



Cheating the Beta Cells to Delay the Beginning of Type-2 Diabetes Through Artificial Segregation of Insulin

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Abstract. In this paper, we focus in an artificial mechanism to detain the beginning of the type-2 diabetes disease in those identified patients which might to be developing a phase of prediabetes. From purely electrical interactions or Coulomb forces between a deployed nano sensor around of beta cells and Calcium²⁺ ions, we propose an artificial entrance of Calcium ions inside the beta-cells allowing them to segregate insulin. The electrical interactions between positively charged insulin inside beta cells is the main assumption of this paper. The permanent segregation of insulin fits well inside of the architecture of advanced networks engineering that contemplates the usage of a bio cyber interface. Therefore, the artificial releasing of granules with repulsive electric forces of insulin becomes a manner to cheat beta cells. This might be also seen as an option to avoid the intake of prediabetes y diabetes pharmacology for large periods. Although the view of this work is theoretical and prospective, it is based entirely in closed-form physics equations that sustain the main claim of this paper: electric interactions driven by charged nano particles would be a window to stop the progress of diseases based on the induced or spontaneous deficit of proteins, hormones and cells that are crucially needed to maintain the human homeostasis.

Keywords: Diabetes · Beta cells · Insulin

1 Introduction

Nowadays, type-2 diabetes becomes a worldwide issue that requires efforts from all angles of the scientific procedures [1]. Essentially, the disease appears due to the anomalous functionality of the beta cell that is not capable to segregate insulin. It has well-defined consequences against the homeostasis in human beings. In fact, the onset of the disease might not have signals, however there is a progressive and in some cases might be called aggressive behavior of the disease in the sense of the degradation of key organs such as kidneys, heart and the vascular system for large terms. Commonly, one sees the existence of two well-defined phases: the prediabetic and diabetic. Normally when the patient presents

lectures of fasting glucose test above 130 mg/dL, the endocrinologist gives a diagnostic of type-2 diabetes. Thus, the diabetic patient has crossed the line that separates the prediabetic and diabetic states and is strongly recommended to intake among various types of pharmacology the well-known metformin. Therefore, patients might to continue with this intake for large periods, however it does not guarantees to locate to the patient away from risk situations [2].

The deficit to segregate insulin is a fact entirely related to the well-known beta cells that are responsible to segregate in an unstoppable manner the granules of insulin. The action to segregate insulin has as previous action the mechanism of depolarization by which the beta cell creates a voltage that allow the entrance of Calcium²⁺ ions [3]. Once these ions reach to enter inside the cell, the insulin is segregated. This process is fully spontaneous and only requires charged ions as external agents to achieve the segregation of insulin. The why beta cells cannot segregate insulin then might be derived from

- the Calcium ions are far away from the beta cells, so there is not physical contact between them, thus insulin remains inside the beta cells and all of them acquire a sterile state.
- the Calcium ions achieve to enter inside the beta cells but are not enough to push out the insulin, so the problem is seen as a lack of volume of Calcium ions [4].

Based on these facts, emerges the idea of cheating in the sense of reconfigure the scenario of insulin segregation but using artificial methods. One of them might be entirely in the territory of physics that can explain the processes of insulin production. Certainly the application of physics principles and subsequently equations, requires the understanding of the phenomenon. Once it is done we can use all those equations that fits well with the dynamics and interactions among the elements of system.

Because in one hand we have the fact of the entrance of Calcium ions through the beta cells, then the physical property that emerges as a key piece to achieve the segregation of insulin becomes the sign of the electric charge of such ions. Thus, we identified that occurs to some extent the processes of electric interactions either outside or inside the beta cell. Although literature have not explained in all the involved processes that are done because the electric charge [5], in this work we claim that the entrance of Calcium²⁺ inside the beta cell involves a scenario of Coulomb interactions essentially between the insulin granules and Calcium ions.

In this manner, while from the physics view we see that the segregation is a purely dynamical situation, then it should be due to the physical causes such as the electric forces between Calcium ions and the electric charge of the insulin still inside of the beta cell. In this paper we propose a mechanism that would inhibit to those prediabetic patients to be apart from a possible acquisition of the disease as well as to avoid the intake of pharmacology. To do that, we present a physics-based scheme that allows us to cheat beta cells targeting their segregation of granules of insulin through the presence of nano device that would controls the volume of segregated granules.

Second section is entirely devoted to the derivation of the main equations that are responsible to the production of insulin. Third section presents the results of paper, while in fourth section the proposal to engage the mechanism of insulin segregation is given. Conclusion of paper is drawn in last section.

2 The Physics Foundations for Cheating

Inside the context of insulin production, we define “cheating” as the action that allows us to stimulate with artificial methods the production of insulin with external nano devices that contain a electric charge. In this view, these proposal would demand the usage of physics equations.

In order to derive equations that would describe the artificial segregation of insulin by the beta cells we assume that

- beta-cell contains a volume,
- beta-cell has a certain density of granules of insulin inside,
- insulin has an electric charge whose sign might not be well defined (For example, Pizarro-Delgado [6] has shown the releasing of insulin in Langerhans islets once were depolarized through an experimental model.),
- insulin would react by electric interactions around,
- beta-cell carry out the processes of depolarization,
- the entrance of Calcium in the beta-cell is a cause for the segregation of insulin.

According to experiments done in the past, insulin is released from beta cell as a response to the processes of depolarization, fact that would suggests that the releasing is strongly based on the electrodynamics of ions more than purely biochemical processes.

Consider ρ_{Ca} as the density of Calcium 2+ ions moving inside the beta cell. Then there is a linear relationship between these ions and the segregation of insulin:

$$\rho_{Ca} = \gamma \rho_I \quad (1)$$

where ρ_I the density of granules of insulin leaving the beta cell and γ a constant of proportionality. When both densities are electrically charges each other then both have a total charge in the sense that

$$Q_{Ca} = \int \rho_{Ca} dV \quad (2)$$

$$Q_I = \int \rho_I dV, \quad (3)$$

thus we can propose a repulsion or attraction force between them by assuming Coulomb interactions [7]:

$$\mathcal{F} = \frac{1}{4\pi\epsilon_0} \frac{Q_{Ca} Q_I}{|\mathbf{x} - \mathbf{x}'|^2}, \quad (4)$$

and the energy that the system expends to apart from each other that is translated as the required energy to move out granules of insulin is given by:

$$\mathcal{W} = \int \mathcal{F} d\mathbf{x} = \frac{1}{4\pi\epsilon_0} \int \frac{Q_{Ca} Q_I d\mathbf{x}}{|\mathbf{x} - \mathbf{x}'|^2}. \quad (5)$$

Clearly this energy is not controllable but while we can control the dynamics of the Calcium ions, then the system is under control. Therefore to impose controllability on the Calcium ions, we need an external agent that acquires the role of exert movement to the Calcium ions located around the beta cells. Prospective and ideas about the deployment of nano devices is seen in [8].

The next step is to represent in a closed-form a solution for each density. In the case when these solution are time-dependent then a good choice is the usage of the diffusion equations as follows

$$\frac{\partial \rho_{Ca}(s, t)}{\partial t} = D_1 \nabla^2 \rho_{Ca}(s, t) \quad (6)$$

$$\frac{\partial \rho_I(s, t)}{\partial t} = D_2 \nabla^2 \rho_I(s, t) \quad (7)$$

where D_1 and D_2 the diffusion constants for both cases. To note that the usage of the diffusion equation demands to assume that the densities have explicit dependence on the time.

2.1 Naive Derivation of the Releasing of Granules of Insulin

We define ρ_R as the density of the released granules of insulin. In virtue of Eq. 1 we write down a generalized relation involving densities

$$\rho_R = \gamma \mathcal{F} \Delta V \Delta T \quad (8)$$

that express the fact that the amount of released granules of insulin depends directly on the constant γ as well as the electric force between the charges inside the beta cell and the charges outside the cell. The exerted granules would also depend on the volume of the cell and the time that takes the electric interaction. Equation 8 becomes the fundamental equation of balance of segregation of insulin by the beta cell. Commonly, classical pharmacology as metformin induces the segregation and it can take a time to reach an optimal value. Thus it the optimal releasing of insulin would depend entirely on time after the biochemical reactions have ended. Thus we can understand this as

$$\frac{d\rho_R}{dt} = \Delta V \Delta T \frac{d(\gamma \mathcal{F})}{dt} + (\gamma \mathcal{F}) \frac{d(\Delta V \Delta T)}{dt} = 0 \quad (9)$$

to find their maximum and minimum values. A straightforward algebra with $d(\Delta V \Delta T) - \Delta V dt = 0$ yields that

$$\gamma \mathcal{F} = \text{Exp} \left[-\frac{t}{\Delta T} \right] \quad (10)$$

When the result is inserted in Eq. 8 we get

$$\rho_R = \text{Exp} \left[-\frac{t}{\Delta T} \right] \Delta V \Delta T \quad (11)$$

turning now to a more realistic interpretation of Eq. 11 we adjudicated to ρ_R the following meaning: the number of granules of insulin per unit of volume and per unit of time, thus

$$\rho_R = \frac{N_R}{\Delta V \Delta T} = \text{Exp} \left[-\frac{t}{\Delta T} \right] \Delta V \Delta T \quad (12)$$

thus the N_R can be written as

$$N_R = \text{Exp} \left[-\frac{t}{\Delta T} \right] (\Delta V)^2 (\Delta T)^2 \quad (13)$$

and with the frequency $\omega = \frac{1}{\Delta T}$ and $N_0 = \Delta V^2$ we have

$$N = N_0 \frac{\text{Exp} [-\omega t]}{\omega^2}. \quad (14)$$

The frequency is clearly understood as the inverse of the periods by which the releasing is done. These periods are determined by the electric interactions between the granules of insulin and the Calcium 2+ ions.

2.2 Full Usage of Physics: Electrodynamics and Diffusion Equations

Inspired on Eq. 8 that encloses the physics of the action of releasing the insulin granules, we consider the electric force as a possible cause to produce displacements and dynamics associated to the charge density. In this manner Eq. 1 can be rewritten as

$$\rho_R = \gamma \rho_{Ca}(\mathbf{r}, t) \rho_I(\mathbf{r}, t) d^3 \mathbf{r} dt \quad (15)$$

where the integration runs over the volumes containing the total charges as $q = \int \rho dV$. We remark the presence of γ that can be perceived as the quantity that is human controllable and to some extent depends on the external physical variables.

In this manner γ is to be defined entirely inside of the territory of the electromagnetic propagation as we shall see along the next sections. In fact, external physical variables might have capabilities to regulate the electric force between the Calcium ions and their effect on the granules of insulin inside the cell. The next steps in this analysis require the following assumptions:

- the variation of the Calcium ions density would have consequences on the cells;
- the density of Calcium ions is controllable by an external device;
- the external device is dependent on the electromagnetic pulses monitored by a bio cyber interface;

- the presence of nano devices around the beta cells do not alter the biochemical reaction inside the Langerhans islets.

In virtue to the previous assumptions we can propose up to 2 well established scenarios:

Scenario I

This first scenario considers that γ is a constant and the density of released granules is in essence dependent on the Coulomb-like character of the interactions that take place inside the Langerhans islets,

$$\rho_R(\omega) = \frac{dN_R}{dV} = \gamma \rho_{Ca}(\mathbf{r}, t) \rho_I(\mathbf{R}, t) \quad (16)$$

so that the number of released granules is derived in a straightforward manner and it reads as

$$N_R = \gamma \int \rho_{Ca}(\mathbf{r}, t) \rho_I(\mathbf{R}, t) dV. \quad (17)$$

Therefore we can estimate the number of granules from the solutions of the diffusion equation for both charge densities. It should be noted that whereas \mathbf{r} describes the vector that defines the position of the Calcium 2+ ion, \mathbf{R} denotes the position of the insulin granule, so the integration runs over the volume $d^3\mathbf{R}$ that would enclose the granules. Concretely, these granules are all those that are being displaced by the Coulomb force exerted by the Calcium ions. Clearly, the repulsion is the case that fits with the action of segregation. Thus, as long as both charge distributions have same electric charge then the repulsion is imminently expected. Subsequently, the exact expression that might be able to estimate the number of released insulin granules is written as

$$N_R = \gamma \int \left[\int \rho_{Ca}(\mathbf{r}, t) d^3\mathbf{r} \int \rho_I(\mathbf{R}, t) d^3\mathbf{R} \right] dV \quad (18)$$

Scenario II

Because the dependence on a frequency as incorporated in Eq. 14 is justified on the basis that the Calcium ions dynamics that would depend of the strength of the electric force intensity between it and an external nano device, then in virtue of Fig. 1 the full electrodynamics of system might be described in terms of the electromagnetic pulses [9] that are sent by the external bio cyber interface to the nano device. Clearly, is the nano device is also a charged object then it exerts electric force either repulsion or attraction on the Calcium ions.

Thus γ encloses information about the electromagnetic pulse intensity. In this manner $\gamma \rightarrow I(\omega, t)$ denoting the well-known function of classical radiation that is sent by the bio cyber interface. Therefore we relate out that the induced releasing of granules of insulin depends entirely on the displacements of Calcium ions. On the other side the charge density of these ions are then fully dependent on the frequency of the pulses ω . Therefore the number of released granules is written in a straightforward manner as:

$$\rho_R(\omega) = \frac{N_R}{dV} = I(\mathbf{r}, \omega, t) \rho_{Ca}(\mathbf{r}, t) \rho_I(\mathbf{R}, t) \quad (19)$$

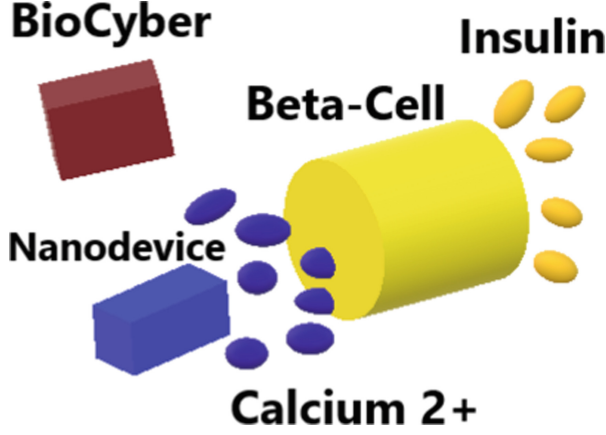


Fig. 1. Schematic representation of the action of cheating beta cells with Coulomb electric forces. The bio cyber interface sends an electromagnetic field characterized by a frequency ω to nano devices whose role is that of exert electric force to the Calcium $2+$ ions to guarantee their entrance the beta cell and therefore to be able to senegregate granules of insulin.

Thus, the net number of released insulin granules by one beta cell is governed by the following master equation:

$$N_R(\omega) = \int I(\mathbf{r}, \omega, t) \rho_{Ca}(\mathbf{r}, t) \rho_I(\mathbf{r}, t) dV dt. \quad (20)$$

Generalizing previous equation for N cells, we have the total for these cells

$$N_R(\omega) = \sum_q \int I(\mathbf{r}, \omega, t) \rho_{Ca}(\mathbf{r}, t) \rho_{I,q}(\mathbf{r}, t) dV_q dt. \quad (21)$$

3 Results and Simulations

To solve the charge densities through the usage of the diffusion equation $\frac{\partial}{\partial t} \rho(\mathbf{r}, t) = D \nabla^2 \rho(\mathbf{r}, t)$ where D the diffusion's constant. For the particular case we search for a methodology that offers a closed-form solution for both the Calcium ions and the insulin granules inside of the beta cells by using standard closed-form techniques for solving the diffusion equations we have assumed that nanodevice and beta cells have a cylindric geometry. Therefore with all this we arrive to analytic solutions as shown below,

$$\rho_{Ca}(r, z, \theta, t) = \sum_{\ell=-\infty}^{\infty} \frac{e^{-\lambda D_C(t-t_0)} \text{Sin} \left(\frac{n_1 \pi z}{z_1} \right) \text{Sin} \left(\frac{n_2 \pi \theta}{\theta_1} \right) J_{\ell}(qr)}{J_{\ell}(qr_1) J_{\ell}(qr_2)} \quad (22)$$

$$\rho_1(r, z, \theta, t) = \sum_{m=-\infty}^{\infty} \frac{e^{-\lambda D_I(t-t_0)} \text{Cos}\left(\frac{n_1 \pi z}{z_2}\right) \text{Cos}\left(\frac{n_2 \pi \theta}{\theta_2}\right) J_m(qr)}{J_m(qr_3) J_m(qr_4)}, \quad (23)$$

where D_C and D_I correspond to the diffusion constants for the Calcium ions and insulin respectively. The quantities r_1, r_2 and r_3, r_4 denote the radial distances in both cylindrical geometries of ion and the receptor beta-cell. All of them were used as boundary conditions for solving the radial part of the differential equations. Below in Fig. 2 both Eqs. 22 and 23 are plotted for $\lambda D(t - t_0) \gg 1$ so the exponential is nearly to 1. The apparition of peaks is perceived as a consequence of the usage of the integer-order Bessel function being these functions the solution to the radial part of the diffusion equation.

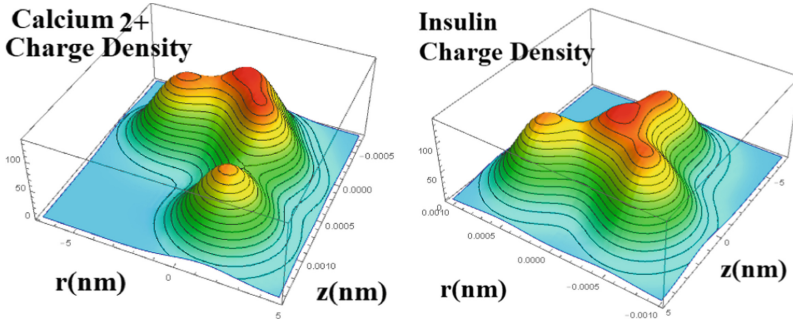


Fig. 2. The 3D plots of Eqs. (22) and (23). Left side: the case where Calcium 2+ by assuming roughly a cylindric flux of Calcium. Right side: the insulin as function of radius and length of the cylindric shape of beta cell.

3.1 The Description of the Electromagnetic Pulse

To model $I(\mathbf{r}, \omega, t)$ accurately, it is required the usage of the Friis equation. We turn now to explicitly define the electromagnetic pulse which is assumed to be emitted by the bio-cyber interface and received by the nanodevice. Intuitively one can assume that the received signal might be modeled at first instance by the Friis-like equation [10] $I(\omega) = I_i(\omega) \frac{A_n A_i}{(d\lambda)^2}$ where A denotes the effective distances whereas d the average separation distance and λ corresponding to the emitted pulse. Therefore we focus on the form of $I_i(\omega)$ as function of the emitted intensity by the bio-cyber interface and can be write down as

$$I(\omega, r, \theta, t) = \frac{A_n A_i}{(d\lambda)^2} e^{-i(\omega t - \frac{2\pi}{\lambda} r)} \eta \frac{|I_0|^2}{8\pi^2 r^2} \sin^3 \theta \quad (24)$$

that it does not depends on the z . To note $|I_0|$ denotes the pulse intensity. Therefore the full flux of released insulin granules per volume and time units dictated by Eq. 19 and together with the solutions Eqs. 22 and 23 becomes entirely dependence from the frequency ω and it is given for $t_0 = 0$ as:

$$\rho_R(\omega) = \int (AI_0)^2 e^{-i(\omega t - \frac{2\pi}{\lambda} r)} \eta \sin^3 \theta \times e^{-\lambda(D_C + D_{IN})t} \times \frac{\text{Sin}\left(\frac{n_1 \pi z}{z_1}\right) \text{Sin}\left(\frac{n_2 \pi \theta}{\theta_1}\right) \text{Cos}\left(\frac{n_1 \pi z}{z_2}\right) \text{Cos}\left(\frac{n_2 \pi \theta}{\theta_2}\right) J_m(qr) J_\ell(qr)}{(d\lambda)^2 8\pi^2 r^2 J_\ell(qr_1) J_\ell(qr_2) J_m(qr_3) J_m(qr_4)} dV dt. \quad (25)$$

resulting that exists there a direct dependence on the pulse intensity and the areas due to the Friis-like approximation.

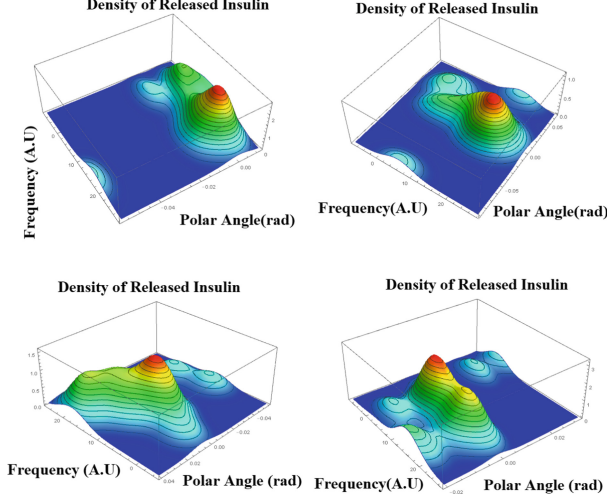


Fig. 3. Plots of Eq. 25. The charge density of the released granules of insulin as function of the frequency (arbitrary units) and the polar angle. Top left panel: the released might be seen as discrete packets, one prominent packet is observed. Top right panel: Secondary packets are segregated apart from the main one. Bottom left panel: packets are segregated as consequence of the increasing of the frequency of pulses. Bottom right panel: frequency can tune the segregation as seen in figure.

The modeling of the pulse intensity is inspired on the one derived from the half-wave dipole approximation [11]. However one can anticipate a clear limitation of the present model as to use intensities that actually would hazard human tissues. So the usage of those intensities over the range of small radiation exposure deserves a wide treatment. Therefore the intensity I_0 is assumed to be fixed and with the lowest values by allowing an acceptable signal reception by the nanodevice [12–14]. We can see that the integration over t , z , and θ turns out to be in a straightforward manner. The integration in the radial component requires a different analysis. Thus as a first task we can anticipate the dependence of the insulin releasing by the beta-cells with respect to the frequency of the arriving pulses to the nanodevice.

In Fig. 3 top and bottom: left and right panels are displayed the 3D distributions from Eq. 25 where the density $\rho(\omega)_R$ is plotted against the polar angle and frequency. Here are displayed the number of released granules of insulin as function of θ and frequency. Clearly the releasing of insulin is given through packets fact that is perceived in the peaks as consequence of the presence of the sinusoid functions \sin and \cos and the Bessel functions. One can also see that this density of granules of insulin decreases with the frequency of communication between the cyber-human interface and nano device [15, 16]. However, one can see the presence of peaks for certain values of frequencies that is interpreted as possible events of hyperinsulinism.

3.2 The Time-Frequency Dependence

The temporal contribution to the integration Eq. 25 can be done quickly. For the sake of simplicity we shall consider the real part so that the integration yields a closed-form expression as:

$$\rho_R(\omega) = e^{-(D_C + D_{IN})T} \frac{[(D_C + D_{IN})\cos\omega T - \omega\sin(\omega T)]}{(D_C + D_{IN})^2 + \omega^2} \quad (26)$$

Equation 26 can be written in a most compact form that would yields another morphologies of the curves of insulin segregation by the beta-cells. Thus, we define $\Delta = \mu\sin\gamma$ and $\omega = \mu\cos\gamma$ that implies that $\mu = \sqrt{\Delta^2 + \omega^2}$ where $\Delta = (D_C + D_{IN})$ so in this manner we have that $\gamma = \tan^{-1} \left[\frac{(D_C + D_{IN})}{\omega} \right]$ and the frequency-dependence of the insulin granules per beta-cell can be written as

$$\rho_R = e^{-\Delta t} \left\{ \frac{(\sqrt{\Delta^2 + \omega^2})\sin \left[\text{Tan}^{-1} \left(\frac{\Delta}{\omega} \right) - \omega T \right]}{\Delta^2 + \omega^2} \right\} \quad (27)$$

In Fig. 4 the density of released insulin as function of time and frequency by following Eq. 27 are plotted. We present two cases where the releasing is done through the emission of well-defined packets (left side) whereas the scenario where the emission is limited to some values of frequencies [17] is seen in right side. The fact that the existence of a oscillatory behavior triggers the idea that the electric energy is governed by a full process of oscillatory dynamics by which a Hamiltonian or Lagrangian can be adjudicated. Therefore the process of cheating might be governed by aspects of energy between the Calcium ions and the insulin inside the beta cells.

3.3 When the Cheating Fails

Of course, not all electric interactions can be successful since the population of Calcium 2+ ions and granules of insulin belong to any well-established statistical distributions. Although this is beyond of the scope of this work, the

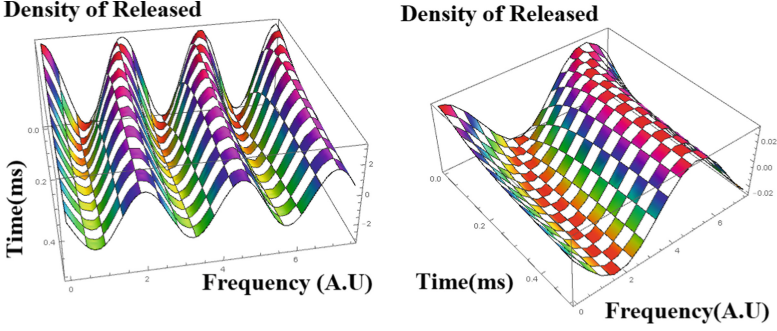


Fig. 4. The insulin density as given in Eq. 27 when $(D_C + D_{IN}) \approx 1.5$. The resulting surfaces contain a successive sequence of peaks for different frequencies and periods as consequence of the usage of the integer-order Bessel functions.

artificial process for cheating might fail for certain times. Thus ρ_R is null when $\sin [\text{Tan}^{-1} (\frac{\Delta}{\omega}) - \omega T] = 0$. As consequence of this, we have that $\text{Tan}^{-1} (\frac{\Delta}{\omega}) - \omega T = 0$. Then we can arrive to $\Delta = \omega \text{Tan}(\omega T)$, as seen before, $T = t - t_0$ is the difference between the first segregation and the subsequent ones, thus one expects that for large times there is also a substantial probability to expect that the expected cheating might fail. Although the Coulomb forces are imminently of character deterministic, the processes to push out granules of insulin from the beta cell might be a process entirely governed by stochastic events. In fact, we can propose a probability distribution function that regulates this segregation and it reads as: $\mathcal{P}(r, \omega) = P_0 \text{Exp} \left[-\frac{r^2 \omega \text{Tan}(\omega T)}{\Delta} \right]$, where P_0 a normalization constant and r the radial distance between the granule of insulin and the Calcium $2+$ ion.

4 Conclusion

Along this paper we have presented a methodology based on physics laws that would allows us to cheat beta cells in order that all of them can acquire capabilities to segregate insulin. This proposal relies entirely on the presence of a nano device that exert electric force on the beta cells in order that the segregation of granules of insulin fulfill the requirement of stabilize the patient to do not surpass the line that separates of being or not being a diabetic patient. Nano devices or nano robots [18] are expected to play a relevant role to improve the quality-of-life of diabetic patients. In the present paper we have obtained simulations that demonstrate the prospectiveness of the proposed method that would cheat beta cells through electrical interactions. Although the procedure

of cheating is not efficient in all, the cheating might be restricted to some values of frequency. The results of this paper would indicate us the potential usage of bio cyber interface as the proposed inside the framework of the Internet of Bio Nano Things [19].

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