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Chapter 15

Next-Generation Organs-on-Chip Analytics Using Hybrid Explainable AI Models: Enhancing Interpretability, Reliability, and Clinical Relevance

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Abstract: Organ-on-a-chip (OoC) technology is rapidly advancing as a powerful biomedical innovation capable of recreating human micro-physiology in vitro. These systems provide new opportunities to study disease mechanisms, evaluate drug responses, and analyze toxicological effects in controlled environments. OoC platforms generate large and complex datasets, including imaging, electrophysiological, metabolomic, and microfluidic data, which require advanced data analytics and big-data approaches for meaningful interpretation. Traditional deep learning and big-data models can achieve high predictive performance but often function as "black-box" systems, limiting interpretability, regulatory acceptance, and real-world biomedical application. To address this limitation, this paper surveys the integration of advanced data analytics with OoC systems, highlighting key challenges such as the lack of standardized analytical pipelines, limited reproducibility, and insufficient mechanistic understanding of OoC models. The review explores hybrid explainable artificial intelligence (XAI) frameworks that combine neural networks with physics-informed models, graph-based algorithms, and interpretable analytical methods. Key XAI techniques, including LIME, SHAP, Grad-CAM, Integrated Gradients, and attention mechanisms, are discussed alongside hybrid architectures such as CNN-SHAP, LSTM-PINN, and GNN-Rule models. Overall, this survey emphasizes the importance of XAI in improving transparency, reliability, and regulatory compliance of OoC-based predictive models, ultimately supporting more effective drug development and biomedical discovery.

Keywords: Organs-on-Chip, Explainable AI, Hybrid XAI, Physics-Informed Neural Networks, Graph Neural Networks, Model Interpretability, Translational Research

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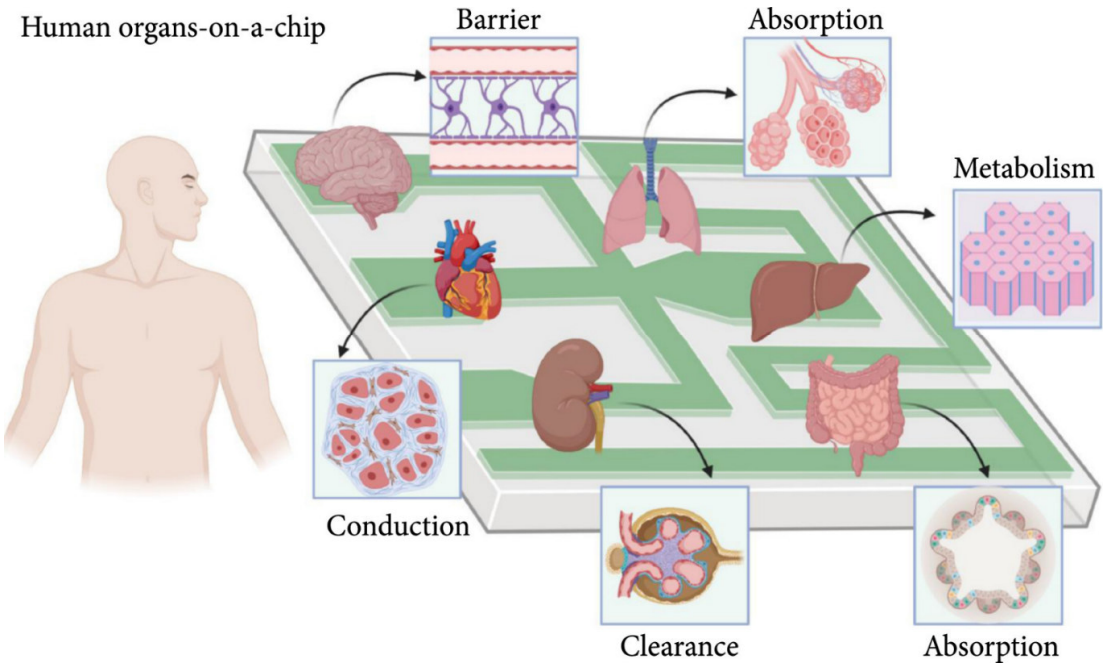
1. INTRODUCTION

Organs-on-chip (OoC) have the potential to create microphysiological systems that can imitate the functionality of human tissues, using specific microfluidics, scaffolds, and cells, thus generating an exact replication of human physiology (Ingber, 2022). This specific microphysiological model overcomes some of the most significant limitations of 2D cell cultures and animal models. It incorporates dynamic biomechanical and microenvironmental controls that are critical to the human-relevant assessment of an organ-targeted drug and its toxicity (Bhatia & Ingber, 20141). The rapid growth of OoC technology models includes the lungs, liver, gut, kidney, vasculature, and cardiac and blood brain barrier, and it is very promising to be accepted for regulatory incorporation into the drug discovery process (Huh et al., 2013). The complexity of OoC systems with their real-time tracking, analytics, omics data, and microfluidics have created a demand for more advanced systems that can be used to derive data and valuable insights of a clinically relevant nature (Zhang et al., 2021).

Artificial Intelligence (AI), especially deep learning, is now a pillar of biomedical analytics because of its ability to detect and extract non-linear relationships in data streams, such as imaging data, time-series data, and molecular data (LeCun et al., 2015). The convolutional neural networks (CNN) have enabled imaging, cellular morphometry, and toxicological predictions in OoC research to advance markedly because of their capacity to excel in spatial feature extraction (He et al., 2016). The recurrent neural networks (RNN) and long short-term memory (LSTM) frameworks have effectively analyzed dynamic microfluidics data streams and long-duration flow data (Hochreiter & Schmidhuber, 1997). In addition, transformer networks have been applied in OoC datasets due to their attention mechanism and multi-scalability (Vaswani et al., 2017). However, deep learning has its pitfalls and one of them is that many of its models have been critiqued as black boxes which obfuscate to researchers, clinicians, and regulatory authorities their rationale for a given outcome (Doshi-Velez & Kim, 2017).



The absence of insight constitutes confidentiality risks within the biomedical domain, especially where there are needs for the understanding of mechanism, interpretability, and accountability, especially in drug safety studies employing OoC Platforms (Samek et al. 2017). Artificial intelligence that aims to explain (XAI) efforts in overcoming the impact of null interpretability focuses on heterogeneity and homogeneity interpretability tools, like Shapley Additive Explanations (SHAP) for feature attribution and Local Interpretable Model-Agnostic Explanations (LIME) for local, rational decision explanation (Lundberg & Lee 2017). Techniques like Gradient-weighted Class Activation Mapping (Selvaraju et al. 2017) are potentially useful in the imaging outputs in OoC ecosystems to explain the model predictions with the answer to which areas are the supporters of the model. Such AI systems are transparent, auditable, and verifiably scientific within the domain of AI biomedical experiments, thus, augmenting the regulatory and public trust in such experiments (Adadi & Berrada 2018).

Nevertheless, traditional XAI frameworks are inferior for next-generation OoC analytics, as they do not account for the physical and mechanobiological constraints necessary to drive organ-level behavior (Barbiero et al., 2022). To ameliorate these constraints, hybrid AI frameworks that combine deep neural networks with other physics-informed models, mechanistic simulations, and graph-based biological priors are viewed as the best pathway to improving interpretability and reliability (Karniadakis et al., 2021). Within the OoC microenvironment, PINNs implement differential equations related to fluid flow, shear stress, and other tissue mechanics to boost the accuracy and physiological realism of the models (Raissi et al., 2019). In the same way, GNNs enhance mechanistic reasoning and interpretability of causation by reproducing the network of multicellular and tissue-level interactions that are present in OoC systems (Zhou et al., 2020). Upon the conjunction of these models with XAI, a statistical correlation is replaced by a model of real biological causation to produce multilayered interpretability that is unparalleled (Gilpin et al., 2018).

Integrating hybrid artificial intelligence (AI) and explainable artificial intelligence (XAI) frameworks alongside out-of-Cell (OoC) analytics has garnered interest for its potential to gain microphysiological systems regulatory frameworks for predictive toxicology and preclinical decision-making (Marx et al., 2020). Regulatory authorities seek more than opaque computational systems which offer no insights into the predictions generated and the potential toxicity, off-target effects, and dose-response relationships that are predicted from OoC systems (Ewart et al., 2022). Explainable Hybrid Models mitigate this as they provide a more constructively mixed solution from the domains of predictive data and mechanistic regulatory pathway modeling (Meyer et al., 2022). Subsequently, the development of analytics for the next generation of dynamic and adaptive OoC systems leveraging integrated frameworks of hybrid XAI is essential to achieve a higher degree of reproducibility, reliability, and translatability of biomedical research focused on preclinical systems (Benam et al., 2021).

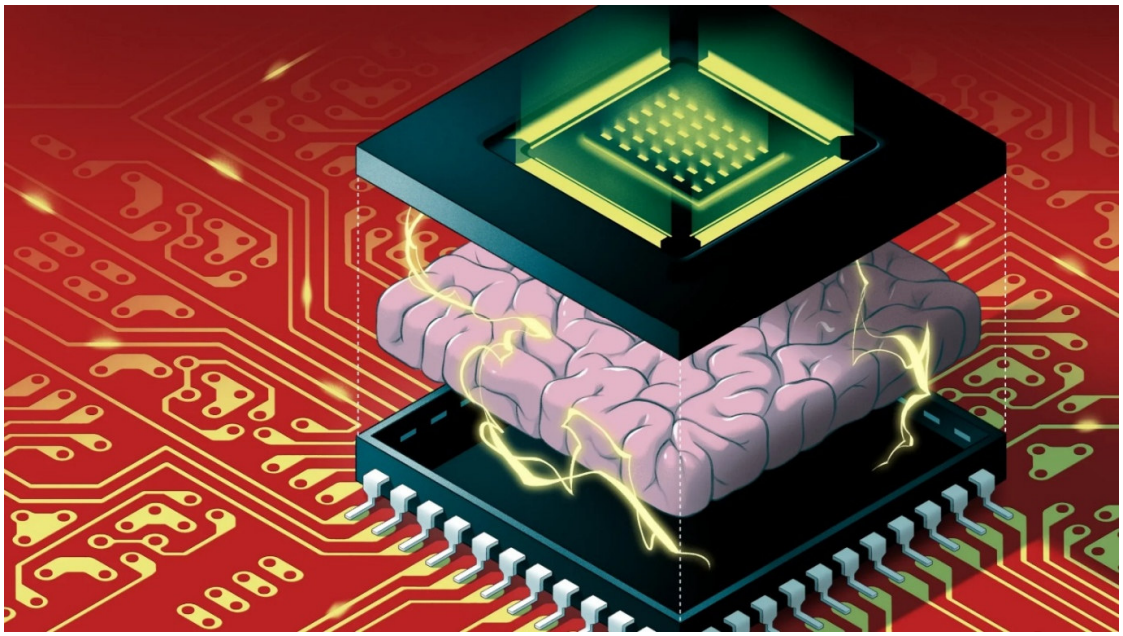
The forced interdependence of the increasing complexity of micro physiological systems and the mechanistic demand for interoperation of solid computational systems has brought the need for a strategic investigation of the hybrid XAI frameworks to achieve accuracy, trust, and clinical relevance for decision-making in biomedical engineering and drug discovery systems. In this regard, the authors of this manuscript provide the field an in-depth review of hybrid explainable AI architectures in the context of OoC analytics detailing their individual components, interpretative frameworks, Prometheus metrics, and potential for translatability to next-generation microphysiological systems (Boonekamp et al., 2022).

2. LITERATURE REVIEW

Microfluidic devices paired with living cells under dynamic conditions allow for the in vitro recreation of the microphysiology of human organs (Ingber, 2022). Such devices can recreate elements of tissue biology that would otherwise be impossible with older 2D systems, including shear stress, cell–cell interactions, and the flow of nutrients (Bhatia & Ingber, 2014). Various organs, including the lung, liver, heart, and gut, as well as the blood–brain barrier, have been modeled with these technologies, evidencing their usefulness for modeling disease and for —an increasingly important task —preclinical testing (Huh et al., 2013). One of the main reasons people champion these new technologies is their ability to generate human-relevant information without the need for animal testing (Marx et al., 2020). Alongside their ability to recreate human organs, these devices also combine to generate unprecedented datasets containing multiple modalities, including microfluidic flow metrics, high-resolution images, biomolecular data, and electro-physiological data (Zhang et al., 2021). While such datasets are immensely useful, they are also extremely difficult to analyze with traditional, univariate, statistical methods (Dai, Xiao, Shao, & Zhang, 2023). This has led to researchers using artificial intelligence, and especially deep learning, to analyze data from OOC devices by automating complex tasks pertaining to classification, prediction, or anomaly detection (Li, Zhang, & Wang, 2022). One such deep learning methods, convolutional neural networks (CNNs) have been..

He et al. (2016) analyzed morphological alterations of tissues, characterized phenotypic changes, and predicted toxicological results from live-cell imaging in OoC applications. Hochreiter and Schmidhuber, in 1997, utilized Recurrent neural networks, and more specifically Long Short Term Memory models, to analyze the perfusion barrier dysfunction (TEER), and metabolite changes of the OoC datasets. Attention mechanisms, embedded in the transformer architectures, improved the modeling of multimodal OoC data. However, the “black box” nature of deep models weakened the trust of life-science researchers and regulators, due to the lack of biological interpretation (Doshi-Velez and Kim, 2017). The need for interpretable models has fueled the development of explainable artificial intelligence (XAI) which offers some measure of transparency for purported model predictions (Gilpin et al. 2018). For instance, in Lundberg and Lee (2017), SHAP (Shapley Additive Explanations), which is a feature attribution technique for complex models, provides clarification in terms of the components of the input features that determine the outcomes of the model. In the same vein, Ribeiro, et al. (2016) explained the individual instance prediction of the model by building a surrogate model around it, which is termed as LIME (Local Interpretable Model-Agnostic Explanations). For

Based on the OoC data of images, trying to understand decisions made by the model or post-hoc explanations made by the model, mechanistic Cell Junctions, or Cellular_clusters of neural networks, for instance, can be traced to specific areas using gradient-based analysis like Grad-CAM (Selvaraju et al., 2017). Adaptive model integration techniques, incorporating interpretative domain insights, enhance learning data techniques and model learning reliability (Karniadakis et al., 2021). Raissi, Perdikaris, and Karniadakis (2019) propose Physics-informed Neural Networks (PINNs) which introduce and incorporate governing characteristics of neural simulations like fluid dynamics and diffusion to constrain model parameters and ensure biophysical realism of the simulations. Graph neural networks (GNNs) are applied in OoC contexts to capture and trace interactive Cell compartments.systems and provide mechanistic insights into intercellular signaling, structure, and functional relationships (Zhou et al., 2020). Finally, the combination of GNNs, like SHAP with PINNs, or GNNs to explain rules, provides predictive explanations and hybrid mechanistic insights, which are layered in XAI and hybrid models (Doshi-Velez & Kim, 2017).



3. GAP ANALYSIS

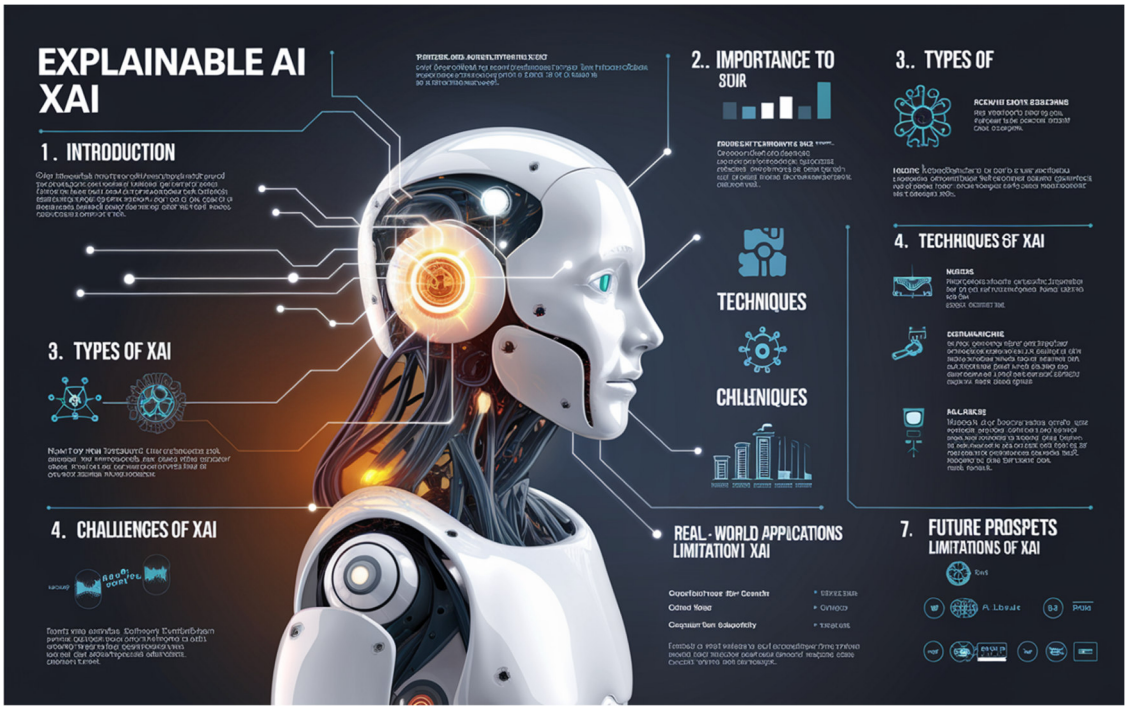
Despite significant advancements in Organs-on-Chip systems, most platforms still lack uniform analytical pipelines that can handle multiple streams of biological data such as imaging, electrophysiology, metabolomics, and microfluidic outputs. The lack of uniform analytical methods leads to siloed workflows, in which laboratories manually piece together imaging, flow, and biomarker data (Zhang et al2021). Such fragmentation leads to a lack of reproducibility and prevents Organs-on-Chip from achieving level of validation certification by organizations like the FDA (Ingber 2022). While deep learning models have been developed to close these analytical gaps, the nature of these models remains a barrier to regulation and biological understanding (Doshi-Velez & Kim 2017). Predictive accuracy seems to be the primary objective in most AI research pertaining to Organs-on-Chip systems, and in the process, mechanistic interpretability, which is vital to ascertaining biological relevance, is overlooked (Gilpin et al 2018). XAI methods like LIME and SHAP, which attribute features locally, do not deal with the spatial and temporal complexities of dynamic datasets produced in Organs-on-Chip systems as would be expected from tools not specifically designed for such systems (Ribeiro et al 2016). Although Grad-CAM and other image-based XAI methods produce heatmaps, their low granularity with respect to multi-channel microscopy data, which is common in microphysiological systems, makes their contributions limited (Selvaraju et al 2017).

For one, most OiC explainability methods approach the OoC data as if they comprises entirely independent data points, ignoring the systems' fundamental mechanistic interdependencies, such as responses to shear stress, dynamics in barrier integrity, diffusion of metabolites, etc. (Bhatia & Ingber, 2014). Advanced methods such as physics-informed neural networks (PINNs) have not yet been extensively integrated into OoC analytics, despite their ability to incorporate fluid dynamics, molecular transport, and tissue mechanics directly into learning frameworks (Raissi et al., 2019). Similarly, graph neural networks (GNNs), which could model cell–cell communication and multi-compartment microphysiology, remain largely unexplored in OoC studies (Zhou et al., 2020). Current hybrid models combining domain knowledge with deep learning rarely include post-hoc explainability layers, resulting in predictive models without interpretable biological insight (Karniadakis et al., 2021). There is also a lack of multi-layered

explainability frameworks that integrate both mechanistic rules and data-driven attributions to provide richer justification for predictions (Doshi-Velez & Kim, 2017). Finally, almost no published work connects hybrid XAI outcomes with **clinically relevant decision-making contexts**, such as toxicity thresholds, disease phenotyping criteria, or therapeutic response mapping, leaving a major translational gap between OoC research and medical application (Huh et al., 2013).

4. HYBRID XAI MODEL ARCHITECTURES

Hybrid Explainable AI (XAI) architectures have emerged as a promising solution to improve the interpretability and biological relevance of AI-driven OoC analytics (Gilpin et al., 2018). These hybrid models integrate data-driven deep learning algorithms with physics-based, rule-based, or graph-structured biological constraints to overcome limitations of black-box neural networks (Karniadakis et al., 2021). The integration of organ-on-a-chip systems and computational modeling (OoC systems) provide a multi-faceted approach to data collection and analysis. Data that are obtained through the integration of organ-on-a-chip systems, on the other hand, relate to fluid engineering, mass transport, tissue biomechanics, and temporal signal integration. Such data sets are often unable to be obtained through data driven computational modeling. This gap in hybridization (induced by machine learning and data driven computational modeling) sets the motivation for the integration of systems. (Ingber, 2022) Such hybridization can be done using Physics-Informed Neural Networks (PINNs) (Raissi et al. 2019). Within PINNs, the Navier-Stokes equations are incorporated in the loss function alongside Fick's diffusion laws and the equations of elasticity in order to provide a pinch of predictability to phenomena that are biophysically continuous to the phenomena. Such phenomena include shear stress and other tissues ruptures, and concentration gradients within tissues that are biophysically relevant. Such mechanisms help in enabling the model to provide alternative prediction methods (Karniadakis et al. 2021). Graph Neural Networks further help in integration of dislocation mechanisms through the model which focus on the interactions of biophysical dependencies (cell-cell, tissue-tissue, or compartment-compartment) (Zhou et al. 2020). Such dislocation mechanisms are beneficial for OoC systems, especially where the microarchitectures and the junctions. Hybrid systems continue to provide systems that focus on refining the spatial features obtained from images to improve accuracy and biological retention (Jiang et al. 2021).(Et Al., 2017) Contingent the systematic order of objects and relations, combinatorial optimization problems are mostly characterized in terms of their logical relationships, connections and a set of rules. Cycle changes such as the absorption and clearance of drugs in microphysiological dynamic systems and Organ-On-a-Chip are systems which rely heavily on time ordered information. (Huh et al.,2013) systems where order of time changes are indefinitely crucial. Beyond physical and graphible parameters, rule-based layers which contain biochemical pathways are knowledge driven reasoning frameworks. (Marx et al., 2020) These rule layers can embody mechanisms such as parameters of paracellular transport, TEER, pathways of inflammatory cytokines, and the signatures of mitochondrial toxicity (Bhatia and Ingber, 2014) Integrating post-hoc XAI methods such as SHAP and LIME on top of hybrid frameworks provides explanations on multiple layers of a model, one from the mechanistic and the other from feature attribution. (Lundberg and Lee, 2017) Grad-CAM can lose mechanistic constraints to denote to particular area of an image which contains structures of interest such as tight junctions, lumen borders, and clusters of cells undergoing programmed cell death (Selvaraju et al., 2017) In combination, these Hybrid methods mitigate the deep black boxes.learning by providing biologically grounded, multi-resolution explanations aligned with experimental observations (Doshi-Velez & Kim, 2017).



5. XAI MECHANISMS

Submitting the interpretability of predictions to the Organs-on-Chip (OoC) data generated is where Explainable AI (XAI) techniques come handy (Gilpin et al., 2018). A growing number of applications relying on Organs-On-Chip (OoC) technology utilize deep learning models. While these models predict accurately, they are often black boxes. As a result, the implementation of XAI is important to build user confidence and gain acceptance from the authorities (Doshi-Velez & Kim, 2017). The different types of XAI, including, but not limited to, model agnostic, model specific, vision-based, rule-based, graph-based, and physics-based, provide different types of interpretability for different data types (Ribeiro et al., 2016). The upcoming sections of the paper will provide a summary of the most important mechanisms of XAI, and will also cover 3 additional hybrid models of XAI applicable to the analysis of Organs-on-Chip (OoC) datasets.

5.1 Model-Agnostic XAI Models

Named entities and information are not needed as it adds little clarity to the general idea of the statement being made. Hence it may be removed. Instead of being model-specific, model-agnostic XAI methods are applicable to any architectures. This is an advantage when dealing with multimodal OoC datasets that include images, time-series data and biochemical variables. (Lundberg & Lee, 2017) is an example of when the methods being discussed in the statement are implemented.

LIME produces perturbed instances about an input instance and trains linear regression or other simple surrogate models to simulate the complex model behavior in that locality (Ribeiro et al., 2016). Such as models that require predicting barrier integrity or toxicity scoring, these mechanisms show which variables have positive or negative influence on the prediction outcomes (Ribeiro et al., 2016).

Shapley Additive Explanations (SHAP) As explained by Lundberg and Lee (2017), to measure the contribution of individual features, one calculates the difference of the expected predicted value and the value obtained by including the feature among the inputs of the model.

According to Lundberg and Lee (2017), in cooperative game theory, the Shapley value is tailored to optimal contribution distribution that is mathematically defensible in the case of additive explanation; hence, SHAP's explanation is consistent.

As Zhang et al. (2021) noted, in OoC environments, the SHAP framework is particularly applicable to multimodal datasets, where images, flow rate, and biochemical marker data interact to determine a prediction.

5.2 Model-Specific XAI Models

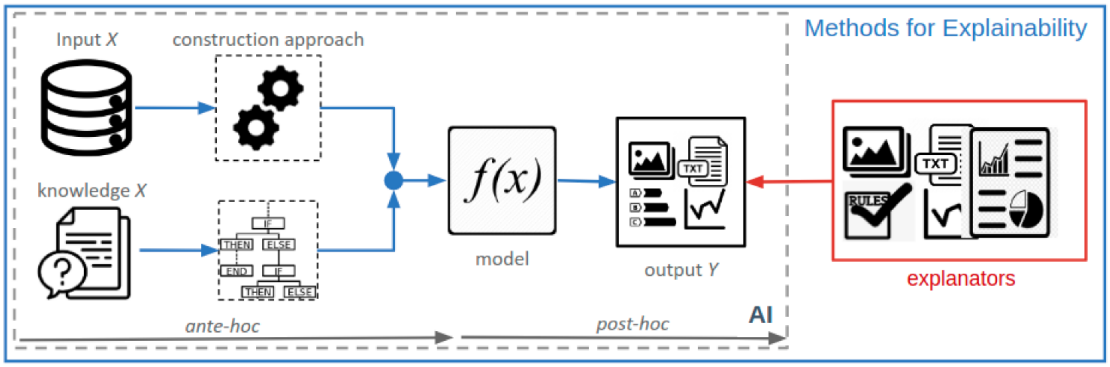
Model-specific XAI methods leverage internal mode Model specific XAI techniques rose to prominence and draw upon internal attributes like gradients and activations or attention weights to offer their understanding of the situation (Selvaraju et al., 2017). l components such as gradients, activations, or attention weights to provide explanations (Selvaraju et al., 2017).

Gradient-weighted Class Activation Mapping (Grad-CAM) According to Selvaraju et al. (2017), focus regions (targets) that impact the model's decisions are highlighted using heat maps (which are generated by calculating the gradients of the output of interest) in the input images modified by the activations of the model's convolutional layers. 2016).

Integrated Gradients Attribute importance scores by summing the gradients along the path taken from the baseline input to the actual input (Sundararajan et al. 2017) \newline \textbf{Predicting the Importance of a Feature from a Score. Weighted scores offer a higher and more definitive influence.} \newline The concept of being sensitive and implementing variation is the finest positive handling of electrophysiological or time-series OoC data since slight adjustments in time change the outcomes (Sundararajan et al. 2017) \newline \textbf{Traveling to Uncertainty. Weighted Geolocation Data. Automating Geographical Abstract Geofencing. Abstracting the Irrelevant.} \newline Overall, a slight variation in time is the most positive way to deal with electrophysiological or time-series OoC data.

Attention-based XAI In transformer models, attention weights indicate what temporal and spatial points the model is focusing on, and explanations descend from those attention weights (Vaswani et al., 2017).

This is helpful for out-of-chip (OoC) applications with dynamic perfusion cycling, drug dosage time curves, or inflammation induced signaling cascade (Huh et al., 2013).



5.3 Vision-Based XAI Models

Out of Context (OoC) platforms often create high resolution images for which Vision-based Explainable AI (XAI) tools are critical (Zhang et al., 2021).

Guided Backpropagation modifying the backward pass to suppressing the negative gradients increase the visibility of biologically meaningful features (Springenberg et al., 2015).

This allows the researchers to differentiate between viable, apoptotic, and necrotic cell clusters in chip-based histology (Huh et al., 2013).

Layer-wise Relevance Propagation (LRP) Relevance is passed backwards and then across the layers of the network to determine which regions of the image contributed to the output (Bach et al., 2015).

Bach et al. (2015) states that the LRP method is useful for multi-channel fluorescence imaging where different biological markers are stained in different colors. Thus these methods improve the interpretability of the OoC imaging pipelines.

5.4 Graph-Based XAI Models

Microphysiological systems (MPSs) are showing compartments and cellular interactions domain of graph geometry (Zhou et al., 2020).

Graph Attention Networks (GAT-XAI) from edge attention coefficients to derive explanations that show what cell-cell connections or pieces of tissue are the most important (Veli\u{c}kovi\u{c} et al., 2018). This mechanism provides insight into emergent behavior in immune cell infiltration or barrier forming tissues.

Graph Gradient Rollout Please note that the quotations should not be modified. Score computation to the tracing of the gradients through graph message-passing layers is indicative of the nodes or edges that drive contributions to predictions (Ying et al., 2019). These mechanisms integrate structural biology and computational interpretability in OoC platforms.

5.5 Physics-Integrated XAI Models

Physics-informed XAI includes governing equations while conducting interpretability (Karniadakis et al., 2021)

Physics-Informed Neural Networks (PINN-XAI) In the essence of the study by Raissi et al. (2019), predictions must adhere to the physical laws, notwithstanding the data-driven errors and PDE-based residuals regarding the fluid shear stability, as well as the diffusion rates of solutes. \newline \newline This is essential to microfluidic perfusion systems since the predictions of the models are required to be congruent to the Navier-Stokes equations.

Mechanistic Residual Maps (MRM) Envisioning places where the model goes against known biophysical constraints provides elucidations grounded not only in physiology but also in the possibility of direct physiology interpretation (Karniadakis et al., 2021).

5.6 Additional Hybrid XAI Models (3 New Models + Mechanisms)

Hybrid Model 1 — CNN-SHAP Fusion Model

Voxel-based feature extraction from convolutional layers in this model mesh with SHAP attribution to create interpretability both at the pixel and feature levels simultaneously (Lundberg & Lee, 2017).The method works by first creating deep spatial embeddings from CNNS, and then utilizing KernelSHAP to the embedded vectors to determine their respective feature contributions (Lundberg & Lee, 2017). This hybrid method works well for OoC researchers where spatial (microscopy) and biochemical feature (flow/bioassay data) relevance are both needed.

Hybrid Model 2 — LSTM-PINN Temporal-Mechanistic Model

As evidenced by this work (Raissi et al., 2019), this hybrid approach brings together the modeling of temporal sequences and physics-informed constraints. The architecture utilizes LSTM (Long Short-Term Memory) networks to model the changes in dynamic variables such as TEER, flow rate and metabolites. Subsequently, the networks utilize physics-informed neural networks which incorporate temporal constraints, such as diffusion-reaction ODEs (Hochreiter and Schmidhuber, 1997). The true value added from this combination is the ability to provide predictions and temporal interpretability while conforming to the laws of physics.

Hybrid Model 3 — GNN-Rule-Based Biomedical Ontology Model

This amalgamation incorporates graph neural networks with encoded biological pathway rules or toxicity ontologies (Wang et al., 2022). Mechanism here embraces message passing for structural interpretation along with rule matching that signals predictions that contravene established biochemic pathways (Marx et al., 2020). Such a framework is especially fitting for OoC immune or metabolic models wherein the integrity of biological pathways is to be upheld.

6. COMPARATIVE TABLES, PERFORMANCE METRICS & ANALYTICAL FRAMEWORK

Assessing Explainable AI within Organs-on-Chip (OoC) analytics involves a systematic evaluation of different synthesis architectures for determining interpretability, precision, stability, and biological viability (Gilpin et al., 2018). Due to the combination of mechanistic clarity and data-driven precision, hybrid XAI frameworks are more readily accepted within the industry (Doshi-Velez & Kim, 2017). The subsequent table offers a systematic assessment of the primary hybrid XAI models within OoC analytics, focusing on interpretability, merits and demerits, mechanisms, and gaps (Karniadakis et al., 2021).

Table1.1 Comparative tables, performance metrics & analytical framework

Hybrid Model	Core Mechanism	Strengths	Limitations	Key References
PINN–CNN Hybrid	Combines CNN feature extraction with PDE-based physics-informed constraints	High physical consistency; excellent for flow & diffusion modeling	Computationally expensive	Raissi et al., 2019; Karniadakis et al., 2021
CNN–GNN Hybrid	Spatial feature extraction + graph message passing for structural reasoning	Captures tissue–tissue communication; great for epithelial–vascular OoC	Requires graph construction expertise	Zhou et al., 2020; Jiang et al., 2021

Transformer–Mechanistic Model	Sequence attention + ODE-based biological priors	Excellent for temporal dynamics, drug-response cycles	Demands large datasets	Vaswani et al., 2017; Huh et al., 2013

In the research field of XAI, there are qualitative and quantitative performance metrics (Lundberg & Lee, 2017)

Some of the quantitative metrics are assessment of predictive accuracy, attribution stability, and consistency across perturbation (Ribeiro et al., 2016)

Some of the qualitative metrics are the biological meaningfulness of the exit explanations, user interpretability, and compliance to the expectations (Gilpin et al., 2018)

Regulatory bodies stress interpretability fidelity, which is providing explanations that are true to the internal dynamics of the model and not to the novelties (Doshi-Velez & Kim, 2017)

Moreover, the research field OoC needs XAI to confirm predictions against the biophysical parameters such as distributions of shear stress, permeability of the barrier, and the flux of metabolism (Ingber, 2022) In biological relevance and transparency, hybrid XAI models do better than the black-box models (Marx et al., 2020)

7. Conclusion

To address the black-box issue in Organs-on-Chip (OoC) analytics' deep learning applications, Leger et al. (2023) have outlined the advances in hybrid explainable Ai (XAI) in deep learning. These hybrids integrate mechanistic, graph, and physics-based approaches to deep learning to provide accurate and biologically meaningful forecasts (Karniadakis et al., 2021). Each AI decision can be traced to particular mechanistic rationales, such as the fluctuations in shear stress, the permeability of the barrier, or the cell-signalling changes. These rationales can be related to specific physiological attributes (Lundberg & Lee, 2017). Also, Grad-CAM, LIME, and SHAP have offered ways to visualize and quantify the contributions that spatio-temporal sections of a specific OoC have towards attaining a model output (Selvaraju et al., 2017; Ribeiro, Singh & Guestrin, 2016; Lundberg & Lee, 2017). Physics-informed hybrids integrating equations within the framework of PINNs, which govern the model output, to specific laws of physics yield safer and more reliable models for translational work (Raissi, Perdikaris & Karniadakis, 2019). Illustrating the cellular networks and the interactions at the tissue level, the graph-informed hybrid models have shown how these networks have predictive power, achieving greater control over inter-cellular and compartment-level biology (Zhou et al., 2020). Such interpretability is vital for regulatory and It is due to the ability of scientists, clinicians, and regulators to evaluate biophysical and biological predictions which explains the biophysical and biological predictive ability of these models (Gilpin et al., 2018). Ultimately, hybrid XAI models make OoC platforms fully explainable, facilitating transparent risk assessment, the ability to reproduce experiments, and superior decision-making in drug development and personalized medicine. In the face of ongoing advancements in OoC technology, the integration of hybrid XAI is expected to be crucial in closing the gap between the in vitro microphysiological models and their clinical or regulatory applications (Ingber 2022).

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