Insulin Delivery in Type 1 Diabetes Mellitus using Multi-Parametric Model Predictive Control

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Type 1 diabetes mellitus (T1DM) is an auto-immune disease characterized by chronic elevation of glycemia due to insufficient endogenous insulin production. Microvascular complications and hypoglycemic events (blood glucose below 60 mg/dL) are common among people with T1DM because the open-loop therapy used is suboptimal, both in terms of insulin dosing and burden. Recent technological advances have led to the availability of continuous glucose monitoring devices, continuous subcutaneous insulin infusion pumps, and rapid-acting insulin analogues, which could be used to form a closed-loop insulin delivery device, or "artificial pancreas". Closed-loop control has been shown to be advantageous over open-loop control in the domain of drug delivery, e.g., the delivery of anesthesia, and thus insulin therapy via closed-loop control is proposed.

We have developed a multi-parametric model predictive control algorithm to control glycemia. Our approach uses an empirical model developed from ambulatory data, explicit constraints developed from clinical expertise, and multi-parametric programming techniques for ease of controller implementation. The control algorithm was tested on ten human subjects as part of a multinational, multicenter collaboration.

The controller demonstrated efficacy in correcting clinically induced hyperglycemia and robustness to disturbances by delivering insulin in response to unannounced meals. No hypoglycemic events occurred. An example of controller performance is shown in Figure 1.

It has been shown that the proposed controller architecture performs well in closed-loop trials. The next stage of clinical trials will attempt to demonstrate robustness to larger meals over longer time periods.

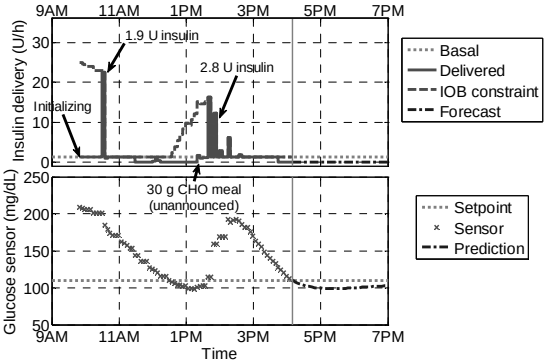

Figure 1: In this clinical trial insulin was delivered in quantities commensurate with the subject's insulin requirements, thus normalizing glycemia after clinically induced hyperglycemia and an unannounced meal.

A Mathematical Model Describing the Pathophysiology of the 3R and 4R Tau Isoforms and Its Implications for Understanding Alzheimer's Disease

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On a molecular level, Alzheimer's disease is characterized by the presence of extracellular plaques and intraneuronal tangles that are composed of tau, a microtubule-associated protein found mainly in neurons. Tau can be phosphorylated at a number of sites and is present in two major isoforms, 3R and 4R tau. Both the isoform type and the phosphorylation state influence the behavior of tau, particularly its interactions with microtubules and its ability to aggregate. In a non-diseased neuron the isoforms are found in approximately equal numbers, and the protein is primarily found in a microtubule-bound, phosphorylated form. In the Alzheimer's afflicted neuron, elevated levels of tau phosphorylation and dissociation from microtubules are observed. The presence of ubiquitin and chaperones in many of the aggregates suggest that defects in chaperone-assisted degradation may be a factor in the accumulation of aberrant tau. Disturbances in the phosphorylation and dephosphorylation of tau have also been noted. The multiple perturbations in the tau pathway make it difficult to determine the significance of specific changes in tau processing with respect to disease development.

To help elucidate the triggers leading to aberrant tau production and aggregation, we have developed a mathematical model that embodies the current state of knowledge about tau's interactions and behavior. The model is formulated as a set of ordinary differential equations with mostly mass-action kinetics, except for the phosphorylation reactions which are described by Michaelis-Menten kinetics. A pseudo-global identifiability method was used to eliminate highly correlated parameters and the remaining parameters were optimized such that the model mimicked the behavior of a healthy neuron. Sensitivity analysis of the model indicates that tau's homeostasis is most vulnerable to ATP depletion and synthesis rates, with moderate sensitivity to the phosphorylation and degradation parameters. To complement our sensitivity analysis, we also establish the minimum requirements for aggregation, determining absolute changes in parameters required to accumulate aberrant tau levels above the critical concentration to support aggregation in the absence of a functional chaperone system.

The model constructed represents a view of the biochemical pathways involving tau protein that is well-supported by the literature in both structure and behavior of a healthy neuron and whose initial analysis provides insight into the underlying causes of tau pathology. It is a foundation on which to build and increase our understanding of the series of events leading to tau aggregation and may ultimately be used to identify intervention points to aid in the treatment of Alzheimer's disease.

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The Effects of Dielectric Thin Film Coating and Surface Chemistry on Induced Charge Electroosmosis

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The emergence of the field of microfluidics in recent years has renewed interest in using electrokinetic flows to transport fluid through the small channel geometries present in microfluidic devices. For example, an AC electrical potential applied across a conductive (metal) surface submerged in an electrolyte have been shown drive time-averaged flows and may prove useful for on-chip mixing and high pressure pumping[1]. This phenomenon, induced charge electroosmosis (ICEO), differs from standard electroomosis in that a critical parameter for determining flow velocity, the surface zeta potential, is directly tunable. Whereas in standard electroosmosis, the zeta potential is usually interpreted from experiments (apply a known electrical field, measure a velocity, calculate the zeta potential), in ICEO the zeta potential is directly related to the applied field strength. Since this allows one to make solid predictions of ICEO flow velocities without resort to empirically determined factors, one might expect excellent quantitative agreement between theory and experiment. However, experiments performed with ICEO and other related phenomena are consistently slower than theory predicts, frequently by orders of magnitude[2]. Here, we present experimental data in which we controllable 'contaminate' the metallic surface with a thin dielectric film, and derive a theory of ICEO that accounts for both the dielectric effects and surface chemistry of the contaminate, both of which act to decrease the flow velocity relative to a clean metal surface. Data for over a thousand combinations of applied electric field strength and frequency, electrolyte composition and dielectric thickness show unprecedented agreement with our theory.

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Bilayer interactions in complex, cationic vesicle dispersions

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Colloidal vesicle dispersions are commonly used in both consumer products and medical applications. Current trends in consumer products are moving toward highly concentrated vesicle dispersions, chalk full of complicated additives and perfumes. Common additives include polymers and polyelectrolytes and are intended to give the product properties desired by the consumer but often upset the stability of the vesicle dispersion and can cause flocculation, creaming, settling and/or phase separation of the solution. The colloidal properties and stability of these dispersions are governed by the interactions between the vesicles and polymers making up the dispersion. To understand the interactions of these complex solutions a model cationic surfactant, di (tallowethyl-ester) dimethyl ammonium chloride, has been chosen. Bilayers made of this surfactant are deposited on mica surfaces using the Langmuir-Blodgett technique and the interactions between the model cationic bilayers are measured in a Surface Forces Apparatus (SFA) under various salt, polymer and polyelectrolyte concentrations. The forces between the cationic bilayers in $CaCl_2$ solution are purely repulsive and follow DLVO theory. We show that the addition of polyelectrolytes has a range of effects on the interactions including screening of the electrostatics due to added charge in the solution, induction of a depletion-attraction between the bilayers due to the excluded volume of the polymer as the bilayers approach each other and even long ranged repulsion do to adsorption of polymer to the bilayers. The effect of electrolyte screening was measured with high molecular weight (>100 kDa) poly(diallyldimethylammonium chloride) (polyDADMAC). The depletion attraction effect was measured with both uncharged 8 kDa PEG and cationic 16 kDa poly(allylamine) (PAA) to fully understand the effect of charge on the interaction. Finally, a simple theory is presented to correlate the SFA measurements to interactions between vesicles, allowing for bending and stretching of the bilayer, with implications to the stability of vesicle dispersions of this kind.

Visualization and Interfacial Microrhoelogy of Phospholipid Monolayers with and without Cholesterol

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Phospholipid monolayers (with and without cholesterol) at the air-water interface serve as model systems for various biological interfaces, e.g. lung surfactant layers and outer leaflets of cell membranes. Although the dynamical (viscoelastic) properties of these interfaces may play a key role in stability, dynamics and function, the relatively weak rheological properties of most such monolayers have rendered their study difficult or impossible. Using a novel technique we have recently developed, we measure the viscoelastic properties of phospholipid monolayers, both with and without cholesterol, at the air-water interface. In particular, our measurements suggest remarkably long relaxation times. Notably, our apparatus enable direct interfacial visualization during the measurement, which enables us to relate the observed interfacial structure and dynamics to the measured viscoelastic behavior. The influence of cholesterol upon these dynamic structures -- and thus rheology -- is visualized, measured and modelled.

Synthetic Red Blood Cells: Drug Delivery and Beyond

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Design and fabrication of drug delivery carriers that enable effective administration of therapeutic agents at the target site and imaging of the diseased tissue in real time is an unmet medical need. Current strategies in carrier design are based either on discovery of new materials or development of new methods for carrier fabrication. Whereas the design of synthetic carriers that meet therapeutic needs has proved challenging, there are several examples of innate objects that deliver biomolecules routinely in the body. In particular, red blood cells (RBCs), the most ubiquitous cell type in the human blood, constitute highly specialized entities with unique shape, size, mechanical flexibility and material composition, all of which are optimized for extraordinary circulation time (~120 days) and biological performance (oxygen delivery). Inspired by this natural example, we synthesized particles that mimic the key structural and functional features of RBCs using a novel fabrication technique. These "synthetic RBCs" can encapsulate drugs and imaging agents. Similar to their natural counterparts, synthetic RBCs also possess the ability to carry oxygen. The synthetic RBCs provide a new paradigm for the design of drug delivery and imaging carriers since they combine the versatility and functionality of natural RBCs with the flexibility and broad applicability of synthetic drug delivery carriers.

Exploiting the selectivity of proteolytic enzymes for site-specific delivery of therapeutic and diagnostic agents

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Proteolytic enzymes play an essential role in regulating and localizing protein activity in many physiological and pathological processes by acquiring high selectively for a protein. The objective of this research is to identify proteolytically cleavable substrates that exhibit fast hydrolysis rates and high selectivity for a protease by targeting the active site and other distinct epitopes or domains on the protease. A two-color cellular libraries of peptide substrates (CLiPS) methodology was used to identify substrates for membrane type-1 matrix metalloproteinase (MT1-MMP), a protease which has been shown by many studies to play a critical role in cancer cell invasion and metastasis. The substrate consensus sequence resulting from quantitatively screening a random pentapeptide library was P-X-G↓L. In order to identify substrates with enhanced activity, a second generation extended focused library was designed and screened under increasingly stringent conditions which resulted in a $M\Phi PLG^{M}/_{L}M^{G}/_{A}R$ consensus motif. Interestingly, identified extended substrates with fastest hydrolysis rates also resolved to be the substrates with highest selectivity for MT1-MMP. These substrates were cleaved by human MT1-MMP with a four-fold higher k_{cat}/K_M than with reported substrates, are efficiently hydrolyzed by murine MT1-MMP and were not hydrolyzed by human plasma. In addition, the soluble FRET substrates constructed from the optimized substrates, but not previous reported substrates, enabled detection of endogenous MT1-MMP activity in human fibrosarcoma (HT-1080) cultures. The substrates were then utilized in the context of a proteolytically-activated masked-antibody (Pro-antibody) model to improve targeting, which resulted in up to 150-fold increase in binding affinity once activated with the protease. These results demonstrate that extended protease substrates can be optimized to enhance *in vivo* selectivity of therapeutic and diagnostic agents.

The Progression of a Novel Liposome-Based Delivery Vehicle Toward In Vivo Drug Delivery

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An optimal drug delivery vehicle should have several universally-desired properties, including the ability to localize at the site of disease, deliver contents at a rate appropriate for maximum therapeutic benefit and retain its contents over this timeframe. Liposome-based drug delivery systems have been widely used as drug carriers in both industry and research, even though content retention and controlled release remain problematic. We have previously demonstrated the *in vitro* viability of the vesosome, a large lipid bilayer enclosing many smaller liposomes, and shown that it is the most suitable candidate for addressing these issues. The external lipid bilayer offers a second barrier of protection for interior components and also serves as the anchor for active targeting components and internal compartmentalization permits customization of separate environments for multiple therapeutics and release triggers, highlighting the vesosome's potential as a single site, single dose, multiple component drug treatment.

In order to use the vesosome for *in vivo* work, it was necessary to modify the composition for extended circulation and to label it to examine the evolution of biodistribution. These issues were addressed by conjugating a near-infrared fluorescent dye to the external membrane, which was also coated with poly(ethylene glycol) (PEG). However, PEGylation of the vesosome required a shift away from established synthesis methods, which resulting in labeled, PEGylated vesosomes that were difficult to purify. Despite this concern, *in vivo* examination of these vesosomes yielded a half-life and biodistribution that was unsurprising for PEGylated micron-size objects. Improvements of up to an order-of-magnitude increase in purity have since been obtained by utilizing smaller molecular weight PEGs. Currently, similar biodistribution and lifetime studies of these new vesosomes are underway. In the near future, experiments have been planned to examine the targeting capacity of functionalized vesosomes as well as how vesosomes compare to vesicles in drug delivery in mice.

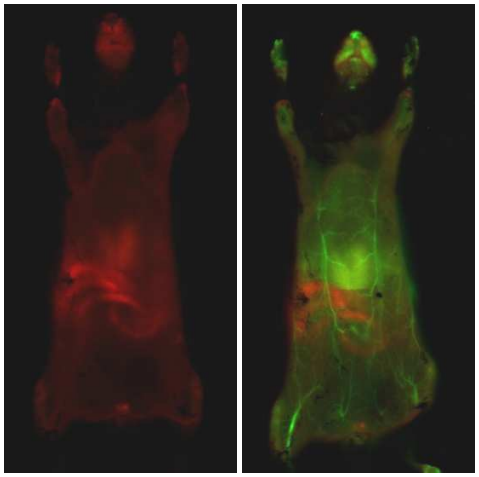

Figure 1: Fluorescent imaging of live, wild-type mouse before and 5 minutes following vesosome injection

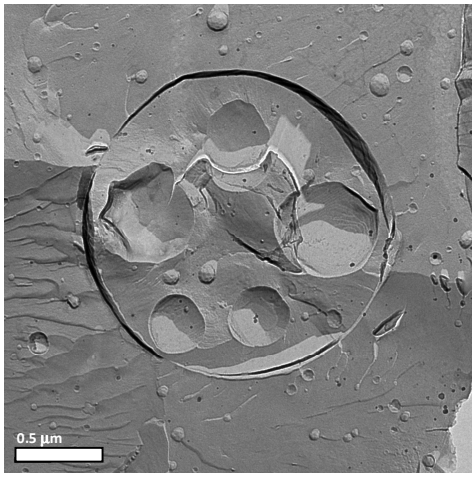

Figure 2: TEM imaging of a replica of a vesosome prepared by freeze- fracture

Rearrangement of Phosphinites on Alumina, and Implications for the Anchoring of Organic and Organometallic Complexes on Oxide Surfaces

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A pincer-ligated iridium complex with a phosphinite substituent at the *para*-position of the pincer ligand, immobilized on γ-alumina, is a highly effective catalyst for the transfer-dehydrogenation of alkanes.[1] The nature of the interaction between the iridium complex and the alumina support was investigated using solid-state ^{31}P MAS NMR spectroscopy, solution-state ^{1}H and ^{31}P NMR spectroscopy, GC/MS, and DFT calculations. The uncoordinated phosphinite substituent is cleaved from the pincer ligand by its interaction with hydroxyl groups on the alumina surface. As a result, pincer complexes become directly anchored to the surface via the aryl ring. The cleaved phosphinite group rearranges to form a phosphine oxide, likely proceeding through a phosphinous acid intermediate, which adsorbs onto the alumina surface. A similar reaction occurs on silica, allowing for ready grafting onto this support as well. A new, general strategy for anchoring homogeneous catalysts and other organic complexes on hydroxyl-terminated oxide supports though the selective cleavage of phosphinite substituents is suggested.

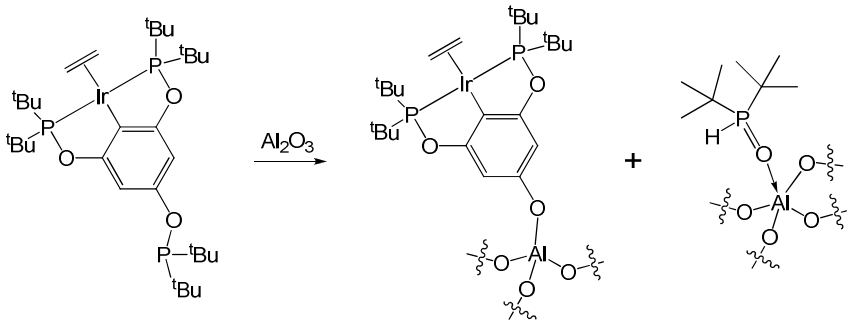

Figure 1: Immobilization of the pincer catalyst [{*p*-OP(^{t}Bu)$_2$-C$_6$H$_2$-2,6-[OP(^{t}Bu)$_2$]$_2$]}Ir(C$_2$H$_4$)] on alumina and generation of (^{t}Bu)$_2$HP=O adsorbed on alumina.

References:

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Molecular Origins of Surface Acidities in Porous Aluminosilica and Aluminosilicate Catalysts

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Porous aluminosilicas and aluminosilicates have been widely used as heterogeneous catalysts and supports, because compared to homogeneous catalysts, their diverse solid-acid properties are often desirable for selectivity and separation reasons. Despite decades of use, however, the molecular origins of their acidic properties, including Brønsted (proton-donating) versus Lewis (electron-accepting) characters and their different strengths, quantities, and distributions, have been challenging to establish and are not well understood. For amorphous aluminosilicas and crystalline aluminosilicates (e.g., zeolites), complicated local compositional and structural order and disorder exist that generally result in a wide distribution of acid sites with different strengths, which are currently difficult to characterize, understand, or control.

Using a complementary combination of synthesis and spectroscopic techniques, we aim to determine the molecular origins of acidic sites in porous aluminosilicas and aluminosilicates. Site-specific adsorption of certain organic bases, according to their molecular sizes and proton affinities, can be used to probe selectively the Brønsted or Lewis characters of solid-acids. Furthermore, by carefully controlling adsorption conditions, different probe molecules can be co-adsorbed, which allow us to establish the mutual proximities of Brønsted and Lewis acid sites and their adsorption-dependent influences on one another. Such characterization and understanding are expected to allow for the optimization of catalysts synthesis conditions to yield solid-acid supports and catalysts with tunable reaction properties. Based on recent characterization of commercial amorphous aluminosilicas, syntheses of mesoporous aluminosilicas have been adapted to increase the reactivity and selectivity of a grafted organometallic catalyst for olefin metathesis. This approach is expected to be general and applicable to a wide range of heterogeneous catalysts in which acid properties are important, including commercially important aluminosilicate zeolites used in the catalytic cracking of petroleum, isomerization, alkylation, and other acid-catalyzed reactions. Optimization of such heterogeneous catalysts is furthermore being directed to improve mass transport, as well as reaction properties, as demonstrated for novel mesoporous zeolites that combine the strong acidity of zeolites with the reduced diffusion limitations presented by mesoporous solids. This characterization and improved molecular understanding will guide the engineering of a new generation of solid-supports and catalysts with tunable reaction and diffusion properties.