Tseng *Nutrition & Metabolism* (2024) 21:65
https://doi.org/10.1186/s12986-024-00840-w

Nutrition & Metabolism

RESEARCH Open Access

Comparative mathematical modeling reveals the differential effects of high-fat diet and ketogenic diet on the PI3K-Akt signaling pathway in heart

Yu-Yao Tseng[1*]

Abstract

Background Obesity is a global health concern associated with increased risk of diseases like cardiovascular conditions including ischemic heart disease, a leading cause of mortality. The ketogenic diet (KD) has potential therapeutic applications in managing obesity and related disorders. However, the intricate effects of KD on diverse physiological conditions remain incompletely understood. The PI3K-Akt signaling pathway is critical for heart health, and its dysregulation implicates numerous cardiac diseases.

Methods We developed comprehensive mathematical models of the PI3K-Akt signaling pathway under high-fat diet (HFD) and KD conditions to elucidate their differential impacts and quantify apoptosis. Simulations and sensitivity analysis were performed.

Results Simulations demonstrate that KD can reduce the activation of key molecules like Erk and Trp53 to mitigate apoptosis compared to HFD. Findings align with experimental data, highlighting the potential cardiac benefits of KD. Sensitivity analysis identifies regulators like Trp53 and Bcl2l1 that critically influence apoptosis under HFD.

Conclusions Mathematical modeling provides quantitative insights into the contrasting effects of HFD and KD on cardiac PI3K-Akt signaling and apoptosis. Findings have implications for precision nutrition and developing novel therapeutic strategies to address obesity-related cardiovascular diseases.

Keywords High-fat diet, Ketogenic diet, Mathematical modeling, PI3K-Akt signaling pathway, Cardiovascular diseases, Precision nutrition, Therapeutic strategies

Introduction

Dietary patterns significantly impact health. High-fat diet (HFD) can induce obesity and significantly elevates morbidity and mortality, primarily through cardiovascular disease (CVD) and diabetes, while also fostering other health problems like cancer, chronic diseases (e.g., osteoarthritis), liver and kidney issues, sleep apnea, and depression [1, 2]. In heart, obesity induced by HFD can induce oxidative stress, apoptosis, pathological cardiac

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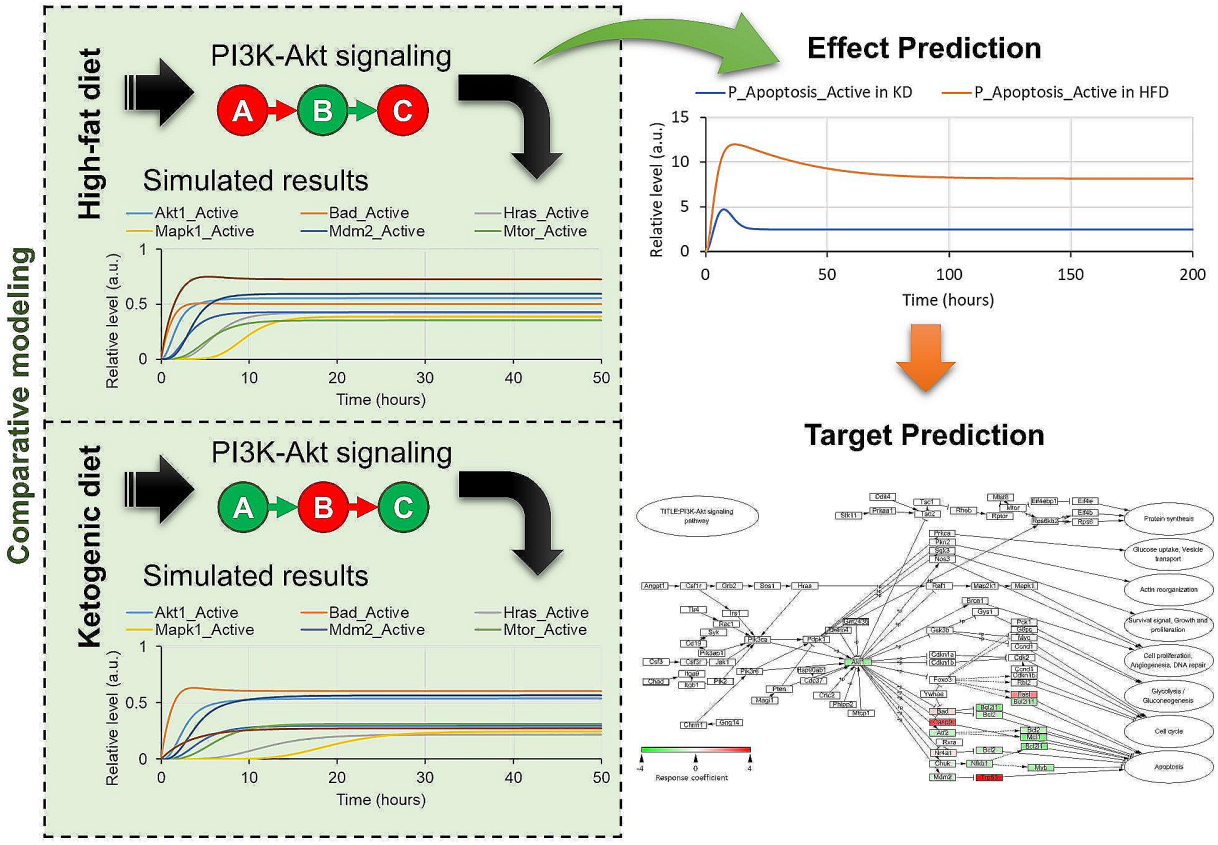
Graphical abstract



remodeling, and heart failure [3–8]. Apoptosis can lead to acute and chronic loss of cardiomyocytes and has a strong correlation with various heart diseases, including myocardial infarction, ischemic heart disease, and heart failure [9, 10].

Ketogenic diet (KD) has been used to reduce the frequency of seizures and improve health conditions during the treatment of obesity, diabetes, and other diseases [11]. KD induces a state of ketosis, predominantly utilizing fat for energy, leading to significant weight loss and improved metabolic markers, though concerns exist regarding nutrient deficiencies and lipid profile alterations [12, 13]. Furthermore, KD's impact on cardiovascular health remains a topic of debate, with studies reporting both favorable lipid profile changes and potential risks, especially in individuals with underlying cardiac conditions [14–16].

HFD and KD effects are closely related to the PI3K-Akt signaling pathway. Evidence has shown that HFD affects the PI3K-Akt signaling pathway and significantly leads to apoptosis in various tissue types, including liver [17], pancreatic β-cells [18], retina [19], brain [20], and heart [7, 21]. In heart, the effects of HFD on the PI3K-Akt signaling pathway is a paradoxical phenomenon and still need to be investigated. HFD exhibits contrasting effects on Akt activation in mouse cardiovascular cells: some studies show activation [22], while others report repression [23, 24]. Further research is essential to unravel the underlying mechanisms. The effects of KDs on the PI3K-Akt signaling pathway are also controversial. KD was found to be able to activate the Akt signaling pathway in type 2 diabetic mice and inhibit apoptosis [25, 26]. However, contrasting evidence is also present in the scientific literature. KD may lead to impairments in PI3K-Akt signaling and increased oxidative stress in mice, potentially exacerbating cardiovascular risks [25]. These findings underscore the complexity of KD's effects on cardiovascular health and the PI3K-Akt pathway, with outcomes varying depending on factors such as diet composition and the patient's medical condition. In summary,

the impact of KD on cardiovascular health, including its effects on the PI3K-Akt signaling pathway, remains a multifaceted topic with evidence of both potential benefits and risks. Further research is needed to elucidate the mechanistic intricacies and to provide comprehensive insights into the precise role of KDs in cardiovascular health.

The PI3K-Akt signaling pathway is the key regulator and is involved in many critical cellular biological processes, including the metabolism of glucose and lipid, cell proliferation, differentiation, growth, and apoptosis [27]. Because of its critical role and applicability for the development of drugs to be used in many diseases, including cancer, inflammation, diabetes, neurodegeneration, and traumatic spinal cord injury, multiple inhibitors and drugs have been developed. The PI3K-Akt signaling pathway is a complex interaction network that contains 364 genes according to the KEGG database. A dynamic quantitative model is necessary to be developed to understand the dynamic status of the mechanisms within the signaling pathway and the effects under certain biological phenomenon or condition. Therefore, we need a quantitative model to simulate the effects of HFD and KD on the PI3K-Akt signaling in heart, to compare the effects under different diet conditions, and to predict the therapeutic effects and adverse effects of KD.

Mathematical modeling is a powerful tool and has been widely used for investigating signaling pathways [28], which are complex networks of molecular interactions that regulate cellular processes. Mathematical models can be used to generate quantitative insights into the dynamics and behavior of signaling pathways, test hypotheses about their mechanisms, and predict their responses and subsequent interactions to different stimuli [29–31]. Abstract models can consider the key features of signaling pathways and detailed models can be used to describe the dynamics of specific pathways in specific organisms [32, 33]. Recently, to construct more comprehensive and precise mathematical models, systematic gene expression profiles have been incorporated into the model [30, 34]. Although many mathematical models of signaling pathways have been proposed, the effects of diet styles on signaling pathways are rarely modeled. Here we propose the first dynamic quantitative models of the PI3K-Akt signaling pathway in heart under HFD and KD conditions. Our model incorporates the majority of the known AKT signaling components and the gene expression profiles from microarray analysis [35, 36]. The signal transduction of PI3K-Akt and the effects of HFD and KD on the PI3K-Akt signaling pathway are successfully simulated in the model. The effects of inhibitors on the PI3K-Akt signaling pathway are also simulated in the model. This model gives a more comprehensive and precise understanding of how diet styles affect signaling and provides a platform for investigating novel therapeutic strategies and administration times.

Methods

Model construction

To model and compare the diet effects on PI3K-Akt signaling in heart, the gene expression profile in HFD and KD was divided by normal diet expression levels and used to consider the initial relative quantity of the inactive components in the model. The expression profile was obtained from the microarray data GSE21368 and GSE150229, which is available on the Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/). For the gene with multiple probes, the reads from the probes are averaged to estimate the expression level.

To capture the pathway structure of mouse PI3K-Akt signal transduction, we use the KEGG database (KEGG ID: mmu04151) to understand the pathway and to design the model. Each of the components in the model is separated into the activated form and the inactivated form to model signal transduction. For simplicity and to maintain a manageable level of complexity, protein expression and degradation reactions are ignored, and there are only two types of reactions: activation/inactivation without regulators and activation/inactivation with regulators. This approach allows us to focus on the key signaling events and regulatory mechanisms within the PI3K-Akt pathway while avoiding the introduction of additional parameters that may not be well-constrained by available data. For activation/inactivation reactions v_i without regulators, the kinetic equation is shown in Eq. (1).

$$v_i = \frac{vmax\_v_i * [Substrate]^{H_i}}{ksp\_{v_i}^{H_i} + [Substrate]^{H_i}} \quad (1)$$

where $vmax\_v_i$ represents the forward maximal velocity of reaction v_i and ksp_v_i represents the half saturation constant of the substrate. H_i is the Hill coefficient of this reaction. The concentration of the substrate is represented as [*Substrate*]. For activation/inactivation reactions v_j with regulators, the kinetic equation is shown in Eq. (2).

$$v_j = \sum_{k=0}^{n} \frac{kcat\_v_{jk} * [Regulator_k] * [Substrate]^{H_{jk}}}{ksp\_{v_{jk}}^{H_{jk}} + [Substrate]^{H_{jk}}} \quad (2)$$

where $kcat\_v_{jk}$ represents the substrate catalytic rate constant of the $regulator_k$ and ksp_v_{jk} represents the half saturation constant of the substrate. H_{jk} is the Hill coefficient. The concentration of the k-th regulator is denoted as [$Regulator_k$]. The kinetic effects of multiple regulators are summed in this equation. The model is

constructed and simulated using the CellDesigner 4.4.2 software [37, 38] (RRID: SCR_007263).

In our model, pathway outputs are represented using the same activation and deactivation equations as other components in the PI3K-Akt pathway. While these outputs may not undergo activation or deactivation in the strictest sense, we use these equations as a proxy for their overall activity, which is ultimately regulated by the activation state of upstream signaling components. For example, the activation of protein synthesis (P_ProSyn) is modeled using Eq. (2), with the regulators being the activated forms of upstream components such as Eif4b, Eif4e, and Rps6. The rationale behind this approach is that the activity of protein synthesis is directly influenced by the activation state of these upstream regulators. We acknowledge that using activation and deactivation equations for pathway outputs is a simplification and may not capture the detailed dynamics of production and degradation. However, we believe that this approach still allows us to investigate the relative changes in pathway output activity under different dietary conditions (HFD vs. KD) and provides valuable insights into the overall behavior of the PI3K-Akt pathway.

Our model consists of 180 species (82 proteins and 8 pathway outputs), 648 parameters, and 180 biochemical reactions. The complete list of the protein components with their respective Entrez Gene IDs is shown in Supplementary Table 1. The initial inactive values of the pathway output components are set to 100. The complete list of the reactions and their regulators in the model are shown in Supplementary Tables 2, 3.

Sensitivity analysis

The apoptosis response coefficients specify how the apoptosis steady state $Apoptosis^{ss}$ change due to a perturbation of an enzyme i initial concentration x_i^0 change.

$$R_i^{Apoptosis} = \frac{x_i^0}{Apoptosis^{ss}} \cdot \frac{\partial\, Apoptosis^{ss}}{\partial\, x_i^0} \tag{3}$$

The sensitivity analysis is carried out by using the COPASI 4.36 software [39] with the function of "sensitivities". The result figures are plotted with the Cytoscape 3.9.1 software [40].

Modeling inhibitor effects on the PI3K-Akt signaling pathway

To model the inhibition effects of Akt1, Bad, and Mdm2 inhibitors on the PI3K-Akt signaling pathway under HFD condition, we decrease the activation of Akt1, Bad, and Mdm2 by multiplying an inhibition constant ki_Akt1_Activation, ki_Bad_Activation and ki_Mdm2_Activation to the rate of Akt1, Bad and Mdm2 activation, respectively. The initial value is set to 1 without inhibition. The kinetic equations are shown as follows:

When the activation reaction has no regulator, the kinetic equation is:

$$v_{i\_inhibition} = \frac{v\max\_v_i * [Substrate]^{H_i}}{ksp\_{v_i}^{H_i} + [Substrate]^{H_i}} \cdot ki\_i\_Activation \tag{4}$$

When the activation reaction involves regulators, the kinetic equation is:

$$v_{j\_inhibition} = \sum_{k=0}^{n} \frac{kcat\_v_{jk} * [\mathrm{Re}\,gulator_k] * [Substrate]^{H_{jk}}}{ksp\_{v_{jk}}^{H_{jk}} + [Substrate]^{H_{jk}}} \cdot ki\_j\_Activation \tag{5}$$

In the kinetic equations, vi_inhibition and vj_inhibition represent the inhibited reaction rates. The inhibition constants for the activation of the respective proteins are denoted as ki_i_Activation and ki_j_Activation.

Results

The PI3K-Akt signaling model

We developed a model of the PI3K-Akt signaling to provide a platform for investigating the effects of HFD and KD on PI3K-Akt signaling. Figure 1 provides an overview of the key components described in this paper. For a detailed diagram including all components, please refer to Supplementary Fig. 1. The core of the model is the PI3K and Akt (highlighted in red) proteins. In addition to the PI3K-Akt signaling pathway, this model also considers critical components related to mTOR (highlighted in blue) signaling pathway, MAPK (highlighted in orange) signaling pathway, FoxO (highlighted in green) signaling pathway, NF-κB (highlighted in cyan) signaling pathway, p53 (highlighted in purple) signaling pathway, ErbB signaling pathway, insulin signaling pathway, VEGF signaling pathway, Toll-like receptor signaling pathway, B cell receptor signaling pathway, JAK-STAT signaling pathway, Focal adhesion and Chemokine signaling pathway. The pathway outputs of this model include protein synthesis (P_ProSyn); cell proliferation, angiogenesis and DNA repair (P_ProAagioDNAre); glucose uptake and vesicle transport (P_GuptakeVesi); actin reorganization (P_ActinRe); survival signal, growth and proliferation (P_SurGroPro); glycolysis / gluconeogenesis (P_Metabolism); cell cycle progression (P_CellCycle); apoptosis (P_Apoptosis). The HFD model and the KD model are available as Supplementary File 1 and Supplementary File 2, respectively.

Modeling the impact of HFD and KD on PI3K-Akt signaling

The simulated results presented in Fig. 2 provide a comprehensive overview of the dynamics of key signaling molecules in the PI3K-Akt pathway under both HFD and KD conditions. The initial concentration of the inactive

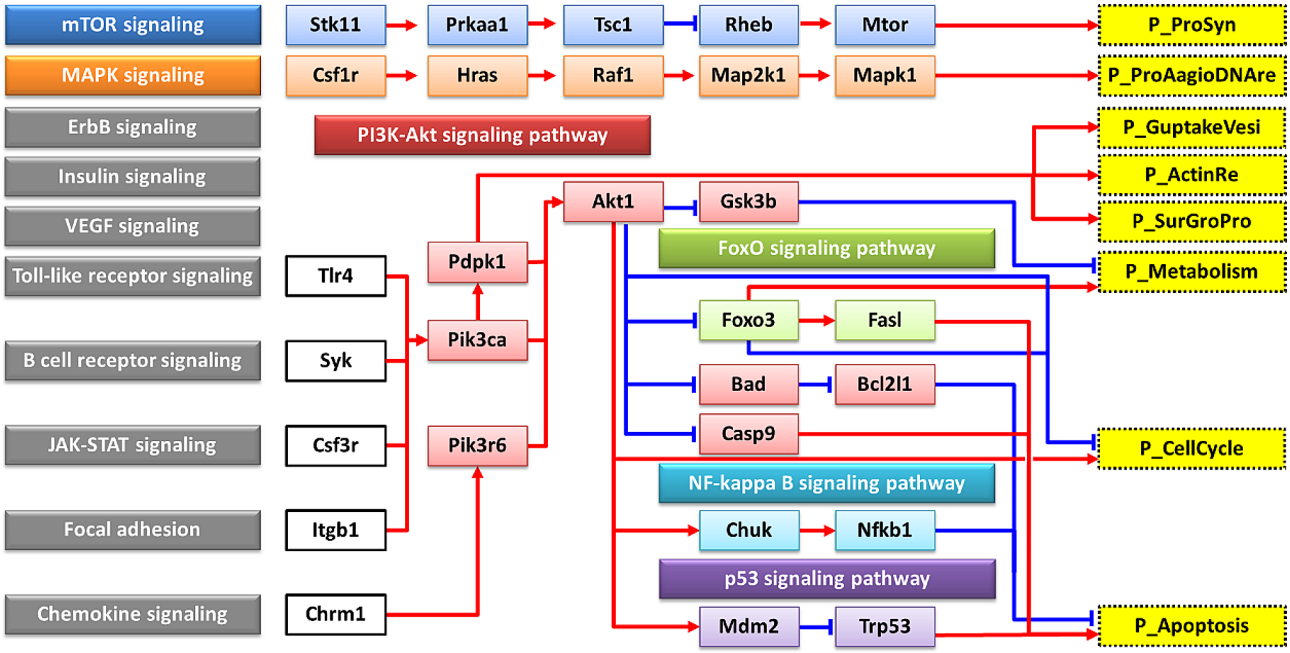


Fig. 1 The simplified scheme of the PI3K-Akt signaling pathway mathematical model. This figure illustrates the core components and interactions within the PI3K-Akt signaling pathway, along with its integration with other critical signaling pathways, such as mTOR (blue), MAPK (orange), FoxO (green), NF-κB (cyan), and Trp53 (purple). The model outputs, depicted in yellow, encompass various cellular processes influenced by these pathways, including protein synthesis (P_ProSyn), cell proliferation, angiogenesis, and DNA repair (P_ProAagioDNAre), glucose uptake and vesicle transport (P_GuptakeVesi), actin reorganization (P_ActinRe), survival signaling, growth, and proliferation (P_SurGroPro), glycolysis and gluconeogenesis (P_Metabolism), cell cycle progression (P_CellCycle), and apoptosis (P_Apoptosis). This schematic serves as an overview of the complex interactions modeled to study the effects of HFD and KD on PI3K-Akt signaling

forms and the genes considered in the model are shown in Supplementary Table 1. The initial concentrations of the active forms are set to 0. To maintain simplicity and ensure consistency in our simulations, we set all parameters to a value of 2, with the exception of the inhibition constants ki_Akt1_Activation, ki_Bad_Activation, and ki_Mdm2_Activation, which were allowed to vary to simulate the effects after inhibition. The use of Hill equations to model the reactions in our study is justified by the fact that the activation and inactivation processes in signaling pathways can be considered as enzymatic reactions.

Under the influence of HFD, our computational model demonstrates distinct activation kinetics for various key components of the PI3K-Akt signaling pathway. Notably, at the early stages, we observe rapid activation of Trp53 (Trp53_active), Bad (Bad_active), and Akt (Akt1_active). As the simulation progresses, the activation of PI3K (Pik3ca_active) and Mdm2 (Mdm2_active) becomes prominent during the middle stages. Finally, during the late stages of the simulation, Mtor (Mtor_active), Ras (Hras_active), and Erk (Mapk1_active) exhibit substantial activation (Fig. 2A). In contrast, when the system is subjected to a KD, we observe a nuanced shift in the activation profiles within the PI3K-Akt signaling pathway. Bad (Bad_active) is rapidly activated during the early stages of the simulation, akin to the HFD condition. However, under KD conditions, Akt1 (Akt1_active), Pik3ca (Pik3ca_active), Trp53 (Trp53_active), Mdm2 (Mdm2_active), and mTOR (Mtor_active) exhibit notable activation during the middle stages. Interestingly, RAS (Hras_active) and Erk (Mapk1_active) demonstrate delayed activation, occurring primarily during the late stages (Fig. 2B). These simulated results show that the KD is able to reduce the activation of Erk, Trp53, and apoptosis in comparison to HFD. Several studies have shown that Erk is activated in HFD [41, 42] and repressed in KD [43]. Trp53 is activated in HFD [44, 45] and repressed in KD [46, 47]. In addition, Trp53 was also found to be closely related to the apoptosis of cardiacmyocytes [48], suggesting that Trp53 plays an important role in the cardiacmyocyte apoptosis in HFD. The simulated results are in agreement with experimental data. Further studies need to be carried out to elucidate the specific molecular mechanisms by which KD exerts its protective effects on cardiacmyocytes, potentially unveiling novel therapeutic targets for mitigating apoptosis and preserving cardiac health in HFD-induced conditions.

Figure 2C depicts the dynamics of apoptosis under both HFD and KD conditions. In this figure, the y-axis represents the relative abundance of apoptotic factors normalized to normal diet conditions. Therefore, values below 1 signify downregulation of a given component compared

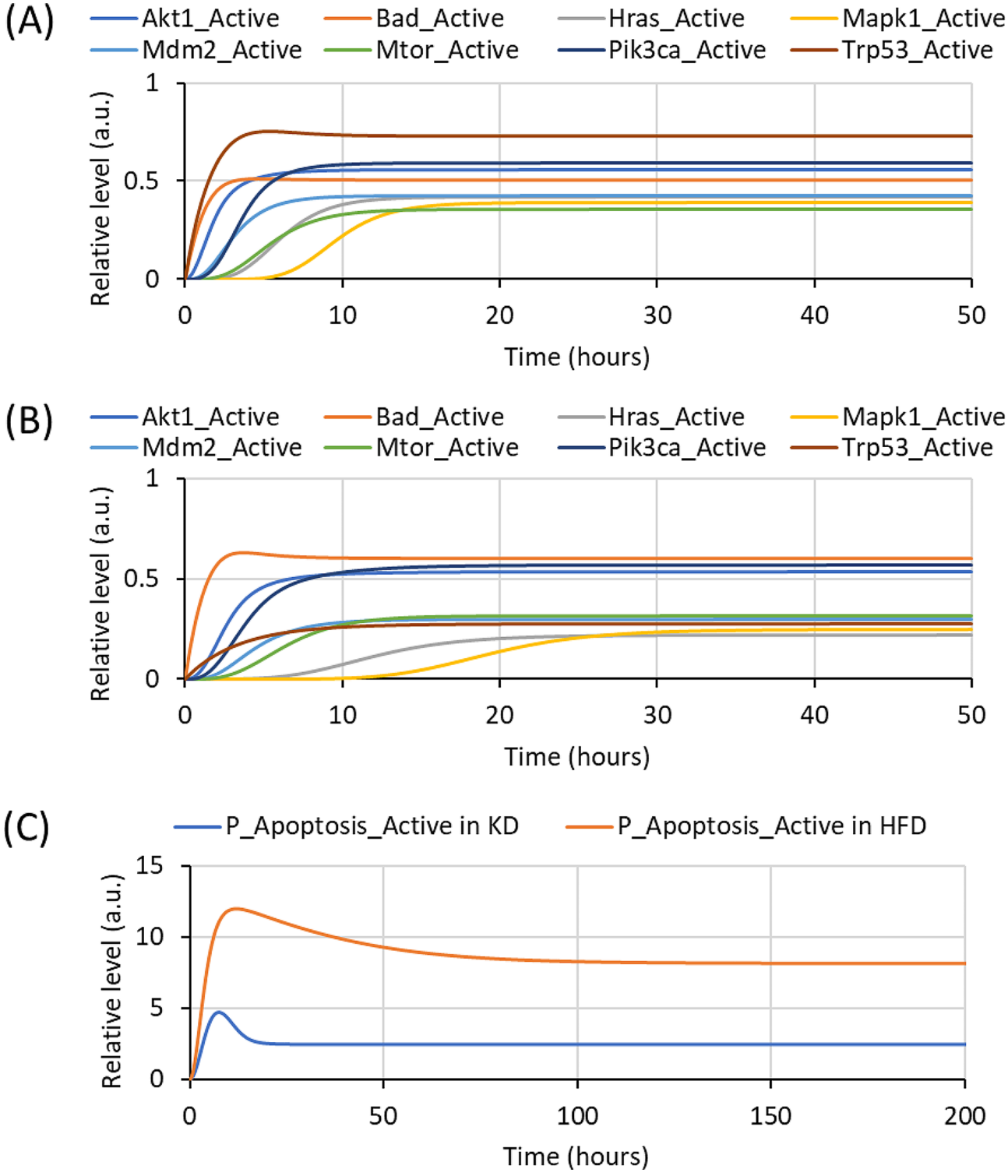


Fig. 2 Modeling high-fat diet (HFD) and ketogenic diet (KD) effects on the PI3K-Akt signaling pathway. **(A)** Under HFD, the model shows early activation of Trp53, Bad, and Akt, followed by PI3K and Mdm2 activation in the middle stages, and Mtor, Ras, and Erk activation in the late stages. **(B)** Under KD, Bad is activated early, while Akt1, Pik3ca, Trp53, Mdm2, and mTOR are activated in the middle stages, and RAS and Erk show delayed activation. **(C)** Apoptosis is activated more rapidly and sustains a higher level in HFD compared to KD, consistent with experimental data

to the control, while levels above 1 indicate upregulation. Consistent with this interpretation, the figure shows that apoptosis is activated more rapidly and sustains a higher level in response to HFD compared to KD. However, it is important to note that both dietary conditions (HFD and KD) result in an upregulation of apoptotic factors compared to the normal diet, with HFD inducing a more pronounced apoptotic response. This observation is in line with previous experimental data [3, 7, 26], which suggests that HFD may have a more significant impact on promoting apoptosis.

We explored different combinations of parameter values (data not shown) and compared the simulated apoptosis activation levels with experimental data from the literature. The current model produces apoptosis activation levels consistent with the relative differences observed in experimental studies. It is important to acknowledge that assigning an arbitrary value of 2 to all parameters, except inhibition constants, is a limitation and prevents the model from being truly quantitative. Obtaining detailed kinetic data for all reactions in a large signaling network is challenging, and the current model serves as a starting point for understanding the relative changes in the system under different conditions. Despite the limitations, our model provides a valuable framework for understanding the complex interplay between dietary conditions and PI3K-Akt signaling in the heart. This work can guide future research, generate testable hypotheses, and contribute to the development of targeted therapies for diet-induced cardiac dysfunction.

Collectively, our model provides valuable quantitative insights into the differential effects of dietary conditions on the intricate dynamics of PI3K-Akt signaling, shedding light on potential mechanisms that warrant further investigation in the context of diet-induced cellular responses.

The apoptosis response coefficient in the HFD model

To systematically quantify how the components in the PI3K-Akt signaling pathway affects the activation level of apoptosis, we carried out the apoptosis response coefficient sensitivity analysis. The apoptosis response coefficients provide insights into how changes in the initial concentration of specific enzymes affect the steady state of apoptosis. Figure 3 illustrates the apoptosis response coefficients for various enzymes in the HFD model. Components with positive apoptosis response coefficients are highlighted in red and components with negative apoptosis response coefficients are highlighted in green. Notably, Trp53 exhibited the most positive apoptosis response coefficient, indicating its pivotal role in promoting apoptosis in response to perturbations. This finding underscores the significance of Trp53 in regulating apoptosis within the context of the HFD model and suggests that targeting Trp53-related pathways could have therapeutic implications. Conversely, our analysis identified Bcl2l1 as having the most negative apoptosis response coefficient in the HFD model. This intriguing result suggests that Bcl2l1 plays a critical role in inhibiting apoptosis under HFD conditions.

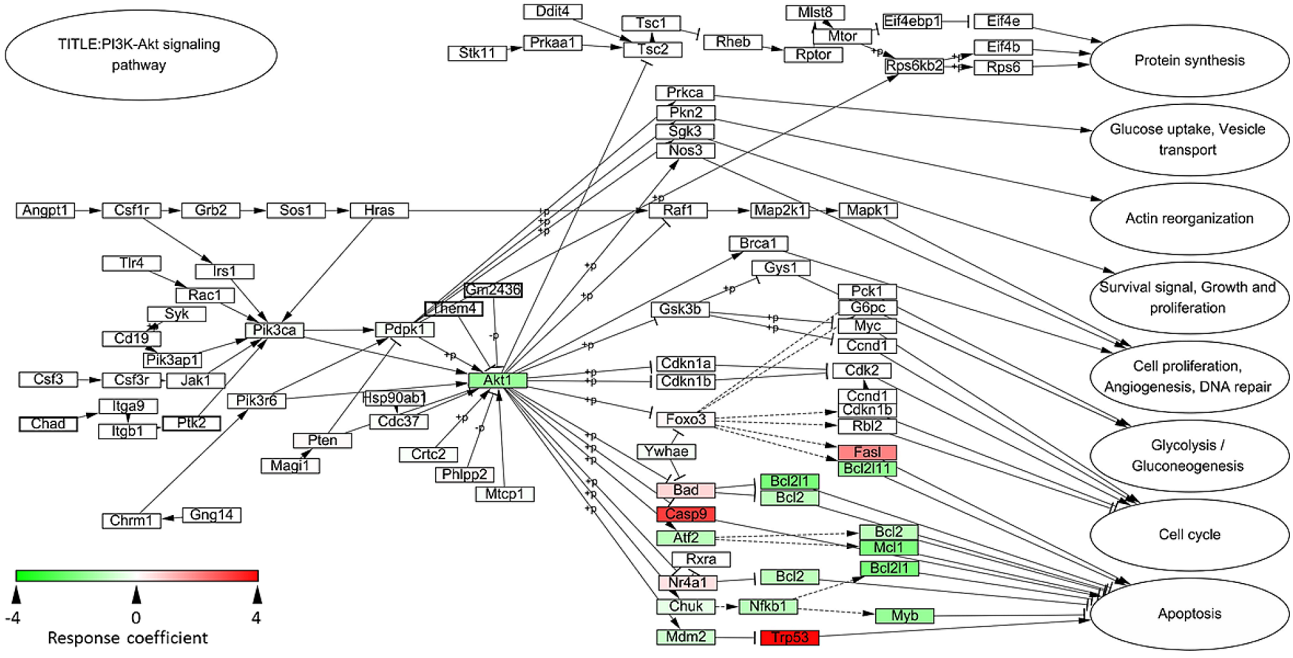


Fig. 3 The apoptosis response coefficient in the HFD model. Trp53 has the most positive apoptosis coefficient and Bcl2l1 has the most negative apoptosis coefficient

Modeling the effects of Akt1, bad, and Mdm2 inhibition on PI3K-Akt signaling in HFD

The apoptosis response coefficient has demonstrated how the components in the PI3K-Akt signaling pathway contribute to apoptosis in HFD. Further investigation is carried out to test the inhibition of critical components against apoptosis. Akt1 is the central component of the PI3K-Akt signaling pathway. Multiple drugs have been proposed to target Akt for various purposes in heart-related diseases [49]. Figure 4A illustrates the simulated consequences of inhibiting the activation of Akt within the PI3K-Akt signaling cascade under HFD conditions. A distinct differential increase in the level of apoptosis occurs when Akt activation is inhibited, both in the initial transient and steady-state phases. These results show that Akt is a key regulator in preventing excessive apoptotic responses induced by HFD. The inhibition of Akt activation appears to exacerbate apoptotic processes, emphasizing its role as a critical anti-apoptotic factor in HFD. Consequently, the use of Akt agonists, such as resveratrol [50], emerges as a promising strategy to mitigate myocardial cell apoptosis, thereby holding potential therapeutic value in ameliorating HFD-associated cardiovascular complications.

The PI3K-Akt signaling downstream Bad protein is a key apoptosis regulator and can induce apoptosis by inhibiting anti-apoptotic BCL-2-family members [51]. In Fig. 4B, computational simulations demonstrate that the inhibition of Bad activation results in a notable differential decrease in the level of apoptosis under HFD conditions, both in the initial transient and steady-state phases. These results are in agreement with experimental data [3, 51] and suggest that activated Bad may play an important role in promoting apoptosis under HFD conditions. Interestingly, our extended simulations revealed non-linear effects of Bad inhibition on steady-state apoptosis levels. While gradual inhibition of Bad (with ki_Bad_Activation from 1 to 0.2) increased apoptosis levels, complete inhibition (ki_Bad_Activation = 0) resulted in a reduced steady-state apoptosis level of 8.07, similar to the level observed without inhibition. This suggests that 100% inhibition of Bad may initially activate apoptosis rapidly, but stronger feedback mechanisms from other components in the model may subsequently inhibit apoptosis, leading to a lower steady-state level. These findings underscore the pivotal role of Bad in mediating apoptosis through the PI3K-Akt signaling pathway, highlighting its potential as a target for therapeutic interventions in HFD-induced obesity. Multiple drugs, such as anthocyanin, dexmedetomidine, and GABA tea, have been proposed to target Bad for various purposes in heart-related diseases [49].

The PI3K-Akt signaling downstream Mdm2 protein is also a key apoptosis regulator and can repress Trp53 and repress apoptosis [52]. Figure 4C shows the simulated consequences of inhibiting the activation of Mdm2 under HFD conditions. A distinct differential increase in the level of apoptosis when Mdm2 activation is inhibited, both in the initial transient and steady-state phases. Again, the inhibition of Mdm2 activation suggests that it may serve as a critical anti-apoptotic factor, exerting its influence to mitigate apoptosis and maintain cellular homeostasis in response to HFD. These results are also in agreement with experimental data [45, 52]. Consequently, the development of Mdm2 agonists emerges as a potential avenue for safeguarding cardiomyocytes against apoptosis in HFD-related scenarios.

Discussion

Obesity has become a global health epidemic and is a major risk factor for various diseases, including cardiovascular diseases such as ischemic heart disease [3, 6]. Understanding the molecular mechanisms underlying the effects of different diets on critical signaling pathways, such as the PI3K-Akt signaling pathway, is essential for developing effective therapeutic strategies and precision nutrition approaches to combat these health challenges. In this study, we developed a comprehensive mathematical model of the PI3K-Akt signaling pathway to investigate how HFD and KD impact this critical pathway in the heart.

Our model incorporates gene expression profiles from microarray data, allowing us to simulate the effects of HFD and KD on the PI3K-Akt signaling pathway with a high degree of accuracy. The model encompasses a wide range of components and reactions, including those related to Mtor, Mapk1, Foxo3, Nfkb1, Trp53, and more, reflecting the complexity of the PI3K-Akt signaling network. This comprehensive approach provides a quantitative and systematic view of the differential effects of dietary conditions on PI3K-Akt signaling.

Our simulations revealed intriguing insights into the dynamics of the PI3K-Akt signaling pathway under HFD and KD conditions. Notably, HFD appeared to induce a more pronounced apoptotic response compared to KD, suggesting that KD may have potential benefits in reducing apoptosis in the context of obesity-related cardiovascular diseases. This finding aligns with previous experimental data and underscores the importance of dietary choices in modulating cellular responses [3, 7, 26].

However, it's essential to recognize that while KD shows promise in mitigating apoptosis and improving metabolic markers in certain conditions, it may not be a one-size-fits-all solution. The usage conditions, benefits, and risks of KD in unique disease statuses should be systematically revisited. For instance, KD has been shown to be effective in reducing seizures in epilepsy patients and

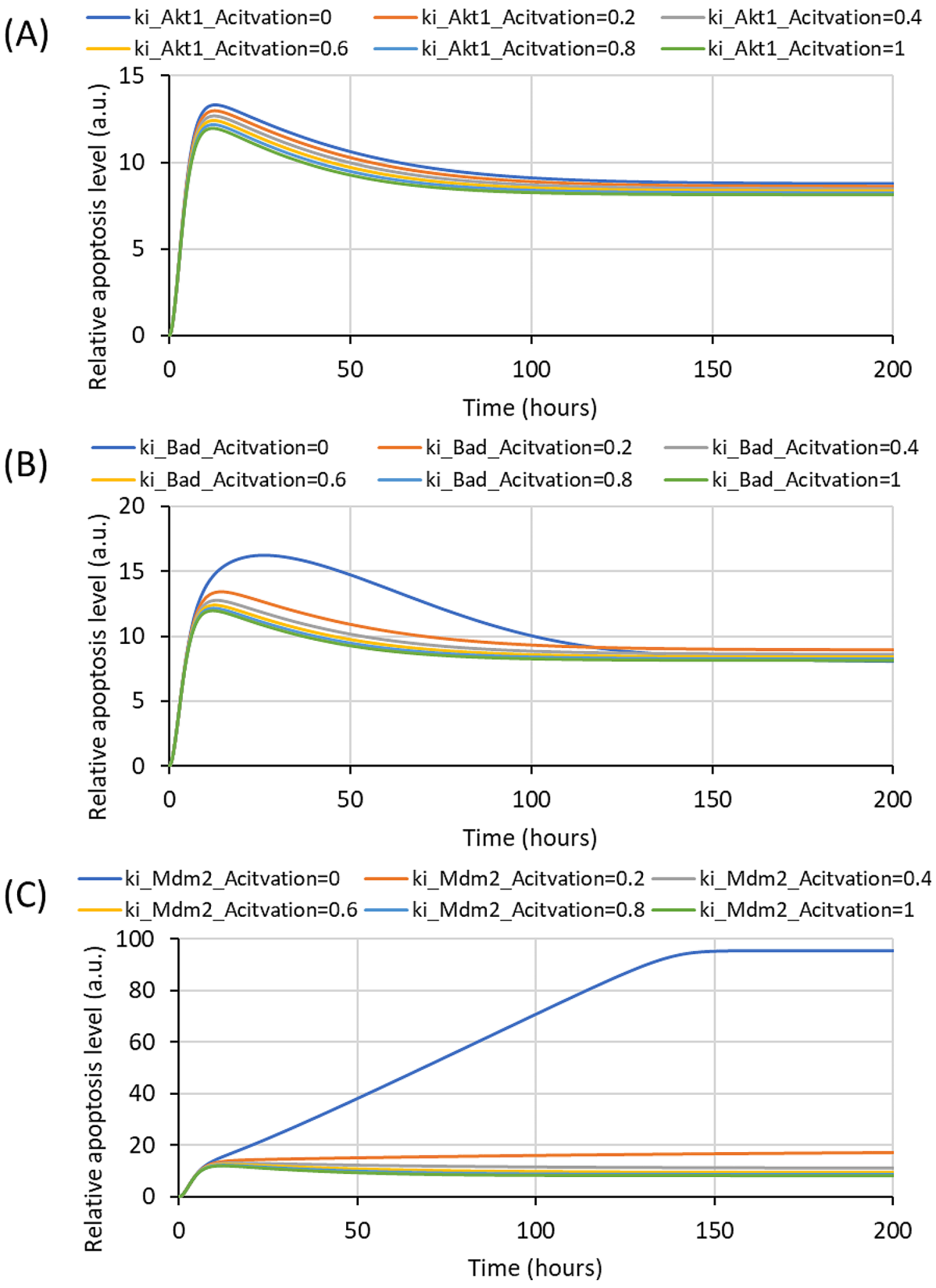


Fig. 4 Modeling the inhibition and activation of critical enzymes affecting apoptosis in HFD Simulated results depicting apoptosis levels upon inhibition of **(A)** Akt activation, **(B)** Bad activation, and **(C)** Mdm2 activation. Akt and Mdm2 inhibition lead to increased apoptosis, while Bad inhibition exhibits non-linear effects on steady-state apoptosis

improving insulin sensitivity in type 2 diabetes [11]. Still, concerns exist regarding potential nutrient deficiencies and lipid profile alterations, especially in individuals with underlying cardiac conditions [25].

Furthermore, our sensitivity analysis identified key PI3K-Akt signaling components, such as Trp53 and Bcl2l1, that play pivotal roles in regulating apoptosis under HFD conditions. Targeting these enzymes or related pathways could offer potential therapeutic avenues for mitigating apoptosis and its associated health risks. A recent study has shown that fortilin, a 172-amino-acid anti-p53 molecule, is able to prevent cardiomyocyte apoptosis and protects the heart against heart failure [53]. Novel therapeutic agents should be developed and further research should be carried out to evaluate their safety and efficacy.

Additionally, we explored the effects of inhibiting critical components of the PI3K-Akt signaling pathway, including Akt1, Bad, and Mdm2, under HFD conditions. Our simulations demonstrated that inhibiting Akt1 activation exacerbated apoptotic processes, highlighting its role as a crucial anti-apoptotic factor. Conversely, inhibiting Bad or Mdm2 activation resulted in a notable decrease in apoptosis, suggesting their potential as targets for intervention in obesity-induced heart diseases.

While our model provides valuable insights into the effects of HFD and KD on the PI3K-Akt signaling pathway, it is important to acknowledge its limitations. The current model relies on arbitrary parameter values, which prevents it from being truly quantitative. To address this limitation and improve the model, future work could focus on:

1. Conducting targeted experiments to measure key reaction rates and protein dynamics, allowing data-driven estimation of critical parameter values.
2. Sensitivity analysis to identify the most influential parameters and prioritize them for experimental measurement.
3. Leveraging available omics data (e.g., transcriptomics, proteomics) to better constrain parameter ranges.
4. Iteratively refining and calibrating the model by comparing simulation results with quantitative experimental data as it becomes available.

By incorporating these strategies, we aim to enhance the predictive power and accuracy of our model, enabling more precise and quantitative insights into the complex interplay between dietary conditions and PI3K-Akt signaling in the heart.

Conclusions

Our mathematical modeling approach provides a valuable platform for understanding the differential effects of dietary conditions on the PI3K-Akt signaling pathway in the heart. These insights have implications for precision nutrition, and the development of novel therapeutic strategies to combat obesity and related cardiovascular diseases. Future experimental studies are warranted to validate our computational predictions and explore the molecular mechanisms driving these observed dynamics further. Ultimately, this research contributes to our understanding of the intricate interplay between diet, signaling pathways, and cellular responses in the context of obesity-related health challenges.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12986-024-00840-w.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Acknowledgements
Not applicable.

Author contributions
Yu-Yao Tseng designed and implemented the research, processed the gene expression data, developed the model, analyzed the results, and wrote the manuscript.

Funding
This research is partially supported by Shih Chien University and Genesys Logic [USC-109-03-02017 and USC-111-05-02001].

Data availability
All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 20 December 2023 / Accepted: 28 July 2024
Published online: 09 August 2024

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