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# Quantifying the Impact of AI on Colorimetric Biosensor Performance: A Focused Metadata Review

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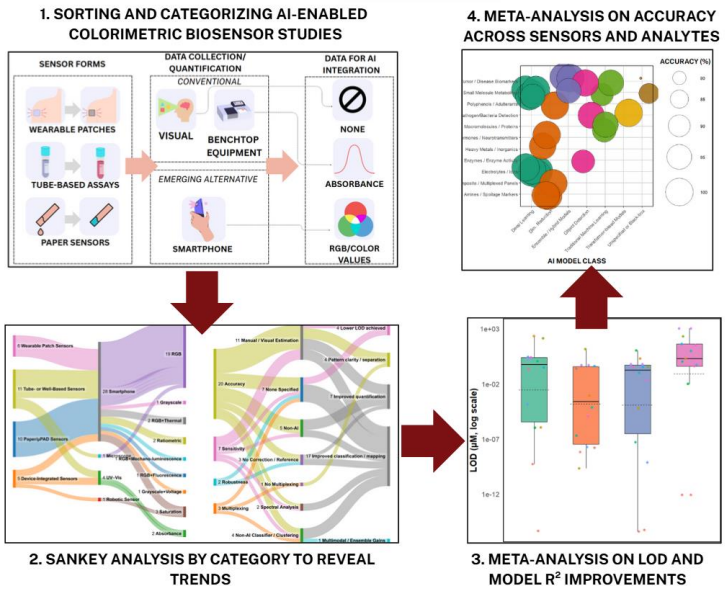
## Graphical Abstract




## Abstract

Colorimetric biosensors offer low-cost diagnostics but often suffer from subjective interpretation, environmental variability, and limited quantification. Artificial intelligence (AI) has emerged as a powerful solution, enabling automated analysis of chromogenic outputs captured via smartphones or imaging systems. This meta-analysis reviews 32 studies (2022–2025) applying AI to colorimetric biosensing, comparing performance across model types, sensor formats (e.g., paper, wearable, tube-based), input modalities (e.g., RGB, absorbance), and analyte classes. Key metrics include classification accuracy, regression strength ($R^2$), and limit of detection (LOD), benchmarked against non-AI and conventional methods.AI-enhanced platforms consistently improved accuracy, with context-specific gains in $R^2$ and LOD, especially for weak or overlapping signals. Smartphone-based RGB systems dominated but required calibration strategies such as CNN-GRU correction and illumination adjustment. Despite promising results, most studies lacked external validation and relied on supervised learning with small datasets. Semi-supervised approaches and standardized benchmarks are needed to ensure generalizability. Beyond analytical metrics, AI offered faster readouts, automated interpretation, and support for multiplexed sensing. Future directions include integrating augmented reality for enhanced usability and applying AI to sensor design and optimization. Collectively, these advances position AI-enhanced colorimetric biosensors as scalable, field-ready diagnostic tools with growing potential for clinical and environmental deployment

Keywords: colorimetric biosensors, artificial intelligence, machine learning, smartphone diagnostics, point-of-care sensing

## 1. Introduction

Lack of accurate, acessible, and rapid diagnostics remain a global issue for healthcare especially in remote, resource-constrained settings where over 47% of the global population lacks access to essential diagnostic tools[1]. While conventional laboratory-based diagnostics remian the gold standard, they require sophisticated equipment, trained personnel, and controlled environments. These limitations contribute significantly to delayed diagnoses and diagnostic errors, which are estimated to cause approximately 371,000 deaths and 424,000 permanent disabilities annually in the United States alone[2]. To address these, portable colorimetric biosensors, which are analytical devices that detect presence of target analytes through visible color changes via enzymatic reactions, nanozyme catalysis, or pH-sensitive dyes, have gained prominence as low-cost, easy-to-use alternatives capable of delivering rapid results without the need for laboratory infrastructure[3]. Google Trends data show that global interest in colorimetry more than doubled from late 2021 to early 2025, reflecting growing attention towards visual-based diagnostics[4]. By translating biochemical interactions into observable color changes, they have found applications in diverse settings from at-home glucose monitoring and pregnancy testing to field-based detection of pathogens and heavy metal ions that might be detrimental to health[5]. Moreover, their compatibility with paper-based substrates, lateral flow formats, and nanozyme-enhanced platforms makes them particularly attractive for decentralized healthcare and environmental monitoring[6]. However, despite their significant improvements over traditional diagnostics, colorimetric biosensors face persistent limitations related to subjectivity in optical result interpretation, arising from variations in ambient lighting, camera resolution, user technique, and perceptual bias, which can significantly affect the accuracy and reproducibility of results[7]. This is a hindrance for their widespread adoption in critical clinical or environmental applications where precision and standardisation are essential.

**Table 1.** Summary of recent reviews on AI-Enabled biosensors and the distinct scope of this work

| Year | Focus | Key Insights |
|---|---|---|
| 2024[7] | AI in biochemical sensors (incl. colorimetric) | Reviewed AI's role across sensing platforms, highlighting accuracy gains and implementation challenges. |
| 2024[3] | AI in electrochemical biosensors | Showed AI improves sensor sensitivity and wearable adaptability. |
| 2024[9] | AI-integrated wound dressings | Reviewed AI-biosensor synergy for wound monitoring and healing prediction. |
| 2023[10] | ML-based sensor arrays for bacterial detection | Surveyed ML-enhanced colorimetric/fluorescent arrays for pathogen classification. |
| 2025 (This review) | AI-enhanced colorimetric biosensors (health & environment) | Conducts first metadata analysis comparing $R^2$, accuracy, and sensitivity across 30+ studies. |

To overcome these challenges, artificial intelligence (AI) has emerged as a transformative solution. By analyzing colorimetric outputs captured via smartphones or imaging devices, AI algorithms provide automated, consistent, and quantitative interpretation of biosensor signals. While previous reviews highlight AI applications in biosensing, few assess its actual performance gains. This review fills that gap through a metadata analysis of recent AI-enhanced colorimetric studies, comparing improvements in sensitivity, accuracy, and regression strength ($R^2$) over traditional and non-AI methods. Table 1 summarizes prior reviews to contextualize this study's contribution.

## 2. State-of-the-art of Current Research

This work conducted a metadata analysis of 32 peer-reviewed studies from 2022 to 2025, sourced via Scopus and Google Scholar using combinations of search terms such as "colorimetric biosensor," "AI," "accuracy," and "sensitivity." Studies were included if they employed artificial intelligence (machine learning or deep learning) for the interpretation of colorimetric biosensor outputs and reported at least one quantitative performance metric (e.g., accuracy, sensitivity, or $R^2$). Data were manually extracted on sensor type, sample source, analyte, AI model, and comparative improvement over non-AI or traditional methods. A comprehensive table detailing these 32 studies is shown in Table S1 (supplementary).

### 2.1. Sensor Architecture – Form Factor, Platform, and AI Data Utilization

Figure 2.4.a shows sensor architectures across the 32 studies prioritized cost-effectiveness, portability, and user-friendliness, which are qualities best demonstrated by paper-based sensors (10 studies), wearable microfluidic patches (6), and tube/well-based formats (11), collectively accounting for over 85% of sensor form factors. In comparison to conventional laboratory-based diagnostics, these form factors drastically reduce overheads in terms of materials and logistics, enabling decentralized testing. Device-integrated sensors (5 studies), while offering superior performance via embedded optics or processors, still lack scalability due to their high cost and need for specialized maintenance. Smartphones were overwhelmingly used for signal collection (28 of 32 studies), outpacing other platforms like scanners (4), robotic sensors (1), and microscopes (1), due to their widespread accessibility, built-in cameras, and ability to process or upload images in real time. This sensor architecture across these studies is visualized in Figure 2.1.

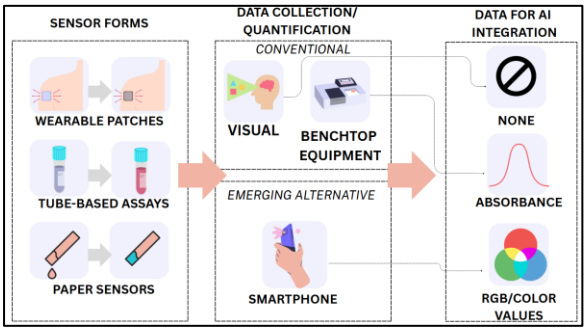



**Figure 2.1.** Architecture of AI-enabled colorimetric sensors

RGB was the main input for AI models (19 studies), followed by grayscale (2), absorbance (3), and multimodal setups like RGB with thermal, mechanoluminescence, or fluorescence (1 each). Its appeal lies in smartphone compatibility and suitability for CNNs that process spatial and color features. Absorbance-based methods are more robust but rely on non-portable, specialized tools. RGB's sensitivity to lighting and device variability reduces reliability without normalization, used in only a few studies (some in Table 2.1).

These steps are key to improving consistency in real-world settings. Overall, the move toward RGB-smartphone-AI systems supports scalable diagnostics, but stronger standardization is still needed to match lab-grade performance.

**Table 2.1** Color correction strategies applied across selected studies

| Study | Color correction applied |
|---|---|
| Wang et al.[11] | Trained a CNN-GRU model to adjust for ambient light and pH variation |
| Ghateii and Jahanshashi [36] | Used flash/no-flash subtraction and lab color space conversion to stabilize lighting conditions |
| Liu et al[42] | Applied pixel-wise color correction using a 24-color checker to calibrate camera-based inputs |

### 2.2 Purpose and Sample Type – Monitoring Targets, Matrices, and Analytes

Figure 2.4.b reveals that sensors are mainly applied to clinical diagnostics (10/32 studies), metabolic monitoring (7), and food safety (6), with fewer targeting pathogens (4), cellular assays (2), or multiplex panels (1). This mirrors the prevalence of accessible samples like urine (4), sweat (3), saliva, and tears, ideal for wearable or point-of-care use. However, this also suggests an application bias, favoring well-characterized analytes in controlled settings. Food and environmental samples (9 studies combined), which present greater matrix complexity and signal noise, remain underrepresented despite being where AI's disambiguation strengths are most needed. Current trends favor feasibility over impact, applying AI where outputs are already interpretable rather than where its value is most critical.

Notably, many AI models have been applied to analytes that already produce vivid and monotonic color changes, such as glucose and pH, where human-readable output is already largely feasible. While this enables automation and precision, it may underutilize AI's potential. As shown in Figure 2.2, analytes like HDL, LDL, and troponin exhibit weaker or grayscale transitions that are far less distinguishable visually. These cases present the strongest justification for AI integration yet remain underrepresented. Rather than reinforcing already discernible signals, AI's role should be expanded to support analytes with ambiguous visual responses, where its capacity for pattern recognition and subtle gradient differentiation can meaningfully extend the reach of colorimetric sensing.

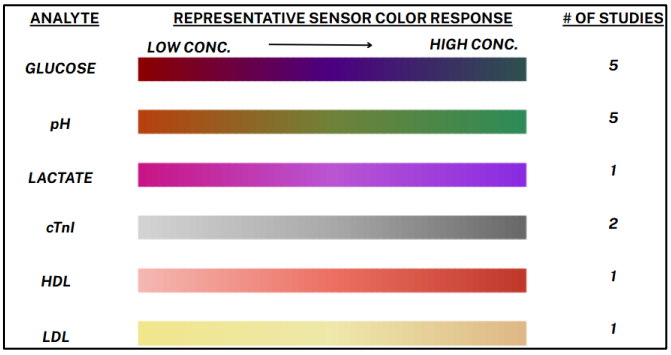



**Figure 2.2.** Colorimetric responses for selected analytes.

### 2.3 AI Use Case and Model – Task Types and Algorithms Employed

AI in colorimetric biosensing has mainly focused on regression (18 of 32 studies) and classification (13), aligning with the direct relationship between color change and either concentration or categorical outcome. Regression typically maps RGB patterns to analyte levels, while classification supports test result interpretation. These applications suit sensors targeting analytes with clear, monotonic color shifts like glucose or pH. However, this also reflects a cautious approach where AI is often applied where signal-response relationships are already well defined. More advanced tasks like clustering, anomaly detection, or multimodal fusion remain rare, despite their potential for handling complex or noisy signals.

Figure 2.3 shows a mismatch between AI task complexity and the models used in reviewed studies. Simpler regression tasks were most common and often addressed with traditional ML models like random forests, even when signals were nonlinear or noisy. Deep learning was more common in classification tasks, particularly for spatial data, but rarely used for complex tasks like object detection or multimodal fusion. For example, Yu et al.[27] used an ANN for RGB-thermal fusion but didn't apply advanced architectures like attention or transformers. Unsupervised methods like PCA or t-SNE were limited to visualization. This suggests model selection is often based on familiarity, not task fit. As a result, underspecified models may limit performance in complex or noisy settings and reduce generalizability outside the lab. Treating model architecture as a key design element, aligned with task demands and supported by benchmarking, will be essential for advancing AI in biosensing.

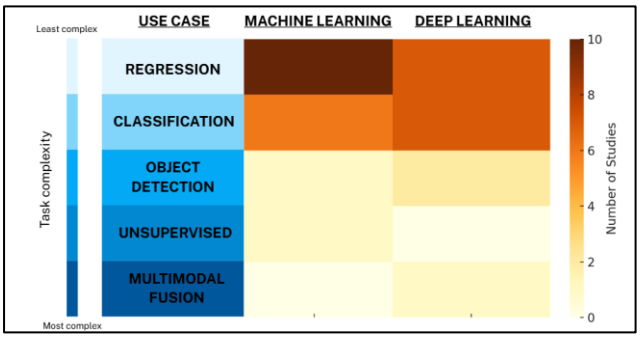



**Figure 2.3.** AI model use by task type, showing ML dominates regression while DL is underused in complex tasks.

### 2.4 Performance Improvement – Gains Attributed to AI and Benchmarks

Across all 32 studies, AI integration was credited with enhancing sensor performance across multiple axes. The most reported gains were improved accuracy (~20 studies), enhanced sensitivity or lower limits of detection (~7 studies), faster or automated interpretation (~3 studies), and improved pattern resolution for multiplexed or overlapping signals (~4 studies). AI enabled detection of subtle analyte differences, automated endpoint interpretation, and separation of overlapping outputs in multi-analyte sensors. While about 7 studies lacked a baseline comparison, those that did consistently showed AI outperforming visual reads, thresholds, or uncorrected data. Table 2.2 highlights four representative examples. Cui et al.[12] used YOLOv5 to improve bacterial classification to 95%.

Yu et al.[27] combined colorimetric and thermal signals via ANN to surpass LOD for cardiac troponin. In Zheng et al's work[16], CNNs reduced assay readout time withing minutes to seconds, while originally taking hours. Ranbir et al[25]. and Singh et al.[30] used PCA-LDA to fully separate volatile amines in meat, showing AI's strength in multiplex detection. These examples illustrate both performance gains and how targeted AI use can expand the utility of colorimetric sensors in real-world settings. However, while showing these gains, a more quantitative approach is required to fully grasp the importance of AI in colorimetric biosensing, as explored in subsequent section.

## 2.4 Meta-analysis of performance improvements

### *2.4.1. Limit of detection (LOD)*

We compared LOD values across studies, as LOD reflects the lowest detectable concentration above background noise and is key to assessing sensor sensitivity. This helps determine whether AI meaningfully improves detection limits in real-world use.

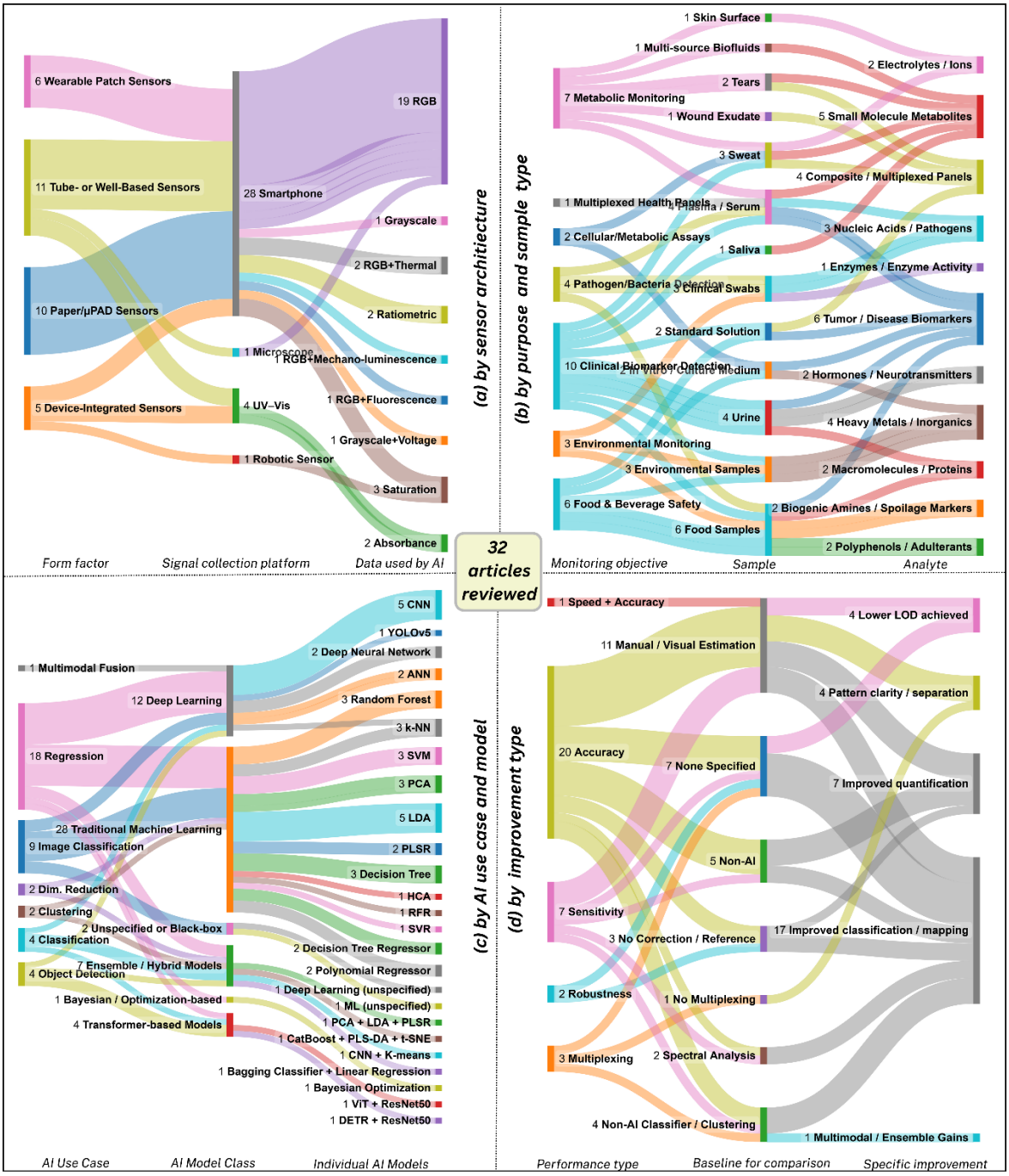



**Figure 2.4** Sankey diagram for AI-enhanced colorimetric biosensor studies sorted by (a) sensor architecture; (b) purpose and sample types, (c) AI use cases, model classes, and algorithms; and (d) performance improvements (comprehensive table in Table S1)

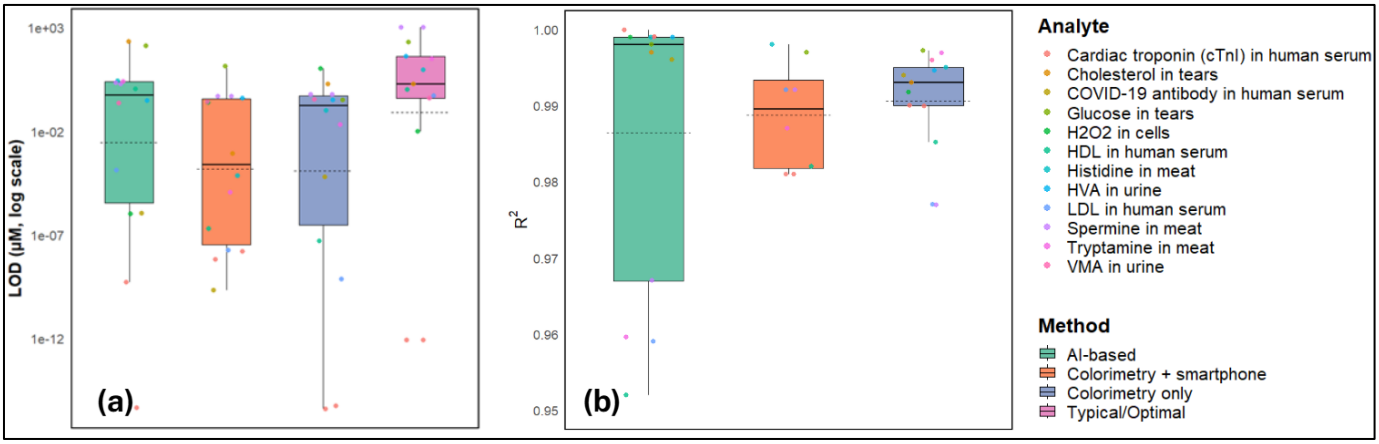



**Figure 2.5.** Log-scale distribution of LOD values across colorimetric detection methods, highlighting analyte-level spread and comparison to typical/optimal reference values

LOD data from AI-enhanced studies were grouped into four categories: AI-based, colorimetry only, colorimetry plus smartphone (non-AI), and typical values in human or food samples. Each analyte within a study was treated as a separate data point. For baseline methods lacking internal controls, LODs were sourced from recent reviews or similar studies. Full data appear in Supplementary Table S1.

As shown in Figure 2.5.a, AI-based platforms had slightly lower median LODs than typical concentrations in human and health samples, highlighting significance in diagnostics, but variability was high across all groups, especially compared to non-AI smartphone-assisted methods. Mann–Whitney U tests (Table S4) showed no statistically significant differences (all $p > 0.15$), indicating that AI alone doesn't consistently improve sensitivity. Outliers like del Real Mata et al's[13] 1 pM $H_2O_2$ detection with a plasmonic sensor and random forest model, or Yu et al's[27] 10.8 pg/mL troponin detection using ANN fusion, highlight AI's potential under optimized setups. However, factors like sensor materials, analyte properties, and sample matrices often have greater influence. AI was most impactful in cases with overlapping or faint color signals, e.g. Cui et al's use of YOLOv5 for low-level bacterial HAase, and Ranbir et al's[25.] and Singh et al's.[30] PCA-LDA models resolving mixed biogenic amines. In contrast, analytes with strong color change like glucose or pH showed minimal LOD gains, though AI improved consistency and automation. These results suggest AI should be applied selectively, especially for low-contrast or nonlinear signals. Broader adoption will require better benchmarking, task-specific AI design, real-world validation, and comparison to regulatory standards or reference methods.

### *2.4.2. Model $R^2$ values*

We included $R^2$ comparisons across studies as it reflects how well a sensor's output follows analyte concentration trends making it an essential indicator of dose-response consistency, even if not a direct accuracy measure. $R^2$ data were grouped by method type (AI-based, colorimetry-only, and smartphone-assisted non-AI) and are summarized in Table S3 and visualized in Figure 2.5.b. AI-based platforms showed higher average $R^2$ values (0.952–0.9999) and wider spread than conventional methods, with several achieving near-perfect calibration under controlled conditions. However, Mann–Whitney U tests (Table S5) indicated these differences weren't statistically significant ($p = 0.075$ vs. smartphone; $p = 0.14$ vs. colorimetry-only), suggesting AI doesn't consistently improve regression fit across all cases. The best $R^2$ values were seen in studies with controlled imaging, high signal-to-noise ratios, or carefully curated datasets. Study 18 reached $R^2 = 0.9999$ for cardiac troponin I using an ANN with thermal and color fusion, while Study 13 achieved robust fits for glucose and cholesterol using ensemble models that corrected ambient lighting. By contrast, non-AI methods, especially smartphone-only approaches, showed greater performance drops under uncontrolled conditions, with $R^2$ values around 0.79–0.80 for LDL and HDL, likely due to lighting variability. These findings suggest AI's greatest strength lies in stabilizing regression under noisy or nonlinear signal conditions. However, high $R^2$ alone is not sufficient. Some colorimetry-only systems still performed well for monotonic, high-contrast analytes, highlighting the continued importance of sensor chemistry. To ensure robust performance, future work should combine $R^2$ with broader metrics like residual analysis, external validation, and real-world testing. Overreliance on $R^2$ may inflate confidence, particularly in the absence of clinical or field verification.

### *2.4.2. Accuracy*

Unlike limit of detection (LOD) and regression metrics such as $R^2$, classification accuracy lacks a consistent universal baseline in biosensing literature. The diversity of decision thresholds, analyte classes, and labeling protocols across studies means that accuracy figures are highly context dependent. As such, we do not compare absolute values across platforms. Instead, we focus on within-dataset patterns observed across sensor architectures, analyte groups, and AI model classes, as summarized in Figure 2.6a and Supplementary Table S6. Overall, AI-enhanced biosensors consistently outperformed non-AI platforms, with the majority of AI-based systems achieving accuracies above 90%, and several reaching the 100% benchmark across diverse sensing contexts. These included both deep learning and hybrid ensemble methods, suggesting the benefits of nonlinear pattern recognition, especially when signal variability or interference is present.

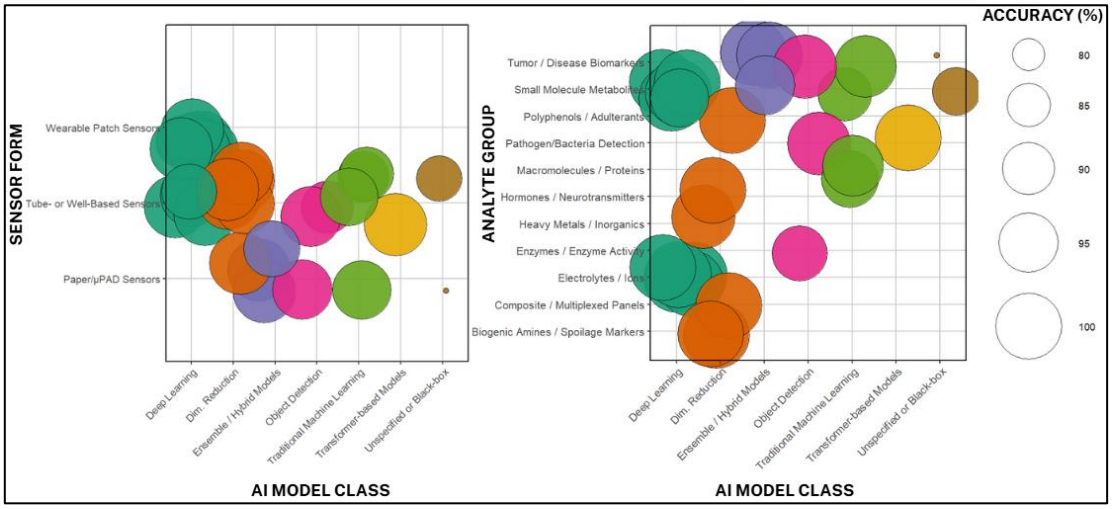



**Figure 2.6.** Bubble plot of classification/quantification accuracy of AI-enhanced colorimetric biosensors, mapped across sensor form factors (left) and analyte groups (right) by AI model class

At the architecture level, wearable patch sensors, when paired with CNN-based models, demonstrated high robustness and accuracy, often exceeding 95% for multi-biomarker sweat patches. Study 14 achieved 100% classification for glucose, pH, and lactate, enabled by a VGG16 CNN that captured subtle differences in spatial signal distributions under ambient conditions. Similarly, paper/µPAD sensors paired with traditional ML models (e.g., Random Forest, SVM) also performed well, particularly for urinary and metabolic analytes, where structured chromogenic arrays generated reproducible color fingerprints. Study 11, for example, achieved 97% accuracy in urinary tract infection classification using an SVM-RF ensemble.Among analyte categories, tumor and cardiac biomarkers benefited most from AI integration. The fusion of thermal and optical signals in Study 18, using an ANN, yielded accurate discrimination of cardiac troponin I (cTnI), reinforcing the strength of multimodal biosensing for critical clinical analytes . Additionally, for biogenic amines, LDA-based models maintained >95% accuracy, even under food matrix variability.

In contrast, non-AI systems, especially those relying on smartphone cameras with simple thresholding or raw RGB interpretation, showed greater susceptibility to lighting inconsistencies, with accuracy often falling to the 85–90% range. These limitations were particularly evident in complex backgrounds like food spoilage detection or overlapping chromophores, where AI methods (e.g., PCA-LDA fusion) restored classification clarity. From the sensor form perspective, tube- or well-based formats showed generally stable accuracy due to controlled optics, though wearable and paper-based formats 6abelled them when enhanced by AI. Notably, the highest accuracies clustered in deep learning and object detection classes (Figure 2.6a left panel), reflecting their superior ability to extract spatial and contextual features from raw image data. Together, these trends suggest that while chemical design and sensor chemistry remain foundational, AI integration—especially through CNNs, hybrid models, and transformer-based architectures—can significantly amplify diagnostic reliability, especially under variable environmental or user-handling conditions. Future work should explore adaptive learning for personalized calibration and establish standardized accuracy benchmarks across sensor classes.

## 3. Synthesis and outlook

*1. On the use of smartphones and calibration needs*- The collected studies make clear that coupling AI with colorimetric biosensors can dramatically enhance their capabilities, turning simple color changes into rich quantitative and actionable data. A unifying theme is the leveraging of ubiquitous hardware, particularly smartphones , as both the data acquisition device and computation platform. This convergence, seen in roughly 90% of the articles, underscores a practical advantage: AI algorithms deployed on consumer smartphones can transform point-of-care diagnostics, allowing immediate analysis in the field. However, this shift toward RGB smartphone-based pipelines brings new challenges in data normalization. Different phone cameras and ambient lighting conditions can skew color readings, requiring robust calibration to ensure reproducibility[67]. Encouragingly, several teams have introduced clever calibration techniques to tackle this issue. For example, cloud-connected analysis frameworks now incorporate hybrid models (CNNs coupled with recurrent networks) to auto-correct for illumination variances and sensor-specific biases. Such approaches (e.g. a multichannel CNN-GRU pipeline) have achieved $R^2$ values ~0.99 by learning to adjust for color temperature differences in images, effectively standardizing results across varying conditions. Moving forward, continued innovation in on-device calibration (from one-time color card references to real-time algorithmic corrections) will be essential to fully capitalize on smartphone-enabled AI sensing.

*2. On generalizability and data-efficient modelling*- Despite the impressive performance gains reported, most studies lack rigorous external validation, highlighting a critical gap between controlled experiments and real-world deployment. Typically, models are trained and tested on the same lab-generated dataset; few works verify that an AI model trained on one device or sample set holds up on others. This absence of external validation and cross-platform testing raises concerns about generalizability, an issue that future research must address by incorporating independent test sets, multi-center trials, or reference sample exchanges. Likewise, the underuse of semi-supervised learning and data augmentation is notable. Many AI models for colorimetric sensing rely on relatively small labeled

datasets, yet few studies leverage the abundance of unlabeled data or synthetic data generation to improve model robustness. Introducing semi-supervised algorithms (which can learn from unlabeled color images) or augmentation techniques (to simulate variations in hue, intensity, backgrounds, etc.) could significantly enhance model resilience to real-world variability at minimal cost. Another insight from our meta-analysis is that AI's added value appears tied less to the analyte type and more to the ambiguity of the signal. In other words, when an assay produces straightforward, high-contrast color changes (e.g. a single intense color shift for a positive result), traditional analysis may suffice. But as the color outputs become more complex, such as subtle gradations, multi-analyte sensor arrays, or overlapping chromatic responses, advanced machine learning yields disproportionate benefits[68]. Indeed, deep learning models excel at deciphering high-dimensional color patterns that humans or simple algorithms struggle to interpret. This trend suggests that future developers should strategically deploy AI in scenarios of inherent signal complexity or uncertainty, where its pattern-recognition strengths are most impactful. It also implies that reporting performance as a function of assay complexity (rather than only by analyte category) could be a more meaningful way to evaluate new AI-enhanced biosensors.

*3. On practical gains: speed, multiplexing, and robustness*- From a practical standpoint, AI-driven colorimetric analysis offers improvements that extend beyond raw analytical metrics, contributing to better usability and reliability of biosensors. One clear advantage is speed: once trained, an AI model can interpret a sensor's color output in milliseconds, potentially enabling near real-time readouts and quicker decision-making in point-of-care settings. In some cases, algorithms can even detect partial color changes before a reaction is fully complete, shortening the time-to-result. Another benefit is the capacity for multiplexed detection, that is, analyzing multiple indicators simultaneously. Traditional colorimetric assays struggle when multiple test spots or mixed-color outputs must be interpreted at once, whereas machine learning can untangle such composite signals with high accuracy. For example, neural network models have distinguished multiple antibody responses in a single assay with ~89% accuracy, outperforming conventional methods by a significant margin[68]. In general, as more analytes are encoded into color-based tests, AI will be instrumental in accurately classifying outcomes across a multidimensional color space. Equally important is the robustness that AI brings: sophisticated models can accommodate variability in sample quality or environmental conditions (such as inconsistent lighting or user handling) better than rigid threshold-based interpretations. Notably, convolutional neural networks have maintained strong performance even when images are noisy or under suboptimal lighting, a resilience crucial for real-world applications. This robustness reduces the incidence of false negatives or false positives caused by minor perturbations, thus improving trust in home or field deployments.

*4. On the horizon: integration with AR/VR and digital design*- Looking towards the horizon, there are exciting opportunities to integrate emerging technologies like augmented and virtual reality (AR/VR) with AI-based colorometric sensing. Early demonstrations have shown that AR smartphone apps can overlay interpretive guidance or even embed fiducial markers into the test to aid real-time result reading. In the future, a user might simply point a phone at a paper sensor and see a quantified result or risk assessment pop up instantly via AR, lowering the barrier to accurate self-testing. VR environments could also serve as training tools, simulating a wide range of colorimetric outcomes for clinicians or as a platform to virtually prototype sensor designs. Moreover, AI itself can be applied beyond analysis – for instance, using machine-learning optimization to design better colorimetric assays (selecting optimal reagent combinations or layout to maximize signal differentiation) or to create digital twins that predict how a sensor will behave under various scenarios. These exploratory directions, while in nascent stages, underscore the expansive potential at the interface of smart algorithms and biosensing. In summary, the future outlook for AI-enhanced colorimetric biosensors is one of continued convergence by merging accessible hardware, powerful algorithms, and user-centric innovations to deliver faster, multiplexed, and more robust diagnostic solutions. The next few years will likely witness not only incremental performance improvements but also a maturing of the field through standardized evaluation protocols, open datasets for model training, and perhaps the advent of intelligent sensors that learn and adapt during use.

## 4. Acknowledgments

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## References

1. Fleming, K. A. et al. The Lancet Commission on diagnostics: transforming access to diagnostics. *Lancet* **2021**, *398*(10315), 1997–2050. https://doi.org/10.1016/S0140-6736(21)00673-5

2. Newman-Toker, D. E. et al. Serious misdiagnosis-related harms in malpractice claims: The "Big Three" – vascular events, infections, and cancers. *BMJ Qual. Saf.* **2023**, *32*, 100–112.

3. Sun, Z., Zhang, B., Tu, H., Pan, C., Chai, Y., & Chen, W. Advances in colorimetric biosensors of exosomes: novel approaches based on natural enzymes and nanozymes. *Nanoscale* **2024**, *16*, 1005–

4. Google Trends. *Colorimetry – Worldwide, 2021–2025*. https://trends.google.com (accessed 4 May 2025).

5. Yang, F.-Q., & Ge, L. Colorimetric Sensors: Methods and Applications. *Sensors* **2023**, *23*(5), 2749

6. Cai, Y., Wang, Y., Wu, Y., et al. Current trends in colorimetric biosensors using nanozymes for detecting biotoxins. *Analyst* **2024**, *149*, 1234–1245.

7. Flynn, C. D. & Chang, D. Artificial Intelligence in Point-of-Care Biosensing: Challenges and Opportunities. *Diagnostics* **14**, 1100 (2024).

8. Nur, S., Salleh, M., Rozan Mohamad Yunus & Halimah Badioze Zaman. Artificial Intelligence−Powered Electrochemical Sensor: Recent Advances, Challenges, and Prospects. *Heliyon* **10**, e37964–e37964 (2024).

9. Prakashan, D., Kaushik, A. & Gandhi, S. Smart sensors and wound dressings: Artificial intelligence-supported chronic skin monitoring – A review. Chemical Engineering Journal 497, 154371 (2024).

10. Yang, C. & Zhang, H. A review on machine learning–powered fluorescent and colorimetric sensor arrays for bacteria identification. Microchimica Acta 190, (2023).

**11.** Wang, Z. *et al.* An artificial intelligence-assisted microfluidic colorimetric wearable sensor system for monitoring of key tear biomarkers. *Npj Flexible Electronics* **8**, (2024).

12.Cui, R. *et al.* AI-assisted smartphone-based colorimetric biosensor for visualized, rapid and sensitive detection of pathogenic bacteria. *Biosensors and Bioelectronics* **259**, 116369 (2024).

13. del Real Mata, C. *et al.* AI-Assisted Plasmonic Enhanced Colorimetric Fluidic Device for Hydrogen Peroxide Detection from Cancer Cells. *Advanced Materials Technologies* **10**, (2024).

14.Sun, S. *et al.* BioCosMe: Lip-based Cosmetics with Colorimetric Biosensors for Salivary Analysis using Deep Learning. *Proceedings of the 2024 ACM International Symposium on Wearable Computers* 32–39 (2024) doi:https://doi.org/10.1145/3675095.3676610.

15.Hassani-Marand, M., Jafarinejad, S. & Hormozi-Nezhad, M. R. An AI-enabled multi colorimetric sensor array: Towards rapid and noninvasive detection of neuroblastoma urinary markers. *Sensors and Actuators B: Chemical* **396**, 134571 (2023).

16. Xin Ting Zheng *et al.* Battery-free and AI-enabled multiplexed sensor patches for wound monitoring. *Battery-free and AI-enabled multiplexed sensor patches for wound monitoring* **9**, (2023).

17. Tong, H. *et al.* Artificial intelligence-assisted colorimetric lateral flow immunoassay for sensitive and quantitative detection of COVID-19 neutralizing antibody. *Biosensors and Bioelectronics* **213**, 114449 (2022).

18. Wansadaj Jaroenram *et al.* One-step colorimetric isothermal detection of COVID-19 with AI-assisted automated result analysis: A platform model for future emerging point-of-care RNA/DNA disease diagnosis. **249**, 123375–123375 (2022).

19. Siew, J., T. Malathi Thevarajah, Chang, S. W. & Khor, S. M. Paper-based multiplexed colorimetric biosensing of cardiac and lipid biomarkers integrated with machine learning for accurate acute myocardial infarction early diagnosis and prognosis. *Sensors and Actuators B Chemical* **394**, 134403–134403 (2023).

20.Yang, J. *et al.* Machine Learning-Assistant Colorimetric Sensor Arrays for Intelligent and Rapid Diagnosis of Urinary Tract Infection. *ACS Sensors* **9**, 1945–1956 (2024).

21.Feng, F. *et al.* Artificial intelligence-assisted colorimetry for urine glucose detection towards enhanced sensitivity, accuracy, resolution, and anti-illuminating capability. *Nano Research* (2023) doi:https://doi.org/10.1007/s12274-022-5311-5.

22. Baştürk, M., Yüzer, E., şen, M. & Kılıç, V. Smartphone-Embedded Artificial Intelligence-Based Regression for Colorimetric Quantification of Multiple Analytes with a Microfluidic Paper-Based Analytical Device in Synthetic Tears. *Advanced Intelligent Systems* (2024) doi:https://doi.org/10.1002/aisy.202400202.

23.Liu, Z. *et al.* Explainable Deep-Learning-Assisted Sweat Assessment via a Programmable Colorimetric Chip. *Analytical Chemistry* **94**, 15864–15872 (2022).

24. Do Hyeon Jung *et al.* Automatic quantification of living cells via a non-invasive achromatic colorimetric sensor through machine learning-assisted image analysis using a smartphone. *Chemical engineering journal* **450**, 138281–138281 (2022).

25.Ranbir, Singh, G., Singh, H., Kaur, N. & Singh, N. Azodye-based colorimetric sensor array for identification of biogenic amines: Food forensics by portable RGB-based signal readout. *Sensors and Actuators B: Chemical* **387**, 133794 (2023).

26. Li, H. *et al.* Porphyrin and pH sensitive dye-based colorimetric sensor array coupled chemometrics for dynamic monitoring of tea quality during ultrasound-assisted fermentation. *Microchemical Journal* **197**, 109813 (2023).

27. Yu, Z., Gong, H., Li, M. & Tang, D. Hollow prussian blue nanozyme-richened liposome for artificial neural network-assisted multimodal colorimetric-photothermal immunoassay on smartphone. *Biosensors and Bioelectronics* **218**, 114751 (2022).

28. Zhang, J. *et al.* Explainable Deep Learning-Assisted Self-Calibrating Colorimetric Patches for In Situ Sweat Analysis. *Analytical Chemistry* **96**, 1205–1213 (2024).

29. Zhu, X., Li, T., Hai, X. & Bi, S. A nanozyme-based colorimetric sensor array as electronic tongue for thiols discrimination and disease identification. *Biosensors and Bioelectronics* **213**, 114438 (2022).

30. Singh, H., Singh, G., Kaur, N. & Singh, N. Pattern-based colorimetric sensor array to monitor food spoilage using automated high-throughput analysis. *Biosensors and Bioelectronics* **196**, 113687 (2022).

31. Feng, H. *et al.* Bimodal Visual Sensors Based on Mechanoluminescence and Biosensing for Artificial Intelligence-Assisted Orthodontics. *Advanced Functional Materials* (2024) doi:https://doi.org/10.1002/adfm.202416437.

32. Zhai, C. *et al.* An enzyme response-regulated colorimetric assay for pattern recognition sensing application using biomimetic inorganic-protein hybrid nanoflowers. *Chemical Engineering Journal* **431**, 134107 (2022).

33. Yang, X. *et al.* A colorimetric sensor array based on peroxidase activity nanozyme for the highly efficient differential sensing of tea polyphenols and Tieguanyin adulteration. *Food Chemistry* **432**, 137265 (2023).

34. Kong, Y. *et al.* Artificial neural network-facilitated V2C MNs-based colorimetric/fluorescence dual-channel biosensor for highly sensitive detection of AFB1 in peanut. *Talanta* **266**, 125056 (2024).

35. Chen, Y. *et al.* Robot-accelerated development of a colorimetric CO2 sensing array with wide ranges and high sensitivity via multi-target Bayesian optimizations. *Sensors and Actuators B: Chemical* **390**, 133942 (2023).

36. Solaleh Ghateii & Amir Jahanshahi. Colorimetric detection of glucose with smartphone-coupled µPADs: harnessing machine learning algorithms in variable lighting environments. *Sensors and actuators. B, Chemical* **400**, 134835–134835 (2024).

37. Hassani-Marand, M., Fahimi-Kashani, N. & Hormozi Nezhad, M. R. Machine-Learning Assisted Multiplex Detection of Catecholamine Neurotransmitters with a Colorimetric Sensor Array. *Analytical Methods* (2023) doi:https://doi.org/10.1039/d2ay01797k.

38. Lee, T. *et al.* A regression-based machine learning approach for pH and glucose detection with redox-sensitive colorimetric paper sensors. *Analytical Methods* **14**, 4749–4755 (2022).

39. Xu, J. *et al.* Machine Learning-Assisted Portable Dual-Readout Biosensor for Visual Detection of Milk Allergen. *Nano Letters* (2025) doi:https://doi.org/10.1021/acs.nanolett.5c01001.

40. Bhatt, S., Kumar, S., Gupta, M. K., Datta, S. K. & Dubey, S. K. Colorimetry-based and smartphone-assisted machine-learning model for quantification of urinary albumin. *Measurement Science and Technology* **35**, 015030–015030 (2023).

41. Mizaj Shabil Sha *et al.* A smartphone-interfaced, low-cost colorimetry biosensor for selective detection of bronchiectasis*via*an artificial neural network. *RSC advances* **12**, 23946–23955 (2022).

42. Liu, W. *et al.* Machine-Learning-Based Colorimetric Sensor on Smartphone for Salivary Uric Acid Detection. *Ieee.org* (2023) doi:https://doi.org/10.21227/8ad0-mw22.

43.Xi, X. *et al.* Preparation of Au/Pt/Ti3C2Cl2 nanoflakes with self-reducing method for colorimetric detection of glutathione and intracellular sensing of hydrogen peroxide. *Carbon* **197**, 476–484 (2022).

44.Peng, Z. *et al.* Rapid colorimetric detection of H2O2 in living cells and its upstream series of molecules based on oxidase-like activity of CoMnO3 nanofibers. *Sensors and Actuators B: Chemical* **382**, 133540 (2023).

45.Kasatkin, A. & Urakov, A. Effect of hydrogen peroxide on erythrocyte temperature in vitro. *Chemico-Biological Interactions* **354**, 109837 (2022).

46.Miri, A., Orouji, A. & Hormozi-Nezhad, M. R. Etched-suppressed gold nanorods providing highly distinctive plasmonic patterns: Towards multiplex analysis of neuroblastoma biomarkers. *Analytica Chimica Acta* **1325**, 343119 (2024).

47.Surasak Kasetsirikul *et al.* Detection of the SARS-CoV-2 humanized antibody with paper-based ELISA. *Analyst* **145**, 7680–7686 (2020).

48.Ulloa-Gomez, A. M., Agredo, A., Lucas, A., Somvanshi, S. B. & Stanciu, L. Smartphone-based colorimetric detection of cardiac troponin T via label-free aptasensing. *Biosensors and Bioelectronics* **222**, 114938 (2022).

49. University of Rochester Medical Center. *Rochester.edu* https://www.urmc.rochester.edu/encyclopedia/content?contenttypeid=167&contentid=troponin (2024).

50. Li, G. *et al.* Colorimetric aptasensors for sensitive low-density lipoprotein detection based on reduced oxide graphene@molybdenum disulfide-ferrocene nanosheets with peroxidase-like activity. *Analytical Methods* (2024) doi:https://doi.org/10.1039/d4ay01648c.

51.Pakira, V., Agarwal, R., Chatterjee, S., Mukherjee, A. & Chakraborty, S. Lipidest: a lipid profile screening test under extreme point of care settings using a portable spinning disc and an office scanner. *Analytical Methods* **15**, 2427–2440 (2023).

52.Johns Hopkins Medicine. Lipid panel. *John Hopkins Medicine* https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/lipid-panel (2024).

53.Chunta, S., Suedee, R. & Lieberzeit, P. A. High-density lipoprotein sensor based on molecularly imprinted polymer. *Analytical and Bioanalytical Chemistry* **410**, 875–883 (2017).

54. Fan, J., Zhou, K. & Wang, J. Glucose Oxidase Coupling with Pistol-Like DNAzyme Based Colorimetric Assay for Sensitive Glucose Detection in Tears and Saliva. *Applied Biochemistry and Biotechnology* (2024) doi:https://doi.org/10.1007/s12010-024-05046-7.

55. Kap, Ö., Kılıç, V., Hardy, J. G. & Horzum, N. Smartphone-based colorimetric detection systems for glucose monitoring in the diagnosis and management of diabetes. *Analyst* **146**, 2784–2806 (2021).

56. Sen, D. K. & Sarin, G. S. Tear glucose levels in normal people and in diabetic patients. *British Journal of Ophthalmology* **64**, 693–695 (1980).

57. Alle, M. *et al.* Gold nanoparticles spontaneously grown on cellulose nanofibrils as a reusable nanozyme for colorimetric detection of cholesterol in human serum. *International Journal of Biological Macromolecules* **201**, 686–697 (2022).

58. Shi, Z. *et al.* Highly sensitive and selective colorimetric and fluorescent dual-readout assay for the analysis of spermine, spermidine and cysteine. *Dyes and Pigments* **220**, 111659 (2023).

59. Wei, Y. *et al.* Smartphone-integrated colorimetric sensor for rapid and highly selective detection of spermine in food based on the laccase-mimicking activity of flower-shaped Mn3O4 nanoparticles. *Microchemical Journal* **198**, 110148–110148 (2024).

60.Naila, A., Flint, S., Fletcher, G., Bremer, P. & Meerdink, G. Control of Biogenic Amines in Food-Existing and Emerging Approaches. *Journal of Food Science* **75**, R139–R150 (2010).

61. Fan, M. *et al.* Highly sensitive detection of tryptophan (Trp) in serum based on diazo-reaction coupling with Surface-Enhanced Raman Scattering and colorimetric assay. *Analytica Chimica Acta* **1119**, 52–59 (2020).

62. Xie, C. *et al.* Fast detection of tryptamine in meat products with azide-functionalized covalent organic frameworks confined in molecularly imprinted polymers. *Food Chemistry* **452**, 139527 (2024).

63.Schirone, M. *et al.* Biogenic Amines in Meat and Meat Products: A Review of the Science and Future Perspectives. *Foods* **11**, 788 (2022).

64. Saadati, A. *et al.* Optical discrimination of histamine and ethylenediamine in meat samples using a colorimetric affordable test strip (CATS): introducing a novel lab-on paper sensing strategy for low-cost ensuring food safety by rapid and accurate monitoring of biogenic amines. *RSC Advances* **14**, 8602–8614 (2024).

65.Wang, J. *et al.* DNAzyme-based and smartphone-assisted colorimetric biosensor for ultrasensitive and highly selective detection of histamine in meats. *Food Chemistry* **435**, 137526 (2024).

66.Michalski, M., Pawul-Gruba, M. & Madejska, A. Histamine contents in raw long-ripening meat products commercially available in Poland. *Journal of Veterinary Research* **65**, 477–481 (2021).

67. Russell, S. M., Doménech-Sánchez, A. & Roberto. Augmented Reality for Real-Time Detection and Interpretation of Colorimetric Signals Generated by Paper-Based Biosensors. *ACS Sensors* **2**, 848–853 (2017).

68.Han, G.-R. *et al.* Machine learning in point-of-care testing: innovations, challenges, and opportunities. *Nature Communications* **16**, (2025).

**Table S1.** Comprehensive table for the 32 reviewed studies on AI-enabled colorimetric biosensor

| Sensor Type | Analyte | Sample Source | Detection Mechanism | Signal collection platform for AI | AI Model | Role of AI (with Subgroup Tags) | Reported LOD | Classification Accuracy | Regression Accuracy (inverted MAE or similar) | Fit Quality ($R^2$ or r) |
|---|---|---|---|---|---|---|---|---|---|---|
| Wearable microfluidic colorimetric sensor [11] | Vitamin C, $H^+$ (pH), $Ca^{2+}$, protein | Human tears | Analyte-induced color change in PDMS microfluidic patch captured as RGB signal for concentration mapping | Smartphone (RGB image capture) | CNN-GRU (1D for pH, 3D for others) | Image-to-concentration regression using CNN-GRU (Regression for Quantification) | Not reported | Not reported | 0.001 (MAE) | $R^2 = 0.998$ |
| Smartphone-based hydrogel colorimetric sensor [12] | Hyaluronidase (Haase) from bacteria | Clinical swabs, food | Hyaluronic acid (HA) degradation triggers CPRG release, reacts with β-galactidose and generates color changes | Smartphone (camera) | YOLOv5 | Object detection and bacteria classification (Image Classification, Object Detection) | 10 CFU/mL | 92% (between gram + and gram -) | Not reported | $R^2 = 0.97$ |
| Microfluidic plasmonic-enhanced colorimetric sensor [13] | $H_2O_2$ | Cancer cell culture medium | Amplex Red reacts with $H_2O_2$ in presence of HRP, forming a pink dye; signal amplified by plasmonic nanostructures | Microscope (image capture) | Random Forest Classifier | Binary classification of $H_2O_2$ levels from RGB image (Image Classification) | 1 picoMolar | 91% (between high and low concentration classification) | Not reported | $R^2 = 0.98$ |
| Lip-applied sensor [14] | pH | Skin surface (via lip application) | Anthocyaninl in lip pigment undergoes pH-triggered color shift captured via selfies | Smartphone (selfie camera) | CNN | Lip color classification into pH levels using CNN (Image Classification) | Not reported | 92% (0.92 | Not reported | Not reported |
| Multicolorimetric sensor array (AuNR-AgNP-based) (Plasmonic, Paper-based) [15] | HVA, VMA (tumor markers) | Human urine | Redox reaction between HVA/VMA and $Ag^+$ causes silver shell formation on Au nanorods, altering LSPR and generating multicolor shifts | Smartphone (RGB image) | PCA + LDA + PLSR | Multivariate regression and classification of tumor markers (Regression, Dim. Reduction + Classification) | 0.22 µM (HVA) and 0.29 µM (VMA) | Not reported | 100% | $R^2 = 0.999$ (HVA) $R^2 = 0.999$ (VMA) |

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| Multiplexed Colorimetric Patch (PETAL) [16] | Temperature, pH, TMA, uric acid, moisture | Wound exudate (rat models) | Colorimetric sensors using liquid crystals, organic dyes, enzymes, and metal ions | Smartphone (patch image) | CNN | Image-based classification of wound biomarkers (Image Classification) | Not reported | 94–96% | (blank) | (blank) |
| PDA-based lateral flow immunoassay (LFIA) (Lateral Flow) [17] | COVID-19 neutralizing antibody | Clinical serum | PDA-NPs conjugated with RBD antigen bind to antibodies; reduced PDA binding causes lighter test line; image processed via T/(T+C) grayscale ratio | Smartphone (test strip image) | Vision Transformer (ViT) + ResNet50 | Band detection and antibody quantification using ViT (Regression, Object Detection) | 160 ng/mL | Not reported | Not reported | Not reported |
| Dual-dye colorimetric RT-LAMP assay (Lateral Flow) [18] | SARS-CoV-2 RNA | Nasopharyngeal swabs | Isothermal amplification causes pH drop, triggering color change in Xylenol Orange and Lavender Green dyes; image analyzed post-reaction | Smartphone or camera (reaction tube image) | DETR-based model (ResNet50 + Transformer) | Tube segmentation and COVID result classification (Object Detection, Image Classification) | 100% (reduced to 83% when diluted) | (blank) | (blank) | $R^2 = 0.998$ |
| Paper-based multiplexed colorimetric biosensor (Paper-based) [19] | Cardiac and lipid biomarkers | Human serum | Targets (e.g., cTnI, HDL, LDL) separated and detected via electrophoresis-induced color change on paper | Scanner or smartphone (paper strip image) | CatBoost + PLS-DA, t-SNE (ensemble) | Color feature extraction and disease classification (Dim. Reduction + Clustering) | CtnI (1.210x10^-5 ug/mL)<br>HDL (435.815 ug/mL)<br>LDL (383.127 ug/mL) | 75.2% for classification of acute myocardial infarction | Not reported | 0.999, 0.9991, 0.999 respectively |
| Urinary disease colorimetric test array (Paper-based) [20] | Urinary disease markers | Human urine | Colorimetric reaction of multiple sensors (metal–organic complexes and chromogenic reagents) with urine | Smartphone (sensor array image) | Random Forest, SVM, kNN | Pattern classification of urinary markers (Image Classification) | Not reported | 97% classification for UTI | (blank) | (blank) |

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| | | | constituents captured via smartphone | | | | | | | |
| Colorimetric sensor using AuNPs[21] | Glucose | Urine samples | Glucose induces color change to AuNP | Smartphone | Image processing and illumination correction for accurate color interpretation across varying lighting conditions | | Not reported | 87.6% accurate glucose concentration prediction | Not reported | Not reported |
| Microfluidic sensor for artificial tears (Microfluidic) [22] | Glucose, cholesterol, pH | Synthetic tears | Gox/ChOx-mediated oxidation produces $H_2O_2$, catalyzing TMB color change via HRP; universal pH indicator used; smartphone captures RGB data | Smartphone (app-integrated µPAD images) | Deep Neural Network (DNN) | Regression for pH/glucose/cholesterol from artificial tear images (Regression for Quantification) | Glucose = 131 uM<br>Cholestrol = 217 uM | 100% | RMS=0.386 | 0.996 (glucose)<br>0.997 (cholesterol) |
| Sweat-based biosensor (Wearable) [23] | Glucose, pH, lactate | Human sweat | Chromogenic reactions triggered by sweat analytes across spatially arranged compartments; color changes recorded via smartphone | Smartphone (microfluidic chip images) | VGG16-based CNN | Color regression of sweat biomarker levels (Regression for Quantification) | Not reported | 100% classification accuracy for all biomarkers in terms of quantity | (blank) | $R^2 = 0.9999$ for three biomarkers |
| HeLa cell-based metabolic colorimetric sensor [24] | Live HeLa cell viability (metabolic activity) | HeLa cell culture | pH-sensitive achromatic dye transitions (black to orange) based on cell density; saturation analyzed via smartphone images | Smartphone (achromatic saturation images) | Mask-RCNN | Quantification of live cell images (Image Classification) | $51 \times 10^4$ cells | 98% | (blank) | $R^2 = 0.959$ |

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| Colorimetric biogenic amine sensor for meat [25] | Biogenic amines | Chicken meat samples | Metal–azodye complex forming a fingerprint-based colorimetric response; analyzed via UV-vis absorbance and RGB imaging | UV–Vis scanner and smartphone (portable strip) | PCA, LDA, PLSR | Colorimetric amine pattern classification (Image Classification) | 0.378 ppm (spermine) | Not reported | 100% accuracy (cross validation), 83% for interference testing | Not reported |
| Tea polyphenol sensor during fermentation[26] | Tea polyphenols | Fermented green tea (w/ ultrasound) | RGB image extraction of CSA and multivariate calibration | Smartphone (RGB image of sensor array) | SVM | Regression and quality tracking for fermentation (Regression for Quantification) | Not reported | Not reported | Rc = 0.886, RMSEC = 0.042 mg/g, Rp = 0.862, and RMSEP = 0.043 mg/g | Not reported |
| Multiplexed troponin sensor (Nanozyme-based) [27] | Cardiac troponin I (cTnI) | Human serum | Cascade nanozyme-based colorimetric and photothermal signals from h-Prussian Blue in TMB-$H_2O_2$ system | Smartphone + thermometer (absorbance + thermal) | Artificial Neural Network (ANN, 3 hidden layers, 64 neurons) | Feature fusion from color and temperature signals for cTnI (Multimodal Fusion) | 10.8 pg/mL | (blank) | (blank) | $R^2$ =0.9965 |
| Sweat ion and pH patch sensor [28] | $Na^+$, $K^+$, pH | Human sweat during exercise | Printed chromogenic reagent zones and reference dye; color change recorded for in-situ analyte detection | Smartphone (sweat patch image with reference dye) | Explainable CNN (with ratiometric self-calibration) | Signal mapping for electrolyte and pH balance (Regression for Quantification) | classified and quantified with 100% accuracy | 100% (≥50 nM) | (blank) | (blank) |
| Thiol-level cancer detection sensor [29] | Thiols (Cys, GSH, Hcy, DTT, MCH, TGA) | Standard solutions | Thiol-induced inhibition of metal ion–TPA@GQD nanozyme peroxidase-like catalysis of TMB-$H_2O_2$ reaction, creating distinct color patterns | UV–Vis reader or smartphone (RGB absorbance pattern) | Linear Discriminant Analysis (LDA) | Clustering of thiol-level profiles for disease classification (Dim. Reduction + Clustering) | 50 nM thiol (not specified) | 100% accuracy to separate and discriminate from different thiols | Not reported | Not reported |

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|---|---|---|---|---|---|---|---|---|---|
| | | | (“fingerprints”) for LDA discrimination | | | | | | |
| Biogenic amine sensor array [30] | Biogenic amines ( tryptamine and spermine) | Meat and cottage cheese | Metal–azophenol complexes (C1–C11) respond to amines with colorimetric “fingerprint” patterns across 10 UV–Vis channels | Smartphone or UV–Vis scanner (sensor array image) | PCA, LDA | Color pattern recognition of food spoilage markers (Image Classification) | Tryptamine 0.40 ppm Histidine 0.42 ppm Spermine 0.45 ppm Spermidine 0.66 ppm | 100% (LDA) | Not reported | $R^2$ = 0.96 (Tryp), 0.97 (Spermine) |
| Bimodal Visual Sensors Based on Mechanoluminescence and Biosensing [31] | Cariogenic bacteria (through pH from lactic acid) | Oral swabs, in vitro culture | Bacterial acid production (colorimetric pH shift via anthocyanin) and tooth pressure via mechanoluminescence | Smartphone (dual-mode mechanoluminescent + color image) | CNN-based model | Segmentation and bacterial profile analysis (Object Detection, Image Classification) | <1 mg/mL (estimated) | 97.7% accuracy in the precise decoupling of visual signals | Not reported | Not reported |
| Heavy metal colorimetric sensor [32] | $Cr^{3+}$, $Fe^{3+}$, $Al^{3+}$, $Ni^{2+}$, $Cu^{2+}$, $Zn^{2+}$ | Water and serum samples | AchE inhibition by metal ions alters enzymatic reaction with chromogenic substrate, producing color shift patterns | UV–Vis spectrophotometer (absorbance scan of arrays) | PCA | Metal concentration regression using pixel intensity (Regression for Quantification) | 0.81 µM, 0.75 µM, 1.06 µM Cu2+, Cr3+, Al3+, | 98% accuracy in p | (blank) | 0.95,0.96,0.99 respectively |
| Tea authentication array sensor [33] | Tea polyphenols, adulterants | Tea infusion samples | TMB-$H_2O_2$ chromogenic system catalyzed by Bpy-Cu and Asp-Cu nanozymes; inhibition by polyphenols alters signal | Smartphone or scanner (nanozyme array image) | LDA, Decision Tree (DT), HCA | Classification of authentic vs adulterated tea via color (Image Classification) | Not reported | Discrimination accuracy was 100%. | Not reported | Not reported |

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|---|---|---|---|---|---|---|---|---|---|
| AFB1 detection in ground peanut samples [34] | Aflatoxin B1 (AFB1) | Peanut extract (ground sample) | Aflatoxin B1 (AFB1) in food (e.g., peanuts) | Smartphone (fluorescent + colorimetric microneedle patch image) | ANN | AFB1 concentration prediction from patch image (Regression for Quantification) | 0.6845 ng mL/1 | (blank) | (blank) | $R^2 = 0.9974$ |
| $CO_2$ strip colorimetric sensor [35] | $CO_2$ | Ambient air (gas sample) | Color change induced by $CO_2$-mediated pH shift, captured as RGB ΔE across a 6-receptor array | Robotic camera and RGB sensor (automated platform) | Multi-target Bayesian Optimization (BO) integrated with robotic plcaatform | $CO_2$ level regression from colorimetric signal (Regression for Quantification) | 400 ppm | (blank) | RMSE = 0.27% | (blank) |
| Paper-based glucose sensor [36] | Glucose | Human plasma | Enzyme-catalyzed colorimetric reaction using glucose oxidase (Gox) and horseradish peroxidase (HRP), with TMB for low and KI for high glucose concentration detection | Smartphone (flash/no-flash image pair) | Ensemble Bagging Classifier (EBC), Linear Regression | Glucose intensity prediction using Lab image values (Regression for Quantification, Classification) | Not reported | 95% (TMB color indicator), 91% (KI color indicator) | (blank) | $R^2 = 0.97$ (high conc), $R^2 = 0.95$ (low conc) |
| Urine neurotransmitter sensor [37] | dopamine (DA), epinephrine (EP), norepinephrine (NEP), and levodopa (LD) | Human urine | Aggregation-based LSPR shift from AuNP interactions at different pH conditions | Smartphone (LSPR color shift image under pH variation) | LDA, PLSR | Catecholamine level estimation using feature-based models (Regression for Quantification, Classification) | 0.3, 0.5, 0.2, and 1.9 mM for DA, EP, NEP, and LD, | 100% (LDA) | (blank) | $R^2 = 0.99$ for 4 analytes |
| Smart μPAD for pH and glucose [38] | pH, Glucose | Aqueous lab-prepared solutions | For pH: Pani-NP undergoes EB to ES state transition; For glucose: Gox generates $H_2O_2$, reducing Pani-NPs, causing color shift (blue→green) | Smartphone (dipstick color image under ambient light) | RFR (best), DTR, SVR | RGB analysis for pH/glucose detection in μPADs (Regression for Quantification) | None reported | (blank) | (blank) | $R^2 = 0.96$ (pH), 0.92 (glucose) |

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|---|---|---|---|---|---|---|---|---|---|---|
| Milk β-lactoglobulin strip (Lateral Flow)[39] | β-Lactoglobulin | Milk | Glucose-fueled EBFC for electrochemical + HRP/ABTS colorimetric detection using smartphone-assisted image processing | Smartphone (colorimetric + voltage strip readout) | Decision Tree (DT), Random Forest (RF), k-NN, SVM | Grayscale intensity detection for β-Lactoglobulin (Regression for Quantification) | 0.0081 ng/mL, | 93% | Not reported | Not reported |
| Albumin detection strip (Lateral Flow)[40] | Albumin | Urine | Protein concentration triggers color change on dipstick; captured by smartphone under varied lighting | Smartphone (dipstick image under varied lighting) | KNN classifier (vs RF, SVM) | Intensity ratio computation for albumin strip (Regression for Quantification) | 4 mg/L | 96% | Not reported | Not reported |
| $H_2O_2$ sensor (Spectrophotometric) [41] | Hydrogen peroxide | Exhaled breath | RGB signal mapping via colorimetric dye response (Eosin blue, $KmnO_4$, Starch-Iodine) | Smartphone (RGB mapping of breath test strip) | ANN Regression | Colorimetric pixel-based regression of $H_2O_2$ (Regression for Quantification) | 0.011 ppm | 94% accuracy for quantification | | 0.941 |
| Saliva uric acid µPAD (Microfluidic) [42] | Uric Acid | Saliva | Prussian blue generation reaction with salivary UA forming blue complex | Smartphone (µPAD salivary test image) | Decision Tree Regressor (ML); Multiple Polynomial Regressor | Color space regression for uric acid quantification (Regression for Quantification) | Not reported | (blank) | MAE=4.2 ppm | Not reported |

**Table S2.** Reported LOD values in AI-based studies, colorimetry only, colorimetry plus smartphone, and typical values in food, human, and environment samples

| **Analyte** | **LOD AI-based ( µM )*** | **LOD colorimetry only*** | **LOD colorimetry plus smartphone (no AI)*** | **Typical values*** |
|---|---|---|---|---|
| H2O2 in cells | 0.000001 µM | 10.24 µM[43] | 0.24 µM[44] | 0.01 µM[45] |
| VMA in urine | 0.22 µM | 0.340 µM | 0.260 µM[46] | 28.7 µM |
| HVA in urine | 0.29 µM | 0.313 µM | 0.397 µM[46] | 41 µM |
| COVID-19 antibody in human serum | $1.07 \times 10^{-6}$<br>(160 ng/mL) | $6.00 \times 10^{-5}$ µM[47]<br>(9 ng/uL) | $2.11x10^{-10}$ uM | None |
| Cardiac troponin (cTnI) in human serum | $5.06\times10^{-10}$<br>(1.210 x 10^-5 ug/mL) | $5.44 \times 10^{-16}$ µM<br>(0.013 pg mL−1) | $1.63\times10^{-8}$ µM 48<br>$3.9X10^{-4}$ µg/ml | 0.02 ng/L[49] |
| LDL in human serum | $1.277 \times 10^{-4}$ µM<br>(383.127 ug/mL) | $7.33 \times 10^{-10}$ µM[50]<br>(2.1999 µg/mL) | $1.77\times10^{-8}$ [51]<br>(5.31 mg/dl) | 0.53[52]<br>(100 mg/dL) |
| HDL in human serum | 1.09 µM<br>(435.815 ug/mL) | 2 mg/dL[53]<br>5.00×10−8 µM | $2.03 \times 10^{-7}$ µM<br>(8.10 mg/dl)[51] | 40 mg/dL |
| Glucose in tears | 131 uM<br>(23.61 mg/L) | 0.32 µM [54]<br>0.05765 mg/L | 13.49 uM[55] | 0.2 mM[56]<br>(360 mg/L) |
| Cholesterol in tears | 217 uM<br>(83.87 mg/L) | 1.9 µM[57]<br>0.7356 mg/L | 0.00085 M | 1.9 µM |
| Spermine in chicken meat | 1.87 µM<br>0.378 ppm | 0.57 uM[58]<br>0.115 mg/L | 0.4644 uM<br>0.094 ug/mL[59] | 988.4 uM<br>200 ppm[60] |
| Cardiac troponin (cTnI) in human serum | 10.8 picogram/mL<br>4.52×10−16 µM | $5.44 \times 10^{-16}$ µM<br>(0.013 pg mL−1) | $.63\times10^{-8}$ uM[48]<br>$3.9X10^{-4}$ µg/ml | 0.02 ng/L[49] |
| Tryptamine in meat | 2.50 µM<br>0.40 ppm | 20 nM[61]<br>0.0032 mg/L | 1.74 µg/L[62]<br>$1.086 \times 10^{-5}$ uM | 5 mg/kg meat[63] |
| Histidine in meat | 2.71 µM<br>0.42 ppm | 0.1 µM[64] | 8 µg/L[65] | 9.0 µM[66] |
| Spermine in meat | 2.22 µM<br>0.45 ppm | 0.57 uM[58]<br>0.115 mg/L | 0.4644 uM<br>0.094 ug/mL[59] | 988.4 uM<br>200 ppm[60] |

**Values* were converted using molar masses

**Table S3.** Reported $R^2$ values in AI-based studies, colorimetry only, and colorimetry plus smartphone

| **Analyte** | **LOD AI-based ( μM )** | **LOD colorimetry only** | **LOD colorimetry plus smartphone (no AI)** |
|---|---|---|---|
| H2O2 in cells | 0.998 | 0.9972 | 0.997 |
| VMA in urine | 0.999 | 0.996 | 0.997 |
| HVA in urine | 0.999 | 0.995 | 0.998 |
| Cardiac troponin (cTnI) in human serum | 0.999 | 0.990 | 0.981 |
| LDL in human serum | 0.999 | 0.9946 | 0.7917 |
| HDL in human serum | 0.999 | 0.9918 | 0.8018 |
| Glucose in tears | 0.996 | 0.994 | 0.995 |
| Cholesterol in tears | 0.997 | 0.993 | 0.993 |
| Spermine in chicken meat | 0.959 | 0.977 | 0.99209 |
| Cardiac troponin (cTnI) in human serum | 0.9999 | 0.990 | 0.981 |
| Tryptamine in meat | 0.9596 | 0.9969 | 0.987 |
| Histidine in meat | 0.952 | 0.9852 | 0.982 |
| Spermine in meat | 0.967 | 0.977 | 0.99209 |

*values correspond to cited studies in Table S2

Table S4. Statistical testing (Mann-Whitney U test) for LOD

| **Pair** | **p-value** |
|---|---|
| AI-based vs Colorimetry + smartphone | p = 0.1610359 |
| AI-based vs Colorimetry only | p = 0.3011529 |
| AI-based vs Typical/Optimal | p = 0.2747575 |

*Statistical testing was conducted using R Studio's Wilcoxon rank-sum tests

Table S5. Statistical testing (Mann-Whitney U test) for $R^2$

| **Pair** | **p-value** |
|---|---|
| AI-based vs Colorimetry + smartphone | p = 0.07539264 |
| AI-based vs Colorimetry only | p = 0.1422894 |

*Statistical testing was conducted using R Studio's Wilcoxon rank-sum tests

**Table S6.**Data for bubble plot analysis with information obtained from Table S5

| AI Subgroup | Analyte | Classification Accuracy | Analyte Group | Sensor Type |
|---|---|---|---|---|
| Object Detection | Hyaluronidase (HAase) | 92 | Enzymes / Enzyme Activity | Tube- or Well-Based Sensors |
| Traditional Machine Learning | Hâ,,Oâ,, | 91 | Small Molecule Metabolites | Tube- or Well-Based Sensors |
| Deep Learning | pH | 92 | Electrolytes / Ions | Wearable Patch Sensors |
| Ensemble / Hybrid Models | HVA | 100 | Tumor / Disease Biomarkers | Paper/Î¼PAD Sensors |
| Ensemble / Hybrid Models | VMA | 100 | Tumor / Disease Biomarkers | Paper/Î¼PAD Sensors |
| Transformer-based Models | SARS-CoV-2 RNA | 100 | Pathogen/Bacteria Detection | Tube- or Well-Based Sensors |
| Unspecified or Black-box | Cardiac and lipid biomarkers | 75.2 | Tumor / Disease Biomarkers | Paper/Î¼PAD Sensors |
| Traditional Machine Learning | Urinary disease markers | 97 | Tumor / Disease Biomarkers | Paper/Î¼PAD Sensors |
| Unspecified or Black-box | Glucose | 87.6 | Small Molecule Metabolites | Tube- or Well-Based Sensors |
| Deep Learning | Glucose | 100 | Small Molecule Metabolites | Tube- or Well-Based Sensors |
| Deep Learning | cholesterol | 100 | Small Molecule Metabolites | Tube- or Well-Based Sensors |
| Deep Learning | pH | 100 | Electrolytes / Ions | Tube- or Well-Based Sensors |
| Deep Learning | Glucose | 100 | Small Molecule Metabolites | Wearable Patch Sensors |
| Deep Learning | pH | 100 | Electrolytes / Ions | Wearable Patch Sensors |
| Deep Learning | lactate | 100 | Small Molecule Metabolites | Wearable Patch Sensors |
| Object Detection | Live HeLa cell viability | 98 | Tumor / Disease Biomarkers | Tube- or Well-Based Sensors |
| Dim. Reduction | Biogenic amines | 100 | Biogenic Amines / Spoilage Markers | Paper/Î¼PAD Sensors |
| Deep Learning | Naâ• º | 100 | Electrolytes / Ions | Wearable Patch Sensors |
| Deep Learning | Kâ• º | 100 | Electrolytes / Ions | Wearable Patch Sensors |
| Deep Learning | pH | 100 | Electrolytes / Ions | Wearable Patch Sensors |
| Dim. Reduction | Thiols | 100 | Composite / Multiplexed Panels | Tube- or Well-Based Sensors |
| Dim. Reduction | Biogenic amines | 100 | Biogenic Amines / Spoilage Markers | Tube- or Well-Based Sensors |
| Object Detection | Cariogenic bacteria | 97.7 | Pathogen/Bacteria Detection | Paper/Î¼PAD Sensors |
| Dim. Reduction | Heavy metals | 98 | Heavy Metals / Inorganics | Tube- or Well-Based Sensors |
| Dim. Reduction | Tea polyphenols | 100 | Polyphenols / Adulterants | Tube- or Well-Based Sensors |

| | | | | |
|---|---|---|---|---|
| Ensemble / Hybrid Models | Glucose | 95 | Small Molecule Metabolites | Paper/Î¼PAD Sensors |
| Dim. Reduction | Catecholamines | 100 | Hormones / Neurotransmitters | Tube- or Well-Based Sensors |
| Traditional Machine Learning | Î²-Lactoglobulin | 93 | Macromolecules / Proteins | Tube- or Well-Based Sensors |
| Traditional Machine Learning | Albumin | 96 | Macromolecules / Proteins | Tube- or Well-Based Sensors |
| Deep Learning | Hâ,,Oâ,, | 94 | Small Molecule Metabolites | Tube- or Well-Based Sensors |

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# Focused Review of Recent Modelling Strategies in Power-to-X Systems for Renewable Energy Storage in Smart Grids

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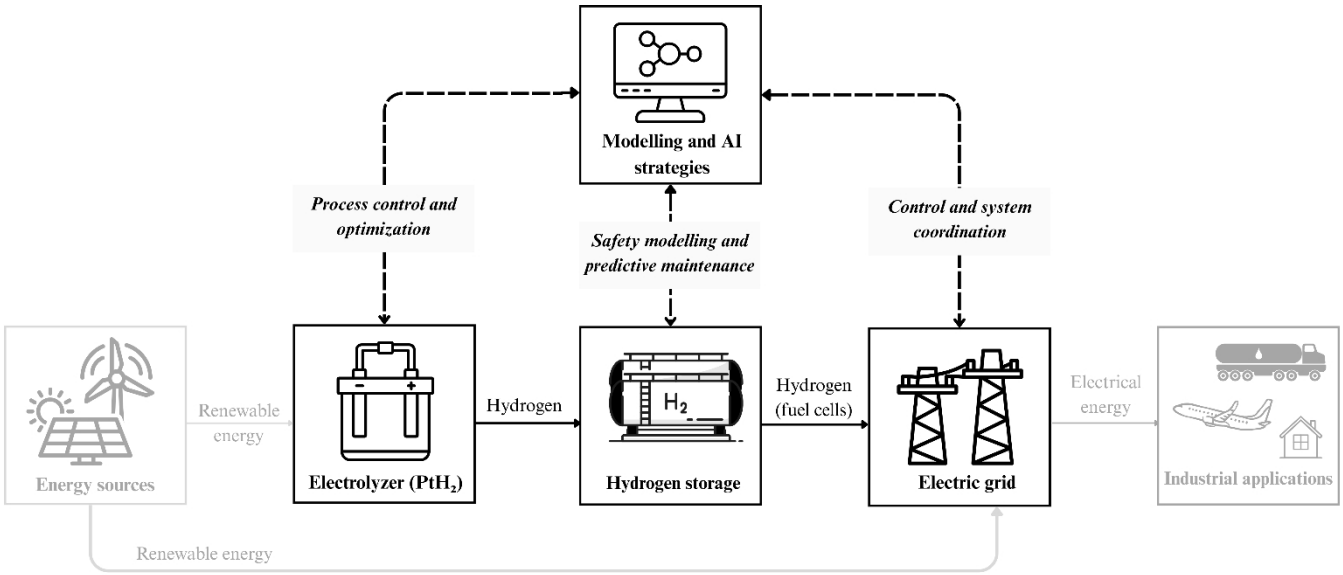
## Graphical Abstract




## Abstract

The variability of renewable energy sources presents a major challenge for maintaining power system stability and long-duration energy storage. Power-to-Hydrogen ($PtH_2$) systems provide a viable solution by converting surplus renewable into hydrogen, which can be stored and used across different sectors. This review focuses on focuses on modelling strategies applied to three core $PtH_2$ processes: hydrogen production via electrolysis, storage, and integration into smart grids. Traditional modelling approaches including computational fluid dynamics (CFD), techno-economic analysis (TEA), process simulation, and linear programming (LP) remain essential for system design but are limited in handling dynamic, real-time operations. In contrast, emerging methods including machine learning (ML), reinforcement learning (RL), surrogate modelling, digital twins, and augmented/virtual reality (AR/VR) platforms offer improved adaptability, predictive control, and operator interaction. However, these tools face limitations related to data availability, computational cost, model interpretability, and integration with existing simulation environments. The review identifies a growing shift toward hybrid modelling frameworks that

combine physical accuracy with data-driven adaptability. Future research should focus on building standardised datasets, developing interoperable modelling platforms, expanding the role of real-time visualisation technologies, and must be supported not only by technical innovation but also by evolving policy for scalable and resilient $PtH_2$-integrated smart grid.

Keywords: Power-to-X (P2X), Power-to-Hydrogen ($PtH_2$), renewable energy storage, smart-grids, advanced modelling, computer simulations, artificial intelligence, machine learning, AR/VR

## 1. Introduction

The global energy transition is accelerating the deployment of renewable energy sources such as solar and wind[1]. However, their inherent variability introduces operational challenges to modern power systems, particularly in ensuring consistent supply and grid stability.[1] Energy storage technologies have become central to enabling reliable and flexible renewable integration.[2]

Power-to-Hydrogen ($PtH_2$) has emerged as a promising long-duration energy storage solution.[3-5] By converting renewable energy into hydrogen via electrolysis, $PtH_2$ enables energy to be stored in chemical form and later utilised across sectors, including electricity, transport, and industrial applications[5]. Unlike conventional battery storage, hydrogen offers higher storage capacity over longer timescales, making it suitable for seasonal balancing and sector coupling.[6]

Recent research has increasingly focused on modelling strategies that support the deployment of $PtH_2$ systems. Advanced simulations and AI-augmented tools are now being used to enable dynamic integration with smart grid, optimise conversion efficiency and assess techno-economic viability, and enable dynamic integration with smart grids.[7-8] Despite increased attention, few reviews have synthesized the full modelling stack from electrolyis to grid-scale integration.[7]

This review aims to synthesise emerging modelling approaches applied to $PtH_2$ systems, with emphasis on processes involving energy conversion, compression and storage, and smart grid integration.

## 2. Modelling strategies across the $PtH_2$ system

$PtH_2$ systems core processes include hydrogen production, storage, and electric grid integration, each requires specialised modelling approaches to optimize performance, cost, and control. This section reviews emerging modelling strategies applied at each stage, with particular emphasis on process-level simulations, safety and reliability, and system coordination models. Comparative summaries and case studies are provided to illustrate how these methods are applied in practice and to highlight their respective advantages and limitations.

### *2.1 Electrolysis process control and optimization*

Hydrogen production via electrolysis is the foundational process in $PtH_2$ systems. Electrolysis enables the conversion of electrical energy typically from renewable energy sources

**Table 1 | Traditional and emerging models used in electrolysis systems control and optimization**

| Type | Approach | Strengths | Limitations | Tools | Ref. |
|---|---|---|---|---|---|
| Traditional | Computational Fluid Dynamics (CFD) | High spatial detail; flow and heat analysis | Computationally expensive | COMSOL, ANSYS | [12,18] |
| | Process Simulation + Techno-economic assessment (TEA) | System-wide modelling; cost-analysis | Rigid to variable input; limited real-time use | Aspen Plus | [13,19] |
| | Numerical optimization | Effective for tuning and design refinement | Requires well-defined objectives | MATLAB | [13,20] |
| | Monte Carlo simulation | Captures uncertainty | Requires many runs; less mechanistic | Python, MATLAB | [14,20] |
| Emerging | Machine Learning (ML) | Fast and adaptive forecasting | Needs large, quality datasets | TensorFlow | [15,21] |
| | Reinforcement Learning (RL) | Real-time adaptive control under fluctuating inputs | Complex training and policy validation | OpenAI Gym, Stable Baselines | [15,22] |
| | Surrogate models | Reduces simulation time; enables real-time control | Accuracy limited to trained domain | GPFlow, surrogateML | [12,15] |
| | AR/VR + Digital twins | Visual diagnostics and operator training | High development cost | Unity | [16,17] |

into chemical energy by splitting water into hydrogen and oxygen[9]. The most common types of water electrolysis technologies include Alkaline Water Electrolysis (AEL), Proton Exchange Membrane Electrolysis (PEM), Solid Oxide Electrolyser Cell (SOEC), Anion Exchange Membrane Electrolysis (AEM).[10] These technologies differ in terms of operating temperature, response time, system complexity, and integration potential with variable power inputs.[10-11] These factors influence the selection and design of appropriate modelling strategies for control and optimization.

Table 1 outlines different modelling approaches applied to electrolysis system control and optimisation. Traditional methods such as CFD are used to analyze thermal gradients, flow behaviour, and gas evolution in electrolyser cells[12]. These models provide high physical accuracy but are computationally intensive and limited to offline analysis. At the system level, process simulation combined with TEA supports performance evaluation and cost estimation under different scenarios.[13] However, these models assume fixed input profiles and are not suited for dynamic control. Numerical optimization is used to refine design and operating parameters but requires well-defined objectives and may converge to local minima.[13] Monte Carlo simulations quantify uncertainties in cost drivers or input variability, though they do not capture time-dependent system dynamics.[14]

To address the limitations of static modelling approaches, recent studies have adopted data-driven methods. ML methods such as Artificial Neural Networks (ANN) was used for predicting stack performance and hydrogen output using operational or simulation data.[15,21] These models improve prediction speed but require large, well-labelled datasets. Reinforcement learning (RL) has also been applied for adaptive electrolyser control under fluctuating power inputs, though it demands complex training environments.[15] Surrogate models, derived from CFD or system simulations, are employed for fast approximation in control applications[12]. These are often integrated into digital twins, which combine physical models with real-time data to support diagnostics and optimisation. Moreover, emerging AR and digital twin platforms provide visual interfaces for system monitoring and operator support. While still limited in deployment, these tools have shown potential for training and real-time fault identification.[16]

A recent study[12] integrated CFD and AI and ML-based modeling for enhanced alkaline water electrolysis cell performance for hydrogen production. CFD was coupled with an ANN surrogate model to predict current density in an alkaline electrolyser, reducing simulation time by over 90% while maintaining accuracy demonstrating the advantage of combining physical and data-driven methodologies.

Traditional models remain essential for system design and validation, while emerging approaches improve adaptability and control. Integrating both supports more efficient and robust electrolysis under variable operating conditions.

### *2.2 Hydrogen storage safety and reliability*

Hydrogen storage refers to the containment of hydrogen following its production, through electrolysis, for later use in

**Table 2 | Traditional and emerging models used in $PtH_2$ hydrogen storage safety and reliability**

| Type | Approach | Strengths | Limitations | Tools | Ref. |
|---|---|---|---|---|---|
| Traditional | Finite Element Modelling (FEM) | Structural stress, fatigue, and failure analysis | High setup time, not real-time | ANSYS, Abaqus | [27] |
| | CFD | Thermal gradient and gas flow simulation | Computationally intensive | COMSOL Multiphysics | [27,28] |
| | Thermodynamic modelling | Pressure–temperature relationships | Oversimplifies dynamic system behaviour | MATLAB | [29] |
| Emerging | ML (SVM, ANN) | Fault and anomaly detection | Data quality and availability | MATLAB, Scikit-learn | [23,30] |
| | Digital twins | Integrated real-time monitoring and simulation | Complex integration, early-stage adoption | Unity, TensorFlow | [31] |
| | IoT-based monitoring and predictive analytics | Real-time condition tracking and decision support | Sensor dependency; integration complexity | IoT sensors, predictive algorithms | [32] |

energy conversion, industrial processes, or transport.[23] Hydrogen produced via electrolysis is commonly stored as compressed gas in tanks or vessels.[24,26] These systems operate under conditions involving high pressure, temperature gradients, and cyclic loading, which introduce risks related to leakage, structural fatigue, and material degradation. While modelling of electrolysis systems often prioritises process optimisation, modelling of storage primarily addresses structural integrity, safety, and system reliability.[23] Predictive modelling supports the identification of failure modes and degradation trends, informing maintenance schedules and system design. As such, current modelling approaches for [illegible] behaviour and enabling condition-based monitoring under variable operating conditions.[25]

Table 2 summarises traditional and emerging modelling approaches applied to hydrogen storage, with a focus on safety, structural reliability, and predictive maintenance. Traditional techniques such as FEM, CFD, and thermodynamic analysis are widely used to assess stress distribution, fatigue, thermal behaviour, and pressure–temperature relationships in storage systems.[27–29] FEM provides detailed insight into structural integrity under cyclic loading, while CFD enables thermal and flow field simulation. Although physically robust, these models are computationally intensive and are not well suited to dynamic or real-time applications. Thermodynamic models offer simplified assessments but may fail to capture transient behaviour under variable conditions. On the other hand, emerging approaches integrate data-driven and system-level methods to improve adaptability and fault prediction. ML algorithms, including support vector machines (SVM) and ANN, have been used for anomaly detection, failure classification, and degradation forecasting from operational sensor data.[23,30] Digital twins extend these capabilities by linking virtual models with live input data to enable real-time condition monitoring and diagnostics. Moreover, IoT-based platforms further support storage reliability by enabling continuous sensor-driven tracking and data-informed decision support. While these methods offer greater responsiveness, they depend on stable data infrastructure and integration with physical systems.[32]

**Table 3 | Traditional and emerging models used for hydrogen storage control and integration with smart grids**

| Type | Approach | Strengths | Limitations | Tools | Ref. |
|---|---|---|---|---|---|
| Traditional | Rule-based dispatch and scheduling | Easy setup for fixed hydrogen dispatch routines | Cannot adapt to real-time or dynamic events | Excel-based | [41] |
| | MILP and LP | Generates optimal hydrogen operation | Rigid, not responsive to live grid or market shifts | Solver, Python | [42] |
| | Deterministic grid simulation | Models grid impact of hydrogen reconversion accurately | Limited for fast, multi-energy coordination | MATLAB | [43] |
| Emerging | Deep RL | Adapts hydrogen control to real-time grid conditions | Needs large training data and careful tuning | Custom RL framework | [44,45] |
| | Digital twins | Aligns physical and virtual hydrogen systems for control monitoring | High setup cost; integration remains complex | MATLAB, LabView | [46] |
| | AR/VR-based visualisation and operator training | Enhances integrity under dispatch and fault scenarios | Not embedded in real-time control; interface dependent | Custom VR platforms | [47,48] |

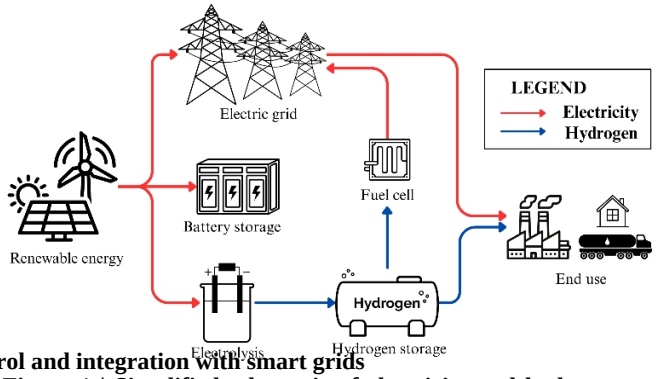



**Figure 1 | Simplified schematic of electricity and hydrogen**

is directed to the grid, battery storage, or electrolysis. The hydrogen produced is stored and later used in end-use applications or reconverted to electricity via fuel cells, which are reintegrated into the electric grid during peak demand periods. *Figure by*

An example of integrating traditional and emerging methods is presented by El-Amin et al.[37], who combined CFD-generated hydrogen dispersion data with machine learning models, specifically Random Forest and SVM, to predict concentration profiles in turbulent buoyant jets. The framework reduced computational load while maintaining prediction accuracy, enabling real-time inference for leak detection and storage safety. The system demonstrated predictive capabilities that enhanced operational safety and informed timely maintenance decisions.

The integration of traditional modelling with AI-based approaches [illegible] safety and reliability of hydrogen storage systems within PtH₂ operations, offering a pathway toward more resilient and intelligent infrastructure.

## 2.3 Smart grid and control coordination

The integration of hydrogen storage into smart grids [illegible] element for grid balancing and providing long-duration seasonal energy storage, offering capabilities for bulk storage and practically infinite energy storage capacity.[10] However, these hydrogen systems, comprising components like electrolyzers, storage tanks, and fuel cells, are inherently complex to operate. Figure 1 provides a conceptual overview of the typical energy flow in PtH₂-integrated smart grid systems and rather than representing a linear process, the diagram aims to foreground the complex, multi-pathway nature of energy conversion, storage, and utilisation in a hydrogen-augmented energy system.[40]

The integration of hydrogen storage into smart grids is important in accommodating the increasing penetration of intermittent renewable energy sources.[39] Hydrogen storage systems such as PtH₂ technologies, which converts excess renewable electricity into storable hydrogen are essential

The complexity of the process coupled with the challenges of integrating variable renewable generation makes modelling techniques indispensable[6]. Accurate and dynamic modelling is essential to characterize efficiency, analyse dynamic behaviour, perform complex optimizations, capture real-world complexities, and manage real-time energy flows.[7,13]. This necessitates advanced control and coordination strategies for optimal operation.[39] Modelling serves as a tool to support the design and evaluation of these control and coordination systems[13] and addressing these challenges effectively requires the application of both traditional and emerging methods.[7,16]

Table 3 summarizes representative traditional and emerging modelling approaches applied in the coordination and control of hydrogen storage systems within smart grid environments. These models vary in computational complexity, real-time adaptability, and integration capacity.

Conventional modelling approaches such as rule-based scheduling, mixed-integer linear programming (MILP) and linear programming (LP), and deterministic grid simulation have historically formed the basis of hydrogen dispatch and grid interaction modelling.[41-43] These techniques are deterministic in structure and generally assume perfect foresight, static grid inputs, and isolated sub-system control. For example, MILP has been used to compute optimal hydrogen operation plans based on pre-defined load forecasts and tariff structures, but lacks responsiveness under real-time fluctuations or market variability.[42] Similarly, deterministic simulation models accurately compute hydrogen reconversion impacts on power system stability and power flow (e.g., voltage deviations), yet are limited in resolving multi-energy coordination or stochastic influences.[43] Furthermore, rule-based dispatch, often implemented in Excel-based methods which provides operational simplicity but cannot adapt to dynamic system feedback or uncertainty.[41] These methods are computationally efficient for system sizing and offline planning but insufficient for online scheduling or integrated sector coupling.

To address these constraints, data-driven and adaptive control methods have been increasingly adopted. Deep RL enable model-free learning of control strategies through interaction with dynamic environments.[44,45] These methods have been shown to optimise hydrogen system dispatch under variable renewable input, demand response signals, and multi-layer objectives (e.g., thermal, electrical, storage). However, effective deployment requires large-scale training data, hyperparameter tuning, and convergence stability management, as seen in the development of actor–critic architectures and dual-network stabilisation.[45] Digital twin frameworks integrates physical system models with real-time sensor data, predictive analytics, and control feedback mechanisms.[46] These systems simulate, monitor, and optimise hydrogen production, storage, and fuel cell systems simultaneously. Although promising, their implementation is constrained by high setup costs, model–data synchronisation issues, and computational overhead—especially in real-time grid-connected applications.[46] On the other hand, AR/VR technologies offer additional operational value by supporting operator situational awareness, particularly during dispatch decision-making and fault management.[47] Platforms such as Verciti provide immersive visualisations of hydrogen operations and enhance safety training for decentralised system operators.[48]

Traditional methods provide guarantees in optimization and deterministic planning, but fail to handle uncertainty, dynamic control, or sector integration. In contrast, AI-driven and hybrid frameworks support adaptable, real-time scheduling but require extensive training, are less interpretable, and lack standardisation for industrial deployment.[41-48] Hybrid models are gaining traction for balancing computational efficiency with physical consistency.[6,44] Recent applications illustrate how traditional modelling can be operationalised through interactive digital environments. For example, Folgado et al.[49] developed a digital twin of a proton exchange membrane (PEM) electrolyser embedded within a MATLAB-based graphical user interface, deployed in a photovoltaic-powered smart grid. The digital twin is based on a deterministic equivalent electrical model and communicates with a PLC via Modbus TCP/IP in real time. This setup enables operators to monitor hydrogen production metrics, assess deviations between simulated and measured performance, and support control decisions. The study highlights how traditional physics-based models can be integrated into real-time, user-interactive systems improving the coordination between hydrogen systems and smart grid operation.

Modelling strategies are shifting from deterministic formulations toward adaptive, interactive frameworks. Case studies such as Folgado et al.[49] demonstrate how equation-based electrolyser models can be embedded in digital twin systems for real-time monitoring within smart microgrids. Future modelling platforms must integrate real-time control logic, data feedback, and intuitive human interfaces to enable scalable hydrogen storage coordination in complex energy systems.

## 3. Challenges and Future Perspective

Emerging modelling and AI-based approaches offer significant advantages over traditional methods in $PtH_2$ systems but remains constrained by several technical and operational challenges. These limitations currently hinder the scalability, real-time deployment, and integration of advanced tools within smart grid environments.

The strong dependence on high-quality data is a primary limitation. ML and RL models require large volumes of well-labelled, high-frequency datasets to train predictive or control agents. In $PtH_2$ applications, this type of data is often

unavailable due to limited sensor coverage, proprietary system architectures, or inconsistencies in temporal resolution. As a result, data-driven models risk overfitting or underperforming in real-world settings, particularly when transferred between systems with differing configurations.[44,45]

Another challenge lies in the computational complexity and training overhead of these models. RL, surrogate model development, and real-time digital twins require significant computing resources for convergence and deployment. For example, actor–critic RL algorithms and physics-informed neural networks (PINNs) demand extended training cycles and often rely on specialised hardware. These resource demands limit the feasibility of deploying such models in real-time, safety-critical environments like hydrogen storage and dispatch control.[45,46]

Model transparency and interpretability also present a barrier to adoption. While AI-based models are effective at pattern recognition and dynamic optimisation, their internal decision logic is often non-transparent. This "black-box" nature makes it difficult for operators and engineers to understand, validate, or troubleshoot behaviour during abnormal conditions. In $PtH_2$ systems, which involve high pressures, thermal gradients, and interdependent components, lack of interpretability can reduce stakeholder trust and pose regulatory challenges.[44]

The integration of AI with traditional physics-based models is another challenge. Hybrid systems that couple data-driven modules with deterministic simulations promise the best of both domains, but remain difficult to implement. Challenges include synchronising time scales, reconciling different data formats, and managing error propagation between subsystems. Few frameworks exist to seamlessly integrate CFD, process simulation, and RL agents within a unified control or optimisation environment.[12,49]

Additionally, operator readiness and system maturity limit the deployment of immersive technologies such as AR/VR and digital twins. These platforms are increasingly used for simulation and training, but rarely serve in active control environments. Visualisation tools and human-in-the-loop interfaces hold promise for enhancing fault awareness and decision support, yet their development is fragmented and lacks standardisation for $PtH_2$-specific applications.[47,48]

Future research must focus on bridging these limitations. First, hybrid models that embed physical laws into learning architectures could improve adaptability without sacrificing interpretability.[6] Second, developing open-source, interoperable frameworks for co-simulation would facilitate integration between AI and physics-based tools. Third, investment in high-resolution, standardised datasets from operational $PtH_2$ systems will be essential to unlock the full potential of machine learning. Fourth, AR/VR platforms and digital twins should be developed with greater emphasis on system interoperability and real-time responsiveness, making them viable for not just training but also active supervision. Lastly, regulatory frameworks must evolve in parallel with modelling innovations. For example, Australia's National Hydrogen Strategy and Guarantee of Origin Scheme are advancing hydrogen certification, dedicated AI governance remains underdeveloped.[53-55] Future modelling research should align with emerging standards for transparency, auditability, and validation.

Emerging modelling technologies can evolve from experimental tools into operational enablers for real-time, adaptive, and resilient $PtH_2$ smart grid coordination by addressing these challenges.

## 3. Conclusion

This review examined modelling strategies for $PtH_2$ systems, focusing on three core processes: production, storage, and grid integration, as a response to renewable energy intermittency. While traditional methods remain essential for system design and optimisation, they lack the adaptability required for real-time coordination and multi-vector control. Emerging strategies offer greater responsiveness but are constrained by data requirements, computational demands, limited interpretability, and challenges in integration with existing physical models.

Future researches should prioritise hybrid frameworks that combine physical accuracy with data-driven adaptability by combining traditional with emerging modelling and AI-based strategies across the $PtH_2$-integrated smart grid system. Moreover, future researches should focus on building standardised datasets, developing interoperable modelling platforms and expanding the role of real-time visualisation technologies. Lastly, modelling must be supported not only by technical innovation but also by regulatory frameworks to promote transparency, auditability, and certification for enabling safe, scalable $PtH_2$ deployment within smart grid.

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## References

 

[1] Hassan, Q. *et al.* The renewable energy role in the global energy Transformations. *Renewable Energy Focus* **48**, (2024).
[2] Prisca, N. & Extension, Kiu Publication. Renewable Energy Storage Solutions: Innovations and Challenges. **3**, 45–48 (2024).
[3] Rezk, H. *et al.* Fuel cell as an effective energy storage in reverse osmosis desalination plant powered by photovoltaic system. *Energy* **175**, (2019).
[4] Nur, G., Ozgur, C. C. & Devrim, Y. A review on the development of the electrochemical hydrogen compressors. *Journal of Power Sources* **494**, 229743 (2021).
[5] Genovese, M. *et al.* Power-to-hydrogen and hydrogentoX energy systems for the industry of the future in Europe. *International Journal of Hydrogen Energy* **48**, 16545–16568 (2023).
[6] Petkov, I. & Gabrielli, P. Power-to-hydrogen as seasonal energy storage: an uncertainty analysis for optimal design of lowcarbon multienergy systems. *Applied Energy* **274**, 115197 (2020).
[7] Mukelabai, M. D., Barbour, E. R. & Blanchard, R. E. Modeling and optimization of renewable hydrogen systems: A systematic methodological review and machine learning integration. *Energy and AI* **18**, 100455 (2024).
[8] Hovsapian, R., Chanda, S., Panwar, M., Agalgaonkar, Y., Sprik, S., Nagasawa, K., Leighton, D. *Power Electronics for Electrolyzer Applications to Enable Grid Services*. National Renewable Energy Laboratory (2023).
[9] Kumar, S. & Lim, H. An overview of water electrolysis technologies for green hydrogen production. *Energy Reports* **8**, 13793–13813 (2022).
[10] Hu, K. *et al.* Comparative study of alkaline water electrolysis, proton exchange membrane water electrolysis and solid oxide electrolysis through multiphysics modeling. *Applied Energy* **312**, 118788 (2022).
[11] Hu, K. *et al.* Grid-Oriented multiphysics model of PowertoHydrogen electrolyzers. *Energy Conversion and Management* **270**, 116264 (2022).
[12] Sirat, A., Ahmad, S., Ahmad, I., Ahmed, N. & Ahsan, M. Integrative CFD and AI/ML-based modeling for enhanced alkaline water electrolysis cell performance for hydrogen production. *International Journal of Hydrogen Energy* **83**, 1120–1131 (2024).
[13] Olivier, P., Bourasseau, C. & Bouamama, B. Modelling, simulation and analysis of a PEM electrolysis system. *8th IFAC Conference on Manufacturing Modelling, Management and Control MIM 2016* **49**, 1014–1019 (2016).
[14] Jang, D., Kim, J., Kim, D., Han, W. & Kang, S. Techno-economic analysis and Monte Carlo simulation of green hydrogen production technology through various water electrolysis technologies. *Energy Conversion and Management* **258**, 115499 (2022).
[15] Allal, Z., Noura, H. N., Salman, O., Vernier, F. & Chahine, K. A review on machine learning applications in hydrogen energy systems. *International Journal of Thermofluids* **26**, 101119 (2025).
[16] Monopoli, D. et al. How to build a Digital Twin for operating PEM-Electrolyser system – A reference approach. Annual Reviews in Control 57, 100943 (2024).
[17] Macharia, S. Harnessing the Power of Virtual Reality for Hydrogen Production and Utilization. *Linkedin.com* https://www.linkedin.com/pulse/harnessing-power-virtual-reality-hydrogen-production-stephen-macharia-jstue (202AD).
[18] CFD LAND. ANSYS Fluent vs COMSOL. https://cfdland.com/ansys-fluent-vs-comsol/ (2024).
[19] Sánchez, M., Amores, E., Abad, D., Rodríguez, L. & ClementeJul, C. Aspen Plus model of an alkaline electrolysis system for hydrogen production. *International Journal of Hydrogen Energy* **45**, 3916–3929 (2020).
[20] Järvinen, L. *et al.* Automized parametrization of PEM and alkaline water electrolyzer polarisation curves. *International Journal of Hydrogen Energy* **47**, 31985–32003 (2022).
[21] Géron, A. Handson machine learning with ScikitLearn, Keras, and TensorFlow: Concepts, tools, and techniques to build intelligent systems. (" O'Reilly Media, Inc.", 2022).
[22] Agos Jawaddi, Siti Nuraishah & Ismail, A. Integrating OpenAI Gym and CloudSim Plus: A simulation environment for DRL Agent training in energydriven cloud scaling. *Simulation Modelling Practice and Theory* **130**, 102858 (2024).
[23] Allal, Z., Noura, H., Salman, O., Vernier, F. & Chahine, K. A Review on Machine Learning Applications in Hydrogen Energy Systems. *International Journal of Thermofluids* (2025) doi:https://doi.org/10.1016/j.ijft.2025.101119.
[24] Züttel, A. Materials for hydrogen storage. *Materials Today* **6**, 24–33 (2003).
[25] Nguyen, B., Roh, H. S., Merkel, D. & Simmons, K. A predictive modeling tool for damage analysis and design of hydrogen storage composite pressure vessels. International Journal of Hydrogen Energy 46, 20573–20585 (2021).
[26] Rezk, H. *et al.* Fuel cell as an effective energy storage in reverse osmosis desalination plant powered by photovoltaic system. *Energy* **175**, (2019).
[27] Wang, L., Zheng, C., Wei, S., Wang, B. & Wei, Z. Thermomechanical investigation of composite highpressure hydrogen storage cylinder during fast filling. *International Journal of Hydrogen Energy* **40**, 6853–6859 (2015).
[28] Melideo, D., Ferrari, L. & Taddei, P. P. CFD simulation of hydrogen storage: Adsorption dynamics and thermal management in cryogenic tanks. *International Journal of Hydrogen Energy* (2025) doi:https://doi.org/10.1016/j.ijhydene.2025.04.426.
[29] Hu, H. *et al.* Thermodynamic modeling and analysis of hydrogen storage systems in hydrogen refueling stations. *International Journal of Hydrogen Energy* **57**, 1101–1110 (2024).
[30] Yang, W., Dong, J. & Ren, Y. Hydrogen Safety Prediction and Analysis of Hydrogen Refueling Station Leakage Accidents and Process Using MultiRelevance Machine Learning. *World Electric Vehicle Journal* **12**, (2021).
[31] Naanani, H., Nachtane, M. & Faik, A. Advancing hydrogen safety and reliability through digital twins: Applications, models, and future prospects. *International Journal of Hydrogen Energy* **115**, 344–360 (2025).
[32] Benson, C., Subbiah, A., Izuchukwu, O., Kamara, S. & Musa. Realtime monitoring using digital platforms for enhanced safety in hydrogen facilitiesCurrent perspectives and future directions. **98**, 487–499 (2025).
[33] Shash, A. Y., Abdeltawab, Noha M, Hassan, D. M., Darweesh, M. & G, H. Y. Computational Methods, Artificial Intelligence, Modeling, and Simulation Applications in Green Hydrogen

 

Production Through Water Electrolysis: A Review. *Hydrogen* **6**, (2025).
[34]Jaribion, A., Khajavi, S., Öhman, M., Knapen, A. & Holmström, J. A Digital Twin for Safety and Risk Management: A Prototype for a Hydrogen High-Pressure Vessel. in 369–375 (2020). doi:https://doi.org/10.1007/9783030648237_34.
[35]Patil, R. R., Calay, Rajnish K, Mustafa, M. Y. & Thakur, S. Artificial IntelligenceDriven Innovations in Hydrogen Safety. *Hydrogen* **5**, 312–326 (2024).
[36]Motiramani, M. *et al.* AIML techniques for green hydrogen: A comprehensive review. *Next Energy* **8**, 100252 (2025).
[37]El-Amin, M. F. & A. Subasi. Forecasting a SmallScale Hydrogen Leakage in Air using Machine Learning Techniques. in *2020 2nd International Conference on Computer and Information Sciences (ICCIS)* 1–5 (). doi:https://doi.org/10.1109/ICCIS49240.2020.9257718.
[38]Lin, R., Zhao, Y. & Wu, B. Toward a hydrogen society: Hydrogen and smart grid integration. *The 7th International Conference on Energy, Engineering and Environmental Engineering* **45**, 20164–20175 (2020).
[39]AlOthman, A. *et al.* Artificial intelligence and numerical models in hybrid renewable energy systems with fuel cells: Advances and prospects. *Energy Conversion and Management* **253**, 115154 (2022).
[40]Dai, S., Shen, P., Deng, W. & Yu, Q. Hydrogen Energy in Electrical Power Systems: A Review and Future Outlook. *Electronics* **13**, (2024).
[41]Huang, C. *et al.* Economic and resilient operation of hydrogenbased microgrids: An improved MPCbased optimal scheduling scheme considering security constraints of hydrogen facilities. *Applied Energy* **335**, 120762 (2023).
[42]Superchi, F., Giovannini, N., Moustakis, A., Pechlivanoglou, G. & Bianchini, A. Optimization of the power output scheduling of a renewablesbased hybrid power station using MILP approach: The case of Tilos island. *Renewable Energy* **220**, 119685 (2024).
[43]Selim, A. *et al.* Hybrid off-grid energy systems optimal sizing with integrated hydrogen storage based on deterministic balance approach. *Scientific Reports* **14**, (2024).
[44]Zhu, W. et al. Deep Reinforcement Learning Based Optimal Operation of LowCarbon Island Microgrid with High Renewables and Hybrid Hydrogen–Energy Storage System. Journal of Marine Science and Engineering 13, (2025).
[45]Ye, J., Wang, X., Hua, Q. & Sun, L. Deep reinforcement learning based energy management of a hybrid electricityheathydrogen energy system with demand response. *Energy* **305**, 131874 (2024).
[46]Feng, Z., Eiubovi, I., Shao, Y., Fan, Z. & Tan, R. Review of Digital Twin Technology Applications in Hydrogen Energy. *CHAIN* **1**, 54–74 (2024).
[47]Scheffer, S. E. S., Alberto, M. A., Roy, D. R. G. J. & Dongen, van. Supporting maintenance operators using augmented reality decisionmaking: visualize, guide, decide & track. *The 33rd CIRP Design Conference* **119**, 782–787 (2023).
[48]Verciti. Immersive Net Zero Skills Training for Hydrogen. *Verciti.com* https://www.verciti.com/ (2025).
[49]Gaspar, F., González, I. & Calderón, A. *PEM Electrolyser Digital Twin Embedded within MATLABBased Graphical User Interface*. 21 (2022). doi:https://doi.org/10.3390/ECP202212676.
[50]Godfrey, N. S., Udemu, C., Hamzat, Abdulhammed K, Darko, C. K. & Quainoo, Kwamena Ato. Smart monitoring and control systems for hydrogen fuel cells using AI. *International Journal of Hydrogen Energy* **110**, 704–726 (2024).
[51]Zhang, T. *et al.* A systematic review of modelling methods for studying the integration of hydrogen into energy systems. *Renewable and Sustainable Energy Reviews* **208**, 114964 (2025).
[52]Prina, M. G., Dallapiccola, M., Moser, D. & Sparber, W. Machine learning as a surrogate model for EnergyPLAN: Speeding up energy system optimization at the country level. *Energy* **307**, 132735 (2024).
[53]Department of Climate Change, Energy, the Environment and Water. Australia's National Hydrogen Strategy. *Dcceew.gov.au* https://www.dcceew.gov.au/energy/publications/australias-national-hydrogen-strategy (2024).
[54]Department of Climate Change, Energy, the Environment and Water. Guarantee of Origin scheme - DCCEEW. *Dcceew.gov.au* https://www.dcceew.gov.au/energy/renewable/guarantee-of-origin-scheme (2022).
[55]Department of Industry, Science and Resources. *Safe and responsible AI in Australia Discussion paper*. https://storage.googleapis.com/converlens-au-industry/industry/p/prj2452c8e24d7a400c72429/public_assets/Safe-and-responsible-AI-in-Australia-discussion-paper.pdf (2023).

 

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# A Focused Review of Modelling and Technological Advances in Organ-on-a-Chip Systems

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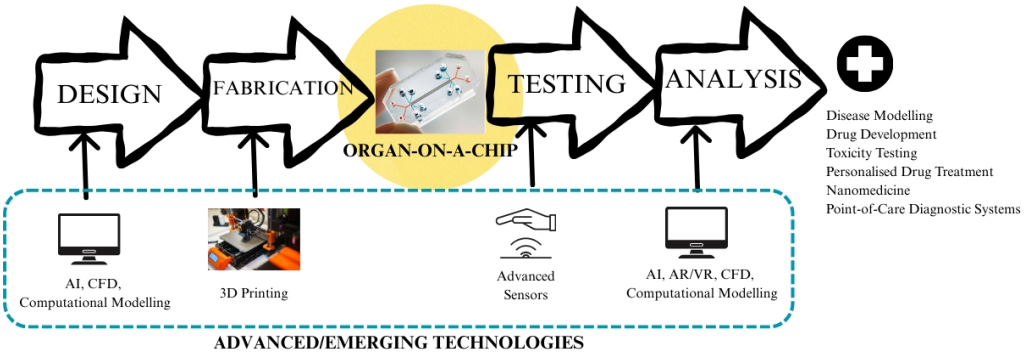
## Graphical Abstract




## Abstract

Organ-on-a-Chip (OoC) technology offers a promising alternative to traditional *in vitro* and animal models by replicating key physiological features of human organs within microfluidic platforms. These systems are increasingly used in drug development, toxicity testing, and disease modelling. However, widespread adoption is limited by challenges such as complex design requirements, scalability issues, data interpretation difficulties, and the integration of diverse technologies. This review explores the role of advanced modelling approaches, such as computational fluid dynamics (CFD), finite element analysis (FEA), pharmacokinetic/pharmacodynamic (PK/PD) models, and artificial intelligence (AI), in addressing these barriers. These tools enable precise simulation, optimization, and data analysis of OoC systems, supporting their design and predictive capabilities. Key challenges identified include limited data quality, computational complexity, organ scaling, and system integration. Modelling solutions, including explainable AI and multiscale simulation, offer pathways to overcome these issues. The integration of emerging technologies like 3D printing, real-time sensing, and automation is also discussed. The review concludes with recommendations for refining existing modelling techniques, improving transparency in AI applications, and supporting interdisciplinary collaboration to drive standardization and regulatory acceptance. These efforts are essential for realizing the full potential of OoCs in biomedical research and preclinical drug development.

Keywords: organ-on-a-chip, OoC, microfluidic, artificial intelligence, AI, machine learning, 3D printing, simulation, computational fluid dynamics, CFD.

## 1. Introduction

The development of sophisticated *in vitro* models has become increasingly important in life science and industry, particularly for applications in medicine, biology, and chemistry.[1] Traditional two-dimensional (2D) cell cultures and animal models struggle to replicate human physiology, hindering data translation and contributing to high drug failure rates.[2-5] This has spurred the evolution of new technologies aimed at creating more biologically relevant systems.[5,6]

Notably selected as one of the "Top Ten Emerging Technologies" by the World Economic Forum[7], The development of organ-on-a-chip (OoC) technology is driven by these limitations of traditional preclinical models.[4,8] OoCs address these limitations by combining advances in microfabrication, tissue engineering, biomaterials, and stem cell engineering to reconstruct key structural, functional, and physiological aspects of human tissues and organs on a chip.[7,9-11] Miniature tissues, cells, or organoids are cultured within the channels and compartments of a microfluidic device.[3,7,11-13] This device, often made of materials like polydimethylsiloxane (PDMS), is engineered with structures such as tiny channels, chambers, and sometimes porous membranes to recreate the organ's microarchitecture.[3,4,7,11,14] The cells may also be embedded within an extracellular matrix analogue or hydrogel inside these compartments. OoC platforms hold promise for various applications, including enhancing our understanding of tissue and organ physiology, modelling diseases (such as cancer), developing and screening drugs, evaluating drug toxicity and efficacy, and facilitating personalized medicine by using patient-derived cells.[3,4,8-11,15,16]

Building upon the foundation of microfluidics, the OoC system has emerged as a biomimetic system.[17] Microfluidics, refers to technologies that manipulate small fluid volumes (mL, nL, pL) within fabricated channels.[1,18] Microfluidic approaches allow for constant miniaturization, automation, and parallelization of processes[1], offering advantages such as low dose requirements, improved sensitivity, efficient processing, great spatial accuracy, good integration, and straightforward control for biological studies.[19] These microfluidic systems can perform several functions, including sample pretreatment, separation, dilution, mixing, chemical reaction, detection, and product extraction, all potentially on a single chip.[18] The precise control offered by microfluidics allows for the emulation of dynamic conditions, such as blood flow, mechanical forces, and concentration gradients, which are crucial for maintaining tissue-specific functions and mimicking the cellular microenvironment.[8,10,11,16]

OoCs are essentially microfluidic cell culture systems designed to precisely replicate the structure and function of a living organ or functional unit *in vitro*.[5,20,21] They can stimulate the tissue or cell microenvironment and regulate crucial parameters like concentration gradients, shear stress, flow

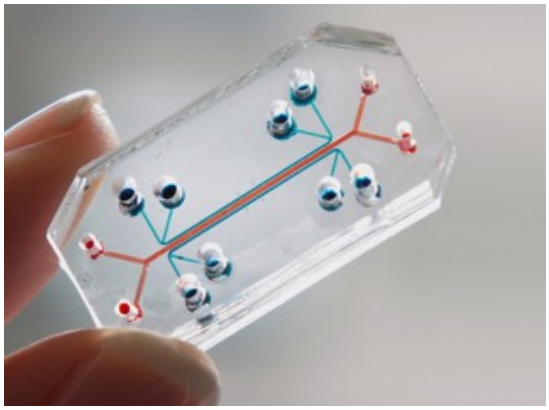


*Figure 1. A lung-on-a-chip. Image by* 허동은교수, *licensed under CC BY -SA 4.0. Source: Link*

[5,17] These platforms integrate microfluidic networks with three-dimensional (3D) tissue-engineered models to recapitulate physiological conditions.[5]

The applications of organ-on-a-chip platforms are diverse and rapidly expanding. They are used as models for studying development and diseases, such as Alzheimer's and schizophrenia, particularly through brain-on-chip models. OoCs play a significant role in drug development, including drug screening and assessing drug release.[2,5,6,18,22,23] They are particularly valuable for toxicity testing, such as evaluating hepatotoxicity, and nephrotoxicity.[5,18] Furthermore, OoCs contribute to personalized medicine by offering functional testing for precision medicine and personalized drug development. They are also explored in the context of nanomedicine for validating the performance and biotoxicity of nanomaterials.[5] Beyond these, OoCs are used to study vascularization of organoids, drug delivery systems, host-microbial interactions, inflammatory processes, and cancer growth and metastasis.[6,23] The technology is even being applied to create point-of-care (POC) diagnostic systems.[18]

The significance of organ-on-a-chip platforms lies in their potential to serve as robust alternatives to animal models, addressing many challenges associated with *in vivo* studies.[2,5] By providing a controlled and realistic environment that mimics human physiology and pathology, OoCs can help reduce the discrepancies observed between preclinical findings and clinical outcomes.[5,18,21] This capability positions them as a fast track for the use of engineered human tissues in drug development and can potentially revolutionize disease modelling and drug testing towards more accurate and personalized healthcare approaches.[18]

Despite the significant progress, the translation of these advanced microfluidic platforms into widespread use, particularly in preclinical validation for clinical applications, still faces limitations and challenges.[5] A critical challenge is the successful integration of biosensor modules into OoCs for automated, continual, and long-term monitoring of various physicochemical and biochemical parameters.[5,18] For complex

applications like pharmacology studies, the development of multiorgan or body-on-a-chip systems is necessary to replicate the interconnections and communication between different organs. However, achieving accurate body scaling and maintaining functional activity across multiple integrated organs is extremely complex.[5] Other challenges include optimizing the design of suitable biomodels, overcoming fabrication complexities associated with microfluidic devices and integrating components like valves and pumps[19], managing potential contamination issues[5], establishing physiologically relevant conditions like oxygen gradients, and bridging the gap between academic research and industrial adoption. Overcoming these challenges is key to unlocking the potential of OoC technology.

Interest in OoC has intensified due to its potential to create more physiologically relevant microenvironments for cell culture, thereby bridging the gap between simplified planar cell cultures and complex human systems.[8,11,16]

Recent breakthroughs and emerging trends are pushing the boundaries of OoC technology, some of which are compared in Table 1 below. A key trend is the move towards integrating multiple individual organ chips into multiorgan-on-a-chip or body-on-a-chip systems, mimicking the physiological coupling and interactions between different organs in the human body.[4,8,16,24] This is particularly beneficial for studying systemic responses, drug metabolism, and complex diseases.[25] Furthermore, there is increasing emphasis on incorporating integrated sensors (mechanical, electrochemical, optical) into OoC platforms for real-time monitoring of cellular behaviors and tissue functions.[8,24,26] Automation and the development of high-throughput systems are also critical for making OoCs more viable for industrial applications like drug screening.[24,26,27] Advances in 3D printing and bioprinting techniques are enabling the rapid fabrication of complex OoC structures and the precise deposition of cells within biomaterial-based scaffolds, creating more realistic three-dimensional tissue architectures.[26] The integration of artificial intelligence (AI), particularly in areas like organoid imaging and data analysis, is enhancing the efficiency and accuracy of OOC-based research, especially for high-throughput drug screening.[9,24] These advancements collectively demonstrate the rapid evolution of OOC technology and its potential to revolutionize biomedical research and drug development.

*Table 1. Comparative Table of Different Modelling Approaches Applied to OoCs.*

| Modelling Approach | Scale | Input | Use | Limitations |
|---|---|---|---|---|
| Computational Fluid Dynamics (CFD) | Microfluidic channels/ devices[28-30] | Geometry, fluid properties, flow rate, solute and solvent parameters, boundary conditions[29,30] | Simulates fluid flow, shear stress, and concentration gradients[28-31] | Complex multiphysics, time-consuming meshing, sensitivity to surface tension and viscosity[29] |
| Finite Element Analysis (FEA) / Finite Element Method (FEM) | Microfluidic devices, bioreactors[29,31,32] | Geometry, material properties, physics modules (e.g., CFD), solute parameters[29,32] | Models mechanical stress, strain, gradient formation, and device refinement[29,31,32] | Requires detailed meshing, complex physics coupling, geometric/parameter coherence[29] |
| Pharmacokinetic/ Pharmacodynamic (PK/PD) & Physiologically-Based Pharmacokinetic (PBPK) | Multi-organ systems (e.g., gut-liver, whole-body)[11,25,28,33-35] | *In vitro*/OoC data (volumes, ADME, flow rates, drug properties)[25,28,33,35] | Predicts drug distribution, toxicity, and human PK/PD profiles; supports *In Vitro-In Vivo* Extrapolation (IVIVE)[11,25,33-35] | Difficult organ scaling, biological/analytical uncertainty, complex model integration[25,33] |
| Artificial Intelligence (AI) / Machine Learning (ML) | Variable (e.g., single-cell to system-level)[5,9,34,36] | Experimental features (e.g., contractility, solubility, oxygen), labeled/unlabeled data[9,34,36,37] | Classifies cells, predicts outcomes, supports toxicology and experimental design[9,25,34,36,37] | Performance depends on data size/quality, model choice, and validation strategy[9] |

This review aims to present the different advanced modelling and analysis techniques that are currently applied and can be applied to OoCs. Section 2 will discuss the current strategies (Section 2.1), and emerging OoC technologies (Section 2.2) with an analysis comparing the technologies (Section 2.3). Section 3 discusses the challenges in OoC

technology (Section 3.1) and how emerging or advanced techniques can help address these challenges (Section 3.2). Finally, Section 3.3 discusses the potential future directions for OoC technology.

## 2. State-of-the-Art in Advanced Modelling Strategies

### *2.1. Current Methodologies*

Current OoC methodologies are grounded in microfluidic platforms, allowing precise control of microscale fluids to mimic physiological conditions.[16] Device fabrication primarily utilizes soft lithography, often with PDMS, known for its biocompatibility and gas permeability.[38] However, alternatives like thermoplastics and natural materials are gaining prominence to address PDMS limitations such as drug absorption.[12] 3D printing and bioprinting are increasingly used for rapid prototyping and creating complex 3D tissue scaffolds.[11]

A key methodology involves reconstituting functional tissues by culturing cells (primary, cell lines, or induced pluripotent stem cells, iPSCs) within the microfluidic chips, often in 3D structures.[10] This requires maintaining a physiologically relevant cellular microenvironment by controlling factors like fluid shear stress, soluble factor concentrations, and cell-matrix interactions.[39]

To capture systemic complexity, multiorgan-on-a-chip systems are developed by connecting multiple organ models, essential for studying drug Absorption, Distribution, Metabolism, Excretion, and Toxicology (ADME-Tox) and inter-organ communication.[4,11,33] These often incorporate vascular networks to simulate blood flow and interactions.[4]

Sensors are being integrated into platforms for real-time monitoring of tissue function and microenvironmental parameters. This facilitates feedback control systems essential for automating high-throughput drug screening.[4,10,11,24,26,39] This drive towards automation and high-throughput screening is critical for the industrial adoption of OoC technology, particularly in drug development.[11,35]

Finally, computational modelling, including fluid dynamics and pharmacokinetic and pharmacodynamic (PK/PD) simulations, plays a vital role in optimizing chip design, predicting parameters, and interpreting experimental data.[33,35,39] Computational platforms such as COMSOL Multiphysics and ANSYS Fluent are commonly used for the design and analysis of microfluidic organ-on-a-chip systems. These *in silico* tools allow for simulations of critical fluid dynamics and transport phenomena necessary for device optimization.[29,30,35] AI is being integrated for enhanced data analysis and image processing. These diverse methodologies collectively contribute to creating and analyzing more physiologically relevant *in vitro* models.[37]

### *2.2. Integration of Emerging Technologies*

OoC technology is a rapidly evolving field that is being significantly advanced by the integration of several emerging technologies with established microfluidic and tissue engineering methodologies.[9,10] This convergence aims to enhance the physiological relevance, functionality, and scalability of OoC systems to better recapitulate human biology and meet the demands of applications such as drug discovery and disease modelling.[4,10]

A prominent area of integration is the development of multiorgan-on-a-chip systems, also referred to as body-on-a-chip, which connect multiple individual organ models using vascular networks within a single microfluidic platform.[4,16,24,35] This mimics the physiological coupling and interactions between different organs in the human body.[35] Such integrated systems are particularly valuable for studying systemic responses, such as drug absorption, distribution, metabolism, and excretion (ADME), as well as complex inter-organ disease mechanisms.[4,16]

Another critical integration involves incorporating integrated sensors directly within OoC platforms.[10,24] Integrated sensors (e.g., mechanical, optical, electrochemical) enable real-time, noninvasive monitoring of tissue function and microenvironmental conditions.[10,24] Examples include electrochemical sensors for detecting relevant biological processes and optical oxygen sensors.

To facilitate the widespread adoption of OoC technology, particularly in pharmaceutical research, there is a significant push towards automation and the development of high-throughput systems. Systemized experimental procedures are being developed to minimize user dependency and improve reproducibility, which are crucial for applications like drug screening.[10,16]

Advances in manufacturing techniques are also being integrated. 3D printing and bioprinting are increasingly used for fabricating complex OoC structures and creating more realistic three-dimensional tissue architectures.[26,40] These methods allow for the precise deposition of cells within biomaterial-based scaffolds and the rapid construction of intricate channel geometries.[26] 3D printing techniques are considered potentially more cost-efficient for OoC fabrication.

Furthermore, AI and computational modelling are being integrated to enhance both the design and analysis phases of OoC research.[9,24,32,35] Computational fluid dynamics (CFD) is used to design optimal microfluidic channel geometries and understand fluid flow patterns.[35] PK/PD modelling helps predict drug behavior and optimize experimental design and sampling.[32] AI is particularly beneficial for tasks such as organoid imaging analysis and processing complex datasets, significantly enhancing the efficiency and accuracy of studies, especially in high-throughput drug screening.[24] Numerical simulation is also used to predict parameters like oxygen concentration and distribution within the devices.[35]

These integrations of multiorgan systems, advanced sensors, automation, 3D printing, and computational approaches are collectively driving OoC technology towards becoming more sophisticated, predictive, and applicable tools for biomedical research and drug development.[9,10]

### 2.3. Comparative Analysis

OoC technologies offer a valuable step towards more physiologically relevant *in vitro* models, providing precise control over the cellular microenvironment and enabling real-time monitoring.[11,41] However, relying solely on traditional experimental methods encounters significant limitations including challenges in achieving industrial scalability, ensuring high reproducibility, accurately replicating complex tissue structures, addressing material compatibility issues, and a lack of widespread standardization.[11,12,42,43] Data acquisition can also be limited by reliance on endpoint assays.[11] The integration of advanced computational modelling and AI is crucial for overcoming these bottlenecks. These *in silico* approaches enable rapid simulation and analysis, providing insights into device design, optimizing parameters for fluid dynamics and transport, and supporting complex analyses like PK/PD modelling.[33,35,38,41] AI and machine learning algorithms further enhance the field by facilitating automated image analysis, cell classification, and predictive modelling based on complex cellular data from OoC systems.[34,44] In the study by Carvalho, et al. [41], a numerical model capable of reproducing the fluid flow behavior within an OoC device was developed and validated. By comparing the model's predictions to experimental results, including qualitative particle paths and quantitative particle velocities, they demonstrated its accuracy and reliability.[41] This synergistic combination of experimental OoC development with advanced computational tools is essential for improving the predictive power and robustness of these platforms.[34]

## 3. Challenges and Future Perspectives

### 3.1. Identified Challenges

Applying advanced modelling techniques, such as numerical simulation and mathematical modelling, to OoC platforms presents several key challenges, summarized in Table 2. These challenges arise from the complexity of replicating human physiology in microfluidic devices and the early stage of standardizing the technology.

*Table 2. Major Challenges in OoC Systems.*

| Challenge | Source | Impact | Modelling Solution |
|---|---|---|---|
| Data Availability & Quality | Data often comes from end-point assays; lacks spatio-temporal resolution. Validation is hard due to low robustness and missing standards. Sampling is limited.[9,11,33,42] | Reduces reproducibility and hinders dynamic analysis. [11,42] | Use of AI/big data analytics for interpretation; optimization of sampling; push for standardized reporting[9,11,33] |
| Computational Complexity | Models are essential but hard to apply; 3D tracking is complex. Analysis must match biology.[9,12,25,41] | Limits predictive accuracy and optimization.[25] | Custom numerical and PK/PD models handle complexity. Tailored analysis improves relevance.[12,25,41] |
| Scalability Issues | Scaling organs and translating data is difficult. Industrial scale-up is limited.[10-12,15,16,25,43] | Affects *in vivo* relevance and slows commercialization.[25] | Use of PBPK scaling models; development of high-throughput and modular system designs.[16,25] |
| Integration of Multiple Technologies | Combines microfluidics, biomaterials, and sensors. Multi-organ signals and system miniaturization are complex.[7,9,10,13,15,26,31,45] | Increases system complexity; hinders functional replication and commercial viability.[9,16,26,42] | Modular design frameworks; collaboration-driven system modelling; incorporation of real-time sensor data into simulations.[9,13,26] |

In addition to these, other challenges include the need for model validation with existing platforms[11,42], the lack of standardization in design, manufacturing, and operating procedures[11,42,43], the requirement for technical skills and user dependency leading to low reproducibility[10,13], limitations of current biomaterials[3,13,15,24], difficulties with sensor integration and data acquisition[9,11,26,42], and the overall engineering limitations in recreating the full physiological complexity of human organs.[9,11,24,42]

### 3.2. Role of Modelling in Addressing Challenges

Advanced modelling techniques are critical for overcoming many of the challenges associated with OoC technology.[25,35] Mathematical and computational models are essential tools for

quantitatively analysing OoC systems and predicting their complex responses.[12] They offer significant advantages over purely experimental approaches, providing insights into fluid flow physics with good precision and accuracy in a rapid and cost-effective manner.[30,41] Computational tools can be used alongside theoretical and experimental methods in microfluidics research.[41] Integrating computational models with OoC experiments provides more quantitative, mechanistic, and physiologically relevant insights than experiments alone.[25] Numerical studies and simulations are performed for optimization purposes, helping to expedite the OoC design process by reducing the need for fabricating numerous prototypes and conducting costly laboratory experiments.[30,41]

Examples from past and current studies demonstrate the impact of these strategies. In the study done by Jeong, et al. [30], numerical approach-based simulation models have been developed to accurately predict *in vivo* levels of shear stress in microfluidic Blood-Brain Barrier (BBB)-on-a-chip models. This prediction, which showed a low error rate compared to experimental results, helps to mimic *in vivo* conditions and establish parameters for successful cell culture, such as tight junction formation. The shear stress model was validated by comparing numerical simulation results with experimental data, achieving a <3% error rate, and demonstrating its reliability in mimicking *in vivo* conditions.[30] CFD and Finite Element Analysis (FEA) are important tools for characterizing biological microflows, predicting biofluid dynamics, and even solid biomechanics.[25] In another study done by Zheng, et al. [35], numerical simulations can also assess the feasibility and efficiency of a microfluidic design before fabrication, reducing experimental trial and error and speeding up the development process. Beyond optimizing design and flow, modelling is used to simulate complex biological behaviors in multicellular constructs, providing critical insights for improving reproducibility or guiding the achievement of desired form and function.[35] Multiscale models for multi-organ or human-on-a-chip systems are more suitable for modelling long-term drug transport and PK/PD effects.[12,34,35] Computational modelling can assist in analyzing, optimizing, and revising the design of 3D culture microfluidic chips, significantly reducing cost and time compared to repetitive experimental measurements.[35] For instance, mathematical models have been used to predict tumor angiogenesis by integrating quantitative experimental data in the study done by Phillips, et al. [37] Furthermore, the integration of machine learning algorithms can accelerate data analysis and image classification in OoC systems, enabling real-time monitoring and automated decision-making in cell culture.[11,34,46] This helps to accelerate preclinical drug screening and disease modelling.[34]

### *3.3. Future Directions*

Advanced modelling techniques are already critical for the quantitative analysis and prediction capabilities of OoC systems, offering speed and cost advantages over purely experimental methods.[28,33,37] Incremental advancements in these methodologies, particularly through enhanced integration of AI and improved visualization, hold significant potential for further progress. Enhanced AI integration, utilizing algorithms like machine learning and deep learning[34,37,44], can accelerate data analysis and interpretation, such as automated image classification and quantitative assessment of cellular responses[34,37], while also refining predictions in areas like drug efficacy and toxicity by improving the estimation of PK/PD parameters from complex data.[33,35,37] The design and optimization of microfluidic devices and experimental protocols can be streamlined by more tightly coupling simulation techniques (e.g., CFD[4]) with AI, allowing for rapid exploration of design parameters, prediction of optimal configurations, and optimization of aspects like sampling times.[14,33,37] Additionally, making AI models more transparent through explainable AI is important for gaining regulatory trust and improving their use in OoC platforms, especially since some deep learning methods are difficult to interpret and can limit understanding in drug development.[47]

Improved visualization techniques, such as layering simulation data onto experimental images or potentially exploring 3D renderings (with techniques like those used for segmented medical images), can enhance researchers' understanding of complex, dynamic processes within the chip, making data interpretation more intuitive and potentially improving reproducibility.[37,44] Projects like ARinBIO explore Augmented Reality/ Virtual Reality (AR/VR) to improve data visualization and collaboration. This initiative seeks to streamline laboratory workflows, reduce errors, and facilitate personalized medicine by providing real-time data visualization and interaction within augmented environments.[48]

Regulation and standardization are crucial for the wider adoption and implementation of OoC technology, as a lack of regulatory consensus on acceptance criteria currently presents a significant hurdle to their use by end-users.[42] International efforts are underway by regulatory agencies and organizations, including the International Organization for Standardization (ISO), which is developing the ISO/AWI 25693 standard.[49,50] This standard, currently under development, specifies requirements for the development process of OoC used for the evaluation of substances, aiming to ensure fitness for purpose and support broader regulatory acceptance.[49]

## 4. Conclusion and Recommendations

This review highlights the critical role of advanced modelling techniques, such as computational fluid dynamics, finite element analysis, PK/PD simulations, and artificial intelligence, in enhancing the design, function, and analysis of OoC systems. These tools enable the replication of complex physiological environments, support data interpretation, and improve predictive modelling for drug development. However, key challenges remain, including limited data quality, computational complexity, scaling issues, and the integration of multidisciplinary technologies. Addressing these barriers is essential for advancing OoC adoption in both research and industrial settings.

Future research should focus on the following priorities to advance Organ-on-a-Chip (OoC) technology:

- Refine current modelling techniques to enhance physiological accuracy and predictive power, especially for multiorgan and systemic models.
- Develop explainable AI frameworks to improve model transparency and build trust for regulatory approval and clinical integration.
- Integrate emerging technologies cautiously, including:
    - Real-time sensor data for continuous monitoring
    - 3D bioprinting for replicating complex tissue structures
    - Augmented and virtual reality tools for enhanced visualization and collaboration
- Ensure compatibility and usability of integrated technologies with biological systems to facilitate practical adoption.
- Promote interdisciplinary collaboration among biologists, engineers, data scientists, and regulators to standardize platforms and accelerate their application in personalized medicine and drug development.

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## References

1 Ali, A. *et al.* in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 1-18 (Academic Press, 2024).
2 Amir, S. *et al.* in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 149-174 (Academic Press, 2024).
3 Farhang Doost, N. & Srivastava, S. K. A Comprehensive Review of Organ-on-a-Chip Technology and Its Applications. *Biosensors* **14** (2024).
4 Driver, R. & Mishra, S. Organ-On-A-Chip Technology: An In-depth Review of Recent Advancements and Future of Whole Body-on-chip. *BioChip Journal* **17**, 1-23 (2023). https://doi.org/10.1007/s13206-022-00087-8
5 Rodrigues, R. O. *et al.* Organ-on-a-Chip: A Preclinical Microfluidic Platform for the Progress of Nanomedicine. *Small* **16**, 2003517 (2020). https://doi.org/https://doi.org/10.1002/smll.202003517
6 Grace Raji, R., Anjali, K. & Kumar, V. B. S. in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 199-213 (Academic Press, 2024).
7 Wu, Q. *et al.* Organ-on-a-chip: recent breakthroughs and future prospects. *BioMedical Engineering OnLine* **19**, 9 (2020). https://doi.org/10.1186/s12938-020-0752-0
8 Ferreira, G. M. *et al.* Numerical simulation, fabrication, and characterization of a heating system for integration into an Organ-on-a-Chip. *Sensors and Actuators A: Physical* **363**, 114699 (2023). https://doi.org/https://doi.org/10.1016/j.sna.2023.114699
9 Koyilot, M. C. *et al.* Breakthroughs and Applications of Organ-on-a-Chip Technology. *Cells* **11** (2022).
10 Cho, S., Lee, S. & Ahn, S. I. Design and engineering of organ-on-a-chip. *Biomedical Engineering Letters* **13**, 97-109 (2023). https://doi.org/10.1007/s13534-022-00258-4
11 Leung, C. M. *et al.* A guide to the organ-on-a-chip. *Nature Reviews Methods Primers* **2**, 33 (2022). https://doi.org/10.1038/s43586-022-00118-6
12 Nahak, B. K., Mishra, A., Preetam, S. & Tiwari, A. Advances in Organ-on-a-Chip Materials and Devices. *ACS Applied Bio Materials* **5**, 3576-3607 (2022). https://doi.org/10.1021/acsabm.2c00041
13 Liu, X. *et al.* Recent Advances of Organ-on-a-Chip in Cancer Modeling Research. *Biosensors* **12** (2022).
14 Grant, J. *et al.* Simulating drug concentrations in PDMS microfluidic organ chips. *Lab on a Chip* **21**, 3509-3519 (2021). https://doi.org/10.1039/D1LC00348H
15 Wang, Y. *et al.* Emerging trends in organ-on-a-chip systems for drug screening. *Acta Pharmaceutica Sinica B* **13**, 2483-2509 (2023). https://doi.org/https://doi.org/10.1016/j.apsb.2023.02.006
16 Azizipour, N., Avazpour, R., Rosenzweig, D. H., Sawan, M. & Ajji, A. Evolution of Biochip Technology: A Review from Lab-on-a-Chip to Organ-on-a-Chip. *Micromachines* **11** (2020).
17 Jacob, S., Kaushik, P. & Parvez, S. in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 309-325 (Academic Press, 2024).
18 Vishwakarma, N. & Singh, S. in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 75-90 (Academic Press, 2024).
19 Shah, M., Prakashan, D. & Gandhi, S. in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 91-112 (Academic Press, 2024).
20 Gupta, V. *et al.* in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 233-249 (Academic Press, 2024).

 

21 Poojary, B. in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 251-259 (Academic Press, 2024).

22 Mukherjee, A. G. *et al.* in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 411-424 (Academic Press, 2024).

23 Chowdary, P., Yadav, D. N., Pogu, S. V. & Rengan, A. K. in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 439-457 (Academic Press, 2024).

24 Huang, Y., Liu, T., Huang, Q. & Wang, Y. From Organ-on-a-Chip to Human-on-a-Chip: A Review of Research Progress and Latest Applications. *ACS Sensors* **9**, 3466-3488 (2024). https://doi.org/10.1021/acssensors.4c00004

25 Sung, B. In silico modeling of endocrine organ-on-a-chip systems. *Mathematical Biosciences* **352**, 108900 (2022). https://doi.org/https://doi.org/10.1016/j.mbs.2022.108900

26 Carvalho, V. *et al.* 3D Printing Techniques and Their Applications to Organ-on-a-Chip Platforms: A Systematic Review. *Sensors* **21** (2021).

27 Ma, C., Peng, Y., Li, H. & Chen, W. Organ-on-a-Chip: A New Paradigm for Drug Development. *Trends in Pharmacological Sciences* **42**, 119-133 (2021). https://doi.org/10.1016/j.tips.2020.11.009

28 Prot, J. M. *et al.* First pass intestinal and liver metabolism of paracetamol in a microfluidic platform coupled with a mathematical modeling as a means of evaluating ADME processes in humans. *Biotechnology and Bioengineering* **111**, 2027-2040 (2014). https://doi.org/https://doi.org/10.1002/bit.25232

29 Menezes, P. D., Gadegaard, N., Natal Jorge, R. M. & Pinto, S. I. S. Modelling human liver microphysiology on a chip through a finite element based design approach. *International Journal for Numerical Methods in Biomedical Engineering* **37**, e3445 (2021). https://doi.org/https://doi.org/10.1002/cnm.3445

30 Jeong, S., Seo, J.-H., Garud, K. S., Park, S. W. & Lee, M.-Y. Numerical approach-based simulation to predict cerebrovascular shear stress in a blood-brain barrier organ-on-a-chip. *Biosensors and Bioelectronics* **183**, 113197 (2021). https://doi.org/https://doi.org/10.1016/j.bios.2021.113197

31 Wang, L. *et al.* A new approach of using organ-on-a-chip and fluid–structure interaction modeling to investigate biomechanical characteristics in tissue-engineered blood vessels. *Frontiers in Physiology* **Volume 14 - 2023** (2023).

32 Filipovic, N., Nikolic, M. & Sustersic, T. in *Biomaterials for Organ and Tissue Regeneration* (eds Nihal Engin Vrana, Helena Knopf-Marques, & Julien Barthes) 753-790 (Woodhead Publishing, 2020).

33 Milani, N., Parrott, N., Galetin, A., Fowler, S. & Gertz, M. In silico modeling and simulation of organ-on-a-chip systems to support data analysis and a priori experimental design. *CPT: Pharmacometrics & Systems Pharmacology* **13**, 524-543 (2024). https://doi.org/https://doi.org/10.1002/psp4.13110

34 da Silva Pereira, J. D. T. *Machine Learning Algorithms and Organs-on-Chips as New Technologies for the Modeling of Human Cardiac Toxicity and Disease*, Universidade do Minho (Portugal), (2022).

35 Zheng, F., Xiao, Y., Liu, H., Fan, Y. & Dao, M. Patient-Specific Organoid and Organ-on-a-Chip: 3D Cell-Culture Meets 3D Printing and Numerical Simulation. *Adv Biol (Weinh)* **5**, e2000024 (2021). https://doi.org/10.1002/adbi.202000024

36 Ibrahim, M., Chakrabarty, K. & Schlichtmann, U. Synthesis of a Cyberphysical Hybrid Microfluidic Platform for Single-Cell Analysis. *IEEE Transactions on Computer-Aided Design of Integrated Circuits and Systems* **38**, 1237-1250 (2019). https://doi.org/10.1109/tcad.2018.2846662

37 Phillips, C. M. *et al.* Towards integration of time-resolved confocal microscopy of a 3D in vitro microfluidic platform with a hybrid multiscale model of tumor angiogenesis. *PLoS Computational Biology* **19**, e1009499 (2023).

38 Silva, D. F. C. *et al.* Design of a microfluidic platform for monoclonal antibody extraction using an aqueous two-phase system. *Journal of Chromatography A* **1249**, 1-7 (2012). https://doi.org/https://doi.org/10.1016/j.chroma.2012.05.089

39 Pisapia, F., Balachandran, W. & Rasekh, M. Organ-on-a-Chip: Design and Simulation of Various Microfluidic Channel Geometries for the Influence of Fluid Dynamic Parameters. *Applied Sciences* **12** (2022).

40 Seyed Zolfaghari, S. H., Pourmand, A. & Kiyoumarsioskouei, A. A low-cost 3D-printing based rapid fabrication procedure for modular microfluidic platform. *Journal of Micromechanics and Microengineering* **35**, 045013 (2025). https://doi.org/10.1088/1361-6439/adc313

41 Carvalho, V. *et al.* Numerical evaluation and experimental validation of fluid flow behavior within an organ-on-a-chip model. *Computer Methods and Programs in Biomedicine* **243**, 107883 (2024). https://doi.org/https://doi.org/10.1016/j.cmpb.2023.107883

42 Teixeira, S. G. *et al.* National reflection on organs-on-chip for drug development: New regulatory challenges. *Toxicology Letters* **388**, 1-12 (2023). https://doi.org/https://doi.org/10.1016/j.toxlet.2023.09.011

43 Candarlioglu, P. L. *et al.* Organ-on-a-chip: current gaps and future directions. *Biochemical Society Transactions* **50**, 665-673 (2022). https://doi.org/10.1042/BST20200661

44 Oliver, C. R., Westerhof, T. M., Castro, M. G. & Merajver, S. D. Quantifying the Brain Metastatic Tumor Micro-Environment using an Organ-On-A Chip 3D Model, Machine Learning, and Confocal Tomography. *J Vis Exp* (2020). https://doi.org/10.3791/61654

45 R, N., Aggarwal, A., Sravani, A. B., Mallya, P. & Lewis, S. Organ-On-A-Chip: An Emerging Research Platform. *Organogenesis* **19**, 2278236 (2023). https://doi.org/10.1080/15476278.2023.2278236

46 Movčana, V. *et al.* Organ-On-A-Chip (OOC) Image Dataset for Machine Learning and Tissue Model Evaluation. *Data* **9** (2024).

47 Gangwal, A. & Lavecchia, A. Artificial intelligence in preclinical research: enhancing digital twins and organ-on-chip to reduce animal testing. *Drug Discovery Today* **30**, 104360 (2025). https://doi.org/https://doi.org/10.1016/j.drudis.2025.104360

48 *Augmented Reality Solutions for Organ-on-Chip applications*, <https://www.gobiond.com/2021/05/01/interview-with-emanuele-borasio-ceo-and-founder-wear-srl/> (2021).


 

49 *ISO/AWI 25693: Biotechnology - Developing process of Organ-on-Chip using for evaluation of substances*, <https://www.iso.org/standard/91185.html> (

50 Centre, J. R. *Setting out a roadmap for standardisation of organ-on-chip technology*, <https://joint-research-centre.ec.europa.eu/jrc-news-and-updates/setting-out-roadmap-standardisation-organ-chip-technology-2025-01-13_en> (2025).

 

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# Focussed Review of Modelling-Driven Innovations in Organ-on-a-Chip Platforms using CFD, AI, and AR/VR

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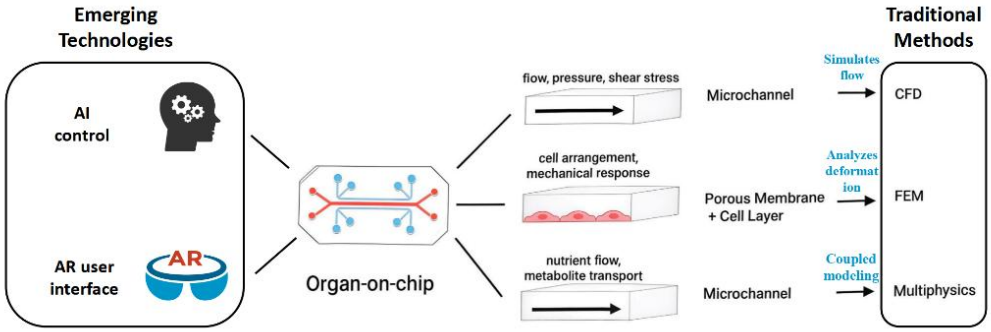
## Graphical Abstract

## Abstract




Organ-on-a-chip (OOC) is an emerging microfluidic platform that mimics key physiological functions of the human body, offering promising tools for drug screening, disease modeling, and personalized medicine (context). This review highlights recent advances in OOC modeling, with a focus on Computational Fluid Dynamics (CFD), Finite Element Analysis (FEM), multiphysics simulation, artificial intelligence (AI), and augmented/virtual reality (AR/VR) (key advance). We summarize the applications of these approaches in fluid dynamics, mechanical responses, chemical transport, and system visualization, explicitly addressing their roles at different modeling layers relevant to chip performance (scope). Finally, we discuss current challenges, including organ complexity, multi-organ integration, validation, and standardization, and propose that future progress will rely on interdisciplinary collaboration, hybrid modeling strategies, and real-time AI integration to accelerate biomedical translation (outlook).

Keywords: Organ-on-a-Chip, Microfluidics, Artificial Intelligence, Biomedical Applications

## 1. Introduction

Organ-on-a-Chip (OoC) is a cutting-edge technology that combines biology and microtechnology, capable of simulating key physiological functions of the human body on microfluidic chips[1,2]. It exactly controls trace amounts of fluid through the use of microchannels to supply cells and tissue structures with a close-to-physiological microenvironment[3]. OOC employs chip-based regulated device systems to supply cells and tissue structures with biochemical and physical environments close to in vivo conditions to allow scientists to experiment on these systems in vitro[4]. This allows scientists to more accurately control the microenvironment in which the cells reside and directly view the reaction of the cells and tissues[5].

In comparison to conventional two-dimensional cell culturing, the scale of the channels in microfluidic systems is comparable to that of cells and more effectively replicates the extracellular microenvironment and the three-dimensional tissue structure[6,7]. It is able to perform precise regulation of mechanical stimulation to the cells, delivery of nutrients and chemical gradients. With these technologies, it is possible to create miniature cavities of precise structures and accurately regulate the molecules and the cells within the microfluidic system to accurately duplicate the organs' microenvironment and replicate the physiological and disease conditions in the body[8]. With this technology, it offers a highly bionic and high-throughput new experimental system for drug screening, disease studies and personalized medicine.

But in order to fully tap the potential of OOC, advanced modeling techniques assume key significance[9]. Modeling not only allows for chip design to be optimized, fluid and cell behavior to be predicted, and the trial-and-error experiment to be minimized but also enhances the reproducibility of the system. CFD, FEM as well as multi-physics field simulation provide valuable information on the flow field distribution, the mechanical stress, the nutrient gradient and the response of the cell within the chip. Meanwhile, recent emerging technologies including AI and AR/VR have continuously improved the precision of designs, data analysis functions, and visual interaction to further enhance the accuracy of modeling.

In the past few years, scientists have constructed various types of organ chips, e.g., the brain[10], heart[11], lung[12] and cancer models[13], and made good performance in various applications. Organ-on-a-chip has become a valuable tool for the academia and industry to study the functions of organs and discover new medicines. For example, the bionic lung chip has effectively duplicated the relationship between human alveoli and capillary structures, offering a new way for drug screening[14].

However, despite the fact that OOC technology is extremely innovative, there are still many challenges[15]. One of the primary challenges is standardization in the process of manufacturing[16]. Up to now, due to the lack of a uniform system of material and techniques, not only does it hinder the reproducibility of experiments but also the mass production and low-cost process. Second, the cooperation and coupling between different chip organs have not yet been effectively integrated, and as a result, it becomes challenging to simulate comprehensive multiple-organ interaction. Likewise, OOC also encounters the problem of medical verification and regulation: how to undergo medical verification and be certified by the US FDA is a primary challenge for the transition of OOC toward application[17].

The aim of this paper is to comprehensively review the modelling approaches for microfluidic platforms in Organ-on-a-Chip (OOC), assess the role of traditional techniques such as Computational Fluid Dynamics (CFD), Finite Element Analysis (FEA), and Multi-Physics Field Simulation (MFSS) in the design and optimisation of OOCs, and explore the innovative breakthroughs brought by the emerging technologies such as Artificial Intelligence (AI), Machine Learning (ML) and Augmented/Virtual Reality (AR/VR). However, existing reviews mostly focus on chip fabrication or biological applications, with less systematic summaries of the synergies of these modelling strategies and their challenges, such as multi-scale coupling, data integration and standardisation issues. By filling this gap, this paper provides ideas and references for the development of OOC in biomedical engineering.

## 2. Modelling and Intelligent Technologies

With the rapid development of organ-on-a-chip (OOC) technology, advanced modeling methods and intelligent technologies are playing an increasingly important role in it. Modeling tools such as Computational Fluid Dynamics (CFD)[18], Finite Element Analysis (FEM), and multiphysics simulation provide reliable theoretical support for chip design, fluid control, and physiological process prediction. Meanwhile, the introduction of emerging technologies such as artificial intelligence (AI), machine learning, and augmented/virtual reality (AR/VR) has greatly enhanced the efficiency of data analysis, design optimization, and visualization. Figure 1 shows how CFD, FEM, and multiphysics relate to key OOC components.

### *2.1 Traditional computational modeling methods*

#### *2.1.1 CFD*

Computational Fluid Dynamics (CFD) is a method based on numerical analysis, which is used to simulate and predict the flow, pressure, velocity, temperature and material transport behavior of fluids (liquids or gases) under different conditions[18].

Hydrodynamic parameters such as shear force, pressure and flow rate can significantly affect the morphology, proliferation, function and survival rate of cells, and thereby

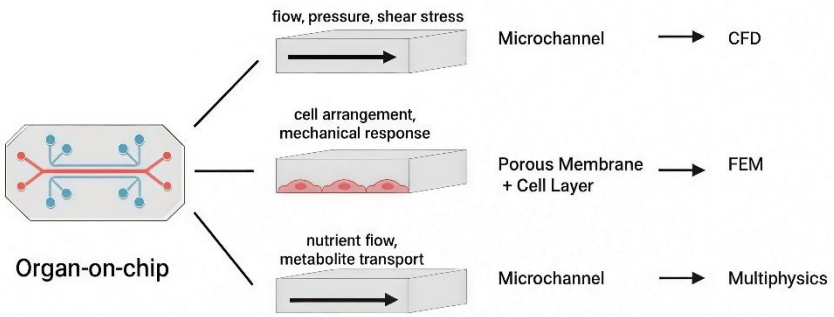



Figure 1. Schematic of Organ-on-a-Chip and modelling methods

play a key role in the overall function and activity of tissues[19]. Microfluidic devices provide a highly promising method for studying these parameters and the fluid behavior in different microchannel structures[20]. Microfluidic devices (MFDS) are made of biocompatible materials and contain tiny channels[21]. Organ-on-a-chip (OOC) utilizes this technology to simulate the microenvironment of specific tissues or organs[22].

Green et al. investigated the influence of channel geometry on cell adhesion by designing microchannels with sharp turns and curved turns and combining them with fluid dynamics simulations. Their results show that the flow velocity and shear stress distribution in the curved and turning microchannels are more uniform, which helps to improve the cell adhesion effect[23].

Bakuova et al. demonstrated through CFD analysis and experiments based on Huh7 cells that the elliptical cavity liver chip has superior flow and filling characteristics compared to the circular cavity chip, and successfully verified the adhesion and continuous growth of cells[24]

However, CFD mainly focuses on fluid systems and is difficult to directly handle the solid deformation of chips or multi-physics field coupling. Moreover, its mesh division and boundary condition setting are complex, the calculation time is long, and it requires powerful computing resources[25].

### *2.1.2 Finite Element Analysis (FEM)*

Finite element Analysis (FEM) is a numerical tool used to predict the mechanical properties in organ-on-a-chip (OOC), capable of simulating the deformation, stress distribution and fluid-structure coupling effects of chip materials. The application of FEM is conducive to optimizing chip design, improving durability and security. However, its modeling is complex and the parameter setting is cumbersome, and it needs to be combined with experimental verification to ensure the reliability of the simulation. Furthermore, at present, many designs still mainly rely on trial-and-error experiments and have not fully utilized the advantages of FEM[26].

### *2.1.3 Multi-physics field simulation*

Multiphysics simulation is an integrated approach used to simultaneously study the interactions among various physical processes such as fluids, mechanics, chemistry, and heat conduction, and is particularly suitable for complex organ-on-a-chip (OOC) systems. Multiphysics simulation not only helps optimize chip design and enhance the physiological relevance of experiments but also provides a powerful tool for the prediction of complex systems.

Jeon et al. utilized multi-physics field simulation combined with experiments to study the effects of fluid flow in the intestinal-liver microarray on intestinal cells and liver cells, optimized the flow velocity and shear force parameters, and explored the effects of fatty acid transport, liver lipid accumulation, and anti-fatty liver drugs[27].

## *2.2 The Application of AI in OOC*

AI, especially machine learning algorithms, can be used to automate chip design and parameter optimization. By training algorithms, researchers can predict in advance which design is the most suitable for a specific biological application, significantly reducing the cost of trial and error. Machine learning is a common method for achieving artificial intelligence, and deep learning is one of the important algorithms among them.

The research by Li et al. indicates that organ-on-a-chip (OOC) systems based on deep learning have demonstrated great potential at multiple levels[28]. Through algorithms such as convolutional Neural networks (CNN) and recurrent neural networks (RNN), image analysis, cell recognition, dynamic tracking, segmentation and functional prediction in the chip can be efficiently achieved, greatly improving the automation level of data processing. In addition, deep learning has also demonstrated significant value in aspects such as the design optimization of microfluidic chips, fluid dynamics analysis, and cell behaviour prediction. This study points out that by integrating deep learning technology, OOC is expected to achieve higher accuracy and efficiency in drug screening, disease modelling, personalized medicine, and multi-organ

Table 1. Summary of modelling tools, applications, advantages, and challenges in Organ-on-a-Chip research

| Tool | Application | Advantage | Challenge | Recent Example |
|---|---|---|---|---|
| CFD | Simulate fluid flow, shear stress, nutrient transport in microchannels | High accuracy, clear physical principles | Complex setup, high computational cost | Barbosa et al. (2024), thermal and fluid flow modeling in OoC[29]. |
| FEM | Analyze mechanical deformation, stress distribution, fluid–structure interaction | Accurate mechanical predictions, good for membrane deformation | Complex meshing, needs precise material data | de Menezes (2020), finite element approach for OoC design[26]. |
| Multiphysics Simulation | Combine fluid, mechanical, thermal, chemical effects | Comprehensive system analysis | High modeling difficulty, long computation time | Jeon et al. (2021), gut–liver-on-a-chip for hepatic steatosis modeling[27]. |
| AI | Optimize design, predict behavior, analyze images | Fast data processing, automated optimization | Needs large, high-quality datasets; limited interpretability | Isozaki et al. (2020), AI integration in lab-on-a-chip systems[30]. |
| AR/VR | Visualization, training, remote collaboration | Improved visualization and interactivity | Limited integration with physical systems | Broek (2025), visualization tool for OoC fibrotic disease model[31]. |

system research, bringing new opportunities for in vitro alternative experiments and precision medicine[28].

Isozaki et al. reviewed the combined application of artificial intelligence (AI) and Lab-on-a-Chip, pointing out that machine learning and deep learning have significantly improved the analytical efficiency and accuracy in aspects such as high-throughput imaging, cell classification, and drug screening[30]. The article also mentioned that algorithms such as Support Vector Machine (SVM) and Convolutional Neural Network (CNN) have been successfully applied in cell cycle analysis and blood cell detection. At the same time, it emphasized future challenges such as model interpretability and data quality.

Lightweight models such as decision trees and embedded machine learning can also be introduced in for real-time control and adaptive tuning[32]. Such methods are faster in computation, consume less power and are more suitable for integration with portable and miniaturised devices.

### *2.3 The Application of AR/VR in OOC*

Augmented Reality (AR) and virtual reality (VR) are visualization and interaction technologies that have developed rapidly in recent years. These two technologies have the advantages of being intuitive, dynamic and highly interactive, which makes them show wide application potential in many scientific research and engineering fields.

Recent works have demonstrated the growing significance of AR and VR in medical applications, including their application in organ-on-a-chip (OOC) studies. For example, VR associated with Computer-aided Modeling (CAM) has been used in tele-surgery to increase the accuracy of operations and collaborative planning[33,34]. In the study of OOC, the use of AR/VR technology can project the Body-on-a-Chip (BOC) system and combine several OOC units to model a whole organism[35,36]. By fusing real-time data and immersive visualization, the use of AR/VR increases the capacity of researchers to track dynamic processes, study drug effects, and tune up experimental protocols without the need for direct physical manipulation. Further, AR/VR also enhances inter-team communications[37].

Although AR/VR has shown great potential in aspects such as visualization, simulation and training, the integration with actual OOC systems still faces some obstacles. Including the limitations of hardware miniaturization and the challenge of real-time data synchronization between virtual and physical systems.

### *2.4 Comprehensive evaluation*

Advanced technologies such as Computational Fluid Dynamics (CFD), Finite Element Analysis (FEM), multiphysics simulation, artificial intelligence (AI), and augmented/virtual reality (AR/VR) are instrumental in the enhanced design and application of organ-on-a-chip (OOC). CFD and FEM offer high accuracy but need complex setup and heavy computing. Multiphysics simulation captures system interactions but is even more demanding. AI brings efficiency and flexibility to design and data analysis but depends on large, quality datasets and often lacks interpretability. AR/VR improves visualization and user

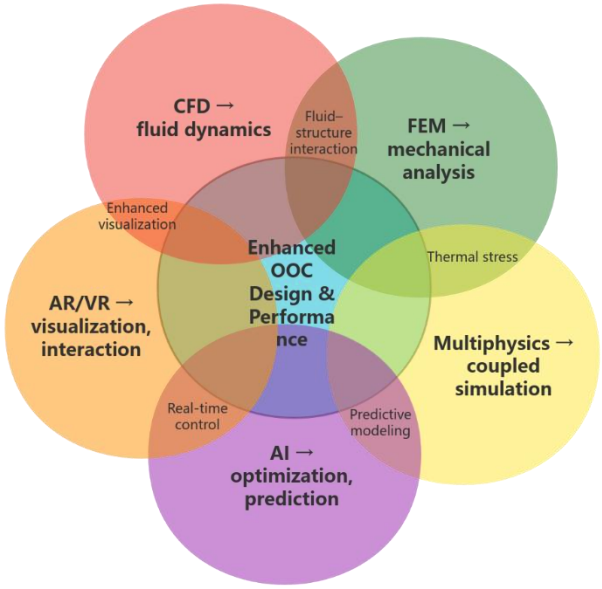



Figure 2. Complementary Modelling Methods in Organ-on-a-Chip

interaction but is still mainly used as a support tool, with limited integration into chip systems.

Table 1 summarizes the main tools, their typical applications in organ-on-chip systems, as well as their respective main advantages and challenges.

To illustrate the complementarity and integration of various modelling approaches in Organ-on-a-Chip systems, Figure 2 presents a schematic Venn diagram highlighting the overlaps and shared roles of CFD, FEM, multiphysics simulation, AI, and AR/VR technologies.

Overall, each technology has its own focus and complementary advantages in OOC. In the future, it is necessary to promote cross-disciplinary integration, combining the rigor of traditional modeling with the predictive ability of AI and the intuitiveness of AR/VR, to achieve a more efficient, intelligent and reliable OOC system, opening up broader prospects for biomedical research and precision medicine.

### *2.5 Validation*

Verification is a key step to ensure that the modeling results accurately reflect the biological performance in the OOC system. For instance, the fluid flow and shear force obtained from CFD simulation can be verified through microparticle imaging velocity measurement (μPIV) or tracer dye experiments[38]. The results predicted by FEM can be compared by observation with a high-resolution microscope or traction microscopy[39]. The prediction of cell behavior or drug response by AI needs to be verified through means such as time series imaging, molecular analysis or histological analysis[40]. Effective verification can not only enhance the credibility of the model, but also identify the deficiencies that need improvement in the model.

Meinicke et al. combined μPIV measurement and CFD simulation to study the single-phase fluid dynamics in porous $SiO_2$ glass foam. In the study, μPIV was used to observe the flow of DMSO in porous structures, and the experimental data were compared with the CFD model reconstructed by X-rays. The research shows that the experimental results are highly consistent with the numerical results, effectively verifying the CFD prediction[41].

## 3 Challenges and Future Perspectives

Although organ-on-a-chip (OOC) technology has made many advancements, it still faces many challenges in practical applications. How to accurately restore the complex structures of human organs and biological interfaces remains difficult[42].

Although traditional modeling methods (such as CFD, FEM, and multiphysics simulation) are accurate in calculation, they are complex in operation and time-consuming. AI offers new approaches to design optimization and data analysis, but it relies on a large amount of high-quality data and has limited model interpretability. AR/VR has improved visualization and interaction, but the deep integration with OOC is still insufficient.

Furthermore, OOC lacks a unified platform and standards, resulting in the difficulty of repeating experiments and integrating and analyzing data. The stable supply of human cells and the development of multi-organ shared culture media are also key bottlenecks for promotion.

Interdisciplinary cooperation among biology, engineering and computational science needs to be strengthened in the future. By integrating modeling, AI and AR/VR, drive OOC to achieve more intelligent and efficient applications. And accelerate its clinical transformation in drug screening, disease research and precision medicine.

## 4 Conclusion and Recommendations

As the core technology of organ-on-a-chip (OOC), the microfluidic platform provides a solid foundation for its application in biomedical engineering. The combination of traditional modelling methods, artificial intelligence (AI), and augmented/virtual reality (AR/VR) has jointly promoted the design optimization, data analysis, and functional expansion of OOC, opening new avenues for fields such as drug screening, disease research, and personalized medicine.

In the future, the development of organ-on-a-chip (OOC) will increasingly rely on close collaboration in the fields of engineering, computing and biology. Hybrid digital twins are expected to combine sensors and AI to achieve real-time monitoring and regulation of OOC for personalized drug screening and disease prediction. Through the real-time feedback system embedded in machine learning (embedded

ML), researchers can adjust the fluid parameters, drug concentrations, etc. of the chip based on real-time data in the experiment, improving the flexibility and physiological relevance of the experiment. These advancements are expected to shorten the transition from the laboratory to clinical practice and promote the wide application of OOC in drug development and personalized medicine.

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## References

[1] Bhatia, S. N. & Ingber, D. E. Microfluidic organs-on-chips. *Nature biotechnology* **32**, 760-772 (2014).
[2] Joseph, X., Akhil, V., Arathi, A. & Mohanan, P. Comprehensive development in organ-on-a-chip technology. *Journal of Pharmaceutical Sciences* **111**, 18-31 (2022).
[3] Whitesides, G. M. The origins and the future of microfluidics. *nature* **442**, 368-373 (2006).
[4] Ronaldson-Bouchard, K. & Vunjak-Novakovic, G. Organs-on-a-chip: a fast track for engineered human tissues in drug development. *Cell stem cell* **22**, 310-324 (2018).
[5] Leung, C. M. *et al.* A guide to the organ-on-a-chip. *Nature Reviews Methods Primers* **2**, 33 (2022).
[6] Halldorsson, S., Lucumi, E., Gómez-Sjöberg, R. & Fleming, R. M. Advantages and challenges of microfluidic cell culture in polydimethylsiloxane devices. *Biosensors and Bioelectronics* **63**, 218-231 (2015).
[7] McLean, I. C., Schwerdtfeger, L. A., Tobet, S. A. & Henry, C. S. Powering ex vivo tissue models in microfluidic systems. *Lab on a Chip* **18**, 1399-1410 (2018).
[8] Tian, C., Tu, Q., Liu, W. & Wang, J. Recent advances in microfluidic technologies for organ-on-a-chip. *TrAC Trends in Analytical Chemistry* **117**, 146-156 (2019).
[9] Low, L. A., Mummery, C., Berridge, B. R., Austin, C. P. & Tagle, D. A. Organs-on-chips: into the next decade. *Nature Reviews Drug Discovery* **20**, 345-361 (2021).
[10] Park, J. W., Vahidi, B., Taylor, A. M., Rhee, S. W. & Jeon, N. L. Microfluidic culture platform for neuroscience research. *Nature protocols* **1**, 2128-2136 (2006).
[11] Lind, J. U. *et al.* Instrumented cardiac microphysiological devices via multimaterial three-dimensional printing. *Nature materials* **16**, 303-308 (2017).
[12] Domansky, K. *et al.* Perfused multiwell plate for 3D liver tissue engineering. *Lab on a Chip* **10**, 51-58 (2010).
[13] Bischel, L. L., Beebe, D. J. & Sung, K. E. Microfluidic model of ductal carcinoma in situ with 3D, organotypic structure. *BMC cancer* **15**, 1-10 (2015).
[14] Lee, S. H. & Jun, B.-H. Advances in dynamic microphysiological organ-on-a-chip: Design principle and its biomedical application. *Journal of industrial and engineering chemistry* **71**, 65-77 (2019).
[15] Tajeddin, A. & Mustafaoglu, N. Design and fabrication of organ-on-chips: promises and challenges. *Micromachines* **12**, 1443 (2021).
[16] Ma, C., Peng, Y., Li, H. & Chen, W. Organ-on-a-chip: a new paradigm for drug development. *Trends in pharmacological sciences* **42**, 119-133 (2021).
[17] Allwardt, V. *et al.* Translational roadmap for the organs-on-a-chip industry toward broad adoption. *Bioengineering* **7**, 112 (2020).
[18] Kamyar, A., Saidur, R. & Hasanuzzaman, M. Application of computational fluid dynamics (CFD) for nanofluids. *International Journal of Heat and Mass Transfer* **55**, 4104-4115 (2012).
[19] Chabanon, M. *et al.* Histological method to study the effect of shear stress on cell proliferation and tissue morphology in a bioreactor. *Tissue Engineering and Regenerative Medicine* **16**, 225-235 (2019).
[20] Pisapia, F., Balachandran, W. & Rasekh, M. Organ-on-a-Chip: Design and simulation of various microfluidic channel geometries for the influence of fluid dynamic parameters. *Applied Sciences* **12**, 3829 (2022).
[21] Solanki, S., Pandey, C. M., Gupta, R. K. & Malhotra, B. D. Emerging trends in microfluidics based devices. *Biotechnology journal* **15**, 1900279 (2020).
[22] Farhang Doost, N. & Srivastava, S. K. A comprehensive review of organ-on-a-chip technology and its applications. *Biosensors* **14**, 225 (2024).
[23] Green, J. V. *et al.* Effect of channel geometry on cell adhesion in microfluidic devices. *Lab on a Chip* **9**, 677-685 (2009).
[24] Bakuova, N. *et al.* Design, simulation, and evaluation of polymer-based microfluidic devices via computational fluid dynamics and cell culture “on-chip”. *Biosensors* **13**, 754 (2023).
[25] Tu, J., Yeoh, G. H., Liu, C. & Tao, Y. *Computational fluid dynamics: a practical approach*. (Elsevier, 2023).
[26] de Menezes, P. D. C. C. *A Finite Element Approach to Design Organ-on-a-Chip Devices*, Universidade do Porto (Portugal), (2020).
[27] Jeon, J. w., Lee, S. H., Kim, D. & Sung, J. H. In vitro hepatic steatosis model based on gut–liver‐on‐a‐chip. *Biotechnology Progress* **37**, e3121 (2021).
[28] Li, J. *et al.* An overview of organs-on-chips based on deep learning. *Research* (2022).
[29] Barbosa, F. *et al.* in *International Conference on Micro/Nanoscale Heat Transfer.* V001T004A014 (American Society of Mechanical Engineers).
[30] Isozaki, A. *et al.* AI on a chip. *Lab on a Chip* **20**, 3074-3090 (2020).
[31] Broek, E. *Building a visualisation tool for an organ-on-a-chip model of fibrotic diseases*, University of Twente, (2025).
[32] Zhao, X., Sun, Y., Li, Y., Jia, N. & Xu, J. Applications of machine learning in real-time control systems: a review. *Measurement Science and Technology* (2024).
[33] Jimenez, J. I., Jahankhani, H. & Kendzierskyj, S. Health care in the cyberspace: Medical cyber-physical system and digital twin challenges. *Digital twin technologies and smart cities*, 79-92 (2020).
[34] Lee, I. *et al.* Challenges and research directions in medical cyber–physical systems. *Proceedings of the IEEE* **100**, 75-90 (2011).
[35] Zhang, B., Korolj, A., Lai, B. F. L. & Radisic, M. Advances in organ-on-a-chip engineering. *Nature Reviews Materials* **3**, 257-278 (2018).

[36] Skardal, A., Shupe, T. & Atala, A. Organoid-on-a-chip and body-on-a-chip systems for drug screening and disease modeling. *Drug discovery today* **21**, 1399-1411 (2016).
[37] Rasheed, A., San, O. & Kvamsdal, T. Digital twin: Values, challenges and enablers from a modeling perspective. *IEEE access* **8**, 21980-22012 (2020).
[38] Lindken, R., Rossi, M., Große, S. & Westerweel, J. Micro-particle image velocimetry (μPIV): recent developments, applications, and guidelines. *Lab on a Chip* **9**, 2551-2567 (2009).
[39] Zielinski, R., Mihai, C., Kniss, D. & Ghadiali, S. N. Finite element analysis of traction force microscopy: influence of cell mechanics, adhesion, and morphology. *Journal of biomechanical engineering* **135**, 071009 (2013).
[40] Panayides, A. S. *et al.* AI in medical imaging informatics: current challenges and future directions. *IEEE journal of biomedical and health informatics* **24**, 1837-1857 (2020).
[41] Meinicke, S., Möller, C.-O., Dietrich, B., Schlüter, M. & Wetzel, T. Experimental and numerical investigation of single-phase hydrodynamics in glass sponges by means of combined μPIV measurements and CFD simulation. *Chemical engineering science* **160**, 131-143 (2017).
[42] Murphy, S. V. & Atala, A. 3D bioprinting of tissues and organs. *Nature biotechnology* **32**, 773-785 (2014).