Modeling the Dynamics of Amyloid Formation of Islet Beta Cells under Therapeutic Interventions and its Role in Discovery of Novel Target for Drug Action

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Abstract - **Islet Amyloid Polypeptide (IAPP or amylin) is a protein which was first discovered in the year 1987. It is co-expressed and cosecreted in the β islet cells of the pancreas along with insulin. IAPP forms amyloid plaques in diseased states like type II diabetes mellitus (T2DM) and Hypertension. These comorbidities play an important role in development of cardiovascular diseases(CVD). Thus, control of amyloidosis is vital in prevention and management of T2DM and CVD. In this work, we model the dynamics of amyloid formation of islet beta cells under therapeutic interventions. According to this model the effects of drug therapy on amyloid formation are given by a system of ordinary differential equations and a partial differential equation. The model is then converted into a system of ordinary differential equations and the equilibrium points are computed and their stability is studied. Also, numerical simulations are performed on the model and we conclude that amyloidosis can be controlled in the presence of therapeutic intervention.**

Key words - IAPP; Diabetes Mellitus; Drug Therapy; CVD; Hypertension

I Introduction

Islet Amyloid Polypeptide (IAPP or amylin) is a protein which was first discovered in the year 1987 [6]. It is coexpressed and cosecreted in the β islet cells of the pancreas along with insulin [5]. IAPP polymerises and forms amyloid fibrils consisting of abnormal extracellular deposits of this protein. Amyloid when present is always abnormal and consists of an insoluble protein precipitate, composed of these IAPP monomers arranged in a β-pleated sheet structure. This Amyloid is a pathological feature of type II diabetes mellitus (T2DM) and studies have shown that the formation of these IAPP oligomers result in β cell loss in T2DM [9].

T2DM is characterised initially by a condition of insulin resistance and later progresses towards insulin dependence. Nearly all type II diabetics exhibit these amyloid plaques in the pancreas composed of IAPP [15]. The severity of the disease appears to correlate with the degree of plaque deposition. Since the islet cells also produce insulin, this accounts for insulin dependence in T2DM. Since insulin and IAPP are cosecreted, as a consequence of their co-regulation, increased insulin requirement as in states of insulin resistance, will lead to increased production of both insulin and IAPP [3]. High concentrations of the monomer protein promote their aggregation and fibril formation and thus insulin resistance is prone to promote islet amyloidosis from IAPP [3]. Many in vitro studies have shown that IAPP fibril formation can cause death of β cells by inducing apoptosis [7]. Already in 1994 it was shown that amyloidogenic human IAPP (hIAPP) is cytotoxic when added to islet cells in vitro, indicating that amyloid formation may directly kill cells. However, more recent studies have provided strong support for the notion that it is the process of amyloid fibril formation, rather than the mature amyloid fibril itself, which is the most cytotoxic [18].

In addition to T2DM, there are studies which show that hyper-

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tension causes functional and structural changes in the pancreatic islet [19]. Hypertension, a multifactorial-polygenic disease, interacts with multiple environmental stressors and results in functional and structural changes in numerous end organs, including the cardiovascular system. We have literature which show various classes of antihypertensive drugs delaying or preventing damage to the vulnerable pancreatic islet, and thus delaying the development of type 2 diabetes mellitus [8]. There is evidence that the various classes of antihypertensive drugs have different metabolic and structural effects, which may ultimately delay, or prevent the onset of the development of T2DM. Thus, hypertension and type 2 diabetes mellitus (T2DM) are common comorbidities that are associated with substantially increased cardiovascular disease (CVD) morbidity and mortality [8]. Hence, theoretical nonpharmacologic interventions represent an important complementary and essential approach to prevention of amyloid formation.

From literature we find that amyloid formation occurs by a process called nucleated polymerisation [16, 17]. The amyloid fibril is not a monomer but a polymer or an oligomer. These amyloid fibrils increase their length by attaching units of IAPP in a string like manner. Once, the fibril is formed, it no longer remains normal like the IAPP monomer. Proteins must properly fold into three dimensional structures in order to carry out their proper functions within the cell and the system. Dysfunctional protein aggregation, intracellular events like misfolding or unfolding of native protein exposes hydrophobic regions. Conformational changes result in unstable intermediates that have a propensity to form oligomers. Oligomers form pathogenic subunits and crossed beta-pleated sheets. In the case of T2DM, amyloid fibrils are formed with subsequent stabilisation by accessory molecules, such as serum amyloid P, perlecan, and apolipoprotein E [10] . When precision folding goes awry, the misfolded, soluble oligomeric proteins begin to accumulate, become toxic, and promote apoptosis [11]. Misfolded IAPP stabilises into crossed beta-pleated formations that are deposited within the adjacent surrounding extracellular matrix, resulting in space occupying lesions within the islets of the pancreas [7]. Once, the fibril is long enough, it wraps into a helical shape called the nucleus and forms stabilizing bond. It then becomes stable. The amyloid polymers can consist of thousands of monomer units [12]. These may split further into two smaller polymers which can lengthen further. If the split polymer or oligomer falls below a critical length, it is unstable and hence it dissociates into normal IAPP monomers. In this work, we model the process of amyloidosis by nucleated polymerisation under the effects of drug therapy. Animal studies, and human autopsy material have directly shown that islet amyloidosis is associated with increased beta cell apoptosis and reduced beta cell mass [8]. These findings support an important role of islet amyloid formation in development of beta-cell failure and ultimately hyperglycemia in T2DM [13]. Being a common pathogenic factor in an otherwise heterogeneous disease, islet amyloid is an attractive target for development of novel therapeutic strategies for T2DM [2]. Harmful effects on islet beta cells and insulin-producing capacity will be prevented by inhibiting aggregation and fibril formation from this amyloidogenic protein by the use of beta sheet blockers [8], heparin sulfate proteoglycan derivatives, serum amyloid P (SAP) inhibitors or vaccination strategies [10]. There are also various classes of antihypertensive drugs which have different metabolic and structural effects, which help in prevention of amyloidosis and thus in turn preventing the onset of the development of T2DM [2].

In this work we model the dynamics of amyloid formation of islet beta cells under therapeutic interventions. According to this model the effects of drug therapy on amyloid formation are given by a system of ordinary differential equations and a partial differential equation. The model is then converted into a system of ordinary differential equations and the equilibrium points are computed and their stability is studied. Also, numerical simulations are performed on the model and we conclude that amyloidosis can be controlled in the presence of therapeutic intervention. This paper is organised as follows: In Section 2, the model which is a coupled system consisting of ordinary differential equations and a partial differential equation is derived . In Section 3, the model is converted into a system of ordinary differential equations and the equilibrium points are computed. In Section 4, the stability of the steady states are studied. In Section 5, the numerical simulations for the model is presented and the conclusions are given in Section 6.

II THE MODEL

In this section, we model the dynamics of polymerisation of human islet amyloid polypeptide (HIAPP or IAPP) in Type II diabetes under the effects of therapeutic interventions. Let $M(t)$

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denote the population of IAPP monomers at time t, $p(x,t)$ be the population of IAPP polymers of length x at time t and $D(t)$ denotes the amount of the drug in the system at time t.

Let A denote the constant rate of production of IAPP monomers in the pancreatic beta cells and g be the constant rate of degradation of the IAPP monomers due to metabolic processes.

r is the conversion rate of IAPP monomers to polymers. The IAPP monomers are converted at a rate proportional to the population of the total number of polymers $\int_{x_0}^{\infty} p(x,t)dx$.

Let $b(x)$ be the binary splitting rate of the IAPP polymers of length x and $f(x,y)$ be the probability density function that a polymer of length y splits into one of length x and another of length $y-x$.

x_0 is the critical length of the polymer below which the IAPP polymer degrades into normal IAPP monomers.

Thus, the rate of change of the monomer population is given by

$$\begin{aligned}\frac{dM(t)}{dt} &= A - gM(t) - rM(t)\int_{x_0}^{\infty} p(x,t)dx + \\ &\quad 2\int_0^{x_0} x\int_{x_0}^{\infty} b(y)f(x,y)p(y,t)dydx\end{aligned}$$

The term $2\int_0^{x_0} x\int_{x_0}^{\infty} b(y)f(x,y)p(y,t)dydx$ is the number of IAPP monomers acquired when a IAPP polymer splits with at least one polymer lesser than the critical length x_0.
The assumption is that such a IAPP polymer dissociates into IAPP monomers. The 2 in the above equation accounts for the binary splitting of the IAPP polymer into two polymers when it's length exceeds the critical length x_0. In our work, we assume the lengths of IAPP polymers to take continuous values for mathematical tractability. Also, from in vitro and in vivo studies (as discussed in refer papers), the polymer lengths are seen to range over large number of IAPP monomers.

$m(x)$ is the constant rate of degradation of the IAPP polymers due to metabolism. k_2 denotes the rate at which the polymer population gets reduced due to the presence of the drug. $-rM(t)\frac{\partial p(x,t)}{\partial x}$ accounts for the loss of IAPP polymers of length x due to lengthening. $2\int_x^{\infty} b(y)f(x,y)p(y,t)dy$ denotes the number of IAPP polymers which are added to the polymer population when longer polymers split into polymers of length x.

Therefore, the rate of change of IAPP polymers is given by

$$\begin{aligned}\frac{\partial p(x,t)}{\partial t} &= -rM(t)\frac{\partial p(x,t)}{\partial x} - (m(x)+b(x)+k_2D(t))p(x,t) + \\ &\quad 2\int_x^{\infty} b(y)f(x,y)p(y,t)dy\end{aligned}$$

k_0 denotes the rate at which the drug is degraded from the system due to metabolic processes and k_1 is the rate at which the drug increases in the system.
Therefore, the rate of change of drug in the system is given by

$$\frac{dD(t)}{dt} = -k_0D(t) + k_1D(t)\int_{x_0}^{\infty} p(x,t)dx$$

Combining the three equations along with the initial conditions and boundary conditions, the model of dynamics of polymerisation of human islet amyloid polypeptide (HIAPP or IAPP) in Type II diabetes under the effects of therapeutic interventions is given by

$$\begin{aligned}\frac{dM(t)}{dt} &= A - gM(t) - rM(t)\int_{x_0}^{\infty} p(x,t)dx + \\ &\quad 2\int_0^{x_0} x\int_{x_0}^{\infty} b(y)f(x,y)p(y,t)dydx \\ \frac{\partial p(x,t)}{\partial t} &= -rM(t)\frac{\partial p(x,t)}{\partial x} - (m(x)+b(x)+ \\ &\quad k_2D(t))p(x,t) + \\ &\quad 2\int_x^{\infty} b(y)f(x,y)p(y,t)dy \\ \frac{dD(t)}{dt} &= -k_0D(t) + k_1D(t)\int_{x_0}^{\infty} p(x,t)dx \\ M(0) &= M_0 \\ D(0) &= D_0 \\ p(x,0) &= p_0(x),\ x_0 < x < \infty \\ p(x_0,t) &= 0,\ t \geq 0\end{aligned}$$

Now, in the above model we make the following assumptions:
Let $m(x) = m,\ b(x) = bx$,
$f(x,y) = 1/y$ *when* $y > x_0$ *and* $0 < x < y$ and
$f(x,y) = 0$ *when* $y \leq x_0$ *or* $y \leq x$

Substituting the above in our model, the model transforms

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into the following:

$$\begin{aligned}
\frac{dM(t)}{dt} &= A - gM(t) - rM(t)\int_{x_0}^{\infty} p(x,t)dx + \\
&\quad bx_0^2\int_{x_0}^{\infty} p(x,t)dx \qquad (1)\\
\frac{\partial p(x,t)}{\partial t} &= -rM(t)\frac{\partial p(x,t)}{\partial x} - \\
&\quad (m+bx+k_2D(t))p(x,t) + \\
&\quad 2b\int_{x}^{\infty} p(y,t)dy \qquad (2)\\
\frac{dD(t)}{dt} &= -k_0D(t) + k_1D(t)\int_{x_0}^{\infty} p(x,t)dx \qquad (3)\\
M(0) &= M_0 \qquad (4)\\
D(0) &= D_0 \qquad (5)\\
p(x,0) &= p_0(x),\ x_0 < x < \infty \qquad (6)\\
p(x_0,t) &= 0,\ t \geq 0 \qquad (7)
\end{aligned}$$

where the constants A, g, r, b, m, k_0, k_1, k_2 are all positive.

III The steady states of the system

In this section, we compute the steady states of our system. For that, we convert our model into a system of ordinary differential equations and compute the steady states of the ODE system [1].

Introduce the functions $P(t) = \int_{x_0}^{\infty} p(x,t)dx$ which denotes the total number of IAPP polymers and $I(t) = \int_{x_0}^{\infty} xp(x,t)dx$ which is the total number of IAPP monomers in the polymers. Now, substituting these functions in equations (1) and (3), we get

$$\begin{aligned}
\dot{M(t)} &= A - gM(t) - rM(t)P(t) + bx_0^2P(t) \qquad (8)\\
\dot{D(t)} &= -k_0D(t) + k_1D(t)P(t) \qquad (9)
\end{aligned}$$

Now integrating equation (2) for $p(x,t)$ between x_0 *and* ∞, we get

$$\begin{aligned}
\frac{dP(t)}{dt} &= -rM(t)[p(x,t)]_{x_0}^{\infty} - mP(t) - \\
&\quad bI(t) - k_2D(t)P(t) + 2b\int_{x_0}^{\infty}\int_{x}^{\infty} p(y,t)dy \\
&= -mP(t) - bI(t) - k_2D(t)P(t) + 2b\int_{x_0}^{\infty}(y-x_0)p(y,t)dy \\
&= -mP(t) - bI(t) - k_2D(t)P(t) + \\
&\quad 2bI(t) - 2bx_0P(t)
\end{aligned}$$

Thus simplifying further, we get

$$\begin{aligned}
\dot{P(t)} &= -mP(t) - k_2D(t)P(t) - 2bx_0P(t) + \\
&\quad bI(t)
\end{aligned}$$

Now multiplying equation (2) with x and integrating for $p(x,t)$ between x_0 *and* ∞, we get

$$\begin{aligned}
\frac{dI(t)}{dt} &= -rM(t)[[xp(x,t)]_{x_0}^{\infty} - \int_{x_0}^{\infty} p(y,t)dy] - mI(t) - \\
&\quad b\int_{x_0}^{\infty} x^2p(x,t)dx - k_2D(t)I(t) \\
&= 2b\int_{x_0}^{\infty} x\int_{x}^{\infty} p(y,t)dydx \\
&= rM(t)P(t) - mI(t) - b\int_{x_0}^{\infty} x^2p(x,t)dx - k_2D(t)I(t) + \\
&\quad b\int_{x_0}^{\infty}(y^2 - x_0^2)p(y,t)dy
\end{aligned}$$

Thus, we get

$$\begin{aligned}
\dot{I(t)} &= rM(t)P(t) - mI(t) - k_2D(t)I(t) - \\
&\quad bx_0^2P(t) \qquad (10)
\end{aligned}$$

Combining equations (8)-(11), we get the transformed system of ODES for our model given by

$$\begin{aligned}
\dot{M(t)} &= A - gM(t) - rM(t)P(t) + bx_0^2P(t)\\
\dot{P(t)} &= -mP(t) - k_2D(t)P(t) - 2bx_0P(t) + bI(t)\\
\dot{I(t)} &= rM(t)P(t) - mI(t) - k_2D(t)I(t) - bx_0^2P(t)\\
\dot{D(t)} &= -k_0D(t) + k_1D(t)P(t)\\
M(0) &= M_0 \geq 0\\
D(0) &= D_0 \geq 0\\
P(0) &= P_0 \geq 0\\
I(0) &= I_0 \geq x_0U_0
\end{aligned}$$

We compute the steady state solutions for the above system of ODEs.

Set $\dot{M(t)} = 0 = \dot{P(t)} = \dot{I(t)} = \dot{D(t)}$
Now, solving $\dot{D(t)} = 0$,

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we get

$$\begin{aligned} -k_0D + k_1DP &= 0 \\ \Rightarrow (-k_0 + k_1P)D &= 0 \\ \Rightarrow \ either\ D &= 0\ or\ (-k_0 + k_1P) = 0 \end{aligned}$$

Case 1: When $D = 0$, the system $\dot{M(t)} = 0 = \dot{P(t)} = \dot{I(t)}$ reduces to the following:

$$\begin{aligned} A - gM(t) - rM(t)P(t) + bx_0^2P(t) &= 0 \\ -mP(t) - 2bx_0P(t) + bI(t) &= 0 \\ rM(t)P(t) - mI(t) - bx_0^2P(t) &= 0 \end{aligned}$$

Now solving the above, we get the disease free equilibrium point as $E_1 = (A/g, 0, 0, 0) = (\tilde{M}, \tilde{P}, \tilde{I}, \tilde{D})$

The disease state equilibrium point is given by $E_2 = (\acute{M}, \acute{P}, \acute{I}, \acute{D})$ where

$$\begin{aligned} \acute{M} &= \frac{(bx_0 + m)^2}{br} \\ \acute{P} &= \frac{bAr - g(bx_0 + m)^2}{mr(2bx_0 + m)} \\ \acute{I} &= \frac{bAr - g(bx_0 + m)^2}{bmr} \\ \acute{D} &= 0 \\ where\ \sqrt{\frac{bAr}{g}} &> bx_0 + m \end{aligned}$$

Case : 2 When $-k_0 + k_1P = 0$, we get the equilibrium to be $E_3 = (M^*, P^*, I^*, D^*)$ where

$$\begin{aligned} M^* &= \frac{A + bx_0^2P^*}{g + rP^*} \\ P^* &= \frac{k_0}{k_1} \\ I^* &= \frac{rM^*P^* - bx_0^2P^*}{m + k_2D^*}\ where\ rM^* > bx_0^2 \\ D^* &= \frac{\sqrt{brM^*} - (m + bx_0)}{k_2}\ where\ \sqrt{brM^*} > (m + bx_0) \end{aligned}$$

IV Stability of the equilibrium points

In this section, we give some results on the stability of the equilibrium points.

Theorem : 1 *The disease free equilibrium* $E_1 = (A/g, 0, 0, 0) = (\tilde{M}, \tilde{P}, \tilde{I}, \tilde{D})$ *is locally asymptotically stable if and only if* $\sqrt{\frac{bAr}{g}} < (m + bx_0)$.

Proof: We compute the jacobian matrix of the system about the equilibrium point E_1. The jacobian matrix is given by

$$\begin{pmatrix} -g & -Ar/g + bx_0^2 & 0 & 0 \\ 0 & -m - 2bx_0 & b & 0 \\ 0 & Ar/g - bx_0^2 & -m & 0 \\ 0 & 0 & 0 & -k_0 \end{pmatrix}$$

The eigen values of the above matrix are

$$-k_0,\ -g,\ -\sqrt{\tfrac{bAr}{g}} - (m + bx_0),\ \sqrt{\tfrac{bAr}{g}} - (m + bx_0)\ .$$

Now, the equilibrium E_1 is locally asymptotically stable if and only if the eigen values of the jacobian matrix have negative real parts. But, all the eigen values will have negative real parts if and only if the condition $\sqrt{\frac{bAr}{g}} < (m + bx_0)$ is satisfied. This proves the theorem.

Theorem : 2 *The disease state equilibrium* $E_2 = (\acute{M}, \acute{P}, \acute{I}, \acute{D})$ *is locally asymptotically stable if and only if* $\sqrt{\frac{bAr}{g}} > (m + bx_0)$ *and* $\acute{P} < \frac{k_0}{k_1}$.

Proof: The jacobian matrix is given by

$$\begin{pmatrix} -g - r\acute{P} & -r\acute{M} + bx_0^2 & 0 & 0 \\ 0 & -m - 2bx_0 & b & -k_2\acute{P} \\ r\acute{P} & r\acute{M} - bx_0^2 & -m & -k_2\acute{I} \\ 0 & 0 & 0 & -k_0 + k_1\acute{P} \end{pmatrix}$$

The characteristic equation of the jacobian matrix is given by

$$(-k_0 + k_1\acute{P} - X)(X^3 + a_1X^2 + a_2X + a_3) = 0$$

where the coefficients

$$\begin{aligned} a_1 &= \frac{-x_0^2b^2(g - 4m) + 6bx_0m^2 + 2m^3 + bAr}{m(2x_0b + m)} \\ a_2 &= \frac{-2b(m + bx_0)(bx_0^2g - Ar)}{m(2x_0b + m)} \\ a_3 &= -g(m + bx_0)^2 + bAr \end{aligned}$$

One eigen value is $X = -k_0 + k_1\acute{P}$ and this eigen value will have negative real part when $\acute{P} < \frac{k_0}{k_1}$.

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To conclude about the other eigen values, we apply the Routh-Hurwitz criterion to the polynomial [4]

$$X^3 + a_1X^2 + a_2X + a_3.$$

Therefore, the other eigen values of the matrix will have negative real parts if and only if

$$a_1, a_2, a_3 > 0 \text{ and } a_1a_2 - a_3 > 0.$$

This condition is satisfied when

$$\sqrt{\frac{bAr}{g}} > (m + bx_0).$$

Hence, the proof.

Theorem:3 *Let*

$$\begin{aligned}
a_1 &= g + rP^* + 2m + 2k_2D^* + 2bx_0 \\
B &= k_1k_2D^{*2} + 2mg + 2gk_2D^* + 2bx_0g + 2mrP^* + \\
&\quad 2k_2D^*rP^* + 2bx_0rP^* + m^2 + 2mk_2D^* + k_2^2D^{*2} + \\
&\quad 2mbx_0 + 2bk_2x_0D^* \\
Q &= brM^* - b^2x_0^2 \\
F &= gk_1k_2D^{*2} + rk_1k_2P^*D^{*2} + k_1k_2bD^*I^* + mk_1k_2D^{*2} + \\
&\quad k_1k_2^2D^{*3} + m^2g + 2mgk_2D^* + gk_2^2D^{*2} + 2mgbx_0 + \\
&\quad 2bgk_2x_0D^* + rP^*m^2 + 2rmk_2P^*D^* + k_2^2D^{*2}rP^* + \\
&\quad 2mbx_0rP^* + 2bx_0k_2D^*rP^* \\
H &= k_1k_2bgD^*U^* + gmk_1k_2D^{*2} + gk_1k_2^2D^{*3} + \\
&\quad rk_1k_2bP^*D^*I^* + rmk_1k_2P^*D^{*2} + rk_1k_2^2D^{*3}P^*
\end{aligned}$$

Then, the equilibrium $E_3 = (M^*, P^*, I^*, D^*)$ is locally asymptotically stable if and only if

$$\begin{aligned}
\sqrt{brM^*} &> (m + bx_0), && (11)\\
rM^* &> bx_0^2, && (12)\\
B &> Q, && (13)\\
F &> Q(g + rP^*), && (14)\\
H &> Q(rP^*) \text{ and} && (15)\\
a_1BF + a_1Q^2(g + rP^*) + a_1^2rP^*Q + 2QF(g + rP^*) &> a_1QF + a_1BQ(g + rP^*) + F^2Q^2(g + rP^*)^2 + a_1^2H && (16)
\end{aligned}$$

Proof: The jacobian matrix about the equilibrium point E_3 is given by

$$\begin{pmatrix}
-g - rP^* & -rM^* + bx_0^2 & 0 & 0 \\
0 & -m - k_2D^* - 2bx_0 & b & -k_2D^* \\
rP^* & rM^* - bx_0^2 & -m - k_2D^* & -k_2I^* \\
0 & k_1D^* & 0 & 0
\end{pmatrix}$$

The characteristic equation of the jacobian matrix is

$$X^4 + a_1X^3 + a_2X^2 + a_3X + a_4 = 0$$

where

$$\begin{aligned}
a_1 &= g + rP^* + 2m + 2k_2D^* + 2bx_0 \\
a_2 &= k_1k_2D^{*2} + 2mg + 2gk_2D^* + 2bx_0g + 2mrP^* + 2k_2D^*rP^* + \\
&\quad 2bx_0rP^* + m^2 + 2mk_2D^* + k_2^2D^{*2} + 2mbx_0 + \\
&\quad 2bk_2x_0D^* - (brM^* - b^2x_0^2) \\
&\stackrel{\text{def}}{=} B - Q \\
a_3 &= gk_1k_2D^{*2} + rk_1k_2P^*D^{*2} + k_1k_2bD^*I^* + \\
&\quad mk_1k_2D^{*2} + k_1k_2^2D^{*3} + m^2g + 2mgk_2D^* \\
&\quad + gk_2^2D^{*2} + 2mgbx_0 + 2bgk_2x_0D^* + rP^*m^2 + \\
&\quad 2rmk_2P^*D^* + k_2^2D^{*2}rP^* + 2mbx_0rP^* + \\
&\quad 2bx_0k_2D^*rP^* - (g + rP^*)(brM^* - b^2x_0^2) \\
&\stackrel{\text{def}}{=} F - Q(g + rP^*) \\
a_4 &= k_1k_2bgD^*I^* + gmk_1k_2D^{*2} + gk_1k_2^2D^{*3} \\
&\quad + rk_1k_2bP^*D^*I^* \\
&+ \quad rmk_1k_2P^*D^{*2} + rk_1k_2^2D^{*3}P^* \\
&\quad - rP^*(brM^* - b^2x_0^2) \\
&\stackrel{\text{def}}{=} G - Q(rP^*)
\end{aligned}$$

Since, the equilibrium point is required to be positive, equations (12) and (13) follow from that. Now, we apply the Routh-Hurwitz condition to the characteristic polynomial of the jacobian matrix about E_3. By Routh-Hurwitz criterion, the eigen values of the matrix will have negative real parts if and only if

$$\begin{aligned}
a_1, a_2, a_3, a_4 &> 0 \text{ and} \\
a_1a_2a_3 - a_3^2 - a_1^2a_4 &> 0
\end{aligned}$$

Now, since all the constants are positive in the model,this $\Rightarrow$ $a_1 > 0$.

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Now, equation (13) $\Rightarrow a_2 > 0$,
equation (14) $\Rightarrow a_3 > 0$,
equation (15) $\Rightarrow a_4 > 0$,
equation (16) $\Rightarrow a_1a_2a_3 - a_3^2 - a_1^2a_4 > 0$
Therefore, the Routh-Hurwitz condition is satisfied and hence all the eigen values of the Jacobian matrix have negative real parts. The negativity of all the eigen values implies that the equilibrium point E_3 is locally asymptotically stable. Hence, the proof.

V Numerical Illustration

Our model can be used for simulations based on data from literature available in similar polymerisation processes. The model parameters are as follows:
$A = 4400$ per day, $r = 0.3$ fibrils per sq. unit per day, $g = 5$ per day, $b = 0.0001$ fibrils per sq. unit per day, $m = 0.04$ per day and $x_0 = 6$ are as given in [14]. $k_0 = 0.1$ per day, $k_1 = 0.0004$ per day, $k_2 = 0.002$ per day
Matlab software has been used to simulate our model. The simulations assume an initial IAPP monomer population $M_0 = 1000$ along with $P_0 = 50$, $I_0 = 500$ and drug values have been chosen from 0 to 8000 units. The graphs thus obtained are presented below.

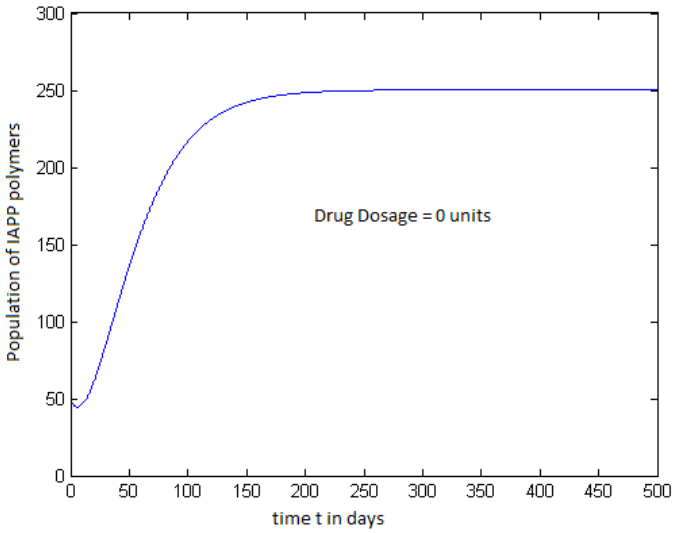

Fig. 1: Drug Dosage = 0 Units

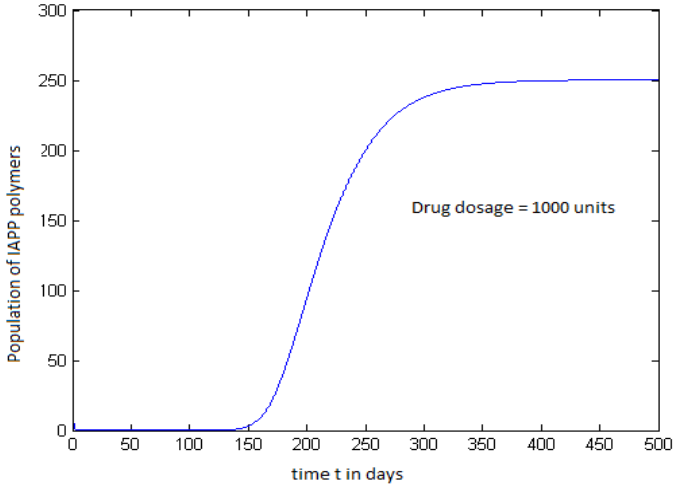

Fig. 2: Drug Dosage = 1000 Units

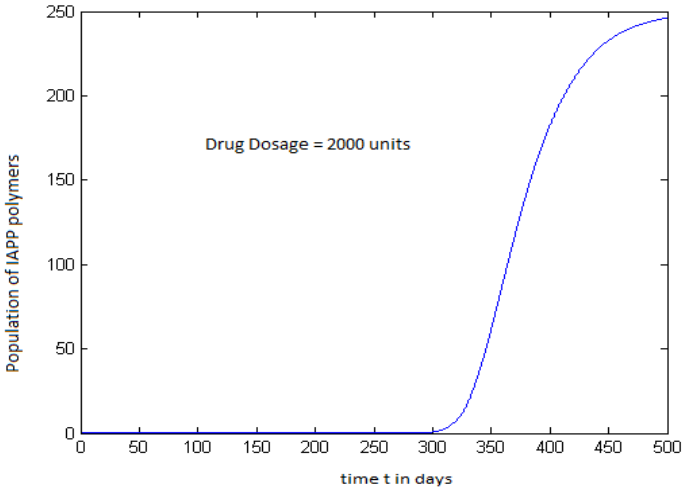

Fig. 3: Drug Dosage = 2000 Units

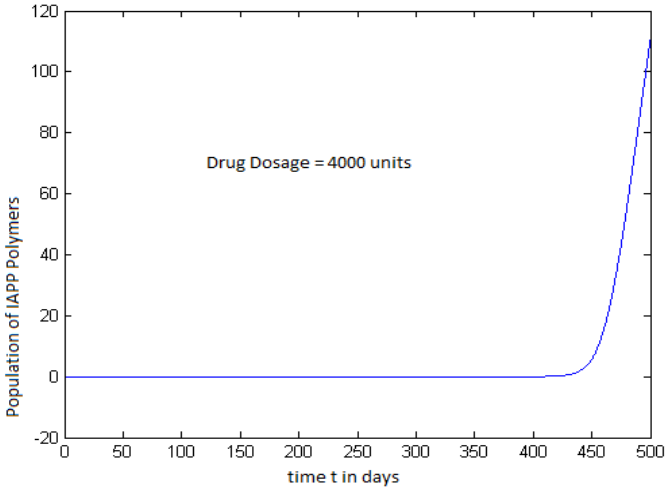

Fig. 4: Drug Dosage = 4000 Units

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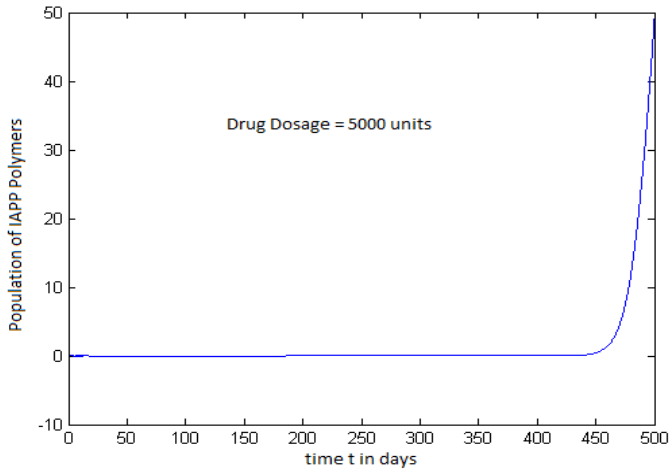

Fig. 5: Drug Dosage = 5000 Units

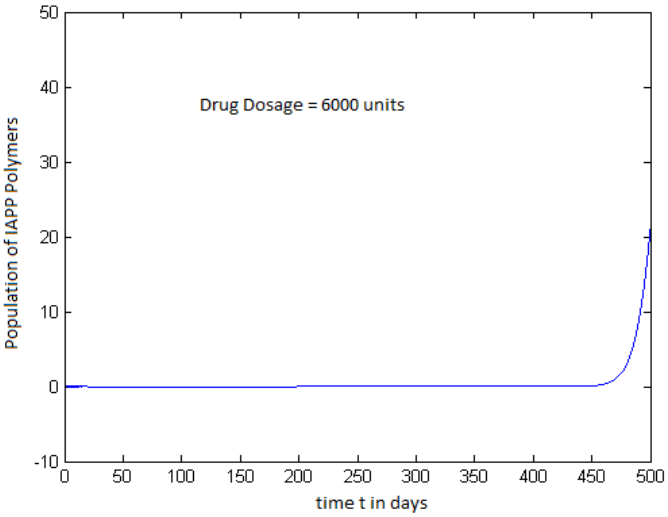

Fig. 6: Drug Dosage = 6000 Units

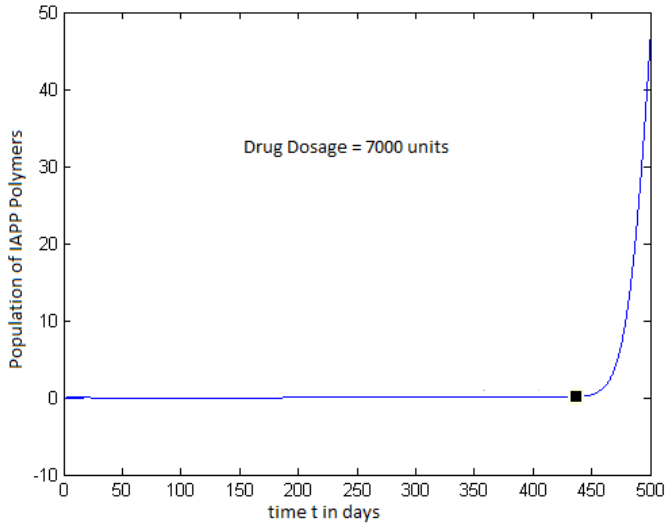

Fig. 7: Drug Dosage = 7000 Units

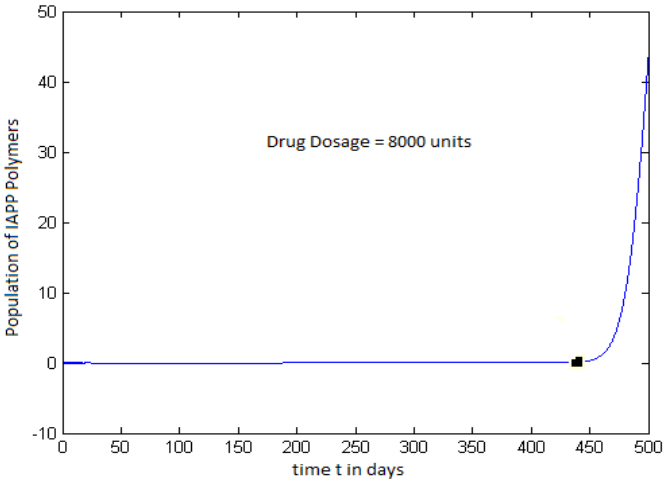

Fig. 8: Drug Dosage = 8000 Units

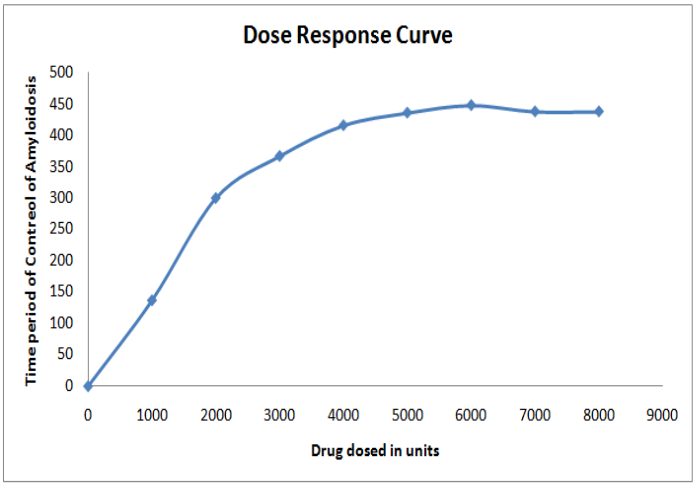

Fig. 9: Dose Response Curve

The above graphs, fig. 1 - 8 give the steady state values of the IAPP polymer population for different levels of drug dosed. We see that as the dose of drug is increased, there is significant control in the polymerisation of IAPP monomers. Hence this prevents the aggregation and fibril formation of this amyloidogenic protein and thus helps in control of T2DM or onset of development of T2DM. We also see from fig. 9 that increasing drug levels beyond 6000 units do not provide any significant reduction in amyloidosis. This will therefore help in arriving at optimum drug levels. The plateuing effect also in this case suggests the presence of fixed number of receptors to which the drug binds before eliciting action thereby giving leads to mechanism of action of the drug.

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VI Conclusions

In this work we have modeled the dynamics of amyloid formation of islet beta cells under therapeutic interventions and have studied the stability of the equilibrium points of the model. We have proved that the steady state solutions of the model are locally asymptotically stable. Also, numerical simulations were performed on the model and we conclude that amyloidosis can be controlled in the presence of therapeutic intervention.

Numeric simulations were performed for different levels of drug administered. The result showed that amyloidosis was prevented / delayed with increasing levels of drug. This, therefore presents new avenues for drug discovery in treatment of T2DM. The simulations also indicated that there was a limit to which the drug can be increased.We found no significant decrease in fibril formation for drug levels above 6000 units. Optimum drug levels and leads to mechanism of action could also be arrived at from these simulations.

Thus the developed model can play a vital role in understanding the mechanism of drug action in drug discovery.

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