Mitochondrial Computational Models and Their Role in Cancer Metabolism: A Survey

Abstract

This survey paper explores the critical role of computational models in understanding mitochondrial energetics and dysfunction, particularly in cancer metabolism. Mitochondria, central to cellular energy production through oxidative phosphorylation (OXPHOS), are pivotal in metabolic processes and cellular signaling. The paper highlights the significance of computational models in simulating mitochondrial processes, integrating metabolic pathways such as glycolysis and OXPHOS, and elucidating key regulatory mechanisms underlying mitochondrial bioenergetics and cellular homeostasis. It emphasizes the impact of fatty acid metabolism on cancer progression and suggests that future research should incorporate computational modeling to further elucidate these processes. The survey identifies targeting mitochondrial processes, especially OXPHOS, as a promising therapeutic strategy for overcoming chemoresistance in cancers like colorectal cancer (CRC). The murburn concept is presented as a framework for understanding mitochondrial oxidative phosphorylation, advocating for research into the roles of diffusible/reactive oxygen species (DROS) in metabolic pathways. The predictive capabilities of integrated models in assessing lung mitochondrial bioenergetics and the development of prognostic tools like OSMTS for hepatocellular carcinoma (HCC) are also discussed. Overall, the paper underscores the transformative impact of computational models in advancing mitochondrial research, offering insights into therapeutic development and improving cancer treatment outcomes.

1 Introduction

1.1 Significance of Mitochondria in Cellular Energetics

Mitochondria are essential for cellular energy production, primarily through oxidative phosphorylation, which is critical for ATP synthesis, the cell's energy currency [1]. This process is closely associated with chemiosmotic energy transduction, effectively modeled using engineering approaches such as bond graph methodology [2]. Beyond energy production, mitochondria play a crucial role in metabolic processes and environmental adaptations, vital for cellular and organismal fitness [3]. The dynamics of mitochondrial membranes significantly influence bioenergetics and signaling pathways, highlighting their importance in cellular processes [4]. Furthermore, the heterogeneous distribution of mitochondria, particularly in cardiomyocytes, affects local metabolite distributions and cellular force dynamics, underscoring their role in metabolic homeostasis [5]. The self-organization and fractal nature of the Krebs cycle exemplify the complexity and efficiency of mitochondrial metabolic processes [6]. Collectively, these aspects illustrate the indispensable role of mitochondria in sustaining cellular energetics and metabolic regulation.

1.2 Importance of Computational Models

Computational models are vital for advancing our understanding of mitochondrial functions, providing a framework to simulate and analyze complex biological systems. They facilitate the exploration

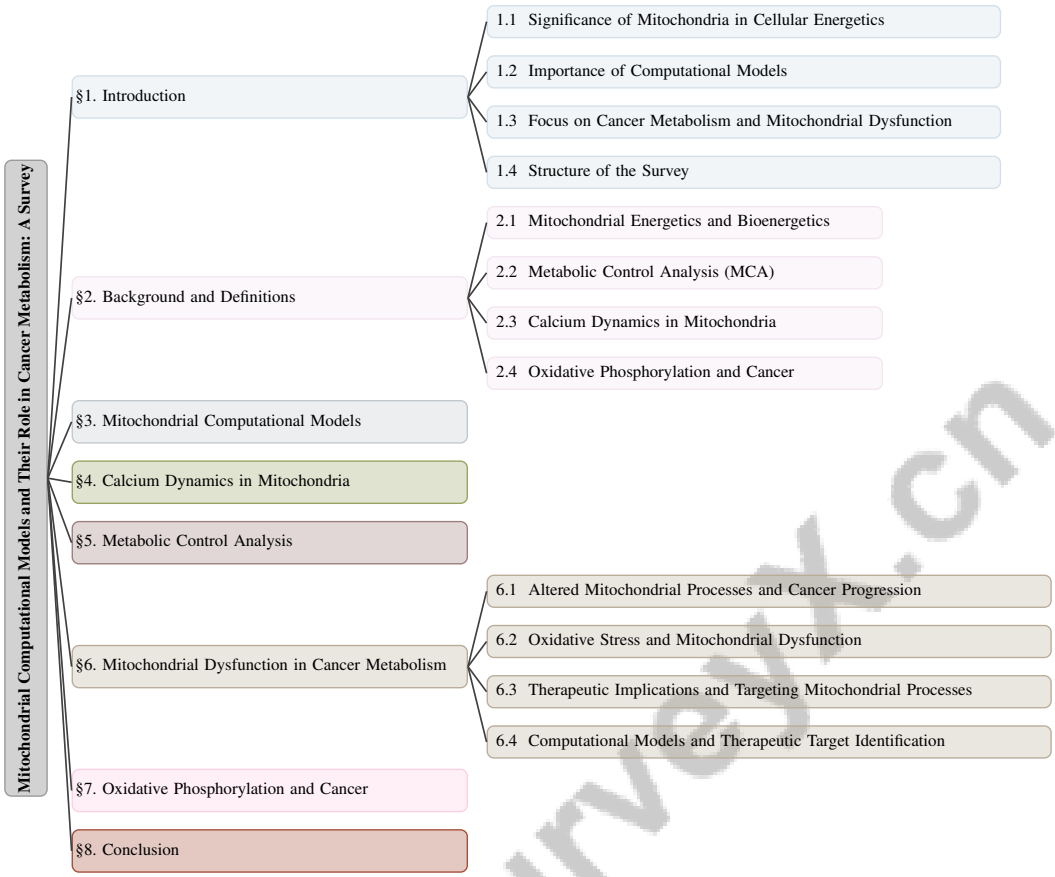


Figure 1: chapter structure

of mitochondrial adaptations essential for maintaining cellular homeostasis and preventing diseases associated with mitochondrial dysfunction [3]. By incorporating thermodynamic constraints, these models yield insights into the bioenergetics of isolated mitochondria, as seen in studies of lung mitochondria [7].

High-resolution computational models enhance our understanding of mitochondrial functional dynamics within cellular environments [5]. They also dissect interactions among key metabolic signaling pathways, such as mTORC1, AMPK, and SIRT1, which are critical in cellular aging and disease progression [8]. Moreover, these models challenge traditional views on energy production, suggesting that glycolysis may be more efficient than oxidative phosphorylation for ATP production when considering the entire mitochondrial proteome [9]. The integration of thermodynamic principles allows for accurate simulation of energy converters, addressing the complexities of coupled fluxes without relying on conductance matching conditions [10].

Innovative methodologies, such as geometric approaches, enhance the development of computational models, providing robust frameworks for analyzing hybrid systems and understanding mitochondrial dynamics [11]. Collectively, these models are indispensable tools that offer profound insights into mitochondrial regulation and potential therapeutic targets, significantly advancing mitochondrial research.

1.3 Focus on Cancer Metabolism and Mitochondrial Dysfunction

Mitochondrial dysfunction profoundly impacts cancer metabolism, influencing tumorigenesis and cancer progression. Mitochondria modulate cell death mechanisms central to tumor development [12]. Cancer cells frequently undergo metabolic reprogramming, exemplified by the Warburg effect, which involves a shift from oxidative phosphorylation (OXPHOS) to glycolysis, even under aerobic

conditions [13]. This adaptation supports rapid proliferation and survival, meeting the metabolic demands of tumor growth.

Altered mitochondrial function, particularly OXPHOS, is evident in various cancers, including those resistant to conventional therapies [14]. For instance, in ovarian cancer, OXPHOS-related metabolic adaptations contribute to chemoresistance, highlighting the need for therapeutic strategies targeting mitochondrial respiration [15]. Additionally, the role of ITGB2-expressing cancer-associated fibroblasts (CAFs) in enhancing glycolysis and lactate secretion illustrates the intricate interplay between mitochondrial function and cancer cell proliferation [16].

Mitochondrial dysfunction is also linked to cancer metastasis. In triple-negative breast cancer (TNBC), copper depletion affects mitochondrial function, influencing metabolism and metastatic behavior [17]. The complex network of mitochondrial signaling, particularly involving the electron transport chain (ETC) and OXPHOS, is crucial for understanding how stress conditions affect mitochondrial function in cancer cells [18]. Alterations in mitochondrial membrane dynamics, including fusion and fission, are vital for maintaining mitochondrial function and are associated with cancer metabolism [4].

The modulation of cellular energy metabolism through OXPHOS is integral to tumor initiation and progression, emphasizing the need for targeted interventions addressing mitochondrial dysfunction in cancer [19]. Impaired mitochondrial oxidative phosphorylation in T cells exposed to persistent antigens limits T cell self-renewal and promotes terminal differentiation, influencing the immune response in cancer [20]. The prognostic benchmark established for hepatocellular carcinoma (HCC) patients highlights the interaction between oxidative stress and mitochondrial function, illustrating the complexity of cancer metabolism [21]. Understanding the modular expression patterns of cancer-associated genes is crucial for enhancing prognostic assessments and treatment strategies in HCC [22]. These insights underscore the significant impact of mitochondrial dysfunction on cancer metabolism, offering promising avenues for therapeutic interventions targeting mitochondrial pathways.

1.4 Structure of the Survey

This survey is structured to comprehensively explore the role of mitochondrial computational models in cancer metabolism. It begins with an introduction emphasizing the significance of mitochondria in cellular energetics and the pivotal role of computational models in elucidating mitochondrial functions, particularly in cancer metabolism and mitochondrial dysfunction. Following the introduction, the survey provides a background overview of key concepts such as mitochondrial energetics, metabolic control analysis, calcium dynamics, and oxidative phosphorylation, establishing a foundation for subsequent sections.

The core of the survey is organized into thematic sections. It first examines mitochondrial computational models, discussing their development, application, and integration of various metabolic pathways for holistic analysis. This is followed by an exploration of calcium dynamics in mitochondria, highlighting stochastic modeling and Monte Carlo simulations. The survey then transitions to metabolic control analysis, elucidating its principles and application in investigating mitochondrial pathways.

Further, the paper investigates mitochondrial dysfunction in cancer metabolism, examining how altered mitochondrial processes contribute to cancer progression and therapy resistance. The discussion extends to oxidative phosphorylation, comparing it with glycolysis and exploring implications for cancer therapy and resistance. Each section builds on the previous one, ensuring logical flow and comprehensive coverage of the topic.

The survey concludes by summarizing key findings and emphasizing the importance of computational models in advancing our understanding of mitochondrial function and dysfunction in cancer. It suggests future research directions and potential applications of these models in therapeutic development. This structured approach ensures a thorough examination of the intersections between mitochondrial computational models and cancer metabolism, providing valuable insights for researchers and practitioners in the field.The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Mitochondrial Energetics and Bioenergetics

Mitochondrial energetics, pivotal for ATP synthesis through oxidative phosphorylation, are central to cellular energy management and homeostasis [1]. This process is influenced by mitochondrial membrane dynamics, affecting signaling pathways [4]. In cardiomyocytes, mitochondrial spatial distribution impacts metabolite concentrations and force production, highlighting the importance of mitochondrial positioning [5]. Recent studies advocate evaluating metabolic pathways via the entire mitochondrial proteome, rather than limited protein subsets, to gain comprehensive insights [9]. Transcriptomic analyses, such as RNA-seq, have furthered understanding of gene expression changes affecting mitochondrial energetics [23].

Computational models are vital for unraveling mitochondrial energetics' complexities. For instance, a bioenergetics model for lung mitochondria elucidates their function in disease contexts [7]. Metabolic control analysis, coupled with thermodynamics, reveals how futile cycles affect equilibrium constants, influencing energy balance [24]. Regulation of mitochondrial energetics involves metabolic signaling pathways adapting to nutrient fluctuations, often modeled using ordinary differential equations [8]. Mitophagy is crucial for maintaining mitochondrial health, with its impairment leading to dysfunction and energy regulation issues [25].

In cancer metabolism, mitochondrial energetics are crucial due to metabolic reprogramming, including fatty acid metabolism alterations and interactions between normal and cancerous cells [26]. Gene expression downstream of AMPK and HIF-1 is vital for metabolic control in hepatocellular carcinoma, illustrating complex regulatory networks [22]. These insights into mitochondrial energetics provide a foundational understanding of cellular energy regulation, with significant implications for health and disease.

2.2 Metabolic Control Analysis (MCA)

Metabolic Control Analysis (MCA) is a foundational framework in systems biology for quantifying how metabolic networks respond to changes in enzyme activities and metabolite concentrations [27]. Initially developed by Kacser and Burns and later expanded by Reder, MCA offers insights into metabolic pathway regulation despite challenges in certain biochemical models [27]. Critiques, such as those by Bagheri and Chaichian, highlight MCA's limitations with discrete enzyme concentration changes, prompting refined approaches [28].

The dynamic and stochastic nature of metabolic networks necessitates advanced modeling techniques for accurate representation [29]. MCA extends beyond static analyses, incorporating time-varying sensitivity coefficients and arbitrary trajectories for a comprehensive understanding of stoichiometric networks [30]. This is crucial for elucidating metabolic control's temporal dynamics in response to perturbations.

In mitochondrial research, MCA is invaluable for dissecting oxidative phosphorylation regulation. By quantifying control within the electron transport chain, MCA identifies potential therapeutic targets, especially concerning mitochondrial dysfunction in diseases like cancer. The integration of MCA with sophisticated models of mitochondrial energetics allows for a thorough examination of mitochondrial function across physiological and pathological contexts, enhancing understanding of cellular energy homeostasis [7, 8, 5].

2.3 Calcium Dynamics in Mitochondria

Calcium dynamics are central to mitochondrial function, impacting bioenergetics and cellular signaling. Regulating mitochondrial calcium is crucial for homeostasis and optimizing ATP production via the Krebs cycle and oxidative phosphorylation [31]. Intracellular calcium dynamics, displaying complex amplitude and frequency modulations, are essential for encoding responses to extracellular signals [32]. Recent imaging advancements have enhanced understanding of mitochondrial calcium dynamics, particularly in neuronal function [33]. In neurons, calcium dynamics influence synaptic plasticity, crucial for learning and memory [34]. The interplay between calcium ions and reactive oxygen species underscores calcium's role in mitochondrial signaling, affecting energy regulation and stress responses [35].

Mathematical models elucidate calcium signaling mechanisms, integrating mechanical effects for comprehensive insights [36]. These models explore how calcium dynamics encode information through modulation methods like amplitude and frequency modulation [32]. The stochastic nature of calcium signaling, captured in various models, emphasizes its role in mitochondrial bioenergetics and cellular adaptation.

Understanding mitochondrial calcium dynamics is vital for elucidating their roles in regulating cellular energy metabolism and signaling pathways, particularly in synaptic transmission and cellular processes like proliferation and apoptosis. This knowledge identifies potential therapeutic targets for diseases associated with mitochondrial dysfunction, where calcium dysregulation is implicated [33, 1, 4, 37, 31].

2.4 Oxidative Phosphorylation and Cancer

Oxidative phosphorylation (OXPHOS) is critical for ATP generation, playing a key role in cellular energy homeostasis [38]. The classical chemiosmotic model of ATP synthesis is complemented by alternative hypotheses, such as the murburn concept, emphasizing diffusible/reactive oxygen species' roles.

In cancer, OXPHOS is linked to metabolic reprogramming, a hallmark of oncogenesis. The Warburg effect, where glycolysis is preferred over OXPHOS even in oxygen-rich conditions, supports rapid cell division and survival under hypoxia [13]. OXPHOS remains crucial in some cancers, contributing to chemoresistance and tumor microenvironment interactions, as seen in ovarian cancer [15]. The complexity of OXPHOS in colorectal cancer underscores the need for comprehensive exploration of its mechanisms [19].

In oral squamous cell carcinoma, cancer-associated fibroblasts exhibit metabolic reprogramming related to OXPHOS, promoting glycolysis and lactate production to sustain tumor growth [16]. This metabolic interplay highlights tumor metabolism's dynamic nature, where metabolites influence gene expression and behavior [12].

Fatty acids in cancer metabolism illustrate the connection between OXPHOS and mitochondrial processes. Fatty acid oxidation provides substrates for the TCA cycle, feeding into OXPHOS and meeting proliferating cancer cells' energetic needs [26]. This adaptability allows cancer cells to thrive under varying conditions within the tumor microenvironment.

Understanding OXPHOS complexes' dynamics and interactions is crucial for elucidating their function in cancer. While single-molecule studies of bacterial OXPHOS complexes offer insights, similar investigations in cancer cells are needed to address knowledge gaps [39].

Exploring OXPHOS in cancer metabolism is essential for developing targeted therapies exploiting tumors' unique metabolic dependencies. By targeting mitochondrial dysfunctions and associated pathways, novel therapeutic strategies may improve cancer treatment outcomes, especially in overcoming resistance to apoptosis-inducing agents [40]. The impaired ability of tumor-infiltrating T cells to self-renew due to persistent antigenic stimulation complicates cancer treatment [20]. Ongoing investigations into OXPHOS underscore its significance as both a fundamental cellular process and a potential therapeutic target.

In recent years, the exploration of mitochondrial dynamics has gained significant attention due to its implications in cellular metabolism and therapeutic interventions. The advancement of computational models has been pivotal in this field, as these models facilitate a deeper understanding of the intricate processes governing mitochondrial function. Figure 2 illustrates the hierarchical structure of mitochondrial computational models, highlighting the development of novel models, integration of metabolic pathways, innovations in imaging and analysis techniques, and applications in cancer metabolism. Each category delves into specific advancements and insights, emphasizing the role of computational models in understanding mitochondrial dynamics, cellular metabolism, and therapeutic potentials. This comprehensive framework not only underscores the complexity of mitochondrial interactions but also serves as a roadmap for future research endeavors aimed at harnessing these insights for clinical applications.

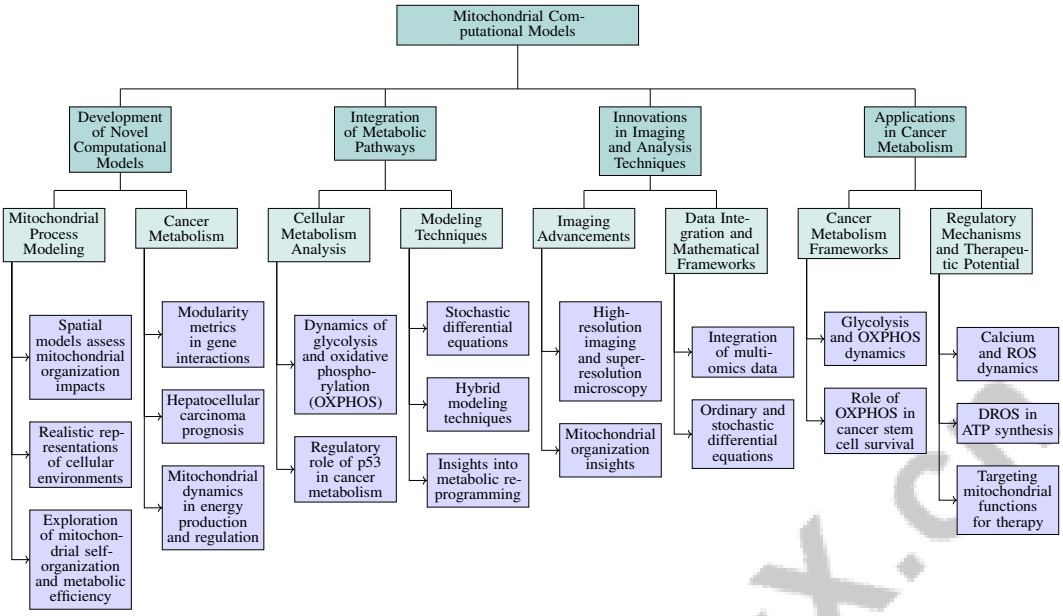


Figure 2: This figure illustrates the hierarchical structure of mitochondrial computational models, highlighting the development of novel models, integration of metabolic pathways, innovations in imaging and analysis techniques, and applications in cancer metabolism. Each category delves into specific advancements and insights, emphasizing the role of computational models in understanding mitochondrial dynamics, cellular metabolism, and therapeutic potentials.

3 Mitochondrial Computational Models

3.1 Development of Novel Computational Models

Advancements in computational modeling have deepened our understanding of mitochondrial processes, integrating spatial models to assess mitochondrial organization impacts on metabolite distribution and force dynamics [5]. These models, incorporating real intracellular components, offer realistic representations of cellular environments, aiding in the exploration of mitochondrial self-organization and metabolic efficiency [6]. In cancer metabolism, models utilizing modularity metrics have been pivotal in understanding gene interactions, particularly in hepatocellular carcinoma prognosis [22]. These innovations reveal how mitochondrial dynamics affect cellular energy production and regulation, enhancing our comprehension of both normal and pathological cellular functions [4, 5, 37].

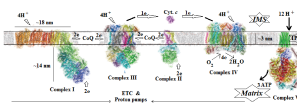
3.2 Integration of Metabolic Pathways

Computational models are instrumental in integrating metabolic pathways, providing a comprehensive analysis of cellular metabolism. These models elucidate the dynamics of glycolysis and oxidative phosphorylation (OXPHOS), especially in cancer metabolism, highlighting the regulatory role of p53 [13]. The incorporation of stochastic differential equations enhances these models, capturing biological variability and complexity [29]. Hybrid modeling techniques have further refined analyses of cellular processes, revealing pathway robustness and control conditions [11, 28]. These models offer insights into metabolic reprogramming, crucial for identifying therapeutic targets in diseases like cancer [8, 22].

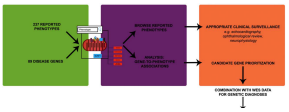
3.3 Innovations in Imaging and Analysis Techniques

Recent imaging and analysis advancements have enhanced computational modeling of mitochondrial dynamics. High-resolution imaging, like super-resolution microscopy, has provided insights into mitochondrial organization, informing accurate computational models [5, 4]. The integration of multi-omics data, such as transcriptomics, enriches these models by capturing cellular regulatory networks

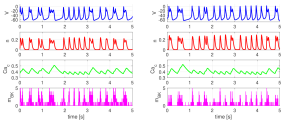
[23]. Mathematical frameworks, including ordinary and stochastic differential equations, have improved simulations of metabolic pathways and signaling networks [8]. These innovations, combining advanced imaging with analytical methods, have deepened our understanding of mitochondrial roles in bioenergetics and disease mechanisms [33, 4, 5, 37, 7].



(a) The Image Represents the Electron Transport Chain (ETC) and Proton Pumps in a Cell[41]



(b) Gene-to-Phenotype Analysis for Genetic Diagnostics[42]



(c) Comparison of V, n, $Ca_c, and m_B kinacardiacpacemakermodel$[11]

Figure 3: Examples of Innovations in Imaging and Analysis Techniques

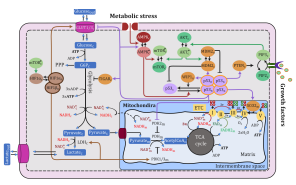
As shown in Figure 3, recent advancements in imaging and analysis techniques have facilitated innovative explorations of mitochondrial processes and genetic diagnostics. The examples highlight the electron transport chain (ETC) and proton pumps, gene-to-phenotype analysis for diagnostics, and parameter comparisons in cardiac pacemaker models, underscoring the potential of advanced methods to enhance our understanding of biological systems [41, 42, 11].

3.4 Applications in Cancer Metabolism

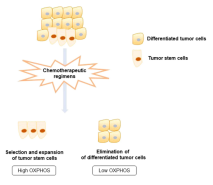
Method Name	Computational Models	Therapeutic Insights	Visual Representations
TGB2-MSW[16]	Metabolic Reprogramming Frameworks	Potential Therapeutic Target	Pathway Models
p53-Metab[13]	Mathematical Framework	Therapeutic Strategies	Visual Tools
CMS[8]	Computational Model	Targeted Therapies	Visual Tools

Table 1: Overview of computational models in cancer metabolism, highlighting their contributions to understanding metabolic reprogramming, therapeutic insights, and visual representations. The table summarizes key methodologies and their applications in elucidating metabolic pathways and potential therapeutic targets.

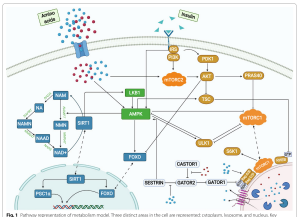
Computational models are crucial for understanding cancer metabolism, particularly metabolic reprogramming in tumor cells. They provide frameworks for analyzing glycolysis and OXPHOS dynamics, highlighting OXPHOS's role in cancer stem cell survival and chemoresistance [15]. Kinetic modeling advancements have optimized bioenergetic outputs, challenging traditional energy production views [10]. Models incorporating calcium and ROS dynamics reveal their influence on mitochondrial function and tumor progression [16]. Computational models have also identified novel regulatory mechanisms, such as DROS in ATP synthesis, and highlighted therapeutic potential by targeting mitochondrial functions [43, 19, 14]. These models deepen our understanding of tumor biology and guide the development of targeted therapies, improving treatment outcomes [22, 13, 26, 37]. Table 1 provides a comprehensive overview of various computational models applied in cancer metabolism studies, emphasizing their role in uncovering therapeutic insights and facilitating visual representations of metabolic processes.



(a) Metabolic Stress and Growth Factors[13]



(b) Chemotherapeutic Regimens and Their Impact on Tumor Stem Cells[15]



(c) The image represents a pathway representation of metabolism model.[8]

Figure 4: Examples of Applications in Cancer Metabolism

As shown in Figure 4, visual representations elucidate complex cancer metabolism processes. The examples highlight metabolic stress, chemotherapeutic impacts on tumor stem cells, and comprehensive pathway models, underscoring the value of visual tools in understanding cancer metabolism and therapeutic strategies [13, 15, 8].

4 Calcium Dynamics in Mitochondria

Calcium dynamics within mitochondria are integral to cellular processes, particularly in energy production and signaling pathways. This section delves into the mechanisms of mitochondrial calcium signaling, emphasizing their stochastic nature and the role of modeling techniques that simulate the probabilistic behavior of calcium ions and their implications for mitochondrial function.

4.1 Stochastic Modeling of Calcium Dynamics

Stochastic modeling offers a detailed framework for simulating calcium signaling in mitochondria, capturing the variability crucial for ATP production and cellular signaling. Baer et al. developed a model focusing on calcium channel dynamics, using stochastic variables to depict activated and inhibited states, aiding in analyzing calcium wave propagation [44]. Kaouri et al. expanded the Atri model into a three-dimensional mechanochemical framework to show how mechanical stimuli influence calcium signaling [36]. De Pittà et al. used bifurcation analysis to identify conditions for amplitude, frequency, and mixed modulation in calcium signaling, illustrating how information is encoded through different modulation methods [32]. Gurung et al. enhanced calcium dynamics modeling with a hybrid PDE-DNN model, integrating deep neural networks with partial differential equations for better representation of ion channel dynamics [45]. Jelbart et al. introduced a heuristic method to identify small parameters in ODEs, refining models to capture the stochastic nature of calcium fluctuations [46].

These stochastic models elucidate the relationship between calcium signaling and mitochondrial metabolism, demonstrating that calcium oscillations can optimize energetic output under various physiological conditions [31, 44]. By exploring the interplay between calcium signaling and mitochondrial processes, these models offer insights into cellular metabolism regulation and potential therapeutic targets for mitochondrial dysfunction-related diseases.

4.2 Coarse-Grained Kinetic Monte Carlo Simulations

Coarse-Grained Kinetic Monte Carlo (CG-kMC) simulations are a powerful tool for modeling calcium dynamics, offering a detailed representation of the stochastic processes governing calcium ion behavior in cellular environments. This method groups neighboring microscopic sites into coarse cells, deriving reaction rates through a local mean field approximation, effectively capturing complex calcium signaling dynamics [47]. In neurons, CG-kMC simulations are particularly relevant, as presynaptic calcium concentration dynamics are influenced by membrane potential changes and ion flux through voltage-gated calcium channels [34]. Incorporating endogenous buffers refines calcium dynamics simulations, enhancing understanding of their contributions to synaptic plasticity and neuronal function.

Integrating physics-based machine learning models into CG-kMC simulations improves accuracy and efficiency by incorporating physical knowledge through candidate functions derived from the chemical master equation (CME) [48]. Advanced analytical techniques, such as evaluating calcium wave generation probabilities using Euler-Lagrange equations, offer quantitative assessments of calcium wave propagation conditions [49]. CG-kMC simulations are essential for understanding the stochastic nature of calcium dynamics, accommodating various physiological parameters influencing calcium behavior. This modeling framework facilitates the exploration of mitochondrial calcium dynamics' roles in synaptic transmission, energy metabolism, and cell fate decisions, identifying potential therapeutic targets for diseases linked to calcium dysregulation, including neurodegenerative disorders and cancer [33, 4, 5, 37, 31].

4.3 Integration of Calcium Dynamics in Bioenergetics Models

Incorporating calcium dynamics into bioenergetics models is vital for understanding the interplay between calcium signaling and mitochondrial energy production. The DBD method estimates effective probability distributions and differential equations from stochastic simulations, facilitating the integration of calcium dynamics into bioenergetics frameworks [48]. CG-kMC simulations further enhance this integration by accurately representing calcium ion dynamics while significantly reducing computational time, enabling the study of larger, more complex systems [47]. Coupling stochastic channel behavior with deterministic calcium concentration dynamics, as proposed in the PDMP model, provides a robust framework for capturing calcium wave dynamics [49]. Baer et al. highlighted the importance of stochastic channel dynamics for realistic calcium wave behavior representation, contrasting with purely deterministic models [44].

Kaouri et al.'s mechanochemical model captures the feedback between mechanical forces and calcium release, providing insights into how mechanical stimuli influence calcium signaling and bioenergetics [36]. The hybrid PDE-DNN model leverages deep neural networks to simplify complex ion channel dynamics while maintaining accuracy, enhancing calcium dynamics integration into bioenergetics models [45]. Future research could expand these models to higher dimensions and incorporate additional biophysical phenomena, as suggested by Tripathi et al., to enhance their biomedical applicability [50]. Such expansions would deepen our understanding of calcium dynamics' multifaceted roles in cellular energy regulation and disease pathogenesis.

4.4 Challenges and Advances in Monitoring Mitochondrial Calcium

Monitoring mitochondrial calcium dynamics presents challenges due to the complex interplay of cellular processes and limitations in current measurement methodologies. Variability in sensor performance and potential artifacts during measurements complicate the accurate tracking of calcium levels within mitochondria [33]. Advancements in imaging technologies have significantly enhanced our ability to observe mitochondrial calcium dynamics in real time, with high-resolution techniques capturing detailed spatial and temporal changes in calcium concentrations [33]. These improvements provide critical insights into calcium's role in mitochondrial processes, deepening our understanding of its influence on cellular energy regulation and signaling pathways.

Novel mathematical and computational models have addressed challenges in studying mitochondrial calcium dynamics. Integrating nonlocal diffusion effects into calcium dynamics models offers a more comprehensive representation of signaling [51]. Stochastic modeling techniques, such as discrete stochastic modeling, reveal new dynamic states that emerge under specific conditions, providing valuable insights into long-term potentiation (LTP) and long-term depression (LTD) mechanisms [44, 34]. The MPEP method, which incorporates noise effects, enhances our understanding of conditions leading to significant changes in calcium signaling and its regulatory mechanisms in mitochondrial function [52]. Hybrid models like the PDE-DNN framework demonstrate improved flexibility and accuracy in modeling calcium dynamics, leveraging machine learning and traditional techniques to simulate mitochondrial calcium dynamics and their cellular impacts [45].

Recent advancements in imaging and modeling, including photonic microscopy and genetically encoded calcium sensors, have improved our capacity to monitor mitochondrial calcium dynamics, particularly in the central nervous system. These innovations are crucial for addressing ongoing challenges in accurately tracking mitochondrial calcium levels, essential for synaptic transmission and astrocyte signaling. Understanding the relationship between mitochondrial dynamics and cellular signaling offers insights into metabolic regulation and potential therapeutic targets in conditions such as cancer. As research progresses, these methodologies promise to overcome existing obstacles and deepen our comprehension of mitochondrial functions in health and disease [33, 4, 5, 36, 37].

5 Metabolic Control Analysis

In systems biology, understanding metabolic pathway regulation necessitates a detailed analytical framework to navigate biological system complexities. Metabolic Control Analysis (MCA) is pivotal in elucidating how variations in enzyme activities and metabolite concentrations influence metabolic networks, offering insights into metabolic regulation.

5.1 Principles and Framework of Metabolic Control Analysis

MCA provides a quantitative framework for analyzing how metabolic network variables respond to changes in enzyme activities and metabolite concentrations. Initially developed by Kacser and Burns, and later refined by Reder with a modified algorithm for control matrix calculations using local elasticities, MCA ensures the Jacobian matrix's full rank by selecting independent rows [27]. This integration of stoichiometric and dynamic data allows for accurate system behavior predictions under various perturbations.

Incorporating stochastic effects, MCA captures the inherent variability in biological systems, particularly in mitochondrial pathways, through mechanisms like stochastic resonance and thermally activated barrier crossing [53]. Bagheri and Chaichian's critique of the flux summation theorem highlights traditional MCA's limitations, advocating for refined approaches that consider enzyme interactions [28]. This aligns with evaluations of metabolic pathways based on the mitochondrial proteome [9].

Qian's exploration of dynamic regulation via futile cycles enriches MCA by allowing modulation of effective equilibrium constants, crucial for cellular homeostasis and metabolic efficiency [24]. However, MCA's focus on steady-state sensitivities underscores the necessity of analyzing non-steady trajectories [30]. Addressing these limitations is vital for a comprehensive understanding of metabolic control in dynamic systems.

The Krebs cycle's structural-functional connections and its synchronization with the respiratory chain further illustrate MCA's insights into metabolic regulation [6]. By integrating stoichiometric, dynamic, and stochastic elements, MCA remains an essential tool in systems biology, offering insights into cellular function and disease progression.

5.2 Applications in Mitochondrial Pathways

MCA is crucial for understanding mitochondrial pathway regulation, highlighting how enzyme activity and metabolite concentration changes affect metabolic networks. Smallbone et al.'s modified MCA approach extends its applicability across diverse biochemical systems, facilitating complex mitochondrial pathway analysis [27]. This universality is essential for dissecting intricate regulatory mechanisms governing mitochondrial bioenergetics and cellular homeostasis.

MCA's focus on enzyme interactions and their evolutionary implications, as discussed by Bagheri and Chaichian, emphasizes the necessity of incorporating these interactions in metabolic control analysis [28]. This perspective aligns with Ingalls' generalization of the Summation and Connectivity Theorems to accommodate dynamic systems, enhancing mitochondrial pathway analysis through temporal dynamics [30].

MCA's application to mitochondrial pathways is further enriched by its integration with therapeutic strategies, such as copper chelation in triple-negative breast cancer (TNBC). Ramchandani et al. highlight copper chelation as a promising therapeutic strategy relevant to mitochondrial metabolic control in cancer cells [17]. This illustrates MCA's potential in guiding targeted therapies by identifying key regulatory nodes within mitochondrial pathways for intervention.

Through insights into enzyme interactions, dynamic system analysis, and therapeutic strategies, MCA provides a robust framework for investigating cellular energy production and metabolic efficiency. This approach facilitates identifying targetable pathways for therapeutic intervention, as evidenced by studies linking mitochondrial dysfunction to conditions like methylmalonic acidemia and cancer, paving the way for innovative treatments and improved patient outcomes [25, 37, 4, 5, 33].

5.3 Challenges and Future Directions

MCA faces challenges limiting its application in complex biological systems. A significant limitation is interpreting sensitivity coefficients in oscillating systems, where results can be unpredictable [30]. This complexity necessitates refined analytical methods to accommodate biological systems' inherent variability and dynamics. Additionally, the modified MCA algorithm may struggle in highly complex or non-linear systems, requiring further refinement and integration with other computational tools [27].

The intricate functions and interconnections of mitochondria complicate developing unified therapeutic strategies targeting mitochondrial dynamics in cancer. This challenge is exacerbated by the insufficient sensitivity of current imaging techniques, limiting real-time visualization of molecular interactions within living cells. Parameter estimation variability for calcium dynamics models complicates modeling due to multiple time-scale phenomena and mechanical stimuli's influence on calcium release dynamics. The complexity of these models increases with the need to incorporate chemical and mechanical effects, as seen in recent extensions including viscoelastic properties and new bifurcation parameters. Consequently, achieving accurate predictions in calcium dynamics presents a significant challenge, necessitating robust methodologies to address individual differences and the mechanisms driving calcium oscillations [48, 44, 46, 34, 36].

A further challenge lies in the insufficient understanding of interactions between mitochondrial dysfunction and programmed cell death pathways, hindering the accuracy and effectiveness of current prognostic models, particularly in heterogeneous diseases like lower-grade glioma (LGG). Recent studies utilizing advanced machine learning frameworks underscore integrating mitochondrial function with various cell death mechanisms to enhance prognostic predictions and guide personalized therapeutic strategies [4, 54, 37]. Current research often lacks comprehensive insights into the precise molecular mechanisms and interactions between mitochondrial signaling and other cellular processes, indicating a need for more detailed investigations.

Future research should focus on refining MCA algorithms and exploring their applicability in more complex biological systems. This includes integrating MCA with other computational tools to enhance its analytical capabilities [27]. Further applications of geometric slow-fast analysis methods to other biological models could yield deeper insights into the complex interactions between stochastic and deterministic elements, advancing metabolic control analysis.

Moreover, MCA studies may not encompass all metabolic pathways, particularly those with intricate interactions beyond the two-enzyme systems typically examined. To effectively address MCA's limitations, it is essential to broaden its application to include more complex metabolic networks. This expansion will facilitate a deeper understanding of metabolic regulation's intricate mechanisms and their significant implications for health and disease, particularly in conditions such as methylmalonic acidemia (MMA) and various cancers, where dysregulated metabolism plays a critical role in disease progression and therapeutic response [8, 25, 22, 5, 26].

6 Mitochondrial Dysfunction in Cancer Metabolism

6.1 Altered Mitochondrial Processes and Cancer Progression

Alterations in mitochondrial processes significantly impact cancer progression by modulating cellular bioenergetics and apoptotic pathways. Mitochondrial dynamics, particularly fusion and fission, are closely linked to cellular energy states, affecting mitochondrial morphology and function under varying energy demands [1, 19]. Cancer cells exploit these dynamics to adapt mitochondrial morphology, supporting rapid proliferation and survival under metabolic stress. The Warburg effect, characterized by a shift from oxidative phosphorylation (OXPHOS) to glycolysis, exemplifies cancer's metabolic reprogramming, providing a competitive advantage through increased ATP yield under high metabolic demand [9]. Such adaptations are crucial for meeting the energetic and biosynthetic needs of proliferating tumor cells.

Mitochondrial content influences apoptotic responses, affecting sensitivity to TRAIL and other therapeutic agents [40]. Dysfunctional mitochondria accumulation can lead to cellular distress, impacting cancer progression through disrupted homeostasis and promoting malignant transformation [25]. Calcium oscillations enhance mitochondrial efficiency under limited substrate availability, supporting the metabolic demands of cancer cells [31]. Understanding these mechanisms elucidates how altered mitochondrial functions contribute to cancer progression by modulating signaling pathways and cellular metabolism [53].

Therapeutic strategies targeting mitochondrial dynamics and bioenergetics offer promising avenues for cancer treatment. Modulating these dynamics may enhance therapeutic efficacy by disrupting metabolic adaptations favoring cancer cell survival and proliferation [37]. However, addressing dose-limiting toxicities associated with potent complex I inhibitors is essential for expanding their

clinical applicability [55]. Targeting mitochondrial processes presents opportunities for developing therapies that exploit the unique metabolic dependencies of cancer cells [40, 37].

6.2 Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress is a key factor in mitochondrial dysfunction, influencing cancer progression and therapy resistance. The murburn concept challenges traditional views by emphasizing the role of diffusible/reactive oxygen species (DROS) in redox reactions and ATP synthesis, suggesting an alternative energy production mechanism affecting cancer metabolism [56, 43]. The interaction between calcium dynamics and oxidative stress is crucial for understanding mitochondrial dysfunction. Mechanical stimuli can suppress calcium oscillations, impacting mitochondrial efficiency and bioenergetics, particularly in cancer cells where altered calcium signaling modifies responses to oxidative stress [36].

Age-dependent feedback mechanisms further complicate the calcium-ROS relationship, with ROS levels initially decreasing with calcium but later exhibiting a positive correlation, exacerbating oxidative stress and influencing cancer progression [35]. Incorporating domain-specific knowledge into machine learning frameworks enhances the study of calcium dynamics and oxidative stress, revealing intricate interactions driving mitochondrial dysfunction in cancer [48]. Regulatory T cells (Tregs) modulate oxidative phosphorylation and fatty acid oxidation, linking mitochondrial dysfunction to immune regulation with implications for cancer progression [57].

Insights into oxidative stress and mitochondrial dysfunction reveal the intricate nature of cancer metabolism, particularly through the Warburg effect favoring glycolysis over OXPHOS. This reliance presents opportunities for therapeutic strategies targeting these vulnerabilities, particularly through modulation of mitochondrial functions to impair cancer cell proliferation and enhance treatment sensitivity [13, 37].

6.3 Therapeutic Implications and Targeting Mitochondrial Processes

Targeting mitochondrial processes in cancer therapy offers a promising strategy to exploit the metabolic vulnerabilities of cancer cells, particularly through modulation of oxidative phosphorylation (OXPHOS) and glycolysis. The expression of ITGB2 in cancer-associated fibroblasts (CAFs) enhances glycolysis and lactate secretion, promoting oral squamous cell carcinoma (OSCC) proliferation by boosting mitochondrial OXPHOS, identifying ITGB2 as a potential therapeutic target [16]. Targeting OXPHOS in estrogen receptor-positive breast cancer (ER+ BC) patients resistant to standard treatments presents a novel approach to overcoming therapy resistance [58].

Modulating the Warburg effect, a hallmark of cancer metabolism, is a critical therapeutic target. Elevated p53 activation can reverse the Warburg effect, suggesting a strategy for targeting metabolic pathways in cancer treatment [13]. Targeting fatty acid metabolism highlights the potential to exploit metabolic dependencies in cancer cells for effective treatments [26]. PHB2's role in colorectal cancer (CRC) progression through mitochondrial function provides insights into novel therapeutic strategies [19].

Enhancing T cell function within the tumor microenvironment offers a novel strategy for improving cancer immunotherapy outcomes, addressing impaired oxidative phosphorylation in T cells exposed to persistent antigens [20]. The MPEP method elucidates the role of noise in wave nucleation, relevant to understanding how altered mitochondrial processes contribute to cancer progression [52]. Future research should focus on integrating additional metabolic pathways and examining pathological conditions affecting calcium-mitochondria interactions to enhance therapeutic strategies [31].

Targeting mitochondrial processes in cancer therapy presents a multifaceted approach to addressing the metabolic adaptations of cancer cells. By focusing on specific vulnerabilities within mitochondrial pathways, such as OXPHOS and mitochondrial dynamics, these strategies may enhance treatment outcomes and effectively counteract resistance mechanisms [14, 40, 37, 55, 13].

6.4 Computational Models and Therapeutic Target Identification

Computational models are vital for identifying therapeutic targets within cancer metabolism by elucidating the complex interactions between mitochondrial processes and cellular signaling pathways.

These models provide a comprehensive framework for understanding how alterations in mitochondrial function contribute to cancer progression and therapy resistance. The interplay between key signaling pathways, such as mTORC1, AMPK, and SIRT1, is crucial for maintaining cellular homeostasis and preventing metabolic disorders, including cancer [8]. Integrating these pathways into computational models enables the identification of potential therapeutic targets that disrupt the metabolic adaptations of cancer cells.

The bond graph approach, combined with the Faraday-equivalent chemical potential, offers a robust framework for understanding energy flows in complex biomolecular systems, providing insights into potential therapeutic interventions [2]. This approach facilitates exploration of energy dynamics within mitochondria, highlighting targets for modulating OXPHOS and reactive oxygen species (ROS) production [14]. Inhibition of OXPHOS through agents like IACS-010759 has shown promise in treating ER+ BC patients resistant to endocrine therapies and CDK4/6 inhibitors, underscoring the therapeutic potential of targeting mitochondrial processes [58].

Age-related dynamics of calcium and ROS, as elucidated by Liu et al., provide a framework for identifying therapeutic targets that address aging's impact on mitochondrial function [35]. These insights are crucial for developing age-specific therapies that mitigate oxidative stress and calcium dysregulation in cancer cells. Integrating these dynamics into computational models enhances understanding of how mitochondrial dysfunction contributes to cancer progression, offering new therapeutic intervention avenues.

Future research should explore the structure of parameter space near heterodimensional cycles, as suggested by Hammerlindl et al., to aid in identifying therapeutic targets in cancer metabolism [59]. Experimental validation of mitochondrial pathway classifiers, such as mtPCDI, could enhance therapeutic decision-making and improve patient outcomes [54]. Extending the MPEP method for identifying therapeutic targets related to mitochondrial dysfunction further exemplifies the potential of computational models in advancing cancer therapy [52].

Computational models are invaluable for identifying therapeutic targets in cancer metabolism, offering insights into the intricate dynamics of mitochondrial processes and their role in disease progression. By utilizing advanced metabolic models, researchers can design targeted therapies that exploit the unique metabolic vulnerabilities of cancer cells, such as their reliance on altered OXPHOS and fatty acid metabolism. This approach aims to disrupt essential energy production pathways for cancer cell growth while enhancing existing treatment effectiveness and improving overall patient outcomes by addressing therapeutic resistance mechanisms [13, 15, 26, 37].

7 Oxidative Phosphorylation and Cancer

The intricate relationship between oxidative phosphorylation (OXPHOS) and cancer metabolism is pivotal in understanding how tumor cells adapt metabolically under diverse physiological conditions. Insights into cancer cell metabolism and energy pathways reveal mechanisms by which cancer cells reprogram their metabolic processes, primarily through alterations in fatty acid metabolism, mitochondrial dynamics, and the Warburg effect. This understanding is crucial for developing targeted therapies against tumor growth and progression [22, 26, 37, 13, 12]. A comparative analysis of glycolysis and OXPHOS elucidates their roles in cancer metabolism and implications for tumor survival.

7.1 Comparative Analysis: Glycolysis vs. Oxidative Phosphorylation

The interplay between glycolysis and OXPHOS is central to understanding metabolic reprogramming in tumor cells. The Warburg effect, where cancer cells prefer glycolysis over OXPHOS even with adequate oxygen, facilitates rapid proliferation, invasion, and therapy resistance. This adaptation supports growth by generating anabolic substrates while minimizing energy production through OXPHOS, often impaired in cancerous tissues. The tumor suppressor p53 regulates this metabolic shift, and its activation can potentially reverse the Warburg effect, highlighting the complex interplay between cancer metabolism and therapeutic responses [9, 37, 55, 13, 12].

OXPHOS complexes exhibit various structural arrangements influencing their efficiency and regulation [39]. While glycolysis provides rapid ATP and metabolic intermediates, OXPHOS offers more efficient energy production, crucial for certain cancer types and conditions. Some cancer cells

rely on OXPHOS for survival and therapy resistance, especially cancer stem cells, necessitating therapeutic strategies targeting OXPHOS in aggressive cancers. Although OXPHOS inhibitors show promise in preclinical studies, challenges like dose-limiting toxicities require a deeper understanding of mitochondrial dynamics in cancer metabolism [55, 14, 37].

The comparative analysis underscores tumor cells' metabolic flexibility, enabling adaptation to environmental and metabolic conditions. Understanding regulatory mechanisms of this metabolic switch is essential for developing therapies exploiting cancer cells' metabolic dependencies. The Warburg effect correlates with increased tumor aggressiveness and poor prognoses, with higher metabolic gene expression modularity linked to advanced hepatocellular carcinoma and greater metastatic potential. p53 activity can reverse the Warburg effect, suggesting targeting glycolysis-promoting pathways may enhance treatment efficacy, particularly in tumors with p53 mutations [22, 13].

7.2 Therapeutic Implications of Targeting OXPHOS

Targeting OXPHOS presents a promising strategy for cancers reliant on mitochondrial respiration. OXPHOS inhibitors like IACS-010759 highlight the potential to exploit this dependency in resistant estrogen receptor-positive breast cancer (ER+ BC) tumors, effectively reducing growth and showcasing the therapeutic potential of targeting mitochondrial processes [58].

The structural dynamics of OXPHOS complexes, differing from bacterial complexes, may influence the effectiveness of OXPHOS-targeting therapies by affecting mitochondrial energy production regulation [39].

Understanding OXPHOS's structural and functional nuances allows for tailored interventions disrupting cancer cells' metabolic adaptations. Selectively targeting OXPHOS combats therapy resistance in aggressive tumors, like ovarian cancer, while minimizing collateral damage to normal cells, which rely less on mitochondrial respiration. This approach leverages cancer cells' metabolic vulnerabilities, potentially leading to more effective and less toxic treatments [55, 15, 37]. Such selectivity enhances OXPHOS inhibitors' therapeutic index, making them valuable in cancer therapy.

7.3 Role of OXPHOS in Cancer Therapy Resistance

Alterations in OXPHOS significantly contribute to cancer therapy resistance, reflecting malignant cells' metabolic flexibility. Cancer cells frequently reprogram their metabolism, adjusting reliance on glycolysis and OXPHOS in response to environmental conditions and therapeutic pressures. This flexibility sustains ATP production and supports biosynthesis necessary for growth and survival. The Warburg effect exemplifies a shift toward enhanced glycolysis, contributing to tumor aggressiveness and treatment resistance. Regulatory mechanisms, including oncogenic pathways and p53, orchestrate these changes, suggesting targeting specific pathways may yield novel therapeutic strategies [13, 26]. This adaptability is a hallmark of therapy resistance, enabling proliferation despite chemotherapeutic agents.

OXPHOS complexes' structural dynamics, from supercomplexes to fluid arrangements, influence efficiency and regulation, allowing cancer cells to modulate energy production in response to interventions [39].

OXPHOS's role in cancer stem cell maintenance and survival emphasizes its significance in therapy resistance. Cancer stem cells, resilient to conventional therapies and pivotal in recurrence, predominantly utilize OXPHOS, making them crucial targets for overcoming resistance mechanisms and enhancing treatment efficacy [14, 37, 55, 13, 15].

The interplay between OXPHOS and other metabolic pathways complicates therapy resistance, particularly due to the Warburg effect, where cancer cells prefer glycolysis for rapid growth. Factors like p53 influence this shift, with its activation potentially reversing the Warburg effect and altering the metabolic landscape underlying resistance. Understanding these interactions is critical for developing therapies to combat metabolic adaptations in cancer cells [9, 13, 38]. Cancer cells' ability to switch between pathways allows adaptation to nutrient availability and therapeutic pressures, maintaining proliferation.

Recognizing OXPHOS's role in therapy resistance is essential for developing therapies disrupting these adaptations. Inhibiting OXPHOS may address resistance mechanisms in aggressive tumors, enhancing outcomes for patients unresponsive to conventional therapies. This strategy leverages tumors' metabolic vulnerabilities, improving efficacy while minimizing adverse effects on normal tissues [14, 15, 55, 13, 58].

7.4 Innovative Perspectives on OXPHOS Mechanisms

Advancements in understanding OXPHOS mechanisms provide insights into cancer metabolism. Cancer cells often exhibit reduced OXPHOS and increased glycolysis, known as the Warburg effect, supporting proliferation and resistance. The tumor suppressor p53 is a key regulator capable of reversing this metabolic alteration, suggesting enhancing p53 activity could redirect metabolism back to an OXPHOS-dominant state. Modulating mitochondrial dynamics presents a therapeutic target, impairing OXPHOS and altering cancer cell sensitivity to chemotherapy. Understanding these interconnections within mitochondrial pathways is essential for developing treatments that disrupt metabolic reprogramming [13, 37].

Alternative hypotheses, like the murburn concept, challenge the classical chemiosmotic model by emphasizing diffusible/reactive oxygen species (DROS) in ATP synthesis, offering new perspectives on mitochondrial energy production, particularly in cancer cells with metabolic adaptations.

OXPHOS complexes' dynamics, from supercomplex formations to fluid configurations, contribute to OXPHOS's functional versatility. This plasticity enables cancer cells to adjust energy production strategies according to metabolic demands and stressors [39].

Integration of OXPHOS with other pathways, such as fatty acid oxidation and glycolysis, underscores its importance in sustaining cancer cells' energetic and biosynthetic needs [26]. The interplay highlights potential for targeting OXPHOS, particularly in cancers reliant on mitochondrial respiration for survival and resistance.

Innovative methodologies, including high-resolution imaging and computational models, advance understanding of mitochondrial dynamics in cancer metabolism. These approaches elucidate how mitochondrial function alterations contribute to growth and resistance, offering new avenues for targeted treatments exploiting cancer cells' metabolic vulnerabilities [41, 14, 37, 55, 15]. Leveraging these perspectives, researchers can further elucidate OXPHOS's role in metabolism and identify strategies for disrupting adaptations supporting tumor growth and progression.

8 Conclusion

The survey illustrates the pivotal contribution of computational models in deepening our comprehension of mitochondrial roles in cancer metabolism. These models provide a comprehensive framework for simulating mitochondrial activities and examining the intricate interplay between metabolic pathways like glycolysis and oxidative phosphorylation. The amalgamation of computational insights with experimental data has been instrumental in unveiling the regulatory mechanisms underpinning mitochondrial bioenergetics and cellular equilibrium, shedding light on cancer cells' metabolic susceptibilities.

Notably, the survey identifies fatty acid metabolism's influence on cancer progression, suggesting that future research should leverage computational modeling to elucidate these processes further. Furthermore, the importance of mitochondrial dynamics in astrocytes necessitates investigations into the regulatory networks that control these dynamics and their implications across various diseases.

Targeting mitochondrial mechanisms, especially oxidative phosphorylation, emerges as a promising avenue to overcome chemoresistance in cancers such as colorectal cancer, where PHB2's role in enhancing mitochondrial oxidative phosphorylation and tumorigenesis is evident. The dynamic nature of mitochondrial signaling and its influence on cancer cell behavior underscores the need for developing therapies that can modulate these processes. Future research should focus on refining mitochondrial targeting strategies, exploring combination therapies, and conducting clinical trials to assess these interventions' efficacy and safety.

The murburn concept offers a valuable perspective on mitochondrial oxidative phosphorylation, advocating for future studies to delve into the roles of diffusible/reactive oxygen species within

various metabolic pathways. Additionally, the predictive power of integrated models in understanding lung mitochondrial bioenergetics highlights the potential for future research to incorporate additional dynamics and cell types.

The emergence of OSMTS as a tool for prognosis prediction in hepatocellular carcinoma highlights its utility in identifying high-risk patients and shaping treatment strategies. Future research could broaden the application of modularity metrics to other cancer types and explore the temporal dynamics of gene expression in hepatocellular carcinoma.

This survey underscores the transformative role of computational models in elucidating mitochondrial function and dysfunction, setting the stage for therapeutic advancements. By harnessing these models, researchers can devise targeted therapies that exploit tumors' unique metabolic dependencies, ultimately improving treatment outcomes and patient care.

References

[1] Joshua G Jackson and Michael B Robinson. Regulation of mitochondrial dynamics in astrocytes: mechanisms, consequences, and unknowns. *Glia*, 66(6):1213–1234, 2018.

[2] Peter Gawthrop. Bond graph modelling of chemiosmotic biomolecular energy transduction, 2017.

[3] Christopher F Bennett, Pedro Latorre-Muro, and Pere Puigserver. Mechanisms of mitochondrial respiratory adaptation. *Nature Reviews Molecular Cell Biology*, 23(12):817–835, 2022.

[4] Marta Giacomello, Aswin Pyakurel, Christina Glytsou, and Luca Scorrano. The cell biology of mitochondrial membrane dynamics. *Nature reviews Molecular cell biology*, 21(4):204–224, 2020.

[5] Shouryadipta Ghosh, Kenneth Tran, Lea MD Delbridge, Anthony JR Hickey, Eric Hanssen, Edmund J Crampin, and Vijay Rajagopal. Insights on the impact of mitochondrial organisation on bioenergetics in high-resolution computational models of cardiac cell architecture. *PLOS Computational Biology*, 14(12):e1006640, 2018.

[6] V. I. Grytsay and I. V. Musatenko. Self-organization and fractality in a metabolic process of the krebs cycle, 2017.

[7] Xiao Zhang, Ranjan K Dash, Elizabeth R Jacobs, Amadou KS Camara, Anne V Clough, and Said H Audi. Integrated computational model of the bioenergetics of isolated lung mitochondria. *PLoS One*, 13(6):e0197921, 2018.

[8] Mehrshad Sadria and Anita T Layton. Interactions among mtorc, ampk and sirt: a computational model for cell energy balance and metabolism. *Cell Communication and Signaling*, 19(1):57, 2021.

[9] Alexei Vazquez. Selective advantage of aerobic glycolysis over oxidative phosphorylation, 2024.

[10] L. A. Arias-Hernández, R. T. Paez-Hernández, and F. Angulo-Brown. A first–order irreversible thermodynamic approach to a simple energy converter, 2007.

[11] Francesco Montefusco and Morten Gram Pedersen. Geometric slow-fast analysis of a hybrid pituitary cell model with stochastic ion channel dynamics, 2023.

[12] Eric S Goetzman and Edward V Prochownik. The role for myc in coordinating glycolysis, oxidative phosphorylation, glutaminolysis, and fatty acid metabolism in normal and neoplastic tissues. *Frontiers in endocrinology*, 9:129, 2018.

[13] Roba Abukwaik, Elias Vera-Siguenza, Daniel Tennant, and Fabian Spill. P53 orchestrates cancer metabolism: Unveiling strategies to reverse the warburg effect, 2024.

[14] Yi Yang, Yahui An, Mingli Ren, Haijiao Wang, Jing Bai, Wenli Du, and Dezhi Kong. The mechanisms of action of mitochondrial targeting agents in cancer: Inhibiting oxidative phosphorylation and inducing apoptosis. *Frontiers in Pharmacology*, 14:1243613, 2023.

[15] Yinjie Wu, Xuewei Zhang, Ziyi Wang, Wanzhen Zheng, Huimin Cao, and Wenjing Shen. Targeting oxidative phosphorylation as an approach for the treatment of ovarian cancer. *Frontiers in Oncology*, 12:971479, 2022.

[16] Xiaoxin Zhang, Yingchun Dong, Mengxiang Zhao, Liang Ding, Xihu Yang, Yue Jing, Yuxian Song, Sheng Chen, Qingang Hu, and Yanhong Ni. Itgb2-mediated metabolic switch in cafs promotes oscc proliferation by oxidation of nadh in mitochondrial oxidative phosphorylation system. *Theranostics*, 10(26):12044, 2020.

[17] Divya Ramchandani, Mirela Berisa, Diamile A Tavarez, Zhuoning Li, Matthew Miele, Yang Bai, Sharrell B Lee, Yi Ban, Noah Dephoure, Ronald C Hendrickson, et al. Copper depletion modulates mitochondrial oxidative phosphorylation to impair triple negative breast cancer metastasis. *Nature communications*, 12(1):7311, 2021.

[18] Corentin Dourmap, Solène Roque, Amélie Morin, Damien Caubrière, Margaux Kerdiles, Kyllian Béguin, Romain Perdoux, Nicolas Reynoud, Lucile Bourdet, Pierre-Alexandre Audebert, et al. Stress signalling dynamics of the mitochondrial electron transport chain and oxidative phosphorylation system in higher plants. *Annals of botany*, 125(5):721–736, 2020.

[19] Lin Ren, Li Meng, Jing Gao, Mingdian Lu, Chengyu Guo, Yunyun Li, Ziye Rong, and Yan Ye. Phb2 promotes colorectal cancer cell proliferation and tumorigenesis through ndufs1-mediated oxidative phosphorylation. *Cell Death & Disease*, 14(1):44, 2023.

[20] Santosha A Vardhana, Madeline A Hwee, Mirela Berisa, Daniel K Wells, Kathryn E Yost, Bryan King, Melody Smith, Pamela S Herrera, Howard Y Chang, Ansuman T Satpathy, et al. Impaired mitochondrial oxidative phosphorylation limits the self-renewal of t cells exposed to persistent antigen. *Nature immunology*, 21(9):1022–1033, 2020.

[21] Yitian Wei, Lujuan Ma, Qian Peng, and Lin Lu. Establishing an oxidative stress mitochondria-related prognostic model in hepatocellular carcinoma based on multi-omics characteristics and machine learning computational framework. *Discover Oncology*, 15(1):287, 2024.

[22] Fengdan Ye, Dongya Jia, Mingyang Lu, Herbert Levine, and Michael W Deem. Modularity of the metabolic gene network as a prognostic biomarker for hepatocellular carcinoma, 2017.

[23] Stella Tommasi, Niccolo Pabustan, Meng Li, Yibu Chen, Kimberly D Siegmund, and Ahmad Besaratinia. A novel role for vaping in mitochondrial gene dysregulation and inflammation fundamental to disease development. *Scientific reports*, 11(1):22773, 2021.

[24] Hong Qian and Daniel A. Beard. Metabolic futile cycles and their functions: A systems analysis of energy and control, 2006.

[25] Zhiyong Chen, Marine Berquez, and Alessandro Luciani. Mitochondria, mitophagy, and metabolic disease: towards assembling the puzzle. *Cell Stress*, 4(6):147, 2020.

[26] Nikos Koundouros and George Poulogiannis. Reprogramming of fatty acid metabolism in cancer. *British journal of cancer*, 122(1):4–22, 2020.

[27] Kieran Smallbone. Metabolic control analysis: Rereading reder, 2013.

[28] Homayoun Bagheri-Chaichian, Joachim Hermisson, Juozas R. Vaisnys, and Gunter P. Wagner. The control of phenotype: connecting enzyme variation to physiology, 2002.

[29] P. Ao. Metabolic network modelling: Including stochastic effects, 2005.

[30] Brian P. Ingalls and Herbert M. Sauro. Sensitivity analysis of stoichiometric networks: An extension of metabolic control analysis to non-equilibrium trajectories, 2002.

[31] Valérie Voorsluijs, Francesco Avanzini, Gianmaria Falasco, Massimiliano Esposito, and Alexander Skupin. Nonequilibrium calcium dynamics optimizes the energetic efficiency of mitochondrial metabolism, 2023.

[32] Maurizio De Pitta, Vladislav Volman, Herbert Levine, Giovanni Pioggia, Danilo De Rossi, and Eshel Ben-Jacob. Coexistence of amplitude and frequency modulations in intracellular calcium dynamics, 2008.

[33] Roman Serrat, Alexandre Oliveira-Pinto, Giovanni Marsicano, and Sandrine Pouvreau. Imaging mitochondrial calcium dynamics in the central nervous system, 2024.

[34] Michael Meyer-Hermann, Frido Erler, and Gerhard Soff. Presynaptic calcium dynamics of learning neurons, 2002.

[35] Weijiu Liu. An age-dependent feedback control model for calcium and reactive oxygen species in yeast cells, 2022.

[36] Katerina Kaouri, Philip K. Maini, and S. Jonathan Chapman. Mathematical modelling of calcium signalling taking into account mechanical effects, 2017.

[37] Kaylee B Punter, Charles Chu, and Edmond YW Chan. Mitochondrial dynamics and oxidative phosphorylation as critical targets in cancer. *Endocrine-related cancer*, 30(1), 2023.

[38] Hélène Lemieux and Pierre U Blier. Exploring thermal sensitivities and adaptations of oxidative phosphorylation pathways. *Metabolites*, 12(4):360, 2022.

[39] Tchern Lenn and Mark C. Leake. Single-molecule studies of the dynamics and interactions of bacterial oxphos complexes, 2015.

[40] Silvia Márquez-Jurado, Juan Díaz-Colunga, Ricardo Pires das Neves, Antonio Martinez-Lorente, Fernando Almazán, Raúl Guantes, and Francisco J Iborra. Mitochondrial levels determine variability in cell death by modulating apoptotic gene expression. *Nature communications*, 9(1):389, 2018.

[41] Kelath Murali Manoj. Mitochondrial oxidative phosphorylation: Debunking the concepts of electron transport chain, proton pumps, chemiosmosis and rotary atp synthesis, 2017.

[42] Joyeeta Rahman, Alberto Noronha, Ines Thiele, and Shamima Rahman. Leigh map: A novel computational diagnostic resource for mitochondrial disease. *Annals of neurology*, 81(1):9, 2017.

[43] Kelath Murali Manoj and Abhinav Parashar. Unveiling adp-binding sites and channels in respiratory complexes: Validation of murburn concept as a holistic explanation for oxidative phosphorylation, 2018.

[44] Markus Baer, Martin Falcke, Herbert Levine, and Lev S. Tsimring. Discrete stochastic modeling of calcium channel dynamics, 1999.

[45] Abel Gurung and Qingguang Guan. Hybrid pde-deep neural network model for calcium dynamics in neurons, 2024.

[46] Samuel Jelbart, Nathan Pages, Vivien Kirk, James Sneyd, and Martin Wechselberger. Process-oriented geometric singular perturbation theory and calcium dynamics, 2021.

[47] Chuansheng Shen and Hanshuang Chen. Coarse-graining the calcium dynamics on a stochastic reaction-diffusion lattice model, 2013.

[48] Oliver K. Ernst, Tom Bartol, Terrence Sejnowski, and Eric Mjolsness. Physics-based machine learning for modeling stochastic ip3-dependent calcium dynamics, 2021.

[49] Gaetan Barbet, James MacLaurin, and Moshe Silverstein. Large deviations of piecewise-deterministic-markov-processes with application to stochastic calcium waves, 2024.

[50] Amrita tripathi and Neeru Adlakha. Finite volume model to study calcium diffusion in neuron involving jryr, jserca and jleak, 2013.

[51] Mostafa Bendahmane, Elmahdi Erraji, and Fahd Karami. Optimal control for nonlocal reaction-diffusion system describing calcium dynamics in cardiac cell. *Mathematical Methods in the Applied Sciences*, 44(6):4802–4834, 2021.

[52] Herve Henry and Herbert Levine. Wave nucleation rate in excitable systems in the low noise limit, 2003.

[53] Solomon F. Duki and Mesfin A. Taye. Stochastic resonance and first passage time for excitable system exposed to underdamped medium, 2018.

[54] Hu Qin, Aimitaji Abulaiti, Aierpati Maimaiti, Zulihuma Abulaiti, Guofeng Fan, Yirizhati Aili, Wenyu Ji, Zengliang Wang, and Yongxin Wang. Integrated machine learning survival framework develops a prognostic model based on inter-crosstalk definition of mitochondrial function and cell death patterns in a large multicenter cohort for lower-grade glioma. *Journal of translational medicine*, 21(1):588, 2023.

[55] Nicole D Machado, Lisa C Heather, Adrian L Harris, and Geoff S Higgins. Targeting mitochondrial oxidative phosphorylation: lessons, advantages, and opportunities. *British Journal of Cancer*, 129(6):897–899, 2023.

[56] Kelath Murali Manoj. Murburn concept: A facile explanation for oxygen-centered cellular respiration, 2017.

[57] Duncan Howie, Stephen Paul Cobbold, Elizabeth Adams, Annemieke Ten Bokum, Andra Stefania Necula, Wei Zhang, Honglei Huang, David J Roberts, Benjamin Thomas, Svenja S Hester, et al. Foxp3 drives oxidative phosphorylation and protection from lipotoxicity. *JCI insight*, 2(3):e89160, 2017.

[58] Rania El-Botty, Ludivine Morriset, Elodie Montaudon, Zakia Tariq, Anne Schnitzler, Marina Bacci, Nicla Lorito, Laura Sourd, Léa Huguet, Ahmed Dahmani, et al. Oxidative phosphorylation is a metabolic vulnerability of endocrine therapy and palbociclib resistant metastatic breast cancers. *Nature Communications*, 14(1):4221, 2023.

[59] Andy Hammerlindl, Bernd Krauskopf, Gemma Mason, and Hinke M. Osinga. Global manifold structure of a continuous-time heterodimensional cycle, 2019.

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