Abstracts

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Dosing Accuracy of Two Disposable Insulin Pens, SoloSTAR and FlexTouch, according to New International Organization for Standardization Requirements

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Objective:
Recently, existing insulin pen options have been extended by the European approval of FlexTouch® (FT; Novo Nordisk, insulin aspart), a prefilled, spring-loaded insulin pen. Furthermore, substantial modifications have been made to the International Organization for Standardization (ISO) requirements for needle-based injection systems. This study (supported by Sanofi) aimed to compare the widely used, manually operated disposable pen SoloSTAR® (SS; Sanofi, insulin glulisine) with FT, according to new ISO 11608-1:2012 requirements for dose accuracy.

Method:
A total of 60 pens from one batch of each pen type were used to test dosing accuracy at minimum (1 U), middle (40 U), and maximum (80 U) doses. Following new ISO requirements, each dose was delivered from the front 1/3, middle 1/3, and rear 1/3 of the pen cartridge in a randomized fashion, with one single measurement of each target dose per pen. Statistical analysis was performed using Student's *t*-test with a 95% confidence level.

Result:
Both insulin pens revealed excellent dosing accuracy, with doses delivered within the limits set by ISO 11608-1:2012. Average values of actual doses of SS were closer to target dose than with FT for all three doses. Differences were statistically significant at middle (p = .009) and maximum (p = .008) dosage levels. Average relative deviation of the actual dose from the target dose, for SS and FT, respectively, was +2.69% and +3.91% at minimum, -0.31% and -0.85% at middle, and -0.45% and -0.84% at maximum dose.

Conclusion:
This study demonstrates the excellent dosing accuracy of SS compared with FT, indicating that the spring-loaded mechanism of FT does not translate into a dosing accuracy advantage versus the manually operated SS.

Eye Safety Using TOUCH Tears Device

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Background:
Diabetes management requires self-monitoring of blood glucose (SMBG). Current methods pose several challenges, most notably, pain from obtaining the sample, which could lead to patient noncompliance with SMBG. An original, tear glucose sensor is presented as an alternative to current SMBG methods. The device was tested to correlate to blood glucose, and the resulting effects on the eye were examined.

Methods:
Four rabbits were tested for blood and tear glucose levels over 7 months. The rabbits were monitored to determine if the sensor was a source of short- or long-term irritation. Following blood sampling, the sensor was briefly applied on right sclera in the nasal and temporal quadrants. The left eye served as the control. Lissamine dye was then applied to both eyes, and photographs were taken. Histogram analysis was performed to evaluate any differences.

Results:
A control experiment showed a 10.71% relative standard deviation (RSD) difference in the nasal quadrant and a 12.66% RSD difference in the temporal quadrant between a right eye with debris on it and a debris-free right eye in the red channel. In the longitudinal study, the right eye displayed an average of a 0.467 tonal value decrease per week more than the left eye.

Conclusion:
The results from the histogram analysis and Excel show that there is no substantial difference between the control eye and the eye to which the sensor was applied. The longitudinal study suggests that there is no significant damage to the eye over time after repeated sensor use.

Effectiveness of Telemedicine for Weight Management in the MOVE! Program

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Objective:
The rate of obesity has reached epidemic proportions, including in our United States veterans (35.5% in 2002–2006). These high rates of obesity have led to the creation of a comprehensive approach to weight management for the veteran population called the MOVE! Weight-Management Program. This study examined the effectiveness of live videoconferencing technology in delivering weight management treatment to groups of veterans in rural populations. (The contents herein do not represent the views of the Department of Veterans Affairs or the United States government.)

Method:
A retrospective cohort study was conducted by chart extraction of data for the years 2008–2010. Treatment included a 12-week MOVE! class series delivered using clinical video telehealth. Data were extracted from the time of baseline weight to one year after baseline weight for the MOVE! group (n = 60) and control group (n = 60) without MOVE! treatment.

Result:
The mean (± standard error of the mean) difference in changes in weight between the groups after adjusting for differences in baseline characteristics was -5.5 ± 2.7 kg (95% confidence interval = -8.0 to -3.0; $p < .0001$), indicating weight loss in the MOVE! group. One year after baseline measurements, the control group gained an average of 2.0 kg, while those completing 1–4 sessions gained 0.8 kg by contrast, those completing 5–8 sessions lost 2.5 kg, and those completing 9–12 sessions lost an average of 5.3 kg. The mean difference between the control group and the MOVE! completer group (9–12 sessions) was -7.3 kg one year after baseline.

Conclusion:
The results indicate that live videoconferencing is an effective method to provide the MOVE! Weight-Management Program to rural Veterans Affairs clinics. Weight loss was maintained for up to one year after treatment. Extending the number of MOVE! sessions after the initial 12 weeks may be beneficial for continued weight loss.

In Vitro Performance Evaluation of a Fluorescence Biosensor for Glucose Sensing: Response and Interference

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Objective:
Recent studies have indicated that implantable optical biosensors based on Förster Resonance Energy Transfer (FRET) can provide high sensitivity in quantifying glucose. However, a standard set of *in vitro* approaches for evaluating optical biosensor response and specificity to glucose has not been established. Towards this end, we reviewed existing glucose meter standards and prior FRET biosensor studies to identify key performance characteristics and test methods. A FRET-based glucose sensor was then fabricated and evaluated with a battery of quantitative, objective methods.

Method:
The biosensor was based on dextran and concanavalin A, labeled with long-wavelength fluorophores. Glucose concentration was calibrated based on donor fluorescence in the 590–617 nm range. Several metrics were determined, including limit of detection, response time, linearity, reversibility, and accuracy. A Clarke error grid analysis was used to evaluate the clinical significance of prediction errors. Interference screening using common sugars followed by dose-response measurements were implemented through paired-difference testing. Several methods for interpreting this data were compared.

Results:
Our biosensor demonstrated a mean error of less than 11% and a limit of detection of 30 mg/dl. A 90% response time of 15 min was observed for a 120 mg/dl glucose change. Maltose concentrations of 40 mg/dl or less produced error levels of less than 10% at the 120 mg/dl glucose level. However, an intermediate maltose concentration of 167.5 mg/dl caused 40 and 114% prediction errors at 120 and 50 mg/dl glucose, respectively.

Conclusion:
This study provides strong evidence of the performance of our FRET-based glucose biosensor. While *in vivo* data are critical for establishing device effectiveness, the test battery implemented here can provide useful insights into device performance and facilitate inter-comparison and optimization.

Evaluation of a Local-Model-Based Calibration Algorithm for Continuous Glucose Monitoring in Subjects with Type 1 Diabetes

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Objective:
Previous works in a limited number of subjects [either healthy or with type 1 diabetes mellitus (T1DM)] showed that local-model-based calibration algorithms (CAs) may improve accuracy of continuous glucose monitoring (CGM). Here, further evaluation is carried out in a larger cohort of patients with T1DM in the postprandial and hypoglycemic states.

Methods:
Continuous glucose monitoring data from the Medtronic Paradigm® Veo™ and paired reference plasma glucose (PG) were collected from two studies. In study 1, 12 patients underwent four mixed-meal tests on different occasions. In study 2, two hypoglycemic clamps were conducted per patient, who simultaneously wore two devices. A total of 19 subjects with T1DM were studied, giving rise to 68 time series, each with a duration of approximately 8 h (6557 paired samples). A dynamic PG prediction model from the CGM electrical signal was identified and integrated into a CA. The prediction model was based on the combination of predictions given by local models that represent, to a variable extent, different metabolic conditions or sensor–subject interactions. An eight-fold cross validation was performed using population and individual normalization of signals.

Results:
Considering population normalization, the new CA improved the accuracy of the estimations as compared with the manufacturer's estimations: mean absolute relative difference (MARD) 18.4% ± 5.2% versus 23.8% ± 16.3% ($p < .05$, analysis of variance). Individual normalization allowed for the identification of two different sensor dynamics for different ranges of normalized glucose, and MARD further improved (13.1% ± 2%; $p < .05$).

Conclusions:
Local-model-based CAs improve accuracy of CGM, either with population or individual normalization. As expected, accuracy is improved to a greater extent when individual normalization is used. However, in this case, estimations of normalization parameters are needed and further validation is required.

Precise and Continuous Subcutaneous Delivery of Exenatide with ITCA 650 Provides Consistent and Sustained Glycemic Control in Metformin-Treated Type 2 Diabetes

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Objective:
We aim to optimize long-term glycemic control, tolerability, and adherence with continuous linear delivery of precise doses of exenatide using ITCA 650 subcutaneous osmotic minipumps and to measure dose-proportional exposure and clinical effects.

Methods:
A highly sensitive, *in vitro* release method that closely mimics human conditions was developed to produce ITCA 650 devices delivering daily doses of 20, 40, 60, and 80 mcg over 3 months. The performance of ITCA 650 was evaluated for up to 48 weeks in a phase 2 dose-ranging study involving 155 type 2 diabetes patients. Patients were randomized to ITCA 650 at 20 or 40 mcg/day or twice-daily exenatide injections (EXinj) for 12 weeks and were subsequently rerandomized to the same or higher dose (60 or 80 mcg/day) of ITCA 650 for the remainder of the study. Patients randomized to EXinj subsequently received 40 or 60 mcg/day of ITCA 650.

Results:
Dose-proportional exenatide exposure was demonstrated with ITCA 650 over 48 weeks. Week 12 hemoglobin A1c (HbA1c) changes were -1.0%, -1.0%, and -0.8% versus baseline (8%) for ITCA 650 at 20 and 40 mcg/day and EXinj; nausea was less frequent with 20 than 40 mcg/day and of shorter duration than EXinj. At week 24, HbA1c was -1.4% from baseline with ITCA 650 at 60 and 80 mcg/day ($p < .0001$); 60 mcg/day offered better glycemic control than 20 or 40 mcg/day and was better tolerated than 80 mcg/day.

Conclusion:
In vitro release accurately predicted long-term exenatide exposures with ITCA 650. In phase 2, ITCA 650 delivered effective exenatide doses to control glycemic parameters and was well tolerated. Subcutaneous placement of ITCA 650 virtually ensures 100% adherence. Phase 3 studies will evaluate a treatment regimen with ITCA 650 at 20 mcg/day for 3 months followed by 6-month maintenance doses of 60 mcg/day.

Early Hypoglycemia Alarm Systems Based on Recursive Autoregressive Partial Least Squares Models

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Objective:
Hypoglycemia is a major challenge of artificial pancreas systems. Early alarms that warn of the potential of hypoglycemia are essential and should provide enough time to take action to avoid hypoglycemia. Many alarm systems proposed in the literature are based on interpretations of recent trends in glucose values. In the present study, subject-specific linear models are introduced as a better alternative to capture glucose variations and predict future blood glucose concentrations. These models are then used in early hypoglycemia alarm systems that notify patients to take action to prevent hypoglycemia before it happens.

Method:
A recursive autoregressive partial least squares (RARPLS) modeling algorithm is proposed to analyze the data from a continuous glucose monitoring system and predict future glucose values. In this model, previous glucose concentrations are used as input to model, and future glucose concentrations, response variables, are predicted. The RARPLS models developed are recursively updated at each sampling step with a moving window size of 1 day in order to adapt the changes in the system. RARPLS models are tested retrospectively using type 1 diabetes subject data collected at the University of Illinois, Chicago. The algorithm is also tested *in silico* prospectively using a Food and Drug Administration-approved metabolic simulator. A Savitzky–Golay filter is used to reduce noise in the continuous glucose monitoring system data. RARPLS models are evaluated in terms of root mean square error (RMSE) and sum of squares of glucose prediction error (SSGPE) and compared with previously proposed time series algorithms. For a continuous glucose monitoring sampling rate of 5 min, 4.45 RMSE and 4.04% SSGPE are obtained for six-step-ahead glucose predictions for RARPLS. For nonrecursive autoregressive partial least squares, RMSE is 6.17 and SSPGE is 4.55%. For nonrecursive and recursive time series models [autoregressive moving average (3,1)], SSPGEs are reported as 10.32% and 5.56%, respectively.

Bayrak cont. ⟶

Bayrak cont. ⟶

Result:
The alarm algorithm is developed based on the future glucose predictions from the RARPLS algorithm. Alarm systems developed are tested retrospectively both using the type 1 diabetes patient data and *in silico* simulations. The performance of alarm systems based on autoregressive recursive PLS is evaluated. Out of 69 hypoglycemia events, 62 of them are detected with average detection time of 28.25 min. Sensitivity of 90% is reported for the early alarm based on six-step-ahead predicted glucose values. False alarm rate is also reported as 0.36 false positive/day.

Conclusion:
The RARPLS algorithm enables the dynamic adaptation of models to intersubject/intrasubject variation and glycemic disturbances. The RARPLS models provide satisfactory glucose prediction with relatively small error. The alarm systems based on RARPLS models have a good performance in prediction of hypoglycemia and, ultimately, in prevention of its occurrence.

Nocturnal Continuous Glucose Monitor Signal Attenuation: An Outpatient Study

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Objective:
Continuous glucose monitors (CGMs) provide real-time blood glucose concentrations that are essential for automated treatment of individuals with type 1 diabetes. Miscalibration, noise spikes, dropouts, or pressure applied to the site (i.e., rolling over in bed) can cause invalid glucose signals. Mistakenly trusting these readings can lead to improper action in real time and confounded metrics in retrospect. We focus on the problem of nocturnal sensor attenuation (NSA) in real time and retrospectively.

Method:
Generally, the start of a NSA is characterized by a sudden decrease in glucose levels that violates physiological limits on rate of change. The end of a NSA occurs at least 15 min later and has an increasingly negative rate of change. The *real-time* algorithm detects the start and end of the NSA using CGM rate of change (first derivative), Kalman filter measurement likelihood, rate of change of CGM increase rate (second derivative), and maximum attenuation time window. The retrospective detection assumes that NSAs are large, high-frequency, negative disturbances to glucose concentrations and uses a weighted least squares fit to the CGM readings and a trust calculation to determine the weighting applied to each reading.

Result:
Both real-time and retrospective detection techniques were tested on the same set of outpatient data of over 100 nights. Because reference glucose values are not available overnight in an outpatient setting, the number of false positives were determined by expert professionals who visually interpreted the data and further fine-tuned the method to better detect the attenuations.

Conclusion:
These methods are useful for detection of and removing NSAs in CGMs. The number of false positives in the real-time NSA prediction method are decreased by fine-tuning the parameter threshold values. Retrospective detection was satisfactory.

ClampArt: Improving the Quality of Glucose Clamps with a Novel, Conformité Européenne-Marked Device

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Objective:
Glucose clamps characterize the time-action profiles of blood glucose (BG)-lowering agents provided that BG levels are kept close to the target throughout the experiments. In manual clamps, BG measurement and adjustments of glucose infusion rates (GIRs) usually occur only every 3–10 min. Automated clamps not only offer a bias-free assessment, but should also improve clamp quality by measuring BG continuously and adapting GIR every minute. However, most automated clamps use the Biostator, a device developed in the 1970s with obvious technical limitations. In this proof-of-concept study, we investigated the performance of ClampArt, a newly developed automated glucose clamp device that uses state-of-the-art technology for continuous BG measurements, GIR calculation, and administration. ClampArt is Conformité Européenne marked and licensed for use in Europe.

Method:
Nineteen subjects received rapid-acting or basal insulin analogs under clamp conditions using ClampArt. The results were compared with previous data obtained with the Biostator using the same insulins in the same patients.

Result:
Technical errors occurred significantly less with ClampArt versus the Biostator (downtime 3% versus 10% of the experiments; $p < .0001$). Furthermore, BG measurements were significantly more reliable with ClampArt as indicated by smaller deviations of the devices' BG level from laboratory reference BG measurements (1.66 versus 1.97 mg/dl; $p < .05$). Blood glucose fluctuations were smaller with ClampArt than with the Biostator [mean maximum deviation of the reference BG from the clamp level 14.0% versus 18.5% ($p < .05$) and minimum deviation 14.7% versus 16.8% (not significant)].

Conclusion:
In comparison with the Biostator, ClampArt significantly improves glucose clamp quality by reducing technical downtimes and increasing the quality of BG measurements and GIR regulation. Further improvements of ClampArt are planned, e.g., through better clamp algorithms.

Can the STAR Protocol Generalize Effectively? Initial Clinical Results in New Zealand and Hungarian Intensive Care Units

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Objective:
We report initial clinical results of the STAR glycemic control protocol at an independent intensive care unit (ICU) in comparison with its first implementation.

Method:
Fifteen pilot episodes (1168 h) using the STAR (Stochastic TARgeted) at Kálmán Pándy Hospital (Gyula, Hungary) are compared with 38 episodes (3763 h) in Christchurch Hospital. Gyula administers insulin as a constant infusion and Christchurch as boluses. Nutrition was controlled by STAR. Measurements were every 1 to 3 h per protocol. Performance was assessed by percentage of (hourly resampled) blood glucose (BG) measurements in glycemic bands for the cohort, safety was assessed by numbers of patients with BG < 2.2 mmol/liter (severe) and percentage BG < 4.0 mmol/liter, and clinical effort was assessed by measurements per day.

Results:
Effort was similar, with 12.8 and 12.4 measurements/day in Gyula and Christchurch, respectively. For performance in Gyula, cohort BG was 6.6 (5.6–7.7) mmol/liter, with 72.7% and 80.43% of BG in the 4.4–7.0 and 4.4–8.0 mol/liter bands, respectively. Also in Gyula, cohort BG was 6.0 (5.4–6.8) mmol/liter, with 72.7% and 80.43% of BG in the 4.4–7.0 and 4.4–8.0 mol/liter bands, respectively, with 2.2% BG < 4.0 mmol/liter. For performance in Christchurch, cohort BG was 6.1 (5.6–6.8) mmol/liter, with 77.8% and 89.43% of BG in the 4.4–7.0 and 4.4–8.0 mol/liter bands, respectively, with 0.87% BG < 4.0 mmol/liter. There were no severe hypoglycemic events. Performance differences were due to one patient in Gyula. Insulin dosing was similar: 2.5 (1.0–4.5) and 3.0 (1.5–4.5) U/h for Gyula and Christchurch, respectively.

Conclusion:
STAR was equally effective in an independent ICU across geographically distinct clinical units, patients, and clinical practice. No significant difference was seen between using constant infusion or bolus insulin delivery. Overall, the STAR framework was readily transposed and achieved very good glycemic control.

User Performance Evaluation of the CONTOUR NEXT Blood Glucose Monitoring System with the CONTOUR NEXT Test Strip

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Objective:
We evaluated performance and ease of use of the CONTOUR® NEXT blood glucose monitoring system (BGMS), which includes second chance sampling and plain language messages, in the hands of health care professionals (HCPs) and untrained users.

Method:
A total of 226 subjects were enrolled (224 completed) aged 23–78 years with type 1 (n = 54) or type 2 (n = 170) diabetes at two clinical sites. Subjects naive to the BGMS tested capillary glucose from their fingertip and palm, and HCPs tested subjects' capillary and venous samples. The BGMS results were compared with YSI reference results. Accuracy was assessed using proposed and current ISO 15197 criteria. Subjects completed questionnaires on ease of use and diabetes management.

Result:
A total of 99.1% of subject finger stick and 96.8% of subject palm results met proposed criteria, 99.5% of subject finger stick and 99.1% of subject palm results met current ISO criteria, and 100% of venous results met both proposed and current criteria. Regression analyses demonstrated strong correlation between BGMS and reference results (adjusted R^2 > 96% for all regressions). For Parkes consensus error grid analysis, 99.5% of subject finger stick results, 99.1% of subject palm results, and 100% of venous results were within zone A (remainder in zone B). Questionnaire results showed that the majority of subjects agreed or strongly agreed the that BGMS was easy to use (94.6%), user instructions were easy to understand (86.2%), meter display was easy to read (96.4%), it was easy to see and understand the results (94.6%), and the meter summary screen could help them understand how they are doing with their diabetes (93.8%).

Conclusion:
The CONTOUR NEXT BGMS met current (2003) and proposed ISO 15197 accuracy criteria and demonstrated ease of use in the hands of untrained users.

Microfocus Computed Tomography: A Novel Method to Assess Insulin Distribution in Subcutaneous Adipose Tissue

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Objective:
Distribution of injected insulin depots in adipose tissue might be an important parameter to predict insulin absorption and onset of insulin action. The aim of the current experiment was to assess insulin distribution measured as surface-to-volume ratio using microfocus computed tomography (μCT).

Method:
Insulin aspart with 10% contrast agent (Iopamiro) added was injected either as a single bolus of 18 IU (1 × 18 IU) or divided into nine boluses of 2 IU (9 × 2 IU) in 12 abdominal skin flaps, explanted maximally 5 h before measurement. Immediately after injection, skin flaps were scanned with μCT. Surface and volume of the resulting subcutaneous liquid depots were measured using three-dimensional reconstruction of μCT images. The volume of interest was selected by a region-growing algorithm; after manual selection of a spot of high-intensity, regions with decreasing levels of intensity were added to the volume of interest until the predefined injection volume (180 ± 1.8 μl) was reached.

Result:
The two injection strategies were applied using the same total volume, and the calculated surface-to-volume ratios of the subcutaneous insulin depots were directly compared with each other. While the measured mean volume of 9 × 2 IU was similar to 1 × 18 IU (179.6 ± 0.96 vs 180.6 ± 0.70 mm^3; $p = .01$), the mean surface was significantly larger (703.6 ± 83.8 vs 396.6 ± 101.1 mm^2; $p < 0.01$). Thus the distributed injection strategy enhanced the surface-to-volume ratio by a factor of 1.8 (3.9 ± 0.48 versus 2.2 ± 0.57).

Conclusion:
Microfocus computed tomography can quantitatively compare the surface-to-volume ratio of subcutaneous insulin depots. For the distributed injection, we found a higher surface-to-volume ratio. Higher surface-to-volume ratio might enhance substance absorption, as a larger surface involves more capillaries. Microfocus computed tomography is a method to analyze injected liquid depots in adipose tissue and describe distribution properties of other injectable drugs.

Insulin Pump Use in 1182 Young Children in the Type 1 Diabetes Exchange Clinic Registry Is Associated with Lower Hemoglobin A1c Levels

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Objective:
In young children with type 1 diabetes mellitus (T1DM), continuous subcutaneous insulin infusion (CSII) has potential advantages over multiple daily injections (MDIs), given irregular eating habits and need for frequent, small insulin doses. The aim of this analysis was to compare clinical outcomes in CSII users versus nonusers in children <6 years of age.

Methods:
We compared demographic and clinical outcome data for 1182 children <6 years of age enrolled in the T1DM Exchange Clinic Registry at 52 U.S. diabetes centers.

Results:
Overall, 390 (33%) were using CSII and 792 (67%) were using MDIs. Mean age (±standard deviation) was 3.7 ± 1.2 years, and mean T1DM duration was 1.4 ± 1.2 years. Continuous subcutaneous insulin infusion use rose from 8% in participants with T1DM duration <1 year to 30% at 1 year and 61% at ≥3 years' duration. In 828 participants with T1DM duration ≥1 year, mean hemoglobin A1c (HbA1c) was lower in CSII users (7.8 ± 0.9; n = 359) than in MDI users (8.4 ± 1.1; n = 469), both overall (p < .001) and when adjusting for T1DM duration, household income, parental education, and number of self-monitored blood glucose readings per day (p < .001). Among 145 CSII users with sufficient HbA1c data, mean HbA1c in the year before pump initiation was higher than HbA1c in the year after pump initiation (8.9 ± 1.2 versus 7.8 ± 0.8; p < .001). A diabetic ketoacidosis (DKA) event (defined as hospitalization with ketones) occurred in 9% (12/134) using CSII ≥1 year and in 7% (35/479) using MDIs (p = .06 when adjusting for HbA1c and socioeconomic status).

Conclusions:
Continuous subcutaneous insulin infusion is a very effective means of achieving improved control of T1DM without increasing the risk of DKA in preschool children with T1DM.

FTY720-Release-Kinetics-Driven Increases in Blood Vessel Growth from Nanofiber Scaffolds for Alternate-Site Islet Transplant

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Objective:
These studies aim to determine the correlation between FTY720 release rate and blood vessel growth, controlled by the choice of polylactic-co-glycolic acid (PLAGA) polymer component. The health of islets *in vitro* using several polymers with and without direct nanofiber contact is also examined.

Method:
The polylactic-co-glycolic acid/polycaprolactone (PCL) fibers were electrospun either with 50:50 or 85:15 PLAGA or other polymers and loaded with FTY720. Images are obtained from dorsal skinfold window chambers.

Result:
Liquid chromatography–mass spectrometry-assisted *in vitro* release data indicate a similar first phase of release; however, the 50:50 formulation continues on this burst release longer than the 85:15 formulation. A total of 77% of the loaded FTY720 remains in the 50:50 formulation, while 82% remains in the 85:15 formulation at 7 days. Blood vessel diameter enlargement correlates with fractional release (125% versus 50%, 85:15 versus 50:50 at day 7). Human islets tested with PLAGA/PCL nanofibers displayed a decrease in viability (propidium iodide and fluorescein diacetate) compared with the media-only controls (68% PLAGA/PCL verses 78% media only). Other polymer types, polyhydroxybutyrate and polyhydroxybutyrate-co-valerate (PHBV), performed better in this assay (75% and 79%, respectively).

Conclusion:
A decrease in culture media pH, driven by acidic PLAGA monomers, may contribute to a loss in islet viability with PLAGA fibers, which is less of an issue with PHBV. However, aggregation of several polymer types indicate that contact with the nanofiber morphology promotes islet health. FTY720 releases at a rate that can drive microvessel growth perhaps by modulation of the inflammatory milieu surrounding the implant. Together, these data demonstrate the ability to control *in vivo* responses based on selection of polymers loaded with FTY720 to suit conditioning of alternate transplant sites.

Insulin Sensitivity Decreases during Menstrual Flow in Premenopausal Women with Type 1 Diabetes Mellitus

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Objective:
It is well recognized clinically that insulin requirements change according to the menstrual cycle in a subset of patients with type 1 diabetes mellitus (T1DM). However, data are still anecdotal, with no large-scale studies in T1DM and limited organized approaches that include this factor in glycemic management. One study in premenopausal women without diabetes demonstrated a decrease in insulin sensitivity (SI) beginning near ovulation and peaking during the second-half (or luteal phase) of the menstrual cycle; estradiol and progesterone levels have been positively associated with measures of SI. We propose to compare hospital SI estimates in T1DM women versus men.

Method:
Eleven T1DM patients were recruited (7 men; 4 premenopausal women) for two liquid mixed-meal SI assessment at the University of Virginia Center for Diabetes Technology. Each patient was admitted twice, approximately 3 weeks apart; admissions were to capture early follicular and luteal phases in cycling patients. Plasma glucose and insulin was obtained frequently and used to assess SI based on the minimal model of glucose kinetics. The relative change in SI was analyzed within each group and compared between control (men) and "treatment" (women) arms.

Results:
Insulin sensitivity estimation led to SI (mean ± standard deviation) of $3.37 \times 10^{-4} \pm 1.18 \times 10^{-4}$ $uU^{-1}/ml/min^{-1}$ across admissions and subjects, and SI increased in three premenopausal women out of four (average relative change +31.7%) compared with three out of seven males (average relative change -13.4%), a significant difference ($p = .014$).

Conclusion:
Currently, there are no patient-oriented tools focused on identifying glucose variability during the menstrual cycle in T1DM. Based on the results presented, such a method for identifying these changes could result in improvement in glycemic control in patients with T1DM affected by variability in glucose regulation during the menstrual cycle.

Extending Threshold-Based Detection of Infusion Set Failures

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Objective:
Undetected infusion set failures can lead to high blood glucose values and ketoacidosis. Set failures can be detected either as departures from the normal controlled glucose levels or as departures from the normal glucose–insulin–meal behavior. Since the risk from set failures stems from elevated glucose levels and the concurrent lack of insulin, we focus on detecting high blood glucose values that result from loss of normal control due to an insulin infusion set failure.

Method:
Currently, most continuous glucose monitors provide high-glucose alarms with the ability to silence alarms for an hour. We improve on the high-glucose alarm as a method for detecting set failures by silencing the set failure alarm for 5 h and ignoring glucose levels that start above 250 mg/dl.

Result:
We tested these methods on 15 outpatient subjects who had a correction bolus that failed to lower glucose levels by at least 50 mg/dl and had subsequent rising glucose levels. The sets failed after a mean duration of 5.3 days. A 300 mg/dl threshold alarm detects 80% of set failures and produces false positive alarms at a rate of 0.73 per day. Our simple alteration to a standard continuous glucose monitor high-glucose alarm detects the same percentage of set failures while lowering the rate of false positives to 0.30 false positives per day. The set failures that do not generate glucose levels above 300 mg/dl can be viewed as less severe failures.

Conclusion:
The current glucose threshold alarms are adequate for detecting insulin infusion set failures but produce a significant number of false positives. Adding a longer silencing period, and silencing obviously false alarms at the start, can reduce the false positives rate by approximately 60%.

Knowledge and Expectation of Meal Announcements in Meal Prior Probabilities for Glucose Control

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Objective:
The timing and size of meals significantly impacts blood glucose levels, requiring appropriate consideration in prediction and control. We present a set of mathematically consistent meal prior probabilities that forecasts the next meal time, adapts current probabilities to meal announcements, and modulates the chance of unannounced meals based on the timing. We integrate this with models to achieve control.

Method:
The priors assume that we know the probability of the next meal time given the last meal time, the percentage of announced meals, and the relation between announced times and when meals appear. From this, we generate the probability of a new meal given knowledge of announcements and of the last meal. To handle the uncertain meal times in the priors, we create seven-state glucose–insulin–endogenous-glucose-production–meal models for variations in the last meal time and which meals are announced. The infused insulin is calculated to lower a confidence bound to a low glucose threshold.

Result:
We validate this controller on the 10 adult patients in the University of Virginia/Padova simulator. Meal size (1.1 g carbohydrate/kg subject) and time announcements are given 15 min before the start of four out of the five meals. The patients are assumed to have not eaten from 10:00 PM to 8:00 AM. We compare the proposed controller with the provided and optimized basal–bolus (BB) control strategies from the simulator; note that the optimized BB strategy represents an idealization that cannot be implemented in practice. Ignoring an outlier patient, we get blood glucose risk indexes of 4.3, 1.2, and 2.8 for the provided BB, optimized BB, and proposed controller, respectively. Likewise, we obtain euglycemic percentages of 82.3%, 98.5%, and 91.6%.

Conclusion:
The proposed meal prior probabilities cleanly incorporate the knowledge and expectation of meal announcements. Further, the priors aid in the achievement of good automatic control.

Use of Redundant Dexcom New-Generation Sensors to Assess Sensor Accuracy and Performance

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Objective:
Recent advances in amperometric glucose sensor technology are critical to the success of artificial pancreas (AP) devices. For such devices, reducing egregious sensor errors that may cause unsafe insulin delivery is of upmost importance. We sought to understand whether the use of duplicate Dexcom G4 sensors would significantly reduce egregious sensor errors and improve overall accuracy.

Method:
Thirty-six adult subjects with diabetes each wore two subcutaneous G4 sensors for 7 days. Here we report results of the 12 h inpatient sessions, which took place on days 1, 4, and 7. Blood glucose was measured every 15 min with a YSI analyzer, and during each session, glucose was deliberately raised and lowered. Sensors were retrocalibrated by YSI once at the beginning of the sessions. Egregious errors were defined as ≥50% deviation from reference glucose.

Result:
As compared with the use of a single sensor, pair-averaging reduced egregious errors by a third, (mean ± standard error of the mean; 2.4% ± 0.9% versus 1.6% ± 0.7%; $p = .04$). Mean absolute relative difference (MARD) for values ≥75 mg/dl also improved with pair averaging versus a single sensor (10.9% ± 1.0% versus 11.4% ± 1.0%; $p < .001$) as did mean absolute difference (MAD) for values <75 mg/dl (9.0 ± 1.0 versus 9.7 ± 1.0 mg/dl; $p < .001$). The percentage of extremely large errors (≥75%) was very low, with a single sensor (mean 0.25%) and even lower (mean 0.11%) with pair averaging.

Conclusion:
Even with a single device, G4 sensors have a low rate of egregious errors. A further reduction in such errors is achieved by averaging the outputs of two sensors. Averaging also improved MARD and MAD. These accuracy benefits are important for optimizing sensor performance and avoiding overdelivery of insulin in future AP systems.

Modeling the Impact of a Standardized Breakfast on Type 1 Diabetes Mellitus Fasting Blood Glucose

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Objective:
The design of a controller for glycemia regulation, in either open or closed loop, relies on models able to describe the effects of a meal intake and an insulin injection on blood glucose dynamics. The purpose of this study was therefore to propose a physiologically relevant yet parsimonious model for carbohydrate action on fasting blood glucose in type 1 diabetes mellitus (T1DM) patients when no insulin is taken.

Method:
Five T1DM subjects were admitted at the clinical investigation center at 7:00 AM, fasting from midnight and served a standardized breakfast containing 40 g carbohydrates at 8:00 AM. The corresponding insulin bolus was administered at 10:00 AM. During the observation period of 8:00–10:00 AM, blood samples were drawn every 10 min to assess glucose concentration utilizing a YSI 2300 STAT Plus blood glucose analyzer. Gain and time constant of the glucose peak for each of the subjects were estimated from data by means of system identification techniques.

Result:
Comparing the output of the model against the actual blood glucose gave a FIT of 85.28% ± 7.21%. Simulating the models with the identified parameters in response to 1 g of glucose produced an increase in blood glucose of 10.02 ± 9.72 mg/dl, with peak time in the range of 3 to 4 h.

Conclusion:
Models of a glucose peak following a standardized breakfast in absence of any insulin taken were estimated from T1DM patient data. The parameters have physiological meaning, being related to the glucose tolerance of each individual, and can be used to describe meal impact in a controller design procedure.

Evaluating the Prevalence of Control Solution Testing in Diabetes Patients Who Self-Monitor Blood Glucose

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Objective:
There is very little information on control solutions made available to the public, and there is a large market for blood glucose monitors (BGMs); hence, this would indicate that there is a large population of uneducated consumers on control solutions. The objective was to explore whether or not patients are using a control solution and, if not, for what reasons.

Method:
The methods used in this project include a survey given to type 1 diabetes patients or to the parents of children with type 1 diabetes. The survey attempted to assess the prevalence of control testing in BGM users or the parents of children who use BGMs. Also, data were collected of control solution availability in 40 pharmacies in San Mateo and six surrounding cities.

Result:
Almost 60% of survey respondents admitted to almost never conducting control tests on their BGMs. Also, it was discovered that only 6 out of 40 pharmacies had any type of control solution in stock.

Conclusion:
It is no surprise that control solution was available in only 15% of pharmacies in seven cities. From the survey, it can be determined that the demand for control solution by diabetes patients who use BGMs is incredibly low. If the survey results and pharmacy data are indicative of national trends, control testing is occurring significantly less frequently than necessary. Published data suggest that control tests are beneficial because they decrease error in readings of blood glucose levels.

"A Worksite Body Weight" Intervention by Telecare

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Objective:
General office staff work long hours with less physical activities, resulting in heavier body weight. In this study, we evaluated the effect of worksite bodyweight intervened by telecare on overweight or obese employees.

Method:
This study recruited employees with body mass index more than 24 kg/m^2 from a company for 8 weeks of long-distance health care. The program includes (1) physician and dietitian clinical visits at initiation and finish and (2) nutrition education by video camera. Through this model, the subjects themselves and health management transmit measurement records to the hospital in real time and deal with employee consulting. Both before and after the intervention, participants collected body weight, waist, blood pressure, triglycerol, and total cholesterol measurements and investigated health knowledge. Statistical analysis was by one-way variation test.

Results:
During 8 weeks of telehealth care services, participants' total body weight and waist measurements decreased by 77.4 kg and 4.21 cm, respectively ($p < .05$); total cholesterol and triglycerol were reduced by 22 and 33 mg/dl, respectively; systolic pressure and diastolic pressure were lowered 8.52 and 13.25 mm Hg, respectively; and average body mass index was reduced by 2.35 kg/m^2 ($p < .05$). All subjects had more correct health knowledge than at initiation.

Conclusion:
It could help management at worksites to increase health knowledge and effectively reduce body weight, waist measurements, cholesterol, triglycerol, and blood pressure of employees by telecare services. We expect to recruit more employees as well as evaluate the effect of worksite body weight intervened by telecare in a long-term study.

Using Observational Data to Inform the Design of a Prospective Effectiveness Study for a Novel Insulin Delivery Device

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Objective:
We aimed to inform the design and assess the feasibility of a prospective effectiveness study evaluating an insulin delivery device among patients with diabetes mellitus (DM) to be conducted within the membership of a U.S. commercial insurer.

Methods:
Providers with ≥1 prescription for insulin between January 1, 2011, and September 30, 2011, were selected from the HealthCore Integrated Research Database. Diabetes mellitus patients with encounters among these providers and continuous eligibility throughout 2011 were identified. Providers were dichotomized into high-volume provider (HVP) and low-volume provider (LVP) groups based on the median number (median#) of DM patients per provider.

Results:
We identified 15,491 HVPs and 15,200 LVPs [median# = 14]. Most HVPs were located in the Midwest (*n* = 6342 [40.9%]) and South (*n* = 5146 [33.2%]), while LVPs were evenly distributed across regions. Over 80% (n = 12,756) of HVPs practiced family/internal medicine, while approximately 6.5% (*n* = 999) were endocrinologists. Metformin was the most commonly prescribed oral antidiabetic (39% ± 13% of patients with ≥1 fill per provider). High-volume providers prescribed insulin to an average of 26% (±14%) of their patients. Patients of HVPs (*n* = 524,086) had similar characteristics to patients of LVPs (n = 79,725), except for geographical dispersion, which followed those of providers. Approximately 66% of patients were aged 18–64 years, and 95% had type 2 DM. Among patients with ≥1 available hemoglobin A1c result during 2011 (*n* = 103,961), 48% (*n* = 50,268) had an average hemoglobin A1c ≥7.0%. Among these uncontrolled patients, 44% (*n* = 22,354) received ≥1 insulin prescription.

Conclusion:
The observed provider/patient populations support the feasibility of the prospective study. Sampling of patients from HVPs is efficient while minimizing bias, as patients are similar in characteristics to those from LVPs. The study also highlights the unmet need for improved glycemic control since approximately half of DM patients are not on goal.

Interference Evaluation of the CONTOUR NEXT Test Strip

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Objective:
A new platform of blood glucose monitoring systems (BGMSs) utilizes the CONTOUR® NEXT test strip containing the flavin adenine dinucleotide-dependent glucose dehydrogenase enzyme in combination with a proprietary electron mediator. Common endogenous and exogenous substances were evaluated for interference effect.

Method:
Interfering substances were tested at glucose concentrations of 80 and 300 mg/dl following the Interference Testing in Clinical Chemistry EP7-A2 guidelines. Interference stock solution was used to create a sample with the highest interfering substance level, at least two intermediate levels, and a blank. Data were analyzed by regression analysis and results were presented as percentage deviation from blank at the maximum therapeutic concentration (MTC) or upper reference value (URV). Results were determined from the glucose level (80 or 300 mg/dl) with the greatest bias.

Result:
Results for the six most common interfering substances showed ≤1% bias at MTC or URV. Acetaminophen, bilirubin, galactose, maltose, and uric acid had no interfering effect on blood glucose measurements at any concentration tested. The system is more sensitive to very high concentrations of ascorbic acid; the high end of the therapeutic range for ascorbic acid is 2 mg/dl. At 10 mg/dl, ascorbic acid can cause a +10% assay bias at 80 mg/dl plasma glucose and approximately 3% bias at 300 mg/dl plasma glucose.

Conclusion:
Study findings showed that common endogenous-reducing substances in blood (e.g., uric acid and bilirubin) or exogenous substances from therapeutic treatments (e.g., maltose and acetaminophen) did not significantly affect the performance of the CONTOUR NEXT test strip. Thus, results obtained with this new BGMS platform can be expected to be accurate in the presence of these interfering substances.

A Comparison of Clinical and Economic Outcomes among Type 2 Diabetes Mellitus Patients Initiating Insulin Glargine Pen versus Vial

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Objective:
This study evaluated the real-world clinical and economic outcomes of type 2 diabetes mellitus (T2DM) patients initiating insulin glargine via pen (PEN) delivery or vial/syringe (VIAL) within a large U.S. managed care population.

Method:
A retrospective cohort study was conducted within the HealthCore Integrated Research Database using administrative claims from April 1, 2007, to September 30, 2011. The index date was set as the earliest PEN or VIAL prescription date. Patients needed ≥6 months preindex (baseline) and ≥12 months postindex (follow-up) health plan eligibility and were required to be insulin naïve with ≥1 oral antidiabetic or glucagon-like peptide-1 at baseline. Propensity score matching (1:1) was used when comparing 1 year outcomes between treatment cohorts.

Result:
Patients in the two matched cohorts (n = 733 in each) were well balanced with regards to demographics (mean age 52 years, 43% female), clinical outcomes [mean glycated hemoglobin (A1C) 9.4%, mean Charlson comorbidity index 0.9], and health care utilization at baseline. Following initiation of insulin glargine, PEN patients were more likely to be persistent (60.6% versus 50.1%; $p < .01$) and adherent (medical possession ratio 0.73 versus 0.57; $p < .01$) and showed lower A1C during follow-up (mean change -1.05 versus -0.73; $p < .01$) compared with VIAL patients. Hypoglycemic events occurred infrequently and at a similar rate across the PEN and VIAL cohorts (3.8% versus 5.2%; $p = .21$). Study drug costs were higher in the PEN group ($1163 versus $762; $p < .01$), but this did not translate into higher total all-cause or diabetes-related costs.

Conclusion:
For T2DM patients newly initiating insulin glargine, these results suggest that using an insulin pen device is advantageous relative to vial/syringe, as it is associated with increased therapy persistence and adherence as well as lower A1C, without increasing total all-cause or diabetes-related costs.

Assessment of Postprandial Glucose Excursions throughout the Day in Newly Diagnosed Type 2 Diabetes Patients

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Objective:
An accumulating pool of evidence points toward postprandial glucose (PPG) as independently linked to multiple complications, and testing of PPG should be added to hemoglobin A1c (HbA1c) and fasting glucose measurements in type 2 diabetes patients. An ongoing debate is questioning how to asses PPG. This observational study looks further into this question in newly diagnosed type 2 diabetes.

Method:
Postprandial glucose characteristics and intravariations/intervariations after breakfast, lunch, and dinner from continuous glucose monitoring were retrospectively analyzed in 86 newly diagnosed non-insulin-treated type 2 diabetes patients.

Result:
A total of 462 registered meals were analyzed. The area under the curve 1–4 h post-meal was significantly larger for breakfast compared with both lunch and dinner ($p < .001$). Time to peak was approximately 90 min and did not differ significantly between meals. However, the distribution of the blood glucose peaks was only near normally distributed among breakfasts, and time to peak had a day-to-day correlation coefficient of 0.60, compared with an insignificant result for lunch and dinner. Breakfast peak PPG was highly correlated to HbA1c ($r = 0.64$) and had a day-to-day correlation coefficient of 0.86 compared with 0.44 (lunch) and 0.74 (dinner).

Conclusion:
This study shows that breakfast is associated with larger and more consistent PPG excursions than seen after lunch and dinner. Self-monitoring of postprandial blood glucose should be evaluated with care. Monitoring of PPG patterns in newly diagnosed type 2 diabetes patients should preferably be obtained approximately 90 min following breakfast for more consistent feedback, reducing day-to-day variations.

Telepodiatry in the Treatment of Lower-Extremity Ulcers

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Objective:
Diabetes is the leading cause of lower-extremity amputations in the United States. This is particularly true among minority populations in the Southwestern states. Risk factors include glucose control, circulation, pedal deformity, regular foot examination, and patient education. Recognition of these variables by a multispecialty health care team leads to significant reduction in lower-extremity ulcers, amputations, and associated health care expenses. Socioeconomic issues in remote locations affect access to care, treatment options, and patient education. In our practice, we have observed that patients with lower-extremity ulcerations fare better when they are seen by a foot specialist earlier and treated aggressively. We propose using telemedicine to evaluate and treat lower-extremity ulcerations in order to provide high-risk patients with early guided care and to improve patient outcomes overall.

Methods:
We created a model for systematic foot examination using Web cameras in remote areas that lack access to podiatrists and other key specialists. The videoconference technique can be used to perform a real-time comprehensive foot evaluation while a patient is being seen in a different provider location.

Results:
Systematic evaluation of ulcer size, depth, location, and other variables can be performed along with input from the local provider regarding vascular perfusion and sensation. This information is correlated to determine wound care regimen, offloading modality, additional tests, specialist referral, and the need for surgical treatment.

Conclusion:
This process allows high-risk populations to receive timely care and prevents morbidity and mortality associated with amputations. Timely ulcer treatment and assessment is cost-effective and has been shown to reduce lower-extremity amputation- related expenses overall.

A Mathematical Model of Glucose–Insulin Dynamics in Critical Care Patients

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Objective:
We evaluated the ability of our composite model of glucose–insulin–fatty acid–exercise dynamics to capture glucose and insulin response in a cohort of 10 critically ill patients.

Method:
We extracted data from 10 patients on the HIDENIC trial, which includes intensive care unit admissions, at the University of Pittsburgh Medical Center between 2007 and 2009. All patients were ≥18 years old without the diagnosis of diabetic ketoacidosis or hyperosmolar state. An insulin–glucose mathematical model by Roy is evaluated. The model was fit to the data by adjusting key parameters in insulin sensitivity and/or those impacting the glucose balance. Quality of fit was quantitated via least squares error between model simulation and measured data. Patients were fit individually, and the resulting parameter profiles were examined over the full set of patients.

Results:
The glucose concentration profiles of HIDENIC patients were well captured by the model of Roy. Given the temporal sparsity of the measurements (sample interval 1–6 h), it is difficult to elucidate the mechanisms impacting glucose response, as insulin sensitivity or glucose balance parameters could be adjusted to yield a quality fit to the data.

Conclusion:
The patient model of Roy is able to represent individual patients from the HIDENIC data set by varying model parameters relevant to the mechanism of disease (insulin sensitivity and glucose utilization). Further evaluation is needed to compare this model to another model by Lin, which has also been shown to match patient data. Future work will evaluate these models for their utility in a closed-loop algorithm controlling patient glucose concentrations *in silico*.

Impact of Transfer Entropy on the Parameter Selection of a Real-Time Adaptive Controller for Glucose Regulation

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Objective:
Recent studies have shown that adaptive control algorithms for glucose regulation in type 1 diabetes mellitus (T1DM) are efficient against interpatient and intrapatient variability. However, they suffer from high sensitivity to initialization and parameter selection. The aim of the study is the individualized tuning of the learning rates for an adaptive control algorithm. The algorithm is used for the run-to-run adaptation of basal and bolus insulin infusion in T1DM.

Method:
Continuous glucose sensor and basal–bolus insulin pump data of 3 days were collected using the educational version of the Food and Drug Administration-accepted University of Virginia T1DM simulator. The transfer entropy was estimated to measure the information flow between bolus insulin infusion and measured glucose concentration. Three transfer entropy zones were identified, and respectively, three learning rate zones were defined in an inversely proportional manner such that lower information transfer was paired with higher learning rate. The methodology was evaluated *in silico* and comparatively assessed with the case of common learning rate tuning using the aforementioned simulator.

Result:
Preliminary results of a 30-day trial on 8 T1DM *in silico* children have shown that the proposed methodology achieved 90% in the A+B regions of the control variability grid analysis within 6 days compared with a respective time of 10 days for the universally tuned algorithm. Furthermore, after 20 days, the individually tuned algorithm reached 96% in the A+B regions compared with 94% for the universally tuned one.

Conclusion:
Transfer entropy might be a useful method for the individualized parameter selection of adaptive control algorithms for glucose regulation in order to improve the performance and increase convergence speed.

Differences in Upper Arm versus Wrist Insertion Sites with a Fluorescence-Based Continuous Glucose Monitor

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Objective:
A continuous glucose monitor that may be inserted subcutaneously for 6 months or longer has been developed. The subcutaneous sensor communicates with a body-worn external reader that reports the sensor glucose to the patient. The system has currently been designed to support insertion in the wrist and in the upper arm, and a 29-day clinical study was designed to evaluate the differences between these two insertion sites.

Method:
Twenty seven sensors were inserted subcutaneously in 18 patients, with some patients undergoing bilateral insertions. Twenty insertions were in the wrist, and 7 sensors were in the upper arm. Over the next 29 days, patients returned to the clinic every 4–7 days for an 8 h read session, during which sensor glucose and temperature were sampled every 2 min by the body-worn reader. Blood was also sampled every 15 min to determine blood glucose using a YSI analyzer. Sensors were removed after 29 days.

Result:
The mean absolute relative difference (MARD) of the sensors inserted in the wrist was 15.2%, and the comparable MARD of the sensors inserted in the upper arm was 14.3%. In subjects who had a sensor in the wrist and another in the contralateral upper arm, the average difference in minimum and maximum temperatures in the upper arm was 4.3 °C, while the average difference was 6.5 °C in the wrist.

Conclusion:
The MARD of the upper arm was lower than that of the wrist. This may be, in part, due to less fluctuation in sensor temperature in the upper arm relative to the wrist.

Improving Overnight Safety of Type 1 Diabetes Subjects: Failure Detection Method of Glucose Sensor–Insulin Pumps System Based on an Average Model

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Objective:
Possible failures of either continuous glucose monitor (CGM) sensors or continuous subcutaneous insulin pumps expose type 1 diabetes patients to possibly severe risks, especially overnight. In a previous contribution, we proposed a failure-detection method (FDM) to detect possible overnight sensor–pump system failures in real time by exploiting CGM and insulin pump data streams. In this contribution, we assess a simplified version of FDM where an average, rather than an individualized, model of the glucose–insulin relationship is used.

Method:
The FDM consists of two main steps: first, a prediction of the future glucose level is obtained through a Kalman-filter estimator based on a model of the glucose–insulin relationship; second, glucose predictions are compared with CGM samples, and a failure alert is generated if the CGM is not consistent with the predictions. The FDM-a and FDM-p implementations of FDM employ, respectively, average and personalized versions of the glucose–insulin relationship model.

Result:
Both FDM-a and FDM-p were tested on simulated data created by using the University of Virginia/Padova type 1 diabetes simulator (US2008/067725), which include three types of failures: spike and transient loss of sensitivity of the CGM and failure of the pump in insulin delivery. FDM-a proved to perform satisfactorily even compared to FDM-p, generating a limited number of false negatives and a number of false positives (~20%) only slightly higher than FDM-p.

Conclusion:
FDM-a performed satisfactorily and similarly as FDM-p, with the significant practical advantage that it does not require going through the data-demanding model individualization phase and is more robust with respect to intraindividual variability. In any case, FDM-a is the approach of choice until enough data for model individualization in FDM-p are collected.

Models for *In Silico* Simulation of Possible Failures of Continuous Glucose Monitoring Sensors

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Objective:
Type 1 diabetes simulators, such as US2008/067725, are widely used to test *in silico* the performance of closed-loop control algorithms for the artificial pancreas. More realistic/challenging simulations could be obtained with a proper description of the continuous glucose monitor (CGM) sensor malfunctionings often experienced in clinical practice. In this study, we propose models of the most common failure episodes that deteriorate CGM device performance.

Method:
We analyzed 24 CGM time series obtained using the Dexcom® SEVEN® PLUS sensor, each lasting approximately 8 h. Blood glucose (BG) references were also collected in parallel. Through the comparison of reference BG and CGM traces, we identified three possible failure types: *disconnection*, i.e., transmitter–receiver connectivity losses; *invalid output*, i.e., sensor self-diagnosed unreliable readings; and *transient loss of sensitivity* caused by pressure on the sensor, leading to sudden drops in sensor reading.

Result:
A two-state (working/faulty) Markov chain, with transition probabilities inferred from the data, proved to effectively describe disconnection and short-in-time invalid outputs. Transient losses of sensitivity were modeled as a square-wave Boolean disturbance, describing pressure on the sensor, subtracted to the sensor output after passing through a first-order low-pass system that models pressure-induced slow changes in the insertion site. Probability distributions of model parameters (pressure duration, system gain, and time constant) were estimated from the data.

Conclusion:
The proposed models proved to be able to effectively capture essential features of three classes of common failures of CGM devices. Thus they can be usefully integrated in type 1 diabetes simulators to allow a more realistic *in silico* testing of artificial pancreas control algorithms and of their robustness against occasional malfunctionings of CGM devices.

Continuous Glucose Monitor *In Vitro* Interference Testing

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Objective:
Continuous glucose monitors (CGMs) are medical devices indicated for tracking and trending of glucose concentrations in interstitial fluid as an adjunct to blood glucose testing. Approved CGMs detect glucose with a glucose oxidase (GOx) electrochemical sensor. Even though GOx enzyme is highly selective for glucose, it can exhibit limited reactivity toward other sugars. This nonspecific GOx reactivity may be a source of interferences and erroneous glucose readings. We present observations of an *in vitro* study on CGM interferences by sugars other than glucose.

Method:
Commercially available CGMs were studied using a specially designed flow-through chamber filled with a buffer solution of known glucose concentrations at 37 °C. Inserted sensors were allowed to warm up and were calibrated according to the manufacturer's instructions. After a stable glucose baseline was obtained, the sugar analyte was added. Analyte concentrations were chosen to be as clinically relevant as possible, based on published literature, given the absence of accepted clinical values in interstitial fluid. Glucose readings in the presence of sugar analyte were compared with baseline readings to determine interference potentials.

Result:
Fourteen sugars and sugar alcohols were screened for interference effects. Under conditions tested, galactose, xylose, and mannose were found to interfere with CGM readings, consistent with the limited reactivity of GOx toward these sugars.

Conclusion:
Our data show that galactose, xylose, and mannose may have the potential to interfere with GOx sensors. However, since *in vitro* data do not always correlate with *in vivo* activity, *in vivo* data are needed to determine the clinical significance of found interferences. The findings and conclusions in this presentation have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any agency determination, guidance, or policy.

Comparison of Three Gastric Emptying Methods Applied Simultaneously to Nine Type 1 Diabetes Patients Suffering Severe Diabetic Gastroparesis

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Objective:
Diabetic gastroparesis is highly prevalent and is believed to have a great impact on glycemic control. A better understanding of the clinical relevance of delayed gastric emptying requires accurate, accessible, and inexpensive methods. This study compares three methods for assessing gastric emptying: (1) paracetamol absorption test, (2) 13C-acetate breath test, and (3) scintigraphy gastric emptying method.

Methods:
Nine type 1 diabetes patients suffering severe symptoms of diabetic gastroparesis were consecutively recruited. Demographic and clinical data, symptom scores, and medication were recorded. After an overnight fast, gastric emptying was measured simultaneously by the three methods in each subject. A liquid meal containing 5 mg/ml paracetamol, 75 mg 13C-natrium acetate, and 20 MBq 99mTc-DTPA was ingested, the subject was placed in the gamma camera, and blood samples for paracetamol and breath tests were obtained. A gamma camera was used until no radioactivity was traced in the gastric region. Blood samples were analyzed for serum paracetamol concentration. Breath samples were analyzed using an isotope-selective infrared spectrometer.

Results:
The data will be presented as percentage retained ventricular contents as a function of time. A gastric-emptying time-retention curve is drawn for each technique, and the results are compared at the 75%, 50%, and 25% retention quartiles demonstrating. The 50% quartile shows superiority for the paracetamol test compared with the breath test. Only the scintigraphy test reveals retention at the end of the test.

Conclusion:
The scintigraphy test detects meal retention in the stomach, whereas the paracetamol test and the breath test do not. The paracetamol test is superior to the breath test in this study. In this study, we found no firm association between gastric emptying rate and symptoms of diabetic gastroparesis.

Concomitant Oral and Subcutaneous Insulin Therapy toward Stabilization of Uncontrolled Type 1 Diabetes Mellitus

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Objective:
We assessed the safety and impact of an orally delivered insulin in combination with standard patient insulin therapy on the stability of glycemic readings in uncontrolled type 1 diabetes mellitus (T1DM) patients.

Method:
The blood glucose profiles of eight T1DM patients [hemoglobin A1c (HbA1c) 7.5–11%] treated with multiple or continuous daily doses of subcutaneous insulin were monitored using a blinded continuous glucose monitoring system (CGMS). During the ensuing 10-day treatment period, patients continued their regular insulin treatment regimen while concomitantly self-administering a single 8 mg capsule of oral insulin (ORMD-0801) three times daily, 45 min before meals. The CGMS continued to record blood glucose concentrations during this phase of the study.

Result:
No adverse events were reported throughout the 15-day study period. Continuous glucose monitoring system data sufficient for analysis were collected from 6/8 subjects. Blood glucose recordings were more frequently below 70 mg/dl during the treatment phase when compared with the pretreatment phase (1.99% ± 0.88% versus 0.45% ± 0.2%, respectively; $p = .06$). In parallel, the frequency of glucose readings >200 mg/dl was 24.4% lower upon addition of ORMD-0801 to the treatment regimen ($p = .026$). ORMD-0801 treatment led to a 16.6% decrease in glucose area under the curve values, with the largest reductions (21.2%) measured between 5:00 and 7:00 PM.

Conclusion:
These findings demonstrate the safety and tolerability of concomitant administration of orally and subcutaneously delivered insulins in uncontrolled T1DM patients. Moreover, the recorded glucose profiles suggest that ORMD-0801 can help promote glycemic control, with a most prominent effect during evening hours. Future studies will be required to measure the full hypoglycemic capacity of this new drug and assess translation of this therapy into reduced levels of HbA1c and diabetes-related complications.

Touch Tears: A Design Alternative to Self-Monitoring of Blood Glucose

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Objective:
Diabetes mellitus is a growing health concern worldwide, with complications often arising from poor patient compliance, particularly with testing blood sugar. This tear-based glucose sensor aims to increase patient compliance to self-monitoring of blood glucose.

Method:
The tear capture method utilizes a polyurethane foam plug, a thermoset plastic fluidic base, and the highly sensitive enzyme glucose dehydrogenase with flavin adenine dinucleotide (GDH-FAD) incorporated on a screen print electrode. Responsiveness of the diagnostic was tested using both bench-top glucose assays as well as *in vivo* testing on New Zealand white rabbits.

Result:
Bench-top data returned a lower limit of detection for GDH-FAD of 2 μM and a sensitivity of 4.5 nA/μM. The *in vitro* glucose assay returned a glucose-to-current correlation with an R^2 of 0.9965, and a concurrent sugar assay showed the GDH-FAD was selective for only glucose and xylose. The animal study showed a 5–10 min lag from blood glucose to tear glucose (TG). A correlation between blood glucose and current from the TG measurements returned an R^2 of 0.64. Lissamine dye testing indicated no observable damage to the eye over a 9-month time frame from use of the sensor.

Conclusion:
The proposed sensor was successfully transferred from the bench-top to *in vivo* testing with acceptable deviations that arise from the limitations of using hand-fabricated devices. No damage to the ocular surface was found from use of the devices, making future clinical trials possible. Future work involves assessing failure modes and standardizing device use and fabrication to minimize variance from hand fabrication of devices. Design improvements will also be reviewed, including a new fluidic design and a better tear capture material.

Automatic Mechanical Infusion Set Prime Reduces Time and Steps and Potentially Improves Safety in Insulin Pumps

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Objective:
The aim is to develop infusion set automatic filling capability for insulin pumps utilizing prefilled insulin cartridges with three goals: simplicity, speed, and safety.

Method:
Through dimensional analysis of prefilled insulin cartridges, a means to quickly and automatically fill an infusion set during the mechanical assembly of the system is designed. The prefilled cartridge is inserted plunger-end first into the pump system. An infusion set with a specifically designed connector is attached via a push and turn motion; this pierces the prefilled cartridge, establishing flow between the cartridge and the infusion set. The attachment motion also seats the cartridge firmly onto the pump drive. As the cartridge is seated, the pump drive pushes the cartridge plunger forward. Approximately 20 U of insulin moves into the infusion set in less than 3 s. The distance between the seated connector and the pump drive is tuned so that the largest compatible infusion set fills with modest overflow over all pump and cartridge tolerances. The design has the benefit of breaking any friction formed between the plunger and the cartridge during storage.

Result:
The design automatically and quickly fills an insulin pump infusion set while meeting the goals of simplicity, speed, and safety.

Conclusion:
Providing pump users with a means to quickly and reliably fill their infusion significantly reduces the time and steps required. This reduction in steps holds potential for reduced errors. As a finite amount of surplus insulin is delivered via this process, the potential for significant overdelivery due to user error is reduced, and the danger from a failure in a pump's reservoir detection system is eliminated.

Innovative Insulin Pump Occlusion Detection Mechanism Offers Improved Sensitivity and Reduces the Amount of Missed Insulin Prior to Detection

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Objective:
The aim is to develop a means to detect occlusion reliably in an insulin pump with improved sensitivity.

Method:
An innovative system that senses increased fluid pressure within the infusion set has been developed. Within a custom infusion set connector, a flexible film is held in fluid communication with the infusion set tubing. As pressure in the infusion set increases because of a blockage, the pressure pushes the film against the backside of a prism contained within the infusion set connector. Normally, the prism will reflect a light beam shined into the prism from the pump system. When the film is pressed against the prism, this reflection is quenched. The drop in returning light is detected by the pump system and indicates a blocked set. The dimensions of the system are tuned to allow the pressures normally seen in insulin pumping to occur without alarm. The insulin contacting parts are replaced with each new infusion set, reducing any risk of contamination by the sensor.

Result:
The design typically detects occlusions at nominal basal rates of 1 U/h within 1.25 missed units. Best case performance is 0.85 missed units, while worst case performance is under 2.3 missed units. This performance should allow the user to address the occlusion prior to significant increases in glucose due to insulin insufficiency.

Conclusion:
Improved occlusion detection sensitivity is needed in insulin pumps. Current systems often cannot detect occlusion until after glucose levels are elevated. By reducing the amount of missed insulin prior to detection, the Pearl insulin pump is designed to help pump users maintain glucose values close to target levels.

Insulin Pump User's Self-Assessment of Ability to Read Their Pump Screen: A Case for Larger Text?

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Objective:
The aim is to determine how current insulin pumps meet users' readability needs

Method:
In an online survey of insulin pumpers conducted in January 2012, 228 participants, recruited from InsulinPumpers.org, responded to the following: Please describe your eyesight as it relates to reading your pump screen: (1) I never need reading glasses, (2) I sometimes need reading glasses, (3) I always need reading glasses, or (4) I cannot read it even with reading glasses.

Result:
A total of 132 participants (58%) indicated that they require reading glasses sometimes or always to read their pump screen. Only 94 (41%) indicated they did not need reading glasses to read their pump screen. When segmented by brand (Animas, Insulet, Medtronic), there is no brand where the percentage of those needing reading glasses was less than 50%. A higher percentage of females 76/124 (61%) needed "help" reading their pump screens than males 56/105 (53%).

Conclusion:
Current pumps do not meet the needs of roughly half of pump users in terms of readability. Given the widespread retinopathy associated with diabetes, it is not surprising to find a large population of pump users with reading difficulties. The safe use of insulin pumps depends upon the user discerning the information presented and executing the desired programming without error. Considering the relatively small letter height used in current pump menus from Animus (2.8 mm), Medtronic (3.0 mm), and Insulet (3.5 mm), the potential for larger text to improve both usability and safety in future pump systems is clear. The Pearl insulin pump, which features larger text at 4.75 mm (a 35% to 60% increase), may offer improved ease of use and reduced user entry errors for many pump users.

Model of Sensor Error from Multiple Simultaneous Continuous Glucose Monitors in the Same Subject

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Objective:
A model of the sensor error is crucial to design reliable simulation scenarios for testing algorithms relying on continuous glucose monitoring (CGM), e.g., artificial pancreas control algorithms. The aim of this study is to develop such a model by using multiple CGM recordings simultaneously measured on the same subject.

Method:
The database consists of 36 data sets collected in 19 adults with type 1 diabetes. Subjects have been recruited at the Oregon Health and Science University (Portland, OR) and admitted for two sessions of 9 h duration each. Glucose concentration was measured simultaneously by four different Dexcom SEVEN PLUS sensors at 5 min sampling. HemoCue Glucose 201 Analyzer plasma samples were collected in parallel every 15 min as reference. Plasma samples were fitted against each of the four CGM traces, exploiting individualized models of plasma-to-interstitium kinetics, calibration, and sensor drift. The four residuals profiles were compared in order to identify the different components of the sensor error.

Result:
The first identified component is the measurement error. In addition, a model error component was identified, which reflects CGM errors due to both plasma-to-interstitium physiological model and technology issues, e.g., calibration/drift. Both components are satisfactorily described by a low-order autoregressive model. Use in simulation of this sensor error model generates realistic profiles.

Conclusion:
The availability of multiple sensor data measured simultaneously in the same subject is key to develop a sensor error model. Our results show that, in addition to measurement error, an additional component is needed to account for physiological and technological uncertainties. This sensor error model will be incorporated in the Food and Drug Administration-accepted University of Virginia/Padova type 1 diabetes simulator.

Physical Activity Information Improves Real-Time Prediction of Glucose Concentration

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Objective:
Prediction of future glucose concentrations from continuous glucose monitoring (CGM) data is a topic of major interest because prediction is used both to generate "preventive" hypoglycemic/hyperglycemic alarms and in closed-loop control algorithms for artificial pancreas applications. Previous contributions demonstrated relationship between moderate physical activity (PA) on glucose excursions. In this analysis, we investigate if PA can be exploited to increase performance of simple linear glucose prediction algorithms.

Method:
Thirteen type 1 diabetes subjects were studied in the clinical research unit at Mayo Clinic (Rochester, MN) for 88 h, during which glycemia was measured with CGM (Dexcom SEVEN PLUS® system), and PA was captured with the Physical Activity Monitoring System (a system with accelerometers and inclinometers that records body movement and posture). Each day, the subjects underwent 4–6 consecutive PA sessions of low intensity, during which they alternated 26.5 min of walking on a treadmill (1.2 mph) with 33.5 min of sitting. We evaluated four linear prediction algorithms based on autoregressive (AR), autoregressive with exogenous inputs (ARX), autoregressive moving average with exogenous inputs (ARMAX), and Box–Jenkins (BJ) models. Prediction horizons (PH) from 5 to 60 min were used.

Result:
Optimal model order was selected on the training test using the Bayesian information criterion. The AR model (no PA exploitation) was used as reference. Average results suggest that no significant increase in the performance is obtained by ARX and ARMAX models, whereas BJ outperforms all other models, especially for PH around 30 min ($p < .05$).

Conclusion:
Simple linear prediction algorithms of future glucose concentration can benefit from information of PA, but the model used should be complex enough to be able to exploit such information.

Analysis of Overnight Continuous Glucose and Sleep Stage Data in Subjects with Type 1 Diabetes in Real-World Conditions

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Objective:
We characterize sleep in type 1 diabetes mellitus (T1DM) and evaluate the feasibility of continuous glucose and sleep stage monitoring outside of the laboratory setting.

Method:
This observational study is part of the DMITRI study conducted at an exercise/leadership training camp. Seventeen T1DM subjects were evaluated: 10 male, 7 female; 19–61 years old; T1DM for 14.9 ± 11.0 years; hemoglobin A1c 7.3% ± 1.3% (mean ± standard deviation). Subjects wore continuous glucose monitors (Dexcom SEVEN PLUS) for 72–120 h and sleep monitors (Zeo Sleep Manager Bedside) for 1–4 nights each. Ten subjects also wore Actiwatch-64 activity monitors throughout the study. Subjects slept unsupervised in dormitories with other camp participants. In total, 22 nights were analyzed for time spent in rapid eye movement (REM), light, and deep sleep; nights with <180 min sleep data (user error or device malfunction) were excluded from analysis. Glycemia (mg/dl) was evaluated as hypoglycemia (≤50), low glycemia (51–70), euglycemia (71–120), high glycemia (121–250), and hyperglycemia (>250).

Result:
Subjects slept 340 ± 54 min per night, with 78 ± 27 min REM, 196 ± 33 min light, and 65 ± 25 min deep (mean ± standard deviation). Glycemia levels during REM: hypo 6.6%, low 5.2%, eu 43.8%, and high 43.5%, and hyper 0.8%. Glycemia levels during light sleep: hypo 5.8%, low 5.6%, eu 39.5%, high 44.2%, and hyper 5.0%. Glycemia levels during deep sleep: hypo 0.9%, low 5.4%, eu 47.1%, high 32.4%, and hyper 14.2%. Significantly less time in hypoglycemia is observed in deep sleep compared with light sleep (p = 2.2e - 4) and REM (p = 8.2e - 4). Zeo sleep data agreed well with Actiwatch-64 data.

Conclusion:
The durations spent in various sleep stages by T1DM subjects are not significantly different from previous studies in healthy individuals. Significantly less hypoglycemia occurs in deep sleep than other stages, though this relationship is not yet understood. The Zeo device is useful for monitoring sleep in an unsupervised setting.

Laser Scanning of Retinal Microvascular Blood Flow for the Detection of Early Neurovascular Dysfunction in Type 1 Diabetes Patients with and without Diabetic Polyneuropathy

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Objective:
In arterial hypertension and diabetes mellitus, laser Doppler scanning of retinal blood flow has been introduced in the evaluation of early retinal pathology. Retinal blood flow regulation is a complex process affected by endothelial and neurovascular modifications. The intention of this study was to investigate morphological and functional changes in retinal microcirculation in type 1 diabetes patients with and without diabetic neuropathy.

Method:
Retinal microvascular blood flow was assessed using scanning laser Doppler flowmetry (Heidelberg Retina Flowmeter, Heidelberg Engineering, Germany) at 670 nm before and after stimulation with flicker light (10 Hz; Photo Stimulater 750, Siemens-Elema AB, Germany). The arterial wall-to-lumen ratio (WLR) was calculated as (arteriole diameter - lumen diameter)/lumen diameter. Neuropathy was assessed using the neuropathy disability score and by quantitative sensory testing.

Results:
Forty-seven subjects were recruited for study participation and stratified to three different groups according to their metabolic and neurological status: (1) group C: nondiabetic subjects without neuropathy (n = 20; age 41.3 ± 8.8 years), (2) group D: diabetes patients without neuropathy (n = 16; age 47.3 ± 7.6 years; diabetes duration 23.5 ± 10.4 years; hemoglobin A1c 7.7% ± 0.6 %), and (3) group DN: diabetes patients with neuropathy (n = 11; age 51.6 ± 8.1 years; diabetes duration 31.6 ± 21.3 years). All subjects were free from diabetic retinopathy as assessed by funduscopy. In patients with diabetic neuropathy, baseline and stimulated retinal microvascular blood was higher and the WLR was lower compared with both other groups. No difference could be found between the nondiabetic control subjects and patients with type 1 diabetes mellitus without diabetic neuropathy. A significant correlation could be observed between the vibration perception thresholds and retinal blood flow (r = 0.39; p = .01) and between temperature perception thresholds and WLR (r = 0.34; p = .03).

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Conclusions:
Our study confirmed early functional and morphological changes in microvascular retinal blood flow. The study indicates an association between peripheral sensory impairment and functional changes in retinal blood flow.

Glycemic Variability during Road Cycling in Elite Athletes with Type 1 Diabetes

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Objective:
We assess glycemic variability (GV) in cyclists with and without type 1 diabetes mellitus (T1DM) during intermittent high-intensity exercise.

Method:
This observational field study evaluated 17 male elite-level cyclists during multiple events. Glycemia was assessed by continuous glucose monitor (CGM; Dexcom SEVEN PLUS). Glycemic variability was calculated using EasyGV for two periods: during races (R) and while not racing (NR). The GV measures were compared between R and NR within and between T1DM and non-DM groups.

Result:
For the T1DM group, n = 9, age 22 ± 4 years, body mass index (BMI) 23 ± 2 kg/m^2, glycated hemoglobin 7.6% ± 1.0%. For the non-DM group, n = 8, age 26 ± 6 years, BMI 23 ± 2 kg/m^2. Races include 85 races (T1DM 39; non-DM 46) over 9676 km (T1DM 3912; non-DM 5764) with 254 h of CGM data (T1DM 101; non-DM 153). Non-races include 1402 h CGM data (T1DM 663; non-DM 739). The T1DM group measures were as follows: glucose mean (mmol), NR = 7.5 and R = 10.3; standard deviation (SD), NR = 2.9 and R = 1.9; continuous overall net glycemic action (CONGA), NR = 6.08 and R=8.79; LI, NR = 12.22 and R = 15.46; J-index, NR = 36.50 and R = 53.21; low blood glucose index (LBGI), NR = 5.85 and R = 1.06; high blood glucose index (HBGI), NR = 7.53 and R = 12.09; glycemic risk assessment diabetes equation (GRADE), NR = 4.99 and R = 11.81; mean amplitude of glycemic excursions (MAGE), NR = 7.02 and R = 0.79; M-value, NR = 11.93 and R = 18.78; and mean absolute glucose (MAG), NR = 4.17 and R = 4.5. The non-DM measures were as follows: glucose mean (mmol), NR = 5.4 and R = 6.1; SD, NR = 0.9 and R = 0.6; CONGA, NR = 4.76 and R = 5.59; LI, NR = 1.08 and R = 1.01; J-index, NR = 12.74 and R = 15.26; LBGI, NR = 2.29 and R = 0.99; HBGI, NR = 0.99 and R = 0.60; GRADE, NR = 0.57 and R = 1.59; MAGE, NR = 2.09 and R = 0.52; M-value, NR = 3.09 and R = 1.20; and MAG, NR = 2.12 and R = 2.07. Both groups' values were consistent with previous reports. All within-group differences (except LI, M-value, and MAG) and between-group differences (except LGBI and MAGE) were significant ($p < .05$).

Conclusion:
In T1DM and non-DM subjects, some GV measures increased while others decreased between R and NR periods. Measures of GV were greater in both R and NR in T1DM subjects versus non-DM. Future studies should assess the impact of greater GV on performance in athletes with T1DM.

Approaching a Truly Noninvasive Glucose Monitor: Calibration Validity

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Objective:
Generally, noninvasive (NI) glucose monitors require calibration with invasive reference prior to conducting measurements. Calibration minimizes the effect of individual quasi-stable factors and sets a baseline for physiological change detection. It is only valid as long as the quasi-stable factors remain unaltered; therefore, recalibration is required periodically. Intervals between recalibrations play a major role in home-use NI devices usability and utilization.

Method:
GlucoTrack® is a NI glucose monitoring device that enables performing frequent spot measurements. Prior to performing measurements, a ~2 h calibration procedure is required. Clinical trials were conducted on 30 subjects to evaluate calibration validity period. Each trial was performed for 4/6 days during 1/1.5 months, accordingly. Day 1 included individual calibration; on days 2–6, full-day measurement sessions took place. In addition, users filled out a questionnaire regarding their satisfaction and general impression from GlucoTrack.

Results:
Analysis of potential degradation in accuracy, as a function of elapsed time from calibration, shows no decrease in accuracy: ARD_{mean} values of 28.0% ± 0.5%, and no less than 97% of the points in the Clarke error grid clinically accepted A+B zones for each fortnight interval were maintained. Feedback shows that 91% found the device comfortable, 88% expressed willingness to use the device on a regular basis, and 97% declared that they will use the device more frequently than an invasive one.

Conclusions:
Clinical trials show feasibility of a simple process with long-term valid calibration (over 1.5 months). Users' feedback indicates satisfaction from GlucoTrack and willingness for utilization. Furthermore, it is believed that long duration of calibration validity and ability to perform frequent spot measurements without the need to continuously wear the device will lead to GlucoTrack becoming a useful home-use self-monitoring of blood glucose solution for persons with diabetes.

Effect of Self-Monitoring of Blood Glucose Calibration Errors on Performance of the Dexcom G4 Continuous Glucose Monitoring System

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Objective:
Currently available continuous glucose monitoring (CGM) systems require calibration with commercially available self-monitoring of blood glucose (SMBG) devices. The Dexcom G4 CGM system was recently tested in a multicenter clinical study with 72 subjects with insulin-dependent diabetes. The G4 CGM system was calibrated twice daily with an Ultra2 blood glucose meter (LifeScan, Milpitas, CA). YSI reference measurements were taken simultaneously per protocol to characterize patient glycemia and sensor performance. The goal of the study was to determine if SMBG errors were a root cause of poor performance observed on some sensors during day 1 of the study.

Method:
Data were obtained from the Dexcom G4 CGM system pivotal study conducted in 2011–2012. Continuous glucose monitoring sensor performance was compared with YSI readings once every 15 min for 12 h on days 1, 4, and 7. All sensors exhibiting mean absolute relative difference (MARD) in excess of 30% on day 1 were reviewed to identify possible SMBG calibration errors as the root cause of poor sensor performance. Seven sensors were identified as having poor performance on day 1 due to large discrepancies between the SMBG calibration values and concurrent YSI reference values. We compared the sensor performance from these seven sensors using calibration values either from SMBG readings obtained by patients with the sensor performance using calibration values from YSI readings obtained by research nursing staff. Sensor performance using YSI calibration values for the CGM system was calculated by postprocessing the data with the same algorithm used with the SMBG values.

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Result:
Approximately 50% of the large errors seen on day 1 of the G4 pivotal study were due to the use of erroneous SMBG values for calibration. The average error was 41.7 mg/dl or 42% compared with temporally matched YSI readings. We will show examples from the seven sensors identified in which use of YSI measurements in place of erroneous SMBG values results in significant improvements in sensor performance. In a typical example, elimination of the erroneous SMBG calibration value and use of the YSI measurement for calibration resulted in a change in MARD on day 1 from 32.8% to 8.4%. In the same case, replacing the erroneous SMBG reading on day 1 with a YSI measurement for calibration changed the overall MARD for days 1–7 from 15.8% to 7.4%.

Conclusion:
A significant portion of the large errors observed on day 1 with the Dexcom G4 CGM system can be attributed to erroneous SMBG measurements used as calibration values. These data suggest that the accuracy of modern CGM devices has improved to such an extent that SMBG errors have become a major root cause of the occasional egregious errors observed in clinical studies. Patients should be strongly encouraged to use the most accurate SMBG devices and rigorously follow best practices for obtaining the most accurate SMBG readings.

Enhanced Vascularization Surrounding an Implantable Continuous Glucose Sensor

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Objective:
The two most common problems that are being observed with *in vivo* experiments of implantable continuous glucose sensors are inflammation and fibrosis. Enhancing vascularization at sensor site improves tissue integration and enhances sensor function.

Method:
The inert, biocompatible materials polydimethylsiloxane (PDMS) and polymethyl methacrylate (PMMA)-coPEGdiMA were selected as housing materials for a near-infrared glucose sensor. Their surfaces are activated by a polydopamine and polydopamine/gelatin type B coating. The surface is then coupled with an antibody that binds to a constitutively expressed and specific endothelial surface molecule (vascular endothelial [VE] cadherin) or constitutively and most expressed endothelial surface molecule (platelet endothelial cell adhesion molecule-1). The presence of the antibody on the surface is measured through radiolabeling of the antibody with iodine. *In vitro* analysis through fluorescent microscopy of a coculture between HFF and HUVEC is used to evaluate their distribution on modified disks. *In vivo* analysis of modified disks in rats and modified coins in goats were performed to evaluate the integration and vascularization of the implants.

Result:
Polydopamine enhances the binding of the antibody to the surface of PDMS and even more to PMMA-coPEGdiMA. In a coculture, only a small enhancement of bound endothelial cells was observed for PDMS-modified surfaces. In the *in vivo* experiments, the presence of the anti-VE-cadherin antibody seems to increase the amount of capillaries and to promote implant integration.

Conclusion:
The results indicate that the modifications applied comprise a promising strategy to increase vascularity around implants, thus enhancing the tissue integration. The risk for capsular fibrosis is, however, still eminent and of importance for any sensor to be applied for *in vivo* use. Future experiments will assess if the enhanced vasculature enables adequate continuous *in vivo* glucose measurements.

Review of Nocturnal Hypoglycemia Risk Factors: Outcome of the HypoMon Home Trials

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Objective:
Nocturnal hypoglycemia is a feared complication experienced by people with type 1 diabetes mellitus (T1DM). The HypoMon (AIMEDICS P/L) is a real-time nocturnal hypoglycemia alarm that detects changes in physiological parameters resulting from the patient's response to hypoglycemia. The goal is to demonstrate that the HypoMon can identify key nocturnal hypoglycemia risk factors in patients who did or did not experience a hypoglycemia event as confirmed by self-monitoring of blood glucose (SMBG).

Method:
Data records from a total of 246 night sessions were collected and analyzed from 9 T1DM patients aged between 10 to 25 years. Patients entered relevant diabetes management data into the HypoMon which checked for physiological signatures associated with hypoglycemia.

Results:
Thirty nights (12%) were identified as low glucose sessions based on the SMBG entered into the device, either at alarm or any other time, with a mean BG of 77 ± 11 mg/dl. A total of 216 (88%) did not alarm nor measured low BG throughout the night sessions, with a mean BG value of 160 ± 54 mg/dl. Common hypoglycemia risk factors were analyzed among both groups. Episodes of hypoglycemia within 12 h of a night session were prevalent in 36% of the alarm nights to that of 22% of non-alarm nights. Similarly, exercise within 12 h of a night session occurred 50% by the alarm nights to that of 31% by non-alarm nights, resulting to a 1.6 times the relative risk factor for the likelihood of hypoglycemia.

Conclusion:
Key hypoglycemia risk factors are identified through the use of HypoMon in the home environment.

GDm-Health: Remote Monitoring for Gestational Diabetes

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Objective:
Effective management of glycemia during gestational diabetes mellitus (GDM) reduces short- and long-term risks to the health of the pregnant woman and fetus. Conventional monitoring involves intensive self-monitored blood glucose (SMBG) measurements with frequent clinic visits (every 2–4 weeks). Our objective is to use m-Health (cell phone based) technology to provide remote monitoring and deliver interventions between clinic visits for women with GDM.

Method:
Each patient uses a blood glucose meter (OneTouch UltraEasy) interfaced to a cell phone via a Bluetooth adaptor (Polytel GMA). New SMBG results are transferred immediately. Software on the phone (Android HTC Wildfire S) collects medication doses, meal tags, and free text comments entered by the patient, transmitting all data to a server. Patients can view graphs of their data on the phone screen, designed to emphasize the relationship between preprandial and postprandial glucose levels. Health care professionals review the data three times per week on a Web site and give rapid, individualized advice via phone calls and text messages. Initial testing of the system has been performed by five pregnant women with GDM.

Result:
The five patients found the system intuitive and helpful. During the first month of testing, they transmitted 753 blood glucose readings. Three patients taking hypoglycemic medication recorded 265 doses, and the health care professionals suggested medication adjustments based on the transmitted data.

Conclusion:
Remote monitoring of patients with GDM appears to be feasible using a cell phone with a Bluetooth connection to a blood glucose meter. The system will now be evaluated with a 50-patient cohort with the aim of providing good care with fewer clinic visits, resulting in time and cost savings for the patients and health service.

Model Predictive Control with Periodic Zones for All-Day Closed-Loop Operation of an Artificial Pancreas

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Objective:
The goal of this work is an artificial pancreas for automated insulin delivery to patients with type 1 diabetes mellitus (T1DM). A crucial element of any *fully* automated artificial pancreas is a strategy to perform safe and effective insulin dosing, and the authors have successfully developed control algorithms that achieve this task. Rigorous testing requires, first, operating controllers for multiday periods and, second, moving trials from clinics to an outpatient environment. The objective of this work is a fully automatic control strategy that enforces safe insulin delivery throughout both day and night.

Method:
The proposed control strategy employs *zone model predictive control*, whereby real-time optimization, based on a model of a human's insulin response, is utilized to regulate blood glucose levels to a safe *zone*. The novelty of the proposed approach is the use of time-dependent zones that *smoothly* modulate the controller correction based on the time of day. Specifically, the proposed controller strategically strives to maintain an 80–140 mg/dl glucose zone during the day, a 110–220 mg/dl zone at night, and a smooth transition of 2 h duration in between.

Result:
Based on a test of 10 *in silico* adult subjects on a typical meal schedule, the proposed controller administers, on average, 7.0% and 2.2% less insulin during the night than current fixed-zone controllers and basal–bolus therapy, respectively, and thereby alleviates the risk of nocturnal hypoglycemia. Furthermore, the proposed controller produces excellent responses to unannounced meals, severe hyperglycemia, and unannounced, self-administered insulin boluses.

Conclusion:
The proposed control strategy is a significant step toward safe and continuous evaluation of artificial pancreases on people with T1DM in an outpatient environment for prolonged periods of time.

IMC-Tuned ePID-IFB: An Improved System to Regulate Glycemia

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Objective:
The proprotional-integral-derivative controller with insulin feedback (ePID-IFB) control algorithm accounts for the ability of plasma insulin to inhibit insulin secretion and has shown promise in clinical trials. It can be tuned by pole placement and individual daily insulin requirements. We developed and tested a modification of this algorithm that incorporates an internal model control (IMC) component.

Method:
A mathematical model of blood glucose (BG) as a function of carbohydrate and exogenous insulin was developed; its parameters are either fixed or are based on individual continuous glucose monitoring and pump data. Individualized mathematical models were used to tune the ePID-IFB by means of IMC. Ten *in silico* adults in the University of Virginia/Padova type 1 diabetes mellitus metabolic simulator were used to compare performance of the generic ePID-IFB controller and the updated, IMC-tuned ePID-IFB. Model behaviors used for comparison included postprandial BG peaks, nadirs, settling times, and the control-variability grid analysis (CVGA) plot.

Result:
The IMC-tuned ePID-IFB outperformed the generic ePID-IFB. The former algorithm reduced 90% of the postprandial BG peaks, nadirs, and settling times and did not result in any hypoglycemic events. The IMC-tuned ePID-IFB glucose responses ended in the A or B zones of the CVGA 90% of the time, while only 70% of the responses from the generic ePID-IFB ended in these zones. The generic ePID-IFB responses included one hypoglycemic event, some strong oscillations, and relatively higher settling times.

Conclusion:
Incorporation of an IMC component into the ePID-IFB algorithm enables fine-tuning of the insulin delivery algorithm on a per-subject basis. The approach is currently being evaluated in an *in vivo* canine model ($n = 4$), and preliminary results are consistent with improvements seen in *in silico* humans.

Two-Dimensional Hindfoot Model for Plantar Pressure Prediction

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Objective:
High plantar pressures have been associated with foot ulceration in patients with diabetes. Treatment usually includes an in-shoe intervention designed to reduce plantar pressure under the heel by using insoles. Finite element (FE) analysis provides an efficient computational framework to investigate the performance of different insoles for optimal pressure reduction. The aim of this study is to design a patient-specific, two-dimensional (2D) FE model of a diabetic hindfoot.

Method:
A 2D FE model of the hindfoot was developed from reconstruction of magnetic resonance images (Simpleware ScanIP-ScanFE, v.5.0 and Rhinoceros v.4.0). Finite element software ABAQUS was used to perform the numerical stress analyses. A diabetes subject [age 72 years; body mass index (BMI) 25.1 kg/m^2] and a healthy subject (age 28 years; BMI 20.2 kg/m^2) were acquired. The foot biomechanics analysis was carried out. Vertical ground reaction forces (Bertec), taken from the midstance phase of the gait, were applied to the FE model. Validation of the pressure state was achieved by comparing model predictions of contact pressure distribution with experimental plantar pressure measures (Imagortesi).

Result:
A nonlinear 2D FE hindfoot model was developed and meshed with quadratic elements. The measured and model-predicted peak plantar pressures of the diabetes subject were, respectively, 682.32 and 602.82 KPa. The values for the healthy subject were 483.63 KPa for the measured peak plantar pressure and 428.63 KPa for the simulated one. The model-predicted structural response of the heel pad was in agreement with experimental results within 10% of error.

Conclusion:
The proposed model will be useful to simulate the different insole material and their contribution in decreasing the plantar pressures.

Combining Continuous Glucose Monitoring with Simultaneous Insulin Infusion in a Transcutaneous Optical Single-Port System

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Objective:
In order to overcome some drawbacks of current glucose monitoring and insulin infusion methods, we developed an integrated catheter for simultaneous glucose measurement and insulin delivery.

Method:
A single-port body interface integrates the glucose sensor into the insulin infusion catheter and thus solves two fundamental technical problems. First, insertion and removal of the sensor impose no additional burden on the patient, and second, the sensor is located in the body for only a short time, thus minimizing biocompatibility issues. The outer surface of the catheter is covered with an enzymatic phosphorescence-based glucose sensor and a reference oxygen sensor. Signals are read out transcutaneously via contactless near-infrared radiation successfully implementing "smart tattoo" technology.

Result:
In previous proof-of-principle studies, we have successfully shown frequency-domain measurements in the near-infrared region in skin and subcutaneous tissue. Furthermore, *in vivo* experiments in pigs demonstrated a good correlation of measured subcutaneous glucose concentrations to reference blood glucose values and that simultaneous insulin delivery at the site of glucose measurement does not affect the measured glucose concentration. In the present study, we used our new integrated glucose-sensitive insulin catheter for subcutaneous insulin infusion and maintained adjusted glucose profiles by intravenous glucose infusion, including hypoglycemic and hyperglycemic episodes (40–250 mg/dl). The insulin infusion rate was adapted to common insulin pumps, and insulin infusion was synchronized with subcutaneous glucose measurement.

Conclusion:
Our single-port device that integrates smart tattoo technology to simultaneously measure glucose and deliver insulin could become the heart of an artificial pancreas and lead to a milestone in diabetes management.

Perioperative Intensive Insulin Therapy Using an Artificial Pancreas with a Closed-Loop System in Hepatectomized Patients

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Objectives:
To reduce postoperative infection and/or surgical site infection (SSI) caused by surgical stress-induced hyperglycemia, perioperative tight glycemic control is recommended. However, intensive insulin therapy (IIT) proposed in 2001 (typical tight glycemic control with a target blood glucose range of 80 to 110 mg/dl) has a major problem of hypoglycemia less than 40 mg/dl, although it decreased morbidity and mortality in surgical intensive care unit patients. The incidence of hypoglycemia in IIT was reported previously ranging from 5% to 20%, and it was leading to often serious neurological disorders and sometimes fatal complications. It has been suggested that IIT-associated hypoglycemia may be solved by closed-loop glycemic controlled devices. To solve this issue of hypoglycemia in IIT, we have used an artificial pancreas (AP) with a closed-loop glycemic control system since 2006 in more than 500 surgical patients.

Method:
We introduce two studies for patients undergoing hepatic resection who were enrolled between 2007 and 2009. The former study is a prospective randomized clinical trial in 88 hepatectomized patients. The latter study is a retrospective comparison study in 150 hepatectomized patients.

Result:
In the former prospective study, IIT using an AP for 44 hepatectomized patients significantly reduces the incidence of SSI compared with conventional insulin therapy with a target blood glucose level of 150 to 200 mg/dl. Also, patients with IIT using an AP had significantly shorter postoperative hospital stays and more cost benefits after hepatic resection compared with those with conventional glycemic control. In the latter retrospective study, IIT using an AP for 74 hepatectomized patients significantly improved postoperative hepatic function compared with conventional insulin therapy with a target blood glucose level of 150 to 200 mg/dl. Of note, in both studies, no one had hypoglycemia even

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though IIT was performed in both studies. Also, IIT using an AP enables us to maintain stable glycemic control near euglycemia with less variability of blood glucose concentration.

Conclusion:
Our established novel tight glycemic control, such as IIT, using an AP is a more effective and safe method compared with conventional glycemic controls because it can improve surgical outcomes and decrease both hyperglycemia and hypoglycemia even in hepatectomized patients.

Accuracy and Precision Evaluation of the CONTOUR NEXT Blood Glucose Monitoring System

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Objective:
The CONTOUR® NEXT blood glucose monitoring system (BGMS) includes second-chance sampling (ability to reapply blood) and plain language messages. This study evaluated technical accuracy and precision of the new BGMS per ISO 15197:2003 section 7.

Method:
For accuracy evaluation, finger stick blood samples from 100 subjects were tested in duplicate using three test strip lots (n = 600). Samples were also tested in duplicate on a YSI 2300 STAT Plus™ reference analyzer. Accuracy was assessed per current ISO 15197:2003 criteria (i.e., percentage of results within ±15 mg/dl or ±20% of the reference result for glucose concentrations <75 and ≥75 mg/dl, respectively). For the precision evaluation, 5 blood glucose concentrations were each tested 10 times (across 3 test strip lots) on 10 individual meters (across 3 BGMS production lots). Additionally, 3 control solutions were tested once on each of the 10 meters on 10 separate days.

Result:
Accuracy assessment revealed that 100% (600/600) of CONTOUR NEXT BGMS results met current ISO 15197:2003 criteria, and 98.2% (589/600) of results were within ±7.5 mg/dl or ±10% of the reference result. Regression analysis demonstrated strong correlation between BGMS and reference results (R^2 = 0.9959). All results were within zone A of the Parkes consensus error grid. Precision testing showed a pooled percentage coefficient of variance (%CV) of 2.1% for the 40 mg/dl blood glucose concentration and 1.3% to 1.4% for concentrations 86 to 323 mg/dl. Control solution testing demonstrated low variability across multiple days (%CV, 1.4% to 1.6%).

Conclusion:
With more than 98% of results within ±7.5 mg/dl or ±10% of the reference laboratory value and low %CV, the CONTOUR NEXT BGMS demonstrated impressive accuracy and precision.

Accuracy Evaluation of a New Platform of Blood Glucose Monitoring Systems with the CONTOUR NEXT Test Strip

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Objective:
We evaluate the performance of a new platform of blood glucose monitoring systems (BGMSs) utilizing the CONTOUR® NEXT test strip in the laboratory and in the hands of users.

Method:
Accuracy of four BGMSs was tested in the laboratory (four studies) and in the hands of users (four studies) in accordance with ISO 15197:2003 sections 7 and 8, respectively. In all studies, BGMS results were compared with YSI reference results.

Result:
Regression analyses of laboratory results demonstrated excellent correlation between BGMS and reference results for all systems (CONTOUR NEXT EZ, y = 0.97*x* + 2.2, R^2 = 0.9964; CONTOUR NEXT LINK, *y* = 0.97x + 2.3, R^2 = 0.9961; CONTOUR NEXT USB, *y* = 0.96x + 2.1, R^2 = 0.9957; CONTOUR NEXT, *y* = 0.97*x* + 1.4, R^2 = 0.9959). In the hands of users, BGMS results showed a similar level of correlation with reference results (CONTOUR NEXT EZ, y = 0.97*x* + 3.78, R^2 = 0.9878; CONTOUR NEXT LINK, *y* = 0.99x + 0.43, R^2 = 0.9926; CONTOUR NEXT USB, *y* = 0.97*x* + 2.11, R^2 = 0.9835; CONTOUR NEXT, y = 0.98*x* + 2.54, R^2 = 0.9850). In the laboratory, >98.7% of results were within ±10 mg/dl (glucose values <75 mg/dl), >98.1% of results were within ±10% (glucose values ≥75 mg/dl), and >98.3% of results were within ±10 mg/dl or ±10% (glucose values <75 and ≥75 mg/dl, respectively) of reference results. In the hands of users, 100% of results were within ±10 mg/dl (glucose values <75 mg/dl), >95.9% of results were within ±10% (glucose values ≥75 mg/dl), and >96.1% of results were within ±10 mg/dl or ±10% (glucose values <75 and ≥75 mg/dl, respectively) of reference results.

Conclusion:
The new platform of BGMSs utilizing the CONTOUR NEXT test strip demonstrated consistently high levels of accuracy both in the laboratory and in the hands of users.

Context-Aware Insulin Pump Systems

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Objective:
With the advent of electronic insulin pump devices comes the risk of third parties *undetectably* altering doses to harm a patient. Contextual information of patient events (e.g., eating, sleeping, or exercise) can be used to protect critical device settings from being changed. Our objective is to augment current devices with detailed contextual information provided by piezoelectric sensors to detect and prevent security breaches.

Method:
A piezoelectric sensor is an inexpensive device that converts a mechanical deformation into a charge. This can be used to detect specific patient events such as eating (e.g., deglutition and peristalsis). An example application of a context-aware system is the blocking of changes to critical device settings while a patient sleeps. If an insulin bolus event is detected while sleeping, this information allows the device to determine that the dosage is harmful, alert the patient, prevent the event from being executed, and log the event to help forensic log investigation (also providing patients better context about blood glucose trends).

Result:
We have built a system using inexpensive piezoelectric sensors to monitor bodily functions and are currently exploring optimized signal processing of resulting signals. After showing a feasible system, manufacturers can eventually integrate piezoelectric sensors with current insertion site and glucose monitoring components. A context-aware insulin pump system will enable improved security (e.g., blocking changes to critical device settings) and better effectiveness (e.g., automatically tagged glucose logs will show how sleeping affects blood glucose levels).

Conclusion:
Recent work has shown that insulin pump system security needs improvement. We are building protection mechanisms by using inexpensive piezoelectric sensors with current insulin pump systems. Contextual information provided by these sensors can provide increased security.

A Bio-Inspired Insulin Bolus

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Objective:
In vitro physiological data of insulin release in beta cells reveal that glucose-induced insulin secretion comprises a transient insulin release (first phase) followed by a gradually developing secondary stimulation (second phase).

This work aims to develop a novel insulin bolus wave inspired by the observed biphasic insulin release to provide more efficient glycemic control for subjects using bolus waves in current subcutaneous insulin infusion pumps (single wave, dual wave, and square wave).

Method:
The bio-inspired insulin bolus (BIB) is composed of an initial single wave (B) at time T0 followed by a trapezoidal shape defined by two insulin infusion rates (R1 and R2) and the corresponding times (T1 and T2). The BIB parameters are optimized for a mixed-meal model library using a composite type 1 diabetes (T1DM) minimal model of glucose–insulin dynamics and a least squares grid search parameter identification technique. The blood glucose risk index (BGRI) was used to assess the performance of the evaluated bolus waves.

Result:
In silico testing shows that the BIB provides better, or equivalent in the worst case, glycemic control (15% average relative BGRI reduction) with respect to other existing bolus waves over 23 tested mixed meals. The BIB showed greater glycemic control improvements in slow absorption meals than fast absorption meals.

Conclusion:
An insulin bolus wave inspired by the physiology of insulin release from the beta cells may help to improve glycemic control in T1DM subjects. Prior individualization of the bio-inspired bolus wave parameters is required for optimal control of different types of mixed meals.

Robust Parameter Estimation of Glucose–Insulin Minimal Models Using Interval Analysis

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Objective:
Minimal models of glucose–insulin metabolism are currently being used in several diabetes-related applications, such as assessment of insulin sensitivity and glucose effectiveness, first- and second-phase pancreatic response, model-based glucose controllers, and model-based fault detection techniques. Robust evaluation of these methods has created a need for bounded error parameter estimation techniques. This work presents an innovative method for guaranteed nonlinear parameter estimation of metabolic minimal models based on interval analysis.

Method:
An efficient vectorial implementation in Matlab of set inversion via interval analysis algorithm (SIVIA) was developed for this purpose. In order to reduce numerical overestimation associated with interval arithmetic, modal interval analysis was employed. Clinical data from standard oral glucose tolerance test (OGTT) and meal tolerance test, as well as *in silico* data, were used to prove the validity of the proposed approach.

Result:
Despite the exponential complexity of the SIVIA, due to its branch-and-bound nature, the proposed implementation, with a tolerance of 1% (stopping criteria), was able to identify the four parameters of the glucose–insulin minimal model (p1, p2, p3, g0) for an OGTT data set with 2% error in plasma glucose measurements and 3% error in plasma insulin measurements in a computation time of 290 s (Intel Dual Core 3.16GHz).

Conclusion:
Set inversion via interval analysis is a suitable tool for robust parameter estimation of the glucose–insulin minimal model.

Formative Evaluation of the Artificial Pancreas System User Interface

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Objective:
Inpatient studies run by engineers for the artificial pancreas (AP) are being replaced by outpatient studies in which the patient assumes control in the operation of AP devices. As a result, human factors studies and usability testing are of paramount importance in the deployment of these systems for home use. This work presents the first formative evaluation of an AP system user interface intended for home use.

Method:
Heuristic evaluation (expert review) was followed by three focus groups with type 1 diabetes patients with varying exposure to diabetes technology (n = 13). Feedback was gathered on various system components addressing user interaction, system features, and capabilities. Change recommendations were prioritized, and users were asked to rate the system on several criteria on an increasing scale from 1 to 5.

Results:
Results indicate high ratings for overall satisfaction (mean 4.77), a very professional "look and feel" (mean 5), and user "understandability" with the system (mean 4.69). Features and functions of the system and preparedness for a clinical trial received slightly lower scores (mean 3.92 and 3.62, respectively). Users indicated the importance in maintaining all existing insulin pump and continuous glucose monitoring device functionalities. In addition, requirements for a user guide suggest the necessity for a thorough explanation of system features.

Conclusion:
New risks associated with interaction between the user and the AP system require a formal human factors analysis and design process to mitigate risk through appropriate interface design and interaction features. The usability tests introduced here lay the groundwork for local and global modes of AP user interface development.

Characterization of Hypoglycemia by Processing Subcutaneous Sensor and Insulin Data

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Objective:
Avoiding hypoglycemia is a key to optimal diabetes management. Continuous glucose monitoring (CGM) is a promising technology, and with subcutaneous glucose readings every 5 min, CGM is a serious candidate for real-time or retrospective hypoglycemia detection. However, sensor inaccuracy in the hypoglycemic range limits the applicability. The objective of this study was to explore features in the sensor data and insulin data suitable for retrospectively characterizing hypoglycemia.

Method:
Seventeen data sets of 10 type 1 diabetes patients were recorded. The patients underwent insulin-induced hypoglycemia, while finger-stick blood glucose and Medtronic sensor subcutaneous glucose were recorded. Several features from sensor data and insulin information were systematically tested, individually and in combination with each other, and feature information content was extracted with SEPCOR and forward selection. The value of a feature combination was determined as the hypoglycemia detection rate in the data set.

Result:
The data set contained 18 hypoglycemic events (one subject experienced two hypoglycemic events). The best features were the sensor glucose value itself, time since last insulin injection, and features derived from linear regression, skewness, and kurtosis of the sensor glucose values in different time intervals. With these features, it was possible to detect hypoglycemia with a sensitivity of 100% (18/18 hypoglycemia detected correct) and one false positive.

Conclusion:
The results indicate that it is possible to characterize and detect hypoglycemia retrospectively by processing only sensor and insulin data. This is a new and unique approach to compensate for the inaccurate sensor data in the hypoglycemic range and thereby improve detection of hypoglycemia. Improved hypoglycemia detection in sensor data could help physicians and diabetologists expedite initiation of necessary measures for improving glycemic control.

Online Insulin Sensitivity Estimation in Type 1 Diabetes Mellitus: Enhancing Glycemic Prediction in the Artificial Pancreas Platform

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Objective:
The objective of this study is to introduce a new method to estimate the insulin sensitivity (SI) of patients online with type 1 diabetes mellitus (T1DM) based on Kalman filtering (KF), which could be used in both insulin dosing correction (open or closed loop) and fault detection schemes, enabling adaptation to varying metabolic states (illness, exercise, and biological rhythms).

Method:
Drawing from the seminal minimal model of glucose kinetics, we designed a novel mathematical description of glucose homeostasis in logarithm space, which enables non-negative SI estimation by linear KF methodology. The KF core model was constructed using the University of Virginia/Padova simulation platform. Two feed-forward models are added informing meal and insulin appearance with the SI parameter replaced by a dynamic equation: enabling KF online estimation based on glucose measurements and insulin injections. Data from eight T1DM patients (two admissions each) with two meals and one exercise period were used to validate the system. Based on estimated blood glucose and remote insulin action states, we used three SI assessments to predict blood glucose: (a) population-averaged SI, (b) patient-specific SI determined during the first meal, and (c) KF estimated SI.

Result:
The resulting mean absolute relative differences (MARDs) of predicted blood glucose are (a) fixed population SI, 18.9% ± 5%; (b) fixed patient-specific SI, 18.7% ± 5%; and (c) variable SI, 17.2% ± 4%. Predictions using methods (a) and (b) were not distinguishable (p = .3), while online SI estimation decreased MARD significantly (p = 2.4e - 5).

Conclusion:
Online estimation of SI is shown to provide more accurate short-term glucose predictions in T1DM patients while maintaining physiologically reasonable values and providing a mean to access key glucose metabolism parameters based solely on insulin injections and frequent glucose measurements.

The Quest for Islet Cell Regenerative Medicine Engineering

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Background:
The success in directing human embryonic stem (hES) and induced pluripotent stem (iPS) cells to differentiate into islet-like cells raises new hopes for cell-based diabetes therapy. It is envisioned that islet cells generated from hES/iPS cells can be used to replace damaged beta cells and restore a patient's near-physiological insulin secretion capability so that homeostatic sugar levels can be maintained in the blood. This, however, has not yet been possible because of the difficulty in generating fully functional beta cells *in vitro*. In many cases, cells differentiated from hES or iPS cells are immature or, in other words, are not suitable for cell replacement therapy. Most islet-like cells derived from hES/iPS cells *in vitro* fail to function normally *in vivo* after transplantation in diabetic animal models. On the other hand, *in vivo* maturation of pancreatic endoderm progenitors presents significant successes. This suggests that more studies need to be done to determine key factors that are required for *in vitro* maturation of hES/iPS cell-derived beta cells.

Method:
In vivo tissue functionality relies upon (at least) three properties, i.e., cell type, extracellular matrix or scaffolds, and hormones and/or other signaling molecules. Thus engineering approaches need to be developed to realize or mimic these *in vivo* microenvironments in order to promote maturation of beta cells *in vitro*.

Results:
Our recent study divulged that *in vitro* maturation of beta cells can be achieved by carefully designing physicochemical cues that mimic *in vivo* microenvironments for cell attachment, proliferation, and differentiation.

Conclusion:
Translation of these studies into technological development will bring cell replacement therapy one step closer to treating diabetes in more controllable clinical settings.

Design and Evaluation of a MicroTip Array-Based Continuous Glucose Monitor

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Objective:
We aim to develop a minimally invasive continuous glucose monitor based on MicroTips to access interstitial glucose.

Method:
An array of hollow silicon MicroTips, approximately 300 μm in length, was attached to a buffer-containing reservoir. A screen-printed, three-electrode amperometric sensor utilizing a platinum–carbon working electrode with immobilized glucose oxidase was situated on the opposite face of the reservoir. Glucose passively diffuses through the MicroTips via the buffer to the sensor. A custom controller was connected to the sensor–MicroTip assembly to operate the sensor. The assembly was applied to human subjects using a spring-loaded applicator. Ten adult subjects with type 1 or type 2 diabetes mellitus had four devices applied to the upper arm or forearm. Six subjects wore devices for 48 h and four subjects for 72 h. Subjects reported to the study site daily for comparative finger stick glucose measurements, taken every 20 min, and underwent glucose excursions into both the hypoglycemic and the hyperglycemic range. Systems were calibrated after a 2 h warm-up period and then once daily with the morning finger stick. Glucose values were calculated using a prospective algorithm that had previously been trained on data from nondiabetic volunteer subjects.

Result:
The mean absolute relative difference for the combined 48 and 72 h data was 16%, with 74% of the readings in the Clarke error grid A region. No lumen clogging or decrease in sensor performance was observed over the 72 h period. Devices were well tolerated, and minimal irritation was observed after device removal.

Conclusion:
A novel MicroTip and sensor technology has been developed that provides clinically accurate continuous glucose readings to diabetes patients over a 3-day duration. This technology provides a pain-free alternative to inserted or implanted continuous glucose monitors.

YSI 2300 STAT Plus Glucose and Lactate Analyzer: Technology, Performance, and Future Developments

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Background:
The YSI 2300 STAT Plus is an established reference method for the measurement of blood glucose in glucometer development and manufacturing quality assurance applications.

Method:
Our presentation will provide an overview of YSI Incorporated, the organization behind the YSI 2300.

Result:
A discussion of the mechanism by which the YSI 2300 measurement is accomplished will be presented, and current performance data will be reviewed, including YSI 2300 precision and linearity performance with a comparison of whole blood and plasma glucose measurements.

In addition, the technology utilized in the YSI 2300 is open for development, with resulting improvements in accuracy, precision, and ease of use.

Conclusion:
Results will be presented demonstrating a path forward with this technology to allow further improvement in the performance of this established reference method.

Development of a Noninvasive Glucose Biosensor for Neonates

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Objective:
The current standard of care for determining glucose levels from an infant is either by a point-of-care testing bedside glucose analyzer and/or one of the laboratory enzymatic methods. In either situation, the infant would be subjected to painful and invasive blood sampling either from an arterial/venous draw or a heel lance. Therefore, a noninvasive method for monitoring glucose would be a breakthrough in the medical management of these sick premature infants who are currently subjected to multiple blood draws.

Method:
Since neonatal skin is underdeveloped, its cutaneous barrier is more permeable than mature skin, and neutral small molecules like glucose could easily diffuse out of the skin. We plan to detect this low concentration of glucose on the skin using a biosensor with improved low-end sensitivity compared with currently used biosensors. In our study, we used the periplasmic glucose-binding protein (GBP) with a single cysteine mutation at L255 labeled with environmentally sensitive dye (acrylodan). The GBP-based assay corresponds to four orders of magnitude higher affinity for glucose than glucose oxidase.

Results:
Cellulose ester nanoporous membrane has been widely used as a substitute for human skin in *in vitro* diffusion studies (e.g., drug delivery and reverse iontophoresis). In our experiments, we used a 10 mm diameter cellulose ester membrane with a 500–1000 Da MW cutoff. Glucose solutions over the range of blood glucose concentration (2–33 mM) were confined within a 5.5 cm length of membrane. The fluorescent GBP biosensor successfully detected glucose on the surface of the membrane that correlated to the glucose concentration of the test solutions.

Conclusions:
The results suggested that mutant GBP L225C labeled with acrylodan can be used to develop a low-cost noninvasive glucose sensor for neonates. Optimum surface washing time and sampling methods were also determined to further develop the protocol for clinical studies. The performance of the optical glucose assay was compared with high-performance anion-exchange chromatography with pulsed electrochemical detection.

Prediction of Exhaustion under Extreme Physical Conditions via Continuous Metabolite Monitoring

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Objectives:
Our aim is to develop a continuous metabolite monitoring system to predict exhaustion under extreme physical conditions. Continuous, real-time monitoring of metabolic level changes during physical exercise can be used as a tool to assess changes in physical condition and predict performance for diabetes patients.

Methods:
Our previously developed coil-type electrochemical sensor was implanted transcutaneously in the dorsal region of normal and diabetic rats, and a wireless transmitter collected data continuously. Microdialysis in the jugular vein and the subcutaneous tissue was used as a reference. Ringer's solution was pumped through the microdialysis probes (CMA Microdialysis), and samples were collected periodically and analyzed for glucose and lactate content (YSI 2300 STAT Plus). Forced exercise was performed on a treadmill (IITC Life Sciences) until exhaustion, and a recovery period was allowed prior to euthanasia (120 mg/kg pentobarbital).

Results:
Glucose and lactate trends indicated immediate activation of both aerobic and anaerobic metabolism, which is typical in transitions from a state of rest to exercise. A short period of aerobic metabolism followed by a switch to anaerobic metabolism during most of the exercise was detected. Interestingly, there was a distinct change in glucose and lactate trends that signaled the exhaustion observed approximately 10 min afterwards. Overall, the metabolic trends obtained by our sensors are more accurate, especially during abrupt changes, while providing real-time data.

Conclusions:
Our results show that concurrent, real-time monitoring of glucose and lactate in the subcutaneous tissue mirrors metabolic changes in the body and can predict exhaustion under extreme physical conditions within a time frame of 10 min. This offers an advantage in diabetes patients by helping manage imminent exhaustion before it fully develops.

Comparative Performance Evaluation of the CONTOUR NEXT Blood Glucose Monitoring System

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Objective:
We compared the performance of the CONTOUR® NEXT blood glucose monitoring system (BGMS), which includes second-chance sampling (ability to reapply blood) and plain language messages, with other systems across a wide range of glucose values, including high and low values.

Method:
Study staff tested finger stick blood samples at three different times from 146 subjects aged ≥18 years with type 1 or type 2 diabetes using the CONTOUR NEXT BGMS and five other systems (Accu-Chek® Aviva Nano, FreeStyle Lite®, OneTouch® Ultra®2, OneTouch® Verio™Pro, and TRUEtrack®). Three samples/subject were collected to test fresh blood. For 100 subjects, an additional sample was collected to be modified to achieve extreme glucose values. Subjects were safely managed to either lower or raise their blood glucose levels to collect samples across a wide glucose range. At least 50 samples were collected in each of the following glucose ranges: <70, 70–180, and >180 mg/dl; extreme levels (<50 or >350 mg/dl) were achieved by blood sample glucose modification. Analyses were performed to compare performance across BGMSs. Subject feedback regarding their attitudes about BGMS accuracy in general and diabetes management were obtained via a questionnaire.

Result:
Analysis of variance results for the low glucose range (<70 mg/dl) will be presented (primary objective) as well as for the middle (70–180 mg/dl) and high (>180 mg/dl) ranges. Additionally, the results of the Parkes error grid analysis and variability analysis will be shown.

Conclusion:
Results from this study are not yet available but will be provided when available.

Critical Role of Macrophage Chemokines in Controlling Continuous Glucose Monitoring *In Vivo*

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Objective:
Our laboratory recently demonstrated that macrophages (MQs) play a central role in compromising glucose sensor function and limiting continuous glucose monitoring (CGM) *in vivo*. It is known that the chemokine CCL2 (monocyte chemotactic protein-1) is a key MQ chemotactic factor at sites of injury and inflammation. Thus we hypothesized that deficiencies in the CCL2 or CCR2 receptor (CCR2) would reduce MQ recruitment to sites of glucose sensor implantation and thereby enhance and extend sensor function and CGM *in vivo*.

Method:
To test this hypothesis, we evaluated CGM in transgenic mice that are deficient in CCL2 or the CCR2 (Jackson Labs) using our murine model of CGM. The mean absolute relative difference (MARD) over a 4-week experiment was utilized to characterize CGM performance and compared with mice sufficient in CCL2 and CCR2 (C57BL/6) using analysis of variance.

Result:
As previously demonstrated, control C57BL/6 displayed loss of sensor function over the 4-week test period as reflected by increasing MARD values. Alternatively, both CCL2-deficient and CCR2-deficient mice failed to display significant increases in MARD values over the 4-week test period. Analysis of variance indicated that, although there was no statistical difference in MARD for these three groups during week 1 and 2, CCL2-deficient (-/-) and CCR2-deficient (-/-) mice have statistically better MARD values in weeks 3 and 4 when compared with C57BL/6 mice.

Conclusion:
These studies indicate that the MQ chemokine CCL2 and the CCL2 play a critical role in controlling sensor function and CGM *in vivo*. These studies suggest that therapeutic targeting of CCL2 and CCR2 may provide a new approach to extending glucose sensor function and CGM in patients with diabetes.

Performance of a Point-of-Care Glycated Hemoglobin Testing Device

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Objective:
Glycated hemoglobin (HbA1c) is a sensitive predictor of the long-term complications of diabetes. Point-of-care testing (POCT) of HbA1c enables a real-time discussion of glycemic status between a health care provider and a person with diabetes and thus may encourage more vigorous control measures that may lead to improved outcomes. Clinical utility of a POCT HbA1c test depends on the availability of accurate test systems. The latest version of Bayer's A1CNow+® device incorporates multiple modifications in manufacturing, calibration, and optics that collectively support its current analytical performance. The objective of this study was to evaluate the performance of the latest version of Bayer's A1CNow+ MULTI-TEST A1C SYSTEM according to the newly tightened National Glycohemoglobin Standardization Program (NGSP) certification criteria.

Method:
As of September 2012, the NGSP criteria for certification were substantially tightened, and the new performance requirements are that 37 of 40 results obtained from an HbA1c device must be within ±7% (relative bias) of the NGSP reference laboratory result. Forty blood samples were analyzed in singleton on Bayer's A1CNow+ over 5 days, and the results were compared with the mean of duplicate results from a NGSP reference laboratory (SRL#9) method (Tosoh G8).

Results:
The results meet the newly tightened NGSP requirements, with 39/40 results being within ±7% (relative bias) of the reference value.

Conclusion:
The current version of Bayer's A1CNow+ system meets the newly tightened NGSP performance criteria and provides accuracy to carry out HbA1c POCT as an aid in the management of diabetes.

Orthogonally Redundant Glucose Sensing: Initial Experiences *In Vitro* and *In Vivo*

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Objective:
One of the major goals for diabetes treatment is to close the loop, i.e., to use a fully automated glucose-sensor-augmented insulin pump. An accurate and reliable sensor has been identified as a necessity for safe closed-loop realization. A reliable sensor in this context must deliver reliable data and have error-detecting functionality, enabling the closed-loop system to take action on erroneous data. Our objective is to develop a continuous glucose monitoring system with sufficient reliability and accuracy for use in a closed-loop system.

Method:
Medtronic's proposed solution to detect failures and deviations in the sensing system is through use of orthogonally redundant sensing. Orthogonally redundant sensing is defined as employing two (or more) fundamentally different technologies to measure the same parameter. Medtronic, in partnership with the Juvenile Diabetes Research Foundation and the Helmsley Foundation, is developing an orthogonally redundant sensing system based on the glucose-oxidase-based electrochemical sensor and a mannose-binding-protein-based optical sensor. The use of two fundamental different glucose recognition principles in combination with two fundamentally different interrogation principles will provide means for an accurate and more reliable measurement, in addition to enabling real-time sensor error and failure detection.

Result:
We will present the initial experiences gained from *in vitro* and possibly *in vivo* testing of a first prototype of the orthogonally redundant sensor and integrated interrogation device.

Conclusion:
The quest for obtaining a safe and reliable sensing system for use in a closed-loop system has started, and orthogonally redundant sensing is one of the paths being pursued by Medtronic.

The Impact of Insurance Coverage and the Family on Pediatric Diabetes Management: A 4-Year Experience

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Objective:
We analyze the relationship between health insurance coverage, family composition, insulin management, and their impact on glycemic control in a pediatric type 1 diabetes population.

Method:
We performed a retrospective chart review of medical records from the Pediatric Endocrinology Clinic at the University of Louisville, Kentucky.

Result:
A total of 893 type 1 patients were included; 305 (34%) publicly insured, 588 privately insured. Publicly insured patients were more likely to use twice-per-day insulin injections (16% versus 11%) or multiple daily injections (MDIs; 67% versus 54%). Mean hemoglobin A1c (HbA1c) level for public patients was 9.26%, compared with 8.42% for private, $p < .0001$. Of the 893 patients, 297 were in single-parent homes (33%). Single-parent homes had significantly higher HbA1c levels than two-parent, 9.04% versus 8.48%, $p < .0001$. Two-parent patients were more likely to utilize a continuous subcutaneous insulin infusion pump (34%) than single-parent (18%). Privately insured patients in two-parent homes with MDI or pump devices had the lowest HbA1c levels.

Conclusion:
Both insurance type and family composition have significant effects on glycemic control and insulin management. Insurance limitations on glucose monitoring and pump devices may play a role in decreased pump usage and monitoring. The social and financial challenges faced by single parents also appear to play an influential role in glucose management. Identifying and addressing major factors influencing glucose control, such as availability of resources, family education, and adult support and supervision, may help improve glycemic control in high-risk diabetes patients.

Oral Medication Adjustment with Telehealth Support for Type 2 Diabetes

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Objective:
We are investigating the feasibility of support for self-titration of oral glucose-lowering medication in type 2 diabetes using a telehealth platform.

Method:
Fourteen type 2 diabetes patients were randomly allocated to two groups. Intervention group patients received a cell phone (Nokia 7230) and a blood glucose meter (OneTouch Ultra) with Bluetooth cradle (t+ Medical) and were asked to perform at least six blood glucose tests per week, of which at least three were required to be fasting. Blood glucose readings were transferred wirelessly to the phone and uploaded to a server. The intervention group used the phone software to review their data after each measurement and self-adjust their medication every 3 weeks based on a treatment plan agreed upon with their physician. Nursing staff reviewed the data via a secure Web site twice per week. Control group patients received routine diabetes care, including physician-directed medication changes. All patients received monthly telephone calls in which lifestyle factors, including diet and physical activity, were discussed and any medication changes were recorded.

Result:
An interim analysis at 6 months showed that six of the seven intervention group patients had adjusted their oral glucose-lowering medication. Four of the seven control group patients had medication changes. The median hemoglobin (HbA1c) reduction was 10 mmol/mol in the intervention group and 5 mmol/mol in the control group, a difference in mean baseline-adjusted HbA1c of 6 mmol/mol ($p = .35$).

Conclusion:
Self-titration of oral glucose-lowering medication in type 2 diabetes with self-monitoring and remote monitoring of glycemia appears feasible. Larger studies are envisaged to determine whether clinical outcomes are improved.

Educational Social Games Embedded in a Telemonitoring Tool for Children with Type 1 Diabetes: A Preliminary Paper

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Objective:
The aim is to develop a telemedicine educational platform for children aged 9–13 years with type 1 diabetes mellitus and conduct a clinical trial that documents the effects hereof on individual diabetes skills and clinical outcomes. This project is a joint consortium effort from Scandinavian and U.S. project partners.

Method:
The proposed system combines social media and video games, creating an educational social game experience. Interfaces to existing electronic diabetes diaries will offer gameplay based on the users' actual treatment scheme. Utilizing reward-driven gameplay, as seen in regular social games, and including the target audience in the design phases will keep players interested and returning to the game and learning about aspects of diabetes. A clinical trial in Danish pediatric departments (control and intervention group) will be performed to document the clinical outcomes. Structured interviews with patients, guardians, and staff will be conducted.

Result:
The study will collect data from both games and the electronic diabetes diary, providing information about daily blood glucose measurements, insulin injections, exercise, and dietary habits, as well as information about time spent playing the game and progress made in game. Hemoglobin A1c will be a primary end point. The results will be used to document potential significant clinical outcomes of system usage. Data from the structured interviews will be analyzed to determine any personal outcomes of system usage.

Conclusion:
Current scientific literature documents a decrease in adherence and quality of self-care when children reach adolescence. This necessitates an alternate approach to diabetes education. This educational approach utilizes social media and video games, both popular and familiar within our target group. Clinical outcomes will be documented in scientific literature in 2012–2015.

Use of a Food and Drug Administration-Approved Type 1 Diabetes Mellitus Simulator to Evaluate and Optimize a Proportional-Integral-Derivative Controller

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Objective:
Clinical studies have shown that the Medtronic proportional-integral-derivative (PID) control with insulin feedback (IFB) provides stable 24 h glucose control but with high postprandial glucose. We coupled this algorithm to a Food and Drug Administration-approved type 1 diabetes mellitus simulator to determine whether a proportional-derivative controller with preprogrammed basal rates (PD_{BASAL}) would have better performance.

Method:
We performed simulation studies on 10 adult subjects to (1) obtain the basal profiles for the PD_{BASAL} controller, (2) define the pharmacokinetic/pharmacodynamic profile used to effect IFB, (3) optimize the PID and PD_{BASAL} control parameters, (4) evaluate improvements obtained with IFB, and (5) develop a method to simulate changes in insulin sensitivity and assess the ability of each algorithm to respond to such changes.

Result:
PD_{BASAL} control significantly reduced peak postprandial glucose [252 (standard error = 11) versus 279 (14) mg/dl; $p < .001$] and increased nadir glucose [102 (3) versus 92 (3) mg/dl; $p < .001$] compared with PID control (both implemented with IFB). However, with PD_{BASAL} control, fasting glucose remained elevated following a 30% decrease in insulin sensitivity [156 (6) mg/dl; different from the target of 110 mg/dl; $p < .001$] and remained below target following a 30% increase in insulin sensitivity [84 (2) mg/dl; $p < .001$]. The PID control returned glucose levels to target in both cases.

Conclusion:
Preprogrammed basal rates provide better postprandial glucose control than PID but are not appropriate for subjects whose basal requirements change with insulin sensitivity. Simulations used to compare different control strategies should assess this variability.

Applying New Support Vector Machine Post-Processing Strategies for the Detection of Correct and Incorrect Measurements in Continuous Glucose Monitoring Systems

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Objective:
Support vector machines (SVMs) are an attractive option to detect correct and incorrect measurements made by real-time continuous glucose monitoring systems (CGMSs), because their learning mechanism usually considers a small subset of patterns to separate failure from fault-free situations. However, the SVM standard is inherently biased toward the majority class when classifying imbalanced data sets. This work is aimed to introduce two strategies of SVM post-processing for imbalanced data sets as in this context. The first approach, called SVM-1, considers improving the geometric mean (G_{mean}) between specificity and sensitivity. In the second approach, SVM-2, the priority is to improve sensitivity rather than improve the accuracy of the overall classifier.

Method:
Twenty-three critically ill patients on insulin therapy were monitored for 72 h using a CGMS. Arterial blood glucose (ABG) samples were obtained following the protocol established in the intensive care unit (ICU). The ABG measurements were synchronized with CGMS measurements, obtaining a data set of 537 samples. The data set was first classified according to International Organization for Standardization criteria (372 correct and 165 incorrect measurements). The SVMs were trained using data provided by the CGMS (electrical signal and glucose estimation), insulin dose, and body temperature.

Results:
The SVMs with Gaussian radial basis kernel (22,750 problems solved) were tuned and validated using five-fold cross validation. Average specificity of 83.0%, 68.1%, and 41.0% and sensitivity of 47.1%, 68.4%, and 80.9% were reported for standard SVM, SVM-1, and SVM-2, respectively. Average accuracy of 72.7%, 68.1%, and 52.3% and G_{mean} of 62.3%, 68.2%, and 57.2% were obtained for standard SVM, SVM-1, and SVM-2, respectively.

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Conclusion:
New approaches of SVMs could be a potential tool to develop a self-monitoring fault detection system for a real-time CGMS, using the information provided by the monitor and incorporating variables about the patient's clinical condition.

PEGylated Photo-Crosslinkable Hydrogels for Long-Term Implantable Glucose Sensors

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Objectives:
The function and lifetime of an implantable continuous glucose monitoring (CGM) device are intimately linked with the stability of the glucose oxidase (GO_x) enzyme, responsible for glucose detection. Enzyme denaturation, loss due to imperfect immobilization, and biofouling-induced pore clogging gradually decrease device stability. Polyethylene glycol (PEG)-based hydrogels offer an opportune venue to minimize biofouling while retaining their highly hydrated state to prevent enzyme denaturation. Here we report the use of a novel PEGylated polymer, capable to afford covalent stabilization with GO_x, and simultaneously photo crosslink in its fully hydrated state. This hydrogel produces CGM sensors with long-term stability and optimal performance.

Methods:
A random copolymer based on PEGylated side chains together with cinnamyl ethyl methacrylate (CEMA) and glycidyl methacrylate (GMA; namely, polyPEGMEM-CEMA-GMA) was synthesized by free-radical polymerization using azobisisobutyronitrile initiator. The polymer was mixed with GOx enzyme and drop casted on the electrode, followed by ultraviolet exposure for crosslinking and 24 h incubation for reaction between the GO_x-amine and hydrogel's GMA-epoxide group.

Results:
Glucose sensors utilizing GO_x-grafted polyPEGMEM-CEMA-GMA hydrogels showed excellent stability during continuous testing for 16 days. Control experiments with a hydrogel lacking the epoxide functionalities indicated that the majority of enzyme leached out within hours. By retaining >65% mole ratio in PEG functionality, these hydrogels provide a good biofouling resistance against serum albumin. The sensors exhibited a sensitivity of 320 nA $mM^{-1}mm^{-2}$, with an apparent Michealis–Menten constant of 25 mM of glucose and limit of detection of 1 μM.

Conclusions:
PEGylated hydrogels with epoxide functionalities to covalently immobilize enzymes were found to provide ideal matrices for implantable glucose sensors. These hydrogels not only retain enzyme activity, but also provide good antifouling properties and afford ease of fabrication via traditional photo-lithography methods.

Shared Care Combined with Telecare Improves Glycemic Control of Diabetes Patients in a Rural, Underserved Community

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Objective:
The effectiveness of shared care combined with telecare in type 2 diabetes patients in an underserved community has not been investigated in Asia. We aimed to investigate this issue.

Methods:
A total of 95 patients with type 2 diabetes who had hemoglobin A1c (HbA1c) > 7% for at least 1 year were recruited from six community health centers in remote Changhua County, Taiwan. All patients were randomly divided into intervention (shared care combined with telecare) and usual care groups for 6 months. Hemoglobin A1c, blood pressure, and lipid profiles were checked at baseline and study end.

Results:
The decrease in HbA1c level was significantly greater in the intervention group than in the usual care group (0.7% + 1.3% versus 0.1% + 1.0%; $p = .03$, after adjusting sex, age, and body mass index) after 6 months of shared care and telecare programs. There were no significant differences in lipid profiles and blood pressure changes between these two groups.

Conclusions:
Shared care combined with telecare could significantly reduce HbA1c levels in type 2 diabetes patients with poor glycemic control in rural, underserved communities. However, further studies should be conducted to clarify the target users and to develop cost-effective and personalized interventions.

Accuracy and Reliability of Current Continuous Glucose Monitoring Systems: A Direct Comparison

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Objective:
We assessed the accuracy and reliability of current continuous glucose monitoring (CGM) systems.

Method:
We studied the Animas Vibe with Dexcom 4a generation sensor, the Abbott FreeStyle Navigator, and the Medtronic Paradigm with Enlite sensor in 18 patients with type 1 diabetes. All three CGM sensors were worn during a clinical research center visit. Patients received a meal with a delayed and increased insulin bolus to induce pronounced postprandial glucose peaks and nadirs. Hereafter, randomization determined which two of the three sensors would be worn at home until end-of-functioning. Patients were instructed to try to reactivate the sensor beyond the manufacturer-specified lifetime. Patients performed at least five reference finger sticks per day. Analysis of variance was performed on all data points ≥15 min apart.

Results:
The mean absolute relative difference [MARD; (standard deviation)] was 19.7 (53.9)% for the Navigator, 20.5 (18.2)% for the Dexcom, and 16.4 (15.6)% for the Enlite (overall $p = .007$), significantly lower for both the Enlite ($p = .001$) and the Navigator ($p = .001$) versus Dexcom. MARD at glucose levels <100 mg/dl was 17.4 (15.2)% for Navigator, 26.6 (25.7)% for Dexcom, and 21.5 (24.0)% for Enlite (overall $p = .005$), significantly lower for both Enlite ($p = .008$) and Navigator ($p = .005$) versus Dexcom. MARD at levels >200 mg/dl was 23.0 (87.6)% for Navigator, 16.6 (13.8)% for Dexcom, and 13.6 (9.4)% for Enlite (overall $p = .104$). Median (interquartile range) time until failure for Navigator was 8.5 (3.5) days, 10.0 (1.0) days for Dexcom, and 8.0 (1.5) days for Enlite (overall p = .075; Dexcom versus Abbot, $p = .042$; Dexcom versus Enlite, $p = .106$). Maximum time until failure was 82 days for Dexcom, 26 days for Navigator, and 15 days for Enlite.

Conclusion:
Sensor accuracy analyzed using MARD ranks better with Abbott and Medtronic devices, while the Dexcom sensor is superior on lifetime when assessed beyond manufacturer recommendations.
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A Novel Algorithm for Processing and Calibrating Continuous Glucose Monitoring Data

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Objective:
The purpose of this study was to develop and evaluate a novel algorithm for processing and calibrating continuous glucose monitoring (CGM) data.

Method:
The algorithm comprises six parts: time shifting to compensate physiological delay between sensor data and blood glucose, rate-limiting filtering to correct signal nonphysiological rate of change, trimmed averaging to decimate the sampling frequency, noise detection to identify the necessity of smoothing based on zero crossing of the signal first-order differences, smoothing to decrease signal roughness, and calibration to convert sensor data from the nanoamp range to mg/dl^{-1} using a robust linear conversion function. To evaluate the algorithm, a Medtronic patented algorithm was implemented, and the performances of the two algorithms were compared using the same 144 data sets [CGM and self-monitored blood glucose measurements (SMBG)] from diabetes patients.

Result:
Compared with the Medtronic algorithm, the median absolute relative deviation of CGM glucose from SMBG glucose was lower in all ranges (9.7% versus 17.6%, 8.9% versus 10.6%, and 7.2% versus 7.6% in the hypoglycemic, euglycemic, and hyperglycemic ranges, respectively), and the delay produced by the new algorithm was 5 min shorter. Furthermore, the new algorithm increased the percentage of the sensor readings (total 18,613 readings) in zone A of Clarke error grid analysis from 81.1% to 84.1% ($p < .0001$; Pearson χ^2).

Conclusion:
The new algorithm appears to decrease the discrepancy between CGM readings and SMBG readings and, as a result, shows promise to enhance the accuracy of commercial CGM devices.

Physical Activity Sensors Are Superior to Heart Rate Monitoring for Real-Time Activity Detection: Implications for Closed-Loop Diabetes Control

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Objective:
We have recently shown that mild/moderate-grade physical activity (PA) influences glucose status in healthy individuals and age/gender matched type 1 diabetes mellitus (T1DM) using continuous subcutaneous insulin infusion. Currently in closed-loop studies, instantaneous heart rate and accelerometers are being evaluated to measure PA. We compared PA measured by accelerometers to instantaneous heart rate output.

Methods:
A total of 23 subjects (11 controls and 12 T1DM) underwent a carefully planned and supervised PA protocol. Where continuous glucose data were captured using Dexcom SEVEN PLUS® continuous glucose sensor, PA data were collected using MSR accelerometers (MSR Electronics GmbH, Seuzach, Switzerland) attached to a participant's body using an elastic belt. The heart rate data were captured on IntelliVue patient monitors (Philips Healthcare, Andover, MA) using finger clip pulse oximeters. The data were compared for two inactive (premeal and meal) bouts and two active bouts to test repeatability. Heart rate and accelerometer data were scaled to a 0% to 100% range based on the participant-specific minimum and maximum values, and intraclass coefficient (ICC) was computed for concordance measures.

Results:
Heart rate profiles by patient were highly variable, whereas accelerometers tracked the study protocol more closely. While the concordance, by ICC, varied considerably by patient, it did not differ statistically between T1DM and controls ($p = .44$). For both controls and T1DM, during active periods, both heart rate and accelerometery output varied appropriately, but during the two sedentary periods, the heart rate data showed more variability ($p = .02$ and $p = .04$, respectively).

Conclusion:
Highly accurate accelerometery shows more accuracy compared with instantaneous heart rate and has more potential for incorporation into closed-loop systems for T1DM.

Evaluation of Enlite Glucose Sensor Performance by Real-Life Glycemic Distributions

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Objective:
To accurately quantify the sensor performance that patients would experience during real-life use, we transformed the average overall mean absolute relative difference (MARD) between sensor glucose and reference blood glucose (YSI) values from in-clinic data. Glucose sensor accuracy is affected by measuring in low, normal, and high glycemic ranges. In clinical studies, patients are artificially driven to low glucose levels to collect a significant number of low glycemic data points. This large number of low glycemic data points leads to an inflated MARD compared with what patients experience in real life.

Method:
The sensor MARD was calculated for each of three glycemic ranges (≤75, >75–180, and >180 mg/dl) using data from abdominal sensors in the Enlite Pivotal Trial. Blood glucose values derived from 1093 patient years of Medtronic CareLink data were grouped into three glycemic ranges to determine the percentage of time spent in each in real life. Finally, the overall real-life MARD was calculated using a weighted average of the three sensor MARDs according to the percentage of time spent in each range.

Result:
MARD values were 17.4%, 12.6%, and 12.0% in the ≤75, >75–180, and >180 mg/dl ranges, respectively. During the clinical study, 23.5% of the YSI values were in the hypoglycemic range, resulting in an overall MARD of 13.6%. The real-life percentages of time spent in each range were 8.1% (≤75 mg/dl), 59.1% (>75–180 mg/dl), and 32.8% (>180 mg/dl). The projected real-life overall MARD was 12.8%.

Conclusion:
Weighting MARD values according to standard glycemic profiles may more accurately represent a patient's real-life sensor performance experience.

A Consensus-Perceived Glycemic Variability Metric

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Objective:
Glycemic variability (GV) is increasingly recognized as a significant component of overall glucose control. Excessive GV may trigger oxidative stress, which has been linked to increased risk of complications. Physicians readily recognize excessive GV in continuous glucose monitoring (CGM) plots; however, there is no automated screen in routine clinical use. One hindrance is the lack of a universally agreed upon way to measure GV. The objective of this study is to provide a consensus-perceived glycemic variability (CPGV) metric that could be routinely applied to CGM data.

Method:
Physicians actively managing patients with type 1 diabetes were recruited at the 2011 Diabetes Technology Meeting. Twelve physicians rated a total of 250 24 h CGM plots as exhibiting low, borderline, high, or extremely high GV. Physician ratings were averaged to obtain consensus and then used as input to two machine learning (ML) algorithms: multilayer perceptrons (MP) and support vector machines for regression (SVR). *In silica* experiments were run using each ML algorithm with either raw or smoothed CGM data and different combinations of 12 descriptive input features. Ten-fold cross validation was used to evaluate the performance of each developed model.

Result:
The SVR models approximated the consensus ratings of unseen CGM plots better than the MP models. When judged by the root mean square error, the best SVR models performed comparably to individual physicians at matching consensus ratings.

Conclusion:
Model refinement continues to develop an accurate and easy-to-use CPGV metric. The new metric could be used as a routine measure of overall glucose control to supplement hemoglobin A1c in clinical practice.

New Continuous Glucose Monitoring System for Artificial Pancreas Research

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Objective:
Performance of continuous glucose monitoring (CGM) systems has significant impact on efficacy and reliability of the artificial pancreas (AP) system. Specific attributes of a CGM system that are critical to an AP are continuous data without large data gaps and reliability. Dexcom's G4® CGM device and the new G4 Receiver Tool DevKit focus on these two needs. DevKit was developed by collaboration between Dexcom and the University of California, Santa Barbara, and Sansum Diabetes Research Institute.

Methods:
Artificial pancreas algorithms use a continuous stream of CGM data to make decisions on insulin and, in some cases, glucagon, and AP algorithms are dependent on the reliability of these data, i.e., without egregious (>30%) errors and without large data gaps (>30min). The Dexcom G4 system and DevKit improve over the previous-generation systems in a number of ways, including enhanced communication, significant reduction in data gaps, and enhanced usability. The new DevKit is a dynamic-link library (DLL) that gives users flexibility to use data as they suit their requirements, significantly simplifying the usability of the DevKit, as AP software can link to the DLLs to get real-time access to effective glycolytic volume and meter records.

Results:
This new system has an improved range (>30 feet), with improved reliability (>99% data availability).

Conclusions:
The DevKit has been validated on Windows. Porting the DevKit to other platforms (e.g., Android) is currently underway. In our testing, the new G4 receiver connected to the AP system platform had a significantly greater range than the previous-generation receiver tool used with SEVEN PLUS. The DevKit is available to all AP groups and enables the use of the accurate and reliable Dexcom G4 system in their studies.

Three-Dimensional Glycemic Variability Diagnostic for Highlighting Patterns of Glycemic Risk through Continuous Glucose Monitoring

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Objective:
Continuous glucose monitoring (CGM) has created new opportunities for measuring glycemic variability (GV) and detecting glucose patterns. To better translate CGM data into insights that enable patients to achieve their glycemic targets and improve clinical outcomes, a novel three-dimensional GV pattern map was developed for use with the Dexcom G4 CGM device.

Method:
The GV pattern map is a graphical rendering of glycemic risk. It highlights patterns of low and high glucose excursions that occur around the same time of day. Detected patterns are shown with an intuitive display that conveys both frequency and severity of excursions. The pattern map allows the patient or clinician to select CGM data across a window of time. The CGM data are then overlaid based on time of day. Each day of CGM data (*y* axis) is plotted separately, between 12:00 AM to 11:59 PM (*x* axis). A "weight" is assigned to each CGM measurement over the range 40–400 mg/dl, where the weight reflects degree of membership in the low or high glucose zone (the lower the glucose, the stronger the membership in the low zone). At each time point, the weighted values from each time series are integrated into a cumulative score. The integrated score is displayed using a shaded coloring scheme (third dimension) that reflects frequency (rate of occurrence) and severity (degree of "low" or "high" excursion).

Result:
The GV pattern map summarizes large quantities of CGM data into an intuitive illustration that conveys how often and by how much glucose excursions travel outside a targeted range.

Conclusion:
The GV pattern map demonstrates how CGM data can be translated into insights that enable improved clinical outcomes. Its clinical validation is underway.

In Vitro Calibration and Accuracy for a Long-Term Implantable, Fluorescent-Based Wireless Glucose Sensor

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Objective:
We present the *in vitro* calibration and accuracy of a fluorescence-based glucose sensor. This sensor is in the early stages of clinical evaluation for long-term implantable continuous glucose monitoring. The *in vitro* characterization and calibrated performance set the basis for a number of parameters that define the transducer's functionality. The objective of this presentation is to show both the calibration process and the accuracy of the sensing system.

Method:
In vitro calibration of the Sensors for Medicine and Science (SMSI) glucose sensor is done at multiple glucose levels, spanning from 0 to 40 mmol, and spanning multiple temperature steps. This process quantitates and verifies the dissociation constant, the percentage signal, and the amount of baseline that are in the system initially, as well as how each of these respond to temperature. This calibration is done as part of the sensor manufacturing process. Further studies were performed to track the changes of these parameters when subjected to thermal degradation, photobleaching, and oxidation to fully characterize our sensor for *in vivo* application.

Result:
In vitro sensor performance is shown to be below 2% mean absolute relative difference at manufacturing as compared with YSI measurements of the various buffer solutions. The testing has also shown that the *in vitro* degradation mechanisms are slow enough such that the sensor signal can transduce glucose past 6 months and maintain an accuracy of less than 5% using fixed rate constants.

Conclusion:
In vitro testing of the SMSI glucose sensor verifies both the model and the performance characteristics that can maintain a high level of accuracy through a period of 6 months or more.

Comparative Analysis of Glycemic Control in Type 2 Diabetes Patients under Pump Therapy with Single and Multiple Daily Basal Rates

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Objective:
Continuous subcutaneous insulin infusion (CSII) is an established and effective treatment in type 1 diabetes, whereas, in patients with type 2 diabetes, CSII treatment is still used on a limited basis. We performed a retrospective analysis of glycemic control in pump users with type 2 diabetes retrieved from the CareLink diabetes management database to determine whether glycemic control achieved with single basal rate (BR) regimen was comparable to results achieved with multiple BRs.

Method:
Data from 244 type 2 CareLink pump users who had used both single and five daily BRs along with continuous glucose monitoring sensors were selected for the analysis. Use of sensor glucose data allowed evaluation of glycemic control with important end points of transient hyperglycemia or hypoglycemia. Mean absolute relative difference values of sensors used in analysis were below 20%.

Result:
Treatment with single or five daily BR regimens resulted in comparable glycemic control. Mean and average maximum sensor glucose values and percentage of time spent in hyperglycemic, euglycemic, and hypoglycemic ranges obtained with two regimens were similar. The mean coefficient of variation of blood glucose was 6.1% ± 2.98% and 6.5% ± 3.84% for single and five BR regimens, respectively ($p < .001$).

Conclusion:
In the type 2 diabetes population treated with pumps, a simplified BR regimen resulted in glycemic control that was comparable in effectiveness to that achieved with the multiple BRs. Moreover, we found less glycemic variability in patients with a single BR as compared with multiple BRs. Thus, in type 2 patients, using multiple BRs does not necessarily improve glycemic control; however, it may be a source of confusion and increased burden for both patients and physicians.

Brain Tissue Oxygenation-Guided Management in Cerebral Edema Induced by Diabetic Ketoacidosis

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Objective:
Type 1 diabetes mellitus is the most common chronic disease of childhood. Diabetic ketoacidosis (DKA) is a well-known complication of diabetes mellitus and can be associated with devastating cerebral edema, resulting in severe long-term neurologic disability. Despite the significant morbidity and mortality associated with this condition, relatively few treatments are recommended for these patients. We present two cases in which they used both intracranial pressure (ICP) and brain tissue oxygenation (PbtO2) monitoring to manage DKA-associated cerebral edema with favorable neurologic outcomes.

Interventions:
The setting for the study was a pediatric intensive care unit in a tertiary care teaching hospital. Two children presented to the emergency room with vague complaints and were found to have DKA. During treatment, both patients became comatose, with head computed tomography scans revealing diffuse cerebral edema and herniation syndrome. Intracranial pressure and PbtO2 monitors were placed to guide therapy.

Results:
Multiple episodes of brain tissue hypoxia were noted in both patients. Intracranial pressure control with intubation, sedation, and hyperosmolar therapy improved episodes of decreased PbtO2 associated with intracranial hypertension. Brain tissue oxygenation was also noted to be significantly less than goal on several occasions, even when ICP was controlled and an age-appropriate cerebral perfusion pressure (CPP) goal was met. Augmentation of CPP above age-appropriate goal with fluid boluses and inotropic agents increased PbtO2 in these instances. Both children had very low Glasgow coma scale scores on admission but ultimately had favorable neurologic outcomes.

Conclusions:
Multimodal neuromonitoring of both ICP and PbtO2 during episodes of clinically apparent DKA-associated cerebral edema allows for detection and treatment of episodes of elevated ICP and/or brain tissue hypoxia that may be of clinical significance.

Diabetes Mellitus: An Alarming Message from the Middle East

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Introduction:
The Arab world covers a vast geographic area, consisting of 23 countries with a combined population of approximately 358 million people. Geographically, this part of the globe is variable, ranging from dry desert areas to lush green land. This part of the globe is also unique for its wide cultural, social, and ethnic variations. Arab countries are well-heeled, with significant oil and natural gas resources, and earn high incomes.

Background:
Socioeconomic progress has brought benefits in the region such as improved access to health care, education, and safe drinking water. This rapid economical change has also set the scene for modern lifestyles activities: people are eating more and exercising less. These changes in the lifestyle cause obesity and metabolic syndrome and are probably responsible for diabetes mellitus. Despite marvelous advancement in medical sciences, diabetes mellitus is still an incurable, lifelong disease and is swiftly increasing in both developing and developed countries.

Result:
Presently, six countries in the Arab world, including Saudi Arabia, Bahrain, United Arab Emirates, Kuwait, Oman, and Egypt, are among the world's highest for the prevalence of diabetes.

Conclusion:
The worldwide prevalence of diabetes mellitus is approximately 7%; however, the prevalence of diabetes in the Arab world is approximately 13.03%, which is almost double the worldwide prevalence.

The Updated University of Virginia/Padova Type 1 Diabetes Simulator

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Objective:
A new version of the type 1 diabetes mellitus (T1DM) simulator has been recently submitted to the Food and Drug Administration (FDA). In fact, recent results showed that there was a margin of improvement, particularly in the ability of the simulator to describe hypoglycemic events and counter regulation. Here we present the new simulator with respect to the version accepted by the FDA in 2008.

Method:
The model of glucose kinetics in hypoglycemia has been improved by assuming that insulin-dependent utilization increases, when glucose decreases below a certain threshold, as the risk function. In addition, glucagon kinetics, secretion, and action models have been incorporated into the simulator. In particular, glucagon kinetics are described with a single compartment model; glucagon secretion is regulated by plasma insulin, plasma glucose concentration below a certain threshold, and glucose rate of change; and plasma glucagon concentration stimulates with some delay in endogenous glucose production. Finally, new rules for determining insulin-to-carbohydrate ratio (CR) and correction factor (CF) of the virtual patients have been implemented to better comply with clinical definitions. A new strategy for virtual patient generation has also been adopted, which is based on clinical parameter plausibility.

Result:
The new simulator shows better performance in describing hypoglycemic events. In addition, the new virtual subjects are representative of the real T1DM population, as demonstrated by the good agreement between real and simulated distribution of patient-specific parameters, such as CR and CF.

Conclusion:
The new T1DM simulator enables more reliable *in silico* testing of closed-loop control algorithms and is a valid tool to provide guidelines for clinical studies.

MIMURA V Dimension Healing on Pico-Nonchemical Technology

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Objective:
MIMURA into H2O cluster of colloidal mineral metals with Nitrogen, Carbon, Toxin, Bacteria, Virus in a cell for mitochondria of healing DNA/RNA of ATP, Apoptosis, Immunity, memory-tip to resolve metabolic failure of body-cells of all internal organs blood(red corpuscle, lymph in leukocyte, plasma), vessels, tissue systemization. All diseases are caused by oxygen deficit and diabetes, cardiac & cancer diseases by cellular oxygen deficit that means the positive electron energy deficit on quantum physics dynamic. Diabetes is a standard bearer of oxygen deficit on insulin that shall guide into incurable diseases.

H2O of hydrogen for oxygen combined with nature positive energy on earth shall sympathize with colloidal minerals, vitamins in amino-protein of mitochondria. As results, processing proteins at amino acid constructive dimensions of phosphoric acid, D-glucose, AT/GC bases, Alpha-helix, Beta-sheet. Integrated DNA/RNA/P53, synthesis enzymes-hormones, noradrenalin &serotonin in Nervous PC12, Alpha wave & spirit, glycol-CD4/CD8. Helper T, Embryonic stem cells, Extra cellular matrix etc., shall have high voltage energy against virus, bacteria, Free radical, cancer DNA RAS21, Toxin, depression, Atomic nucleus at negative energy under nature principle.

Method:
(M) MIMURA Energy Water: 1~ 1.5L per day for QOL, drink/cook/take a bath. Quality: Much oxygen, Non-oxidization, Non-free radical, Nano-cluster, Hardness CaCO3/Mg over 50% down for melt-soft, Colloidal-minerals & NO3/SO4-compound, Low-surface tension, High-penetration, High-electric conduction, Self-destruction of bacteria & virus, Air infective protection, ammonia resolution, Smell methane volatilization, pH for low, Ion radiation (S) Super ATORU Liquid: 40 ~60 cc per day. Morning/Evening huge oxygen & colloid minerals energy in nano- tornado cluster of low pH.

Mimura cont. ⟶

Mimura cont. ⟶

Result:
(M) for 3 months: Diabetes w/hypertension, Atopy, Kidney stone, Menstrual dark HDA1C 6.7% - 5.8%, Skin normal, Stone melt, blood fresh color No pain. (M & S) for 4 months: 1)Before HIV/RNA 373,455/ml CD4 148 After 20 days - 186,915/ml CD4 62 and healing for Healthy Fat. 2) Cancer(Brain Glio-Blastome Multiformae Stage3) w/ diabetes. After 2 months – Restrain& Stop tumor-expand and decrease for Recovery w/ refresh hair, skin 3) Diabetes w/ hypertension and cardiac & kidney diseases & much neutral fat: Before glycogen 270 After 2months 110 for healthy recovery. 4) Myocardial & Cerebral infarction, Cancer (Breast/ Womb/ Stomach), Leukemia, Hepatitis, Vertebra carries, Articular leumatism, Arthritis, Neuralgia, Alzheimer, Alcoholic etc since 1997 R&D on clinical tests.

Conclusion:
M&S would be able to extend the average of healthy life span for 22 century's hope.

Kaiser Permanente Diabetes Technology: Innovation to Reduce Inpatient Hypoglycemic Events

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Objective:
We aim to reduce incidents of hypoglycemia in the hospital setting by effectively utilizing electronic systems and implementing improvements as a result of trend analysis, observations, and fact finding.

Method:
Point-of-care test (POCT) glucose results obtained from hospitalized individuals are recorded in our electronic medical records (HealthConnect). Data extracted from this system allow for real-time application of standardized algorithm for hypoglycemia treatment. Also, the ability to collect historical data on a large scale allows for quality, risk, and specialist teams to assess patterns and implement strategies for patient safety and quality of care.

Result:
Over a period of 19 months, statistical analysis exhibits a reduction in hypoglycemic episodes during hospitalization by 8% and 1.5 episodes per day of diabetes patients. This practice proves to shorten the duration of a hypoglycemic event and reduce complications of prolonged reoccurrences in a timely manner. To further prevent hypoglycemic episodes, multidisciplinary root cause analysis teams are created. Findings are disseminated to primary care, hospitalist, and specialty providers, including nursing administration, as a tool to educate and further raise awareness in both the inpatient and outpatient setting.

Conclusion:
The frequency of hypoglycemic episodes varies; however, there is greater prevalence and complication if untreated in a timely manner. An immediate ability to access patient charts through HealthConnect and extract real-time POCT results has allowed staff to become engaged in effective and timely treatment of abnormal glucose levels. The invaluable information stored in HealthConnect has served as a vehicle for the organization to adopt a continuous improvement model. Incorporation of plan–do–study–act models in daily operations permits the institute to develop specific, realistic protocols and sustainable targets.

Glycemic Variability Is Associated with Subclinical Atherosclerosis in Type 2 Diabetes

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Objective:
The contribution of glycemic variability to macrovascular complications remains unclear, thus we investigated the association between glycemic variability and cervical and/or intracranial atherosclerosis in type 2 diabetes patients.

Method:
Ninety-three type 2 diabetes patients with a hemoglobin A1c of 8.6% ± 2.0% and a median (interquartile range) diabetes duration of 9 (4.5–13.5) years underwent magnetic resonance angiography (MRA) and carotid ultrasound assessment to evaluate the cervical and intracranial atherosclerotic lesions and to quantify carotid intimamedia thickness (IMT) as subclinical atherosclerosis index. Glycemic variability was calculated as the standard deviation of blood glucose (SDBG) values and mean amplitude of glycemic excursion from 3-day continuous glucose monitoring data.

Result:
Sixty-four patients (68.8%) presented with cervical and/or intracranial lesions on MRA. The common carotid artery and the intracranial portion of the internal carotid artery were most susceptible to plaque formation. Age and diastolic blood pressure were significant and independent predictors for cervical and/or intracranial lesions. SDBG value (r = 0.384; p = .04) was positively correlated with carotid IMT and remained significant in multivariate regression analysis, but only among subjects without atherosclerotic lesions (n = 29).

Conclusion:
Glycemic variability is associated with subclinical atherosclerosis in type 2 diabetes. Improved glycemic variability control may reduce the risk of atherosclerosis.

Real-World Experience Managing Obesity and Metabolic Syndrome with an Ileal Brake Hormone-Releasing Substance in Comparison with Roux-en-Y Gastric Bypass

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Background:
Roux-en-Y gastric bypass (RYGB) hormonally mediates inflammation and rapidly improves glucose, insulin resistance, and hepatic function. These changes precede weight loss. Delivery of oral food materials to the distal small intestine would be expected to mimic the predominant effect of RYGB through actions on the "ileal brake." We are developing Brake™, an oral carbohydrate compound formulated for release in the small intestine. In our present work, we compare RYGB and Brake for restorative effect on weight and metabolic biomarkers.

Methods:
In separate protocols, RYGB and Brake subjects were followed to identify changes in excess body weight (EBW), blood pressure [systolic blood pressure (SBP)/diastolic blood pressure (DBP)], cholesterol [low-density lipoprotein (LDL)/high-density lipoprotein (HDL)/triglycerides (TG)], fasting plasma glucose (FPG), homeostasis model of assessment of insulin resistance (HOMA-IR), hemoglobin A1c (HbA1c), liver [aspartate aminotransferase (AST)/alanine aminotranferease (ALT)], and renal function [serum creatinine (SCr)]. Subjects with baseline elevation in ≥1 metabolic biomarker and follow-up sampling were included in comparative analyses assessing metabolic restoration, medication discontinuation, and safety.

Results:
RYGB subjects had profound restoration in all metabolic parameters: EBW (38%), SBP (100%), DBP (100%), LDL (94%), HDL (69%), TG (96%), FPG (100%), HOMA-IR (83%), HbA1c (100%), AST (100%), and ALT (100%), while reducing need for antihypertensive, antihyperlipidemic, and antidiabetic medications. Brake subjects demonstrated restorative effects similar to RYGB: EBW (40%), SBP (59%), DBP (100%), LDL (72%), HDL (140%), TG (92%), FPG (64%), HOMA-IR (46%), AST (73%), and ALT (68%), but medications were not commonly discontinued. No change in SCr was detected in RYGB or Brake.

Monte cont. ⟶

Monte cont. ⟶

Conclusions:
While not as profound as RYGB, Brake induced significant weight loss and improvements in blood pressure, lipids, glucose, and insulin resistance. Liver enzymes improved significantly in both groups. Our future work aims to optimize the Brake formulation and release mechanism to maximize hormonal response from the small intestine.

Pharmacokinetics, Pharmacodynamics, and Local Toleration of Recombinant Human Insulin-Based Ultra-Rapid-Acting Formulations BIOD-123 and BIOD-125 Compared with Insulin Lispro

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Objective:
We evaluated the pharmacokinetics, pharmacodynamics, and local injection site toleration of BIOD-123 and BIOD-125 compared with insulin lispro (IL).

Method:
These formulations were evaluated in a single-center, double-blind, randomized, three-period cross-over trial in 12 patients with type 1 diabetes. Each patient received injections of 0.20 U/kg of blinded test insulin in a randomized treatment sequence. Pharmacodynamics were assessed with euglycemic glucose clamps. Injection site toleration was evaluated using a 100 mm visual analog scale and relative and absolute severity scales. Injection site edema and erythema were systematically assessed using the Draize scale.

Result:
Both BIOD-123 and BIOD-125 were associated with significantly faster time to 50% maximal insulin concentrations compared to IL (9.8, 12.4, and 27.0 min, respectively; $p < .05$). Peak metabolic effects were comparable between the formulations. Metabolic effect washout times were modestly longer for BIOD-123 and BIOD-125 than for IL, although these differences were not statistically significant (286.7, 284.2, and 260.7, respectively). Visual analog scores were 3.6, 6.8, and 1.8 mm, respectively, p = not significant for BIOD-123 to IL comparison. Relative and absolute severity and Draize scores were not different between the formulations.

Conclusion:
BIOD-123 and BIOD-125 were associated with more rapid absorption, similar peak metabolic effects, and modestly longer, nonsignificant washout times compared with IL. All injections were well tolerated and comparable in intensity to IL.

Reduced Glycemic Excursions with Recombinant Human Hyaluronidase Pretreatment and Continuous Subcutaneous Insulin Infusion in Type 1 Diabetes Mellitus

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Objective:
Pretreatment with recombinant human hyaluronidase (rHuPH20) provides a consistent ultrafast pharmacokinetic/glucodynamic profile over infusion set life. This study compared the glycemic response to a solid meal challenge between continuous subcutaneous insulin infusion (CSII) with rHuPH20 pretreatment and without pretreatment.

Method:
A randomized two-way crossover study in subjects with type 1 diabetes mellitus (T1DM) who use CSII compared 150 U of rHuPH20 administration upon infusion set placement to sham injection. Subjects were administered intravenous insulin and/or glucose to stabilize premeal glucose to 110 mg/dl and received the same prandial insulin bolus dose at the start of four identical solid breakfast meal challenges in each study phase. Glucose response was measured by YSI, and p values were obtained from a repeated measures analysis of variance model with a compound symmetric covariance matrix.

Results:
Based on interim data, rHuPH20 pretreatment provided a 67% reduction in prandial hyperglycemia (0–2 h area under the curve > 180 mg/dl) from 2051 to 675 min/mg/dl, $p < .0001$. Mean peak postprandial glucose was reduced from 210 to 178 mg/dl ($p = .0004$), with comparable reductions in 60, 90, and 120 min values from 184 to 143, 175 to 134, and 162 to 131 mg/dl, respectively (all $p \leq .001$). Hypoglycemia was identical with both treatments.

Conclusion:
Pretreatment with rHuPH20 dramatically reduced prandial hyperglycemia following solid breakfast meals for T1DM patients on CSII.

Clinical Feasibility Study of a Percutaneous Optical Fiber Glucose Sensor

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Objective:
Current continuous glucose monitoring (CGM) systems exhibit a rather short lifetime. We present data of a novel CGM system (FiberSense) with improved duration of action and accuracy, based on a fluorescent biosensor placed on the tip of an optical fiber.

Methods:
FiberSense was inserted in the subcutaneous abdominal and upper arm tissue of 10 patients and compared with capillary blood glucose measured by a laboratory method and a commercial CGM system placed on the contralateral abdominal area. Blood glucose was altered during measurement sessions of 4–5 h by administration of insulin and carbohydrates, followed by periods of home-use conditions. Fluorescence was measured using a miniaturized photometer. Two-point calibrations as well as one-point calibrations were performed daily.

Results:
FiberSense was clinically well tolerated at both placement sides for up to 28 days without complications or signs of inflammation. The pooled data exhibit a mean absolute relative difference superior to the commercial CGM system used during the same measurement times. Mean absolute relative difference changed only marginally over the course of the trial.

Conclusions:
The present clinical feasibility study proves the capability of FiberSense to replace current CGM systems, with the possibility to extend the duration of action to 28 days.

A Collaborative Approach: Insulin Pump Therapy for 790 Children in Kazakhstan

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Background:
Insulin pump therapy improves glycemic control and quality of life in children with type 1 diabetes and has been used in many countries around the globe. This technology was introduced in Kazakhstan in 2011. Medtronic diabetes was awarded a government contract to provide insulin pumps, supplies, and provider education/support for 790 children, 5–15 years of age, and to initiate therapy with the goals of ensuring patient safety and improving glycated hemoglobin levels.

Method:
A collaborative model was developed to allow children to be cared for in 16 regions across the country. A pediatric endocrinologist and a nurse [health care provider (HCP)] were identified in each region, and a lead HCP was appointed in the cities of Astana and Almaty. Systematized training consisted of two world-expert pediatric endocrinologists coming to Kazakhstan and HCPs attending out-of-country training, seminars/visits by local and U.S. Medtronic employees with medical degrees, and data management with CareLink Therapy Management Software and local databases. A geographic- and experience-based physician self-support program was also implemented to provide a surveillance program to ensure optimal long-term clinical outcomes.

Result:
The first child was started on pump therapy in February 2012, and by June 2012, there were 420 children using this technology. Regional HCPs are initiating and adjusting therapy with no serious adverse events to date.

Conclusion:
Collaboration among patients, families, providers, government, and industry is critical to the successful introduction of insulin pump therapy in children in countries without previous experience with diabetes technology. Development of local expertise is required when using advanced technologies for successful diabetes management in children.

Simulating Glycemic Variability in Critically Ill Burn Patients

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Background:
Computer simulation is poised to be an invaluable tool in the development and validation of protocols for tight glycemic control (TGC) in critical care settings, providing a safe means of evaluating sensitivities to target ranges, sampling intervals, and blood glucose (BG) measurement accuracy. Reflecting the known effects of the stress hormone epinephrine, we have developed a mathematical model of BG variability in the intensive care unit, in which stress action (SA) is reflected as a time-varying effect superimposed onto otherwise normal models of endogenous glucose production and insulin-dependent glucose uptake.

Method:
Using BG, insulin, and screening data from 154 patients treated in a burn unit with a TGC protocol, we have identified a matching set of 86 *in silico* patients (derived from noncritically ill patients in the University of Virginia/Padova simulator) and 212 associated SA curves. Randomly recombining *in silico* patients to SA curves and running the same TGC protocol, we compared simulated BG outcomes to those for the original population, focusing on per-patient percentage of time in range (%TIR), percentage of time in hypoglycemia (%THYPO), average blood glucose (ABG), median blood glucose (MBG), average daily risk range (ADRR), mean absolute glucose change per hour (MAG), and mean insulin per hour.

Result:
For real patients and simulated patients, respectively, means of %TIR (39.1% versus 42.5%), %THYPO (0.78% versus 0.59%), ABG (116.7 versus 118.2 mg/dl), MBG (113.6 versus 115.2 mg/dl), ADRR (13.9 versus 14.1), MAG (14 versus 14.5 mg/dl), and mean insulin (7 versus 6.5 U/h) were not significantly different at the $p = .05$ level.

Conclusion:
The resulting simulator is able to meet important clinical outcome criteria, enabling its use in testing insulin protocols *in silico* before use in patients.

Effect of Three-Week Pramlintide Treatment on Meal-Related Glycemic Excursions during Closed-Loop Control

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Objective:
Meal-related blood glucose (BG) excursions in type 1 diabetes mellitus (T1DM) typically exceed target levels during open- and closed-loop (CL) insulin delivery because of delays in insulin absorption/action and inappropriate increases in plasma glucagon. We previously demonstrated that low-dose (30 mcg) pramlintide injections in drug-naïve T1DM subjects mitigated glycemic excursions during CL control. Our current objective was to evaluate the effect of higher dose and longer duration treatment with pramlintide on BG excursions during CL control.

Method:
Subjects underwent two 24 h admissions: first with CL alone and 3–4 weeks later with closed-loop + pramlintide (CL+P). Between admissions, pramlintide was initiated at 15 mcg/meal and increased gradually to 60 mcg/meal prior to the second admission. During CL control, target glucose was 120 mg/dl; identical meals were provided for both study days. No pre-meal manual boluses were given. Reference BG excursions, defined as incremental glucose rise from premeal to peak, were compared between admissions.

Result:
Among eight subjects (four males, age 16.9–23.2 years, hemoglobin A1c 7.2% ± 0.6%), mean BG was 1 49 ± 40 mg/dl during CL+P and 148 ± 45 mg/dl during CL. Closed-loop + pramlintide was associated with delayed time to glucose peak (3.1 ± 0.8 versus 1.7 ± 0.6 h; $p = .0001$) and reduced glycemic excursion across all meals (55 ± 50 versus 95 ± 33 mg/dl; $p = .0002$) compared with CL alone. The higher dose and longer duration of treatment significantly improved the magnitude of glycemic excursions compared with our previous single-day 30 mcg/dose treatment study (88 ± 42; $p < .02$).

Conclusion:
Compared with low-dose, single-day treatment, a higher dose of pramlintide and longer duration of treatment was safe and effective and had a significantly greater effect on BG excursions during CL insulin delivery. Current studies are investigating inhibitory effects of pramlintide on meal-stimulated glucagon secretion.

Analytical Accuracy Evaluation of the Contour XT Blood Glucose Meter

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Objective:
Our aim was to assess the analytical accuracy of the CONTOUR® XT meter, which uses the CONTOUR Next test strip with a flavin adenine dinucleotide-dependent glucose dehydrogenase enzyme in combination with a proprietary electron mediator and algorithm based on current and proposed ISO 15197 section 7 guidelines.

Methods:
Fingertip capillary blood samples from 100 subjects were tested in duplicate using three test strip lots (n = 600). Corresponding plasma samples were tested in parallel using a YSI analyzer as laboratory reference. Accuracy was assessed based on ISO 15197:2003, section 7, standard guidelines (i.e., percentage of results within ±15 mg/dl of the mean YSI reference result for samples with glucose concentrations <75 mg/dl and ±20% for samples with glucose concentrations ≥75 mg/dl) and proposed more stringent guidelines.

Results:
One hundred percent of results <75 or ≥ 75 mg/dl were within ±15 mg/dl or ±20% of the reference method. For values <75 mg/dl, 100% of the results were within ±10 mg/dl, and for results ≥75 mg/dl, 99% of the results were within ±10% of the YSI value. A total of 99.2% of results <100 or ≥ 100 mg/dl were within ±10 mg/dl or ±10% of the reference. For values <100 mg/dl, 98.4% of the results are within ±10mg/dl, and for values ≥100mg/dl, 99.5% of the results were within ±10% of the YSI value. Regression analysis showed good correlation between meter results and YSI laboratory reference results (R^2 = 0.9964). Parkes consensus error grid analysis showed that 100% (600/600) of results were within zone A.

Conclusion:
Findings from this study showed that the performance of the CONTOUR XT meter met and exceeded accuracy guidelines based on the current and proposed more stringent International Organization for Standardization standards.

Dynamic Electrochemistry Corrects for Hematocrit Interference in Blood Glucose Meters for Patient Self-Testing

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Background:
Hematocrit (HCT) is known to be a confounding factor that interferes with many blood glucose measurement technologies, resulting in wrong readings. Dynamic electrochemistry has been identified as one possible way to correct for these potential deviations. The purpose of this laboratory investigation was to assess the HCT stability of four blood glucose meters known to employ dynamic electrochemistry (BGStar and iBGStar, Sanofi; WaveSense Jazz, AgaMatrix; and Wellion LINUS, Wellion) in comparison with three other devices (GlucoDock, Medisana; OneTouch Verio Pro, LifeScan; and FreeStyle InsuLinx, Abbott-Medisense).

Method:
Venous heparinized blood was immediately aliquoted after draw and manipulated to contain three different blood glucose concentrations (60–90, 155, and 310 mg/dl) and five different HCT levels (25%, 35%, 45%, 55%, and 60%). After careful oxygenation to normal blood oxygen pressure, each of the resulting 15 different samples was measured six times with three devices and three strip lots for each meter. The YSI Stat 2300 served as laboratory reference method. Stability to HCT influence was assumed when less than 10% difference occurred between the highest and lowest mean glucose deviations in relation to HCT concentrations [hematocrit interference factor (HIF)].

Results:
Five of the investigated self-test meters showed a stable performance in this investigation: BGStar (HIF 4.6%), iBGStar (6.6%), Wavesense Jazz (4.1%), Wellion Linus (8.5%), and OneTouch Verio Pro (6.2%). The two other meters were influenced by HCT (FreeStyle InsuLinx 17.8%; GlucoDock 46.5%).

Conclusions:
Hematocrit values can vary widely in community patient populations (25–60%) and may be influenced by daily activities, e.g., exercise, stay in mountains, or hemodialysis. In this study, all meters employing dynamic electrochemistry as used in the iBGStar device were shown to reliably correct for potential HCT influence on the meter results.

Influence of Oral Uptake of Ascorbic Acid and Acetaminophen on Performance of Blood Glucose Meters for Patient Self-Testing

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Background:
The aim of this study was to investigate blood glucose measurement accuracy of several blood glucose monitoring systems for patient self-testing after intake of ascorbic acid and acetaminophen in high doses.

Method:
The study was performed with 22 patients with type 1 diabetes (10 female, 12 male; age (±SD) 47 ± 11 years; disease duration 18 ± 10 years; hemoglobin A1c 7.1% ± 0.7%; hematocrit 45% ± 4%). The patients participated in 4 days of experiments with oral application of 100, 200, and 2000 mg of ascorbic acid and 1000 mg of acetaminophen in random order. Blood samples for assessment of glucose and substance levels were drawn every 30 min for 4 h and after 5 h. A YSI Stat 2300 (glucose oxidase method) served as capillary reference method. The following meters were tested: BGStar and iBGStar (Sanofi), Accu-Chek Aviva (Roche Diagnostics), and OneTouch Ultra2 (LifeScan).

Results:
Maximum acetaminophen concentration (11 mg/liter) was reached 30 min after uptake. The mean paired differences versus YSI for blood glucose values >75 mg/dl at this time point were -5 ± 24 mg/dl for iBGStar (BGStar, -1.5 ± 24 mg/dl; Accu-Chek Aviva, 5 ± 27 mg/dl; and OneTouch Ultra2, 6 ± 28 mg/dl). Maximum ascorbic acid concentrations seen after 180 min were 8.5 mg/liter (100 mg), 9.1 mg/liter (200 mg), and 25.3 mg/liter (2000 mg). Mean paired deviations during these experiments for blood glucose values >75 mg/dl were -8 ± 14 mg/dl for iBGStar (BGStar, -5 ± 15 mg/dl; Accu-Chek Aviva, 2 ± 14 mg/dl; and OneTouch Ultra2, 6 ± 18 mg/dl). All meters stayed within the International Organization for Standardization accuracy criteria in these experiments.

Conclusions:
All four tested blood glucose meters showed no clinically relevant interference by acetaminophen or ascorbic acid, even when ingested in high doses. The underlying technologies [e.g., dynamic electrochemistry in case of (i)BGStar] seem effective to correct for these potential confounding factors.

Diurnal Pattern of Hepatic Insulin Action in Healthy Individuals

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Objective:
We have demonstrated that, in healthy individuals, whole body insulin sensitivity (S_I) is higher at breakfast (B) than lunch (L) or dinner (D). The objective of this study was to determine whether there was a diurnal pattern to parameters of postprandial hepatic insulin sensitivity (S_I^L) and glucose effectiveness (GE^L).

Methods:
We studied 20 healthy volunteers with normal fasting glucose and hemoglobin A1c. Identical triple tracer mixed meals were ingested during B, L, or D in randomized Latin square order on three consecutive days. Endogenous glucose production (EGP) profiles were interpreted with a model that assumes that EGP suppression is made up of three components: one proportional to basal glucose concentration (GE^L), one proportional to positive glucose rate of change (K_{GR}), and one proportional to delayed (constant rate k_1) insulin concentration. The S_I^L and S_I^{LD} (index accounting for insulin action dynamics) were derived from model parameters.

Results:
S_I^L was different among meals ($p < .001$): 4.1 ± 0.5, 6.1 ± 0.7, and 6.8 ± 0.8 10^{-4} dl/kg/min per μU/ml for B, L, and D, respectively. *Post hoc* comparisons showed that S_I^L was lower at B than L or D ($p < .001$ for both comparisons). This was accompanied by a higher rate k_1 at B ($p = .002$). In contrast, there were no differences in S_I^{LD}, GEL, or K_{GR} among meals ($p = .063$, $p = .15$, and $p = .39$, respectively).

Conclusions:
Our data demonstrate the existence of a diurnal pattern to postprandial *hepatic* insulin action in healthy nondiabetic individuals that is in contrast to the pattern observed for *whole body* insulin action. If present in type 1 diabetes, such information may need to be incorporated into the simulator for artificial pancreas testing.

Remote Monitoring of Artificial Pancreas: A Web-Based Application for Home Trials

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Background:
Recent developments in the artificial pancreas (AP) for type 1 diabetes patients have resulted in clinical trials performed outside of the hospital. Going home implies specific protocol and system adaptations to ensure patient safety, including remote monitoring. We present a novel tool allowing simultaneous monitoring of multiple patients in home settings.

Method:
We investigated existing systems designed for hospital studies, listed common features, defined required parameters, and performed interviews of experienced nurses, engineers, and clinicians. The resulting application was then focused to provide a robust architecture and a user-friendly interface.

Result:
We developed a Web-based application, entitled DiAs Web Monitoring (DWM), which includes two major features: (1) data collection that ensures reception and storage of data sent by AP systems and (2) data display to allow real-time monitoring of a detailed single subject or a summary of several diabetes patients simultaneously. Quantities such as continuous glucose measurements (CGMs) and insulin delivery are displayed in a main chart, which refreshes every minute. An alert module has also been integrated that helps detect adverse events such as hypoglycemia, CGMs, and pump failures. Released in December 2011, DWM has since successfully monitored 22 patients under closed-loop glucose control, representing more than 40 cumulated days of monitoring. An important step was achieved in June 2012 with the monitoring of five patients simultaneously.

Conclusion:
Early phase investigations of AP systems in home environments require specific monitoring tools to ensure patients' safety. DiAs Web Monitoring demonstrates full ability to cover these needs and offers new possibilities to accelerate AP development, allowing (i) simultaneous real-time remote monitoring of multiple patients, (ii) remote alarms following system failures and/or glycemic imbalance, and (iii) real-time data backup.

Soluble Nonaqueous Glucagon Formulations for the Treatment of Severe Hypoglycemia

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Objective:
Severe hypoglycemia remains a significant unmet medical need. Recent studies estimate that 6% to 10% of deaths of patients with type 1 diabetes are attributable to hypoglycemia. Administration of glucagon is effective in reversing severe hypoglycemia. However, development of a simple, ready-to-use glucagon product has been hampered by the property of glucagon to spontaneously assemble into fibrils in aqueous solution. Thus currently approved products (Lilly, Glucagon for Injection; Novo Glucagen®) are based on lyophilized formulations. The need for reconstitution has made these products difficult to administer in emergency situations, and thus they are infrequently used.

Method:
We have developed a soluble glucagon formulation based on biocompatible, nonaqueous solvents.

Result:
These formulations effectively suppress the fibrillation of glucagon observed in aqueous solutions, even at high concentrations and temperatures. Further, the chemical stability of glucagon in these formulations is similar to that of dry powders. Nonaqueous solutions of glucagon (5 mg/ml) have been demonstrated to be free of fibrillation after incubation at 40 °C for 2 months (compared with just hours for aqueous solutions). Additionally, minimal chemical degradation of glucagon is observed in nonaqueous solutions (apparent degradation rate at room temperature is ~0.25%/month). Comparative pharmacology studies in a rodent model show the nonaqueous solutions of glucagon to have equivalent pharmacokinetics and pharmacodynamics to aqueous formulations. Similar to aqueous solutions, injection of nonaqueous formulations of glucagon show rapid absorption (T_{max} ~5 min) and elevation of glucose levels (within 15 min).

Conclusion:
These data support the development of a ready-to-use rescue pen for severe hypoglycemia as well as a glucagon formulation suitable for a bihormonal (insulin–glucagon) infusion pump.

Treatment of Obesity with Closed-Loop Gastric Stimulation Device

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Background:
We study the efficacy of a closed-loop gastric stimulation (GES) system with integrated intake and activity sensors for weight loss and behavior modification in obese subjects.

Method:
The abiliti® system was implanted in 31 subjects ($35 \geq$ body mass index ≤ 55 kg/m^2). The therapy is multipronged, including GES to produce satiety through the activation of vagal afferents and behavior modification therapy through feedback of sensor data: intake events from a transgastric sensor and physical activity from a triaxial accelerometer. The sensor-triggered stimulation targets therapy to meals and potentially reduces sensory habituation. The meal therapy was built with periods of varying parameters to produce reduction of consumption. In addition, the therapy is tailored to the patient by adjusting the stimulation parameters based on symptom response as measured by a visual analog scale (VAS) and design of individualized allowed and disallowed eating periods to promote consumption on a regular schedule.

Result:
The weight loss outcomes at 12 months of therapy are mean percentage of excess weight loss 28.7% (95% confidence interval, 34.5% to 22.5%). Individualized programming of the stimulation parameters resulted in moderate or above response on the VAS in all patients (predominant symptoms were satiety and gastric pressure). The average weekly exercise duration increased from 126 to 334 min/week from baseline to month 12. All subjects reduced their number of sensed intake events at month 12 compared with baseline. The subjects who obtained >25% excess weight loss also reduced their eating outside of the allowed meal times.

Conclusion:
The results of a new stimulation therapy algorithm using abiliti® system in obese subjects show that the therapy is well tolerated by the subjects and effective in changing eating and exercise behavior and producing weight loss.

Home Medical Monitoring System: A Brief Case for Computer-Naïve Patients and Providers

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Objective:
The aim is to design a clinical tool for the direct integration of patients' home blood pressure (BP), pulse, and blood glucose (BG) all in one, with direct connectivity to the electronic medical record (EMR).

Method:
This is a self-contained, compact, wireless-based, tablet-sized portable unit used to compute daily values or aggregates and integrate in real time the patients' medications and export them directly into the patients' office-based EMR. Progress notes can be generated on a daily or weekly basis. Clinic-based interaction, medication titration, and diagnostic tests are interposed in real time to maintain linearity in care.

Result:
Patients with diabetes mellitus, hypertension, chronic kidney disease, and coronary artery disease are managed using home BP and BG for day-to-day care. Hypertension, like diabetes mellitus, is based more on aggregate home BP readings. In our contemporary practice, integrating this type of information for medication titration is labor intensive. Patients depend on several schemes to report for achieving target goals and maintaining their follow-up care. Compiling and integrating these data with medicine titration and diagnostic tests in a linear flow is arduous. Computer-based technology via the Internet or other means is expensive and far from being patient friendly. Ascot Technology has devised a wireless system with the unique ability to directly log in the patient's test results. Medical clinic interaction is displayed with a similar friendly format at the patient's site.

Conclusion:
We believe patients with chronic illnesses can be managed with greater intensity using the home medical monitoring system. Furthermore, we have, for the first time, a simple briefcase-sized tool for use by a patient's family or any care giver without having to depend on Internet-based home monitoring equipment or frequent office visits.

On-Demand Online Specialist Assistance from Hospital to General Practice: Telemedical Treatment of Diabetic Foot Ulcers

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Background:
We assessed the effects of implementation of on-demand online telemedical specialist assistance from hospitals to general practice in order to optimize the course of treatment of diabetic foot ulcers.

Method:
A priori conventional (historic) treatment courses for 30 individual patients were registered with regard to (1) time lines for diagnosis and treatment, (2) delay in first contact to foot ulcer specialist, and (3) delay in first screening for diabetes late complications and contact to a diabetologist. After implementation of telemedicine, all patients with diabetic foot ulcers in six general practices were consecutively recruited, and clinical data and pictures were documented in the Internet-based communication system, thereby time-stamping all events to be compared with the "historic" data. All parties (patients, relatives, staff in general practices and hospitals) are subjected to focus group interviews and questionnaires describing satisfaction/dissatisfaction and advantages/disadvantages with the current treatment and treatment in this study. More than 40 patients will have been included from January 1, 2011, to December 31, 2012.

Result:
Preliminary results reveal (1) great patient/relative satisfaction sparing the patient transport to hospital and allowing treatment in more comfortable and well-known surroundings, (2) satisfaction in general practice with on-demand assistance but reluctance with regard to implementing the communication system, (3) satisfaction among hospital staff as patients are stratified according to severity, and (4) overall diminished delays in diagnosis, treatment, and first contact to specialists.

Conclusion:
On-demand online specialist assistance from hospitals to general practices is feasible. In our study, treatment was optimized and patients and relatives were satisfied overall, as was hospital staff. Barriers include reimbursement issues and apprehension toward yet another technology to be implemented.

Clinical Assessment of a Novel Bio-Inspired Artificial Pancreas in Subjects with Type 1 Diabetes Mellitus

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Objective:
A mathematical model of beta-cell physiology derived from physiological experiments has been implemented in a novel bio-inspired controller for closed-loop insulin delivery in type 1 diabetes mellitus (T1DM). *In silico* data show very good control, and presented here are the first clinical data in subjects with T1DM.

Method:
The closed-loop system consists of a subcutaneous glucose sensor (Enlite, Medtronic), a novel bio-inspired glucose controller, and a subcutaneous insulin pump (Accu-Check Combo Spirit, Roche). The control algorithm is implemented on a microchip installed in a handheld device and allows communication between the three components of the system. Subjects with T1DM have been recruited and have been assessed in a 6 h closed-loop fasting study.

Result:
The closed-loop system was evaluated over 6 h in 6 male subjects [mean (standard deviation [SD]) age 45 (12) years, duration of diabetes 24 (9) years, hemoglobin A1c 57 (10) mmol/mol, body mass index 27 (5) kg/m^2]. The mean (SD) plasma glucose was 7.4 (1.6) mmol/liter. The mean (SD) sensor glucose was 6.8 (1.7) mmol/liter, low blood glucose index 1.3 (1.0), and high blood glucose index 3.1 (3.2). Control-variability grid analysis showed 100% of points in zones A+B (17% zone A, 50% upper B zone, 33% lower B zone). Mean average (SD) insulin dose was 1.1 (0.6) U/h, and the maximum and minimum bolus delivered at any point was 1.1 and 0.1 U, respectively.

Conclusion:
The bio-inspired closed-loop artificial pancreas achieves normoglycemia without hypoglycemia in subjects with T1DM. No adverse events occurred. The system is being further assessed in overnight control and mealtime scenarios in subjects with T1DM.

Recommendations for Insulin Dose Calculator Risk Management

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Objective:
Several studies have shown the usefulness of an automated insulin dose bolus advisor (BA) in achieving improved glycemic control for insulin-using diabetes patients. Although regulatory agencies have approved several BAs over the past decades, these devices are not standardized in their approach to dosage calculation and include many features that may introduce risk to patients. Moreover, there is no single standard of care for diabetes worldwide and no guidance documents for BAs, specifically. Given the emerging and more stringent regulations on software used in medical devices, the approval process is becoming more difficult for manufacturers to navigate, with some manufacturers opting to remove BAs from their products altogether.

Method:
A comprehensive literature search was performed, including publications discussing diabetes, BA use and benefit, infusion pump safety and regulation, regulatory submissions, novel BAs, and recommendations for regulation and risk management of BAs. Also included were country-specific and international guidance documents for medical device, infusion pump, medical software, and mobile medical application risk management and regulation. A practical risk management exercise was performed utilizing a BA currently marketed in the United States.

Result:
No definitive worldwide guidance exists regarding risk management requirements for BAs, specifically. However, local and international guidance documents for medical devices, infusion pumps, and medical device software offer guidance that can be applied to this technology. Additionally, risk management exercises that are algorithm-specific can help prepare manufacturers for regulatory submissions.

Conclusion:
This article discusses key issues relevant to BA use and safety and recommends risk management activities incorporating current research and guidance.

An Analysis of Insulin Pump Display Accessibility Based on Font Size, Contrast, and Reflection Properties

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Objective:
The objective of this study was to quantify the display quality of the five available insulin pumps on the market based on font size, contrast, and reflection properties.

Methods:
The Michelson contrast, reflection factors, and font sizes of five insulin pumps were selected and measured using the optics laboratory developed by the American Foundation for the Blind's office in Huntington, WV. The measuring apparatus was based on the Video Electronics Standards Association Flat Panel Display Measurement 2 standard and consisted of a camera, an integrating sphere, a luminance meter, and a personal computer.

Results:
Two of the five insulin pumps contained backlit color liquid crystal display (LCD) displays. These displays exhibited very high contrast in office lighting (typically 80–90%), but high ambient illumination caused a significant contrast degradation (reduced to 10–20%). The other three pumps contained reflective, monochrome LCDs. These displays exhibited low contrast in all lighting conditions (40–50%), but the contrast was not reduced by high light levels when there was no specular reflection. The font sizes among the devices were reasonably consistent with the bolus volume, averaging 8.0 mm (22.6 point), and the menus averaged 3.0 mm (8.5 point).

Conclusions:
Contrast and font size determine the baseline accessibility of a display for low-vision users. The reflection properties determine how a display performs in different levels of light. Color LCDs exhibit the greatest level of readability in dark and office lighting conditions. The reflective LCD displays exhibit lower contrast levels but are typically more readable in sunlight conditions. The font sizes for the menus of all of the pumps are small, at an average of 3.0 mm or 8.5 point equivalent. The American Printing House for the Blind recommends 18-point font for low-vision users.

Continuous Insulin Infusion and Glycemic Control in Type 1 Diabetes before and after Total Thyroidectomy for Graves Disease

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Objective:
Uncontrolled hyperthyroidism may lead to persistent tachycardia even after correction of metabolic acidosis and dehydration, leading to masking of resolution of diabetic ketoacidosis in type 1 diabetes. We present the changes seen in average glycemic control in a person with type 1 diabetes mellitus and coexistent Graves disease before and after total thyroidectomy.

Method:
A 22-year-old female with a history of type 1 diabetes for 3 years on an insulin pump for the past 2.5 years was diagnosed with hyperthyroidism due to Graves disease. She had an Omnipod insulin pump, and her diabetes was poorly controlled. Her initial glycated hemoglobin (A1C) was 10.6, with wide variability in blood glucose readings. Her blood glucose readings (in mg/dl) were prebreakfast 224 (±45), prelunch 299 (±97), predinner 248 (±24), bedtime 264 (±54), and midnight (12:00 AM) 340 (±52). She was initially treated with antithyroid medications, but she developed a rash on the methimazole, which necessitated a total thyroidectomy.

Result:
Her perioperative and postoperative course was uneventful, as she was treated with intravenous insulin during that time. Six months after surgery, she underwent a 72 h glucose monitoring with the help of a continuous glucose monitoring system. Her average glucose was ranging between 53–187 mg/dl, with 4% of the time above the higher limit of 100 mg/dl and 8% of the time below the lower limit of 70 mg/dl. Her A1C had fallen to 8.5.

Conclusion:
Treatment of Graves disease leads to substantial improvement in glycemic control in type 1 diabetes in the short and long term. The impact of excess thyroid hormone on hyperglycemia needs to be emphasized.

Foot Biomechanics Model for Diabetic Ulcer Prevention

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Objective:
High plantar pressures have been associated with foot ulceration in patients with diabetes. Therefore, characterization of elevated plantar pressure distributions can help identify diabetes patients at risk of foot ulceration. Finite element (FE) monitoring of internal deformations and stresses in the plantar pad is required to identify elevated deformation/stress exposures. The aim of this study is to design a patient-specific, multiscale FE model of a diabetic foot.

Method:
A three-dimensional (3D) multiscale FE model that couples a biomechanical foot model (BFM) and a biological tissue model (BTM) was developed. The BFM quantifies the links between internal structures and external pressures on the foot. The BTM considers the ulcerated region, composed of a necrotic core and a more peripheral zone containing the surrounding soft tissues. The BFM was developed from 3D reconstruction of magnetic resonance images (Simpleware ScanIP-ScanFE, v.5.0). Finite element software ABAQUS was used to perform the numerical stress analyses. A diabetes subject (age 72 years, body mass index 25.1 kg/m^2) was acquired. Foot biomechanics analysis was performed. Ground reaction forces (Bertec), taken from the midstance phase of the gait, were applied. Validation of the pressure state was achieved by comparing model predictions of contact pressure distribution with experimental plantar pressure measures (Imagortesi).

Result:
A nonlinear 3D FE foot model was developed and meshed with tetrahedral elements. The model-predicted structural response of the plantar pad was in agreement with experimental results.

Conclusion:
The development and validation of the proposed methodology will be a relevant contribution in increasing knowledge regarding the biomechanical alterations resulting from diabetes.

Know Your Blood Glucose: Differences between Perceived versus Measured Blood Glucose Test Results in People with Type 2 Diabetes

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Objective:
Research suggests one reason people do not test their blood glucose (BG) levels is they believe they know their BG levels without testing. People use these perceptions to make decisions about their self-care practices, including insulin dosing. This study assessed the difference between self-reported BG values, estimated BG values, and BG values as measured on a BG meter.

Methods:
Subjects ≥18 years old with type 2 diabetes (n = 297) attending one of two Taking Control of Your Diabetes conferences were asked questions about testing behaviors and perceived BG level. Study staff then performed a finger stick BG measurement.

Results:
A total of 77% of subjects reported that their body tells them without testing if their BG is low or high, and 71% made decisions about their diabetes without testing. A total of 58% of subjects estimated BG values that were not accurate based on proposed more stringent accuracy criteria (within ±15 mg/dl or ±15% at glucose concentrations <100 and ≥100 mg/dl, respectively). Time since last BG test, time since last meal, testing frequency, and hemoglobin A1c had no effect on the results. After finger stick testing, nearly all (99%) felt knowing their BG by checking could help them make different diabetes decisions. A total of 96% of subjects agreed or strongly agreed that knowing their BG by checking could help them recognize and treat low BG values, while 68% of subjects agreed or strongly agreed that knowing their BG value by checking could help them prevent low BG values.

Conclusion:
These findings suggest the importance of regular BG testing rather than estimation of BG values to help people with diabetes make better informed decisions for effective diabetes management.

Performance Evaluation of the Contour Next USB Blood Glucose Meter System in the Hands of Users

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Objective:
Our aim was to assess the performance of the Contour Next USB blood glucose meter system (BGMS) in the hands of intended users. This BGMS has built-in data management software (DMS) and a universal serial bus plug for direct computer connection to view results within the DMS.

Methods:
A total of 207 subjects, 18 to 82 years old, with diabetes, were enrolled. More than half had only a high school education. Untrained subjects learned to use the BGMS by reading materials provided and tested finger stick and palm alternate site samples. Reference samples were tested on the YSI 2300 STAT Plus™ analyzer. Accuracy was assessed based on current ISO 15197:2003 and proposed more stringent criteria (i.e., within ±15 mg/dl or ±15% of the reference result for samples with glucose concentrations <100 and ≥100 mg/dl, respectively). Subjects completed questionnaires on diabetes management, the ease of use of the BGMS, and the user guide instructions.

Results:
A total of 99.5% of capillary finger stick results and palm results met ISO 15197:2003 criteria, and 98.5% of capillary finger stick results and 99.0% of palm results met the proposed more stringent criteria. Based on questionnaires, 7% of the subjects report using DMS at home, while 48% only download at the doctor's office, and 29% do not know about DMS. Of the 7% who use DMS at home, 43% use it daily and 21% use it only to prepare for a doctor's appointment. The majority of subjects agreed or strongly agreed that the BGMS was easy to use (96%), and intuitive (89%), and that it was easy to see and understand the test results (99%).

Conclusion:
Contour Next USB with built-in DMS was shown to be accurate, intuitive, and easy to use in the hands of intended users.

Improved Performance of Continuous Blood Glucose Monitoring Using Intravenous Microdialysis and the Enhanced Ionic Reference Technique

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Objective:
Intravenous microdialysis has become an attractive approach for glucose monitoring. Alterations of the recovery limit its application. It has been shown that the recovery of ions can be used to partially compensate recovery changes of glucose [ionic reference technique (IRT)]. The study objective was to investigate if the performance of blood glucose monitoring using intravenous microdialysis can be improved by using the enhanced ionic reference technique (eIRT).

Method:
Twenty healthy subjects (age 26.4 ± 3.7 years, body mass index 24.2 ± 2.3 kg/m^2) participated in this 24 h study. Thirty-nine microdialysis probes were placed in the peripheral veins of their arms. Blood glucose was clamped to different target levels (90–180–130–90 mg/dl) over a period of 6 h each. Dialysate was analyzed for glucose and ions enabling the eIRT, which takes into account the different mass transfers of glucose and ions.

Result:
A total of 3218 paired glucose readings were analyzed. The data revealed a correlation coefficient *r* of 0.60/0.82/0.82, a mean absolute relative difference (MARD) of 45.8/22.1/21.6%, and a predicted error sum of squares (%PRESS) of 50.3/26.8/26.4% for dialysate glucose, dialysate glucose corrected with the IRT, and dialysate glucose corrected with the eIRT, respectively. In 85% (33 out of 39 systems), the IRT and eIRT improved the correlation coefficient of blood glucose and the calculated glucose. In 67% (26 out of 39 systems), the MARD and %PRESS was best using the eIRT.

Conclusion:
The IRT/eIRT improves the performance of the intravenous microdialysis. Since the overall ion concentration can be estimated by the electrical conductivity, we will combine intravenous microdialysis with glucose and conductivity sensors to develop a continuous glucose monitoring system.

Assessment of Postprandial Glucose Turnover in the Presence of Moderate Physical Activity Using a Stochastic Deconvolution Method

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Objective:
Model-independent estimate of postprandial glucose turnover requires multiple tracer experiments to realize a tracer-to-tracee ratio (TTR) clamp. However, keeping TTR constant is almost impossible in practice, thus fluxes are derived with Steele or Radziuk models, which need the calculation of TTR rate of change. Regularized deconvolution can be employed to calculate the derivative of the noisy TTR. However, inherent assumptions on stationarity of unknown signal are critical, because even a moderate physical activity causes sudden changes in glucose concentration and fluxes.

Method:
Twelve healthy subjects received a mixed meal containing 75 g of carbohydrates labeled with [1-^{13}C] glucose. [6,6-$^{2}H_2$]glucose and [6-3H]glucose were infused intravenously to mimic endogenous glucose production and meal rate of appearance, respectively. Four exercise sessions of 15 min (spaced out by 5 min rest) started 120 min later at 50% maximal oxygen uptake. Plasma tracer concentrations were measured frequently, and TTR time courses were calculated. Derivative of TTR was obtained by a stochastic deconvolution method, ignoring or taking into account the nonstationarity introduced by physical activity. To do so, a random-walk model with rate of variability different in presence or absence of exercise was used. Fluxes calculated in both cases were then compared.

Result:
Accounting for TTR derivative, nonstationarity allows a better fit of reconvoluted TTR to data and, thus, a more robust estimate of glucose fluxes.

Conclusion:
We have proposed a method to accurately calculate TTR rate of change, and thus assess postprandial glucose turnover, in the presence of moderate physical activity.

Carbohydrates on Board to Assess the Fraction of Meal Carbohydrates Entering the Circulation

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Objective:
Type 1 diabetes patients calculate the insulin still active in the body (insulin on board) before injecting premeal or correction bolus in order to avoid insulin overdosing, which may lead to hypoglycemia. This is needed because subcutaneous insulin absorption is a slow process that lasts several hours after administration. Similarly, knowing the amount of carbohydrates that have still to appear after a meal could be useful to understand whether more carbohydrates or insulin are needed for maintaining glycemic control. Here we present the carbohydrates on board (COB) concept, which, given the amount of carbohydrates ingested at time t_m, evaluates at each time $t > t_m$ the percentage of carbohydrates not yet absorbed by the gastrointestinal tract.

Method:
The COB function is based on a model of oral glucose absorption, which describes the transit of glucose through the gastrointestinal tract. Model parameters can be varied to account for different meal compositions (e.g., high versus low carbohydrate content), use of drugs decelerating gastric emptying (e.g., pramlintide), or subject-specific conditions (e.g., normal versus impaired gastric motility).

Result:
Time courses predicted by the COB model for the conditions described are calculated.

Conclusion:
The new COB function is proposed, which, given the amount of carbohydrates ingested with a meal, provides the amount of glucose not yet absorbed by the gastrointestinal tract at each time after the meal. Carbohydrates on board could be useful to optimize insulin therapy. In addition, it could be incorporated into a tool recently proposed to estimate insulin sensitivity from continuous glucose monitors and pumps, allowing us to extend its use when consecutive meals are not fully absorbed.

Can Use of an Automated Insulin Bolus Advisor Improve Adherence to Multiple Daily Insulin Injection Therapy?

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Objective:
People with insulin-treated diabetes often do not follow and/or adjust their insulin regimens as needed. Key contributors to treatment nonadherence are fear of hypoglycemia, lack of self-efficacy, and inconvenience/complexity associated with insulin dose determination. We designed a study to determine if use of an automated bolus advisor (BA) can improve adherence in patients treated with multiple daily injections (MDIs) of insulin.

Method:
The Automated Bolus Advisor Control and Usability Study is a 6-month, prospective, randomized, multinational trial to determine if automated BA use improves glycemia in poorly controlled subjects treated with MDI therapy. The primary end point is change in hemoglobin A1c (HbA1c) at 6 months. Secondary outcomes are changes in other glycemic measures (e.g., glycemic variability), therapy adherence (e.g., use of rule sets and BA use), frequency of adjustments to proposed bolus amounts, and psychosocial measures (e.g., hypoglycemia fear, depression, diabetes-related distress).

Result:
A total of 218 subjects (type 1 diabetes mellitus $n = 202$; type 2 diabetes mellitus $n = 16$) were randomized to control or BA use. Characteristics are mean (standard deviation) age 42.4 (13.3) years, HbA1c 8.9 (1.2), diabetes duration 17.6 (11.1) years, and established on MDIs 11.2 (8.8) years. Baseline data revealed that fear of hypoglycemia was common, with 39.4% of participants reporting that they "often" or "always" reduce their insulin dose to avoid hypoglycemia. Hypoglycemia fear was correlated with increased problem areas in diabetes, higher mean blood glucose, increased depressive symptoms, and reduced diabetes treatment satisfaction.

Conclusion:
Findings from a recent survey suggest that BA use positively alleviates hypoglycemia fear and improves self-efficacy relevant to MDI therapy. Randomized trials are needed to confirm these perceptions and determine whether BA use improves clinical outcomes. Our study is designed to make these assessments. Trial registration available at www.ClinicalTrials.gov (NCT1460446).

Can Use of an Automated Insulin Bolus Advisor Improve Glycemic Control in Patients Failing Multiple Daily Insulin Injection Therapy?

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Objective:
Because manual calculation of bolus insulin dosages can be complex and time-consuming, many people rely on empirical estimates, which can result in persistent hypoglycemia and/or hyperglycemia. Use of automated bolus advisors (BA) has been shown to be useful in helping insulin pump users safely improve glycemic control; however, use of this technology in patients treated with multiple daily injections (MDIs) of insulin has not been well studied. We designed a trial to determine if use of an automated BA can improve clinical and psychosocial outcomes in MDI-treated patients.

Method:
The Automated Bolus Advisor Control and Usability Study is a 6-month, prospective, randomized, multinational trial to determine if automated BA use improves glycemia in poorly controlled subjects treated with MDI therapy. The primary end point is change in hemoglobin A1c (HbA1c) at 6 months. Secondary outcomes include change in time spent within blood glucose in target range, therapy adherence, use of rule sets, BA use, frequency of adjustments to proposed bolus amounts, frequency/severity of hypoglycemia, and self-monitoring of blood glucose test frequency. Self-care behaviors and psychosocial issues will also be assessed.

Result:
A total of 218 subjects (type 1 diabetes mellitus n = 202; type 2 diabetes mellitus n = 16) were randomized to control or BA use. Characteristics are mean (standard deviation) age 41.0 (13.4) years, HbA1c 9.1 (1.2), diabetes duration 17.5 (11.3) years, and established on MDIs 11.5 (9.0) years. Mean time from diagnosis to MDI initiation was 6.6 (9.3) years.

Conclusion:
Automated BA use may help MDI-treated patients safely achieve good glycemic control. Findings from a recent survey suggest that BA use positively addresses both safety and lifestyle concerns; however, randomized trials are needed to confirm these perceptions and determine whether BA use improves clinical outcomes. Our study is designed to make these assessments. Trial registration available from www.ClinicalTrials.gov (NCT1460446).

Can Real-Time Calculation of Glycemic Variability Parameters Represent a Further Means to Improve Patient Management in Intensive Care Units?

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Background:
The effectiveness of tight glycemic control (TGC) protocols, as a means for reducing patient mortality and morbidity in intensive care units (ICUs) is controversial and has been extensively debated. Nonetheless, most TGC studies agree that mortality in ICUs is more significantly correlated to glycemic variability (GV) than to the average blood glucose (BG) value. Despite these evidences, GV parameters are not routinely used as further criteria to cross check the efficacy of an implemented TGC protocol, mainly because their calculation is performed retrospectively.

The advent of continuous glucose monitoring (CGM) systems with reliable performance even in ICU environments may open the possibility to calculate GV parameters in real time. We discuss features and possible benefits of a novel algorithm (real.time.GV, A. Menarini Diagnostics) specifically developed for providing real-time access (update frequency = 1 min) to a number of GV indexes.

Method:
The data collected by the GlucoMenDay CGM system (A. Menarini Diagnostics) on 20 type 1 diabetes patients were used to calculate both the real-time value and trend of several GV parameters—including standard deviation, continuous overall net glycemic action, mean amplitude of glycemic excursions, high blood glucose index, and low blood glucose index—using the real.time.GV algorithm.

Result:
For each patient datum analyzed in the present study, the real-time profile of each GV index has been compared with the corresponding CGM profile. The results obtained for several case studies will be presented and discussed in detail.

Conclusion:
The CGM devices implemented with the real-time calculation of GV parameters feature may become one of the most valuable tools for supporting the application of TGC in ICU patients.

Detecting Unusual Continuous Glucose Monitor Measurements: A Stochastic Model Approach

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Background:
Hyperglycemia and hypoglycemia have been associated with negative outcomes in critically ill adults and infants. Blood glucose (BG) measurements used to diagnose these glycemic abnormalities are often taken several hours apart. Continuous glucose monitors (CGMs), with their ~5 min sampling period, offer the potential to better monitor glucose levels. However, there have been concerns regarding the accuracy and reliability of these devices in critically ill patients. This study uses CGM data from neonatal infants to develop a tool that will aid clinicians in identifying unusual CGM behavior, retrospectively or in real time.

Method:
Continuous glucose monitor data from 50 neonatal infants were used to construct a nonparametric stochastic model based on the kernel density method. The stochastic model was used retrospectively to classify the measurement-to-measurement change in CGM output, with an emphasis on highlighting unusual CGM measurements. A percentile value determined by the model was assigned to each CGM measurement. The percentile values were then used to color code the CGM trace, conveying the outlier information quickly and efficiently.

Result:
The stochastic model contained over 67,000 CGM measurements spread across a glycemic range of ~36–216 mg/dl. A five-fold validation was Monte Carlo simulated 25 times to ensure the model fit. The stochastic model and classification proved capable of highlighting unusual hypoglycemic events in the CGM output (potential sensor artifacts), as well as possible sensor degradation.

Conclusion:
Overall, while BG measurements are required to make definitive conclusions about glycemic abnormalities, the stochastic classification provides another level of information to aid users in interpretation and decision making. Furthermore, in the real-time application, clinical protocols might use stochastic information to justify an added BG measurement to clarify a potentially significant event.

Simulated Provider Training Improves Diabetes Management

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Objective:
Medical procedure simulation training is common, but we describe and evaluate software for an innovative cognitive-based simulation training (SimCare Diabetes).

Method:
SimCare Diabetes, the culmination of three federally funded randomized controlled trials (RCTs), uses simulated learning cases that replicate real and challenging clinical vignettes. The provider engages in patient care using a Web-based interactive electronic-health-record-like interface over longitudinal patient encounters. The software captures effects of treatment actions using physiologic modeling and uses evidence-based rules algorithms to critique them. The first two RCTs evaluated the effects on actual patients of practicing providers. The last RCT evaluated an 18-case comprehensive learning curriculum as an adjunct to traditional training in primary care residents (n = 341). Outcomes in these trials included hemoglobin A1c (HbA1c), provider management skills (simulated assessments of appropriate and safe treatment decisions), knowledge testing (multiple choice test), self-reported confidence (Likert scale), and satisfaction.

Result:
The first two RCT interventions (a 1–3 h time commitment of practicing providers) demonstrated a mean HbA1c reduction of 0.19% in actual patients (p = .04) and a 10% reduction in metformin prescriptions for patients with contraindications (p = .03). In the third trial, an average of 32% of intervention and 9% of control residents achieved composite clinical goals for glucose, blood pressure, and lipids on four simulated assessment cases. Knowledge scores were above 50% for 71% of intervention and 34% of control residents, and overall diabetes management confidence was above average for 79.4% intervention and 43.9% of control, $p < .001$. Satisfaction was high; 88% of practicing providers and 91% of resident physicians would recommend to colleagues.

Conclusion:
Evidence supports the use of case-based simulated diabetes education to improve patient outcomes and diabetes management of primary care practicing providers and resident physicians.

Bolus Calculation for Type 1 Diabetes Mellitus Patients Using Prediction and Selection

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Objective:
Patients with type 1 diabetes mellitus have to solve an optimization problem every day to determine the insulin doses needed to stabilize their blood glucose (BG) concentration.

The proposed control algorithm aims at assisting multiple dose injection (MDI) patients to decide on the needed bolus insulin doses to stabilize BG.

Method:
The controller decides upon the doses and times for insulin boluses to be administered by comparing time and dose combinations from a given set. The comparison is made based on an asymmetric cost function that evaluates the risk of a certain BG concentration. To determine the insulin boluses, BG predictions and a linear state space model that describes the patient dynamics are used. For evaluation, an implementation of a virtual patient is used.

Results:
For a simulated patient, the controller stabilizes the BG concentration to the normal range (70–80 mg/dl) with high blood glucose index = 4.33 and low blood glucose index = 1.53. The simulated continuous glucose monitoring system was in the normal range 79% of one day, compared with 76% using standard recommended dosage.

Conclusion:
The control algorithm proposed here determines the bolus insulin doses to keep the BG concentration in a safe range. This could be valuable to help MDI patients with choosing the correct doses.

The Value of Admission Glycemic Variability Revealed by Continuous Glucose Monitoring System as a Risk Factor of Major Adverse Cardiac Events after Acute Myocardial Infarction

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Objective:
Dysglycemia is associated with poorer prognosis in patients with acute myocardial infarction (AMI). Whether admission glycemic variability is more important than prior long-term glucose metabolism is unknown. The aim of study is to investigate the prognostic value of admission glycemic variability and glycosylated hemoglobin (HbA1c) levels in AMI patients.

Methods:
We measured HbA1c and glycemic variability on admission in 222 consecutive patients with diagnosed AMI. Glycemic variability, indicated as the mean amplitude of glycemic excursions (MAGE), was determined by a continuous glucose monitoring system. The MAGE was categorized as <3.9 or ≥3.9 mmol/liter and HbA1c as <6.5% or ≥6.5%. Participants were followed up with prospectively for 12 months. The relationship between MAGE, HbA1c, and major adverse cardiac events (MACEs) was analyzed.

Results:
In the 222 enrolled patients with AMI, the rate of MACEs by MAGE category (<3.9 or ≥3.9 mmol/liter) was 8.4% and 24.1%, respectively (p = .002); MACEs rate by HbA1c category (<6.5% versus ≥6.5%) was 1 0.7% versus 18.7%, respectively (p = .091). On multivariate analysis, high MAGE level was significantly associated with incidence of MACEs (heart rate 1.942; 95% confidence interval 1.044–3.613; p = .036), but HbA1c level was not (heart rate 1.522; 95% confidence interval 0.841–2.757; p = .165).

Conclusions:
Elevated admission glycemic variability appears more important than prior long-term abnormal glycometabolic status in predicting 1-year MACEs in patients with AMI.

Development and Evaluation of Proportional-Integral-Derivative Controllers for Glucose Control in People with Type 1 Diabetes Mellitus

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Objective:
The aim of this research is to develop and evaluate a novel, model-based proportional-integral-derivative (PID) control design method to achieve normoglycemia with an artificial pancreas. A key objective is to utilize a simple, control-relevant model that can be personalized for individual subjects based only on clinical information that is readily available, such as total daily insulin (TDI).

Method:
The proposed PID design method is based on the internal model control (IMC) approach and a simple dynamic model that has a single adjustable parameter that is personalized based on the subject's TDI.

Result:
The proposed controller design method was evaluated in an *in silico* study using the University of Virginia/Padova metabolic simulator. Ten simulated subjects were used to determine a conservative value of the single IMC design parameter. This value provided good postprandial responses and a reasonable degree of robustness for changes of ±50% in the insulin sensitivity. Then 10 additional subjects were simulated in a validation study that included three meals (50, 40, and 50 g carbohydrate) during a 24 h period. The PID controllers based on the personalized models performed better than controllers based on a fixed model. For the validation study, the average amount of time that the glucose concentration was in the desired range (70–180 mg/dl) was 88% for the personalized models and 83% for the fixed models. Similarly, the average values for the 180–250 mg/dl range were 10% and 16% for the personalized and fixed models, respectively. Neither design method resulted in hypoglycemia (<60 mg/dl).

Conclusion:
Simulation studies have demonstrated that the proposed controller design method based on personalized models is practical and superior to controllers based on a fixed model.

Glucose Meter Links to Apple Mobile Devices

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Objective:
LifeScan has developed a new glucose meter with the capability to transmit data wirelessly to a patient's iPhone®, iPod touch®, or iPad® via Bluetooth® technology. In order to evaluate the user acceptance of the new meter, a clinical evaluation was conducted.

Method:
We enrolled 168 participants [86 male/82 female, mean age 41.6 years (range 12.4–68.6 years), 99 (58.9%) with type 1 diabetes, and 69 (41.1%) with type 2 diabetes], assessed user acceptance by questionnaire, and calculated the percentage of favorable and very favorable responses (i.e., 4 or 5) on a 5-point scale (n = 168 responses per question).

Result:
The study showed uniformly positive results, including 94.0% found the meter easy to use, 95.8% found that it was easy to see high and low patterns with the application, 94.6% found it easy to review blood sugar readings in the application, 92.3% stated that the application made it easier to identify patterns than using a paper logbook or scrolling through their current meter's memory, 93.5% stated it was easy to send results from the meter to the Apple device, and 80.4% stated that the application prioritizes the information needed for conversations with their doctor

Conclusion:
The data suggest that this new system is well accepted by people with type 1 and type 2 diabetes across a broad age range. This system advances mobile health technologies for people with diabetes.
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The ASPIRE-2 Study of Automatic Insulin Suspension: Design, Methods, and Interim Baseline Characteristics

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Objective:
The ASPIRE-2 study aims to examine the safety and efficacy of hypoglycemia-triggered insulin pump suspension during long-term, in-home use. The study's design and methods, along with baseline characteristics of subjects enrolled as of June 20, 2012, are presented.

Method:
The study is expected to randomize 260 subjects aged 16–70 years with type 1 diabetes. All subjects are provided with a Medtronic Revel insulin pump, Enlite glucose sensors, and a Bayer Contour NextLink blood glucose meter before entering a 4–6 week run-in period. Subjects with sensor glucose (SG) evidence of two nocturnal hypoglycemic episodes (defined as SG < 65 mg/dl for >20 min between 10:00 PM and 8:00 AM) during a specific 2-week window of the run-in period are randomized to group A [Veo insulin pump with low glucose suspend (LGS) feature set to suspend insulin when a low glucose threshold is reached] or group B (Revel insulin pump, no LGS capability) during the treatment period. For safety, glycated hemoglobin values at the beginning and end of the treatment period will be compared to test the hypothesis that LGS is not associated with glycemic deterioration. For efficacy, the event area under the curve will be used to demonstrate the reduction of nocturnal hypoglycemia when LGS is turned on.

Result:
As of June 20, 2012, 247 subjects have been screened and enrolled at 18 investigational centers, and 101 subjects have been randomized at 13 centers (52 to group A, 49 to group B, 40.2% male, age range 22–70 years, mean ± standard deviation age 44.45 ± 11.6 years).

Conclusion:
Results of the ASPIRE-2 study may help quantify the safety and glycemic benefits of the LGS feature during long-term, in-home use.

Evaluation of a Novel Artificial Pancreas: Closed-Loop Glycemic Control System with Continuous Blood Glucose Monitoring

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Objective:
A closed-loop glycemic control system using an artificial pancreas has been applied with many clinical benefits in Japan since 1987. To update this system, incorporating user-friendly features, we developed a novel artificial pancreas (STG-55). The purpose of this study is to evaluate the new model of artificial pancreas (STG-55) regarding usability and performance of blood glucose measurement and glycemic control compared with the conventional artificial pancreas (STG-22) *in vivo* in animal experiments.

Method:
There are several features for usability improvement based on the design concepts, such as compactness, a display monitor, batteries, guidance function, and reduction of the time for preparation. We examined correlations of both blood glucose measurements using Clarke error grid analysis and compared glucose infusion rate (GIR) during glucose clamp between the two systems.

Results:
The results showed strong correlation between both blood glucose concentrations (Pearson's product-moment correlation coefficient 0.97; n = 1636). Clarke error grid analysis showed that 98.4% of the data fell in zones A and B, which represent clinically accurate or benign errors, respectively. The difference in mean GIRs was less than 0.2 mg/kg/min, which was considered clinically similar. The clinical data showed sufficient glycemic control, maintaining appropriate glucose range without any hypoglycemia.

Conclusion:
The new model of artificial pancreas STG-55 showed improvement of usability and good accuracy in terms of blood glucose measurements and sufficient glycemic control performance compared with the conventional artificial pancreas and also showed sufficient glycemic control clinically. Closed-loop glycemic control using the novel artificial pancreas would be useful for surgical and critical patients in intensive care units, as well as diabetes patients.

Closed-Loop Control of Insulin Pumps with Multivariable Adaptive Models

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Objective:
The objective of this work is to develop subject-specific models that can capture a subject's daily glucose variations, predict his/her future glucose excursions, and automate insulin infusion by using model-based closed-loop control. A subject's metabolic, physical activity, emotional stimuli, and lifestyle conditions are known to have a significant effect on glucose metabolism and daily glucose excursions. We use such physiological signals measured continuously with a multisensor body monitor and the subject's recent glucose history from a continuous glucose sensor with calculated insulin-on-board information, to develop the proposed subject-specific models and control algorithms.

Method:
The subject-specific glucose prediction model is developed using measurements from a glucose sensor and physiological signals from a multisensor armband. The frequent data from the sensors are analyzed by time-series methods. Adaptive system identification consists of an online parameter identification using the weighted constrained recursive least squares (WCRLS) method and a time-varying forgetting factor method that changes the importance of history of measurements adaptively. It estimates model parameters that enable the adaptation of the model to intersubject/intrasubject variation and glycemic disturbances. Generalized predictive control methods with insulin-on-board information are used to determine insulin infusion flow rates.

Result:
The control algorithms based only on glucose measurement information are tested by using simulators. The multivariable control systems are tested in clinical studies. Errors in glucose concentration predictions are reduced by building multivariable models that use information from the armband, compared with predictions done solely on glucose measurements. The use of a constrained optimization method prevented unstable models. With a time-varying forgetting factor, a better identification performance with lower computational load is obtained. Both control systems are successful in regulating glucose concentrations in response to various meal and exercise disturbances.

Turksoy cont. ⟶

Turksoy cont. ⟶

Conclusion:
Models developed are linear, low order, and easy to identify, which makes them good candidates for use in closed-loop control with an automated insulin pump. The WCRLS and the time-varying forgetting methods enable the dynamic adaptation of the models to intersubject/intrasubject variation and glycemic disturbances. Use of insulin-on-board information in control contributes to prevention of hyperinsulinemia (or hypoglycemia).

Identification of Motifs in Continuous Glucose Monitor Data in Type 1 Diabetes

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Objective:
We computationally identify motifs in continuous glucose monitor (CGM) data from subjects with type 1 diabetes mellitus (T1DM), thereby simplifying CGM data for additional analyses.

Method:
A total of 4000 h of CGM data from 26 T1DM individuals were analyzed. Linear approximations replaced missing subsequences ≤15 min (those >15 min were replaced with null data). CGM data motifs were identified via a novel algorithm that intakes windows of six consecutive data points and an upper bound, returning motifs and labels for each window. Within the algorithm, repeated K-means intakes feature vectors, K, and percentage bound and outputs a list of K-means, and score intakes centers and feature vectors and outputs a score corresponding to each feature vector, accounting for both distance and rate of change (RoC).

Result:
With an upper bound of 20, percentage bound of 0.99, and initial K of 8, several hundred motifs are generated from approximately 4200 feature vectors. Motif shapes are diverse and generally display RoC ≤ 2 mg/dl/min. A total of 13% of motifs have a RoC > 3 mg/dl/min, while 12% of the vectors also have a RoC > 3 mg/dl/min, suggesting good fit of motifs to the raw data. In fact, over 99% of the original CGM data was within the upper bound of a motif, as measured by score. Comparing the general motifs against an individual's data, however, yields 68% accuracy.

Conclusion:
This approach identifies many motifs in CGM data, potentially reducing the data's complexity six-fold; to improve algorithm performance, we plan to consolidate redundant motifs. We hope to sample this method on more individuals' data sets and compare the motifs generated to those generated by the "general" data set, as our preliminary data suggest the presence of non-general motifs that may constitute a "CGM fingerprint."

A Cost-Weighted Metric for Evaluating the Analytical and Clinical Accuracy of Glucose Sensors

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Background:
Glucose monitoring systems are developed using calibration algorithms that optimize both accuracy and their ability to provide best quality of care to their patients. Objective functions that set to minimize metrics such as mean absolute relative difference (MARD) and mean absolute difference (MAD) are deficient in their ability to assess the impact of treatment decisions and clinical error based on sensor output and rely on a separate error grid analysis (EGA). This work introduces and evaluates a numerical metric that spans the full glucose space and assesses both accuracy and clinical error for both single-point and continuous glucose readings.

Method:
This metric incorporates a weighting for the error of a data point to the reference glucose along with a cost of providing misleading diagnosis to the patient. This weighting varies depending on whether the reference is in the hypoglycemic, hyperglycemic, or euglycemic range. This cost-weighted metric is evaluated on several simulated data sets to test its ability to detect a decrease in overall sensor accuracy and performance when compared with the set of MAD, MARD, and EGA.

Result:
An example of a subset of the data shows that simulations with a decrease in Clarke A+B zones do not directly translate to an increase in MAD or MARD. The cost-weighted metric that will be presented does have a quantitative impact from each of these. Since it bundles both analytical and clinical accuracy in to a single number, it is also enabling the optimization of an algorithm for a continuous glucose monitoring system.

Conclusion:
This metric enables the convergence of the beneficial analytical features of the traditional MARD and MAD metrics in with the clinical features of the Clarke error grid.

Generation of Macroscopic Porosity in Outer Hydrogel Membranes to Offset Sensitivity Drifts in Implantable Glucose Sensors

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Objectives:
Biofouling and tissue inflammation present two major challenges for realizing long-term implantable glucose sensors. Following sensor implantation, proteins and cells adsorb on its surface not only to inhibit glucose flux, but also to signal a cascade of inflammatory events that eventually leads to permeability-reducing fibrotic encapsulation. Herein, we show that the permeability reduction due to biofouling can be offset by the continuous generation of macroscopic porosity through microsphere degradation in outer dexamethasone-eluting composite coatings.

Methods:
Implantable glucose sensors utilizing enzymatic detection of glucose were coated with dexamethasone-containing polylactic-co-glycolic acid microspheres/polyvinyl alcohol (PVA) hydrogel composite. Sensors and composite films were incubated in either phosphate-buffered saline (PBS) buffer or in porcine serum to let the microsphere degrade. Variation in sensor sensitivity and composite's glucose permeability as a function of incubation time was investigated.

Results:
In the absence of proteins (PBS buffer), a monotonic increase in glucose permeability (150%) has been observed over a 1-month period concomitant with sensor sensitivity. Scanning electron microscopy has revealed that this increase is due to the continuous creation of voids (macroscopic porosity) following microsphere degradation, which is assisted by the rigidity of PVA hydrogel that prevents its complete collapse onto the voids. In the presence of proteins (porcine serum), while biofouling clogs the microporosity of the hydrogel, this is offset by the generated macroscopic porosity following microsphere degradation. This results in a two-fold recovery in sensor sensitivity as compared with blank PVA-hydrogel-coated devices.

Conclusions:
These findings suggest that the concept of macroscopic porosity can reduce sensitivity drifts due to biofouling and, at the same time, is synergistic with current efforts to mitigate negative tissue responses through localized and sustained drug delivery.

Tissue Classification and a Volumetric Model from Magnetic Resonance Imaging: A Novel Method for Diagnosis and Therapy of the Diabetic Foot

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Background:
Magnetic resonance (MR) imaging of soft tissues can be utilized to describe diabetic ulcer composition and produce a volumetric model. This provides the physician with an efficient method of determining the depth, size, and composition of the ulcers. This can support crucial clinical decision making and scientific evaluation of other noninvasive diagnostic methods. This pilot study was performed on healthy subjects before including diabetes patients. We aim to develop an accurate method to produce a volumetric model of the foot (and diabetic foot ulcers) from MR images.

Methods:
MR images were acquired from a 1.5T Siemens Achieva scanner with a grey scale resolution of 256 × 256 pixels. Three-dimensional (3D) ultrafast T1 weighted gradient echo scan sequence (MPRAGE) was used to record the images of the foot anatomy. Combining the scans with the 3D T2 weighted sequence (NATIVE SPACE), the characteristics of ulcer tissue can be acquired. The MR images showed ghosting artifacts and background noise elements, which were eliminated by filtering techniques. The filtered images were processed with the level set method, allowing segmentation of the foot. A volumetric model of the foot was calculated and described on this basis with a polynomial mesh.

Results:
Image processing combined with MPRAGE sequencing makes it possible to create a volumetric model of the scanned foot of a healthy person.

Conclusion:
Magnetic resonance imaging combined with image processing methods offer the possibility to classify tissues and create volumetric models. This study is the initial step toward a volumetric model of a diabetic foot ulcer. Our results show that MR images can provide the data needed to create a volumetric model with the depth, size, and tissue composition of a diabetic foot ulcer.

Blood Glucose Control in the Intensive Care Unit: LOGIC-Insulin versus Leuven Nurse

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Objective:
Tight glycemic control (TGC) in critically ill patients is difficult, labor intensive, and associated with increased hypoglycemia rate. The LOGIC-Insulin computerized algorithm has been developed to assist nurses in titrating insulin to maintain blood glucose levels between 80 and 110 mg/dl (normoglycemia) and to avoid severe hypoglycemia (<40 mg/dl). The objective was to clinically validate LOGIC-Insulin, compared with TGC-experienced nurses.

Method:
In the LOGIC-1 single-center controlled clinical trial, a heterogeneous mix of 300 critically ill patients were randomized, by concealed computer allocation, to either nurse-directed glucose control (Nurse-C) or to algorithm-guided glucose control (LOGIC-C). The primary outcome measure (efficacy) was the glycemic penalty index (GPI), a measure that penalizes hypoglycemic/hyperglycemic deviations from normoglycemia with low values, indicating effective TGC. The incidence of severe hypoglycemia (<40 mg/dl) and the sampling interval served as safety and workload outcome measure, respectively.

Result:
Baseline characteristics of 151 Nurse-C patients and 149 LOGIC-C patients and study time did not differ. Average blood glucose (Nurse-C, 107 ± 11 mg/dl; LOGIC-C, 106 ± 9 mg/dl; p = .36) was similar. The GPI decreased from 12.4 [interquartile range (IQR) 8.2–18.5] in Nurse-C to 9.8 (IQR 6.0–14.5) in LOGIC-C ($p < .0001$). While the proportion of patients who had a severe hypoglycemic event was not decreased (Nurse-C, 3.3%; LOGIC-C, 0%; $p = .060$), LOGIC-C (32.2%) lowered the incidence of mild hypoglycemia (<70 mg/dl) compared with Nurse-C (48.3%; $p = .0048$). The interval between blood glucose measurements was slightly shorter in LOGIC-C (2.2 ± 0.4 h) compared with Nurse-C (2.5 ± 0.5 h; $p < .0001$).

Conclusion:
The computerized algorithm LOGIC-Insulin improved efficacy of TGC without increasing the rate of hypoglycemia compared with glucose control by expert Leuven nurses. This work was funded by IWT-TBM-100793, IOF-HB/10/039, and FWO-G.0557.08; LOGIC-1 ClinicalTrials.gov number, NCT01420302).

Continuous-Glucose-Monitoring-Informed Correction Bolus Advisor for Multiple Daily Injection Treatment of Type 1 Diabetes

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Objective:
Recent clinical and outpatient studies have illustrated the potential of continuous subcutaneous insulin infusion (CSII)-based closed-loop control of type 1 diabetes. However, it is unclear whether patients on multiple daily injection (MDI) therapy can benefit from the associated algorithmic developments. Taking advantage of the ability to estimate the patient's metabolic state using both continuous glucose monitoring (CGM) and insulin delivery in real time, we have developed a model-based, patient-adapted correction bolus advisor and hypothesize that it can be used to extract significant improvements in hemoglobin A1c (HbA1c) when used in conjunction with conventional meal-related insulin corrections.

Method:
Incorporating a pharmacokinetics/pharmacodynamics model of long-acting insulin within the University of Virginia/Padova simulator, we have tested the mealtime correction bolus advisor within a population of *in silico* MDI patients who, under conventional therapy, achieve a HbA1c of 7.98% (±0.512% standard deviation). The advisor was tested under a two-day protocol involving three meals on the first day, two meals on the second day, and daily long-acting insulin injections at 6:00 AM. The performance measures compared were HbA1c and low blood glucose index (LBGI), among others.

Result:
With mealtime correction doses computed using the CGM-informed advisor, under "nominal" absorption of the basal insulin dose, mean HbA1c was improved from 7.98% to 6.79% ($p < .0001$) without substantially increasing the risk of hypoglycemia: LBGI increased from 0.001 to 0.594 ($p < .0001$). Even under ±25% variability in the basal insulin pharmacokinetics model parameter, the system improves HbA1c by at least 0.75% on average, keeping mean LBGI below 1.1.

Conclusion:
Our results indicate that CGM-informed algorithmic MDI therapy is a promising alternative to future CSII-based artificial pancreas systems, potentially appealing to tech-savvy patients who prefer not to use insulin pumps.

A Paradox of Defective Peripheral C/Aδ Nerve Fiber Dysfunction and Increased Central Cognitive Function in Painful Diabetic Neuropathy

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Objective:
At least one out of four patients with diabetes develop neuropathic pain. There is no established mechanism for the development or absence of pain, which may be spontaneous or nociceptive and may have central or peripheral cognitive involvement. Contact heat-evoked potential stimulation (CHEPS), with central recording, allows for the evaluation of both central and peripheral functional integrity.

Methods:
We examined subjective and objective measures of central and peripheral cognitive function in 12 patients with painful diabetic neuropathy (PDN) and 20 patients with nonpainful diabetic neuropathy (NPDN) using quantitative sensory testing, physical examination, CHEPS, and nerve conduction studies (NCS). CHEPS results were recorded and analyzed to determine interpeak amplitude (IA).

Results:
PDN patients had higher neurological symptom scores than NPDN patients (3.38 ± 0.35 and 1.90 ± 0.29, respectively; $p = .001$). PDN patients had a higher frequency of numbness compared to NPDN patients (95% and 67%, respectively; $p = .033$), and NCS showed no large nerve fiber abnormality. In contrast, compared with controls, both PDN and NPDN groups had impaired vibration detection threshold and touch pressure perception (healthy controls = 15.8 ± 2.81 μ, PDN = 39.8 ± 7.59 μ, and NPDN = 39.6 ± 7.22 μ; $p = .002$ and $p = .013$, respectively) in support of a peripheral nerve dysfunction. PDN patients had significantly lower CHEPS IA responses than NPDN patients at the lower back (18.5 ± 1.81 and 31.7 ± 7.88 μV, respectively; $p = .049$), with no difference in verbal ratings of stimuli. Paradoxically, PDN patients had a higher heat pain threshold (16.7 ± 0.41°C) than NPDN patients (14.2 ± 1.17 °C; $p = .023$).

Vinik cont. ⟶

Vinik cont. ⟶

Conclusion:
Thus, this study shows that PDN is distinguished from NPDN by increased heat pain thresholds, higher rates of numbness, and reduced physiologic measures of C-Aδ nerve fiber function. Our results indicate a peripheral nerve dysfunction and enhanced central cognitive processing contributing to pain. This suggests that pain therapies should focus on improving the peripheral defect as well as mitigating the central cognitive processing of pain signaling.

Evaluating the Sudoscan as a New Diagnostic Tool for Painful Diabetic Neuropathy and Autonomic Dysfunction

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Objective:
Major clinical manifestations of diabetic neuropathy are autonomic dysfunction and pain. The aim of this study was to evaluate Sudoscan™ as a tool for assessing autonomic neuropathy and neuropathic pain.

Methods:
The Sudoscan measures the electrochemical skin conductance (ESC) of the hands and feet through reverse iontophoresis. Sudomotor function was evaluated in 72 patients to determine its relationship with pain and autonomic dysfunction. Time and frequency quantitative autonomic function testing (QAFT) was used to determine sympathetic, parasympathetic, and autonomic balance. Quantitative sensory evaluations of hot, cold, pressure, and vibration perception were assessed, and symptomatic pain was recorded using a visual analog scale (numerical rating two-point scale). Results are reported as mean ± standard error.

Results:
Patients with two abnormal QAFT ratios (expiratory-to-inspiratory < 1.09, Valsalva < 1.19, postural < 1.093) were compared with those with normal QAFT ratios. An ESC < 60 was considered an abnormal Sudoscan reading. Those with a normal QAFT had a significantly higher mean ESC (78.85 ± 3.06) versus those with an abnormal QAFT (57.4 ± 6.21; p = .0073). Patients with abnormal ESC values had significantly higher baseline LFA values (11.34 ± 5.93 versus 1.64 ± 0.33; p = .0076) and sdNN intervals values (61.00 ± 13.08 versus 32.38 ± 4.08; p = .0075), which measure parasympathetic and sympathetic function. Higher rmSSD values (59.57 ± 15.93 versus 22.45 ± 3.81; p = .0018), a measure of parasympathetic function, were also observed. Patients with abnormal ESC readings also had significantly higher mean pain ratings of 7.4 ± 1.17 versus 1.47 ± 0.61 (p = .0002) in patients with normal ESC readings.

Conclusions:
Sudoscan is able to detect autonomic activation and identify pain susceptibility. The significant difference found in pain ratings in patients with abnormal sudorimetry suggests that the peripheral sympathetic autonomic nervous system plays a role in painful diabetic neuropathy and may aid in patient selection for autonomic therapeutic intervention.

Association of Self-Monitoring of Blood Glucose Use on Glycated Hemoglobin and Weight in Newly Diagnosed, Insulin-Naïve Adult Patients with Type 2 Diabetes

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Objective:
Clinical trials have shown that self-monitoring of blood glucose (SMBG) combined with patient education and medication titration can lead to improvements in glycated hemoglobin (A1C) and weight reduction in recently diagnosed non-insulin-using type 2 diabetes mellitus (T2DM) patients. This study assessed the association of SMBG with achieving long-term clinical outcomes in these patients in a real-world clinical setting.

Methods:
Using electronic medical records (2008–2011), we selected a population of adult patients recently diagnosed with T2DM not receiving insulin who were SMBG users and a population of non-SMBG controls with similar demographic and clinical characteristics using propensity score matching. Outcomes compared between the two groups were (1) proportion of patients with a baseline A1C ≥ 7% achieving an A1C < 7% and (2) proportion of patients achieving a ≥5% reduction in weight from baseline.

Results:
Of the 589 patients (~53% female; mean age ~64 years) identified in each group, 113 in each group had a baseline A1C ≥7% (mean, 8.2%). The SMBG users were more likely to achieve A1C < 7% (3 months 24.8% versus 15.0%; 6 months 46.0% versus 32.7%; 12 months 58.4% versus 38.9%; 36 months 84.0% versus 70.0%; all $p < .05$) and to do so faster (median 6.5 versus 20.5 months; log rank $p = .0016$). The mean baseline weight was ~205 lbs. ($n = 400$ SMBG; $n = 403$ non-SMBG). Self-monitoring of blood glucose was associated with faster weight reduction (median time to achieve a ≥5% reduction 23.5 versus 35.9 months for SMBG and non-SMBG, respectively; log rank $p = .0005$).

Conclusions:
In newly diagnosed T2DM insulin-naïve patients, SMBG users had an improved rate of achieving long-term glycemic control and weight loss in a real-world clinical setting, suggesting that SMBG plays a role in achieving clinical improvement with these patients.

Cloning a Day of Individual Type 1 Diabetes Mellitus Subjects from the Food and Drug Administration-Accepted Simulator by a Bayesian Approach

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Objective:
The model included in the Food and Drug Administration-accepted type 1 diabetes mellitus (T1DM) simulator has not yet been identified on T1DM individuals because, given the complexity of the model, its identification would require the availability of experiments with multiple tracers. Here we propose a Bayesian identification method of the model from plasma glucose and insulin concentrations only, exploiting the knowledge of the a priori model parameter distribution.

Method:
The database consists of 15 T1DM subjects, recruited within the AP@Home FP7-EU project (data from the Cardiovascular Health Research Unit, Montpellier and Academic Medical Center, Amsterdam) who received dinner, breakfast, and lunch (respectively 80, 50, and 60 g of carbohydrates) on three occasions (one open loop and two closed loop) for a total of 20 h per session. The model is identified using the Bayesian maximum a posteriori technique, where the a priori parameter distribution is that of T1DM simulator. In addition, diurnal variability of a few parameters describing glucose absorption and insulin-dependent utilization is allowed to improve model adherence to data.

Result:
The model well describes glucose traces. Absorption parameters at breakfast are significantly different from those at lunch and dinner, reflecting a more rapid dynamic of glucose absorption, possibly due to the different meal composition. In addition, insulin-dependent glucose utilization varies in each individual but without a specific pattern.

Conclusion:
These results prove the robustness of the model structure and, indirectly, the validity of the model parameter distribution included in the simulator. The method for the identification of the glucose–insulin model allows us to describe the glucose time course during a day and to estimate the parameter of each T1DM subject from plasma glucose and insulin concentrations.

Specificity Is the Central Problem of Noninvasive Glucose Measurement, but It Can Be Solved by Mid-Infrared Spectroscopy

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Objective:
Technologies for noninvasive glucose measurement yield convincing results if tested in a controlled laboratory environment. However, they reveal weak reproducibility under daily life conditions. The major reason for that is the lack of specificity of the physical principles used, such as near-infrared spectroscopy, skin impedance, optical coherence tomography, Raman spectroscopy, and others. Thus the correlation between the instrument signal and the blood glucose value is not robust and reliable enough to be used by the diabetes patient on a day-to-day basis. The technology we proposed relies on the specific fingerprint of the glucose molecule in the mid-infrared (MIR) and is based on infrared quantum cascade lasers and photoacoustic (PA) detection. With this technology, we observe a strong correlation between PA signals and blood glucose ($r > 0.9$) for a wide glucose range (50–300 mg/dl).

Method:
Our MIR noninvasive glucose analysis was tested with patients subjected to physical exercise, fluid loss, exposure to fluid, and change of skin composition.

Result:
No influence on MIR signals was observed upon these manipulations. After a deprivation of 0.5 liter water induced by exercise, PA signals continued to follow glucose as they did after water exposure by drinking or after the removal of layers of the stratum corneum of the skin.

Conclusion:
Our data provide strong evidence that the use of our proposed MIR-based noninvasive glucose measurement does not suffer from unspecific effects that are characteristic for daily life. In this respect, this technology differs from the other approaches.

DialBetics: Smart Phone-Based Self-Management for Type 2 Diabetes Patients

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Objective:
The purpose of the study is (1) to develop a partially automated system to interpret patients' data—with interactive communication of findings—achieving diabetes management without increasing the physician's workload and (2) to evaluate the potential role of the system in diabetes self-management among type 2 diabetes patients.

Method:
DialBetics is composed of four modules. (1) Data transmission: patients' data—blood glucose, blood pressure, body weight, and pedometer counts—are measured at home and sent to the server twice a day. (2) Evaluation: data are automatically evaluated following the Japan Diabetes Society guideline's targeted values; DialBetics determines if each reading satisfies guideline requirements and then sends those results to each patient's smart phone. (3) Communication: (a) the patient's voice/text messages about meals and exercise are sent to the server; (b) message processing; (c) advice on lifestyle modification, matched to the patient's input—foods and exercise— is fed back to each patient. (4) Dietary evaluation: patients' photos of meals are sent to the server; the nutritional values of their meals are calculated by dietitians and sent back to each patient.

Result:
DialBetics was tested with five type 2 diabetes patients [age 63.8 ± 4.4 years; body mass index 24.1 ± 4.8 kg/m^2; hemoglobin A1c (HbA1c) 6.9% ± 0.7%] and found to be effective in modifying lifestyle and improving self-management. Diabetes control was improved (p = .04), and patients started exercising more and eating healthier food.

Conclusion:
DialBetics may lead to better control of diabetes, improving patient lifestyle by offering continuous suggestions for improvements. To validate if diabetes control was improved by change of HbA1c, a randomized controlled trial—50 patients for 3 months—is in progress. So far, 24 patients have been registered.

Accuracy of the Contour Next Link Blood Glucose Meter System in the Hands of Users

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Objective:
This study assessed the performance of the Contour Next Link in the hands of users. This blood glucose meter system (BGMS) can communicate with specific Medtronic insulin pumps. It uses a FAD-GDH enzyme test strip with a proprietary electron mediator.

Method:
A total of 110 subjects aged 19 to 86 years with type 1 (n = 37), type 2 (n = 63), or type unknown (n = 10) diabetes participated. Untrained subjects learned to use the BGMS using the labeling materials provided and tested finger stick and palm alternate site testing (AST) samples. All results were compared to YSI 2300 STAT Plus™ Glucose Analyzer reference results. Subjects completed a questionnaire on the ease of use of the BGMS and clarity of user guide instructions.

Results:
Overall, the meter met both current ISO 15197:2003 and proposed more stringent accuracy criteria, with more than 99% and 96% values from finger stick and AST samples, respectively, falling within ±15% or ±15 mg/dl. For finger stick values < 100 mg/dl, 100% were ±10 mg/dl of reference value, and 99% of values ≥ 100 mg/dl were ±10% of reference value. By Parkes error grid analysis, 100% of capillary results were in zone A; 97.2% of palm results were in zone A, and the remainder were in zone B. Based on questionnaire results, the majority of subjects agreed or strongly agreed that the BGMS was easy to use (91.8%), user instructions were easy to understand (86.4%), and meter display was easy to read (95.5%) and see and understand the results (98.2%).

Conclusion:
The Contour Next Link BGMS demonstrated ease of use and impressive accuracy in the hands of users, which is important for a meter that enables communication with an insulin pump.

ITCA 650 for Zero-Order Continuous Delivery of Exenatide at Its Therapeutic Levels for 12 Months

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Objective:
We aim to deliver exenatide at therapeutic levels with zero-order release profiles from ITCA 650, exenatide in DUROS® devices, for 3, 6, and 12 months.

Method:
The DUROS drug delivery device provides continuous administration of therapeutic molecules at steady rates for long durations. The DUROS device is an osmotic minipump consisting of a sterile titanium cylinder (4 by 44 mm) that is placed subcutaneously. Exenatide was formulated into the devices. *In vitro* delivery of exenatide was evaluated at 37 °C and characterized by reversed-phase high-performance liquid chromatography and ultraviolet methods. Stability of exenatide at 40 °C was also characterized using multiple methods to ensure exenatide in the DUROS devices is stable for at least 12 months.

Result:
ITCA 650 was successfully manufactured for clinical studies to deliver exenatide at therapeutic levels of 20, 40, or 60 mcg/day for durations of 3, 6, and 12 months. ITCA 650 exhibited zero-order *in vitro* release profiles at expected exenatide release rates over the designed delivery durations. The *in vitro* formulation release studies demonstrated that the expected delivery rates reached steady state rates quickly, within 2 h, after initiation. No overdose was observed over the entire delivery durations (3, 6, and 12 months) from each device for more than 3000 devices studied. Stability of exenatide in ITCA 650 was maintained at 40 °C for 3 years. The bioactivity of the exenatide in the formulations was comparable with its reference standard at all time points.

Conclusion:
ITCA 650 was successfully manufactured in various strengths for clinical studies. It delivered exenatide at continuous and consistent rates at desired therapeutic levels for up to 12 months. ITCA 650 showed desired stability at 40 °C. ITCA 650 is not required to be stored at refrigeration conditions.

Noninvasive Continuous Glucose Monitoring by Multisensor System: Improved Accuracy Using an Elastic Net Regression

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Objective:
An approach for noninvasive continuous glucose monitoring was assessed using a combination of the Solianis Multisensor system and a multivariate linear regression model identified with the least absolute shrinkage and selection operator (LASSO). The aim of this work is to improve accuracy exploiting the elastic net (EN) technique for model identification.

Method:
Data from 45 experimental sessions were considered, during which Multisensor data and reference blood glucose were acquired in parallel. Half of the experiments were used for model identification, and the remaining for model test. The model was identified with EN regression, a technique minimizing a cost function given by the sum of the residual sum of squares plus a regularization term given by the combination of an absolute norm and a squared norm over the coefficients of the linear model.

Result:
The EN model shows a 9.5% root mean square error reduction (from 63.1 to 57.1 mg/dl) and a 7.6% reduction of the mean absolute relative difference (from 38.1% to 35.2%) with respect to the LASSO. The achieved point accuracy [93% of points in zone A+B of the Clarke error grid (CEG)] is not yet comparable with that of minimally invasive devices, but glucose trends are estimated sufficiently well (around 85% of points in zone A_R+B_R of the continuous CEG).

Conclusion:
An improvement in the accuracy of estimated glucose profiles by the Multisensor system is achieved by EN regression even though it is not yet comparable with that of enzyme-based needle sensors. The Multisensor technology is potentially suitable to integrate sparse self-monitoring of blood glucose readings with glucose trend information, resulting in a useful solution as a potential adjunctive device in diabetes monitoring.

Antidiabetic Efficacy of a Proinsulin–Transferrin Fusion Protein in Mice

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Objective:
The purpose of this study was to evaluate a proinsulin (ProINS)–transferrin (Tf) fusion protein *in vivo*. Our previous studies have shown that ProINS–Tf was converted to active insulin (INS)–Tf via the Tf–Tf receptor-mediated pathway in hepatoma cells. We hypothesized that this fusion protein can be administered as a prodrug and be converted to a biologically active protein with liver selectivity. Administration as an inactive prodrug with selective liver action conceivably reduces hypoglycemia, desensitization, mitogenicity, and metabolic side effects seen with other INS analogs.

Methods:
His-tagged ProINS–Tf was expressed and purified from HEK293 cells. *Ex vivo*-activated INS–Tf was generated by trypsin digestion of purified ProINS–Tf. The pharmacokinetics, hypoglycemic efficacy, and gluconeogenic/glycogenolytic liver-enzyme levels were determined following administration in streptozotocin-induced diabetic mice.

Results:
Pharmacokinetic studies determined a delayed absorption (t_{max} = 5.5 h) and prolonged half-life ($t_{1/2}$ = 7.29 h) compared with ProINS (t_{max} = 0.3 h, $t_{1/2}$ = 0.5 h). ProINS–Tf demonstrated a delayed hypoglycemic efficacy following subcutaneous administration, reaching a maximum effect (84% reduction in blood glucose levels) at 8 h, which was maintained until the latest 12 h time point. The effect at 8–12 h was similar to INS at 2 h. The activity of ProINS–Tf was also delayed following intravenous administration, while *ex vivo*-activated INS–Tf had immediate activity, indicating the requirement of *in vivo* conversion to elicit a biological response. Finally, after assessing the bioactivity profile and the effect of ProINS–Tf in reduction of gluconeogenic/glycogenolytic enzyme levels, the results indicated that its effect was liver specific.

Conclusion:
ProINS–Tf showed a slow, but sustained, *in vivo* hypoglycemic efficacy and long plasma half-life. Therefore, ProINS–Tf can potentially be administered as an inactive prodrug with sustained Tf-mediated activation in the liver.

Physical Activity Measured by Physical Activity Monitoring System Device Correlates with First- and Second-Order Glucose Concentration Derivatives

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Objective:
Quantification of the effect of physical activity (PA) on glucose concentration and its variability is a challenging topic. In the present study, we evaluated possible correlations between PA, measured using the Physical Activity Monitoring System (PAMS; a system with accelerometers and inclinometers for recording body posture and movement) and first- and second-order derivatives of glucose concentration measured by the Dexcom SEVEN PLUS® continuous glucose monitoring system.

Method:
A total of 13 type 1 diabetes and 17 control subjects were studied in the Clinical Research Unit at Mayo Clinic (Rochester, MN) for 88 h. Each day, subjects underwent 4–6 consecutive sessions of low-intensity PA, during which they alternated 26.5 min of walking on treadmill (1.2 mph) with 33.5 min of sitting. First- and second-order glucose derivatives were estimated using a Bayesian smoothing procedure. Their correlation with PAMS output was assessed at various delays in the range of 0–60 min.

Result:
We found that, in diabetes subjects, glycemic concentration decreases during PA and increases during rest sessions. The decreasing effect is maximum after 15 min of PA, while the increasing effect is maximum after 15 min of rest. Furthermore, we found that, when glucose is decreasing, PA makes it decrease more rapidly, while, if glucose is increasing, PA makes it stop increasing and start decreasing or increase less rapidly. Results on control subjects are similar, but the correlation is inferior (in absolute terms), and the effects of PA start after only 5 min.

Conclusion:
We demonstrate that low-intensity PA correlates with fluctuations of glucose concentrations and, in particular, has the effect of lowering glucose concentration or makes it increase less rapidly.

Prediction-Based Alerting Methods Could Reduce Number and Duration of Hypoglycemic Events: An *In Silico* Quantification

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Objective:
Prevention of hypoglycemia is pivotal in type 1 diabetes treatment. Prediction of future glucose concentration based on continuous glucose monitoring (CGM) data, combined with algorithms for the generation of (preventive) hypoglycemia alerts, could help in mitigating, and sometimes even avoiding, hypoglycemic events. Here we quantify *in silico* the potential reduction in number and duration of hypoglycemic events obtainable by treating hypoglycemia (through ingestion of carbohydrates) on the basis of alerts generated by exploiting glucose predictions obtained by a recently presented neural network approach.

Method:
We generated 50 *in silico* CGM time series through the University of Virginia/Padova type 1 diabetes simulator (US2008/067725). The simulation scenario consisted of 2 days, three meals/day, with random variability on meal carbohydrates and insulin dosages. To quantify the potential reduction of hypoglycemia occurrence, we compared number and duration of hypoglycemic events when hypoglycemic treatment (15 g of carbohydrates) is administered on the basis of either the actual CGM value or the 30 min ahead-of-time glucose prediction obtained via the neural network.

Result:
Without any alert, each subject experienced, on average, two hypoglycemic events/day (with 121 min of duration, lowest glucose value 53 mg/dl). Hypoglycemia alerts generated by actual CGM reduce the number of hypoglycemic events to 1.6 per day (38 min each, lowest glucose 62 mg/dl), while hypoglycemia alerts generated using the predicted glucose further reduces the hypoglycemic events to less than 0.5 per day (21 min each, lowest glucose value 67 mg/dl).

Conclusion:
In silico simulation suggests that generation of hypoglycemia alerts based on glucose prediction algorithms significantly reduces number and duration of hypoglycemic events with respect to hypoglycemia alerts based on the actual CGM readings.

Integrated Self-Monitoring of Blood Glucose System: Comparative Handling Evaluation of the First and Second Generation

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Objective:
The overall usability of systems for self-monitoring of blood glucose (SMBG) is essential to ensure regular measurements of blood glucose (BG) done by the patients. The strip-free Accu-Chek® Mobile system incorporates a test cassette with 50 tests on a continuous tape. Additionally, it provides an attached lancing device with a drum containing six sterile lancets. In this handling evaluation study, handling characteristics of the Accu-Chek Mobile system (second generation) were compared with the previous system (first generation).

Method:
Fifty-six participants with type 1 diabetes [19 male, 37 female; age 48.9 ± 12.5 years; 24.7 ± 14.2 years on insulin therapy; daily 5.6 ± 1.6 BG measurements (mean ± SD)] were included in this study; 52 participants were evaluated as per protocol population. During 10 days, both Accu-Chek Mobile systems were used alternately for daily SMBG. The conduct of single handling steps, separately for BG meter and lancing device, was assessed using a visual analog scale (VAS) from 0–10 cm (0 cm = easy, 10 cm = difficult). Weight/acoustic volume of both systems were assessed using a VAS from 0–10 cm (0 cm = light/quiet, 10 cm = heavy/loud).

Result:
Handling of BG meter and lancing device was considered easier with the second-generation system than with the first-generation system [BG meter 1.76 ± 1.07 versus 2.05 ± 1.18 cm; lancing device 1.35 ± 0.83 versus 1.68 ± 0.92 cm (mean ± SD)]. The second-generation system was assessed as lighter and quieter than the first-generation system [weight 3.94 ± 2.39 versus 4.9 ± 2.2 cm, acoustic volume 3.54 ± 1.71 versus 3.92 ± 1.72 cm (mean ± SD)].

Conclusion:
The overall usability of the Accu-Chek Mobile system (second generation) was indicated to be more preferable to the first-generation system.

ProAct Study: Glycemic Control in Patients with Type 1 Diabetes during Transition of Continuous Subcutaneous Insulin Infusion Systems under Daily Routine Conditions

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Background:
In the longer course of continuous subcutaneous insulin infusion (CSII) treatment, patients experience switches to newer insulin pump systems on a regular basis. In Europe, usage time of insulin pumps is dependent on the approved longevity of the device and on national reimbursement regulations. The purpose of this real-world study was to investigate the impact of a transition from older pumps to the Accu-Chek® Combo system on glycemic control in different patient populations.

Method:
A total of 164 patients [95 female, 69 male; age (mean ± standard deviation) 39.8 ± 14.5 years; hemoglobin A1c (HbA1c) 7.84% ± 1.14%] were enrolled by 61 centers into this uncontrolled prospective trial with a 6-month observation period and performed at least one follow-up visit (intend-to-treat population). Parameters of glycemic control (HbA1c, frequency of hypoglycemia) were measured at baseline, after 3 months, and at end point. Changes from baseline were analyzed for the whole group and for subgroups stratified by CSII treatment experience or by the baseline quality of glycemic control.

Results:
Glycemic control remained stable or improved slightly after transition to the new insulin pump. There were no significant changes in the frequency of hypoglycemic events in the entire population or in any of the investigated subgroups. Well-controlled patients (HbA1c < 7%) remained stable during the transition process from one system to the other, and moderately controlled patients (HbA1c 7–8%) showed a trend toward better glycemic control. Patients with an insufficient glycemic control (HbA1c > 8%) showed a significant reduction in HbA1c over time, with a delta > 0.5% HbA1c ($p < .01$).

Conclusions:
Transition from older pump systems to the Accu-Chek Combo system under real-world conditions resulted in stable glycemic control with improvements in some of the analyzed subgroups. Patients who showed the highest benefit in glycemic control were those with shorter CSII experience and patients with insufficient glycemic control at the time of the switch to the new pump.

Performance of a Microdialysis-Based Continuous Glucose Monitoring System for Hospital Care

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Objective:
Combining intravenous microdialysis with online glucose analysis for continuous glucose monitoring (CGM) may prove to become an important development to achieve tight glycemic control in hospitalized patients without blood loss, measurement delays, or frequent manual interventions. In this study, we evaluated the performance of a microdialysis-based CGM system for up to 48 h use.

Method:
Twenty-one healthy adult subjects were connected to one or two CGM systems. Blood glucose was sampled automatically without blood loss by means of microdialysis every 1–2 min. The dialysate containing the sampled glucose was analyzed immediately by an online glucose sensor. This sensor was calibrated once every 24 h. Reference blood samples were taken manually and analyzed using a laboratory glucose analyzer every 10–60 min. The subjects consumed meals or glucose was administered orally or intravenously to analyze the accuracy of the CGM system over a range of blood glucose concentrations.

Result:
A total of 1796 paired sensor-reference data points were evaluated. Mean relative deviation was 9.4%, and 91.4% of data points were accurate according to the ISO 15197 criteria. Accuracy in the hypoglycemic range is notoriously difficult to achieve, but the first results with this new system are very encouraging: 94.6% of the sensor values below 75 mg/dl were within 15 mg/dl of the reference value. Clark error grid analysis showed that 99.4% of the data points were located within the accurate and acceptable zones.

Conclusion:
This study shows that CGM using microdialysis in blood is feasible for up to 48 h and provides reasonably accurate glucose results with only a once-daily calibration. Improved calibration and/or referencing strategies may increase the accuracy of the system further in future studies.

United States Inpatient Glucose Levels in 2011: The RALS Report

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Objective:
Inpatient glucose management remains controversial with conflicting conclusions regarding the efficacy of controlling inpatient glucose levels and the optimal range for various patient populations. Aggregate data from a national survey of U.S. hospitals was collected in order to gain insight into the current practice of regulating inpatient glucose. Medical Automation Systems, now known as Alere Informatics Solutions, has been producing a national benchmark of inpatient glucose results since 2006. The latest data for 2011 are presented here.

Method:
Data were collected by streaming deidentified patient point-of-care glucose results over a secure connection to a central server located in Charlottesville, VA. Data from 700 participating hospitals were aggregated and parsed by intensive care unit (ICU) and non-ICU patients to provide participants with a benchmark of their hospital's results compared with the aggregate.

Results:
The RALS Report database has approximately 1 billion patient data points. Trend data for the past 6 years reflect the changes in hospital practice as it relates to inpatient glucose control. Results include mean glucose, hypoglycemia, and hyperglycemia rates in critical care and non-critical care inpatient settings.

Conclusion:
Aggregate data from a national survey of U.S. hospitals provides valuable insight into the current approach in regulating inpatient glucose and a useful benchmark for individual hospitals. Ongoing studies are needed to determine whether glucose control impacts better patient outcomes and to determine the optimal target range for various patient populations.