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Stimuli Sensitive Polymers and Self Regulated Drug Delivery Systems: A Very Partial Review

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Abstract

Since the early days of the *Journal of Controlled Release*, there has been considerable interest in materials that can release drug on an “on-demand” basis. So called “stimuli-responsive” and “intelligent” systems have been designed to deliver drug at various times or at various sites in the body, according to a stimulus that is either endogenous or externally applied. In the past three decades, research along these lines has taken numerous directions, and each new generation of investigators has discovered new physicochemical principles and chemical schemes by which the release properties of materials can be altered. No single review could possibly do justice to all of these approaches. In this article, some general observations are made, and a partial history of the field is presented. Both open loop and closed loop systems are discussed. Special emphasis is placed on stimuli-responsive hydrogels, and on systems that can respond repeatedly. It is argued that the most success at present and in the foreseeable future is with systems in which biosensing and actuation (i.e. drug delivery) are separated, with a human and/or cybernetic operator linking the two.

Keywords

stimuli sensitive; self regulated; hydrogels; pH sensitive; glucose sensitive

I. Introduction

“Stimuli responsive” and “self regulating” drug delivery systems have captured the imagination of researchers, in large part because they suggest a means to mimic the physiological homeostatic feedback mechanisms that are essential for health. As dysregulation of homeostasis is a feature of many diseases such as diabetes and cancer, the design of systems that target drugs in space and time to re-establish homeostasis has been pursued by numerous groups. Self regulating systems also permit those with an engineering bent to think of drug delivery in terms of closed loop (feedback) control *versus* open loop control. These two control philosophies are illustrated in Figure 1. In open loop control, the

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control and delivery scheme a predetermined control program governs drug release. In closed loop control, physiological information is gathered and fed back to the controller, which alters the rate of drug release. Although the controller and delivery device are pictured as being separate, their realization may be in a device whose release characteristics are either programmed (open loop) or responsive to physiological signals (closed loop). Discovering means to build sensitivity to endogenous and external physical and chemical stimuli into drug delivery systems has provided a problem that can be attacked using physical, chemical, and engineering ingenuity, particularly in the area of polymers.

A large fraction of delivery drug systems are stimuli responsive, at least in a trivial sense. For example, one would not wish a tablet to release its contents until it is ingested and exposed to the aqueous environment of the GI tract, which is a kind of stimulus but not very interesting. On the other hand, oral delivery systems in which release is triggered by exposure to a particular pH range characteristic of a locale in the GI tract are more interesting [1-3]. It should also be recognized that during the course of drug release, the device might create a “stimulus” that modulates its own release properties. For example, autoacceleration of degradation of poly(lactic-co-glycolic acid) and poly(ortho ester) polymers, mediated by accumulation of acid products, is a mechanism underlying the delayed bursting of drug release from these systems [4]. As this phenomenon is a result of the material’s intrinsic kinetic properties, it would not ordinarily be considered to be the result of an external stimulus.

It has been fashionable to call responsive drug release systems “intelligent” or “smart,” reflecting nomenclature that has arisen in the materials literature. Although these terms may have a certain sex appeal, they do not seem appropriate, insofar as their definition might imply some cognitive capabilities. No material has passed the Turing test [5]. We avoid such anthropomorphic terminology, as it places too high expectation on the materials and seems demeaning to sentient beings.

In order to narrow the scope of this review, we focus on systems that respond repetitively to a stimulus, releasing drug in a programmed manner each time. Thus we will ignore the very extensive literature on systems that release drug only once in response to a stimulus, depleting their contents. The pH-regiospecific oral drug delivery systems already mentioned fall into this category, as do most reported responsive systems, and it might be argued that we are being too restrictive. After all, many circulating nanoengineered drug delivery systems have been designed to release their cargo only when receiving a localized stimulus such as heat or light, and repetitive application of the stimulus can lead to multiple release events as the depleted material is replaced by fresh material at the point of stimulation. Furthermore, useful systems may lie dormant for long periods until a critical event, such as inflammation, occurs, which triggers release.

This review is structured as follows. In section II we briefly review some nonpolymeric systems used for automatic feedback controlled drug delivery. These may be regarded as “competitors” to the polymeric systems that are normally studied in the controlled release field. In section III, biodegradable systems and monolithic systems with repetitive “on-off” capability are discussed. Section IV reviews stimuli responsive hydrogels, which have a

long history of theoretical and experimental development. Sensing and release actuation modalities involving swelling and shrinking of hydrogels are discussed in Section V. Systems proposed to utilize such hydrogels in closed and open loop repetitive release systems are reviewed in section VI. Finally, section VII will suggest directions that should be pursued if stimuli sensitive hydrogels are to be useful in feedback controlled drug delivery. We will argue that in the foreseeable future, human decision making is likely to be present in the feedback loop.

II. Nonpolymeric systems

Self regulation occurs whenever monitoring of the effects of a dosing history causes a change, or feedback, to the subsequent dosing pattern. This process of “dose titration” is common in both inpatient and outpatient clinical practice, and there need not be any advanced technology except for reliable record keeping and some pharmacokinetic calculations. This practice is typically “low frequency” since observations and corrections may occur on the time scales of days, weeks, or months. Cancer chemotherapy may be one area in which relatively sophisticated models of dosing and monitoring are of importance, due to the severity of side effects [6].

There has been considerable research, however, into automatic control algorithms and instrumentation in the domains of anesthesia and critical care [6-10]. In this case, patient’s vital signs, including blood pressure, tidal volume, heart rate, cardiac output, EKG, EEG, and blood chemistry (including pH, pO_2 , and pCO_2) can be monitored nearly continuously, and the critical state of the patient is such that sudden changes in these signs require rapid attention and compensation. In most cases, a system of alarms can alert attending staff when these variables exceed tolerable limits, but there has been interest in automating the infusion of drugs that maintain blood pressure and heart rate close to a chosen set point. Such controllers can operate by simple PID (proportional, integral, derivative) control algorithms, in which the present levels, recent time averages, and slopes of physiological variables are combined in calculating infusion rates. More sophisticated systems can update, or adapt their control dynamics by probing the patient’s dynamic response. Neural net and fuzzy logic based controllers have also been considered. Neural nets are nonlinear, multilayered learning schemes, while fuzzy logic algorithms combine several kinds of data that are classified into intervals. The latter approaches may emulate what anesthesiologists do without necessarily giving it a name.

Type I diabetes probably represents the best known disease in which tight closed loop regulation is needed [11]. Following ingestion of carbohydrate, blood sugar levels start to increase drastically. While this increase is not in itself life threatening, glucose should be quickly converted to glycogen for storage. Conversion is mediated by insulin, which is normally secreted from the beta cells of the pancreas when the body senses or anticipates an increase in blood glucose level. Insulin also officiates in the delivery of glucose to tissues for utilization. However, too much insulin leads to hypoglycemia, with acute effects such as coma and death. In normal glucose regulation, insulin secretion is reduced to a low basal rate when glucose levels fall into the normal range. By this means average glucose levels remain within the normal range, but with a safety margin that prevents hypoglycemia.

Type I diabetics do not secrete adequate insulin, causing a persistent average state of hyperglycemia, accompanied by a variety of degenerative sequelae over time, including blindness, neuropathy, and loss of extremities. Thus exogenous insulin must be provided, and traditional delivery systems involved injections around meal times. In recent decades the situation has improved tremendously, with advances in glucose sensor technologies, accurate pumps, chemical modifications to insulin that improve its performance, better catheters, and improved understanding of glucose/insulin dynamics [12]. The ultimate goal is to mimic the closed loop control that is effected by a healthy functioning pancreas. (We note in passing that a whole parallel endeavor using transplanted pancreatic islets is underway. Unfortunately, issues of adequate supply of donor islets and challenges associated with immunoisolation have limited this approach [13-19].)

Early studies of an “artificial beta cell” involved a (volunteer) patient lying on a hospital bed [20-23]. The patient’s blood glucose was sampled frequently and analyzed off line, with results fed into a computer. Using a “minimal model” of the patient’s glucose/insulin dynamics [24], infusion schedules were calculated, and these were administered through an i.v. line. While of little practical use for ambulatory patients, this system was useful in validating algorithms. It can also be regarded as a precursor for critical care monitoring of blood glucose.

All aspects of closed loop insulin therapy have been the object of intensive research. A wide variety of increasingly noninvasive electrochemical and optical approaches to glucose sensing have been proposed [25-30]. On the actuation side, precision pumping, the synthesis of insulins that do not clog catheter lines, and the ability to store, retrieve and analyze blood glucose time series, has improved therapy substantially. Presently, the most advanced systems consist of a small electrode tipped with glucose oxidase, which pierces the skin and transmits, by radio, the sensed glucose concentration to the pump controller (e.g. Medtronic Guardian® REAL-Time CGM, Dexcom G4™ PLATINUM). Figure 2 presents a cartoon of these systems. The pump controller reports the present glucose level, and can store and report preceding glucose time series. With this information, the patient can make informed decisions regarding rate and amount of insulin to be delivered. Data can be downloaded or transmitted over the internet, permitting *post hoc* analysis by a physician or by a cadre of experts. Perhaps the most important benefit of the sensor-pump system is that the patient and physician can track, over time, the efficacy of dosing decisions, along with the effects of aging, exercise, diet, and other behavioral variables. This benefit may also extend to Type II diabetes therapy, in which behavior is a strong determinant of disease.

Present glucose sensing electrodes must be changed every three days due to fouling and loss of function. Thus, skin must be breached at a new site, and not all patients are satisfied with this inconvenience. Recently, a fully implantable bioelectrochemical sensor system with telemetry has been shown to function faithfully for over a year in a pig model [31].

One element that is lacking in even the most advanced commercial systems is an intrinsic algorithm to compute the dosing schedule [6, 9, 32-40]. Such an algorithm would completely close the loop and take the patient out of the picture. While many believe that such a fully closed loop system will be the final *piece de resistance*, there are some reasons

for caution [12]. A patient's sensitivity to insulin is known to exhibit diurnal oscillations [41-43]. Factors such as exercise, which are not easy to quantify, are also important. The body's glucose regulation is determined not only by insulin, but also by glucagon, which mediates glycogen depolymerization. Finally, incretin factors such as glucagon like peptide (GLP-1), which are secreted even before food is absorbed into the blood are also involved in glucose regulation [44]. Thus, a system that makes its control decisions based on blood glucose time series alone may fail unexpectedly. It is also important to note that continuous monitors present a delayed blood glucose signal, due to transport limitations in surrounding tissues and sensor fouling [32, 45]. These considerations will be reiterated below, when the proper role of glucose sensitive polymers and hydrogels is discussed.

The annual dose of insulin is approximately one gram, and totally implantable pumps have been envisioned. Such pumps must be absolutely failsafed against leakage or dumping, however, since an overdose of insulin is fatal.

Besides insulin, many hormones are known to be secreted in an episodic, pulsatile manner [46-49]. Because their periodicities are scaled in hours rather than days, they are called *ultradian*, and it has been postulated that temporal variation is part of their signaling function, since different hormone receptors and downstream pathways may exhibit variant dynamics of desensitization, down regulation, and restoration. In most cases it has not been established yet that hormone replacement therapies should mimic the endogenous patterns. One exception exists, however. Gonadotropin releasing hormone (GnRH), also known as leuteinizing releasing hormone (LHRH) is a decapeptide hormone that is secreted in rhythmic pulses from the hypothalamus in both males and females, with periods of 1-2 hours [50-52]. In sexually mature males, GnRH is released with near constant period, while in females its release period differs during the follicular and luteal phases of the reproductive cycle. When GnRH is released, it is transported portally to the anterior pituitary gland, where it stimulates release of leuteinizing hormone (LH) and follicle stimulating hormone (FSH). These peptide hormones then stimulate release of gonadal steroid hormones, e.g. estrogen, progesterone, and testosterone, which regulate sexual and reproductive function.

In females, feedback loops from these downstream hormones regulate the period between secretory pulses over the menstrual cycle [53]. In males, sexual development is arrested when the pulsatile regime is not established [54]. Importantly, it has been shown that when this hormone is lacking, it must be replaced not only in level but also in pulse pattern for it to be effective [55, 56]. In fact, when GnRH or its analogues are administered continuously, there is a shutdown of reproductive function due to down regulation of GnRH receptors [57, 58].

Replacement therapy for GnRH is used for fertility treatments, and to induce sexual maturation. Electromechanical pumps (e.g. Zyklomat®, Ferring Laboratories) are the current standard of care. The pumps are charged with GnRH formulations, and deliver the hormone in pulses whose width and interpulse interval are set. Treatment periods last over months or years, and the hormone needs to be administered many times per day. The inconvenience of pumps has motivated research into less invasive methods of GnRH delivery. Since the hormone is relatively small (MW 1183) and its dose is very low (1.25 µg/

pulse), both the nasal and iontophoretic transdermal routes have been studied [59-64]. Even if these routes are feasible, however, the high dosing frequency is a practical drawback.

Given the low dose requirement, rapid clearance, and nonlethality (relative to insulin), it may be speculated that an implantable GnRH pulsating system would be valuable. Later in this review a stimulus sensitive hydrogel/enzyme system for rhythmic pulsed release of GnRH will be discussed. In the context of physiology, this system runs open loop, but its internal mechanism is closed loop, or self regulated, justifying its inclusion in this review.

A caveat regarding long term implantable GnRH systems is that the peptide, while highly stable in the dry state, has a relatively short (24 hr) stability half life in water, so any implantable device must have a mechanism for “quantally” dissolving only that drug that is to be released in a given pulse, or at least within a few hours. A possible example is the MicroCHIPS system in which individual drug doses are stored in separate wells of a silicon device, and hermetically sealed by gold films [65-67]. These seals are rapidly melted by an electrical current under microprocessor control, and the solid drug in a single well is free to dissolve. If the release can be rapidly pulsed, and the nearly 4500 doses required yearly can be placed in a single device, then such a system might be considered beneficial.

The purpose of this section was to point out that self regulated, episodic drug delivery based on stimuli responsive polymers faces competition. We now turn to episodic release systems in which polymers are fundamental actors. Stimuli-sensitive hydrogels will be our main focus, but first we briefly discuss other polymer systems.

III. Biodegradable and Monolithic Systems

Following the introduction of recombinant proteins in the 1970's, there was a surge in interest in delivering these molecules from implantable polymer matrices, due to their potency, short half pharmacokinetic half-lives, and the intractability of oral dosing [68, 69]. The simplest of these systems released drug continuously. Since it was known that hormones such as insulin and GnRH require episodic, pulsatile delivery, methods for modulating drug release were pursued.

In the first such system, pursued by the Langer group [70, 71], magnetic beads were impregnated into porous monolithic polymer matrices containing protein powders. When exposed to strong, low frequency magnetic fields, the beads were agitated, exerting stresses on the surrounding polymer, either driving convective flow in the pores or causing ruptures, leading to pulses of protein release. These studies, while crude by present standards, provided the first example of external modulation of drug delivery from polymeric implants. Interestingly, the magnetic motif has been revived in recent years due to the popularization of superparamagnetic iron nanoparticles (SPIONS). In one example [72], a porous alginate sponge is dispersed with SPIONs. Applying a strong, external magnetic fields causes this sponge to squeeze, releasing its contents. As will be discussed below, high frequency electromagnetic fields can stimulate drug release through a local heating mechanism, which causes hydrogels to swell or shrink.

A relatively simple self regulated glucose responsive monolithic system for episodic insulin delivery was studied by Brown et al. [73, 74] Two elements were involved in the system's response to glucose. First, glucose oxidase, in conjunction with gluconolactonase and catalase were used to convert glucose to hydrogen ion (H^+), leading to a drop in pH inside the pores of the monolith. Second, the pH dependence of the solubility of insulin was engineered such that a drop in pH would lead to enhanced dissolution and diffusional release of insulin. A problem with this system was diminishing returns with time, since the diffusion distance inside the pores increased. Pursuing another idea, Brownlee and Cerami [75], and Kim et al. [76, 77] investigated a system in which glycosylated insulin was complexed with ConA. Free glucose displaced the insulin from the ConA binding sites, in a glucose concentration dependent manner.

Around the same time, biodegradable polymers were receiving increased attention, the goal being surface controlled erosion, which would provide better control of release patterns than was provided by bulk eroding systems. During this period, the poly(orthoester) [78] and poly(anhydride) [79] systems were developed. In both cases, erosion was acid catalyzed, ensuring pH dependence. By including glucose oxidase and its accompanying enzymes, pH response could be converted to glucose response, as above. Under the ideal surface erosion scenario there would be no increase in diffusion distance with each pulse. Unfortunately, however, the attenuation of pH changes by physiological buffers would limit the ability of these systems to respond quickly. Ultrasound was also shown to stimulate enhanced release from biodegradable polymers [80].

In a recent study, pH-sensitive biodegradable acetal crosslinked dextran particles containing glucose oxidase, catalase, and insulin, half of them coated with alginate and the other half coated with chitosan, were mixed together to form a shear thinning gel that could be injected through a syringe needle [81]. The gel held together due to electrostatic forces between the oppositely charged coated particles. This system showed the ability to release insulin when challenged with hyperglycemia and turn off release when blood glucose returned to normal. The glucose oxidase catalyzed lowering of pH could affect insulin release rate in three ways: 1) change in insulin solubility, 2) loosening up of the gel due to increase in positive charge on the chitosan-coated particles and decrease in negative charge on the alginate-coated particles, and 3) acid-catalyzed degradation of the acetal crosslinks. Because this system erodes, it will eventually disappear without need for retrieval. Furthermore, only a small number of doses need to be injected at a time.

IV. Stimuli Responsive Hydrogels

Hydrogels, as water swollen crosslinked polymer networks, are particularly responsive to their environment due to three forces that determine their swelling [82-84], illustrated in Figure 3. The first swelling force is mixing with water, which is due primarily to the gain in translational entropy that water molecules enjoy when they invade the polymer network. However, the degree to which polymer chains and water intersperse is determined by their physicochemical compatibility, which has both enthalpic and entropic components. The hydrophilicity *versus* hydrophobicity of polymer chains is determined by the presence of polar, nonpolar, and hydrogen bond donors or acceptors groups in the constituent

monomers, which determine their enthalpic and entropic interactions with water; by temperature, which determines the relative importance of enthalpy and entropy, and by the presence of solutes that may alter water structure or adsorb onto the polymer chains, altering their hydrophilic/hydrophobic balance [85, 86].

The second force determining swelling in hydrogels is polymer elasticity. As polymer chains are linked together, they cannot disperse in water, and therefore they stretch and rearrange when the network swells in water. This leads to a rubber-like restoring force, which has been shown to be primarily entropic in nature. On the other hand, if a hydrogel is prepared in water and water is removed, the hydrogel shrinks and chains become relatively confined. Thermal (entropic) forces resist this confinement, again providing a restoring force. The primary determinant of the elastic force is the number density of elastically active chains connecting crosslinks in the hydrogel, which in turn depends on the crosslink density and the average number of chains per crosslink, excluding dangling ends and loops. The elastic force increases with temperature.

For electrically neutral hydrogels, the mixing and elastic forces are sufficient to determine swelling. The earliest model of swelling of polymer networks, due to Flory and Rehner [87], combined the Flory-Huggins theory for polymer/solvent mixing with the affine model for polymer elasticity. This model has since been elaborated in numerous ways [84, 88], but it remains useful in providing a succinct account that can be fitted to experimental data.

When the hydrogel contains ionized groups, a third, ion osmotic force is present. This force is also called the electrostatic force, and when properly analyzed these forces are essentially the same. Except for the smallest nanogels, hydrogels can be considered macroscopic in size with respect to the Debye screening length [83], which is approximately 1 nm in physiologic solutions. As a result, the hydrogel must be essentially electroneutral everywhere except at its interface with the external solution, where an electrical double layer is present with thickness of a few Debye lengths [89]. In order to enforce electroneutrality, an excess of counterions (ions whose charge is opposite to the charges fixed to the hydrogel network — Na^+ in Fig. 3b) is drawn into the hydrogel, while coions (ions whose charge is of the same sign to the fixed charges — Cl^- in Fig. 3b) are expelled to a lesser degree. This situation is analogous to the well known Donnan equilibrium [90, 91] that is set up when a semipermeable membrane separates charged colloids from aqueous salt solutions. In fact, the charged hydrogel acts both as the colloid and the membrane. The Donnan distribution of counterions and coions leads to an excess of mobile ion inside the hydrogel compared to the external solution, and an accompanying osmotic swelling force. This ion osmotic force, balanced against the polymer/water and elastic forces already discussed for electrically neutral hydrogels, determines the swelling of ionized hydrogels.

The relevance of Donnan equilibrium theory to the swelling of biological hydrogels was recognized as early as 1916 by Procter and Wilson [92], and it was explicitly combined with Flory-Rehner theory in Flory's 1953 *Principles of Polymer Chemistry* [82]. For highly charged and highly swollen hydrogels, in which polymer chains are separated by distances comparable to a Debye length, it was shown by Katchalsky and coworkers [93-95] that the ideal Donnan theory overpredicted swelling, since localization of counterions near

polyelectrolyte chains is not accounted for. In the 1950s and 1960s, this group studied polyelectrolyte (polyacrylic acid) hydrogels as “mechanochemical” (the term now is “chemomechanical”) engines that could perform mechanical work by shrinking and swelling in response to increases and decreases, respectively, in ionic strength of the external medium [96-100]. This effect of ionic strength can be interpreted alternatively in terms of changes in ion osmotic pressure or in terms of “screening” of the charges fixed to the polymer network [91].

When the hydrogel contains acidic or basic groups, then degree of ionization and swelling is a function of pH and ionic strength, as first studied by Michaeli and Katchalsky [101] and later by Hasa et al. [102]. This work can be regarded as setting precedent for work on pH-sensitive hydrogels conducted within the context of controlled release and other applications, starting in the 1980s [1-3, 103-110]. For these hydrogels, the Flory-Rehner-Donnan theory was augmented to include mass action (Langmuir) equilibria between hydrogen ions and pendant acid or base groups inside the hydrogel [103].

In the intervening period, work by Tanaka and coworkers at MIT [111-119], and by investigators at the Institute for Macromolecular Science in Prague [120-122], investigated conditions under which hydrogels could undergo first order volume transitions. In particular, Tanaka showed that substituting a small amount of sodium acrylate into a polyacrylamide hydrogel causes the latter to undergo substantial shrinkage, at constant temperature, when a critical composition of a water/acetone cosolvent was reached. This transition was reversible, and could be converted to a thermal transition, with the transition temperature depending on water/acetone content. The transition could be explained, qualitatively, using the Flory-Rehner-Donnan theory. This work, although it could not be directly applied to drug delivery due to the presence of acetone in the swelling medium, was the beginning of what might be called “modern” gel research, in which numerous physical and chemical techniques were brought to bear. Since that time, it has become essentially impossible for any investigator to follow the whole literature on hydrogels.

One of the most important discoveries related to stimuli sensitive hydrogels was the behavior of poly(N-alkyl acrylamides) as a function of temperature. Of these, poly(N-isopropyl acrylamide) (pNIPAM) has been the most thoroughly studied [123]. When synthesized as uncrosslinked systems, these polymers are miscible with water in all proportions at low temperatures, but phase separate and precipitate from solution with increasing temperature. While a so called lower critical solution temperature (LCST) and composition (volume fraction of polymer) exists, the threshold temperature for phase separation is relatively independent of polymer composition. When crosslinked into hydrogels, precipitation behavior is converted to strong deswelling [124, 125]. This inverse behavior is characteristic of the hydrophobic effect, which is attributed to breakup of and release of low entropy water “clathrate” structures that form around hydrophobic parts of polymer sidechains, with increasing temperature [126, 127]. This phenomenon appears to be very cooperative in pNIPAM hydrogels, in which the volume change is precipitous near 33 °C. This collapse temperature can be decreased by copolymerizing NIPAM with hydrophobic groups such as butyl methacrylate [128-130], and it can be increased by incorporating more hydrophilic groups such as acrylamide [131]. When ionizable groups are incorporated

at small degrees of substitution (<10%), the transition temperature depends on degree of ionization which, in turn, depends on pH [111, 132]. Conversely, a small change in pH can lead to a sharp change in volume, at constant temperature [133, 134].

When temperature is held constant, the transition pH depends jointly on the pKa of the acid or base groups, and the hydrophobicity of the polymer [104, 135, 136]. In fact the transition pH can be shifted away from pKa by several units, by co-incorporating increasingly hydrophobic moieties. For example, in one study [137] pNIPAM hydrogels were substituted with a series of n-alkylacrylic acids (acrylic, methacrylic, propylacrylic, butylacrylic). With increasing length of the α -alkyl chain, the transition pH increased by approximately 0.5 units per added methylene group, even though all of these monomers have essentially the same pKa when not included in the copolymers. Replacing carboxylic acid monomers with vinylated sulfonamides can also provide hydrogels with pKa and hence transition pH values much closer to the physiologic range [138, 139].

The inverse temperature behavior of hydrogels has also been studied extensively by Urry et al [140, 141], using variants of a repeated polypeptide motif from elastin, a very hydrophobic biopolymer. Using peptide synthetic and recombinant methods, essentially perfect control of peptide sequence (secondary structure) is achieved, and the chains adapt β -spiral configurations, providing a substrate for long range ordering of water [142]. The chains are radiation crosslinked. These are very strong hydrogels that exhibit a pronounced inverse volume transition, which can be converted to mechanical work. The transition temperature (T_t) has been shown to be exceptionally sensitive to peptide substitution (<5%), to the point where a hydrophobicity scale can be assigned to all amino acids based on T_t . Similarly, incorporation of acidic and basic amino acids, at very low substitution, leads to drastic pH sensitivity, and the transition pH (i.e. pKa) can be modulated over several units by varying the hydrophobicity of proximal amino acids. Urry has demonstrated that the pH effect can be attributed to alteration of polymer/water interaction as manifested in T_t , rather than the Donnan osmotic pressure effect discussed previously [143-145]. Another interesting feature of these systems is that amino acids with intrinsic degradation kinetics can be incorporated, leading to changes in swelling over time.

Besides hydrophobicity, hydrogen bonding has been utilized as a means to amplify and possibly shift pH-driven phase transitions. Carboxylic acids are not only ionizable, but they can form complexes with hydrogen bond acceptors. Polyethylene glycol (PEG)-based monomers have proved especially useful, as they stabilize the protonated form of a pendant $-\text{COOH}$ group, forming a hydrophobic complex [146, 147]. When the proton dissociates, the PEG group is released, which can then hydrogen bond to water and promote swelling. Since the $-\text{O}-$ groups are lined up in PEG, this release is likely to be cooperative. Other hydrogen bond acceptors include carbonyl, amine, amide and pyrrolidone groups.

As discussed above in the context of pH-sensitive degradable polymers, incorporation of glucose oxidase, gluconolactonase and catalase can be used to convert changes in glucose concentration to changes in pH. Incorporating these enzymes into pH-sensitive hydrogels renders them glucose sensitive. A more direct way to accomplish this is to incorporate monomers that complex with glucose, leading to physical and chemical changes in hydrogel

structure. To this end, hydrogels containing monomers with phenylboronic acid (PBA) groups on their sidechains have been investigated [148, 149]. The boron atom on PBA is attached to a phenyl ring and two -OH groups in a trigonal geometry, as shown in Figure 4a. One of its valence orbitals (sp^3) is bare, and the phenyl ring delocalizes the other electrons. Thus PBA is an excellent Lewis acid, which complexes with Lewis bases such as OH^- and N: groups. The most commonly studied PBA, methacrylamidophenylboronic acid (MPBA) acts, when in a hydrogel, as an acid with $\text{pK}_a \approx 8.5$ [150, 151]. At physiologic pH and in the absence of glucose, only a small fraction of the MPBA units are ionized. However, when complexation occurs the boron atom now has three coordinating -OH groups along with its link to the phenyl ring, so it takes on a tetragonal geometry. In this configuration, two of the -OH groups can form bisbidentate condensation complexes with cis diols residing on sugars, including glucose. Condensation is reversible, but when glucose is present it stabilizes the ionized boronate. Thus the apparent pK_a is reduced, the hydrogel ionizes, and the hydrogel becomes more polar and swells. These processes are completely reversible—when glucose is removed the hydrogels shrink back to its original size.

In another application, hydrogels are formed from interpenetrating networks of polymers containing PBA sidechains and chains containing closely spaced -OH groups such as poly(vinyl alcohol) (PVA) [152, 153] (Figure 4b). In the absence of glucose, condensation occurs between the ionized PBA groups and the polymerized -OH groups, and the hydrogel shrinks. Upon introduction of glucose, however, these condensates are replaced by glucose-PBA condensates, the two types of chains dissociate and the hydrogel swells.

The PBA-based strategy, as described so far, has problems regarding specificity. Other carbohydrates also form complexes with PBA groups. For example, fructose binds to ionized MPBA with about 40 times more avidity than glucose [154]. Lactate is another interfering species [155]. Since glucose is much more abundant than fructose and lactate in the blood, this is probably a minor problem. Of more concern is the fact that pH in the blood can vary, especially during diabetes. Since the mechanism described above relies on an acid-base binding step, the degree of swelling depends jointly on pH and glucose concentration [151, 156]. The latter problem can be averted, in principle, either by lowering the pK_a of PBA by increasing the electron withdrawing character of the groups attached to or neighboring the phenyl ring [157-159], or by incorporating Lewis base groups such as amines into the hydrogel, which can take over the role played by OH^- ions [148, 151, 160]. With these modifications, the PBA group is mostly charged at pH 7.4. In this case, binding of glucose does not alter charge substantially, so it does not cause a swelling increase. Interestingly, however, glucose can bind to two PBA moieties on separate polymer chains, adding a covalent but reversible crosslink to the network and increasing its elastic retractive force (Figure 4c). In this regime the hydrogel *shrinks* with increasing glucose concentration and reswells when glucose concentration decreases [161-164]. Shrinking usually only occurs to a certain point, however, since at high enough glucose concentrations the PBA sites become flooded with bound glucose and are unable to form crosslinks. The hydrogel then swells. The shrinking mechanism must therefore be tuned such that reswelling only occurs above the range of glucose concentrations of interest.

Another problem with PBAs is that they are subject to deborylation in the presence of reactive oxygen species (ROS), especially H_2O_2 [165] which may compromise their viability as long term components of implantable sensors and actuators. Recently it was shown, however, that this problem can be mitigated by immobilizing platinum catalysts that remove ROS [166]. Catalase may have the same effect.

Besides PBAs, concanavalin A (conA), a plant lectin, binds avidly to glucose and carbohydrate polymers of glucose such as dextrans, and to vinyl polymers with glucose side chains [167-170]. At low free glucose concentrations, each of the four binding sites can attach to a polymer chain, forming a crosslinked hydrogel. This hydrogel loosens up in the presence of free glucose, which displaces some of the chains from the ConA. Again, these reactions are reversible.

Similar ideas have been tried with molecular species besides glucose. Miyata and coworkers demonstrated a number of ways in which antigen-antibody fragment interactions can be used to control hydrogel swelling [171-177]. For example, if the antigen is bound to one chain and the Fab fragment of its corresponding antibody is bound to another chain of a hydrogel, then the two will create a strong noncovalent crosslink. The noncovalent bond will be displaced and the crosslink broken when free antigen is introduced, leading to swelling of the hydrogel. Withdrawal of free antigen causes the noncovalent bond to reform, and the hydrogel shrinks back to its original state. Similarly, crosslinks based on DNA hybrids that are attached to separate chains can be broken up reversibly by free chains containing one of the hybridized sequences [178, 179]. Finally, aptamer interactions appear to be an interesting way to control the rigidity, and perhaps swelling, of a hydrogel [180-182]. Since aptamers can be raised against many small molecules, this approach may be particularly useful in the future.

We conclude this section by mentioning some other methods to control swelling by altering the crosslink structure of a hydrogel. Wang et al. synthesized hydroxypropylmethacrylate (HPMA) hydrogels containing crosslinks based on protein coiled-coil motifs [183]. The coiled-coils were stiff at low temperature, but melted at higher temperatures, leading to a collapse of the gel. Chemically controlled swelling changes due to reversible folding transitions of protein crosslinkers has also been demonstrated. Ehrick et al. demonstrated glucose driven transitions due to conformational changes in glucose sensitive protein [184], and calcium sensitive swelling of hydrogels containing calmodulin (CaM) [185]. A similar CaM driven calcium dependent system, using a different hydrogel, was described by Murphy et al. [186]. Finally, Yuan et al. attached a mutated adenylate kinase to HPMA, and showed that hydrogels based on this combination shrink in the presence of ATP [187]. These studies suggest that molecular control of hydrogel swelling is a field that is still ripe for further exploration.

V. Sensing and Signal Transduction by Swelling and Shrinking

We turn now to methods by which repetitive swelling and shrinking of hydrogels can be used in self regulated drug delivery [188]. We will first consider sensing of hydrogel swelling, which can be used in conjunction with a “delivery” arm. Then, we will show how

externally applied stimuli can be used to modulate release from hydrogels inside the body. Closing the loop between sensing and release will be the topic of section VI.

Changes in volume or weight are the most obvious means to measure swelling. Clearly, continuous direct measurement of these parameters is impractical. Moreover, hydrogel swelling and shrinking rates should be rapid if they are to be useful for monitoring purposes. Since the time constants for mass transfer and poroelastic relaxations involved in size change scale as the square of the smallest dimension [189-191], the latter should be as small as possible, at least until chemical reactions such as enzymatic conversion, binding/release of solutes to the hydrogel, and reversible crosslinking become rate limiting. Response rate can sometimes be improved by using porous hydrogels [192-194]. Since the goal is for the hydrogel to take up minimal volume, practical sensing of hydrogel swellings state requires an accompanying readout mechanism. These considerations take us into the realms of micro- and nanotechnology.

An elegant surrogate for volume measurement is to synthesize hydrogels containing regularly spaced arrays of colloidal sized silica particles or polystyrene beads [157, 195, 196]. The spacing between the beads corresponds to optical wavelengths, and as the hydrogel swells or shrinks, a red or blue shift, respectively, in the diffraction of visible light is observed. Colloid array-embedded -PBA hydrogels have been proposed as sensors that can be placed in the front of the eye, in order to monitor glucose in the tear film. The short term correlation of tear film glucose levels with that in blood is not completely reliable, however, and this system would probably be most useful for long term monitoring [197]. Systems in which holograms are embedded in the hydrogel have also been investigated [155, 198].

Another method to measure the volume of a very small hydrogel is to place it onto the tip of a fiber optic connected to a monochromatic light source [179, 199-201]. The hydrogel then acts as a Fabry-Perot interferometer, with light reflected at the interface between the hydrogel and the external environment interfering with the incident light, with a phase shift depending on the hydrogel's diameter. This system has been tested successfully with pH-, glucose-, and DNA-sensitive hydrogels. It was proposed that these systems, covered with a suitable blood compatible protecting material, could be used as indwelling monitors of metabolites in the blood.

Micromachined microcantilever systems provide another means for rapid readout. In one such system, a pH-sensitive hydrogel was polymerized and bonded on top of a microcantilever beam [202, 203]. Swelling of the hydrogel increased the weight load and created stress on the beam. In another system, both pH- and glucose sensitive hydrogels were polymerized below the beam, pushing it away from the base as the hydrogel swelled [204]. In both cases, deformation of the beam was monitored by optical interference, and rapid response with excellent sensitivity was noted. Unfortunately, this kind of readout is difficult to realize *in situ*.

For implantable sensing of small molecules, it is necessary to mechanically isolate the hydrogel from the host tissue, and also to prevent large molecules from entering the hydrogel. This observation has prompted a few groups to confine the hydrogel in a chamber,

between a thin but solid nanoporous membrane and a sensing element. In these systems, free swelling is replaced by nearly isochoric sensing of the hydrogel's swelling pressure, which arises because free swelling is frustrated by confinement [205]. In one system, readout is by changes in piezoresistance of the sensing element below the hydrogel. Examples involving hydrogels that are primarily sensitive to glucose, pH, and ionic strength have been published [206-211]. Since glucose sensitive hydrogel based sensor may also be sensitive to pH, having a pH-sensitive microsensor by its side can be used to provide compensatory information. As presently designed, this system requires an implanted electrical source. In another system, the hydrogel pushes down on the top plate of a hermetically sealed microcapacitor that is integrated with a microinductor coil [212-214]. Changes in capacitance lead to a change in the electromagnetic resonant frequency, which is sensed remotely by a radio frequency (RF) impedance spectrometry. Multiple sensors of this kind, each with its own resonant frequency range, might be integrated into a single device.

Confining a hydrogel into a cavity is difficult in practice, as its dimensions must exactly match those of the cavity into which it is placed. If the hydrogel is too small, a "dead" space will be present, and there will be no swelling pressure to measure. If it is too large, then there will be an extra "jamming" stress. Recently, a simple method to measure hydrogel swelling in a small cavity has been proposed, which avoids these difficulties [215]. In this method, commercially available SPIONs, embedded in polystyrene microspheres, are dispersed in the hydrogel during synthesis. The hydrogel is bonded on top of a microinductor, but is otherwise free to swell into the cavity under the membrane. The microinductor has a constant stray capacitance, and hence a defined resonance frequency, which is probed remote RF stimulation. The magnetic permeability of the hydrogel changes as it swells and shrinks, altering the lines of magnetic flux and hence the inductance and resonance frequency. The latter system has been shown to provide relatively rapid and reproducible pH determinations.

Very low electromagnetic fields are needed to sense changes the volume of SPION impregnated hydrogels. Much higher intensity fields can be used to control hydrogel swelling, if the hydrogel is temperature sensitive. Thus, SPIONs have been incorporated into PNIPAM and other hydrogels, and it has been shown that these hydrogels contract when stimulated, due to heat generated by Néel or Brownian relaxations [216-219]. This heat is very localized, and need not affect surrounding tissues. Another way to provide localized heating is to incorporate gold nanoparticles into the hydrogel, which heat up plasmonically when stimulated at particular NIR wavelengths [220]. As a final possibility, heating can be generated by focused ultrasound.

How can swelling and shrinking of a hydrogel alter drug release properties? The earliest investigated and most obvious method is to utilize the increase in mesh size that accompanies swelling, since diffusion through the hydrogel is dependent largely on the ratio of drug diameter to mesh size [188, 221, 222]. Other effects besides swelling may be present, however. For example, hydrophobic, hydrogen bonding, and electrostatic interactions between drug and the hydrogel may alter the partitioning and diffusion characteristics of drug in the hydrogel, and all of these interactions may be altered upon application of the controlling stimulus [221, 223, 224]. When the hydrogel contracts

strongly, release can be increased (an inverse effect) due to squeezing of the internal contents and resulting advective flow [225, 226]. In addition, as water leaves, drug becomes more concentrated and closer to the surface, which also may increase release rate.

The inverse effect between hydrogel swelling and drug release also can be achieved by utilizing the hydrogel as a valving element. Here the hydrogel, usually micro- or nanosized, is placed in a confined space with inlets and outlets. When the hydrogel is swollen, it completely fills the space, either completely or substantially blocking drug diffusion. When the hydrogel shrinks, some of the space is opened up for diffusion [227]. This mechanism can also be used to gate convective transport of drug. One relatively simple way to achieve gated transport is to cast a dispersion of nanosized (~500 nm) hydrogels in an ethylcellulose solution and evaporate the solvent, leaving behind a hydrogel-impregnated thin membrane. The volume fraction of the nanogels should be high enough that connected (percolating) paths connect the two sides of the membrane. Wu and coworkers used this technique with hydrogels containing copolymers of NIPAM and methacrylic acid, and demonstrated both thermal and pH control of insulin permeation [228, 229]. Recently, Hoare et al. demonstrated that thermosensitive hydrogels containing SPIONs, when incorporated in a thin membrane, can rapidly gate the transport of fluorescent FITC-dextran when a high frequency magnetic field is applied [230].

Hydrogels can also be incorporated into micromachined structures to provide valving and gating functions. Silicon, glass, and polymeric substrates have been studied [231, 232]. Polymer substrates can be hard or soft, with polydimethylsiloxane (PDMS) being a favored soft polymer due to its ease in molding and surface modification. In early studies, Beebe and coworkers polymerized pH-sensitive hydrogels around posts in microfluidic channels, enabling them to gate fluid flow [233-235]. Serksen et al. (see above) incorporated gold nanoparticles into thermosensitive hydrogels, which were then confined in microchannels. Stimulation with infrared light generated local heat, shrinking the gels and enabling flow. In the work reported by Ehrick et al. (see above), swelling and shrinking of small hydrogels as a function of glucose or calcium ion concentration was used to block and unblock microchannels.

In the systems described in the previous paragraph, flow was in plane. To fabricate a more membrane-like structure, Baldi et al. created a network of cylindrical pores crossing a thin membrane [236]. At the middle of each pore was a narrow cylindrical post that was suspended by silicon tethers attached to the outer pore wall. The whole structure was etched from a silicon wafer. Both thermo- and pH-sensitive hydrogels were polymerized into the pore gaps. These hydrogels filled the pores, but retracted around the inner cylinders when stimulated, providing a means for controlling cross planar flow. Clearly, the thermosensitive version of this system could be rendered susceptible to magnetothermal stimulation by incorporation of SPIONs.

Very recently, there has been interest in self-folding or “origami” polymers. These systems typically consist of layers or patches that swell in response to a stimulus, mechanically coupled to other layers/patches that are unresponsive. Upon application of the appropriate stimulus, swelling or shrinking of the sensitive component leads to a swelling stress

mismatch and bending of the couple. While early versions of this idea required layering of materials with different swelling response characteristics [237, 238], advances in feed gradient polymerization [239], polymerization under graded photomasks [240], and multiphoton polymerization techniques [241] have permitted much more precise control. Using these methods, it is possible to determine flat sheet geometries that fold up into specified three dimensional shapes. In the controlled release arena, the first systems were polymeric caps that would curl up and unveil underlying drug [238]. More advanced box-like systems have been demonstrated, with most of the motion occurring at photopolymerized hinge regions [242].

VI. Closing the Loop

In the previous section, the sensing and delivery arms were discussed separately. Implantable systems for drug delivery might contain one or the other arm, are both. When only one arm is included, a nonpolymer based system could be used as the other arm. For example, a hydrogel based sensor with wireless telemetry could be implanted to monitor blood levels of a target metabolite over time, while delivery of the therapeutic countermeasure would be by simple injection or by an electromechanical pump. Conversely, an implanted polymer-controlled delivery device could be activated remotely when the patient or caregiver senses the need. Both kinds of devices could be implanted, with the human operator acting between the sensing and delivery arms, leading to closed loop control. In more “complete” systems, an automatic control algorithm could be used in place of the human operator. In all these systems, there is likely to be some electronics involved.

However, what has intrigued many researchers in the controlled release field from the start is the potential of an implantable device to provide closed loop control due to its intrinsic structure and properties, with no internal or external electronics involved. Such devices would act as both sensors and actuators. For now, we will ignore basic philosophical issues, already brought up in the context of fully automated systems, and consider some of the intrinsic closed systems that have been studied for about three decades. We will return to these basic concerns in the concluding section of this review.

The primary focus of most research on intrinsic implantable closed loop systems has been insulin delivery for treatment of Type I diabetes [243, 244]. This should be of no surprise, because closed loop therapy is needed to provide the tight control of blood glucose levels that is needed for long term reduction of morbidities associated with hyperglycemia, and for avoidance of the acute dangers of hypoglycemia. However, it should also be noted that the glucose-insulin system provides the ideal “test bed” for closed loop studies. Glucose is abundant at high concentrations in the blood (>3 mM in the normoglycemic and hyperglycemic states), so it is readily available to provide a large signal to a sensor. It is also remarkable that enzymes and complexing agents such as –PBAs are available and work over the concentrations ranges of physiological interest. Analytes that are characteristics of other disease states, such as antigens and ions, tend to be present at much lower concentrations, and most polymeric systems to date that respond to such stimulants can only do so at higher concentrations than are seen physiologically. In this section we review some intrinsic closed loop glucose-insulin systems. We also discuss another application of glucose-based sensing

and actuation in which rhythmic, pulsatile release of GnRH is achieved, even though the level of external glucose does not change with time.

The idea of using a hydrogel to mediate insulin release in response to changes in glucose concentration was introduced, almost simultaneously, by Ishihara et al. [245, 246] and by Kost, Ratner, and Horbett [247-251]. Both groups copolymerized dimethyaminomethacrylate (DMAEMA) with a neutral comonomer, to produce a polybase hydrogel that swells with decreasing pH, with greatest sensitivity just below physiologic pH. To convert pH-sensitivity to glucose sensitivity, glucose oxidase and catalase were covalently immobilized to the hydrogels. Since glucose oxidase as purchased usually contains gluconolactonase, this enzyme was probably also immobilized. In the presence of these three enzymes, the following reactions occur:

Since the pKa of gluconic acid is about 3.8, it is completely dissociated above pH 6, so one H^+ is produced for every glucose molecule that is consumed. The H^+ ion, in turn, binds to the tertiary group on DMAEMA ($\text{pKa} \approx 7.9$), leading to hydrogel swelling and increased permeation of insulin through the hydrogel.

Notice that half of the O_2 molecule is also consumed. This is important, since O_2 is present at much lower concentration than glucose, so the glucose oxidase catalyzed reaction may become oxygen limited, hence less sensitive to glucose concentration changes. To a partial degree, the higher diffusion coefficient of oxygen compared to glucose compensates for the relative sparsity of free O_2 . In addition to preserving half of the oxygen, catalase protects the enzymes from oxidation [252]. This, combined with the stabilization of enzymes that is afforded by immobilization [253], function to enhance the lifetime of the enzymes. Also, the enzymes can all be incorporated in excess, so that the reactive function remains even after a large fraction of the enzymes have been deactivated [254].

In the absence of buffers, very low pH values can be obtained, when the membrane is exposed to glucose in unbuffered solution, but it was computationally predicted, and experimentally confirmed, that when physiological buffers are included, pH in the membranes does not go below about 6.8; hence, the need for a membrane whose sensitivity lies between 6.8-7.4 [247, 255]. Since the original studies, attempts have been made to optimize the polymer swelling response using different ionizable and neutral monomers to better locate pH sensitivity and swelling differential between the ionized and neutral states [256]. It has also been shown that the oxygen debt problem can be mitigated, at least partially, by lowering access of glucose to the enzymes compared to oxygen [255].

The mechanism of insulin release modulation in the DMAEMA based system is variation of mesh size of the hydrogel as a result of swelling and shrinking due to the internal pH change. Unless very thin hydrogels are used, this mechanism is slow, since the partition coefficient and diffusivity of insulin in the hydrogel are low. As discussed previously, response time can be improved by embedding micronized hydrogels in a porous substrate membrane and using them as valving elements. In this case they must shrink when insulin delivery is called for. The latter approach has been advanced furthest by Gordijo et al. [257, 258], who embedded NIPAM-methacrylic acid microgels, along with glucose oxidase and catalase and MnO₂ nanoparticles in a glutaraldehyde-crosslinked albumin membrane. The purpose of MnO₂ was to react with H₂O₂ in such a way as to completely restore the O₂ that is consumed in the glucose oxidase reaction. This reaction is consumptive and not catalytic—hence it is ultimately limited by the stock of MnO₂. The membrane capped a small silicone tube containing the insulin suspension, which may also have provided an extra route for O₂ access to the reactive membrane. This system was shown to be successful in providing repeated pulses of delivery of insulin *in vitro* in response to elevations of glucose level. Limited *in vivo* tests in diabetic rats demonstrated that this system could respond to a single glucose challenge.

The use of –PBA containing hydrogels in self-regulated glucose delivery has also been studied, first using PVA-MPBA membranes by Okano, Kataoka and coworkers [149, 259-261]. Kataoka et al. later studied copolymer hydrogel membranes consisting of NIPAM and MPBA [262]. The charge transition and polarity transition of the –PBA moiety was amplified by the LCST response of the NIPAM, leading to a sharp transition in swelling and permeability, and hence delivery of insulin across the membrane. It was found however that this behavior could only occur at pH 9.0. To bring the behavior down to physiologic pH, Matsumoto et al. replaced MPBA with 4-(1,6-dioxo-2,5-diaza-7-oxamyl)-PBA, whose electron withdrawing properties increased the acidity of the PBA moiety [159]. Micro- and nanoparticles consisting of –BPA hydrogels and containing insulin have also been studied as potential depot or circulating systems [263, 264].

A complete closed loop delivery system based on a crosslinked ConA-dextran hydrogel (see above) was reported recently by Taylor and coworkers [265]. A thin hydrogel system was layered between two porous cellulose nitrate (Millipore) membranes, and this sandwich was screw clamped between two polycarbonate elements, one a fluid chamber containing insulin solution and the other a perforated mesh. This device was implanted into the omentum of diabetic rats, and was shown to provide good control of glycemia over several days. Evidence was provided that the omentum grew into the perforations, perhaps providing intimate contact between the device and the blood supply.

A system to convert hydrogel swelling and shrinking to modulation of fluid flow, with application to closed loop insulin delivery, was studied by Siegel, Ziaie, and coworkers, in a system that bears resemblance to the microfabricated glucose sensor described in section V [161, 204, 266]. A poly(MPBA-co-acrylamide) hydrogel was confined between a solid porous membrane and a flexible PDMS diaphragm, under which a solid silicon embossment opened and closed a microfluidic channel. The idea was to connect this channel to a pressurized insulin solution, whose flow would be gated on an off. A major design flaw was

that the hydrogel swelled and closed the channel as glucose concentration increased. This problem could be solved, however, by using a –PBA based hydrogel that shrinks appropriately with increasing glucose concentration.

We now turn to the problem of using rhythmic swelling and shrinking of hydrogels to provide periodic, pulsed delivery of hormones. This mode differs from the normal closed loop systems discussed so far, which might be considered feedback compensators that respond to concentration changes of an analyte such as glucose. As will be shown, glucose at constant concentration can be used as a “fuel” to provide rhythmic swelling/shrinking cycles, analogous to a strobe light, which functions by alternating a slow buildup of electrical charge with a rapid discharge when a threshold is reached. The inspiration for the rhythmic system came from chemical and biochemical oscillators, the study of which has matured since the 1960s [49, 267-270]. Most of the nonbiochemical oscillators are based on redox reactions of toxic inorganic species, and hence are not relevant for drug delivery. However, a growing and interesting literature has arisen based on combinations of such oscillators and hydrogels, in which hydrogel swelling and shrinking plays a causative or modulating role in the oscillatory behavior [271-277].

A bench scale prototype for glucose driven rhythmic delivery of GnRH was demonstrated by Siegel and coworkers [278-282]. In this system, a poly(NIPAM-*co*-MAA) hydrogel membrane separates a chamber containing containing GnRH, glucose oxidase, catalase, and gluconolactonase from an external glucose solution held at constant concentration, with pH set to 7.0. At high pH values inside the chamber, MAA units are charged and the membrane is swollen, permitting glucose entry, where it is rapidly converted to gluconic acid, which dissociates to free H^+ and gluconate $^-$ ions. The H^+ diffuses into the hydrogel membrane and neutralizes the MAA units, and the membrane collapses to the point where its permeability to glucose is strongly attenuated. Now, conversion to H^+ in the chamber is also severely reduced. Eventually, H^+ dissociates from the pendant $-COO^-$ groups on the membrane and is neutralized by the external medium. The hydrogel then reswells, bringing the system back to its initial state where it is poised to repeat the cycle. As the hydrogel swells and shrinks, it gates release of GnRH from the system, with rhythmic pulses separated by dead periods. Rhythmicity can be monitored by tracking pH in the chamber.

A feature of the poly(NIPAM-*co*-MAA) membrane is its bistable, hysteretic pH response—the membrane collapses at a lower pH value than where it reswells [283]. Between these two pH values the swelling state of the hydrogel depends on its most recent history. This feature is crucial, since a monotonic relation between pH and swelling would likely lead the system to a stationary state, at a pH value where swelling is such that inward glucose flux and outward H^+ flux are balanced at all times.

It is important to emphasize that the cyclic behavior of the GnRH releasing system is driven by external glucose at a *constant* level and is functionally open loop, but its function relies on an internal closed loop feedback instability caused by the interaction between the enzyme driven reaction and the swelling/shrinking behavior of the hydrogel. Such instabilities are common in electrical and chemical/biochemical oscillators, and instability in this context need not be considered undesirable. However, nonlinear oscillators can be very sensitive to

small changes in operating conditions. For example, diurnal and higher frequency fluctuations in external glucose level will lead to some modulation of the system's interpulse interval [281, 284, 285].

The prototype oscillator, while demonstrating the principle of rhythmic hormone delivery, has several deficiencies. First, it must be scaled down in size to make implantation possible. Second, gluconate⁻ ion accumulates inside as time increases, leading to buffering of the pH changes inside the chamber and slowing of the oscillations. Third, the oscillator's performance is challenged in the presence of physiological buffers. Fourth, it was found that in order to speed up the oscillations and prevent the system from slowly drifting to a stationary state without oscillations, marble (CaCO₃) had to be added to the chamber. The mechanism by which marble accomplishes this task is described in the original papers. While modeling studies suggest that many of these problems can be mitigated by reducing system size and altering properties of the hydrophobic polyelectrolyte hydrogel membrane [286, 287], much work will remain before this prototype system can advance to *in vivo* studies.

VII. Conclusions

In section II we pointed out that systems coupling electrochemical sensors with electromechanical actuators such as pumps have reached a state of advancement that exceeds what has been achieved by the polymer based systems that are typically studied in the controlled release community. This is understandable, since the many of the former systems are derived from a more mature technological base. Much more research will be needed if the polymeric devices are to catch up. If they can, there may be benefits of simplicity and the ability to circumvent some disadvantages of the more advanced systems.

Nevertheless, there are some common lessons. At this stage, we believe that completely automatic closed loop delivery systems, especially for Type I diabetes treatment, are unlikely to be accepted in the near future. As indicated in section II, there still is much to be learned regarding glucose/insulin dynamics, along with the roles of other hormones such as glucagon and incretins such as GLP-1. Interindividual variations, circadian rhythms, and the effects of exercise on glucose/insulin dynamics are all important inputs that should be included in specifying the insulin delivery program, regardless of the kind of system that is used. Moreover, delays between actual blood glucose changes and the values of glucose concentration sensed in the tissues, along with the intrinsic low pass filtering that accompanies delays, will be compounded with delays in sensor response. In this regard, interjection of the human operator, perhaps assisted by well designed advisory software (as might now be programmed as an app on a smart phone) into the feedback loop seems, at present, to be the best way to provide adaptive, informed behavior that can learn from its own mistakes. Whether this kind of approach is regarded as closed loop or information driven open loop is probably immaterial.

To confine the scope of this review, we have not covered circulating nanosystems that can target specific tissues or even cell types within tissues. These systems can respond to local biochemical conditions, or they can be regionally stimulated by externally applied energy.

Theranostic systems, in which the condition to be treated, and the delivery and/or local impact of a therapeutic can be imaged, may provide future examples of therapies that are effectively closed loop.

A complete review of papers published in the areas of stimuli sensitive polymers and self regulated drug delivery systems would reference thousands of articles, and the present attempt has had a much narrower focus. Apologies are made to those whose contributions were not adequately recognized. Like many other very good but difficult ideas in therapeutics, the field has experienced a long period of gestation, during which some of the original expectations and assumptions have had to be modified. Nevertheless, the lessons learned in the study of responsive polymer systems have led to new ideas and potential applications.

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Figure 1.

Contrast between open and closed loop drug delivery. In open loop delivery, the system releases drug in a programmed fashion determined by the control. Delivery impinges on the physiological response, which also depends on the drug's pharmacokinetic (PK) properties. In closed loop delivery, physiological and PK information is fed back to the controller, which alters its "commands" to the delivery system. While the controller and delivery system are represented as separate components, the control aspects may be intrinsic to the delivery device.

Figure 2.

Current implementation of quasi-closed loop feedback control of insulin delivery. A small electrode senses glucose and transmits it to the controller by radio waves. The controller records glucose time series, providing it to the operator (patient or caregiver), who then instructs the pump, through commands to the controller, regarding insulin delivery program. Glucose time series can be stored or transmitted for further analysis.

Figure 3.

a) Stimuli that can cause reversible swelling and collapse (shrinking) of hydrogels. b) Three forces determining hydrogel swelling, and the factors affecting them. T is temperature, pH and other concentrations refer to external aqueous medium, pK_a is acidity constant of ionizable groups. Polymer elasticity: filled circles are permanent crosslinks, while crosslink in center is reversible. Polymer/solvent interaction: lattice representation of solvent and polymer is not intended to be realistic. Ion osmotic pressure: Here ionization is due to $\text{COOH} + \text{NaCl} \leftrightarrow \text{COO}^- + \text{Na}^+ + \text{HCl}$ reaction.

a)

b)

c)

Figure 4.

a) Phenylboronic acids are charged in the presence of Lewis bases such as OH^- , and the charge is stabilized by bidentate condensation of molecules containing cis diols (e.g. sugars) depicted as orange ovals. Charging of hydrogels containing PBA's causes them to swell. b) Polymer chains in a hydrogel containing PBA, a chains containing a high density of pendant OH groups, such as poly(vinyl alcohol) (PVA) form crosslinks, shrinking the hydrogel. These crosslinks can be displaced by free sugar molecules, causing the hydrogel to swell. c) Glucose contains two sets of diols that can complex with PBA chains. At high pH values where the PBA units are highly charged, this can lead to formation of bisbidentate binding and crosslink formation. At high glucose concentrations, this mode is suppressed since all PBA sidechains are occupied by glucose molecules. The pH at which these mechanisms

operate can be lowered by incorporating amines into the hydrogel, which serve as Lewis bases (:N-) that take over the function of:OH⁻.