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REVIEW ARTICLE

Microneedle-Based Automated Therapy for Diabetes Mellitus

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Abstract

This article discusses the use of microneedles in automated diabetes therapy systems. Advanced bioengineered systems have the potential to close the loop between diagnostic and therapeutic elements of diabetes treatment, thus constituting a "smart" system. Prevalent insulin therapies, and most glucose sensing techniques, involve the transfer of physical entities through the skin. Micromachined needles (microneedles) can achieve this in a noninvasive or minimally invasive manner while contributing various other technological merits. The dynamics of autonomous diabetes therapy systems include highly complex interdependencies between the various physical and biological entities involved, thus warranting multidisciplinary research initiatives. The iterative development of a noninvasive, bioengineered interface such as microneedles necessitates a better understanding of the human skin, its molecular architecture as a polymer film, and its role as a functional biological unit. This review addresses application-specific requirements of a microneedle-based interface system specifically for autonomous diabetes therapy. Key design issues and related parametric interdependencies specific to this application are discussed.

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Introduction

Currently about 250 million people in the world suffer from diabetes mellitus. Exogenous insulin replacement is the primary form of treatment for type 1 diabetes, and it is also used in cases of advanced untreated type 2 diabetes.[1,2] Insulin therapy requires periodic monitoring of blood glucose levels combined with intermittent injections of insulin to optimize the blood glucose levels while minimizing the risk of hypoglycemia. A number of insulin preparations are currently available whose onset and duration of action can vary widely. Combining a short-acting preparation with a longer-acting one is often required to treat patients with insulin resistance or those whose glucose levels gyrate over wide ranges. Unfortunately, manual administration of the insulin is essentially an "approximate therapy." The dynamics of natural production of insulin are highly complex and nonlinear; the conventional method cannot replicate the optimum insulin levels accurately either quantitatively or temporally. Moreover, an unignorable factor in the manual technique is the possibility of human error or patient noncompliance.

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Abbreviation: (ISF) interstitial fluid

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Advanced bioengineered systems have the potential to close the loop between diagnostic and therapeutic elements of diabetes treatment, thus constituting a "smart" system.[3] Prevalent insulin therapies, and most glucose sensing techniques, involve the transfer of physical entities through the skin. Traditional approaches used to collect biofluids or delivery drugs include needle puncture, electroporation or vaporization, or removal of the stratum corneum through gels or tapes. Micromachined needles (microneedles) can enable collection of the same information, with significantly less trauma to the tissue, and have the potential of even eliminating it. This review addresses those factors important in the design of such a system. In particular, the design of microneedle systems is reviewed.

Autonomous Diabetes Therapy Systems

Autonomous insulin therapy systems that automatically monitor the glucose levels and intermittently inject the requisite amount of insulin at appropriate times can address many of the problems associated with manual techniques.[4–6] At the broadest level, a generic device consists of the following parts: (a) a glucose sensor (diagnostic component), (b) an insulin delivery mechanism (therapeutic component), and (c) a feedback mechanism that bridges between glucose sensing and insulin delivery units (control component). **Figure 1** depicts the elements of a prototypical microneedle-based diabetes therapy system.

Currently there is an assortment of stand-alone glucose sensors and insulin delivery mechanisms available or being developed. Not all types of glucose sensors and insulin delivery devices are conducive to use in autonomous systems. The diagnostic and therapeutic units of choice should fulfill the following criteria:

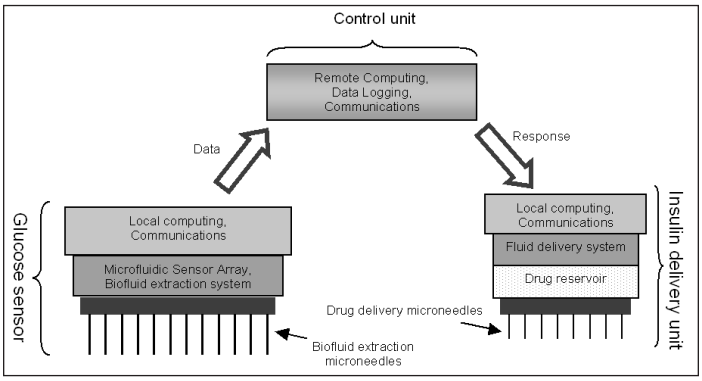

Figure 1. Elements of the prototypical microneedle-based diabetes therapy system.

a. Require minimal intervention on part of the patient
b. Be extremely reliable
c. Preferably be minimally invasive or completely noninvasive

Stand-alone glucose sensors vary extensively in their approach, implementation, or complexity. Typical variables are as follow.

a. Fluid being extracted—blood[7] and interstitial fluid (ISF)[8]
b. Degree of invasiveness—highly invasive (implantable sensors[9]), moderately invasive (finger stick type[10]), or noninvasive (extracorporeal watch type[11])
c. Sensing technique (colorimetric,[12] electrochemical,[13] ultrasound,[14] dielectric spectroscopy,[15] near infrared[16])

Insulin delivery mechanisms vary based on their method of administration, namely intravenous injection,[17] subcutaneous injection,[18] intraperitoneal injection,[19] or nasal delivery.[20] Of these, the subcutaneous injection mechanism is the most prevalent due to accurate dosage control and moderate to low levels of invasiveness.

The feedback mechanism, or the control unit, is the most critical component of the automated insulin therapy device. The dynamics of glucose absorption and insulin production are highly complex. Translating empirical data and available knowledge on internal metabolisms into efficient mathematical equations and control algorithms is not an easy task. Ideally, the program should allow for a patient-specific tailoring of the glucose level vs insulin delivery scheme in order to closely match real metabolic activities. In general, two kinds of feedback control algorithms are being used.[21]

a. Closed-loop control—only uses feedback from the glucose sensor. No external interaction.
b. Partially closed-loop control—uses feedback from glucose sensor, as well as the physician's assessment of the patient's requirement. **Figure 2** depicts the control diagram of a typical partially closed-loop therapy model.

Open-loop control schemes are also being used for preprogrammed therapy.[22] These schemes control the insulin delivery mechanism based solely on the physician's input. As they do not provide for any feedback from the glucose sensor, they can only be regarded as partially autonomous systems.

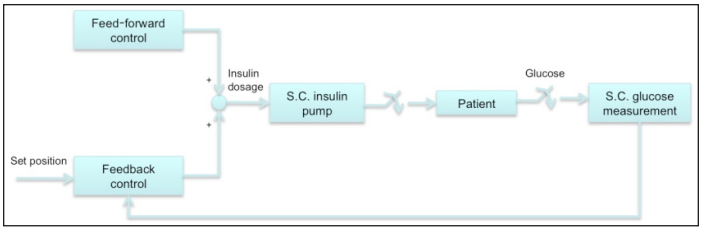

Figure 2. Typical control flow of partially closed-loop insulin therapy models.[21] S.C., subcutaneous.

Microneedle-Based Skin Interface Systems

Even though noninvasive glucose monitoring has greatly improved recently,[23] the techniques used by these devices still lag in accuracy as compared to direct electrochemical glucose measurements. This is because these devices rely on inexact mathematical algorithms. Accurate calibration of these devices is problematic due to varying lipids, proteins, and water levels in humans. Although noninvasive techniques remain an option for glucose sensing, administration of insulin necessitates at least minimal invasion

Traditional methods of subcutaneous insulin injection or biofluid sampling employ hypodermic needles. Although utilitarian, this method causes undesirable pain and tissue trauma. This is particularly troublesome in the case of diabetes where frequent sampling and drug delivery are required. One solution to these problems is the use of microneedles, a minimally invasive skin interface tool.

Microneedles are microscopic needles capable of piercing the skin and creating micrometer-sized perforations. Perforations of micrometer dimensions are large enough to allow macromolecules such as insulin to pass through. The microneedles are long enough to penetrate the outermost layer of skin. However, depending on the application, either they do not penetrate deep enough to reach the underlying nerves, thus being totally painless,[24] or they just graze the tips of nerves, causing sensation but reducing pain nevertheless.[24a]

System Architecture of Microneedle-Based Diabetes Therapy Device

Microneedles form the generic abiotic front-end interface to the biotic domain. The use of microneedles imposes certain architectural requirements pertaining to the autonomous device. The micrometer size domain of microneedles (~10 to 500 μm in diameter) necessitates the use of microfluidic components and microelectromechanical systems technologies. At the microscale, effects such as laminar flow, diffusion, fluidic resistance, surface to volume ratio, and surface tension become dominant,[25] thus scaling or shrinking of traditional large devices cannot be done. Microfluidic-based versions of components, e.g., chambers, channels, pumps, valves, and mixers, are required. It should be noted that a natural predilection toward smaller device footprints has led to the use of microfluidics in even nonmicroneedle-based autonomous sensors.

An advantage of using microfluidics, apart from smaller device size, is the convenience of adding communication and data logging capabilities. The glucose sensor and the insulin delivery unit need not be physically located at the same position on the patient's body and may interact wirelessly with each other. The unit may record raw and significant data, which can be analyzed later by a physician or researcher. Historical data can also be actively utilized by more complex algorithms such that the insulin delivery scheme is dynamically tailored based on past conditions or responses. Advanced systems in the future might follow a node-based approach for global-level monitoring and incorporate distributed computing algorithms and low-power communication protocols at those nodes.

Anatomy of Skin: Diabetes Therapy-Specific Perspective

To understand the nuances involved in interfacing with skin, one needs to understand its anatomy from an application-specific perspective; in this case, microneedle-based diabetes therapy. The skin hosts simultaneously occurring complex physiological, biomechanical, and biochemical processes. These are brought about by tissues within its two layers: the dermis and the epidermis. The epidermis is the tough and waterproof outer layer of the skin that protects the body's interior from foreign substances. The underlying dermis is a thicker layer and is responsible for imparting strength and elasticity to the skin. **Figure 3** illustrates the cross-sectional view of human skin.

An estimated 90% of the epidermal cells are "keratinocytes." They produce keratin, a tough, fibrous, intracellular protein. Keratinocytes are stacked in layers. The youngest cells occupy the lower layers while older cells are present in the upper ones. The lower layer cells multiply continually and migrate to the upper layer. By the time the cells move up to the outermost layer (stratum corneum) of the epidermis, they are dead, completely filled with keratin, and are continually sloughed.

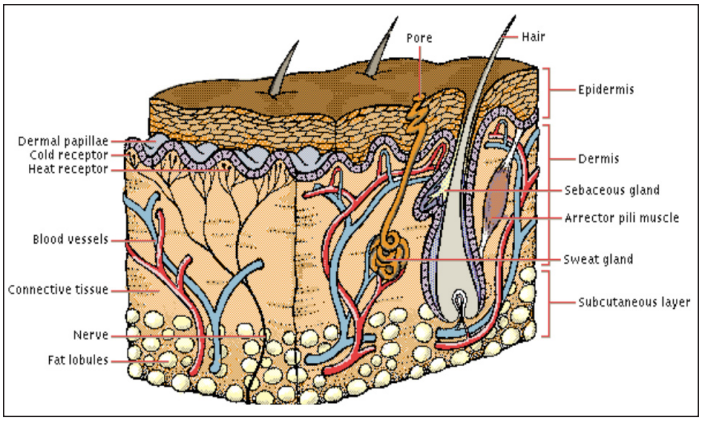

Figure 3. Cross section of skin.[26]

The stratum corneum in particular dominates various design considerations, especially the micromachined interfaces. This layer is a thin, flexible, high impedance bio-polymer composed of interconnected "dead" cells called corneocytes. This complexly organized, anucleate, 15- to 20-μm-thick, biopolymeric structure is essential to life and serves to couple the organism to the environment. This structure is particularly well developed in humans who lack a protective mantle of fur. The stratum corneum precludes passive transdermal delivery of insulin, as its molecules are too large (~50 Å in diameter) to pass through. Thus, the key requirement to develop the microneedle interface is that the stratum corneum needs to be ruptured for successful insulin delivery.

Glucose (molecular mass 180 daltons, ~1 Å in diameter) is present in both blood and ISF below the stratum corneum. The epidermal layer, from approximately 40 to 400 μm depth, contains ISF that can be sampled for glucose measurements. Blood capillaries are present just below the epidermis at penetration depths of about 400 μm. Nerve cells tips are also found at the same depth as capillaries.

Microneedle Design for Autonomous Diabetes Therapy Systems

An application-independent optimum design for microneedles does not exist. Design selection is highly application specific and involves simultaneous consideration of multiple parameters. Common design variables include geometric features (length, diameter, shape), choice of material, array layout, and physical architecture (beveled tip, conical, side-opened). There is always a trade-off among the various output characteristics, such as fragility, biocompatibility, penetration force, fluid flow rates, ease of fabrication, and cost. Application-specific requirements of diabetes therapy systems necessitate that certain microneedle characteristics have higher priority. Key design issues and related parametric interdependencies specific to diabetes therapy systems are discussed next.

Microneedles for the Glucose Sensing Component

Glucose sensing can be done by sampling either blood or ISF. The choice of the biofluid sampled is the primary factor determining microneedle design. Numerous studies have been performed on differences between blood glucose levels in blood and ISF.[27–29] It has been generally observed that a time lag exists in the distribution of glucose from blood to ISF. Estimates of the lag time range from 0 to 45 minutes.[28] However, once equilibrium is reached, blood and ISF glucose levels correlate highly. In order to understand design variations between blood extracting microneedles and ISF extracting microneedles, it is important to understand physiological differences between blood and ISF.

Microneedles for Interstitial Fluid Sampling. The depth of microneedle penetration needs to be in the approximate range of 50–150 μm to extract ISF. At these depths, microneedle insertion is painless.[24] Such a low microneedle height requirement translates to a higher latitude in design variations. Microneedles have two possible failure scenarios: fracture or buckling. In general, shorter needles, of the same diameter and material, can withstand higher pressures without failing. Thus, needles composed of relatively lower strength material, e.g., silicon dioxide, can be used for ISF sampling. Silicon dioxide is also highly biocompatible, an additional advantage. Reduced height allows for smaller needle diameters without inducing buckling.[30] A smaller tip diameter results in a much higher ratio of fracture force vs insertion force into skin.[31] This increases the margin of safety for employing microneedles without failure. Microneedle lumen diameters for ISF sampling can typically be as low as 10 μm.

A small microneedle diameter coupled with the low density of ISF induces extremely high capillary forces. Capillary forces also increase with higher hydrophilicity of the microneedle material. This facilitates extraction of the fluid even without a pumping mechanism. Unfortunately, the flow rate through the microneedle declines with decreasing diameter.[32] Thus, an initial latent time exists before the microneedles are filled with ISF.[33] Most commercial ISF glucose sensors require around 0.5–2 μl of fluid,[34] and this figure is continuously decreasing. In order to increase flow rates, an array

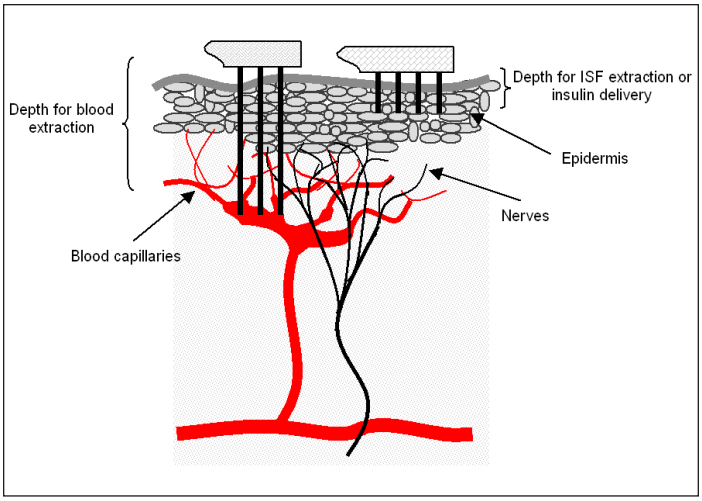

Figure 4. Relative insertion depths of microneedles.

of microneedles is used to achieve the required flow. Vacuum pump-assisted ISF sampling using microneedles in humans has been demonstrated and shown to successfully track changing glucose levels following insulin injection with a time lag of less than 20 minutes.[35]

Microneedles for Blood Sampling. Blood capillaries are present just below the epidermis. Generally, blood microcapillaries are found at penetration depths of about 400 μm. The nerve tips are also present in the same depth vicinity. Thus some microneedles within the array might just graze the topmost nerve cells. However, the extremely small diameters and controlled shank length reduce the odds of encountering a nerve or of stimulating it enough to induce much pain.[36,37] Research that explored the effect of microneedle design on pain in humans found that needles ranging from 480 to 1450 μm in length resulted in pain scores 5 to 40% of a 26-gauge hypodermic needle.[24a] **Figure 4** depicts the relative insertion depths of microneedles used for blood or ISF sampling.

In order to extract blood without significant pain, microneedle shank lengths need to be around 400–900 μm. At these lengths the microneedle needs to be built using higher strength materials such as metal or silicon. A common model used by researchers is the dimension of the female mosquito proboscis.[38,39] The microneedle diameter needs to be large enough to allow convenient passage to the largest blood cells. Also, the larger length necessitates larger diameters to preclude needle failure via buckling. Typical microneedle diameters have to be at least 50 μm wide. Even though capillary action alone can be enough to extract blood, factors such as higher fluid density, larger conduit diameter, and material of choice can mitigate the effect. In such a case, a microfluidic pumping device is needed to generate negative pressure.[38]

Microneedles for the Insulin Delivery Component

Insulin can be delivered into the epidermal region, and thus these microneedles have the same length requirements as those required for ISF sampling. In order to regulate the delivery of insulin, the delivery component would need to incorporate a pumping mechanism controlled via the feedback unit. The active pumping scheme removes the dependence on capillary force. This obviates restriction on material choice based on degree of hydrophilicity. Various kinds of microneedles have been built using polymers,[40,41] metals,[42,43] silicon dioxide,[44,45] and silicon.[46–48] An insulin molecule being small in size, any suitable lumen diameter of microneedle can be chosen and typically ranges from 10 to 100 μm at the tip.

For fluid infusion, flow rates of greater than 1 ml/hour for a single microneedle have been demonstrated.[49] Even with modest rates, and employing a needle array, the requisite amount of dosage can be transferred easily via microneedles. Reduction of glucose levels by insulin delivery using microneedles has been exhibited successfully in animal models.[42,50] Studies have shown a 47–80% drop in glucose levels by 0.05–0.5 units of insulin delivered in this way.

Microneedle Array Design

Deciding the microneedle array specifications (pitch, size of array) is as important as design of the individual microneedle. Microneedles can sometimes get clogged by tissue being trapped in a needle lumen during insertion (beveled-tip[51] or side-opened[52,53] needle designs minimize these effects). Employing numerous needles minimizes the influence of individual needle failures or passage blockages. Also, as mentioned earlier, use of an array formation increases fluid flow rates. The flow rate increases linearly with the number of microneedles in the array. However, care has to be taken not to place needles too close to each other, as otherwise a "bed-of-nails" effect can result in the skin being pushed down uniformly without penetration.[54] Generally, microneedles are placed more than 200 μm apart, and array size can be as small as a few microneedles to hundreds.

Fluid flow through a microneedle is generally assumed to be laminar. It largely depends on the pressure difference across the needle and is set by the microfluidic

pump and the capillary forces. Unfortunately, a fluid-mechanical description of the skin has not been established yet, and thus modeling flow through a microneedle is a complex task, which is complicated further by the fact that biofluids generally exhibit non-Newtonian behavior. Various nonlinear *in vivo* effects, such as liquid absorption in the epidermis, hindrance to fluid motion due to the presence of cells, and saturation, play a role in fluid dynamics. Furthermore, there are present pressure losses due to flow down a microneedle. These can be attributed to entrance losses, drag on the duct walls, and losses as a consequence of specific microneedle geometry (expansions, bends, etc.).[55] Nevertheless, simplified modeling of fluid flow can be used to obtain rough estimates of design variables. To model fluid flow in microneedles, the basic modified Bernoulli equation is often used as an approximation. **Equation (1)** depicts this relation:

$$\Delta p = \mu \frac{128}{\pi} \frac{qL}{D^4} + \rho \frac{8(K_1 + K_2)}{\pi^2} \frac{q^2}{D^4}, \quad (1)$$

where Δp is the pressure drop, q is the flow rate, K_1 and K_2 are macroscopic values that represent inertial minor losses in piping systems, ρ is the density of liquid, μ is the viscosity, D is the diameter of the needle, and L is the length. To establish rough flow rates in microneedles, the Hagen–Poiseuille relation, depicted in **Equation (2)**, is used. This equation describes slow viscous incompressible flow through a constant circular cross section:

$$Q = \Delta p \left(\frac{\pi r^4}{8 \mu L} \right). \quad (2)$$

For n microneedles, the net flow rate gets multiplied by a factor of n.

Application-Specific Considerations and Challenges

Microneedle design for autonomous diabetes therapy needs to account for the nature of application. Microneedles should be robust enough to withstand repeated penetration and extended use without failure. Microneedle reliability is highly crucial as their failure can lead to incorrect or even failed dosage. Even though microneedle insertion and failure force studies have been done,[31,43] extensive characterization of their durability is needed to accurately ascertain their practical lifetime.

Due to prolonged use requirements, the degree of biocompatibility also becomes an important factor. This necessitates that the microneedles comply with stringent precision requirements and adhere to high quality control. The biocompatibility of materials needs to be established clinically. Although silicon is relatively versatile for microneedle fabrication, its degree of biocompatibility can lag as compared to certain metals. Microneedles made of biodegradable polymers[40,41] should also be explored further.

An automated diabetes therapy device constitutes a safety-critical system. The system intends to distance human intervention from its functionality by removing patient and physician from the active loop. The nature of application opens up an assortment of technical, ethical, and legal issues. A discussion of these issues is beyond the scope of this review. However, they would need to be addressed when this technology is put into application.

Technical Merits of Microneedle Use for Diabetes Therapy

Relatively painless insertion and ease of use translate to reduced risk of patient noncompliance and human error. Furthermore, it is speculated that microneedle use would demand minimal medical training. These benefits are especially welcome considering their relevance to diabetic children.

Some researchers believe that the small volumes of insulin passing through the microneedles via auxiliary pumping systems allow for precise quantitative control and continuous delivery. Traditional therapy schemes assume only infrequent administration of insulin and thus need to employ slow-releasing synthetic analogs to replace a basal supply of insulin. Unfortunately, these slow-acting insulins also take longer times to start taking effect. This prevents effective predictions of future blood glucose profiles.[56] By allowing controlled injection over an extended period of time, it becomes possible to deliver short half-life insulin more frequently. Thus the insulin concentration can be maintained within the therapeutic window more accurately.

Alternative to Microneedles

A few noninvasive alternatives to microneedle-based interfaces are currently being developed.[57] Most promising techniques include iontophoresis,[58] electroporation,[59] and use of low-frequency ultrasound.[60] All of these methods can potentially be used for autonomous diabetes therapy systems and, at times, have been shown to have great value to this application. It is imperative that multiple approaches to the same issue are explored simultaneously to expedite the obsolescing of conventional methods.

Conclusion

The dynamics of autonomous diabetes therapy systems include highly complex interdependencies between the various physical and biological entities involved, thus warranting multidisciplinary research initiatives. Optimum utilization of this technology depends on our capacity to identify and resolve, qualitatively and quantitatively, the various parametric entities involved. Successful clinical implementation would entail overcoming numerous challenges in areas of design, fabrication, electronics integration, packaging, deployment, testing, and data interpretation, among many others. The development will necessitate integration of broad advances in a wide variety of fields, namely microfluidics, clinical medicine, cell and molecular biology, physiology, anatomy, microfabrication, information technology, and signal processing.

The confluence of emerging disciplines promises to bridge the biotic (organism) and abiotic (environment) realms in unanticipated ways. The iterative development of a noninvasive, bioengineered interface such as microneedles necessitates a better understanding of the human skin. Seamless coupling to the body surface demands better knowledge of the molecular architecture of the skin as a polymer film and its role as a functional biological unit.

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