Glucose Regulation through Cooperative Molecular Communication

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Abstract—In Type 1 diabetes, the pancreatic beta cells responsible for producing insulin are destroyed by the immune system. Insulin is needed to activate an insulin-dependent glucose transporter, which is responsible for taking glucose into the muscle cell for metabolism. Recent advancements in nanotechnology, bioengineering, and synthetic biology are leading to the artificial beta cell (ABC) closer to reality. In this paper, we model glucose regulation by ABCs as a cooperative molecular communication system, in which the glucose source is seen as the transmitter and the muscle as the receiver. The last absorbs the glucose in the presence of insulin, and the ABC is modeled as a decode-and-forward relay that detects glucose molecules and releases insulin in response. Using this model, we analyze the end-to-end system performance for ABC-assisted glucose regulation by providing closed-form expressions for the probabilities of hyperglycemia and hypoglycemia and the error probability of the system. In addition, we present simulation results for quantifying performance and validation of the analysis.

Index Terms—Cooperative molecular communication, decode-and-forward relay, error probability, glucose, insulin

I. INTRODUCTION

Molecular communications (MC) have numerous advantages over electromagnetic and acoustic communications for biomedical applications. These advantages include the small size of the system components, energy efficiency and bio-compatibility. As a result, MC can be used in a plethora of biomedical applications, such as early tumor detection and smart drug delivery [1]. Moreover, enabled by the use of nanomachines, MC systems are promising to contribute to the Internet of Bio-Nano Things.

In order to increase the transmission range, several works have considered a cooperative MC system (CMCS), where signals from both direct and relay-assisted link are considered to decode the transmitted bit. For instance, in [2], an equal-gain combining scheme was employed in a 3D diffusive drift channel, by optimizing the number of molecules and the decision threshold. Also, the authors of [3] used an energy detection method for the diffusion-based MC network and obtained the optimal position of the relay node. Additionally, in [4], the error performance of the CMCS was optimized among distributed receivers and, in [5], a symbol-by-symbol maximum likelihood detection was proposed for the considered CMCS.

In general, a network of nanomachines in biological system such as the human body performing complex tasks is envisioned to accomplish early detection and treatment of some of the most widespread chronic diseases such as diabetes [6], [7]. Type 1 Diabetes is a chronic autoimmune disease characterized by hyperglycemia and the lack of insulin. More specifically, as described in [6], when a meal is introduced, glucose is released into the bloodstream. The glucose molecules bind to specialized pancreatic cells known as beta cells. After glucose reception and a series of chemical reactions, beta cells produce insulin that moves through circulatory system. When an insulin molecule locates a muscle or an adipose cell binds to a receptor, a major insulin dependent glucose transporter is enabled to transport glucose into the cell, which is then used for metabolism. Finally, after glucose storage, the concentration of glucose into the blood drops. However, the number of pancreatic beta-cells, which are the only cells in the body that can synthesize and release insulin, diminishes, as the person’s age progresses. As a result, if pancreatic beta-cells do not exist, there will be no insulin production, causing unregulated high blood glucose levels.

Recent advancements in nanotechnology and in synthetic biology have led to the creation of artificial beta cells (ABCs), which can secrete insulin and hence substitute pancreatic beta-cells [8]. In this paper, we introduce an information-theoretic approach to model the insulin secretion system via ABCs, which to the best of the authors’ knowledge has not been proposed in the literature, yet. More specifically, insulin secretion and glucose absorption can be modeled as a CMCS, where glucose is the information received by the beta cell, which uses the decode and forward (DF) protocol and retransmits insulin. The muscle or the adipose cell, which serves as the receiver, utilizes the two parallel channels of glucose and insulin and absorbs glucose based on the result of an AND gate. It should be highlighted that, from an information-theoretic aspect, the investigated CMCS can be considered as a two-input two-output binary communication system. To this end, we derive analytical expressions for the probability of hyperglycemia and hypoglycemia and, consequently, the error probability of the investigated system, which can be considered as the probability of erroneous decision at the muscle cell. Finally, simulations validate the analysis and illustrate the performance of the considered system.

II. BIOLOGICAL AND COMMUNICATION MODEL

In this section, we focus on developing an abstract communication-theoretical model that captures some key biological aspects of glucose absorption by the muscle cell.
A. Biological Aspects

Glucose Source: A mechanism that allows glucose to exit the blood vessel is to enter peripheral endothelial cells through fluid-phase endocytosis. Once inside the cell, it may remain unphosphorylated within vesicles of the endocytic system and eventually be transported across the cell through exocytosis [9]. When vesicles fuse with the cell membrane in exocytosis, glucose is released immediately in the extracellular fluid in a discrete way [10].

Channel: After glucose molecules are released by exocytosis, they enter the extracellular fluid which is the space between the endothelial cell and the muscle cell [11]. According to [12], approximately 75% of the extracellular fluid in skeletal muscle is composed of water.

Muscle Cell: In order to absorb the glucose, the GLUT-4 glucose transporter protein needs to be translated from intracellular vesicles to the cell surface membrane of muscle cell. This process is insulin-dependent, meaning that insulin signaling triggers the translocation of GLUT-4 to the cell surface [11]. In addition, the percentage of GLUT-4 transporters on the plasma membrane is regulated by the concentration of insulin, which follows a sigmoidal dose-response curve [13].

B. Biological Conditions

From a communication perspective, depending on the ability of ABCs and the muscle cells to perform correct molecule detection, the following conditions may occur.

Hyperglycemia: A condition, in which glucose concentration in blood vessels is above the normal range, is called hyperglycemia. This occurs, e.g., in Type 1 Diabetes, where the pancreatic beta-cells, which are responsible for the insulin secretion, are destroyed by the immune system.

Hypoglycemia: Conversely, when the blood glucose level becomes too low (e.g., due to too much glucose absorption), the corresponding biological condition is called hypoglycemia.

In this paper, we focus on glucose regulation via insulin generation by ABCs, which serves as a treatment for Type 1 Diabetes.

C. End-to-end Channel Model

Next, we model the insulin-dependent absorption of glucose and its regulation by ABC molecules as a cooperative relay channel. This information-theoretic model enables us to analyze the end-to-end system performance which is relevant for assessing the treatment of Type 1 Diabetes. In particular, we consider a diffusion-based MC network which consists of a transmitter representing a glucose source (node 1), a DF relay representing an ABC (node 2), and a receiver representing a muscle cell (node 3). We also consider a stationary liquid environment with uniform temperature and viscosity. Considering that glucose is released through exocytosis, we model the activation of the glucose source by a binary process considered as on-off keying (OOK) modulation, releasing $Q_1$ molecules of glucose with probability $\pi_1$ for the transmission of bit 1 and zero molecules with probability $\pi_0$ for bit 0. The molecules released by the transmitter are assumed to make Brownian motion following the Fick’s law and propagate towards both the ABC and the muscle cell with diffusion coefficient $D_1$.

If the ABC detects glucose molecules transmitted by the glucose source, it releases insulin molecules, which, from a communication system’s point of view, can be interpreted as a DF strategy with OOK modulation. More specifically, after decoding the information by the glucose source, the ABC performs OOK and transmits to the muscle cell $Q_2$ insulin molecules for bit 1 with diffusion coefficient $D_2$ and zero molecules for bit 0. It is assumed that the ABC is a passive receiver not absorbing glucose molecules in order not to interfere with glucose propagation and not to affect the received signal at the muscle cell, which is in line with [8], where the ABC does not interact with glucose propagation.

Furthermore, the muscle cell is assumed to be an absorbing receiver, which absorbs insulin whenever available whereas absorbs glucose only if sufficient concentration of insulin is simultaneously available. In addition, molecules absorbed by the muscle cell are removed from the environment.

To this end, we consider 3 subsystems, the glucose source to ABC system denoted as (1,2), the glucose source to muscle cell system denoted as (1,3), and the ABC to muscle cell system denoted as (2,3). The number of the received molecules for each receiving node at the $k$-th arrival is given by

$$y_{(a,b)}[k] = N_{(a,b)}^c[k] + N_{(a,b)}^p[k] + N_{(a,b)}^o[k],$$  \hspace{1cm} (1)

where $a \in [1,2]$, $b \in [2,3]$, $N^c$ represents the number of molecules released at the $k$-th arrival from the ABC or the glucose source, $N^p$ represents the inter symbol interference (ISI) for previous transmissions, $N^o$ represents the external noise and $k$ is used to compactly describe the operation of the proposed system in the two time slots. Specifically, for the $n$-th transmission, the glucose transmission occurs at time $k = n$, while insulin transmission occurs at time $k = n + 1$.

1) Glucose to ABC System: As a passive receiver, the ABC is assumed to be able to count the number of molecules within its volume at any time instant, while propagating molecules diffuse through it. The probability of observing a glucose molecule inside $V_2$ at time $t$ is given by [14, eqs. (34), (35)]

$$F_{(1,2)}(t) = \begin{cases} \frac{V_2}{(4\pi D_1 t)^{3/2}} \exp \left( -\frac{d_{(1,2)}^2}{4D_1 t} \right), & r_2/d_{(1,2)} \leq 0.15 \\ \frac{1}{2} \left( \text{erf} \left( \tau_2 \right) + \text{erf} \left( \tau_0 \right) \right) + \sqrt{\frac{D_1}{d_{(1,2)}^2}} \left( e^{-\tau_2^2} - e^{-\tau_0^2} \right), & r_2/d_{(1,2)} > 0.15 \end{cases},$$  \hspace{1cm} (2)
where \( r_s = \frac{r_2 + d_{1,2}}{2\sqrt{D_1}}, \) \( r_a = \frac{r_2 - d_{1,2}}{2\sqrt{D_1}}, \) \( r_2 \) is the radius of the sensing volume of the ABC, \( d_{1,2} \) is the distance between the glucose source and the center of the receiver, \( T \) is the time between arrivals, and \( \text{erf}(\cdot) \) denotes the error function.

At the ABC, the received signal at the current arrival follows the Binomial distribution [14], i.e.,

\[
N^c_{(1,2)}[n] \sim B \left( Q_1 W_1[n], F_{(1,2)} \right),
\]

(3)

where \( W_1[n] \in \{0, 1\} \) is the bit sent from the transmitter at the \( n \)-th arrival and \( F_{(1,2)} = F_{(1,2)}(IT + t_s) \) with \( T \) being symbol duration and \( t_s = \frac{d_{1,2}}{6\sigma_1} \) being the sample time. The ISI is described as the sum of Binomial random variables [3], i.e.,

\[
N^p_{(1,2)}[n] \sim \sum_{i=1}^{L} B \left( Q_1 W_1[n - i], F_{(1,2)} \right),
\]

(4)

where \( L \) denotes the ISI length of the channel. The external noise follows the normal distribution [3], i.e.,

\[
N^\sigma_{(1,2)}[k] \sim N \left( \mu_{(1,2)}, \left( \sigma^2_{(1,2)} \right) \right). \]

(5)

When \( Q_1 \) is sufficiently large and \( Q_1 F_{(1,2)} \) is not zero, (1) can be approximated for system (1,2) by [3]

\[
y_{(1,2)}[n] \sim N \left( Q_1 W_1[n] F_{(1,2)}, Q_1 W_1[n] F_{(1,2)} \left( 1 - F_{(1,2)} \right) \right) + \sum_{i=1}^{L} N \left( Q_1 W_1[n - i] F_{(1,2)}, Q_1 W_1[n] F_{(1,2)} \left( 1 - F_{(1,2)} \right) \right) + N \left( \mu_{(1,2)}, \left( \sigma^2_{(1,2)} \right) \right).
\]

(6)

2) Insulin or Glucose to Muscle Cell System: In the following subsection, both systems with the absorbing receiver, i.e., systems (1,3) and (2,3), are described. For either glucose or insulin transmission and a specific time period, the molecules hitting the receiver can be described by [15]

\[
F_{(a,3)}(t) = \frac{r_3}{r_3 + d_{(a,3)}} \text{erfc} \left( \frac{d_{(a,3)}}{4D_a t} \right),
\]

(7)

where \( r_3 \) is the radius of the receiver, \( d_{(a,3)} \) represents the distance from the center of node \( a \) to the surface of the receiver, and \( \text{erfc}(\cdot) \) denotes the complementary error function. It is worth noting that for the glucose molecules the absorption depends on whether insulin is present.

The received signal at the receiver follows the Binomial distribution [14], i.e.,

\[
N^c_{(a,3)}[k] \sim B \left( Q_a W_a[k], F_{(a,3)} \right),
\]

(8)

where \( F_{(a,3)} = F_{(a,3)}(IT) \) and \( W_a[k], a \in \{1, 2\} \) denotes for a = 1 the bit transmitted by the glucose source and for a = 2 the bit transmitted by the ABC. The ISI is represented by the sum of Binomial random variables, i.e.,

\[
N^p_{(a,3)}[k] \sim \sum_{i=1}^{L} B \left( Q_a W_a[k - i], q_{(a,3)} \right),
\]

(9)

where \( q_{(a,3)} = F_{(a,3)}^{(i+1)} - F_{(a,3)}^{(i)} \). The external noise follows the normal distribution [15], i.e.,

\[
N^\sigma_{(a,3)}[k] \sim N \left( \mu_{(a,3)}, \left( \sigma^2_{(a,3)} \right) \right). \]

(10)

When the system is sufficiently large and \( Q_a F(T) \) is not zero, (1) can be approximated by [15]

\[
y_{(a,3)}[k] \sim N \left( Q_a W_a[k] F_{(a,3)}^{(1)}, Q_a W_a[k] F_{(a,3)}^{(1)} \left( 1 - F_{(a,3)}^{(1)} \right) \right) + \sum_{i=1}^{L} N \left( Q_a W_a[k - i] q_{(a,3)}^{(i)}, Q_a W_a[k - i] \right) \times q_{(a,3)}^{(i)} \left( 1 - q_{(a,3)}^{(i)} \right) + N \left( \mu_{(a,3)}, \left( \sigma^2_{(a,3)} \right) \right).
\]

(11)

III. ERROR PROBABILITY ANALYSIS

The information-theoretic description of the considered CMCS corresponds to a discrete channel with two binary inputs and two binary outputs. The first input-output pair corresponds to the direct link between the transmitter (glucose source) and the receiver (muscle cell), while the second pair corresponds to the cooperative link, i.e., between the relay (ABC) and the receiver. The receiver decides to absorb glucose if it detects both glucose and insulin, i.e., when both outputs are equal to one. In this direction, the receiver absorbs glucose based on the result of an AND gate, thus the detected symbol, i.e., glucose absorption, is obtained by

\[
z = \hat{y}_{(1,3)} \times \hat{y}_{(2,3)},
\]

(12)

where

\[
\hat{y}_{(1,3)} = \mathbb{I} \left[ (1 - W_1) y_{0(1,3)} + W_1 y_{1(1,3)} \geq \xi_{(1,3)} \right],
\]

\[
\hat{y}_{(2,3)} = \mathbb{I} \left[ (1 - W_2) y_{0(2,3)} + W_2 y_{1(2,3)} \geq \xi_{(2,3)} \right],
\]

\( \times \) is the modulo 2 multiplication and \( \mathbb{I} \) is the indicator function. Also, considering that \( W_2 \) denotes the \( \hat{y}_{(2,3)} \), i.e., the detected symbol at the ABC, the detected symbol in (12) also depends on the detection at the ABC, as expected. Thus, \( z = 1 \) when glucose is absorbed by the muscle cell and \( z = 0 \) when it is not absorbed. Also, \( \xi_{(a,b)} \) is the threshold and \( \hat{y}_{(a,b)} \) represents the information bit detected by the receiver in system \((a, b)\). Moreover, using binary hypothesis testing for the two types of receivers in (6) and (11), where \( H_0 \) represents the absence of molecules and \( H_1 \) denotes the presence of molecules, \( y_{x(a,b)} \) is given by

\[
H_x: y_{x(a,b)} \sim N \left( \mu_{x(a,b)}, \sigma^2_{x(a,b)} \right),
\]

(13)

where \( \mu_{x(a,b)} \) is the mean for bit \( x \in \{0, 1\} \) and system \((a, b)\), while \( \sigma^2_{x(a,b)} \) is the corresponding variance, which for the case of the passive receiver, i.e., system (1,2), are given, respectively, by [3]

\[
\mu_{x(1,2)} = x Q_1 F_{(1,2)} + \pi_1 Q_1 \sum_{i=1}^{L} F_{(1,2)}^{(i)} + \mu_W^{(1,2)},
\]

(14)

\[
\sigma^2_{x(1,2)} = x Q_1 F_{(1,2)}^{(0)} \left( 1 - F_{(1,2)}^{(0)} \right) + \pi_1 \sigma_W^{(1,2)} \sum_{i=1}^{L} \left( F_{(1,2)}^{(i)} \right)^2 + \pi_1 Q_1 \sum_{i=1}^{L} F_{(1,2)}^{(i)} \left( 1 - F_{(1,2)}^{(i)} \right) \left( \sigma^2_{x(1,2)} \right).
\]

(15)

Likewise, for the absorbing receiver they are given by [15]

\[
\mu_{x(3)} = x Q_a F_{(a,3)}^{(1)} + \pi_1 Q_a \sum_{i=1}^{L} q_{(a,3)}^{(i)} + \mu_{x(3)}^{(a,3)},
\]

(16)
\[ \sigma_{x(a, 3)}^2 = xQ_a F_{(a, 3)}^{(1)} \left(1 - F_{(a, 3)}^{(1)}\right) + \pi_1 \pi_0 Q_a^2 \sum_{i=1}^{L} \left(q_{(a, 3)}^{(i)}\right)^2 \]

\[ + \pi_1 Q_a \sum_{i=1}^{L} q_{(a, 3)}^{(i)} \left(1 - q_{(a, 3)}^{(i)}\right) + \left(\sigma_{\theta}^{(a, 3)}\right)^2. \] (19)

In the following theorem, we provide the probability of hyperglycemia, i.e., glucose is falsely not detected, and hypoglycemia, i.e., glucose is erroneously absorbed.

**Theorem 1:** The probabilities of erroneous decision at the muscle cell, at the \((n + 1)\)-th arrival, leading to hyperglycemia or hypoglycemia, are given, respectively, by

\[ P_{\text{hyper}}[n + 1] = 1 - Q \left( \frac{\xi_{(1, 3)} - \mu_{1, (1, 3)}}{\sigma_{1, (1, 3)}} \right) \times \left[ 1 - Q \left( \frac{\xi_{(2, 3)} - \mu_{1, (2, 3)}}{\sigma_{1, (2, 3)}} \right) \right] \left[ 1 - Q \left( \frac{\xi_{(1, 2)} - \mu_{1, (1, 2)}}{\sigma_{1, (1, 2)}} \right) \right] \] (20)

\[ P_{\text{hypo}}[n + 1] = 1 - Q \left( \frac{\mu_{0, (1, 3)} - \xi_{1, (1, 3)}}{\sigma_{0, (1, 3)}} \right) \times \left[ 1 - Q \left( \frac{\mu_{0, (2, 3)} - \xi_{1, (2, 3)}}{\sigma_{0, (2, 3)}} \right) \right] \left[ 1 - Q \left( \frac{\mu_{0, (1, 2)} - \xi_{1, (1, 2)}}{\sigma_{0, (1, 2)}} \right) \right] \] (21)

where \( Q(x) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{x} e^{-\frac{t^2}{2}} dt \) is the Gaussian \( Q \) function.

**Proof:** The proof is provided in the Appendix.

**Remark 1:** The probability of erroneous decision at the muscle cell, at the \((n + 1)\)-th arrival, which is defined as the error probability of the considered CMCS, can be obtained as

\[ P_{\text{er}}[n + 1] = \pi_1 P_{\text{hyper}} + \pi_0 P_{\text{hypo}}, \] (22)

which can be expressed in closed form through substituting (20) and (21) in (22).

**IV. SIMULATIONS**

In this section, numerical results validate the theoretical analysis and illustrate the performance of the considered CMCS. It should be mentioned that the numerical results were acquired through Monte Carlo with \(10^6 \) realizations, aiming to simulate the communication process. The diffusion coefficients of the glucose and insulin molecules are calculated by \( D = (k_B T_0) / (6\pi \eta R) \), where \( k_B = 1.38 \times 10^{-23} \) JK\(^{-1}\) is the Boltzmann’s constant, \( T_0 \) is the temperature in K, \( \eta \) is the (dynamic) viscosity of the fluid and \( R \) is the radius of the molecule [14]. The hydrodynamic radius of the glucose and insulin molecules are 0.38 nm and 2.86 nm, respectively [16]. The viscosity of the water is \( 0.6915 \times 10^{-3} \) kg/(m·s) for body temperature \( 37^\circ\)C [17]. As a result, the diffusion coefficients of the glucose and insulin molecules can be calculated as \( D_1 = 864.12 \) \( \mu \)m\(^2\)/s and \( D_2 = 114.81 \) \( \mu \)m\(^2\)/s, respectively. In addition, \( r_2 = 0.4 \) \( \mu \)m, \( r_3 = 0.2 \) \( \mu \)m and \( Q_2 = cQ_1 \), where \( c \ll 1 \), thus the number of molecules released by the glucose source is much greater than the insulin molecules released by the ABC. Also, the thresholds are chosen as the maximum

**Fig. 2.** Error probabilities

**Fig. 3.** Impact of insulin molecules release
determines the corresponding probabilities. The results suggest that the threshold should be prudently selected at the ABC to prevent negative health effects, because it can lead to erroneous decision of muscle cell and potentially cause hypoglycemia or hyperglycemia. It should be highlighted that this insight is in line with the results in [8], where the appropriate utilization of ABCs mitigates these two conditions.

V. CONCLUSION

In this paper, we have proposed a generic model of a CMCS that captures some key biological aspects of glucose absorption. More specifically, through the ABC, insulin can be regulated based on the glucose levels. Furthermore, considering that false decision at the muscle cell can lead to hyperglycemia or hypoglycemia, we have provided a closed-form expressions for the probabilities of hyperglycemia and hypoglycemia and the error probability of the considered system. From the numerical results, it can be concluded that, a big spike in glucose, i.e., high concentration of glucose molecules can improve the system’s error performance and, thus, controlling the insulin molecules and the threshold at the ABC is crucial for minimizing the error at the muscle cell. Future work may include modeling glucose transport through the capillaries, adding drift to the model and including endocytosis uptake as a more realistic model for muscle cell absorption.

APPENDIX

The receiver decides erroneously to absorb glucose or not, leading to hypoglycemia or hyperglycemia, respectively. Thus, the corresponding probabilities are given by

\[ P_{\text{hyper}} = Pr(z = 0|W_1 = 1) = 1 - Pr(\hat{y}_{(1,3)} = 1|W_1 = 1)Pr(\hat{y}_{(2,3)} = 1|W_1 = 1) \]  

(23)

and

\[ P_{\text{hypo}} = Pr(z = 1|W_1 = 0) = 1 - Pr(\hat{y}_{(1,3)} = 0|W_1 = 0)Pr(\hat{y}_{(2,3)} = 0|W_1 = 0), \]  

(24)

where

\[
\begin{align*}
Pr(\hat{y}_{(2,3)} = x|W_1 = x) &= Pr(\hat{y}_{(2,3)} = x|W_1 = x, W_2 = x)Pr(W_2 = x|W_1 = x) \\
&\quad + Pr(\hat{y}_{(2,3)} = x|W_1 = x, W_2 \neq x)Pr(W_2 \neq x|W_1 = x).
\end{align*}
\]

(25)

Depending on the transmission bit, the error probability for system \((a, b)\) is given by

\[ Pr(\hat{y}_{(a,b)} = 1|W_a = 0) = \frac{Q\left(\frac{\xi_{(a,b)} - \mu_0(a,b)}{\sigma_0(a,b)}\right)}{Q\left(\frac{\xi_{(a,b)} - \mu_1(a,b)}{\sigma_1(a,b)}\right)}. \]

(26)

and

\[ Pr(\hat{y}_{(a,b)} = 0|W_a = 1) = 1 - Q\left(\frac{\xi_{(a,b)} - \mu_1(a,b)}{\sigma_1(a,b)}\right). \]

(27)

Substituting (25), (26), and (27) in (23) and (24), (20) and (21) are derived, respectively, which completes the proof.

REFERENCES


