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AI-Powered Multi-Omics Analysis for Novel Diabetes Biomarker Discovery: Interlinking Metabolomic, Genomic, and Proteomic Networks

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Diabetes mellitus is a multifactorial metabolic disease that involves multiple complex molecular interactions ranging from genetic predisposition, proteomic alteration, and metabolic disturbance. Traditional single-omics approaches have been unable to capture the systemic landscape of diseases, including the understanding of disease onset, progression, heterogeneity, and response to treatment. Recent progress in multi-omics integration with the aid of artificial intelligence (AI) and machine learning (ML) has made biomarker discovery a revolution by mapping interconnected biological networks. This review provides a synthesis of the current state of progress in genomics, transcriptomics, proteomics, and metabolomics integration using AI-driven computational frameworks for the discovery of predictive, diagnostic, and prognostic biomarkers in diabetes. We discuss analytical pipelines, tools of network biology, deep learning architectures, the issues of clinical translation, ethical concerns, and future aspects of precision diabetology.

Keywords: Artificial intelligence; Biomarkers; Diabetes; Machine learning; Mapping.

Diabetes mellitus is a rapidly increasing health problem throughout the world due mainly to sedentary lifestyles, unhealthy diets, genetic predisposition, and ageing. There are both Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM), which both have a profound molecular heterogeneity, including dysregulated pancreatic beta cell function, chronic inflammation, insulin resistance, and widespread metabolic imbalance.[1] Conventional biomarkers - such as fasting glucose, HbA1c, insulin, and C-peptide - give only a limited view of the physiology and evolution of disease. They are not able to address the variability at the patient level and cannot predict the early course of the disease and complications with enough precision.[2] Multi-omics technologies are revolutionizing this landscape by allowing these various layers of genome, epigenome, transcriptome, proteome, metabolome, lipidome, and microbiome to be explored at the same time. When combining them with state-of-the-art artificial intelligence (AI), such data sets can identify previously unknown molecular signatures and disease subtypes.[2] Multi-omic approaches using AI are suitable for systematic mapping of biological pathways by identifying the mechanisms

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that connect the genetic predisposition to proteomic alterations and downstream changes in metabolism. This review expands on the concept of using a multi-omics integration enabled by AI to provide a refined and network-level understanding of the pathogenesis of diabetes and to identify predictive, diagnostic, and prognostic biomarkers for precision diabetology.

The Molecular Complexity of Diabetes: A Multi-Layered Systems

Genomic and Epigenomic Landscape

The genomic structure of diabetes shows that there is a complex interaction of inherited loci of susceptibility and environmental regulation shifts that together lead to the breakdown of glucose homeostasis. More than 400 genetic loci have been identified by genome-wide association studies (GWAS) for the risk of diabetes, and some high-impact variants located in the genes TCF7L2, FTO, and KCNJ11 have provided mechanistic information on the biology of the disease.[3] Variants in TCF7L2 interfere with Wnt signaling pathways that are important for insulin granule exocytosis, and mutations in FTO regulate adiposity-associated insulin resistance by affecting energy balance and adipocyte differentiation. Similarly, KCNJ11, which encodes the Kir6.2 subunit of ATP-Sensitive potassium channels in â-cells, influences the voltage-dependent insulin release, mutations in which are directly associated with impaired excitability of â-cells.[4] In addition to the static genetic predisposition, diabetes is also strongly influenced by epigenomic dysregulation-in the form of epigenome-wide association studies (EWAs) which have shown aberrant DNA methylation of locations at the promoters of key metabolic genes such as PPARGC1A (mitochondrial biogenesis), INS (insulin production) and ABCC8 (sulfonylurea receptor) and which contribute to the progressive dysfunction of beta cells. [5] In addition, histone modification patterns, such as decreased H3K9 acetylation, are associated with loss of b-cell identity and loss of transcription of insulinogenic pathways. Non-coding RNAs add to this complexity of regulation; miRNA, such as miR-375, regulates insulin secretion and beta-cell mass, and miRNA-146a regulates inflammatory cascades that are at the centre of insulin resistance.[6] Artificial intelligence and machine learning frameworks provide improved methods of interpreting these multi-layered datasets and provide integration of GWAs' findings with EWAs, chromatin accessibility maps, and ncRNA regulatory networks.[7] This allows causal regulatory elements to be predicted, nodes of gene-environment interaction to be identified, and genomic-epigenomic signatures that more accurately identify inter-individual variability in susceptibility to and progression of diabetes to be discovered.

Transcriptomic Alterations

Transcriptomic profiling has greatly contributed to the understanding of diabetes by recording dynamic changes in gene expression in pancreatic, hepatic, adipose, and muscle tissues - each of which plays a crucial role in glucose homeostasis. RNA-sequencing analysis in pancreas islets from patients with diabetes consistently shows the down-regulation of insulin biosynthesis genes such as INS, PDX1, and MAFA[8] and up-regulation of endoplasmic reticulum (ER) stress-related transcripts such as DDIT3 and XBP1, reflecting the exhaustion of the â-cells and maladaptive stress responses. In peripheral tissues, skeletal muscle transcriptomics show downregulation of oxidative phosphorylation genes and mitochondrial electron transport genes, as a sign of impaired metabolic flexibility. Adipose tissue is known to have increased expression of pro-inflammatory cytokines (IL6, TNF, CXCL5) and decreased expression of adipose-inducing factors like PPARG, which contribute to systemic insulin resistance.[9] Single-cell transcriptome analyses have further increased the resolution of complexity to reveal the existence of heterogeneous beta cell subpopulations, some of which appear to be selectively vulnerable to glucotoxic and lipotoxic injury. In addition, noncoding transcripts (long noncoding RNAs, lncRNAs such as MALAT1, H19; microRNAs, miR-29a, miR-124) are dysregulated and modulate important pathways such as insulin secretion, adipogenesis, and inflammatory signaling. Artificial intelligence-based transcriptomics integration models, such as autoencoders and graph-based deep learning models, allow the detection of subtle co-expression modules and gene signatures that predict glycemic deterioration and, therefore, could be potential therapeutic targets and early biomarkers.

Proteomic Perturbations

Proteomic studies are a source of functional information on the pathophysiology of diabetes by characterizing changes in circulating and tissue-specific proteins that directly mediate metabolic and inflammatory processes. In Type 2 diabetes, the defects in insulin signal transduction are reflected in decreased phosphorylation of insulin receptor substrate-1 (IRS-1) and decreased AKT activation and reduced glucose uptake in skeletal muscle and adipose tissue.[10] Chronic low-grade inflammation also contributes to the metabolic dysfunction, as demonstrated by elevated systemic levels of tumor necrosis factor-á (TNF-á), interleukin-6 (IL-6), C-reactive protein (CRP), and other cytokines that interfere with insulin receptor function through serine kinases such as JNK and IKKb. Beyond the inflammatory mediators, the altered secretion of adipokines, such as the reduced secretion of adiponectin and the increased secretion of leptin and resistin, will impact the lipid metabolism, the efficiency of mitochondria, and insulin responsiveness.[11] Mass spectrometry-based proteomics has identified multiple markers of diabetes, including FGF21, clusterin, RBP4, and several heat shock proteins, pointing to dysfunction in stress response mechanisms, mitochondrial dysfunction, and protein homeostasis. Post-translational modifications (PTMs) are another important dimension: glycation, carbonylation, and oxidative modifications to hyperglycemia affect enzymatic activity and enhance the loss of â-cells.[12] AI-enabled proteomic integration, especially convolutional neural networks and graph neural networks, is used to enable pattern recognition across high-dimensional datasets to find multi-protein signatures associated with the early onset of diseases, insulin resistance subtypes, and risk of microvascular and macrovascular complications. These proteomic fingerprints derived from AI have a better predictive performance as compared to traditional biomarkers.

Metabolomic Signatures

Metabolomics are unique metabolite patterns linked to specific biological conditions, such as metabolic dysregulation in diabetes. Numerous studies show different metabolic disturbances before the appearance of the clinical picture, such as an increase in branched-chain amino acids (BCAAs: leucine, valine, isoleucine), which indicate impaired amino acid catabolism and predict the development of insulin resistance in the future.[13] Dysregulated lipid metabolism is a key player in the development and pathogenesis of diabetes, with high levels of ceramides, diacylglycerols, acylcarnitines, and FFA's playing a role in mitochondrial dysfunction, lipotoxicity, and lowered insulin sensitivity.[14] Metabolomic profiling analysis also reveals changes in glycolytic metabolites, metabolomics of the tricarboxylic acid cycle, and ketones, suggesting impaired oxidative metabolism and the greater use of alternative energy resources. Gut microbiota-derived metabolites (short-chain fatty acids (SCFAs), secondary bile acids, indole metabolites, and trimethylamine-N-oxide (TMAO)) are becoming known as regulators of hepatic glucose production, systemic inflammation, and insulin sensitivity.[15] These metabolic signatures are often found years before the diagnosis is made, proving to be a very powerful tool for early diagnosis. Methods like clustering algorithms, multi-view learning, and metabolic network modelling are some artificial intelligence techniques that model the metabolomics source aimed at genomic and proteomics layers to reveal the metabolic subnetwork in relation to disease phenotypes.[16] Feature reduction methods using artificial intelligence assist in identifying discriminative panels of metabolites that can discriminate prediabetes, early insulin resistance, and â-cell failure progression with a higher accuracy than clinical metrics alone.

Diabetes is not a single pathway disease; it happens through a complex interaction of genomic, epigenomic, transcriptomic, proteomic, metabolomic, microbiomics, and environmental levels. Each of the layers brings a unique insight into the underlying mechanisms of insulin resistance, as well as â-cell dysfunction and chronic metabolic imbalance. Understanding these different levels of interconnection between biology allows for more precise biomarker discovery as well as individual treatment strategies. At the genetic level, there are variants in several key genetic loci, such as TCF7L2, FTO, IRS1, and SLC30A8, that give a baseline risk by affecting insulin signaling, â-cell development, as well as glucose homeostasis. However, this inherited predisposition is further influenced or determined by epigenomic changes DNA methylation, histone

remodelling, and miRNA regulation, that react to obesity, inflammation, diet, stress, and early-life exposures. These epigenetic changes translate into transcriptomic changes at the pancreatic islets, liver, adipose, and muscle tissues, identified as disruptions in oxidative stress pathways, ER stress, mitochondrial activity, inflammation, and insulin secretion. Proteomic changes reflect these transcriptional changes into functional consequences that are manifested as altered levels of circulating cytokines, adipokines, transporters, and enzymes involved in metabolic imbalance. Metabolomic profiles provide an additional snapshot of real-time biochemical disruption of the biochemical processes, such as amino acid, lipid species (e.g., ceramides), ketone bodies, and microbiome-derived metabolites, which provide sensitive metrics of disease stage and treatment response. Contributing to this complexity, dysbiosis of the gut microbiome with low diversity, a decrease in the number of short-chain fatty acid (SCFA)-producing bacteria, and an increase in the number of bacteria producing endotoxins modulate host metabolism and systemic inflammation, and consequently, insulin resistance. Overlying all these layers, environmental and lifestyle factors like diet, physical activity, sleep, stress, pollution, socioeconomic status, etc., continuously influence each of the dimensions of the omics and interact with genetic and epigenetic predispositions. Together, these intertwining networks of molecules and environments represent a complex systems biology framework that describes the actual complexity of the pathogenesis of diabetes.

AI and Machine Learning in Multi-Omics Integration for Diabetes

Classical Machine Learning Approaches

Classical machine learning (ML) techniques are still considered as a basic tool in early-stage multi-omics exploration in diabetes research, because they are easy to interpret, robust, and relatively cheap to compute. Algorithms like Random Forests can efficiently manage the heterogeneous genomic, proteomic, and metabolomic inputs that allow the identification of the most important biomarkers that have high predictive value and stable importance scores across cross-validation folds. These models are good for modelling non-linear relationships and interactions between features, as well as for the initial screening of diabetes-associated metabolic pathways or gene signatures.[27] Support Vector Machines (SVMs) try to add more to the table and provide classifiers with high accuracy that could discriminate glycemic states, prediabetes risk profile, or insulin resistance phenotypes, even for moderately sized datasets. Regularized regression techniques, such as LASSO and Ridge regression, are techniques that fine-tune the selection of biomarkers by adding penalty terms that reduce the size of the coefficients of the less informative biomarkers, increasing the model sparsity and stability.[28] These techniques assist in isolating a minimal, but biologically-meaningful, panel of features, e.g., key metabolites or transcriptional regulators, in which a consistent association with the phenotypes of the disease is observed. Overall, while traditional ML approaches are useful as primary preliminary tools to help reduce the dimensionality and identify relevant biological patterns to prepare multi-omics data sets for deeper deep learning-based integrative frameworks.

Deep Learning Approaches

Deep learning (DL) has been at the forefront of integration among the different types of omics because of its capacity to handle thousands of variables for every type of omics, and to uncover complex, non-linear patterns without the need for extensive manual feature engineering. Autoencoders, specifically variational autoencoders (VAEs), can compress high-dimensional omics data into low-dimensional latent spaces with the key feature of maintaining the necessary biological variation.[29] These latent representations help to cross the omics by getting metabolomic, genomic, and proteomic features in an integrated embedding. The Convolutional Neural Networks (CNNs) are especially suitable for structured omics data, e.g., proteo-metric mass spectrometry peaks or metabolite-metric spectra, in which spatial, intensity, or frequency dependencies are present. CNNs can be used to pick up subtle biochemical changes related to early dysglycemia or â-cell dysfunction. Recurrent Neural Networks (RNNs) such as the Long Short-Term Memory (LSTM) and Gated Recurrent Units (GRUs) architectures are good for analysing temporal (or longitudinal) data sets, to capture dynamic changes in glucose metabolism data, gene expression rhythms, and disease progression trajectories.[30] The advent

of multi-modal transformer models further helps to strengthen the multi-omics fusion by learning the association among different layers in context through self-attention mechanisms. These models bring together many different omics inputs, DNA variants, protein abundance, and metabolite concentrations together in one predictive model.[31] Transformers have shown state-of-the-art performance in the prediction of diabetes onset, patient subgroup stratification, and candidate biomarkers that interact across the molecular layers.

Graph Neural Networks (GNNs)

Graph Neural Networks (GNNs) provide a powerful framework in which biological systems, which by their nature function via interconnected regulatory, metabolic, and signaling networks, can be analyzed. In multi-omics integration, GNNs represent either genes, proteins, or metabolites as nodes, and edges represent functional relationships that are related to a gene, protein, or metabolite, such as transcriptional regulation, protein-protein interactions, metabolic conversions, or signaling cascades.[32] Unlike traditional methods that consider biomarkers as independent features, GNNs represent the topological and relational structure of omics data, which allows for identifying hub nodes or highly connected molecules that are central to the pathogenesis of diabetes.[33] For instance, GNN-based network analyses can identify critical mediators between genomic changes (variants) and downstream gene-level proteomic dysregulation and metabolic dysfunctions (e.g., lipid accumulation or oxidative stress). These models can also be used to predict how perturbations affecting specific nodes spread through the network to affect insulin signaling, â-cell survival, or inflammatory pathways.[34] Through learning both node-level features and network topology, GNNs play an important role in improving biomarker discovery, through which molecular clusters and subnetworks identified and learned are more predictive of disease than single omics variables.

Systems Biology and Network-Based AI

Network-based AI approaches use multi-omics data as part of systems-level models of the hierarchical and dynamic organization of biological processes that underlie diabetes. These methods are used to reconstruct complex interaction networks that involve the insulin receptor signalling cascades, lipid metabolism fluxes, mitochondrial bioenergetic pathways, and immune-metabolic crosstalk.[35] Using some of the techniques, such as probabilistic graphical modeling, Bayesian networks, and dynamic systems reconstruction, the AI can determine how the genetic variants, which are identified from genomics or GWAS, modulate the downstream proteomic pathways and ultimately reform the metabolic phenotypes.[36] For example, a variant that affects a transcription factor, TCF7L2, can be computationally modelled to predict the downstream effect on insulin secretion mechanisms, oxidative phosphorylation proteins, and metabolomic signatures associated with this variant. Systems-level AI also enables pathway perturbation to be simulated, and allows prediction of how therapeutic interventions (e.g, GLP-1 agonists, SGLT2 inhibitors) modulate network behaviour across multiple layers of the omics.[37] By capturing synergistic interactions and cross-talk between genomic, proteomic, and metabolic pathways, network-based AI is found to provide mechanistic insights that go beyond correlation and supersede mechanistic biomarker discovery. This integrative systems biology perspective is required to understand the complexity of diabetes and make reliable and biomarker discoveries that have strong mechanistic underpinnings.

The integration of multi-omics data in the healthcare field of diabetes requires analytical frameworks that can accommodate high dimensionality, biological complexity due to some cross-layer interactions. Classical machine learning methods like Random Forests, SVM, and Penalized Regressions are good baseline method that allows robust feature selection and initial biomarker discovery across various genomic, proteomic, and metabolomics layers. Deep learning methods add further capabilities to this through the presentation of latent biological signatures, learn non-linear molecular relationships, and modelling time signatures from longitudinal omics trajectories by such architectures as autoencoders, CNNs, RNNs, and multi-modal transformers. Complementing these, graph neural networks (GNNs) provide a biologically intuitive approach to the representation of molecular interactions, since they propose the nodes of interconnected networks, the nodes being genes, proteins, and metabolites, which allow elucidating mechanisms in pathways involved in

insulin resistance, â-cell function, and metabolic inflammation. Systems biology and network-based AI frameworks also improve the interpretability of the data through reconstruction of insulin signaling cascades, metabolic flux pathways, as well as multi-layered regulatory networks, allowing for to determination of causality and even predictive simulation of molecular perturbations. Together, these complementary approaches to AI and machine learning can be used in a cohesive toolkit that enables effective and mechanistically-informed integration of multi-omics data to accelerate the discovery of clinically relevant biomarkers and therapeutic targets for diabetes.

Integration Strategies for Multi-Omics Data

Fusion-Based Frameworks

Fusion-based integrative frameworks are the backbone of multi-omics analytics by specifying the algorithmic joining of heterogeneous data sets, i.e., genomic variants, transcriptomic profiles, proteomic abundances, and metabolomic signatures. Early fusion methods combine the raw feature matrices of the different omics layers into one single comprehensive set and allow unsupervised analyses such as clustering, patient clustering, and exploratory correlation discovery.[51] This method respects the Granularity of data, but may ssuffer from noise buildup or the imbalance of scale, and is hence best suited for high-quality data sets, with similar feature distributions. Intermediate (latent-space) fusion, widely used in the modern deep learning model, is to compress each omics data set into a latent embedding, representing the inherent structure and cross-omics relationship.[52] These embeddings (which are created using autoencoders, multimodal transformers, or variational inference) help improve the predictive accuracy by matching molecular interactions on a systems level, often surpassing the simple approaches based on simple concatenation. Late fusion combines the predictions or decision outputs of independently trained omics-specific models and is therefore ideal for situations where datasets differ in their sample size, batch effects, or measurement noise. This strategy allows modality-specific strengths to be preserved while breaking up model stacking, ensemble learning, and hierarchical integration is flexible.[53] The combination of both types of frameworks creates a strong structural framework for effective biomarker discovery and disease subtype recognition.

Multi-View Learning

Multi-view learning is based on the idea that each of the different omics modalities is our complementary "view" of the underlying biological system and that genomic regulation, protein abundance, and metabolite flux reflect different but highly related aspects of diabetes pathophysiology.[54] These algorithms, including multi-view canonical correlation analysis, co-training architectures, and multi-kernel learning, help in extracting cross-view correlations, as well as shared predictive signatures that are independent of the population and experiment platform. By making use of both common and unique information sources, multi-view frameworks produce biologically consistent molecular signatures and make biomarker identification more robust while less sensitive to noise in any of the individual omics layers.[55] The models produced are ideal for identifying stable metabolic or regulatory markers linked to insulin resistance, beta-cell stress, or inflammation, which will provide insight not only in mechanistic terms but also in a generalizable manner applicable to different cohorts.

Probabilistic and Bayesian Models

Probabilistic and Bayesian frameworks are important to reveal causal relationships in complex multi-omics data sets. Bayesian networks, hierarchical models, and probabilistic graphical models are used by deducing directional pathways mapping how perturbations at one molecular level propagate to another.[56] These models are formal representations of biological dependencies, such as the impact of genomic variants on transcriptional regulation, the downstream effects of altered protein abundance on signaling networks, and the metabolic effects of enzymatic dysregulation. Such causal modelling helps scientists go beyond the discovery of biomarkers that are associated with each other and move towards finding mechanistic drivers of dysglycemia, mitochondrial dysfunction, lipid imbalance, or chronic inflammation.[57] Bayesian inference also enables the integration of prior biological knowledge to incorporate curated pathways or previously experimentally validated interactions and hence make the results biologically plausible and more reliable for translation to

Table 1. The Molecular Complexity of Diabetes: A Multi-Layered Systems Framework

DataLayer	Key Components	Pathophysiological Role	Representative Alterations in Diabetes	Clinical/Research Implications
Genomic[17]	SNPs, gene variants, polygenic risk loci	Predisposed to â-cell dysfunction, obesity, and insulin resistance	Variants in *TCF7L2*, *MTNR1B*, *KCNJ11*, *FTO*	Early risk prediction; genetic stratification
Epigenomic[18]	DNA methylation, histone marks, non-coding RNAs	Environment-driven tuning of gene expression	Altered methylation at *INS*, *PPARGC1A*; miR-375 dysregulation	Identifies reversible molecular changes; targets for interventions
Transcriptomic[19]	Gene expression profiles, lncRNAs, and mRNA signatures	Reflect dynamic cellular responses	Inflammatory transcriptomic signatures, â-cell dedifferentiation markers	Diagnosis of metabolic stress: pathway-level insights
Proteomic[20]	Signaling proteins, cytokines, kinases, and secretome	Executes metabolic pathways and inter-tissue communication	Reduced IR/AKT phosphorylation; elevated FGF21, RBP4, CRP	Predictors of insulin resistance and complications
Metabolomic[21]	Amino acids, lipids, ceramides, gut metabolites	End-point readout of metabolic flux	Branched-chain amino acids ‘!, ceramides ‘!, and SCFAs altered	Sensitive markers for early metabolic shifts
Lipidomic[22]	Fatty acids, phospholipids, sphingolipids	Regulate insulin sensitivity, membrane dynamics	Sphingolipid imbalance; DAG accumulation	CVD risk stratification; insulin resistance profiling
Gut Microbiome[23]	Bacterial taxa, microbial enzymes, and metabolites	Modulates inflammation and glucose homeostasis	Reduced diversity; altered SCFA and bile acid metabolism	Dietary and probiotic therapeutic approaches
Immunomic[24]	Cytokines, immune cell signatures	Chronic inflammation is driving insulin resistance	TNF-á, IL-6, MCP-1 elevation; innate immune activation	Inflammation-targeted therapeutics
Single-Cell & Spatial Layers[25]	Cell-type–specific expression, spatial localization	Resolves tissue heterogeneity	â-cell subcluster stress states	High-resolution biomarker discovery
Digital & Physiological Layer[26]	Wearables, CGM, physiological signals	Real-time metabolic monitoring	Altered glycemic variability patterns	Dynamic and adaptive biomarker systems

Table 2. AI and Machine Learning Approaches for Multi-Omics Integration in Diabetes

Section	AI/ML Approach	Core Features	Role in Multi-Omics Integration	Diabetes-Specific Applications	Pros	Cons
Classical	Random Forests[38]	Non-linear decision trees; feature importance	Identifies discriminative omics features	Ranking top genomic, proteomic, and metabolite predictors of insulin resistance	Robust to noise; handles non-linear relationships; interpretable feature importance	Can overfit; limited scalability with very high-dimensional omics
Machine Learning	Support Vector Machines (SVMs)[39]	Margin-based classification	Integrates moderate-sized multi-omics data	Classifying glycemic states (normoglycemic, prediabetic, diabetic)	Strong performance in high-dimensional data; effective with small samples	Kernel selection is critical; limited interpretability
Approaches	LASSO / Ridge Regression[40]	Penalized regression; sparse model	Dimensionality reduction across omics layers	Selecting minimal biomarker panels for early T2DM prediction	Produces compact, interpretable models; reduces overfitting	Assumes linearity; may miss complex biological interactions
Deep	Autoencoders[41]	Latent-space embedding	Compresses each omics type into shared features	Identifying hidden molecular patterns underlying â-cell dysfunction	Effective for unsupervised integration; captures non-linear structure	Latent features are difficult to interpret; data-hungry
Learning	CNNs[42]	Pattern recognition	Converts omics into spatial/structured formats	Detecting pathway signatures in proteomic and metabolomic spectra	Powerful pattern detection; high predictive accuracy	Requires artificial data structuring; limited biological interpretability
Approaches	RNNs / LSTM[43]	Temporal modeling	Integrates longitudinal omics with CGM data	Forecasting metabolic deterioration over time	Captures temporal dynamics; suitable for disease progression studies	Computationally intensive; prone to overfitting with small cohorts
	Multi-Modal Transformers[44]	Cross-attention across data types	Learns relationships between entire omics layers	High-accuracy prediction of diabetes onset and treatment response	State-of-the-art integration; models long-range dependencies	Very high computational cost; limited explainability
Graph Neural	Biological GNNs[45]	Node–edge representation	Models gene–protein–metabolite interactions	Identifying network hubs driving insulin resistance and inflammation	Biologically intuitive; captures interaction topology	Requires high-quality interaction networks; complex training
Networks (GNNs)	Heterogeneous GNNs[46]	Mixed omics graph structures	Connects regulatory, metabolic, and signaling layers	Mapping multi-omics trajectories leading to â-cell failure	Integrates diverse data types naturally; strong systems-level insight	Model complexity; limited standardization across studies
Systems Biology & Network-Based AI	Network Reconstruction Models[47]	Predictive and mechanistic mapping	Builds integrated insulin signaling and metabolic networks	Simulating genomic variant impact on proteomic cascades	Mechanistically interpretable; hypothesis-driven	Sensitive to model assumptions; incomplete biological knowledge
	Constraint-Based Metabolic Models (CBM)[48]	Flux balance analysis	Links proteomics ’! metabolomics	Predicting metabolic bottlenecks associated with hyperglycemia	Quantitative metabolic insight; grounded in biochemistry	Requires curated metabolic networks; static assumptions
	Multi-Layer Network Integration[49]	Unified molecular networks	Fuses omics layers for systemic interpretation	Identifying cross-layer biomarkers for early diagnosis	Comprehensive systems view; biomarker discovery	Integration complexity; data heterogeneity issues
	Perturbation & Causal Inference Models[50]	Simulate molecular interventions	Tests how gene/protein changes propagate	Predicting targets for improving insulin sensitivity	Supports causal reasoning; translational relevance	Requires strong priors; limited by experimental validation

Table 3. Ethical and Regulatory Concerns

Aspect	Key Issue	Ethical Concern	Indian Regulatory / Governance Context	Implication for AI–Multi-Omics in Diabetes
Data Privacy & Security	Handling sensitive genomic and metabolomic data	Risk of re-identification and misuse	DPDP Act, 2023	Requires informed consent, secure storage, and controlled data sharing
Research Ethics	Use of human multi-omics data	Participant autonomy and transparency	ICMR Ethical Guidelines; IEC approval	Mandatory ethical oversight and disclosure of future data use
Algorithmic Bias	Non-representative training datasets	Potential health inequities	ICMR guidance (emerging AI ethics)	Need for diverse, multi-centric cohort validation
Model Interpretability	"Black-box" deep learning models	Limited clinician trust and accountability	CDSCO / ICMR emphasizes transparency	Hampers clinical acceptance without explainability
Explainable AI (XAI)	Lack of transparent decision logic	Difficulty in clinical justification	Regulatory expectation for traceability	Supports safer risk stratification and therapy decisions
Clinical Deployment	AI tools for diagnosis or prognosis	Patient safety and reliability	CDSCO (Medical Devices Rules, 2017; SaMD)	Requires analytical and clinical validation
Data Sharing	Cross-border omics data transfer	Ownership and consent concerns	DPDP Act, 2023	May restrict international collaborations
Accountability	Responsibility for AI-driven outcomes	Unclear liability	IECs, CDSCO oversight	Necessitates clear governance and monitoring frameworks

biological applications.[58] Thus, probabilistic models are one of the pillars for mechanistic interpretation and hypothesis generation in the context of multi-omics.

Cloud, Federated, and Privacy-Preserving AI

As international cohorts of diabetics build up ever larger multi-omics databases, often comprising terabytes worth of genomic sequences, single-cell transcriptomes, proteomic spectra, and longitudinal metabolomics that can be scaled computationally, they have become essential. Cloud-based pipelines have made it possible to have high-performance on-demand computational capacity for one to process such massive datasets, harmonize datasets, and analyse them, while supporting reproducible workflows.[59] Federated learning has been a revolutionary concept that allows several institutions to co-train AI models without the need to transmit raw patient data and maintain privacy while avoiding regulatory constraints. Complementary privacy-preserving technologies, such as secure multiparty computation, homomorphic encryption, and differential privacy, have made it possible to perform sensitive omics data analysis in encrypted data without the disclosure of individual-level data.[60] As a collective, these infrastructures support ethical, scalable, and globally distributed AI-driven multi-omics research, which integrates population-scale datasets that are needed to data mine biomarkers and stratify individuals with diabetes at the population scale, where meaningful results will be obtained.

AI-Identified Biomarkers and Molecular Signatures in Diabetes

Genomic Biomarkers

Advances in Artificial Intelligence (AI)-integrated genomic analysis have led to a revolution in the way that diabetes risk variants are discoverable through the availability of a deep understanding of complex GWAS datasets. Some of the risk-associated SNPs identified by machine learning frameworks are those that regulate insulin secretion, including those in MTNR1B, which influences â-cell melatonin receptor signaling, and GLIS3, which regulates â-cell development and insulin transcription.[61] AI models are also picking up the interactions between genes and the environment, and genes and lifestyle, to show how the predisposition of genes is altered by diet, obesity, disruption to the circadian rhythm, or exposure to metabolic stressors. Importantly, polygenic risk scores (PRS) that are enhanced with AI now incorporate non-linear interactions and include epigenomic and transcriptomic modifiers, which allow susceptibility to diabetes to be predicted with high resolution years before a diabetic state occurs. These enriched PRS frameworks enhance the risk stratification in order to identify the high-risk individuals early and support a personalised prevention strategy [62]

Proteomic Biomarkers

Proteomic profiling enhanced by AI gives mechanistic insights into dysregulated protein networks of diabetes progression. Large-scale phosphor proteomics data demonstrate massive decreases in activation of the insulin receptor (INSR) and phosphorylation of AKT, signatures known to be highly correlated with insulin resistance seen in the whole body. AI algorithms are also consistently able to identify inflammatory proteins, such as CRP, complement factors, and peptides associated with cytokines, as key early predictors of metabolic deterioration. [63] Among the circulating biomarkers, two proteins that act as regulators of lipid and glucose metabolism, FGF21 and RBP4, which are associated with adipose-liver metabolic cross-talk, appear to be robust markers of insulin resistance and â-cell stress.[64] By examining correlations between different proteins, network topology, and pathway activation profiles, models that are driven by a machine learning system identify signatures of multiple proteins that are more effective at the prediction of glycemic deterioration, progress to type 2 diabetes, and therapeutic response than traditional single-protein biomarkers.

Metabolomic Biomarkers

AI-assisted metabolomics identifies metabolic disorders that predict early metabolic collapse and diabetes. Machine-learning models have shown that ceramide subclasses are strong predictors of cardiometabolic complications, revealing the role in lipotoxicity, mitochondrial dysfunction, and beta-cell death. Additionally, clusters of branched-chain amino acids (BCAAs), aromatic amino acids, and acylcarnitines are known to be early metabolic fingerprints of developing insulin resistance when observed years before the onset of clinical hyperglycemia.[65] AI models also

emphasize the role of gut-derived metabolites of microbiota, such as short-chain fatty acids, secondary bile acids, and indole metabolites, which regulate hepatic glucose production and body inflammation. These metabolic signatures have been compiled into high-performance predictive metabolic risk panels with excellent translational potential for early screening as well as monitoring of intervention.[66]

Integrated Multi-Omics Biomarker Panels

With the integration of genomics, proteomics, and metabolomics, AI produces comprehensive biomarker panels that cover the complexity of diseases more than any other layer of the omics. Multi-omics fusion approaches have resulted in the creation of genomic-metabolomic signatures that can identify biologically distinct subgroups of patients with prediabetes and allow them to be stratified early in the disease. Proteogenomic profiles are used to further distinguish individuals based on the rate of â-cell decline by providing a link between transcription factors, post-translational modifications, and metabolic readouts.[67] In the field of therapeutic research, integrated panels are used to predict the phenotypes of drug response, for example, the prediction of metformin responders based on the proteomic patterns of the AMP Kinase family in combination with mitochondrial metabolite signatures. These multi-layer biomarkers are consistently better predictors than conventional clinical indices (e.g., HbA1c, fasting glucose, and HOMA-IR) with an improved power to predict early changes, and to predict long-term metabolic trajectories. [68] Consequently, integrated omics-AI signatures are emerging as the future clinical tools for the personalized risk assessment, diagnosis, and treatment planning of diabetes.

Clinical Applications of AI-Based Multi-Omics in Diabetology

Early Diagnosis and Risk Prediction

AI-enabled multi-omics-and-things technology paradigm of early diagnosis by detecting disruption of metabolism far before conventional clinical disruption will result in Integrated models using genomics, epigenomics, proteomics, and metabolomics that can effectively predict progression from prediabetes to diabetes that providing a significant lead time for intervention to prevent diabetes. By analysing B-cell transcriptomic stress signatures, mitochondrial proteomic changes, and metabolite flux changes, AI can detect early B-cell dysfunction and subclinical insulin resistance, which typically remain asymptomatic for years. These predictive systems can identify high risk even if fasting glucose and HbA1c are in the normal ranges, therefore they allow a proactive lifestyle and pharmacological intervention.[69] As a result, multi-omics signatures are emerging as early-warning biomarkers, which will change risk assessment from successive to pre-emptive clinical practice.

Precision Classification of Diabetes

Traditional diabetes division into type 1 (T1DM) and type 2 (T2DM) diabetes does not reflect the wide biological heterogeneity across the spectrum of the disease. The use of AI-enabled multi-omics integration has enabled data-driven subtyping, which has shown different mechanistic clusters of diabetes. These are severe insulin-resistant diabetes (SIRD), which is characterized by severe hepatic insulin resistance and a high burden of fat liver disease (NALD); mild obesity related diabetes (MOD), which is associated with metabolically flexible obesity; and severe autoimmune diabetes (SAID), which is associated with immune-mediated destruction of beta cells.[70] Each of the subtypes has distinctive genomic, proteomic, metabolic, and immunological profiles, which are the objective of specific management strategies. For example, some individuals who fall under SIRD may benefit from insulin sensitizers, while SAID subgroups may need early immunomodulatory therapy.[71] The classification guided by AI, therefore, enables personalised clinical decision-making and transcends the treatment algorithms.

Predicting Complications

The development of complications associated with diabetes is highly variable, and early prediction is important for management. AI-enhanced multi-omics tools for the identification of early molecular markers of diabetic nephropathy-albuminuria-associated proteomic panels, extracellular matrix proteins, and metabolite signatures associated with renal oxidative stress. For diabetic retinopathy, lipidomic and metabolomic predictors, including dysfunctional sphingolipids, branched-chain amino acids, and metabolites of oxidative stress in the retina, are early signs of

microvascular damage.[72] Similarly, multi-layer inflammatory signatures combining cytokines, complement factors, and inflammation markers derived from metabolites accurately predict the risk of cardiovascular disease in diabetes. These models can be used to map individual trajectories of development of complications years before clinical symptoms appear, which can be used to provide tailored screening intervals and targeted preventive therapies to reduce long-term morbidity.[73]

Personalized Treatment Response

AI-enabled pharmacogenomics and proteogenomic integration are making way for personalised diabetes therapy. Predictive models that include genomic variants such as SLC22A1 are used to predict metformin response, that is, to identify patients who will respond favourably to metformin with optimal glycaemic control and those who will need other regimens.[74] Similarly, inflammatory proteomic signatures and gut-metabolic signatures also correlate with differential response to GLP-1 receptor agonists, which helps in the process of personalized drug selection. AI models also use renal metabolomic signatures and sodium-handling pathways to predict the efficacy of SGLT2 inhibitors to guide their use in individuals who may get the most cardiovascular or renal benefit.[75] By determining who will and will not respond to therapy before initiating treatment, these types of approaches reduce trial-and-error prescribing, minimize adverse effects, and aid in optimizing dose. Ultimately, personalization using AI to tailor therapies to individual patient needs ensures the most effective therapy is being offered to each patient based on their unique biology profile.

Challenges and Limitations

Data Heterogeneity

One of the biggest challenges for the integration of multi-omics is that of the massive heterogeneity present across datasets due to variations in biological sampling, the sequencing platforms, and analytic protocols being employed. Variability in sample collection procedure, e.g., fasting status, tissue source, storage conditions, is the source of pre-analytical noise that makes the comparison between cohorts difficult.[76] Similarly, sequencing platforms, mass spectrometry platforms, and the library preparation strategies are quite different among the different laboratories, which leads to the existence of batch effects and may mask real biological signals. Population-based differences of factors like ethnic background, diet, comorbidities, and environmental exposures further contribute to the variability in molecular profiles to decrease the generalisability of biomarkers derived from AI.[77] Without rigorous harmonization and standardization, the integration of studies with high-quality cross-studies is a challenge, which limits the reproducibility and clinical scale of multi-omics models.

Computational Constraints

Multi-omics datasets are highly-dimensional, sparse, and noisy, which present huge computational challenges for AI-based analysis. Deep learning models, especially transformers, variational autoencoders, and graph neural networks, need a lot of computational power in terms of high-memory GPUs or TPUs, software pipeline optimizations, and parallel processing infrastructures.[78] Furthermore, the good model training requires large samples, which are not always present in multi-omics studies focused on a specific disease, giving rise to the problems of avoiding overfitting and ensuring the robustness of the models. These computational constraints can hinder the timeline of working on the models, restrict availability to resource-limited research environments, and cannot be done without specialized know-how in bioinformatics, A.I. engineering, and systems biology.[79] As a result, the use of advanced multi-omics tools and artificial intelligence (AI) is not evenly developed and deployed across institutions.

Biological Interpretability

Despite the power of their predictive ability, however, many AI models are "black boxes," with limited interpretability with regard to clinical/biological decision-making. Clinicians and translational researchers need clear models that reveal the role of particular molecular characteristics in predicting how things will go. [80] Without mechanistic clarity, it is hard to perceive the difference between disease and statistical association (causal driver). In order to fill this void, there is also a growing demand for explainable AI (XAI), feature attribution techniques, and biologically-based modelling strategies to explain regulatory mechanisms and molecular networks.[81] Moreover, the predicted

biomarkers and interactions need to be validated experimentally in cell-based assays and animal models and in human cohorts, so that AI-generated hypotheses are made of actual biological processes. The fact that the pipelines that connect artificial intelligence outputs to in vitro validation are not presently standardized, however, means that the translation of these biomarkers is inhibited from rapid uptake.

Ethical and Regulatory Concerns

The exponential growth of AI-enabled multi-omics analytics brings up all sorts of ethical, regulatory, and societal concerns. High-dimensional omics data contain significant privacy risks, especially if genomic information can be re-identifiable by computational inference. Bias in datasets - due to the result of overrepresentation of certain ethnic groups or socioeconomic backgrounds, may propagate into model predictions and make fairer predictions, potentially increasing health inequalities.[82] Furthermore, there is a lack of standardized workflows for multi-omics generation, integration, and reporting, which makes the evaluation of regulations difficult. As of right now, there are few FDA or EMA-approved AI-multi-omics tools for clinical use, and this reflects the regulatory difficulties involved in assessing dynamic, probabilistic, and continuously evolving AI systems.[83] Dealing with these concerns will require extensive standards, open algorithms, and robust safeguards for patient data.

Limited Clinical Translation

Despite promising findings, most biomarkers identified through AI algorithms, known as multi-omics, have yet to be translated into common practice. The high cost of omics profiling, such as whole genome sequencing, single cell assays, and high-resolution proteomics, is a major barrier to implementation in standard healthcare settings.[84] Additionally, many proposed biomarkers have not been prospectively validated in large groups of multi-ethnic cohorts, which would be required for drug approval and clinical trust. Hospitals - and clinical labs - are often not set up to implement multi-omics AI pipelines, due to technical inadequacy of technology infrastructure, computational resources, and human resources with the required expertise and knowledge base; this delay in translation is in addition to the challenges associated with developing pipelines that use genomics, brain imaging, and electrocardiograms (for atrial fibrillation) as input and employ machine learning to identify disease risk.[85] Consequently, although multi-omics technologies have an exceptional potential for precision diabetes medicine, implementation of the technologies will require a concerted effort in funding, infrastructure development, regulatory alignment, and clinical education.

Ethical and Regulatory Concerns

Model interpretability, data governance, and regulatory compliance are crucial ethical considerations in AI-driven multi-omics research related to diabetes. The use of sensitive genomic, proteomic, and metabolomic data raises concerns about privacy, re-identification, and data ownership. Therefore, it is essential to strictly adhere to the Digital Personal Data Protection (DPDP) Act of 2023 and follow the informed consent practices outlined by the Indian Council of Medical Research (ICMR). Algorithmic bias is another significant issue, especially in genetically and metabolically diverse populations like India. This highlights the need for representative, multi-centric datasets and transparent reporting. Additionally, the limited interpretability of many deep learning models poses challenges to clinical trust and accountability, making explainable AI (XAI) frameworks critical for regulatory approval and clinical decision-making. From a regulatory perspective, AI-based multi-omics tools intended for diagnosis or prognosis may be classified as software as a medical device under the guidelines of the CDSCO. This classification requires rigorous validation and post-deployment oversight. Overall, addressing these ethical and regulatory challenges is essential for the responsible translation of AI-enabled precision diabetes medicine into clinical practice.

Future Directions

Single-Cell and Spatial Multi-Omics technologies are a significant breakthrough in the understanding of the microarchitecture of cells that underlie diabetes. However, it can now be profiled in detail on an individual basis with single-cell RNA sequencing (scRNA-seq), ATAC-seq, and multi-modal assays, showing previously unknown differences in insulin secretion ability, stress vulnerability, and regenerative capacity among pancreatic â-cells.[86] Such strategies can distinguish distinct â-cell subpopulations, such as the immature

subpopulation, the stressed subpopulation, the dedifferentiated subpopulation, and the senescent subpopulation, each with a different contribution to diabetes. Spatial transcriptomics also provides the broader context of the results by mapping the anatomical architecture and transcriptional states of cells in intact pancreatic islets, and enables the researcher to measure the effect of physical proximity to á-cells, ä-cells, immune infiltrates, or fibrotic areas on â-cell behaviour.[87] These spatially resolved datasets provide the ability to reconstruct cell-cell communication networks, cytokine gradients, and paracrine signalling perturbations in response to metabolic stress in cells coupled with single-cell proteomics and metabolomics. Combined, the single-cell and spatial multi-omics offer an unprecedented molecular resilience and increase biomarker selectivity as well as the identification of early cellular changes that can be observed before functional deterioration.

Multi-Omics Digital Twins is a new paradigm of precision diabetes medicine. Digital twins are computational replicas of individual patients, which integrate genomic, proteomic, metabolomic, microbiome, lifestyle, and clinical data to simulate individual patient metabolic physiology.[88] These in silico models enable real-time prediction of an individual's response to certain types of dietary patterns, physical activity regimens, drug combinations, or environmental stressors. Through the integration of multiple layers of omics, digital twins can model intricate molecular interactions that are responsible for insulin sensitivity, â-cell workload, hepatic glucose output, and lipid flux.[89] This makes it possible to provide very personalized lifestyle recommendations, optimize dosing strategies, and detect early on metabolic inflection points that could lead to the progression of the disease. Additionally, digital twins can be used to test therapeutic interventions virtually reducing trial and error prescribing and reducing adverse effects.[90] The continued development of predictive models with adaptive artificial intelligence that use increasingly new wearable and biochemical data will ensure that digital twins will be considered a cornerstone of next-generation cancer treatment.

Explainable AI (XAI) tackles one of the most important constraints to clinical adoption of multi-omics-based machine learning systems, namely the opacity of complicated models. While deep learning and transformers are very good at predicting diabetes risk and finding new biomarker patterns, they are frequently "black boxes" which give little insight into the biological reason why they make certain predictions.[91] XAI techniques, including SHAP (Shapley Additive Explanation), attention heatmaps, and (causal) interpretability frameworks, can help identify the importance of individual genes, proteins, metabolites, or pathways in the risk assessment or treatment recommendations.[92] For instance, using XAI, one can determine which variants in the genome are the most important for a given predictive signal or identify which proteomic features differentiate responders from non-responders to a given therapy. Such transparency not only helps to build confidence among clinicians it also supports regulatory assessment because the use of AI for clinical decision-making is increasingly requested by regulatory agencies to provide a mechanistic basis for these decisions. By combining the accuracy of prediction with biological interpretability, XAI will facilitate the acceleration of the translation of the multi-omics biomarkers into clinical practice.

Integration with Wearables and Continuous Monitoring: bringing together of multi-omics data and digital health technologies in the form of continuous glucose monitoring (CGM), smartwatch-derived bio-signals, dietary trackers, and microbiome sensors is paving the way for real-time precision metabolic modelling.[83] Wearables enable real-time generation of unrestricted streams of physiological information containing glucose trends, heart rate variability patterns, physical activity patterns, sleep cycles, and stress indicators, which can be combined with molecular profiles to create adaptive biomarker systems. AI models can correlate the variation in CGM readings with the metabolomic signature, inflammatory proteins, or genetic predispositions and can give us a dynamic and individualised prediction of the glycemic responses. Emerging technologies like gut biosensors and digital dietary mapping add a wealth of data to these regulatory databases in almost real time in the form of mealtime composition and microbiome activity.[93] The fusion of these various sources of information enables building closed-loop systems which can continually refine

risk assessments, predict glycemic excursions, and inform about personalized dietary or medication adjustments.[94] Ultimately, combining multi-omics and wearable analytics will be the answer to shifting diabetes care from static measurements towards being proactive, data-driven, and real-time managed.

CONCLUSION

The integration of artificial intelligence and multi-omics technologies is transforming our view of diabetes into a complex and systems-level disease caused by closely interrelated genomic, epigenomic, proteomic, metabolomic, and environmental interactions. This can be achieved through the use of analytically driven approaches that employ Artificial Intelligence to derive biologically meaningful patterns from large-scale and heterogeneous datasets and shape the discovery of early-stage biomarkers, mechanistic pathways, and clinically actionable endotypes. Deep learning, graph-based models, and multi-view fusion strategies, strategies use unprecedented capacity to map disease networks, to identify hubs of interactions, and to predict the metabolic trajectories long before the clinical onset. Furthermore, emerging innovations, such as single-cell and spatial multi-omics, digital twin simulations, explainable AI, and continuous biosensor integration, hold out the promise of providing highly personalized and adaptive models of disease prediction and intervention. Despite great progress, issues around data standardisation, data interpretability, data computational requirements, and data translational readiness still hinder widespread clinical implementation. Solutions to such barriers will consist of international consortia of multi-omics, regulatory reform, and developments in explainable and privacy-preserving AI. This AI-enabled therapy offers multiple clinical advantages in diabetes management through integrating the multi-omics longitudinal biomarker data for early risk stratification and treatment optimization. This will provide a more precise therapy, glycemic control, reduced adverse drug events, and personalized therapies, and is expected to play a pivotal role in précised diabetes care and improved long-term patient outcomes. Overall, the use of AI-based, multi-omics research is positioned to usher in the next generation of precision diabetes medicine and to enable the earlier diagnosis and personalized optimization of therapy delivery and improved patient outcomes for diverse patient populations, both in the long and short term.

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