Adaptive Closed-Loop Control Provides Blood-Glucose Regulation Using Dual Subcutaneous Insulin and Glucagon Infusion in Diabetic Swine

Firas H. El-Khatib, Ph.D., John Jiang, B.S., and Edward R. Damiano, Ph.D.

Abstract

Background:
In order to stave off deleterious complications of the disease, the ultimate task for people with diabetes is to maintain their blood glucose in euglycemic range. Despite technological advancements, conventional open-loop therapy often results in prolonged hyperglycemia and episodic hypoglycemia, in addition to necessitating carbohydrate counting, frequent glucose monitoring, and drug administration. The logical conclusion in the evolution of exogenous insulin therapy is to develop an automated closed-loop control system.

Methods:
Eleven closed-loop control experiments were conducted in four anesthetized diabetic pigs, with carbohydrate loads simulated by intravenous glucose administration through ear-vein catheters. Type 1 diabetes-like pathology was induced using intravenous administration of cytotoxin streptozotocin. The augmented model-predictive control algorithm accounts for the accumulation of subcutaneous insulin, which is critical in avoiding excessive insulin dosing.

Results:
Control results consistently showed successful blood-glucose regulation to euglycemic range within 80–120 minutes after intravenous glucose loads, with no incidence of hypoglycemia. This is consistent with a negative oral glucose tolerance test for diabetes and is the optimal postprandial regulation that can be achieved with subcutaneous insulin administration. Results also demonstrated the potency of subcutaneous glucagon in staving off episodic hypoglycemia and revealed efficacy of the control algorithm in coping with a twofold variation in subject weights, while simultaneously overlooking erratic blood-glucose fluctuations.

Conclusions:
Using an automated adaptive glucose-control system, we show successful blood-glucose regulation *in vivo* and establish, definitively, the plausibility and practicality of closed-loop blood-glucose control using subcutaneous insulin and glucagon infusion in type 1 diabetes. The control system strikes an intricate balance between tight blood-glucose control and optimal drug consumption, while simultaneously maintaining emphasis on simplicity and reliability.

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Author Affiliation: Department of Biomedical Engineering, Boston University, Boston, Massachusetts

Abbreviations: (BG) blood glucose, (GPC) generalized predictive control, (IV) intravenous, (STZ) streptozotocin, (SC) subcutaneous

Keywords: counterregulatory hormone, hyperglycemia, hypoglycemia, infusion pump, *in vivo*, predictive control, swine

Corresponding Author: Edward R. Damiano, Ph.D., Associate Professor, Department of Biomedical Engineering, Boston University, 44 Cummington Street, Boston, MA 02215; email address *edamiano@bu.edu*

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Background

Type 1 diabetes is a chronic life-threatening disease that is characterized by a total failure of the pancreas to deliver insulin, thereby rendering the body incapable of regulating blood glucose (BG). The consequential, untoward, conditions of hyperglycemia and hypoglycemia can have serious acute and chronic deleterious consequences. Hypoglycemia may result in acute complications, including convulsions, seizures, and coma, which can lead to brain damage, paralysis, and death, in addition to other more subtle chronic neurocognitive deficits. While hyperglycemia can have acute complications, it also has a causal relationship with many long-term complications, including vascular disease, renal complications, vision disorders, nerve degeneration, and skin disorders. Risks for such complications are elevated by three- to fivefold with diabetes.[1–3] The World Health Organization estimates that diabetes affects about 185 million people worldwide, with ~20 million individuals (~6% by population) afflicted in the United States (~10% of these have type 1 diabetes).

The ultimate task for people with diabetes is to maintain their BG levels in euglycemic range in order to avoid prolonged hyperglycemia, while at the same time minimizing episodic hypoglycemia. This has been affirmed and quantitatively assessed by the Diabetes Control and Complications Trial Research Group,[1,4] who showed that the single most important determinant for minimizing all long-term complications of type 1 diabetes was to maintain BG close to euglycemic range. They further established that the tighter the control, the fewer and less severe the complications. One method of achieving this objective involves developing an integrated glucose-control system, enabled by a continuous glucose monitor and subcutaneous (SC) drug infusion pumps.[5] Such a system would automate the management of type 1 diabetes, obviate the need for a central patient contribution, involve continuous BG monitoring, and ultimately lead to better BG regulation.

Research efforts to develop such systems have been ongoing for decades, with the Biostator design of Clemens being one of the earliest.[6] Like most glucose-control systems,[7–13] the Biostator assumed the intravenous (IV) route for drug infusion and, like most dual-infusion systems,[14–16] used dextrose as the counterregulatory agent to insulin. While IV infusion results in faster drug bioavailability than SC infusion, its associated heightened risks of infection, embolism, or thrombosis, render the SC route more practical for ambulatory usage.[5,17] The SC route, however, poses an additional challenge due to the gradual absorption of the infused drug into the bloodstream. The finite absorption

rate (with peak effect on BG at ~45–60 minutes and total SC consumption after ~5–6 hours) presents the possibility of excessive drug accumulation in the SC tissue, which can have a cumulative effect of impending hypoglycemia in the case of insulin,[17] an event that must be safeguarded against in any practical glucose control system.

This study presents a novel closed-loop control system that uses automated SC administration of insulin and glucagon by two infusion pumps to provide effective BG regulation in type 1 diabetes. Note that this is the first closed-loop control study in 30 years to employ administration of both insulin and glucagon, the last study being that by Marliss *et al.* in 1977, which, in contrast to our study, employed IV administration of both drugs.[9] In essence, the hormone glucagon serves as a counterregulatory agent in closed-loop control, which provides a key preventative measure against hypoglycemia.[18] Unlike dextrose or other fast-acting sugars, exogenous glucagon effectively mimics[19] and compensates[20] for a physiologic process in which the body's glucose reserves are utilized to raise BG and, in contrast, does not introduce exogenous glucose into the bloodstream. Another measure that we employ to prevent occasions of impending hypoglycemia is to have the control algorithm keep track of and act in light of the accumulation of SC insulin, as governed by its *in vivo* pharmacokinetics.

Materials and Methods

Diabetic Swine Model

In light of similarities between pig and human in terms of skin, lipid content, SC tissue structure, and metabolism,[21,22] a diabetic swine model was used in all of our experiments. Our control experiments could not have been conducted in healthy swine, since such subjects are able to regulate their BG by secreting endogenous insulin, which would interfere with our experimental results and would present a confounding factor in assessing and verifying the overall efficacy of our system. Our diabetic swine model[21] shows compelling symptoms that resemble a type 1 diabetes-like pathology, including elevated fasting BG levels and elevated postprandial BG levels (note that euglycemic range in pig is ~30–80 mg/dl) (see **Figure 1**). Overall, the presented experiments utilized four diabetic pigs to provide a total of 11 closed-loop experiments. The pig numbers assigned by the supplier for these four pigs, namely #7, #9, #11, and #13, were retained for future association because some of these pigs (with the same numbers used here) appear in El-Khatib *et al.*[18] Note that a total of six

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pigs were used to attain the results of this study (pigs #8 and #10 were excluded in the early stages of the study after showing adverse responses in their vitals when kept under anesthesia using isoflurane).
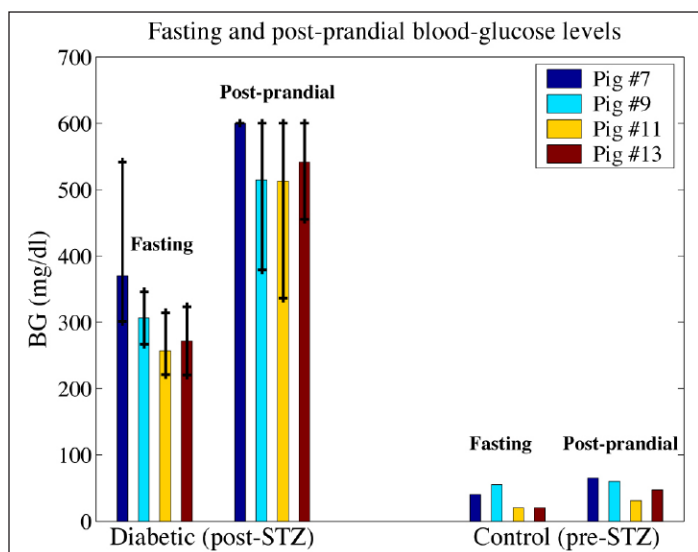

Figure 1. Average fasting (20 hours) and postprandial (2-4 hours) BG levels in health (pre-STZ) and diabetic (post-STZ) swine, with BG ranges shown for post-STZ pigs. Note that euglycemic range in healthy pig is ~30–80 mg/dl. The average fasting BG value across all four pigs increased after STZ treatment by an order of magnitude, from 34 mg/dl (control) to 319 mg/dl (diabetic); the average postprandial BG value also increased by an order of magnitude, from 51 mg/dl (control) to 533 mg/dl (diabetic). Note that BG levels below and above the range of the meter are recorded as 20 and 600 mg/dl, respectively.

Induction of Type 1 Diabetes in Swine

All experiments were reviewed and approved by the Institutional Animal Care and Use Committee at Boston University (#AN-14568). Male Yorkshire swine, weighing ~15 kg each (10–12 weeks of age and weaned), were obtained from a breeder and housed together. After a few days of acclimation, during which the pigs were checked for parasites or disease and their overall health was confirmed to be in good status, a type 1 diabetes-like pathology was induced. The induction was achieved using ß-cell cytotoxin streptozotocin (STZ) doses of 50–70 mg/kg, mixed in fresh cold Na-Citrate buffer solution to give a concentration of 100 mg/ml, with pH adjusted to 4.5 using glacial acetic acid, and administered IV to each pig (0.5 ml of solution per 1 kg body weight) via ear-vein catheters once a day for 3 consecutive days. To carry out the injection procedure, the pigs were anesthetized (anesthesia procedure is described later in the protocol for closed-loop experiments), and their ears were subsequently swabbed with 70% isopropyl alcohol prior to venipuncture. Ears were alternated on each day of STZ administration, using a different vein, or a different location on a used vein for successive doses. Pigs were ready for experiments to commence about 2 weeks after injection with STZ.

Drug Infusion and BG Monitoring

For the SC delivery of both insulin lispro (Humalog, Eli Lilly) and glucagon (Eli Lilly), two customized Bluetooth-enabled Deltec CoZmo infusion pumps (Smiths Medical MD, Inc.) were used, one for each drug. The same two infusion pumps were used in each experiment on each diabetic pig, whereby fresh insulin (Humalog) was drawn from a refrigerated vial and fresh glucagon was prepared from a standard kit on the same day of each experiment. The CoZmo pump's cartridge can hold 300 U of either drug, i.e., insulin or freshly reconstituted glucagon, and can deliver variable SC bolus quantities in less than a minute. Our pumps were retrofitted with Bluetooth adapters that were hardwired onto their internal serial (RS-232) ports. This customization allowed wireless pump access from a laptop computer and enabled remote bolusing of SC insulin and SC glucagon doses down to the finest mechanical resolution of the device (0.005 U or 50 nl). For measurements of BG, an *in vitro* hand-held whole-blood glucose meter was used (One Touch Ultra, Johnson and Johnson), with blood samples obtained from ear pricks (capillary BG) or venous blood draws. All BG measurements, whether capillary or venous, were made with the same glucometer, with all test strips coming from the same lot.

Intravenous Catheterization

Two ear-vein catheter lines were established in each experiment. One was used to administer a continuous IV drip of saline, in order to prevent dehydration, as well as to administer an IV glucose drip, which was composed of glucose dissolved in a saline bag to a concentration of 20% and placed on a IV pole. The IV glucose was allowed to drip from the saline bag, with the rate of administration controlled by a valve, in order to simulate a meal. The second catheter was established in order to sample BG levels. Blood samples were taken every five minutes. The catheter insertion sites were located near the extremity of the ears, which were first shaved and scrubbed with antiseptic.

Infusion-Set Insertion

Before fixing the infusion sets onto the pig, the insertion site area was shaved with regular razors and scrubbed with antiseptic. Typical insertion sites were on the pig's back, around the shoulder area. The commercially available Silhouette infusion sets (Medtronic MiniMed) were inserted using a Sil-serter (Medtronic MiniMed). Once the infusion-set cannulae (~1.5 cm long) were inserted, their trochar needles were withdrawn and discarded. The soft tapered flexible cannulae that remained in the SC tissue were inserted at an angle of ~30° and penetrated ~0.5 cm below the skin.

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Closed-Loop Glucose-Control Experiments

A control algorithm automated the computation and periodic administration of SC insulin–glucagon doses based on either capillary of venous BG measurements. For initial preparation prior to each experiment (i.e., shaving, sensor insertion, and infusion set insertion), the animals were briefly sedated (30–45 minutes). Sedation was achieved with an intramuscular injection of Telazol (6 mg/kg) mixed in saline to give a concentration of 100 mg/ml, and administered while the pigs were inside their stalls. General anesthesia was maintained using ~2.5% isoflurane in conjunction with an oxygen flow rate of 2 liter/min administered through a nose cone using an ISOTEC 4 animal anesthesia machine (SurgiVet, Smiths Medical Veterinary Division). Note that anesthesia using a nose cone characteristically differs from intubation in that no tube is placed in the trachea, and no forced ventilation is applied (the animal is breathing autonomously). In each experiment, the animal's vitals, including respiration, heart beat, oxygen level, and temperature, were monitored and recorded continually, and the level of anesthesia was adjusted to ensure that vitals remained in normal range. All presented results pertain to experiments where the animal's vitals remained continually in normal range. Finally, the animal's BG was monitored and found stable for ~30–45 minutes while under anesthesia before commencing each closed-loop experiment, suggesting that the employed anesthesia technique presents minimal stress and does not alter BG per se (however, the responsiveness to SC insulin or SC glucagon might potentially differ when under anesthesia, but any alterations in the required doses, if any, will be transparently compensated for by the controller).

Analytical Methods

We employed the generalized predictive control (GPC) algorithm to automatically govern the SC administration of insulin and glucagon formulations [input signal $u(t)$] for the purpose of regulating the output BG concentration [output signal $y(t)$] online. The control algorithm optimizes the multistage quadratic cost function

$$J_{GPC} = \sum_{k=N_d}^{N_m} \delta_k \, \| C \, (r_{t-k} - y_{t-k}) \|^2 + \sum_{k=0}^{N_u} \lambda_k \, (\Delta u_{t-k})^2, \qquad \textbf{(1)}$$

where N_d and N_m are, respectively, the minimum and maximum (output) prediction costing horizon limits, N_u is the control horizon bound, δ_k is the weighting on prediction error, λ_k is the weighting on control signals, and the integrator $\Delta := 1 - z^{-1}$, with z^{-1} playing the role of a one-step delay operator.[24,25] The first term of the objective function of **Equation (1)** reflects the desire to steer measurements y_t to cluster around the reference signal r_t, i.e., the set point target glucose level in our case. This is done concurrently with the second term's optimization, which penalizes swings in the control signal, i.e., the subcutaneous drug doses in our case. By replacing y_t in **Equation (1)** with a vector counterpart, namely $\vec{y}_t := (y_t, \, s_f \, q_t)\text{T}$, where q_t denotes the online outstanding amount of insulin in the SC tissue and s_f is a relative scaling factor, minimizing the accumulation of SC insulin is effectively augmented as an additional objective in the cost function. Solving the resulting matrix cost function online therefore recovers the optimal control signal that continually strikes a balance among all three objectives, and therefore simultaneously (1) optimizes the controller's aggressiveness, (2) minimizes insulin accumulation in the SC depot, and (3) regulates glucose concentration to the reference set point. Note that the scaling factor, s_f, and the relative ratio between the weight factors, δ and λ, serve as key tuning "knobs" that can vary the aggressiveness of the control response. Further details about the control algorithm are provided in the Appendix.

The GPC algorithm is used in conjunction with a linear empirical input–output subject model,[23–25] which is recursively adapted online. When the system is online, recent input and output signals [$u(t)$, $y(t)$] are fed continually into the subject-model block, thereby recursively adapting the parameters of the subject model and generating updated output predictions. In comparison with a desired reference, and in view of past input–output signals, the controller computes the input control signal, $u(t)$. The input signal is translated into an insulin or glucagon dose, which is then physically administered to the subject via the SC infusion pumps. The glucose monitor then provides the latest output measurement, $y(t)$, to complete the cycle, which is then executed anew.

Results

Figure 1 shows fasting (20 hours) and postprandial BG levels in four diabetic pigs. Note that while euglycemic range is ~30–80 mg/dl in pig, the average fasting BG value across all four pigs increased by an order of magnitude, from 34 mg/dl (control) to 319 mg/dl (diabetic); the average postprandial BG value also increased by an order of magnitude, from 51 mg/dl (control) to 533 mg/dl (diabetic). Results of **Figures 2–4** show successful *in vivo* closed-loop BG regulation in anesthetized diabetic pigs in response to various (initial) hyperglycemic states, as well as glucose loads, which were administered IV to simulate a meal. A summary of the results from all closed-loop BG control experiments is tabulated in **Table 1**.
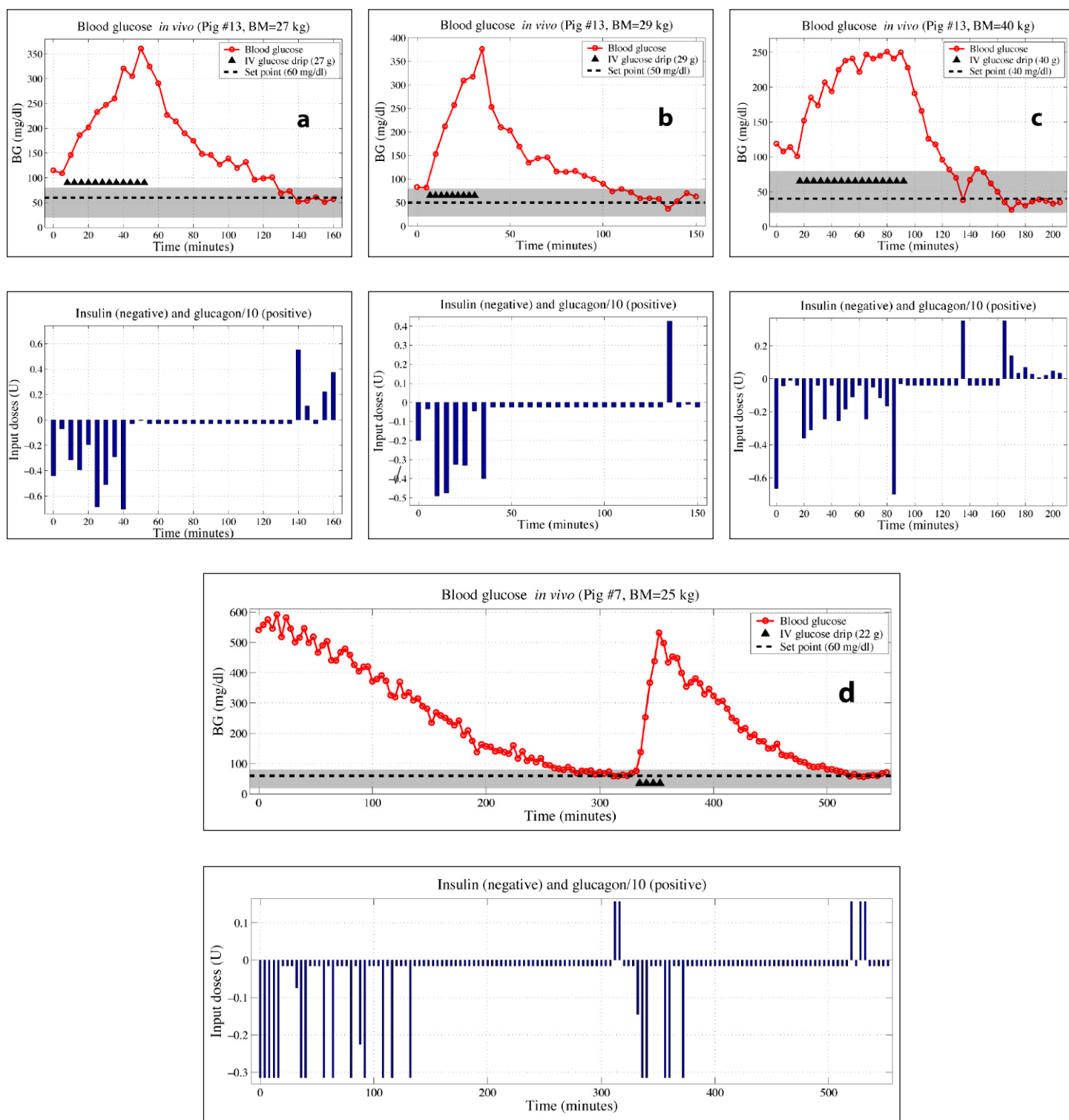
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Figure 2a, b, c and d. Top panels in each pair show online control of BG *in vivo*, while bottom panels in each pair show insulin–glucagon doses, which were administered automatically by the governing control algorithm (scales differ between panels). All plots report BG sampled from venous draws, with euglycemic range (~30–80 mg/dl) for pig indicated by the shaded region. In order to limit the duration under anesthesia to approximately four hours in survival experiments, high fasting BG levels were initially reduced by IV insulin to moderately hyperglycemic levels prior to starting the experiments, except in the case of the relatively long experiment in pig #7 (see panel d), which was nonsurvival by design. All control experiments commenced with virtually constant BG, with essentially no outstanding insulin in the bloodstream or SC tissue.
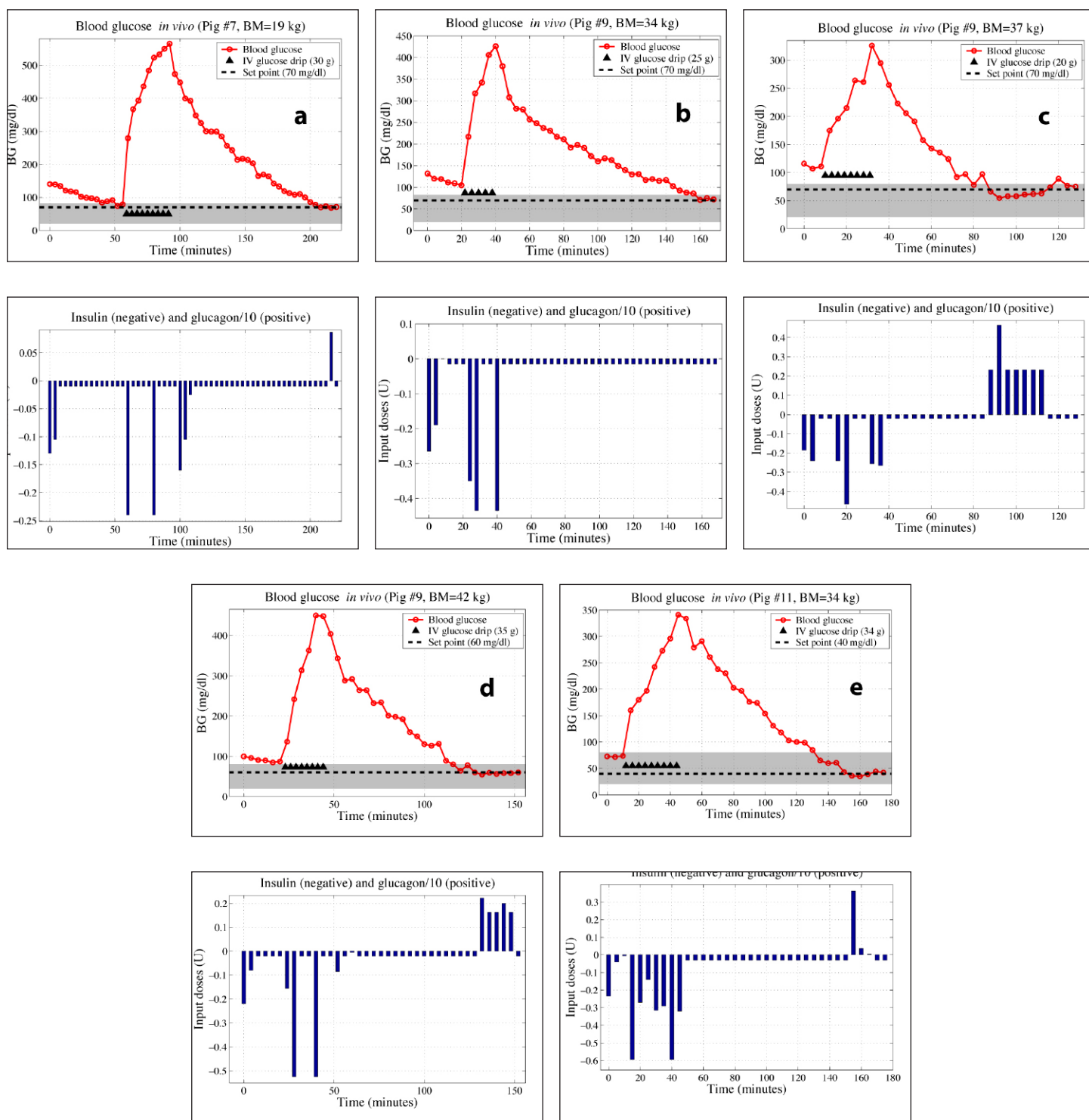
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Figure 3a, b, c, d and e. Same interpretation as in **Figure 2**. It is noteworthy that controller aggressiveness can be tuned in advance to provide either a rapid return to euglycemic range with an extensive need for glucagon to stave off hypoglycemia (e.g., see panel c) or a more conservative return with little to no glucagon required (e.g., see panels a and b). In concept, this demonstrates the feasibility of attaining prolonged closed-loop glucose regulation with near-physiologic levels of glucagon.
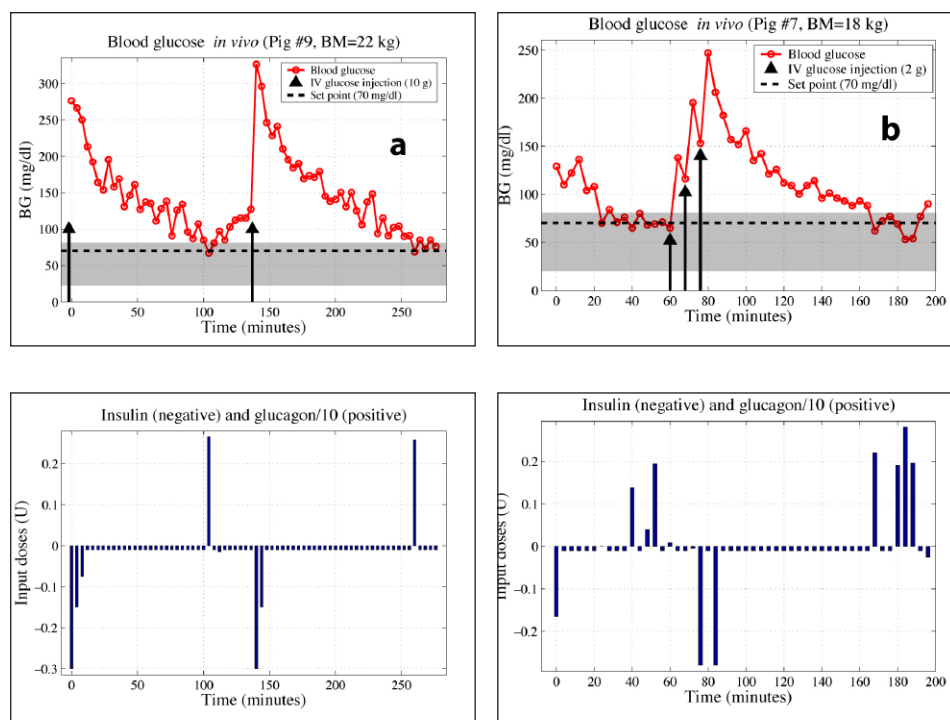
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Figure 4. Same interpretation as in Figures 2 and 3 except that capillary BG is controlled, where each isolated arrow denotes an IV glucose bolus. Note the restraint in controller action to the relatively pronounced erratic fluctuations in BG, an attribute of the augmentation of the control algorithm with SC insulin accumulation. Without such augmentation, any classical control algorithm would inevitably result in an overdose of insulin. Note, particularly, that raw proportional–integrator–derivative control would dose aggressively (and potentially excessively) around changes in sign of the time derivative of BG, even when not indicative of the general BG trend, such as the case between ~50 and 100 minutes and ~200 and 250 minutes in panel a.

Pig	BM (kg)	Duration (mins)	BG_{max} (mg/dl)	BG_{min} (mg/dl)	Set point (mg/dl)	Insulin (U)	Glucagon (U)	IV glucose (g)	Δt to range (mins)
#9	22	296	326	67	70	1.61	5.24	10	~100
#7	18	196	247	53	70	1.12	12.6	6	~80
#9	34	168	426	70	70	2.23	0.00	16	~100
#7	19	220	565	68	70	1.48	0.86	30	~100
#9	37	128	326	55	70	2.05	18.6	20	~50
#7	25	552	592	57	60	8.11	7.82	22	~120
#9	42	152	450	54	60	2.14	9.10	35	~75
#13	27	160	361	51	60	4.18	28.0	27	~80
#13	29	150	376	37	50	2.84	4.26	29	~70
#11	34	175	341	35	40	3.56	4.04	34	~90
#13	40	205	251	24	40	4.12	7.33	40	~40

Table 1. Summary of *in vivo* Closed-Loop Control Experiments[a]

[a]Note that euglycemic range in pig is 30-80 mg/dl.

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Discussion

Ultimately, the task of any BG controller is to regulate BG to within euglycemic range (~30–80 mg/dl in the case of pig) in the shortest time possible without causing hypoglycemia. Our results show successful BG regulation to euglycemic range (~30–80 mg/dl) within 80–120 minutes in the wake of simulated meals with no instances of hypoglycemia. Moreover, our results demonstrate (i) successful BG regulation by our control algorithm, despite an almost twofold variation in weight across four pigs; (ii) efficacy of SC insulin and SC glucagon in our diabetic pigs, particularly the efficacy of glucagon in staving off impending hypoglycemia (see **Figures 3b** and **3c**, and **Figure 3c–3e**, in particular); (iii) successful BG regulation to euglycemic range (~30–80 mg/dl) using different set point values (40, 50, 60, and 70 mg/dl in **Figures 2** and **3**); (iv) effective steering of BG to set point within euglycemic range in all of our experiments; and (v) successful BG regulation, despite different rates of IV glucose administration. The rationale behind variability in the chosen set point values, as noted in (iii), was to span most of euglycemic range (~30–80 mg/dl) in the pig and to demonstrate the fine ability of our controller to flexibly steer BG, at will, to cluster around different preset target values within euglycemic range. Furthermore, it is noteworthy that while IV glucose typically causes a faster BG rise than that caused by an oral meal uptake, the rate of IV glucose administration was modulated in experiments that involved continual drips and the drip duration was extended over a period of time in order to resemble that of a regular meal.

It cannot be overemphasized that besides requiring only the subject's weight for the purpose of initialization, the online operation of the control algorithm is solely based on regularly sampled BG, without any additional input requirement, such as carbohydrate counting, physical activity, or other user feedforward information that is required by other systems.[10,13,26,27] Our success with closed-loop glucose control is a testament to our correct insight into BG dynamics, the adequacy of the diabetic swine model as a platform for glucose control,[21,22] proper mathematical formulation, and the anticipated inherent power and robustness of adaptive model predictive control.[10,12,28] Moreover, a crucial element in the control system lies in the effectiveness of glucagon in countering otherwise excessive insulin administration and averting impending hypoglycemia,[18] as is evident whenever the BG concentration fell below a predefined set point. In terms of its stability in solution, the practicality of using glucagon for a period of several days at room temperature (which would be required of any closed-loop system that

uses glucagon) has been demonstrated in diabetic swine *in vivo*.[18]

Of profound importance is the controller's restraint from administering insulin in response to erratic yet physiological BG fluctuations, which particularly occur near mild hyperglycemia (see **Figure 3** in particular). This restraint owes back to the fact that the control algorithm is inculcated with knowledge of pending insulin action. While BG is descending en route to euglycemic range, the controller will exercise critical restraint by frequently refraining from administering additional insulin and will simply emulate a basal-rate delivery of insulin (based on the subject's weight), which is analogous to that used in conventional open-loop insulin therapy. The basal-rate delivery of insulin plays an effective role in BG control, specifically by providing (after an initial transient) a steady compounded accumulation effect that simulates normal physiological function, which the pancreas uses to maintain a basal metabolic regulation of BG. Moreover, the controller continually oversees the BG descent and can provide further corrective action should BG undergo a further rise, is stalled, or is slowed down to a point that warrants additional insulin, i.e., when the BG rise outweighs the aggregate effects of the outstanding insulin in the SC depot (see **Figures 2–4**). All of those elements must be handled simultaneously, with no overreaction to coarse variations or erratic fluctuations that are not necessarily indicative of the general BG trend (see **Figure 3**). These fluctuations can otherwise have a serious confounding influence in BG control *in vivo*, which could result in significant insulin overdosing if raw classical control methods (such as proportional–integral-derivative control) are employed without account for SC accumulation of insulin.

We have demonstrated the practicality and plausibility of an automated closed-loop control system for robust glucose regulation in type 1 diabetes *in vivo*. In particular, our system (i) depends only on the subject's weight for initialization, (ii) requires only a stream of regularly sampled BG for online operation, without any feedforward information about the subject's activity (e.g., carbohydrate consumption, level of physical activity, health status), (iii) employs subcutaneous dual infusion of both insulin and glucagon, (iv) overlooks erratic BG fluctuations that are not indicative of the general BG trend, (v) exercises critical restraint from administering excessive insulin doses, and (vi) effectively regulates BG over at least a twofold variation in subject weight. Such a closed-loop system has potential utility in a critical-care setting[29–31] where BG can be obtained with a continuous BG monitor introduced into a peripheral IV catheter. However, the system can

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also be developed and adapted to provide long-term utility in ambulatory care using either an implanted continuous BG monitor or, alternatively, a continuous interstitial-fluid glucose monitor where interstitial-fluid glucose can be correlated with and projected onto their corresponding BG values.

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Appendix: An Augmented Adaptive Model-Predictive Control Algorithm for Blood-Glucose Regulation in Diabetes

Glucose-Control System

Schematic Control Paradigm

The model-predictive control (MPC) strategy employed in the glucose-control system is described schematically in the paradigm of **Figure A1**. When the system is running, recent input and output signals, u_t and y_t, respectively, are continually passed to the subject-model block, thereby internally updating the subject model and generating updated output predictions $\hat{y}_{t+k|t}$. By comparison with desired future reference set point values, r_{t+k}, future error signals are computed and passed to the controller block, which, in view of past input–output signals, synthesizes a control signal $u_{t|t}$. The input signal $u_{t|t}$ is physically administered to the subject via infusion pumps and is also passed to the subject-model block. The glucose monitor then provides the latest output measurement, y_t, to complete the cycle, which is then executed anew.

Empirical Subject Model

An option for the subject model is one of empirical form,[1,2] which may possibly be obtained through system identification performed on input–output data generated from open-loop glycemic control of the subject.[3] Representation for a subject model having a single-input single-output autoregressive moving average with an exogenous input (ARMAX) structure is given by

$$A(z^{-1})\, y_t = z^{-d}\, B(z^{-1})\, u_t + C(z^{-1})w_t, \tag{A1}$$

where u_t denotes the (input) insulin–glucagon doses, y_t denotes the (output) glucose concentration deviation from the reference set point, w_t is a white Gaussian noise sequence, d is the inherent system time delay (dead time), z^{-1} plays the role of the unit delay shift operator, and the scalar polynomials A, B, and C are given by

$$A(z^{-1}) = 1 + a_1 z^{-1} + a_2 z^{-2} + \dots + a_n z^{-n},$$

$$B(z^{-1}) = b_0 + b_1 z^{-1} + b_2 z^{-2} + \dots + b_m z^{-m},$$

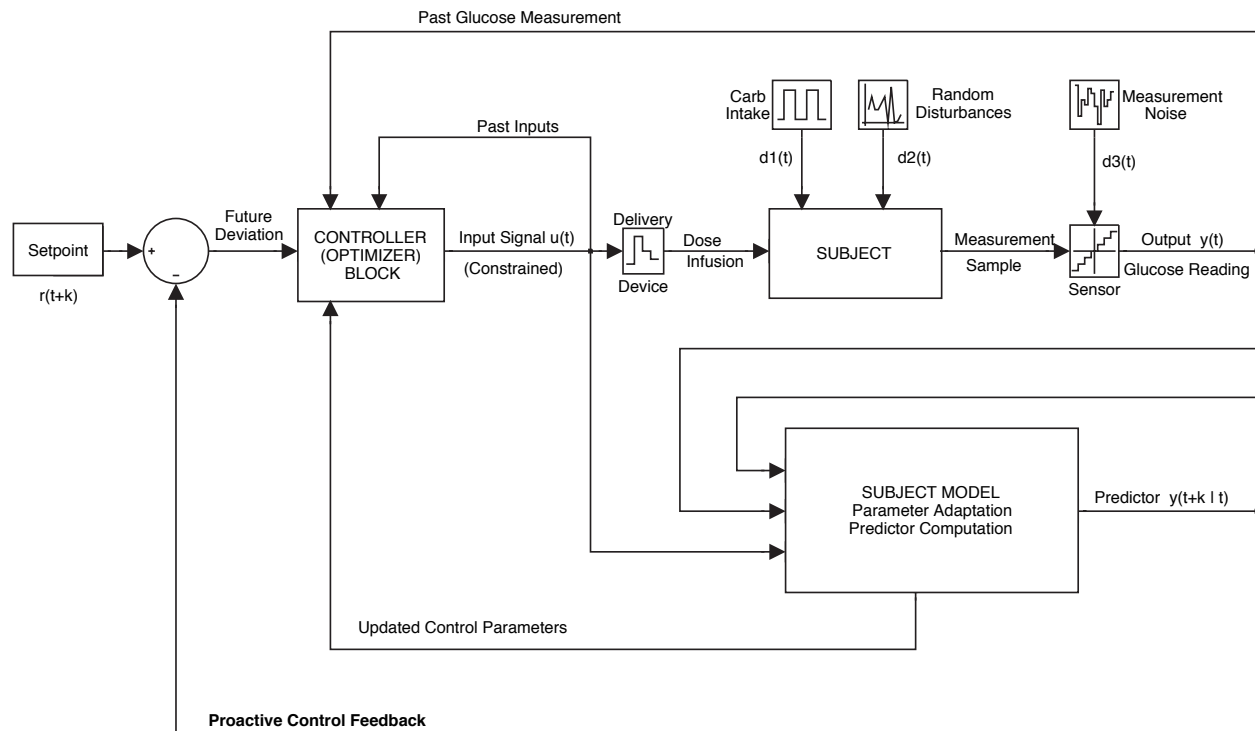$$C(z^{-1}) = 1 + c_1 z^{-1} + c_2 z^{-2} + \dots + c_p z^{-p}.$$

Figure A1. A paradigm depicting the logical flow in the integrated glucose-control system, governed by adaptive MPC strategy.

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The orders and delay of the model may be determined beforehand from an off-line system identification analysis.[3] The identified model is then employed online in the integrated control system, whereby the model parameters are not statically stipulated, but are dynamic, in the sense that they are recursively updated.[1,2,4] Recursive (online) parameter estimation of a model such as **Equation (A1)** may be facilitated by rewriting the model in regressor form,[5] namely

$$y_t = \theta^T \, \psi_t + w_t, \tag{A2}$$

where the regressor, ψ_t, and parameter vector, θ, are, respectively, given by

$$\psi_t := [-y_{t-1} \dots -y_{t-n} \, u_{t-d} \dots u_{t-d-m} \, w_{t-1} \dots w_{t-p} \,]^T,$$

$$\theta := [\, a_1 \dots a_n \, b_0 \dots b_m \, c_1 \dots c_p \,]^T. \tag{A3}$$

With online parameter estimates packed in a time-varying version of vector θ, namely θ_t, and the estimate $\hat{w}_t := y_t - \psi_t^T \theta_t$ used in lieu of w_t in ψ_t, the extended least-squares method described by Lai and Wei[5,6] follows the scheme

$$\theta_t = \theta_{t-1} + \frac{P_{t-1} \, \psi_t}{1 + \psi_t^T \, P_{t-1} \, \psi_t} \, e_t, \tag{A4}$$

$$P_t = P_{t-1} - \frac{P_{t-1} \, \psi_t \, \psi_t^T P_{t-1}}{1 + \psi_t^T \, P_{t-1} \, \psi_t}, \tag{A5}$$

where $e_t := y_t - \psi_t^T \, \theta_{t-1}$, and P_0 is taken to be a positive definite matrix. As such, the subject model parameters can be recursively estimated in real time and passed to the online control algorithm, thereby providing an indirect adaptive control strategy.[1,2,6,7]

Basic Predictive Control

For the online glucose control algorithm, we propose generalized predictive control (GPC), which optimizes the multistage quadratic cost function[7,8] given by

$$J_{\mathrm{GPC}} = \sum_{k=N_d}^{N_m} \delta_k \, \| C \, (r_{t+k} - y_{t+k}) \|^2 + \sum_{k=0}^{N_u} \lambda_k \, (\Delta \, u_{t+k})^2, \tag{A6}$$

where N_d and N_m are, respectively, the minimum and maximum (output) prediction costing horizon limits, N_u the control horizon bound, δ_m the weighting on prediction error, and λ_n the weighting on control signals. For control action with an integral effect,[7,9] predictor formulation and control design are based on

$$A(z^{-1}) \, y_t = z^{-k} \, B(z^{-1}) \, u_t + C(z^{-1}) w_t / \Delta, \tag{A7}$$

with the corresponding Diophantine separation identity[6,7] given by

$$\frac{C}{A\Delta} = E_k + z^{-k} \, \frac{F_k}{A\Delta}, \tag{A8}$$

where F_k is the remainder polynomial corresponding to the *monic* quotient polynomial E_k, the former and latter being of respective orders n and $k-1$ in z^{-1} or, specifically, $F_k = f_0 + f_1 \, z^{-1} + \dots + f_n \, z^{-n}$ and $E_k = 1 + e_1 \, z^{-1} + \dots + e_{k-1} \, z^{-(k-1)}$. The best predictor $\hat{y}_{t|t-k}$ is then defined[6,7] to satisfy

$$y_t = \hat{y}_{t|t-k} + E_k \, w_t, \tag{A9}$$

which yields

$$C \, \hat{y}_{t+k|t} = G_k \, \Delta \, u_{t+k-d} + F_k \, y_t, \tag{A10}$$

where $G_k := E_k B$. Note that G_k is order '$m+k-1$' in z^{-1} and can be written as $G_k = g_0 + g_1 z^{-1} + \dots + g_{m+k-1} z^{-(m+k-1)}$, with $g_0 = b_0$, since E_k is monic for all k. To implement the GPC algorithm,[6-8] **Equation (A10)** is rewritten as

$$C \, \hat{y}_{t+k|t} =$$

$$\sum_{i=0}^{k-d} g_i \, z^{-i} \Delta \, u_{t+k-d} + (G_k - \sum_{i=0}^{k-d} g_i z^{-i}) \, \Delta \, u_{t+k-d} + F_k \, y_t,$$

where the first term on the right-hand side contains the only $k-d$ future terms (containing the sought control signal) for any k. Taking contributions over the output and control horizons, a matrix-form equation can be developed in the form of (refer to Comacho and Bordons[7] for details)

$$y = Gu + G'u + F \, y_t, \tag{A11}$$

and rewritten as

$$y = Gu + f, \tag{A12}$$

where f includes the last two quantities in **Equation (A11)**, which are available at time t as being either directly measurable or dependent only on past measurements. With $\delta_m = 1$ and $\lambda_n = \lambda$, **Equation (A6)** can be rewritten as

$$J_{\mathrm{GPC}} = (G + f - r)^T \, (G + f - r) + \lambda u^T u, \tag{A13}$$

where r is the vector holding future set points, namely $r = [C \, r_{t+d} \; C \, r_{t+d+1} \dots \; C \, r_{t+N+d-1}]^T$. Further manipulation of **Equation (A13)** leads to

$$J_{\mathrm{GPC}} = \tfrac{1}{2} \, u^T \, Hu + b^T \, u + f_0, \tag{A14}$$

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where

$$H = 2 (G^T G + \lambda I), \quad b^T = 2(f - r)^T G,$$

and

$$f_0 = (f - r)^T (f - r).$$

The unconstrained vector u minimizing J_{GPC} can be found by inspection[7] of **Equation (A14),** and is given by

$$u_{GPC} = -H^{-1}b = (G^T G + \lambda I)^{-1} G^T (r - f). \tag{A15}$$

Since $G^T G \geq 0$, **Equation (A15)** gives a unique solution, provided $\lambda > 0$. Only the first control move is of interest at t, namely

$$\Delta u_t = [\,1\,0\,0\,...\,0\,] (G^T G + \lambda I)^{-1} G^T (r - f). \tag{A16}$$

The control increment or move in **Equation (A16)** is thus zero if the current setting and desired outcome coincide, that is, if $r - f = 0$, as it should.[7] Finally, to deal with nonsquare horizons, which would only be permissible for $N_u < N_y$, G is replaced by G_{Nu}, where G_{Nu} is composed of the first $N_u + 1$ columns of G, and u is replaced by u_{Nu}, which contains the first $N_u + 1$ elements of u, with everything else kept the same.[7] Note that the generalized minimum variance control, with $N_y = N_u = N - 1 = 0$, is a special instance of GPC with square horizons.[1,2,10]

Augmented Control Algorithm

Because excessive accumulation of insulin* in the subcutaneous tissue could be detrimental, and because the insulin concentration essentially depends on the input control signal, a formulation estimating the subcutaneous accumulation of insulin can be augmented to the raw control cost function of **Equation (A6)**, with its minimization viewed as an additional control objective in the optimization process. The resultant online control signal will therefore simultaneously (i) optimize the controller's aggressiveness, (ii) minimize insulin accumulation in the subcutaneous depot, and (iii) regulate glucose concentration to a preset set point. The mathematical formulation providing a measure for the subcutaneous accumulation of exogenous insulin can be derived based on nominal temporal values pertaining to its pharmacokinetics, i.e., its time course of activity from subcutaneous tissue into plasma, in terms of its absorption rate, peak absorption time, and overall time of action (perfusion into plasma). This has already been analyzed in the literature,[11] and the permeation of insulin from the subcutaneous tissue into plasma is known to possess a typical profile, with the nominal values of its characteristic parameters being predominantly dependent on the kind of insulin used. Note that because the coupling, in the augmented objective function, between the subcutaneous accumulation of insulin and the glucose output, y_t, is only through the input signal, u_t, the multiple-output system is diagonal and the two subsystems can be decoupled as far as parameter adaptation for the y_k-system is concerned (see Comacho and Bordons[7] for details on multiple-output single-input GPC).

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* Accumulation of glucagon is not crucial, poses no risk, and is to a lesser extent, in light of its substantially faster absorption and bioavailability.[12]

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