Algorithme et technologie

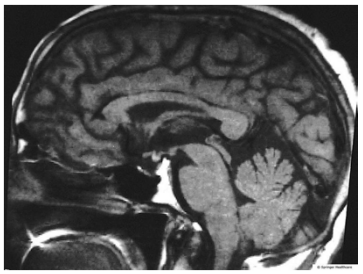
- **CGMS** : capteurs sous-cutanés simples d'utilisation

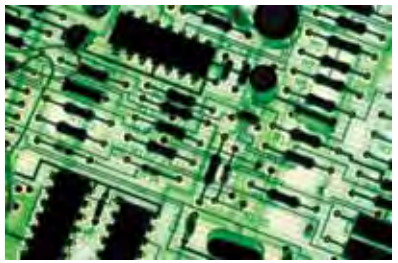
  → Décalage entre la concentration de glucose sous la peau et celle du sang (5-18 minutes)

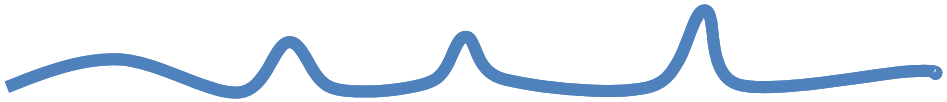
- **Pompes sous-cutanées** : administrent de l'insuline en sous-cutané

  → Délai avant que l'hormone atteigne la circulation sanguine.

Réflexion







« In silico experiments »

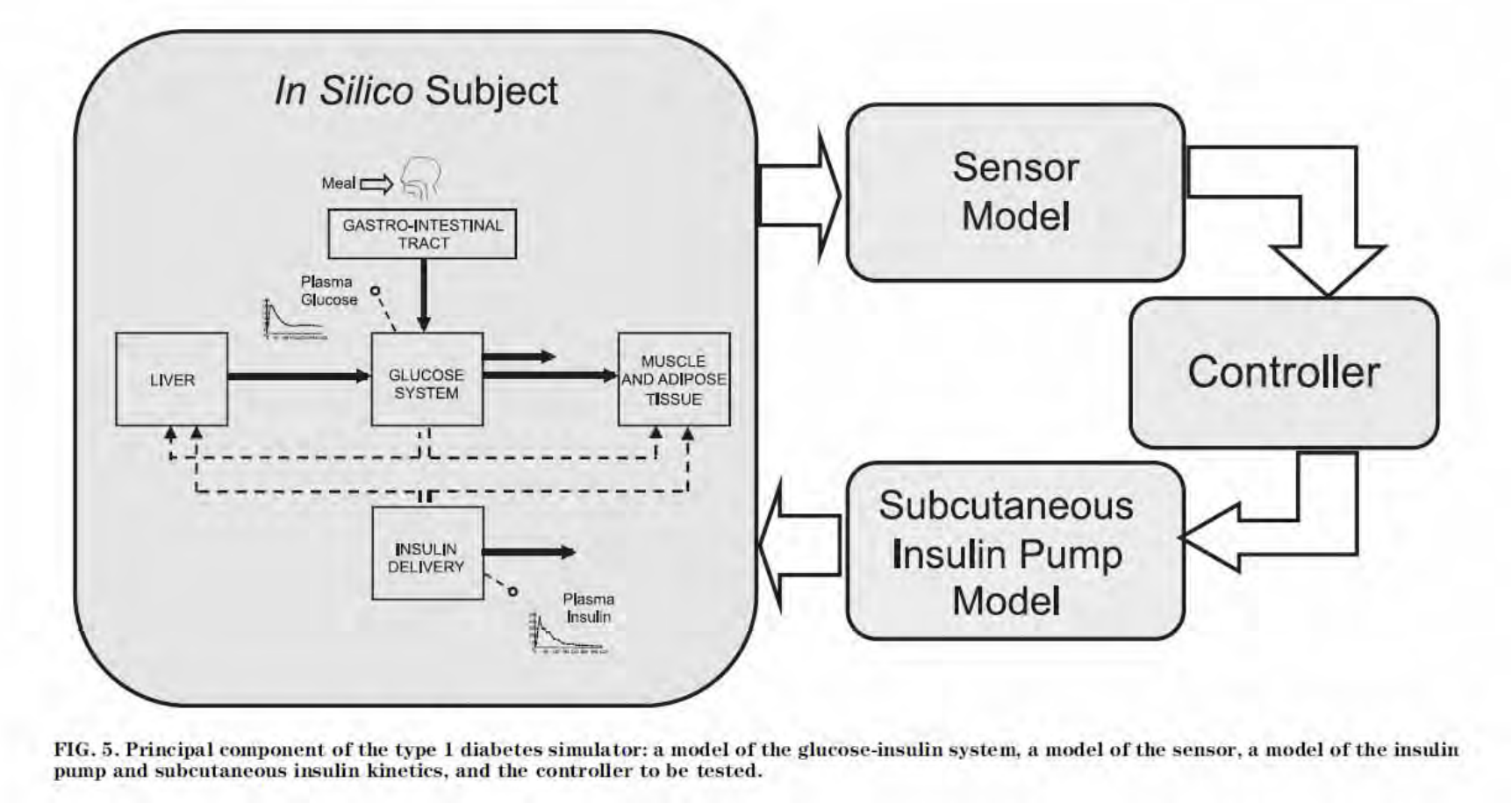


FIG. 5. Principal component of the type 1 diabetes simulator: a model of the glucose-insulin system, a model of the sensor, a model of the insulin pump and subcutaneous insulin kinetics, and the controller to be tested.

Les projets existants de pancréas artificiel sont le fruit d'une innovation incontestable :

→ Remplacement des modèles animaux classiques par des modélisations mathématiques ***« in silico »***

« commande prédictive »

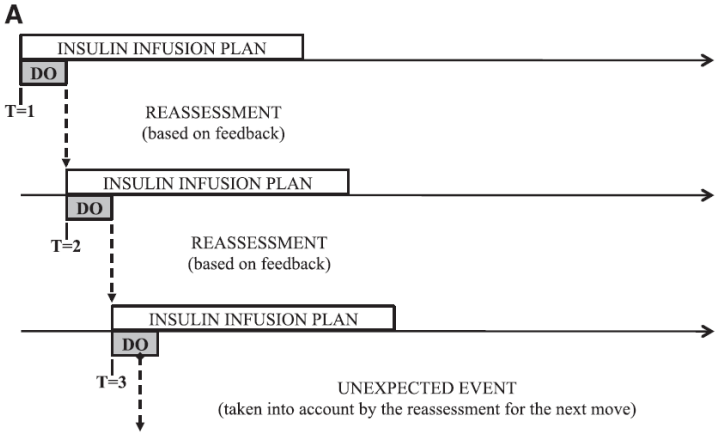


FIG. 4. *A*: The concept of MPC. At each step, future glucose levels are predicted and insulin delivery strategy is mapped several steps ahead. Then, the first insulin delivery step is implemented, and the situation is reassessed with new glucose data. The process is very similar to a chess game in which several moves are planned ahead, and after the implementation of the first move the position is reassessed given the response of the opponent. *B*: The critical stage of the famous chess game between Leonid Stein (white) and Lajos Portisch (black), Stockholm, 1962 (courtesy of Leon Fabri, University of Virginia).

Planification et anticipation minutieuse des étapes à franchir.

Solutions :

- Le pancréas artificiel doit intégrer un **algorithme** qui prend en compte les décalages de temps liés au CGMS et au passage de l'insuline sous-cutanés.
- Les algorithmes les plus élaborés : **« commande prédictive »** permettent de prévoir les actions avec plusieurs étapes d'avance (jeu d'échecs).
- Intelligence artificielle : auto-apprentissage de la machine de la routine quotidienne d'un patient et optimiser la performance en conséquence.

ETUDE pilote

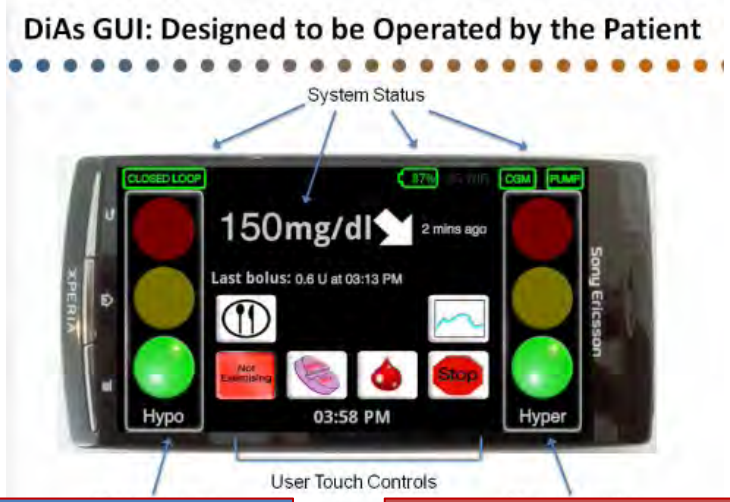
- **ETUDE PILOTE :**
  - 2 patients (1 dans chaque pays : France et Italie)
  - 18 heures à l'extérieur, dont une nuit à l'hôtel
  - Smartphone Xperia de Sony : appareil de contrôle de leur glycémie.

- **Le smartphone** : connecté avec CGMS (du commerce) via bluetooth et transmet les instructions à la pompe à insuline, affiche à écran:
  - mesures de glucose
  - vitesse de perfusion

  Envoie les données à l'équipe de l'étude lui permettant ainsi de surveiller à distance la performance du système.

- **L'algorithme de contrôle** : averti le patient avant de manger ou de faire du sport, contribuant ainsi à éviter d'importantes variations du taux de glucose.

Système pancréas artificiel



Zone d'hypoglycémie

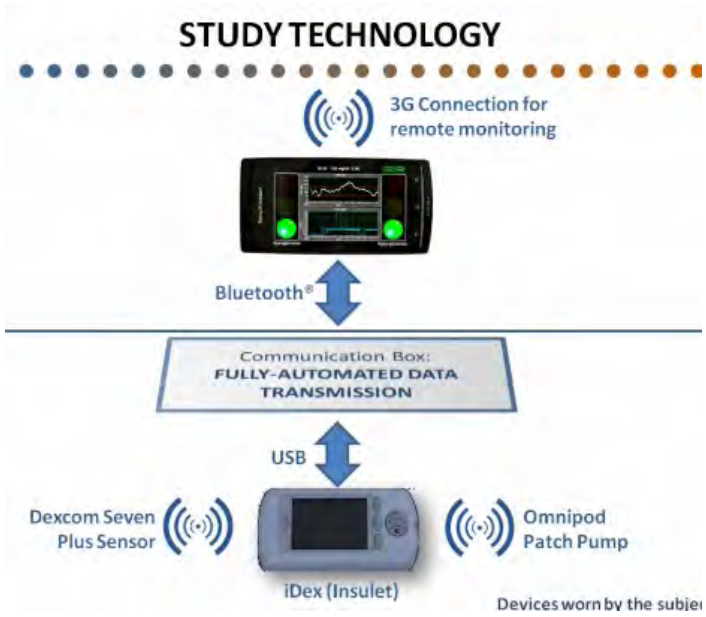
Zone d'hyperglycémie

Tracé CGM

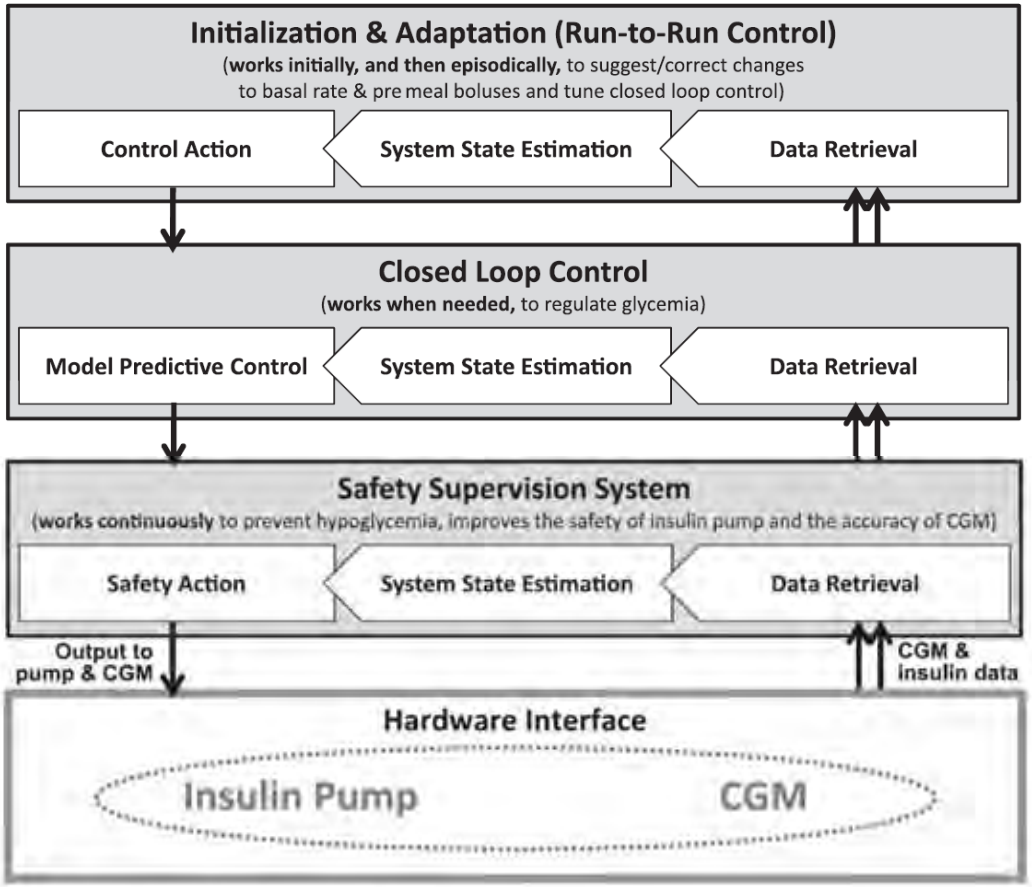
Historique bolus

insuline basale

Profile basal



Modélisation des étapes



'IG. 6. Modular architecture for sequential AP development.

Diabetes Care Symposium

ORIGINAL ARTICLE

Feasibility of Outpatient Fully Integrated Closed-Loop Control

First studies of wearable artificial pancreas

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Claudio Cobelli, PhD[3]
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Patrick Keith-Hynes, PhD[1]
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Marie-Josée Pelletier, MD[2]
Jérôme Place, MSc[2]
Daniela Bruttomesso, MD, PhD[3]
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Alessio Filippi, MD[3]
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Angelo Avogaro, MD, PhD[3]
Francis J. Doyle III, PhD[5]

OBJECTIVE—To evaluate the feasibility of a wearable artificial pancreas system, the Diabetes Assistant (DiAs), which uses a smart phone as a closed-loop control platform.

RESEARCH DESIGN AND METHODS—Twenty patients with type 1 diabetes were enrolled at the Universities of Padova, Montpellier, and Virginia and at Sansum Diabetes Research Institute. Each trial continued for 42 h. The United States studies were conducted entirely in outpatient setting (e.g., hotel or guest house); studies in Italy and France were hybrid hospital–hotel admissions. A continuous glucose monitoring/pump system (Dexcom Seven Plus/Omnipod) was placed on the subject and was connected to DiAs. The patient operated the system via the DiAs user interface in open-loop mode (first 14 h of study), switching to closed-loop for the remaining 28 h. Study personnel monitored remotely via 3G or WiFi connection to DiAs and were available on site for assistance.

RESULTS—The total duration of proper system communication functioning was 807.5 h (274 h in open-loop and 533.5 h in closed-loop), which represented 97.7% of the total possible time from admission to discharge. This exceeded the predetermined primary end point of 80% system functionality.

CONCLUSIONS—This study demonstrated that a contemporary smart phone is capable of running outpatient closed-loop control and introduced a prototype system (DiAs) for further investigation. Following this proof of concept, future steps should include equipping insulin pumps and sensors with wireless capabilities, as well as studies focusing on control efficacy and patient-oriented clinical outcomes.

Diabetes Care 36:1851–1858, 2013

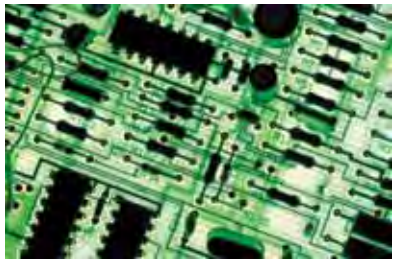
of artificial pancreas technology for home use. To help facilitate this goal, the Food and Drug Administration has recently issued a guidance document to help industry and academic institutions achieve approval for outpatient evaluations of artificial pancreas technology as efficiently as possible. These studies necessarily begin in highly supervised hospital settings and progress through early feasibility, transitional, and, finally, pivotal trials, each with step-wise reduction in monitoring requirements as system performance and functionality are established under normal and stress conditions.

The components of the contemporary closed-loop control have been developed over the past 40 years, including subcutaneous insulin pump technology (1,2), continuous glucose monitoring (CGM) (3,4), and subcutaneous closed-loop control involving CGM coupled with insulin pump via a control algorithm (5–12). A comprehensive review of past and present research is presented in a recent Perspectives in Diabetes (13). However, the artificial pancreas control algorithms used by virtually all studies so far were based on laptop computers wired to a CGM and an insulin pump, a system limiting free movement and too cumbersome to be used beyond hospital

1ère ETUDE de faisabilité

- 20 patients en France, en Italie et aux Etats-Unis
- Résultats: le système a fonctionné de manière fiable et les niveaux de glucose sont restés dans une fourchette sûre.
- L'équipe prévoit maintenant de réaliser d'autres essais dans des hôtels avec un algorithme plus agressif visant à contrôler la glycémie plus précisément.

Etapes franchies en 2013



« In silico experiments »

Medical Android OS

DiAs (Diabetes Assistant)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

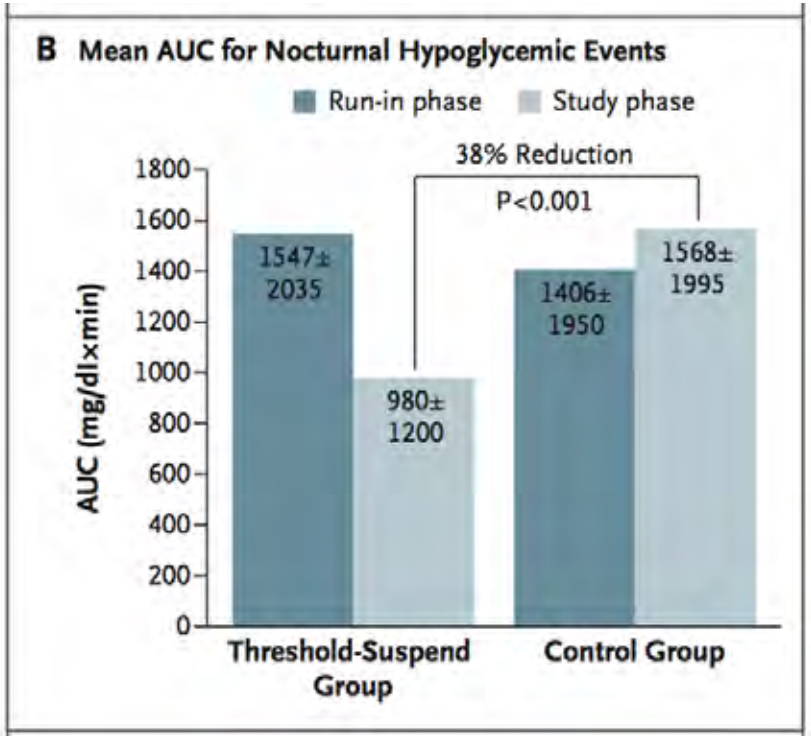
Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia

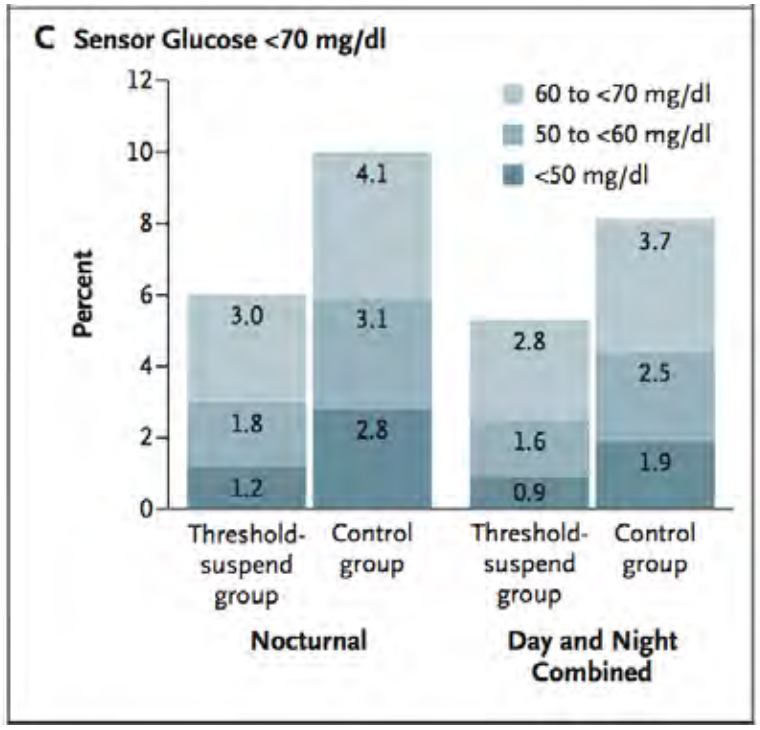
Richard M. Bergenstal, M.D., David C. Klonoff, M.D., Satish K. Garg, M.D., Bruce W. Bode, M.D., Melissa Meredith, M.D., Robert H. Slover, M.D., Andrew J. Ahmann, M.D., John B. Welsh, M.D., Ph.D., Scott W. Lee, M.D., and Francine R. Kaufman, M.D., for the ASPIRE In-Home Study Group*

ABSTRACT

This article was published on June 22, 2013, at NEJM.org.

Hypoglycémies





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Hypoglycémies

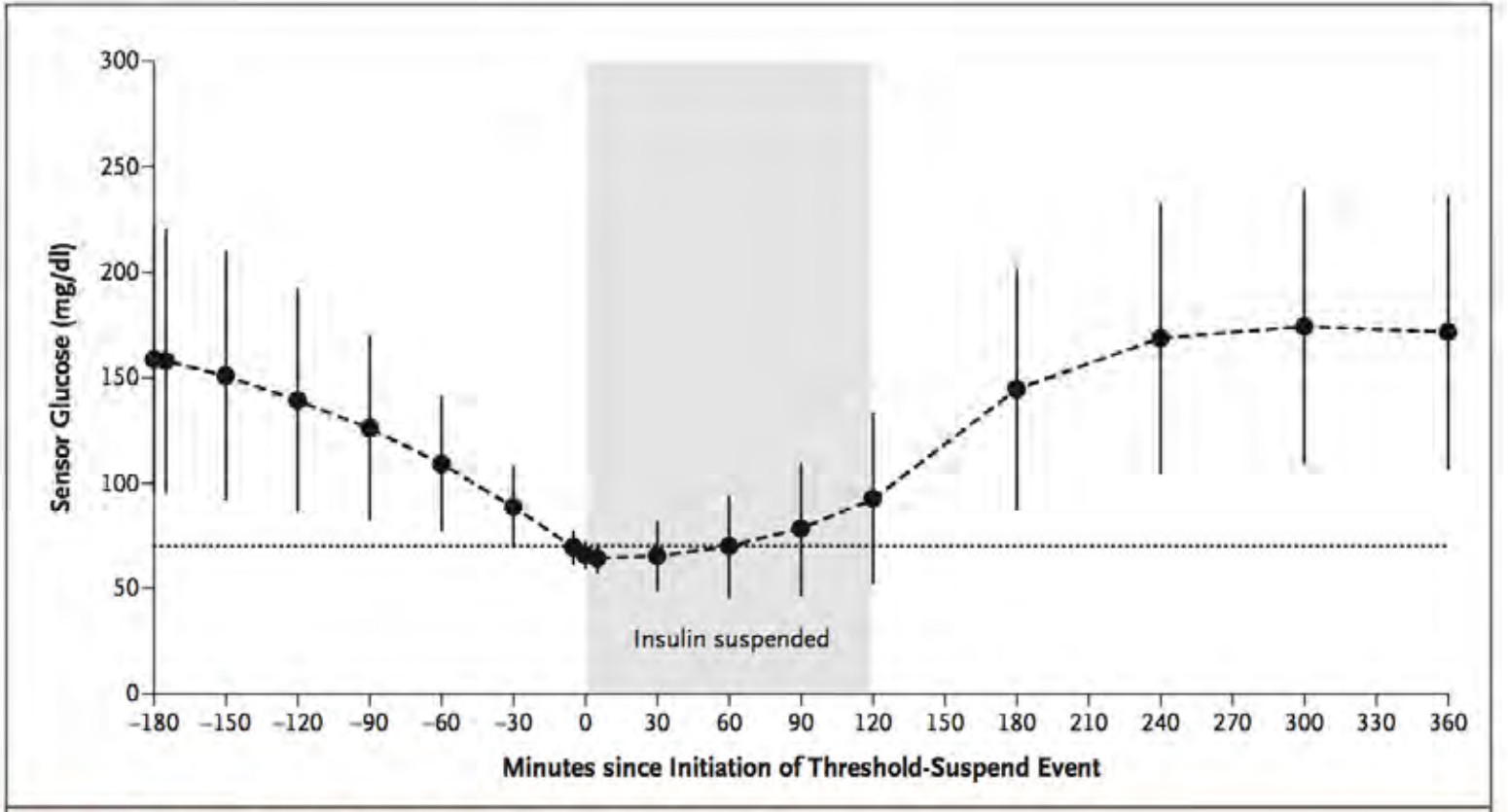


Figure 3. Sensor Glucose Values during Threshold-Suspend Events.

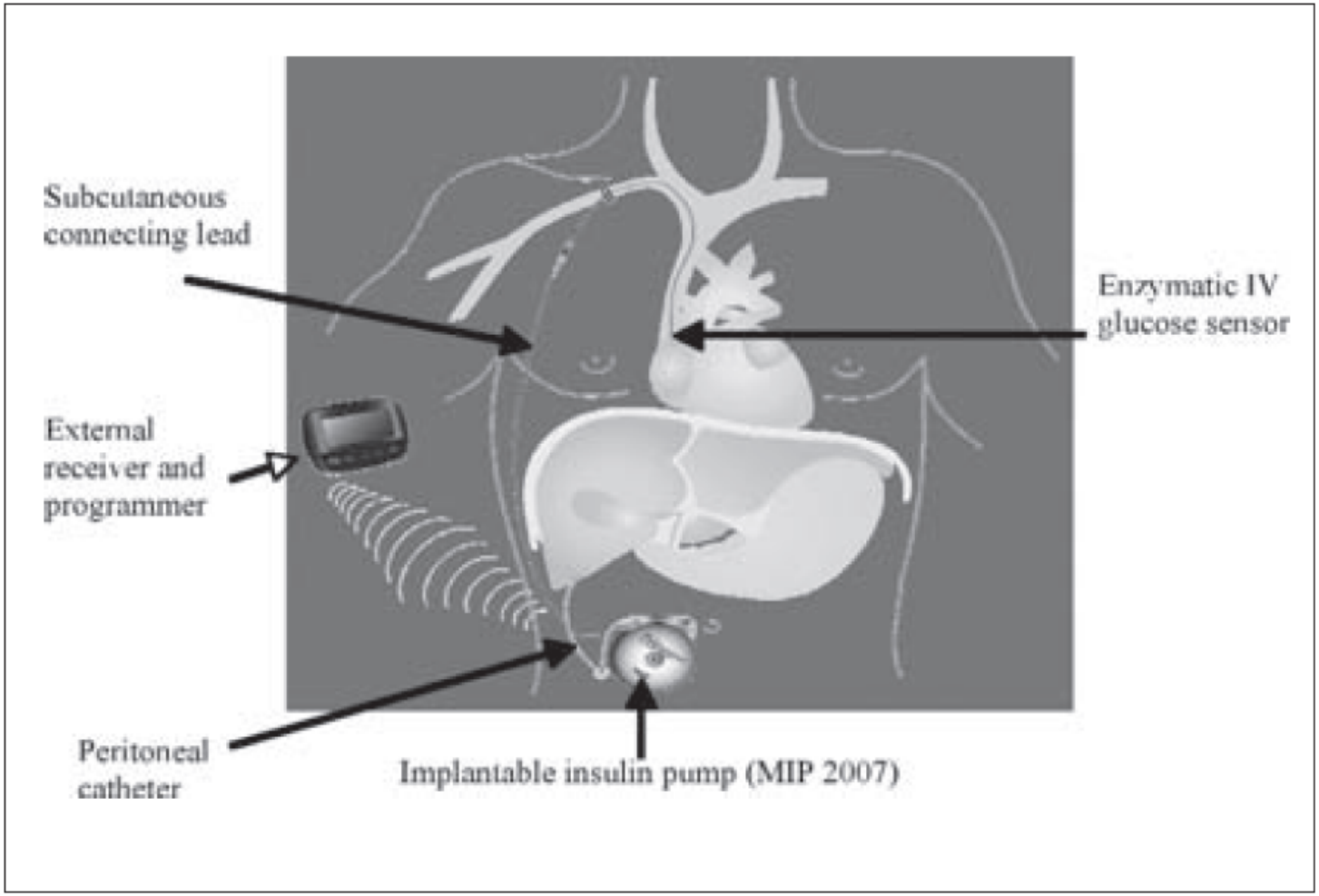
Shown are mean (±SD) sensor glucose values during 1438 nocturnal threshold-suspend events lasting for 2 hours. Time 0 indicates the time that the pump suspension started, and 120 minutes indicates the resumption of insulin delivery. The dotted line is at 70 mg per deciliter. See Figure S3 in the Supplementary Appendix for the percentages of sensor glucose values in various ranges at 2 and 4 hours after the beginning of nocturnal 2-hour threshold-sus-

This article was published on June 22, 2013,
at NEJM.org.

Conclusions

- Plusieurs études multi-centriques dédiées au pancréas artificiel.
- L'équipe de chercheurs français (Montpellier), italiens (Padoue et Pavie) et américains (Californie et Virginie) ont mis en place le premier système en boucle fermée hors hôpital.
- L'algorithme mathématique développé permet le maintien d'une glycémie stable grâce à des adaptations de la délivrance d'insuline coordonnées aux variations du tracé glycémique mesurées et transmises par le CGM.
- Le couplage des dispositifs existants (pompes et CGM) repose sur une application micro-informatique installée sur un téléphone portable de dernière génération.

Pancréas artficiel



Injectable Nano-Network for Glucose-Mediated Insulin Delivery

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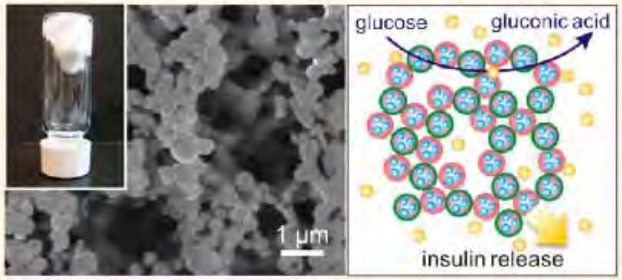
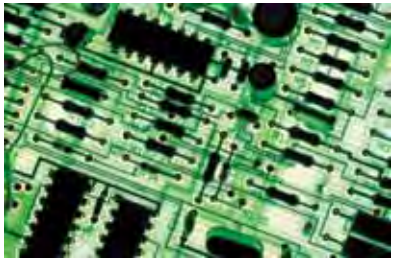
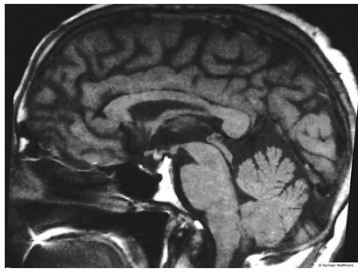
ABSTRACT Diabetes mellitus, a disorder of glucose regulation, is a global burden affecting 366 million people across the world. An artificial "closed-loop" system able to mimic pancreas activity and release insulin in response to glucose level changes has the potential to improve patient compliance and health. Herein we develop a glucose-mediated release strategy for the self-regulated delivery of insulin using an injectable and acid-degradable polymeric network. Formed by electrostatic interaction between oppositely charged dextran nanoparticles loaded with insulin and glucose-specific enzymes, the nanocomposite-based porous architecture can be dissociated and subsequently release insulin in a hyperglycemic state through the catalytic conversion of glucose into gluconic acid. *In vitro* insulin release can be modulated in a pulsatile profile in response to glucose concentrations. *In vivo* studies validated that these formulations provided improved glucose control in type 1 diabetic mice subcutaneously administered with a degradable nano-network. A single injection of the developed nano-network facilitated stabilization of the blood glucose levels in the normoglycemic state (<200 mg/dL) for up to 10 days.



KEYWORDS: drug delivery · diabetes · insulin · glucose-responsive · closed-loop · nano-network





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