally and Non-Invasive Techniques, Devices and Sensors. Sensors 2019, 19, 800

Optical measurement of glucose concentration

- Raman Spectroscopy
- Surface Plasmon Resonance
- Optical Polarimetry
- Optical Coherence Tomography
- Terahertz Time Domain Spectroscopy
- Thermal Spectroscopy
- Photo-Acoustic Spectroscopy
- Electromagnetic Sensing
- Bioimpedance Spectroscopy
- Metabolic Heat Conformation

Reference: Villena Gonzales, W.; Mobashsher, A.T.; Abbosh, A. The Progress of Glucose Monitoring—A Review of Invasive to Minimally and Non-Invasive Techniques, Devices and Sensors. Sensors 2019, 19, 800

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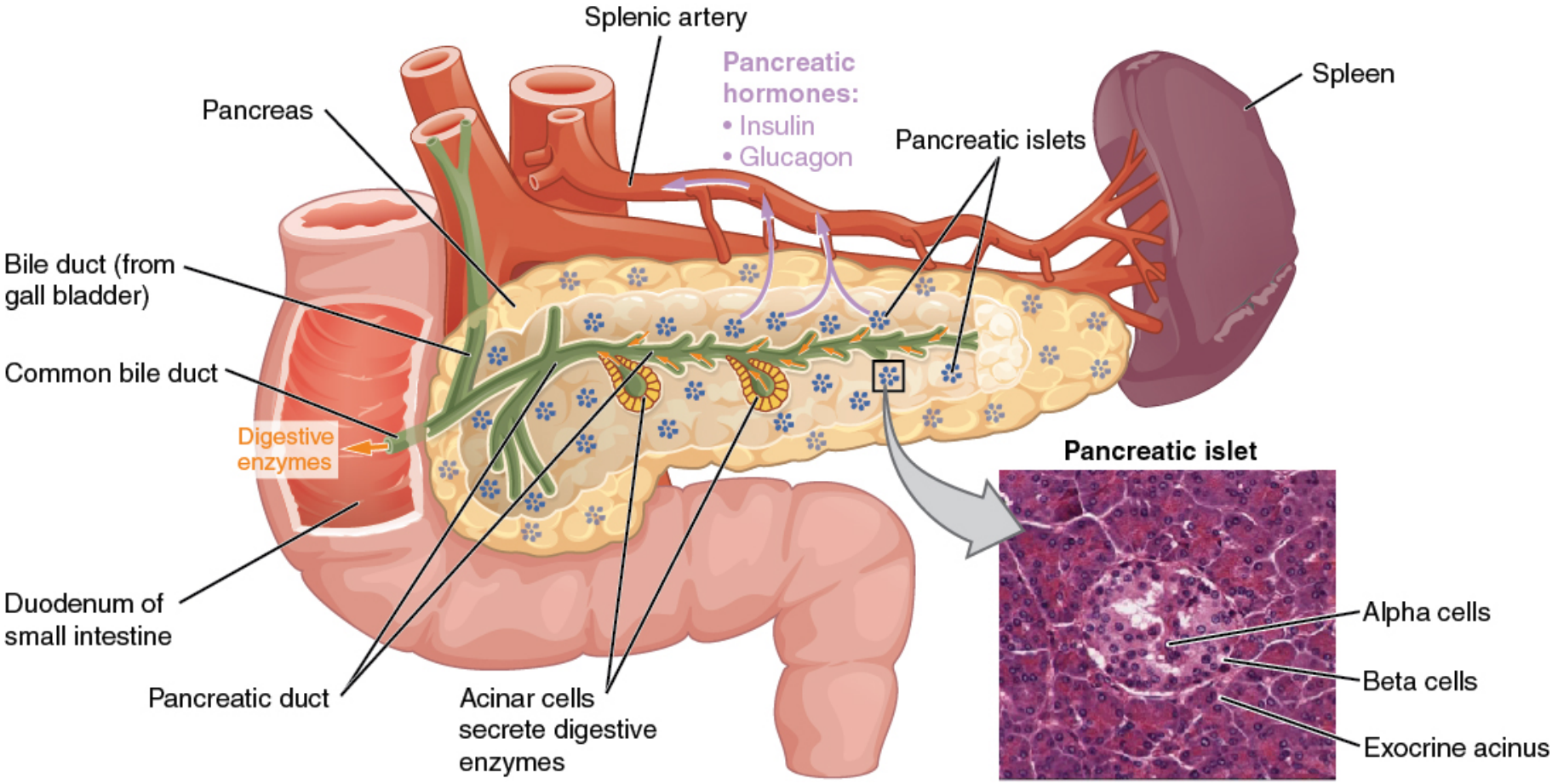
Biology-Based Research

Brief Overview

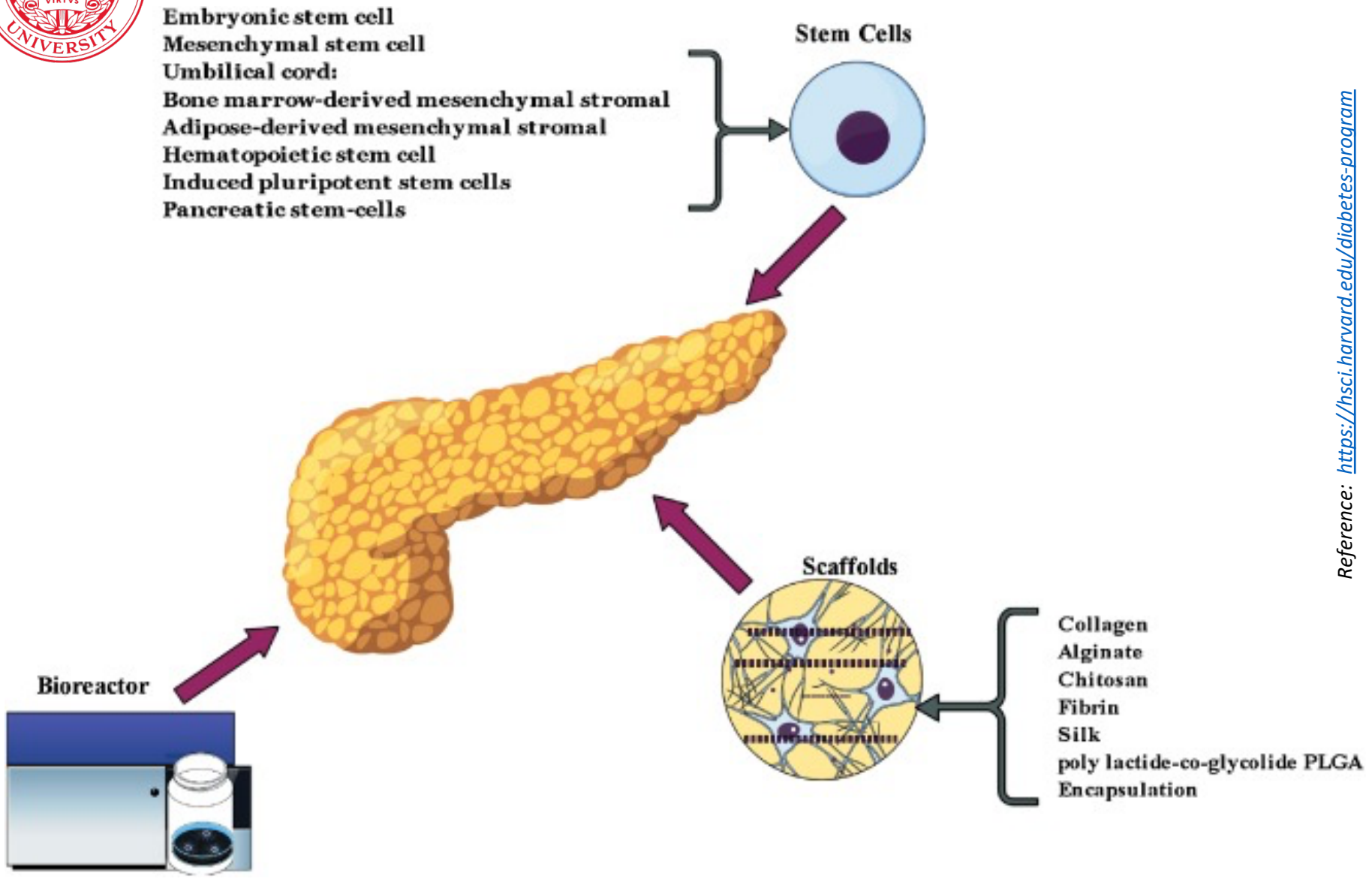
Duodenum and Pancreas



Reference: OpenStax College, "Anatomy & Physiology, Connexions", Jun 19, 2013. Available online: http://cnx.org/content/col11496/1.6/

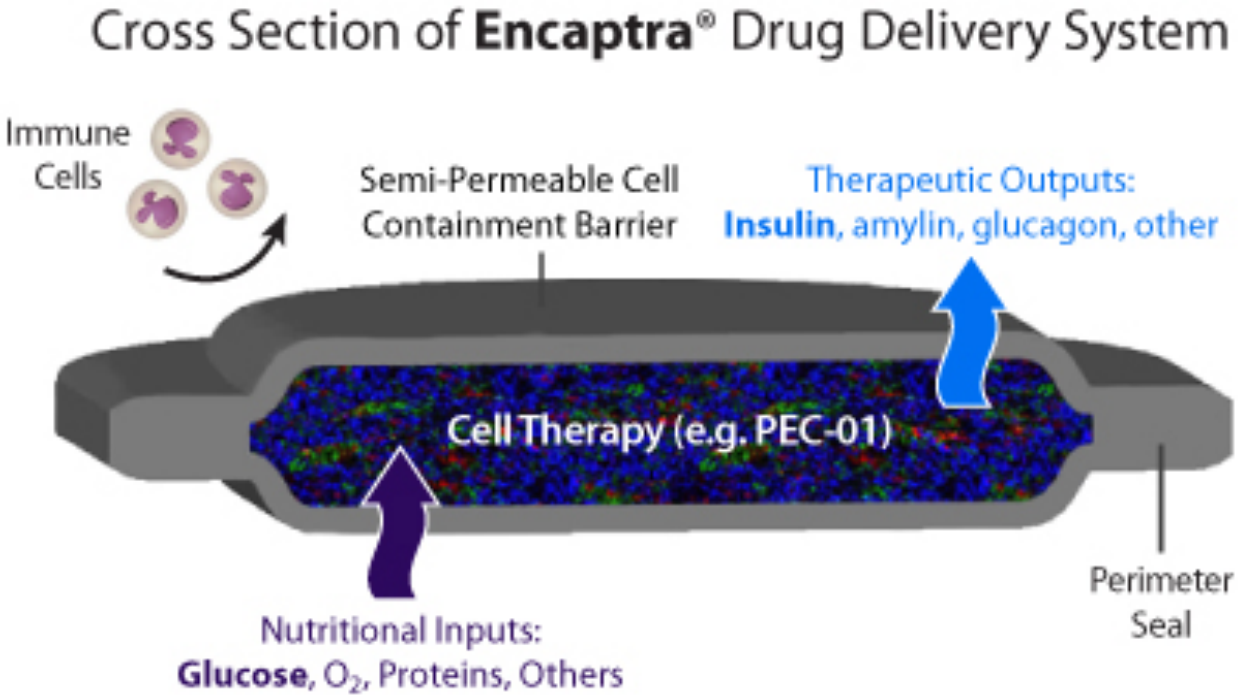
Stem Cell Therapy

HARVARD STEM CELL INSTITUTE
1000 scientists. One goal. Discovering cures.



Reference: https://hsci.harvard.edu/diabetes-program

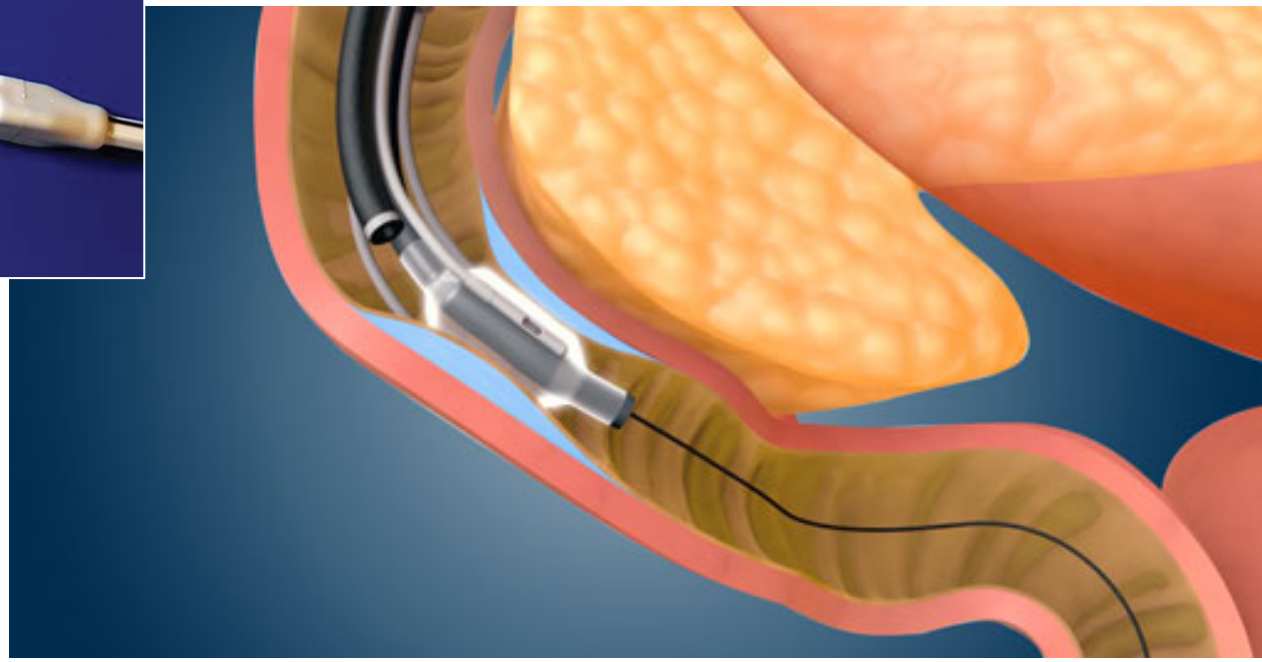
Implantable Cell Therapy



https://viacyte.com

Reference: *https://www.jdrf.org/blog/2013/11/04/study-shows-promise-for-implantation-of-encapsulated-islets-2/*
See also: *http://news.mit.edu/2016/pancreatic-cells-diabetes-treatment-insulin-injections-0125*

Duodenal Mucus Resurfacing



https://www.fractyl.com/revita-dmr/

Reference: Cherrington, et al. "Hydrothermal Duodenal Mucosal Resurfacing Role in the Treatment of Metabolic Disease." Gastrointestinal Endoscopy Clinics of North America, 27(2), 299-311, 2017

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Conclusion

Research opportunities in diabetes care

Areas of opportunity for new research and product development for diabetes care:

a) Non-invasive glucose measurement technologies.

b) Long-term continuous glucose monitoring.

c) Higher fidelity mathematical models for simulation of glucose metabolization in the human body, and

d) Incorporation of more variables, such as exercise and stress, into these physiological models.

e) Control algorithms for automated insulin with higher precision and lower computational complexity.

f) Machine learning algorithms for proactive interventions.

g) New cell therapies.

h) New minimally invasive surgical procedures for T2D remission.

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Muchas gracias!

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https://www.linkedin.com/in/carlosomorales/

Biografía del conferencista

Carlos Omar Morales comenzó su carrera profesional en México como ingeniero en electrónica. Después de estudiar física en la Benemérita Universidad Autónoma de Puebla, Carlos Omar vino por primera vez al INAOE para estudiar óptica en 1992, donde comenzó a explorar computación óptica y descubrió las posibilidades del procesamiento de imágenes digitales para control de calidad en aplicaciones industriales. Con apoyo del CONACYT, Carlos Omar fundó Axon Electro-Fotónica en 1993, la cual fue la primera empresa de su tipo en Latinoamérica. Para 1997, los productos de Inspección Óptica Automática diseñados y fabricados por Axon eran vendidos en Norteamérica, Europa, y Asia. En 1999, Omar vendió su compañía y se mudó a Boston para estudiar Sensores Ópticos y Robótica en el Instituto Tecnológico de Massachusetts (MIT). La empresa COGNEX, actualmente el líder mundial de visión artificial, lo invitó a emigrar a Estados Unidos en forma permanente. Comenzó diseñando sistemas de visión para guiar robots industriales en Detroit, y dos años después trabajó en su primer proyecto médico: un endoscopio digital ingerible. En 2005, se convirtió en el líder de arquitectura de sistemas implantables y monitoreo cardiaco con Boston Scientific. En 2010, fue contratado por la división de Diabetes de Johnson & Johnson como director técnico del Proyecto Páncreas Artificial, y en 2016 fue nombrado director mundial de tecnología avanzada e innovación para la división de diabetes de Becton Dickinson en Boston.

Por 25 años, Carlos Omar Morales ha colaborado en forma cercana con instituciones académicas como INAOE, Northeastern, Harvard, y el Instituto Tecnológico de Massachusetts (MIT). En colaboración con académicos de MIT, Carlos Omar es co-autor del libro “Avances en el diseño de plataformas para familias de productos”, publicado por Springer en 2014.

Para contactarlo: carlos.morales@sloan.mit.edu

Evolución del Páncreas Artificial y Áreas de Investigación para el Futuro

RESUMEN

La condición médica conocida como diabetes mellitus se ha convertido en uno de los más graves problemas de salud mundial de los últimos años. La solución tecnológica conocida como “Páncreas Artificial” se perfila claramente como el nuevo estándar terapéutico para pacientes diabéticos, por lo que ha sido un área de investigación muy activa en los últimos 10 años. Durante este tiempo, avances en las áreas de sensores implantables y sofisticados algoritmos de control automático para dosificación de insulina han hecho posible el lanzamiento del primer producto comercial en 2017. Actualmente, varios fabricantes de equipo médico están finalizando estudios clínicos para solicitar aprobación de agencias reguladoras y unirse a este mercado naciente. Sin embargo, aún queda mucho por hacer. En esta plática, el conferencista presentará un bosquejo histórico del desarrollo de las tecnologías asociadas con el Páncreas Artificial y el estado actual de estos sistemas. Adicionalmente, se presentarán los retos científicos y tecnológicos actuales cuya solución representarían avances adicionales en esta dirección, así como enfoques alternativos que también podrían resolver el problema de control de glucosa. En este problema multidisciplinario convergen la biología, química, electrónica, matemáticas, teoría del control, e informática con el objetivo común de aliviar los terribles problemas asociados con la diabetes.

Duración: 30 minutos de presentación y 10 minutos de preguntas y respuestas.