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Research Article

Computational Network Modelling of hIAPP-Induced β-Cell Toxicity Reveals Key Signalling Pathways in Type 2 Diabetes

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Abstract

Human islet amyloid polypeptide (hIAPP) oligomers are increasingly recognized as central mediators of β-cell dysfunction and toxicity in type 2 diabetes mellitus (T2DM). Islet amyloidosis is a chronic condition developed during the course of T2DM and it is characterized by the deposition of toxic hIAPP aggregates in pancreatic β-cells. Although, islet amyloidosis in not a condition that has gone unaddressed however, the intricate biological processes that the toxic hIAPP oligomers intervene with to mediate β-cell toxicity are yet to be fully elucidated. In this study, we employed systems metabolism and computational biology approach to mathematically reconstruct and investigate the dynamics and hIAPP-mediated β-cell toxicity axis using SimBiology MATLAB. The signalling network was reconstructed using a number of enzyme kinetics and parameters which provided a computable framework of all the signalling components giving us valuable insights to predict and replicate the best behavioural outcomes of the biological system. Sensitivity analysis, Principal Component Analysis (PCA), Flux analysis, Model reduction and cross-talk point determination accurately captured the dynamics of the entire system and identified key components (RAGE, PKC, ROS, CytoC, PERK, IRE1, ATF6, Ca2+ influx), interactions, and processes (insulin resistance, glycation, autophagy defect, ER and mitochondrial stress, apoptosis) driving its pathogenic behaviour.

Keywords: hIAPP, Islet amyloidosis, T2DM, β-cell dysfunction, SimBiology MATLAB

1. Introduction

Islet amyloidosis is a chronic condition developed during the course of prolonged hyperglycaemia in Type II Diabetes Mellitus (T2DM). It is characterized by the accumulation of amyloid deposits formed through aggregation of amyloidogenic peptide known as Islet Amyloid Poly-Peptide (IAPP) within the Islets of Langerhans causing their loss of function and mass. IAPP aggregates are attributed to defective glucose regulation, mitochondrial and endoplasmic reticulum (ER) stress, increased β-cell toxicity, dysfunction and apoptosis; and are best characterized by their physiological role in being able to inhibit insulin secretion causing insulin resistance through a direct paracrine effect on the β-cells [1]. IAPP deposits in the pancreas of a T2DM patient were first described in 1901 as hyaline lesions however, were later described as proteinaceous amyloid plaques in 1961 [2,3]. Proteinaceous plaques are mainly formed due to aberrations in protein folding mechanisms leading to misfolded protein aggregates and deposits in the cells causing severe damage to the organs and surrounding areas [4].

IAPP exhibits endocrine, paracrine and autocrine functions. Human IAPP (hIAPP) is expressed as an 89 amino acid pre-pro-peptide and post-translationally 22 amino acids are cleaved from the N-terminus to give a 67-amino acid peptide called proIAPP. proIAPP is then altered in the lumen of ER by forming a disulphide bond between cysteines at position 2 and 7. This altered peptide is transported to the Golgi Complex to be packed in the secretory granules and further be cleaved into a final 37 amino acid peptide modified by amidation at the C-terminus [5]. Under normal physiological conditions this active form of hIAPP is co-expressed, co-processed and co-secreted with insulin in a molar ratio of 1:100 to regulate blood glucose levels; however, during chronic hyperglycaemic conditions this ratio is heavily altered [6,7]. Extensive evidences suggest that hIAPP oligomerizes intracellularly as a result of incorrect processing of proIAPP in the secretory granules and released as deposits into extracellular space when β-cells degenerate. Apart from the physicochemical alterations, perturbations in the biological processes also hold a significant weight in the oligomerization of hIAPP leading to loss of β-cell mass [8].

The rationale of this study is that persistently elevated blood glucose levels place a heavy metabolic burden on β-cells creating glycolytic overload. As a compensatory mechanism excess glucose is rapidly metabolized to meet

insulin synthesis demands and by default synthesizing hIAPP along with insulin. The proteostatic environment is usually maintained when the secretory granules release their contents, however, when there is a higher demand for insulin, the cytosolic pool of hIAPP will also rise and there will be greater chance of aggregation and deposition of aggregates around β-cells. Despite the considerable research available linking hIAPP with T2DM, hIAPP misfolding, deposits as plaques throughout different parts of the body little amount of research is available on the integrative role of toxic hIAPP oligomers as central regulators of β-cell toxicity. In this study we elaborate and corroborate the role that toxic hIAPP oligomers may have in contributing towards aberrant functioning of several biological processes that lead to insulin resistance, ER and mitochondrial stress, autophagy failure, inflammation and β-cell death during T2DM. Although these molecular processes represented in the model have each been individually reported in the context of T2DM, very few has been said with respect to their regulation by toxic hIAPP oligomers. The mechanistic novelty of the present study lies in their systems-level integration. Rather than proposing a new signalling pathway, the model reveals how these processes are dynamically coupled, organized and driven by a limited set of event reactions that act as tipping points for β-cell failure. Sensitivity analysis, PCA, and flux profiling consistently identifies a compact subset of molecular species and reactions that disproportionately govern network behaviour, demonstrating that β-cell toxicity emerges from coordinated pathway convergence rather than parallel independent dysfunctions. The perturbations in these signalling pathways are subject to two major events firstly the changes in the blood glucose levels and its influence on the oligomerization of hIAPP. Understanding the impact of these events on the tempering of various metabolic and biological processes will prove to be crucial in following the evolution and reach of the disease. Our study mainly focuses on deciphering the hIAPP mediated β-cell toxicity axis in islet amyloidosis during T2DM, which could offer new insights in developing precision and targeted therapies for this condition.

1.1. The hIAPP Mediated β-cell Toxicity Axis

Once, the glucose uptake is levelled up through the GLUT1 transporters it is rapidly converted to pyruvate through sequential enzymatic steps of glycolysis. Pyruvate is an essential node that connects the mitochondrial TCA cycle and glycolysis [9]. Additional regulatory features of this metabolic signalling are initiated by continuous glucose influx where anaplerotic flux converts back oxaloacetate to phosphoenolpyruvate via phosphoenolpyruvate carboxylase. This phosphoenolpyruvate can re-enter glycolysis cycle producing pyruvate in a feedback loop where recurrent cycling of oxaloacetate-PEP-pyruvate feeds into α-ketoglutarate production. Increased production of α-ketoglutarate acts as a metabolic signal for secretory granules to promote the release of stored insulin and hIAPP monomers [9,10]. Apart from this under conditions of chronic metabolic burden excessive glucose is shunted into secondary metabolic pathways most notably the polyol pathway where the aldose reductase reduces glucose to sorbitol which is then oxidized to fructose pushing it back into the glycolysis cycle. During this reaction methylglyoxal a highly reactive dicarbonyl molecule is generated as a byproduct which functions as a glycating agent in altering the structural conformations of hIAPP monomers speeding up its oligomerization. As a result, soluble hIAPP monomers are transformed into insoluble toxic oligomeric assemblies characterized by β-sheets [11,12]. Notably, the hIAPP oligomers rather than the mature fibrils are the prominent mediators of cellular toxicity and their formation can be influenced not only by the intrinsic amyloidogenic properties but also extrinsic molecular factors and non-canonical processes that promote protein misfolding [4].

Once formed these hIAPP oligomers engage in cellular toxicity by two mechanisms including receptor mediated interactions and non-receptor mediated events (Figure 1). The receptor for advanced glycation end products (RAGE) can bind hIAPP oligomers due to its oligomerization being enhanced by glycation. RAGE is not only involved in eliciting signalling responses leading to inflammation and apoptosis but also plays a crucial role in causing insulin resistance during T2DM. Interaction of hIAPP oligomers with RAGE leads to the recruitment and activation of protein kinase C (PKC), which carries out IRS1 phosphorylation at serine/threonine residues. This impairs normal IRS1 functioning and damages the insulin mediated PI3K/AKT signalling inhibiting glucose uptake and metabolism, thus, leading to insulin resistance in β-cells [13,14]. Parallelly, β-cell apoptosis characterized by release of cytochrome C (CytoC) and activation of caspases is mediated by hIAPP-RAGE signalling. PKC activates NADPH oxidase (NOX), which takes up hydrogen from NADPH formed in mitochondria and releases a reactive oxygen species (ROS) harmful to the cells. ROS production mostly occurs through the electron transport chain in mitochondria however, activated PKC triggers the stress-related JNK/p38 signalling pathway which stimulates NOX for ROS generation in β-cells [15]. The activated JNK mediates β-cell apoptosis by activating a range of events leading to mitochondrial and ER stress, ROS formation and production of pro-inflammatory cytokines.

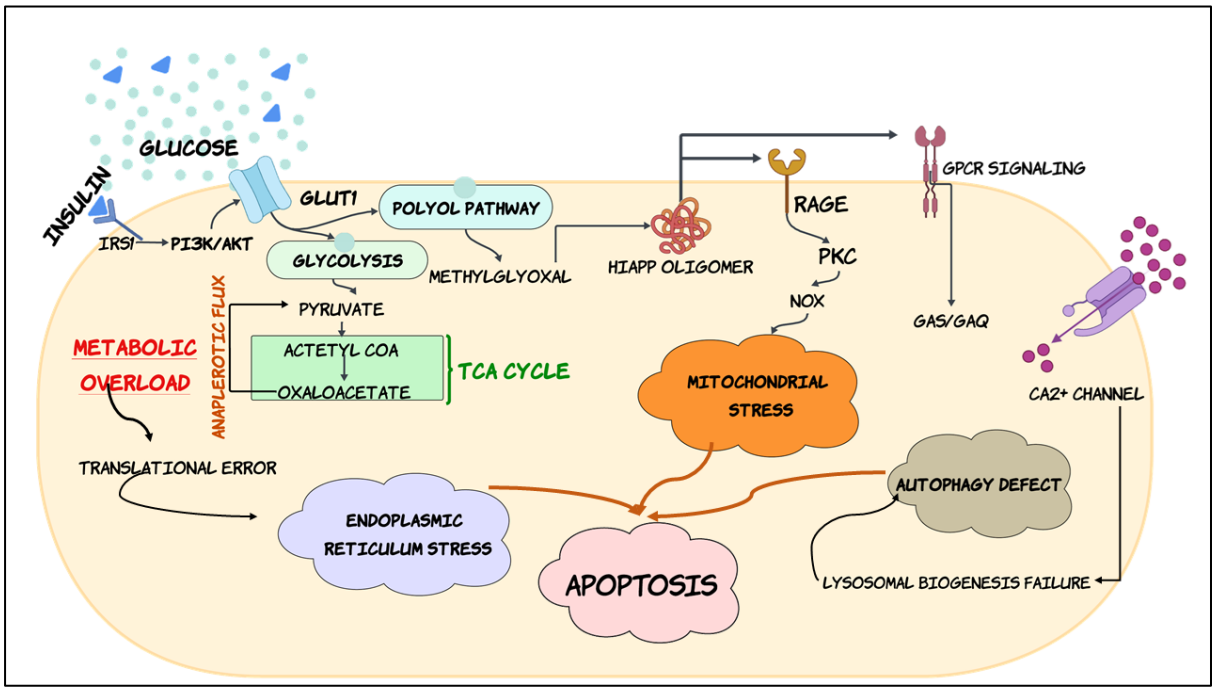

Figure 1: Overview of the hIAPP-Mediated β-cell Toxicity Axis During T2DM

CytoC initiates the intrinsic apoptotic cascade by binding to the APAF1 forming the apoptosome assembly activating caspase 9 for cell death [12]. Additionally, it also acts as signalling molecules that participates in the activation of NLRP3 inflammasome. Inflammasome formation triggers the activation and release of pro-inflammatory cytokines such as IL-1β, IL-6, IL-18 and TNFα. Systemic release of these cytokines induces islet inflammation that plays a major role in β-cell dysfunction and apoptosis activation [16,17]. Through NF-κB-mediated transcription pro-inflammatory cytokine expression is amplified, recruiting immune responses that worsen β-cell injury. These cytokines initiate an inflammatory response that does not act in isolation; rather, it primes β-cells for apoptosis by enhancing Fas receptor expression on their surface. Thus, inflammation, oxidative stress, and failed proteostasis converge to channel β-cells toward programmed cell death, making apoptosis an inevitable point.

As the demand for insulin becomes chronic, the biosynthesis and secretion process may eventually overload the protein folding capacity of the ER leading to the saturation of chaperon BiP and activation of the unfolded protein response (UPR) which senses the activation of PERK, IRE1α, and ATF6. Chronic nutrient stress will uncouple translational control from protein folding capacity of the ER leading to its dysfunction, miss-processing of proIAPP and proInsulin and accumulation of misfolded protein cargo in the β-cells [12-18]. Under physiologically normal circumstances, autophagy maintains β-cell proteostasis by degrading excess proInsulin and IAPP monomers through lysosomal clearance. This elevates the levels of cyclic AMP (cAMP) through hIAPPs interaction with calcitonin receptors increases Ca2+ levels intracellularly leading to disruption of lysosomal membranes and preventing its fusion with the autophagosomes for degradation of misfolded protein cargo [4,19,20].

Ultimately, the toxicity of hIAPP oligomers establishes a pathological cascade converging various metabolic and biological processes. These events not only contribute to the degeneration of pancreatic functions but also intensifies the systemic insulin resistance and chronic hyperglycaemic conditions. Recent evidence reveals that chronic hIAPP toxicity induces loss of β-cell identity, a process characterized by dedifferentiation toward progenitor-like states. Transcription factors essential for β-cell identity, including PDX1 become downregulated under sustained hIAPP stress, while disallowed genes are aberrantly expressed. This identity loss represents a critical mechanism contributing to β-cell failure, as dedifferentiated cells lose glucose-responsive insulin secretion capacity [21]. Based on such existing biological data to get a greater insight into this intricate pathological axis, we reconstructed a kinetic model interpreting this signalling network using a systems and computational biology approach which emphasizes its key molecular interactions [22]. For this purpose, we have used Systems Biology Markup Language – based MATLAB SimBiology Toolbox R2024b. Through the mathematical model we have thus, worked two extremely important objectives: firstly, to contribute to a deeper understanding of the biological events under study in a manner that is simple to be replicated in silico and conveyed; secondly, to make it possible in the future to design in vitro and in vivo experiments that specifically track the predicted features (vital cross-talks) of this biological system in order to follow the reach of the pathological network.

2. Methodology

2.1. Data Preparation

To decipher and reconstruct the hIAPP mediated β-cell

toxicity axis fragmented data was gathered through thorough literature reviews and signalling database searches such as KEGG and GEO Dataset (hsa04930, hsa00010, hsa00020, hsa04151, hsa04024, hsa04020, hsa04933, hsa04210, hsa04930, hsa04141, hsa04140, GSE135276, GSE164416, GSE118139.) [4, 12, 13, 18, 19, 23-28]. The curated literature and transcriptomic datasets were selected based on established roles in β-cell metabolism, stress responses, dysfunction and survival; comparing non-diabetic and T2DM conditions. The molecular networks and expression trends were validated against KEGG pathway structure prior to model reconstruction.

2.2. Quantitative Modelling and Simulations

Quantitative modelling of biological reactions was done using SimBiology Model Builder; it involves the application of appropriate kinetic rate laws, parameter estimation, and initial component concentration (https://in.mathworks.com/help/simbio/). The kinetic rate laws implemented in the SimBiology Toolbox for the reconstructed models were as follows: 1) The Law of Mass Action, was applied to association and dissociation reactions where the rate is directly proportional to reactant collision or interaction frequency. 2) The Henri-Michaelis-Menten equation, was employed for phosphorylation, dephosphorylation, and ubiquitination reactions this allows for the abstraction of complex enzyme-substrate intermediates into a saturable rate law. 3) Hill's kinetic equation was applied for gene expression reactions transcription and translation reactions in the system where the rate with n=1 depends on the availability of the template (DNA/mRNA) and the saturation of the synthetic machinery (Polymerase/Ribosomes) Table 1. Initial concentrations of signalling components were determined considering experimentally known concentrations from the literature, indicating that a cell can secrete 103 -106 signalling molecules [29]. Simulations of the mathematical model were performed using the Stiff Deterministic ODE15s solver type for 100 seconds time units in SimBiology Model Analyzer, which generates the first-order non-linear ODEs, that provides a state versus time graph for each node (molecule/species) to determine their dynamic behaviour in the system over time defining the mathematical framework used in SimBiology [30-32]. This discrete transition depends on the conditions applied i.e., the reaction rate (V_{max}), and the concentration of the substrate (K_{max}) at a given time.

Kinetic Rate Laws	Type of Reactions	Rates and Parameters
Law of Mass Action	Association and Dissociation Reactions (e.g. Receptor Ligand binding reactions)	1/ (molecule x second)
Henri's Michaelis Menten Reaction	Phosphorylation, Dephosphorylation and ubiquitination reactions (e.g. Insulin signalling, RAGE, GPCR, Autophagy, Apoptosis and Stress signalling pathways)	Vmax = molecule/second Kmax = molecule
Hill's Kinetics	Transcription and translation reactions (e.g. Reactions in the nucleus)	Vmax = molecule/second Kmax = molecule n = 1

Table 1: Parameter Table Representing Kinetic Rate Laws, Type of Reactions and Reaction Rates

2.3. Trigger Events

A per the SimBiology User Guide documentation provided by Mathworks, in addition to simulations, species in the model can be assigned trigger events such that they demonstrate a discrete transition in their concentration regulating the final outcome of the system (https://in.mathworks.com/help/simbio/ug/event-object.html). In SimBiology we need to use a combination of relational and logical operators to execute a trigger event. In addition to Event objects an EventFcns property needs to be specified which occurs when an event is triggered. The EventFcns property of an event specifies a condition that is time – dependent or time – independent. For example, at a time >= 25 seconds, and at a species concentration of X = 150 molecule per second will trigger an event where post 25 seconds the axis will switch from its normal functioning depending on the change in concentration of the species X. In our model we have employed time – dependent simulation of trigger events which allowed us to specify the EventFcns property with respect to change in concentration and parameters associated with the species at given time = 20 seconds or 50 seconds.

2.4. Sensitivity Analysis

In order to determine the interdependence of the components and robustness of the biological network, sensitivity analysis of the mathematical model was carried out [33,34]. In our current work, we have performed Local Sensitivity Analysis (LSA) for the reconstructed model. The SimBiology Toolbox uses the Sundails solver type to perform the LSA by integrating the primary ODE of the model with the auxiliary differential equations to determine the sensitivity coefficient for every species/component in the system. Thus, the time-dependent sensitivities for a species, say x, with regard to its parameters y and z, are expressed as dx/dy and dx/dz, where the numerator denotes sensitivity output and the denominator denotes sensitivity input. Through sensitivity analysis we generated a high-dimensional adjacency matrix (137 × 137), capturing pairwise sensitivities among

all model components. This matrix was further used to compute score coefficients for principal component analysis (Supplementary data) (https://in.mathworks.com/help/simbio/ug/global-local-sensitivity-analysis-gsa-lsa-simbiology.html).

2.5. Principal Component Analysis

Principal Component Analysis (PCA) is a well-known method for simplifying large multi-component biological networks by eliminating background noise and randomness from the network. PCA was calculated using sensitivity scores for each signalling component with respect to another in the system using the MATLAB function "score coefficient = princomp A," where A = m*n matrix. The variance in sensitivities of each signalling component in the system is represented by the principal component score coefficient [35].

2.6. Flux Analysis

One of the best methods for identifying most important reactions in the system that could be involved in disease aetiology is through comparative flux analysis. The flux analysis determines the productivity of each reaction, and their contribution to the outcome of the biological system. In our study, we have used COPASI (4.45) a biochemical network simulator to compute the flux [35,36]. The reconstructed signalling network was exported in Systems Biology Markup Language (SBML) format. Ordinary differential equations (ODEs) describing the reaction kinetics were numerically solved to estimate molecular fluxes for individual reactions.

2.7. Model Reduction

Model reduction is a method for streamlining biological networks by removing biochemical reactions that don't significantly affect the dynamics of the whole system. By minimizing extraneous parameters that are not contributing maximally to enrich the phenotype of the biological axis, model reduction makes it easier to anticipate the final outcome of the system by making the mathematical model more comprehensible [37]. In order to accomplish this in a systematic approach, we have combined the results of flux analysis and sensitivity analysis for filtering out reactions with low flux and sensitivity levels that have negligible impact on the output of the network.

2.8. Crosstalk Point Determination

A cross-talk point is a bridge between two or more biological signalling pathways that have been reconstructed. It is created when a single component or metabolite of the biological axis can regulate or is regulated by various signalling cascades [38]. The cross-talk point in our study was computed for the reconstructed biological axis of hIAPP-mediated β-cell toxicity, by subtracting the in-degree of a node (species) across the overall network from the out-degree of a node (species) in a specific signalling pathway, producing a positive non-zero value.

3. Results

The reconstructed mathematical model elucidated that the interactions between hIAPP oligomers and β-cell receptors prompted the activation of various metabolic and biological processes in the hIAPP-mediated β-cell toxicity axis. The pathogenicity of this axis was mediated through the generation of methylglyoxal, ROS and activation of PKC, cAMP, CytoC, NLRP3 and p62. This led the entire axis through events that facilitated the β-cell toxicity, dysfunction and loss of β-cell mass.

3.1. Reconstruction of Signalling Cascade and Simulations

The signalling cascade was reconstructed using SimBiology Model Builder. The mathematical model represented four compartments: β-cell, nucleus, mitochondria and endoplasmic reticulum (Table 2). Each compartment consisted of a set of reactions influenced by receptor-ligand interaction of insulin as well as hIAPP oligomers (Figure 2). To simulate the entire signalling cascade, SimBiology Model Analyzer and the Ordinary Differential Equation (ODE15s) solver were used. This solver generated first-order non-linear ordinary differential equations (ODEs) to depict the pathogenicity and toxicity induced by hIAPP oligomers in β-cells over a duration of 100 seconds. The same solver was used to simulate the trigger events. The simulation generated concentration-versus-time graphs to visualize the dynamic changes in the concentrations of various molecular components within the hIAPP-mediated β-cell toxicity axis. The axis yielded significant outputs that corresponded to key biological features of β-cell dysfunction and toxicity in T2DM. These outputs including insulin resistance, altered glucose metabolism, mitochondrial and ER stress, defective autophagy, inflammation and apoptosis were governed by key signalling intermediates and transcription factors such as AP1, PDX1, NF-κB and STAT3.

Sr. No.	Compartment	Components
1	Beta Cell	98
2	Endoplasmic Reticulum	11
3	Nucleus	7
4	Mitochondria	21
5	Total Number of Species	137
6	Total Number of Reactions	97
7	Total Number of Parameters	195

Table 2: Summary of Compartments, Species and their Respective Parameters

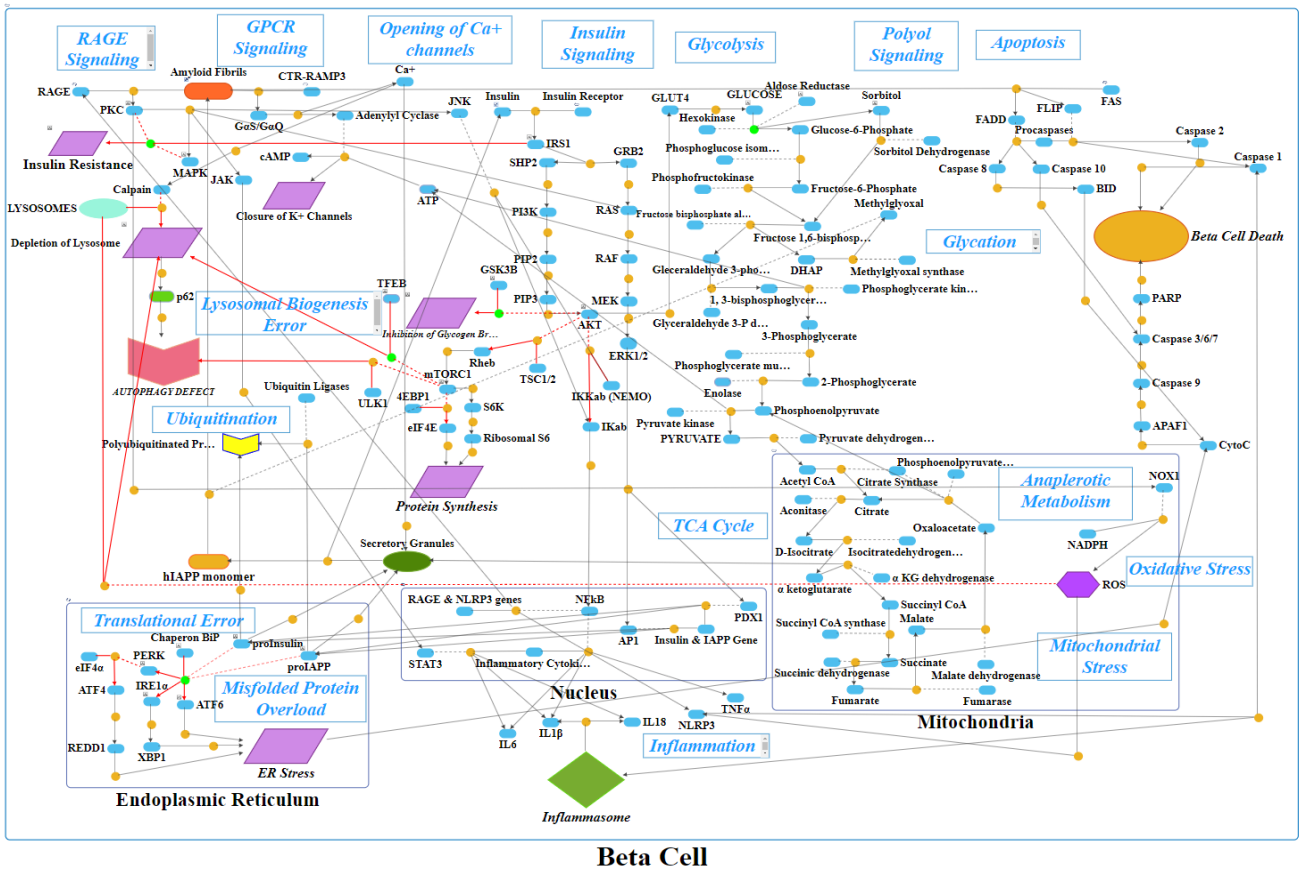

Figure 2: Reconstructed Mathematical Model Depicting the hIAPP-mediated β-cell Toxicity Signalling Axis during T2DM. The Model Consists of Four Compartments Including Beta Cell, Nucleus, Endoplasmic Reticulum and Mitochondria. All the Signalling Components/Species are Connected across these Compartments

3.1. Trigger Events

The trigger events were applied to track the evolutionary behaviour of biological processes and the reach of pathological effects of hIAPP oligomers mediating β-cell toxicity. In total five crucial reactions of the axis were subjected to trigger events which played a major role in the control of disease state. This helped us track the parametric alterations of various species affected by the event as well as the species undergoing the event itself. The list of reactions subjected to trigger events are summarized in Table 3. These reactions were associated with the processes like insulin resistance, glycogen breakdown, autophagy defect, glycation and ER stress. GLUCOSE + Aldose Reductase → Sorbitol becomes kinetically significant only during extreme hyperglycemia. This reaction was selected as a trigger event as it is not a normal signaling event and concentration trigger is used to activate the pathological axis as this pathway further activates methylglyoxal which facilitates oligomerization of hIAPP. Regulation of PKC at physiologically normal conditions does not affect insulin signalling and glucose metabolism. However, hyperactivation of PKC through hIAPP oligomer and RAGE interactions plays an important role in escalating insulin resistance by eventually hindering the uptake of glucose in β-cells. Parallelly, since the body is under nutrient stress due to hyperglycaemic conditions β-cells are signalled to increase the production and secretion of insulin, this puts the endoplasmic reticulum through unfolded protein response signals that upregulate ER stress associated ATF6, PERK and IRE1α. Additionally, AKT blocks the GSK3B under normal insulin signaling. Insulin resistance removes this inhibition leading to halt in glycogen storage which puts the islets through starvation and eventually death. Autophagy, one of the critical processes involved in hIAPP regulation is impaired due to defects in lysosomal biogenesis via mTORC1 expression. Physiologically, nutrient fluctuation allows mTORC1 oscillation permitting TFEB nuclear translocation and lysosomal biogenesis, chronic hyperinsulinemia and nutrient overload maintain constitutive mTORC1 activity. This creates a “lock” mechanism that permanently phosphorylates TFEB, sequestering it in the cytoplasm. This trigger event defines the failure of compensatory clearance, leading to the irreversible accumulation of toxic hIAPP oligomers. All these events culminate to remodel the normal physiological signalling to work in a pathological manner.

Sr. No.	Trigger Event Reactions
1	GLUCOSE + Aldose Reductase -> Sorbitol
2	PKC & MAPK + IRS1 -> Insulin Resistance
3	proIAPP & proInsulin + Chaperon BiP -> PERK + ATF6 + IRE1α
4	mTORC1 + TFEB -> Depletion of Lysosome
5	AKT + GSK3B -> Inhibition of Glycogen Breakdown

Table 3: List of Reactions Subjected to Trigger Events

3.2. Principal Component Analysis:

Principal Component Analysis helped in identifying key molecular species that have the greatest impact on the overall dynamics and behaviour of the signalling system disregarding those species with background noise as they are involved in reactions with least effect. By considering the sensitivity profiles and score coefficients of all components in the interconnected axis principal components were identified having significant fluctuations. Figure 3 graph represents the principal component score coefficients vs the components. The components having highest score coefficients between 0.8 to 1.0 are highlighted in the graph. Numerical PCA scores for all 137 components are provided in the Supplementary Data. Through PCA analysis in addition to recognized T2DM hallmarks such as insulin resistance, it detected several elements that are likely to exert substantial effect on the regulation of pathogenicity of hIAPP oligomers in inducing β-cell toxicity. Notably, we observed the involvement of hIAPP monomers and intermediates of metabolic signalling such as methylglyoxal and αketoglutarate which facilitated oligomerization kinetics. PKC, IRS1, REDD1 and XBP1 involved in insulin resistance and ER stress response were also highlighted. Processes and events like GPCR signalling, Ca_{2+} influx relating to autophagic defect, inflammation and β-cell death were corroborated with to the identification of GαS/GαQ, calpain, p62, NLRP3 and caspases as principal component species in the axis (Figure 3). Besides the standard components, our analysis revealed numerous model-specific molecules depending on trigger events and sensitivities, that emerged as significant principal components that enhanced the interpretability of their roles played in governing the system, ensuring minimal loss of information.

3.3. Flux Analysis

In order to have a closer look at every reaction in the axis with respect to its kinetics (V_{max}, K_{max}) and what role it plays in shaping the biological system we have computed molecular flux for every reaction. Amongst the total number of reactions involved in the biological network we considered reactions with high molecular flux to be crucial as these usually play a vital role in defining the outcome of the system having a substantial impact on the dynamics and behaviour of biological processes (Figure 4). By identifying these high flux reactions, we gained insights into the key molecular processes and interactions that drive the network towards pathogenicity and inevitable disease progression. Reactions with molecular flux ranging from 500 mol/s to 1200 mol/s observed for processes like apoptosis through activation of caspases and APAF1, inflammation, autophagic defect through lysosomal depletion and p62 inclusions, glycation, mitochondrial and ER stress through generation of ROS and activation of cytoC are summarized in Table 4.

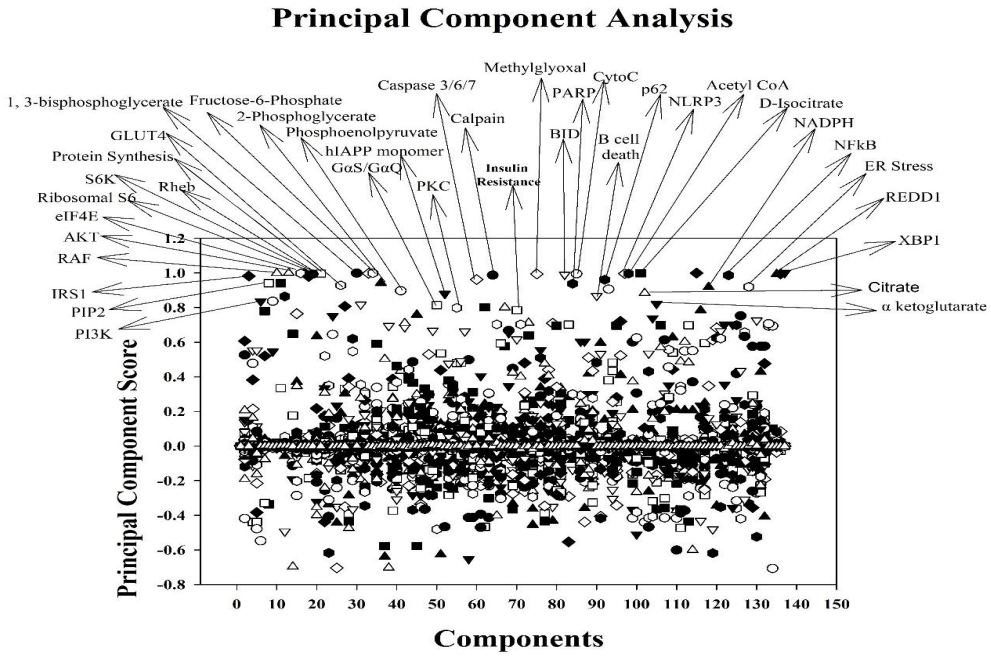

Figure 3: Principal Component Analysis Depicting Components with High Sensitivities and PCA Score Coefficients

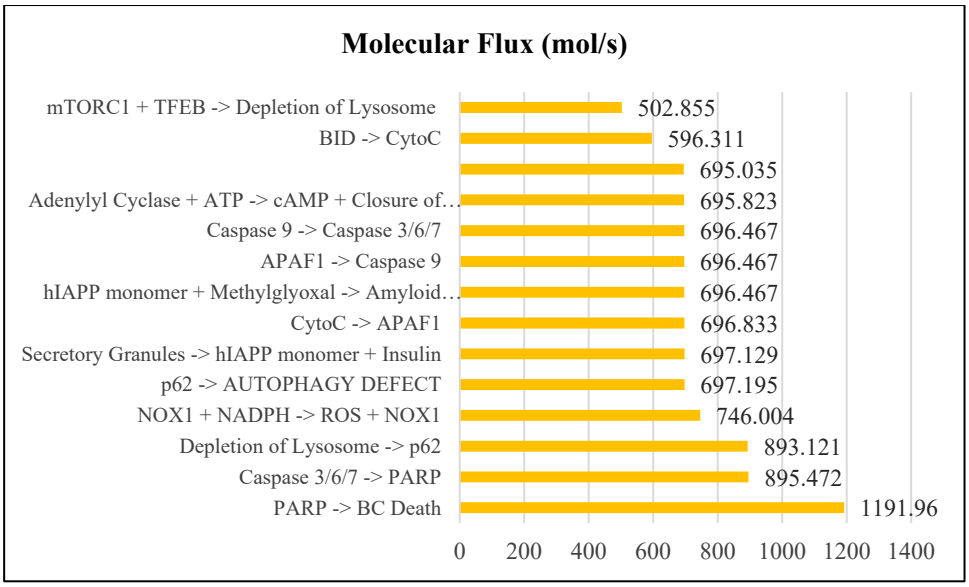

Figure 4: High Molecular Flux Reactions Identified from the Reconstructed hIAPP-mediated β-cell Toxicity Signalling Axis

Sr. No.	Reactions	Molecular Flux (mol/s)
1	PARP -> BC Death	1191.96
2	Caspase 3/6/7 -> PARP	895.472
3	Depletion of Lysosome -> p62	893.121
4	NOX1 + NADPH -> ROS + NOX1	746.004
5	p62 -> AUTOPHAGY DEFECT	697.195
6	Secretory Granules -> hIAPP monomer + Insulin	697.129
7	CytoC -> APAF1	696.833
8	hIAPP monomer + Methylglyoxal -> Amyloid Fibrils	696.467
9	APAF1 -> Caspase 9	696.467
10	Caspase 9 -> Caspase 3/6/7	696.467
11	Adenylyl Cyclase + ATP -> cAMP + Closure of K+ Channels	695.823
12	DHAP + Methylglyoxal synthase -> Methylglyoxal	695.035
13	BID -> CytoC	596.311
14	mTORC1 + TFEB -> Depletion of Lysosome	502.855

Table 4: List of High Flux Reactions in the System Governing the Fate of the Axis

3.4. Model Reduction

Model reduction is aimed at simplifying the system for better comprehensibility and understanding. The goal of model reduction is to retain essential species and interactions to achieve a robust and concise model for precisely replicating and predicting the outcome of a biological system. The model reduction was thus, adopted for the reconstructed hIAPP-mediated β-cell toxicity axis to eliminate extraneous elements and parameters aiding its precise prediction. The 3D Quasi-potential landscape graph was generated considering the molecular flux, sensitivity and concentration of species over the time duration of 100s (Figure 5). The graph exhibited a peak-like pattern, which effectively demonstrated the concentration of high flux reactions and principal components at the top of the peak. The species with low molecular flux, sensitivity and concentration descended from the peak and were distributed at the bottom of the plot. The model reduction peak thus, represented the focal point of the network's dynamics and the most influential components within the system.

3.5. Crosstalk Point Determination

Cross-talk points serve as critical hubs where various signalling pathways converge through molecular components, allowing for extensive communication and coordination across distinct biological processes. Within

the reconstructed mathematical model for hIAPP-mediated β-cell toxicity axis, a total of eight cross-talk points was identified communicating across crucial signalling pathways. These cross-talk points include caspases, cytoC, IL1β, PKC, NLRP3, ATF6, PERK and IRE1 (Figure 6). Each of these species represents a point of convergence or intersection of insulin signalling, glycolysis, polyol signalling, TCA cycle, GPCR signalling, RAGE signalling, autophagy, ER stress, and Mitochondrial stress and apoptosis in the hIAPP-mediated β-cell toxicity axis culminating to facilitate the pathogenicity of the disease.

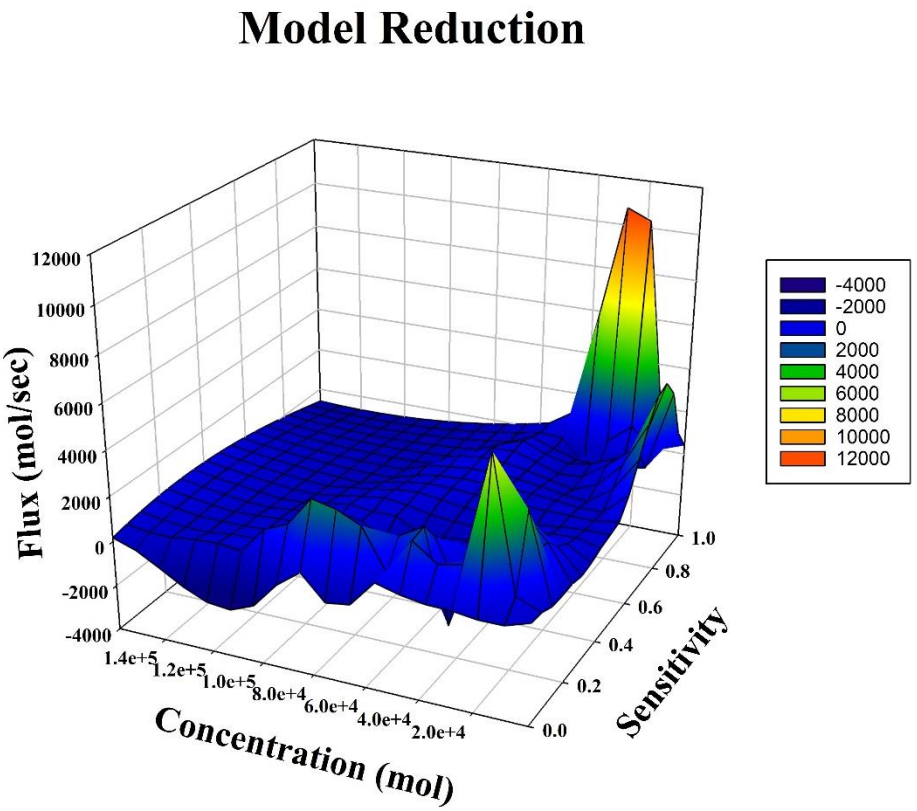

Figure 5: 3D Quasi-Potential Landscape Graph Representing Model Reduction. The Peak-like Pattern Reflects Concentration of High Flux Reactions and Principal Components at the Top of the Peak. X-axis = Sensitivity Score, Y-axis = Molecular Concentration and Z-axis = Molecular Flux

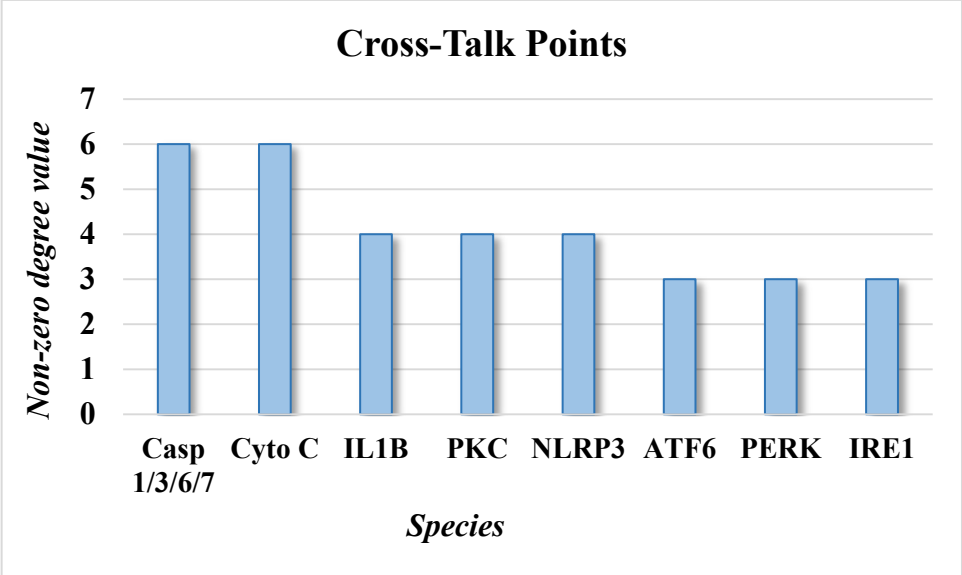

Figure 6: Crosstalk Points

4. Discussion

In our present study we have investigated the hIAPP-mediated β-cell toxicity axis through mathematical modelling using computational tool – MATLAB SimBiology ToolBox. The MATLAB SimBiology Toolbox is a potent tool widely used in systems and computational biology for mathematical modelling and simulation of complex biological systems. It offers a comprehensive platform to replicate, reconstruct, analyse and capture the multifaceted dynamics of intricate biological processes [39]. Our mathematical model facilitated the quantitative identification of signalling intermediates, metabolic switches, and feedback loops that collectively drive β-cell dysfunction and apoptosis. The hIAPP-mediated β-cell toxicity axis in T2DM is characterized by the dysregulation of several biological processes that culminate to apoptosis and contribute to loss of β-cell mass. The reconstructed signalling network captured the convergence of metabolic stress pathways, proteotoxicity, cellular homeostasis and inflammatory signalling as emergent properties of the system. Our data highlights the activation and aberrant expression of crucial signalling intermediates such as PKC, IRS1, REDD1, XBP1, PERK, IRE1, ROS, cytoC, GαS/GαQ, calpain, p62, NLRP3, interleukins and caspases as a whole system that augment the pathogenic effects of hIAPP oligomers. The parameter estimation and model simulations were regulated in such a manner that the mathematical model could mimic the behaviour of the signalling events taking place in the β-cell during the course of islet amyloidosis in T2DM. A key insight provided by the model was the identification of trigger-event reactions. In mathematical modelling of biological networks an event describes a particular process discretely transitioning from its normal functioning and progresses towards an abnormality. These transitions occur when a customized time and concentration condition becomes true. Such conditions are defined as Event objects in the model as they have the trigger property that must be true for an event to execute. For instance, if a specific simulation time is considered as a triggering object, then at that time the amounts/values/parameters of a particular species are changed in such a way that an event occurs. In response to the dynamics of the events in the system certain other species are affected even though they are not tied to the triggering time or concentration. The reactions or species participating in triggering events are of great importance as they ultimately govern the fate of the biological processes causing it to switch or transition between normal and pathological forms during disease condition. The trigger events used in this model represent the 'tipping points' where a healthy β-cell begins to fail. The trigger event reactions were associated with the processes like sorbitol production, PKC hyperactivation and insulin resistance, activation of UPR intermediates, autophagic defect and β-cell starvation representing critical switches that drive the β-cell from adaptation to dysfunction during the course of disease. We selected the five reactions mentioned in Table 2 because they act like biological switches that are only flipped under the extreme conditions and concentrations. For example, the shift in glucose metabolism mechanism from glycolysis to sorbitol production and the activation of PKC represent the first stage of the disease, where high glucose and hIAPP aggregates force the cell's metabolism to go off-track. This leads to a pathogenic cycle where the cell tries to produce more insulin to compensate, but instead causes ER stress because the cell's protein-folding machinery (BiP) becomes overwhelmed. These, trigger event reactions incorporated into the system signifies the control of the disease state and function as bottleneck reactions that heavily influence network stability. The use of trigger events helped us in tracking the evolutionary behaviour of biological processes and the reach of pathological effects of hIAPP oligomers mediating β-cell toxicity.

According to various factors, including the biochemical process involved, the kinetic law used, and the set of parameters the components are subjected to, the sensitivity analysis of the model provided information about the most important signalling species that have a significant impact on the output of the entire system. Sensitivity analysis provides in-depth understanding of how mathematical models should be operated to best mimic the behaviour of biological networks and events, where each component of the signalling cascade is sensitive to the action of others. Using SimBiology we computed time-dependent sensitivities of all species depending on their initial concentration and parametric values. Additionally, highly linked species in the biological network that tend to convey the most information from one end to the other were identified using PCA. The identified molecular species had strongest influence on the pathological behaviour of the axis; these included methylglyoxal-induced fibril formations, ER stress sensors (PERK, IRE1, ATF6), mitochondrial amplifiers (cytochrome c, ROS), metabolic intermediates (methylglyoxal, α-ketoglutarate), lysosomal depletion and autophagy-associated molecules (p62, Gαs/Gαq, calpain, NLRP3, caspases) as key pathogenic regulators driving disease progression. Thus, because of their importance in establishing the phenotype of the biological axis, removing them from the network might cause the network to collapse. The rate at which a metabolite or a signalling component is synthesized is also very important. In light of the fact that this rate will ultimately determine the outcome of the system, a higher rate of the reaction implies greater flux which is important for the axis to maintain its nature. Flux analysis, provided a quantitative rationale for the dysregulated expression of signalling intermediates emphasizing high molecular flux reactions involved in regulating glycation processes, formation of toxic amyloid intermediates, lysosomal depletion, autophagic defect, mitochondrial stress and β-cell death. While these processes have been individually described in experimental studies, our model demonstrates how their coordinated activation under extreme metabolic stress drives a systemic collapse of β-cell homeostasis. The reactions identified as high flux under steady-state conditions were enriched for pathways and processes highlighted by sensitivity and PCA analyses, indicating consistency between network topology. This supports the robustness of the model-derived conclusions and underscores the functional importance of these reactions in shaping disease progression. Next, the quasi-potential landscape graph for model reduction demonstrated a peak-like structure which indicated the concentration of high flux reactions and principal components at the peak of the dome. The entire model was reduced by 86% retaining only the essential components and interactions, involved in facilitating the dynamic outcome

of the biological system (Figure 4). Despite this reduction, the model preserved the pathological behaviour of the full system. Sensitivity analysis, PCA and flux analysis confirms the fidelity of the reduced model retaining the dynamics of the pathological axis. Time-resolved concentration profiles of key output species, highlighting various signalling intermediates exhibits steady-state behaviour, as detailed in the Supplementary Data. The reduced model thus, identifies a minimal set of components sufficient to recapitulate β-cell failure, thereby enabling more focused experimental validation and therapeutic exploration. The systems-level reconstruction further pointed critical cross-talk molecules facilitating the inter-communication among different biological processes that helps us trace the reach of the axis and nature of the dynamic activities of the system. The cross-talk points such as IL-1β, NLRP3, cytochrome c, caspases, and RAGE came out as nodal regulators that integrate signals from multiple pathways and processes involved in shaping the pathogenicity of toxic hIAPP oligomers in β-cells.

When viewed among existing literature, these model-driven findings align with known features of T2DM pathophysiology, including progressive β-cell loss, ER stress, mitochondrial dysfunction, autophagic defect and insulin resistance. One of the most crucial processes – autophagy, where polyubiquitinated proteins are destined for degradation through ubiquitin binding p62/sequestosome 1 (SQSTM1) which itself gets degraded in autophagosome along with the cargo. During islet amyloidosis defective autophagy in β-cells results in accumulation of p62 forming cytoplasmic inclusions as an indicator of impaired autophagic flux. Our model captures the highlight of this defective process which is linked by the malfunctioning of many other processes in the system. Thus, the strength of the present study lies in integrating these processes into a single quantitative framework that is easy to interpret and reveals the hierarchical organization and dynamic interdependence. While prior studies have implicated hIAPP oligomers in β-cell toxicity, our model provides mechanistic insight into how metabolic overload, proteostasis failure, autophagic defect, imbalance in K^+/Ca^{2+} concentrations, translational errors and inflammatory responses collectively drive disease progression.

Type 2 Diabetes Mellitus remains a significant global health issue due to its widespread occurrence, as well as its morbidity and mortality rates. The rapid pace of economic growth, urbanization, and abrupt lifestyle shifts have contributed and will keep contributing to the increasing global burden of T2DM [40]. Current estimates suggest that over 530 million adults are affected, with projections indicating that this number could exceed 780 million by 2045 if effective prevention and treatment strategies are not implemented [41]. T2DM extends beyond hyperglycemia, representing a complex multisystem disorder associated with cardiovascular, neural, renal, and hepatological complications. These collectively contribute to increased global disability and premature mortality rates [42]. A hallmark of T2DM is the progressive reduction in pancreatic β-cell function and mass, primarily driven by the advancement of islet amyloidosis. Islet amyloidosis is characterized by the accumulation of amyloid fibrils, predominantly composed of human islet amyloid polypeptide. It is estimated that amyloid deposits are present in over 90% of patients with longstanding T2DM, highlighting their critical role in the disease pathology [12]. Far from merely being inert aggregates, hIAPP oligomers are cytotoxic species that disrupt β-cell membranes, induce oxidative and ER stress, cause insulin resistance, and initiate apoptotic cascades [43,44]. The toxic effects of hIAPP oligomers on β-cells are multidimensional. Their interaction with receptors activates toxic signalling intermediates that facilitate calcium influx, leading to autophagy defects and mitochondrial dysfunction through ROS generation. Additionally, in line with metabolic overload, oligomers induce ER stress by overwhelming its protein folding capacity and activating unfolded protein response signalling through PERK, IRE1, and ATF6 [23].

Although, islet amyloidosis in not a condition that has gone unaddressed however, the intricate mechanisms that the toxic hIAPP oligomers intervene with to mediate β-cell toxicity are yet to be fully elucidated. Certain reports suggest that hIAPP oligomers can cross the blood-brain barrier and have been shown to deposit in the brain, kidneys, heart, and liver of individuals with T2DM, where they contribute to neuroinflammation, nephropathy, cardiomyopathy, and hepatic dysfunction [45-47]. These extraprancreatic effects explain the high mortality risk associated with T2DM highlighting the importance of developing new therapeutic approaches that address amyloid toxicity at its origin, rather than focusing solely on insulin sensitization in diabetic patients. Despite advances in diabetes management, current therapies largely fail to address the hIAPP aggregation or proteostasis defects. While the therapies like metformin improve insulin sensitivity and reduces hepatic glucose production, it does not effectively prevent amylin fibril formation or restore autophagic function, which may explain the continued progression of β-cell loss in patients despite receiving therapeutic care. The broader perspective of our systems-level analysis extends beyond pancreatic β-cells. Reports of hIAPP deposition in extrapancreatic tissues suggest that similar mechanisms may underlie systemic complications of T2DM. By identifying central regulatory hubs such as RAGE signaling, GPCR-mediated calcium influx, and autophagy–lysosome dysfunction, our model highlights potential combinatorial therapeutic targtes that may mitigate amyloid toxicity at its source rather than addressing downstream metabolic symptoms alone. Our findings provide a comprehensive framework that consolidates diverse experimental observations into a single mechanistic narrative. The mathematical model for the hIAPP-mediated β-cell toxicity axis was reconstructed using a number of enzyme kinetics and parameters which provided a computable framework of all the signalling components giving us valuable insights to predict the best behavioural outcomes of the system. The findings point toward potential combinatorial therapeutic strategies employed to modulate the receptor activities of RAGE and GPCR pathways. RAGE blockade has shown protective effects in models of atherosclerosis, neurodegeneration, and other diabetic complications suggesting that similar benefits may be achievable in the context of β-cell amyloidosis. Restoring autophagic flow and preventing lysosomal biogenesis errors can be one of the approaches used to modulate calcium influx by targeting the calcitonin receptor or GPCR signalling. The growing prevalence of this chronic condition, coupled with the

underappreciated role of hIAPP deposits and toxic oligomers, highlights the urgent need for innovative strategies that can protect β-cell functionality and improve long-term outcomes.

5. Conclusion

While the present study provides a systems-level framework for understanding hIAPP-mediated β-cell toxicity, several limitations should be acknowledged. The model is primarily constructed from curated literature and publicly available transcriptomic datasets, and therefore depends on the accuracy and completeness of existing biological knowledge. Although sensitivity analysis, PCA, and flux profiling provide robust internal validation, direct experimental validation of individual model predictions was beyond the scope of the current study. Consequently, further refinement of the model will require stepwise experimental validation of key regulatory components and trigger-event reactions through targeted in vitro and in vivo studies. Such experimental fine-tuning will enable optimization of kinetic parameters and improve the physiological fidelity of the model. Once adequately validated, the model may serve as a predictive platform to explore therapeutic target modulation and simulate β-cell responses under pathological conditions.

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The Preprint

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Conflicts of interest

The authors have no conflicts of interest to declare.

Data availability

Data will be made available on reasonable request.

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