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Review article

AI-enabled organoids: Construction, analysis, and application

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ABSTRACT

Organoids, miniature and simplified *in vitro* model systems that mimic the structure and function of organs, have attracted considerable interest due to their promising applications in disease modeling, drug screening, personalized medicine, and tissue engineering. Despite the substantial success in cultivating physiologically relevant organoids, challenges remain concerning the complexities of their assembly and the difficulties associated with data analysis. The advent of AI-Enabled Organoids, which interfaces with artificial intelligence (AI), holds the potential to revolutionize the field by offering novel insights and methodologies that can expedite the development and clinical application of organoids. This review succinctly delineates the fundamental concepts and mechanisms underlying AI-Enabled Organoids, summarizing the prospective applications on rapid screening of construction strategies, cost-effective extraction of multiscale image features, streamlined analysis of multi-omics data, and precise preclinical evaluation and application. We also explore the challenges and limitations of interfacing organoids with AI, and discuss the future direction of the field. Taken together, the AI-Enabled Organoids hold significant promise for advancing our understanding of organ development and disease progression, ultimately laying the groundwork for clinical application.

1. Introduction

Organoids are three-dimensional structures that mimic the architecture and functions of various organs [1]. They are grown *in vitro* from stem cells or other precursor cells and have been used to study the development and behavior of different organs, as well as for drug screening and disease modeling [2,3]. Organoids are highly valued for their ability to recapitulate the complex microenvironments and functions of different organs, making them valuable tools for studying the mechanisms of disease and for testing potential treatments [4,5]. However, organoids research is still in its infancy, with preliminary exploration of construction strategies, assessment, and application methods, and shortcomings and deficiencies such as insufficient active properties of the construction matrix material, significant differences in cell composition and ratio compared to natural tissue, and lack of spatial characteristics [6].

Organoids research mainly includes three key aspects: construction strategies [7], data analysis [8], and efficacy verification [9]. Among them, construction strategies are crucial for the success of organoids construction. Construction strategies cover three aspects: the selection of matrix material s [10] (elastic modulus, porosity, degradability, etc.), the exploration of cellular culture conditions [1] (temperature, humidity, etc.), and the screening of various growth factors [11] (WNTs, BMPs, etc.). As can be seen, the construction of organoids involves multiple materials, external stimuli, factors, and their interactions. At present, conventional construction techniques are based on literature speculation (e.g., the selection of growth factors) and continuous *in vitro* experiments (e.g., the synthesis of matrix materials) to explore the best

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strategies, which are not only costly and time-consuming but also have a low success rate [12]. Multiple immunofluorescence imaging and multi-omics data analysis (genomics, metabolomics, single-cell omics, etc.) are important evaluation methods for organoids and can effectively assess the functionality of organoids *in vitro* [13]. However, image data analysis is often limited by the multifocal and heterogeneity of organoids, making it difficult to quickly and accurately determine the spatial characteristics of organoids, while multi-omics data have diverse non-structured, semi-structured, and heterogeneous architecture characteristics, making the data volume extremely large and posing great challenges to traditional analysis methods. Therefore, there is an urgent need for new technical means to break the traditional research paradigm, quickly and efficiently optimize the construction strategies and data analysis methods of organoids, and achieve precise and efficient repair efficacy verification for organoids research.

Artificial Intelligence (AI) is a field of computer science that aims to develop computer systems that can perform tasks that typically require human intelligence, such as visual perception, speech recognition, decision-making, and language translation [14]. AI systems can be trained on large data sets to make predictions, classify objects, and perform other complex tasks. Machine learning, a cutting-edge technology derived from the development of artificial intelligence, is a multidisciplinary field that combines computer science, mathematics, philosophy, control theory, determinism, and other disciplines [15,16]. Machine learning studies the simulation or implementation of human learning activities through computers and is one of the most intelligent and cutting-edge research fields in artificial intelligence. For example, in the field of material preparation, it has been reported a method and strategy based on machine learning for the bottom-up self-assembly of colloidal and nanoparticle soft materials [17]. In the field of data analysis, Takahashi et al. employed unsupervised machine learning to accurately estimate survival probabilities in non-small cell lung cancer, identifying novel survival-linked subtypes through analysis of six multi-omics datasets from the Cancer Genome Atlas [18]. In the field of clinical applications, Google published a paper in 2016 describing the application of machine learning in diabetic retinopathy screening, which was rated as one of the most influential papers of the past decade [19]. The machine learning algorithm proposed can explain the signals of diabetic retinopathy in retinal photos, helping doctors screen more patients in resource-limited situations. Another example is the establishment of a machine learning model to label abnormal X-ray images, distinguishing between normal and abnormal chest films, and demonstrating good generalization ability for unseen lung diseases (such as COVID-19) [20].

One area of research that is of particular interest is the intersection of organoids and AI. For example, AI algorithms can be used to analyze large amounts of data generated by organoids experiments [21], allowing for a more comprehensive and efficient analysis of the data. Additionally, AI algorithms can be trained on images of organoids [22], allowing for the rapid and accurate analysis of organoid structure and function. This can provide valuable insights into the mechanisms of disease and the development of new treatments. Another important aspect of interfacing organoids with AI is the potential for the development of new and improved organoid technologies. For example, AI algorithms can be used to optimize the growth conditions of organoids [23], leading to the creation of more functional and physiologically relevant organoids. Furthermore, AI algorithms can be adopted to predict the differentiation of stem cells into specific cell types, leading to the creation of more complex and sophisticated organoids [24–26]. One of the studies validates that, a convolutional neural networks (CNN) model-DenseNet121 could accurately predict kidney organoid differentiation derived from human induced pluripotent stem cells based on the analysis of simple bright-field images of kidney organoids. This noninvasive and nondestructive prediction method may accelerate the transition of kidney organoid technology "from the bench to the bedside [25].

Although AI has been used in the field of organoids research, to the best of our knowledge, there has been no systematic review summarizing the integration of AI and organoids. With this in mind, the second section will provide a brief introduction to the development history of organoids, along with their application scenarios and challenges faced. The third section will delve into the history of AI, its classification, and its application scenarios in medicine. The fourth section will focus on the detailed application of AI in organoid research, encapsulating the essence of AI-Enabled Organoids. This section will elaborate on four aspects: rapid screening of construction strategies, cost-effective extraction of multiscale image features, streamlined analysis of multi-omics data, and precise preclinical evaluation and application. Lastly, we will briefly discuss the advantages and limitations of AI-Enabled Organoids. Throughout the review, we will provide a comprehensive overview of the field of interfacing organoids with AI and to encourage further research in this area.

2. Overview of organoids

2.1. Definition and brief history

The term "organoids" combines "organic" and the suffix "-oid", signifying natural, self-organizing structures resembling native organs [27]. Originating from stem cells, these 3D constructs mimic organ properties yet are not true human organs [28]. Proposed in 1907, the term gained traction in 2009 [29] when Hans and his team cultured the first intestinal organoids [30]. Since then, the field has rapidly advanced (Fig. 1).

Over the last decade, significant milestones have been achieved [31–33]. In 2011, gut and retinal organoids were first cultivated from stem cells [34,35]. The following year saw the development of retinal organoids from human pluripotent stem cells [36]. In 2013, brain, liver, kidney, and pancreas organoids were successfully grown [37]. Prostate and lung organoids followed in 2014 [38,39], and mammary gland, fallopian tube, and hippocampus organoids in 2015 [40–42]. In 2020, snake venom gland organoids were successfully cultivated [43].

In 2022, Tokyo Medical and Dental University initiated the world's first clinical trial transplanting stem cell-derived organoids into humans for treating ulcerative colitis [44]. This pioneering work in regenerative medicine is under safety validation and positions organoid technology as a Nobel Prize contender.

2.2. Applications of organoids

Due to the highly accurate mimicry of real organs in structure and function, organoids have great potential for understanding the complex functions of human tissues and organs and for preclinical disease treatment [45–47]. Their utility extends from high-throughput drug screening to intricate disease modeling, and some have even reached the stage of clinical translation (Fig. 2). Specifically, organoids have been employed to simulate complex tumor microenvironments by co-culturing with immune cells, thereby advancing our understanding of cancer biology [48,49]. They also serve as platforms for drug discovery, enabling researchers to assess the efficacy and toxicity of new therapeutic agents. For example, liver organoids can be used to study the metabolism of drugs, and to identify new targets for drug development [50]. In the realm of regenerative medicine, organoids offer the potential for creating functional tissues suitable for transplantation and other therapeutic applications [51–53].

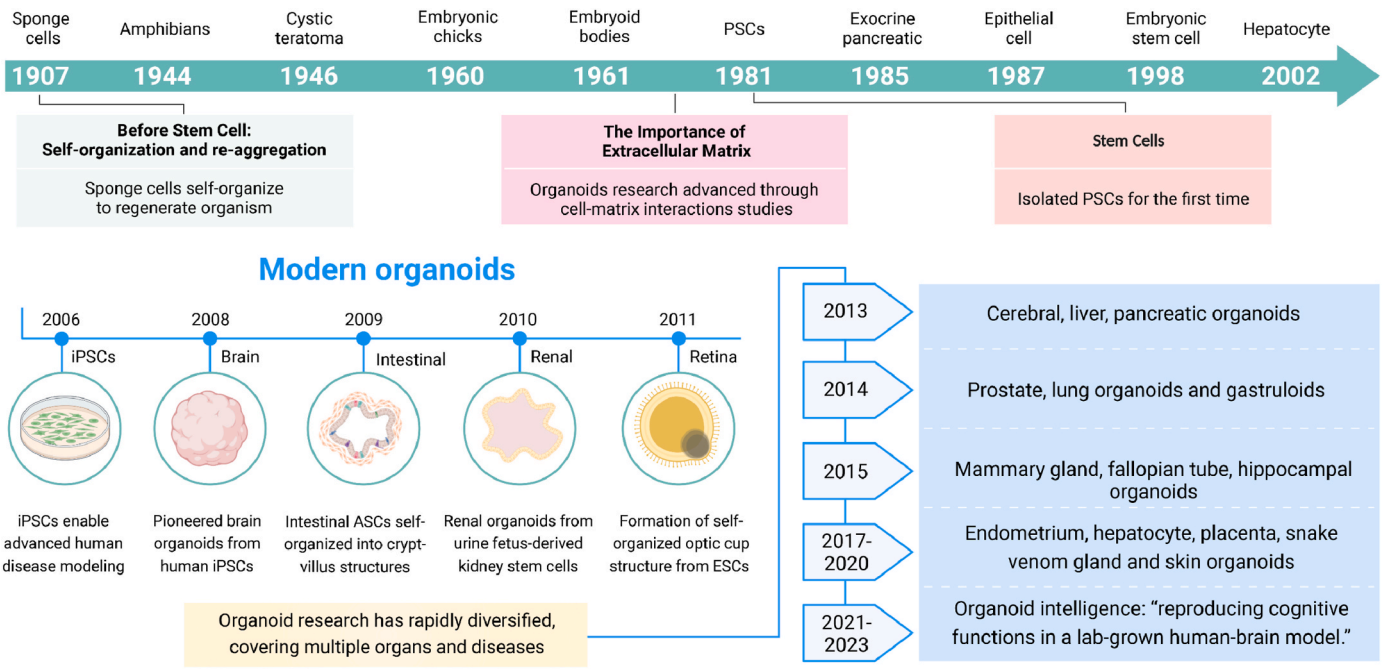

Fig. 1. A brief history of organoids.

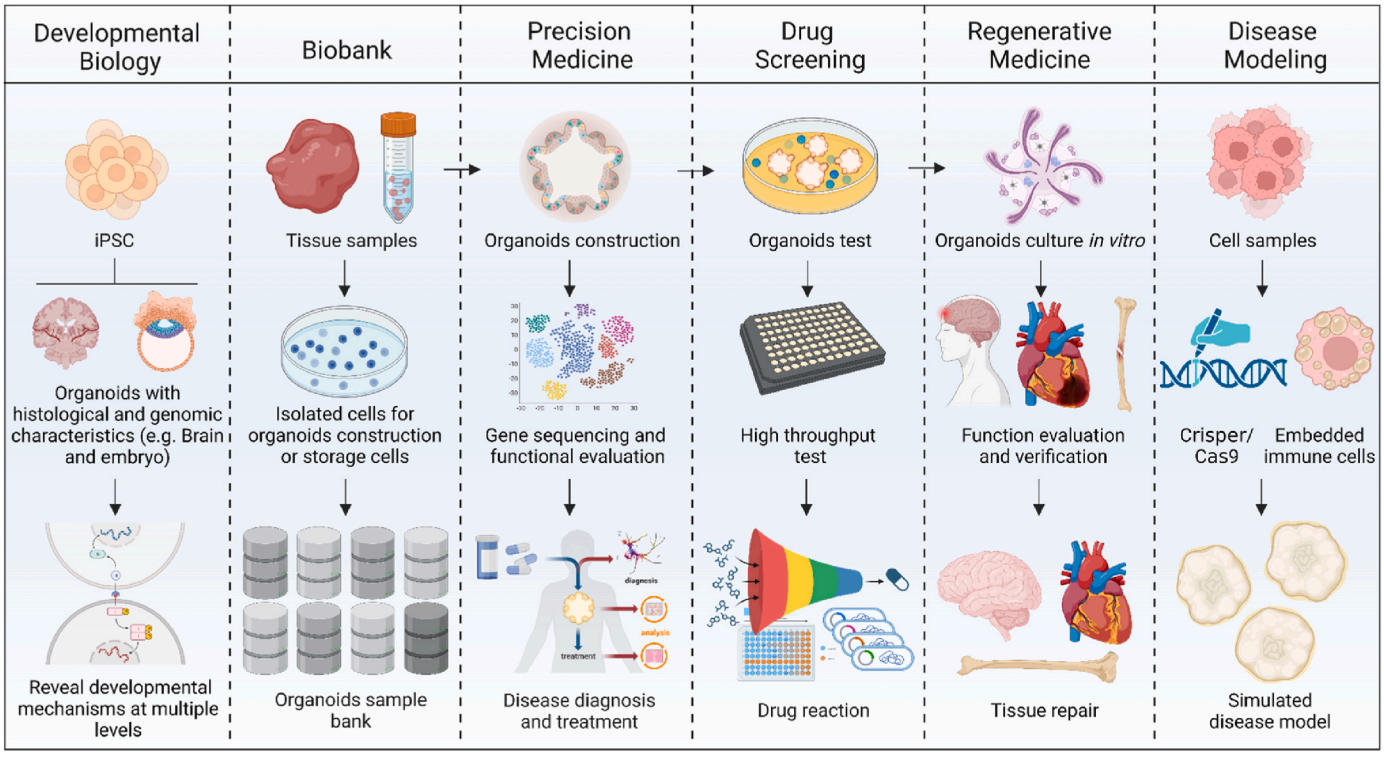

Fig. 2. Applications of organoids.

Furthermore, they are instrumental in studying human developmental biology, providing invaluable insights into the mechanisms underlying various diseases, including genetic disorders and infectious diseases. For example, brain organoids can be used to study the development of the human brain and the underlying mechanisms of neurological disorders [54,55]. The continual refinement of organoid technology is expected to yield groundbreaking advances in these fields, thereby deepening our understanding of human biology and paving the way for innovative treatments.

2.3. *Challenges and limitations*

Organoid technology, a significant advancement in biomedical research, faces multifaceted challenges, particularly in the areas of

construction, data analysis, and applications. In the construction phase, the selection of matrix materials is paramount. Currently, the field largely depends on Matrigel, an animal-derived extracellular matrix, which is fraught with issues such as poor reproducibility, variability, and potential immunogenicity [56]. The emergence of synthetic/hybrid hydrogel matrices offers a promising avenue, boasting advantages like cost-effectiveness and a closer resemblance to the native structures of human organs. However, the intricate nature of synthesizing these hydrogels, given their varying chemical compositions and cross-linking mechanisms, adds a layer of complexity, requiring iterative optimization processes.

In the realm of data analysis, the field is plagued by a lack of standardized protocols and real-time monitoring techniques [57,58]. This absence of standardization introduces significant variability into the system, which is further exacerbated by manual handling and subjective interpretation of data. The lack of automation in the culture process and data analysis contributes to inconsistencies that hinder the organoids' translational potential.

Lastly, the application of organoids faces its own set of challenges, including ethical considerations and economic constraints. As organoids become increasingly complex, ethical concerns surrounding their potential to mimic human consciousness or perceive pain, particularly in cerebral organoids, become more pressing [59]. Additionally, the high costs associated with specialized culture media, growth factors, and labor-intensive procedures make scaling up and clinical translation a resource-heavy endeavor [60].

In summary, while organoids offer unprecedented opportunities for advancing our understanding of human biology and disease, they are encumbered by a range of challenges from their construction and data analysis to their ethical and economic implications. These challenges must be systematically addressed to unlock the full potential of organoid technology.

3. Overview of AI

3.1. Definition and brief history

AI, originating in computer science, aims to emulate human-like cognitive functions such as visual perception and decision-making [61]. It is an interdisciplinary domain, integrating computer science, mathematics, and psychology among others [62]. Its relevance has surged in diverse sectors like medicine and finance [63]. The history of AI can be traced back to the 1950s [64] (Fig. 3), when John McCarthy coined the term "AI" in 1956 at Dartmouth College [65]. Early AI research was rule-based, exemplified by the Logic Theorist developed by Newell and Simon in 1955 [66]. The focus shifted to machine learning in the 1970s, introducing algorithms like neural networks [67]. The 1990s marked advancements in natural language processing, facilitated by the burgeoning World Wide Web [68].

Recent milestones include AlphaGo [69], AlphaFold [70], and ChatGPT [71]. Additionally, the rise of big data has made it possible to train AI algorithms on large amounts of data, leading to improved performance in various tasks. Today, AI is being applied in a wide range of fields, and its potential for future applications is limited only by our imagination. Further research in AI will likely lead to even greater advances in the field, and it will be exciting to see what the future holds for this rapidly growing field.

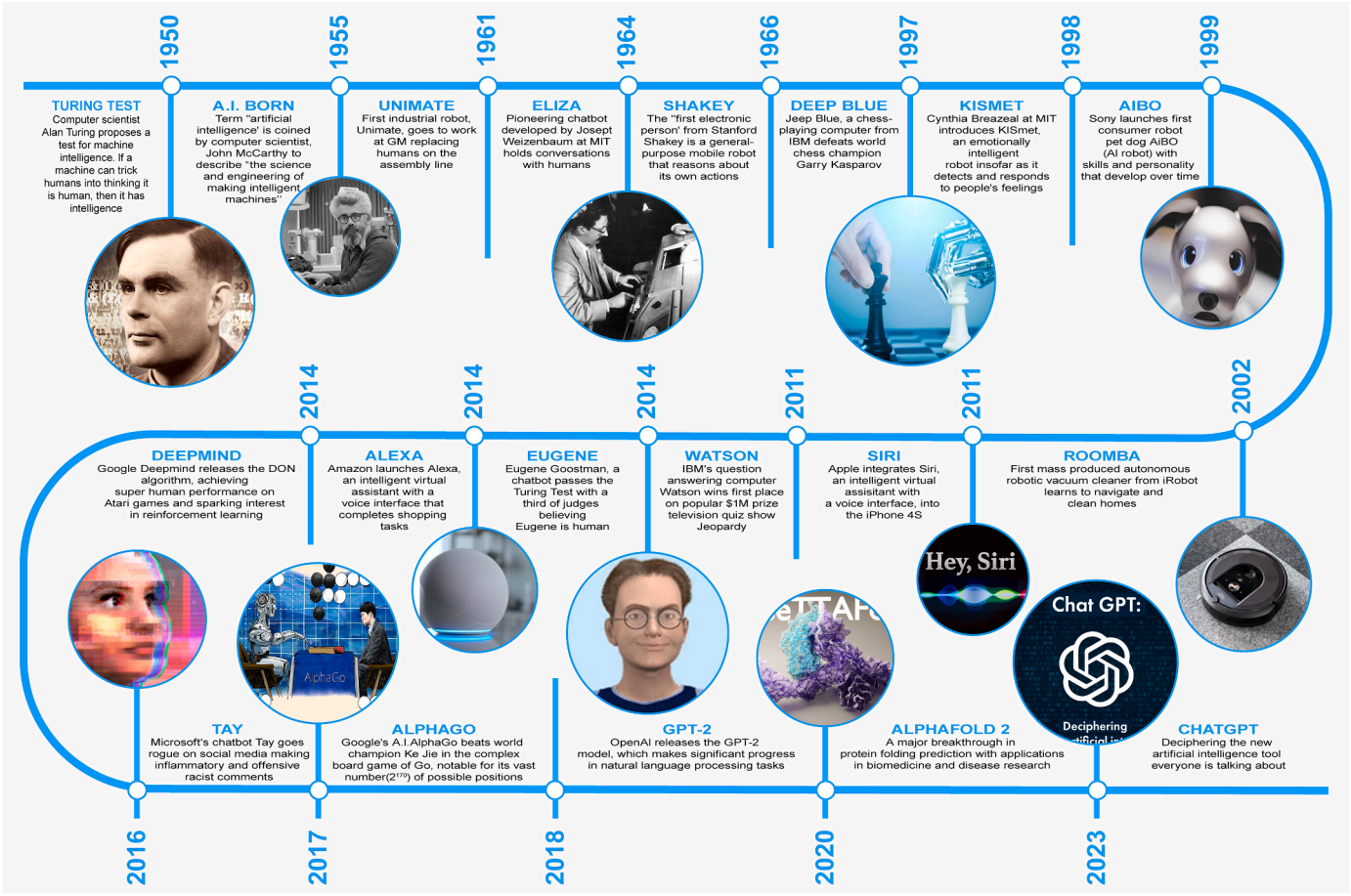

Fig. 3. A brief history of AI development.

3.2. Types of machine learning

AI aims to emulate human cognitive functions for tasks requiring intelligence, such as natural language understanding and decision-making [72]. Machine learning, a subset of AI, employs algorithms to iteratively learn from data, thereby automating decision-making and prediction [73]. It serves as the foundation for most AI applications today. There are several types of machine learning, each of which can be used to solve different problems (Fig. 4a). The main types of machine learning include:

Supervised learning: Utilizes labeled data to train algorithms for predictive tasks. Common algorithms include linear and logistic regression, as well as decision trees [74].

Unsupervised learning: Operates on unlabeled data to discover inherent patterns. It is often used for clustering and dimensionality reduction, with algorithms like k-means and principal component analysis [75].

Reinforcement learning: Involves algorithms learning through environmental interaction, aiming to maximize rewards over time. It is commonly applied in robotics and control systems [76].

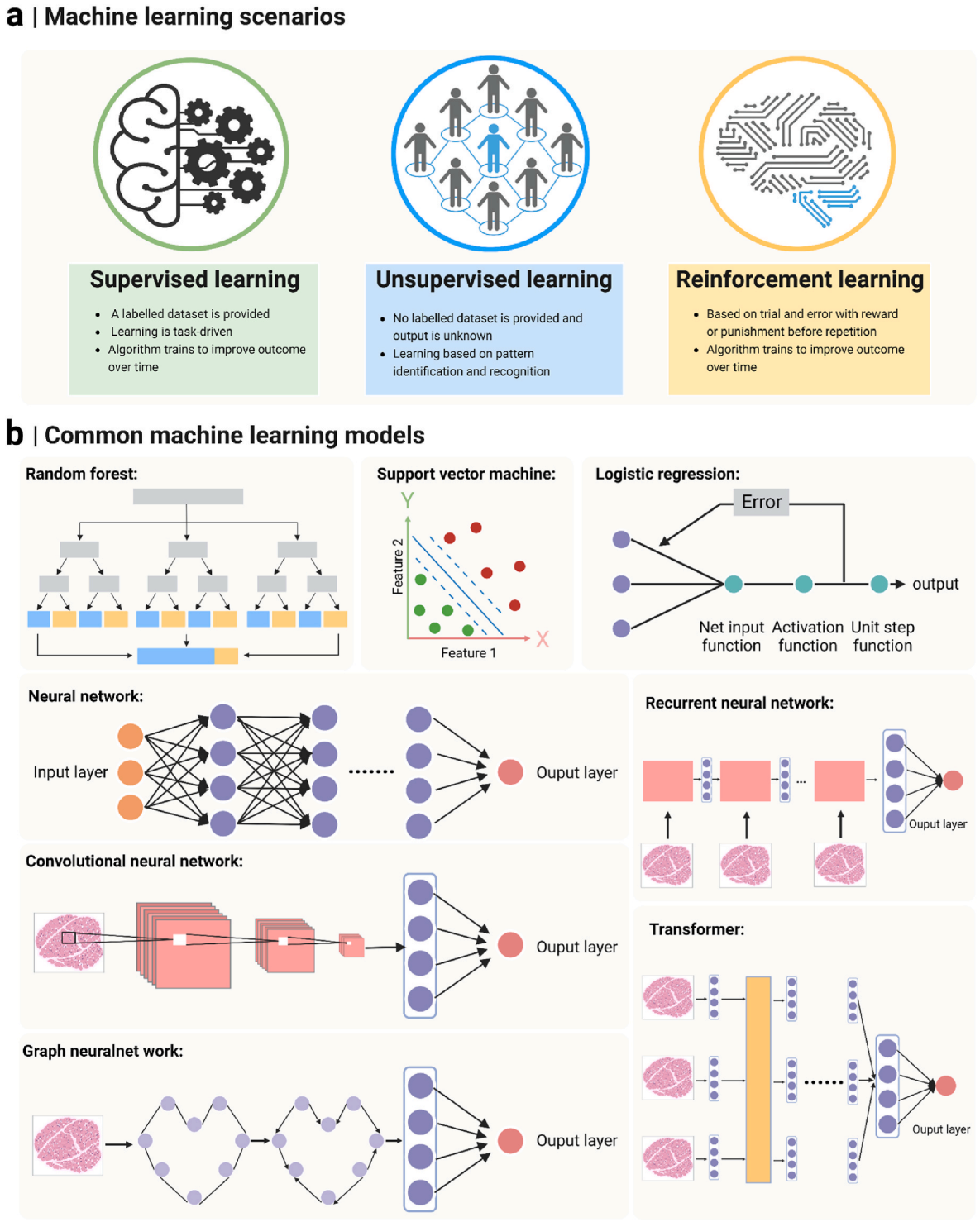

Fig. 4. A brief introduction of machine learning. (a) The main types of machine learning. (b) Common machine learning models.

In summary, machine learning provides the tools and methodologies that allow AI systems to learn from experience, adapt to new situations, handle vast amounts of data, improve performance over time, and accomplish complex tasks that were previously out of reach. It is the engine that powers the current AI revolution and will likely continue to play a pivotal role in the future developments of the field.

3.3. Common machine learning models

There are several common machine learning models, each with its own strengths and areas of application. Here are a few (Fig. 4b):

Random Forests: An ensemble method using multiple decision trees on data subsets; outputs are averaged for regression or voted for classification [77]. Random Forests are often used for disease classification and risk prediction. For instance, a study proposes a cloud-random forest (C-RF) model for assessing the risk of coronary heart disease (CHD), demonstrating superior classification performance over traditional models like CART, SVM, CNN, and RF, with an accuracy of 85% and an AUC value of 0.85 based on the Framingham dataset [78].

Support **Vector Machines (SVM)**: Models for both regression and classification, excelling in high-dimensional data handling [79]. SVMs are commonly used in medical imaging, particularly in the classification of images for diseases like cancer [80]. They are also used in genomics for gene expression classification [81].

Logistic Regression: A statistical model for binary classification, employing the logistic function to model probabilities [82]. Logistic regression is widely used to identify risk factors for diseases [83]. It is also used in predictive modeling for patient outcomes [84].

Neural Networks: Versatile models adept at high-dimensional, structured data like images and text [85]. Deep learning models, a subset of neural networks, are increasingly used in diagnostic applications, including the interpretation of medical images such as X-rays and MRIs [86].

Recurrent Neural Networks (RNNs): Designed for sequence data, these networks contain loops for information persistence [87]. RNNs are used in natural language processing tasks in healthcare, such as medical report generation and predictive text functionalities in electronic health records [88].

CNNs: Specialized for image tasks, they learn spatial feature hierarchies [89]. CNNs are predominantly used in medical image analysis, including the detection and diagnosis of various diseases like cancer through histopathological images [90].

Graph Neural Networks (GNNs): Operate on graph data, capturing node dependencies for tasks like node and graph classification [91]. GNNs are used in drug discovery for predicting molecular interactions and in the analysis of biological networks [92].

Transformers: Rely on self-attention, excel in sequential data tasks, and are highly parallelizable [93]. Transformers are used in medical language understanding tasks, such as automated medical coding and extraction of medical entities from unstructured text [94].

3.4. Advantages and limitations

In the biomedical fields, AI serves as a double-edged sword, offering groundbreaking advancements while posing significant challenges. On one hand, AI revolutionizes personalized medicine by leveraging vast datasets to identify optimal treatments based on individual genetic makeup [95]. It also accelerates drug discovery by predicting molecular interactions, thereby reducing both time and financial costs [96]. Furthermore, AI enhances healthcare accessibility in underserved regions and streamlines administrative processes, improving overall system efficiency [97,98]. It also acts as a decision-support tool for clinicians, particularly in image-based specialties like radiology [99,100]. On the other hand, the technology's effectiveness is heavily dependent on the quality and availability of training data [101]. Biased or incomplete datasets can result in flawed predictions. The "black box" nature of AI algorithms, especially deep learning models, hampers transparency and trust among healthcare professionals [102]. Additionally, AI systems often lack generalizability, performing inconsistently when applied to diverse populations with varying genetics and healthcare practices [103]. Ethical and regulatory challenges, such as accountability for AI errors and ensuring equitable healthcare outcomes, add another layer of complexity [104]. In summary, while AI holds the promise of revolutionizing biomedicine, its successful implementation requires overcoming data, ethical, and regulatory hurdles. A balanced approach that addresses these challenges is crucial for unlocking its full potential in this domain.

4. AI-enabled organoids

4.1. Overview of AI-enabled organoids

With the preceding discussion as foundation, interfacing organoids with AI is an emerging field in the organoids research. By interfacing these organoids with AI, researchers aim to create more sophisticated and accurate models of human organ function and disease. This can provide a powerful tool for drug discovery, disease diagnosis, and treatment development. Herein, we aim to expound upon the paramount importance of AI for the advancement and augmentation of AI-Enabled organoids. Our focus is guided by five pivotal dimensions: rapid screening of construction strategies, cost-effective extraction of multi-scale image features, streamlined analysis of multi-omics data, and precise preclinical evaluation and application (Fig. 5). The discourse within these domains furnishes us with an all-encompassing framework to probe deeper into the potential of AI, thereby facilitating an expedited and optimized development of AI-Enabled Organoids.

In the first instance, rapid screening of construction strategies serves as an effective tool for pinpointing optimal experimental designs and implementation strategies. Secondly, cost-effective extraction of multi-scale image features empowers us to dissect and comprehend the structure and function of organoids from a myriad of viewpoints and hierarchical levels. Thirdly, streamlined analysis of multi-omics data is instrumental in grasping the intricacies of organoids across numerous facets such as gene expression, proteomics, and metabolomics. In the penultimate place, precise preclinical evaluation and application offer critical insights to forecast the performance and impact of AI in real-world clinical settings. Lastly, we will explore strategies to put these theories into practice more effectively, thereby harnessing the full potential of AI in the evolution of AI-Enabled organoids.

4.2. Rapid screening of construction strategies in AI-enabled organoids

In the context of organoid research, construction strategies refer to the methodologies and techniques used to create these miniaturized and simplified versions of organoids. AI can play a crucial role in this process by helping to optimize these strategies. Machine learning algorithms can analyze large amounts of data to identify the most effective methods for synthesizing matrix gel, discerning the spatial structure of matrix gel, fine-tuning cell culture conditions, identifying active inducing factors, and assessing external stimuli. This can lead to more efficient and higher quality organoid construction.

As depicted in Fig. 6a, historically, the field of matrix gel research has evolved through three major scientific paradigms. Empiricism: Traditional methods focus on iterative adjustments of parameters like monomer selection and cross-linking methods. While effective, this approach is resource-intensive. Theory: The second paradigm shift involved structure-performance models that apply principles of kinetics and thermodynamics to understand matrix gel formation. However, these models are not universally applicable. Computation: The advent of computational methods like density-functional theory (DFT) and classical molecular dynamics (MD) simulations marked the third paradigm, providing atomic-level insights but requiring substantial computational resources.

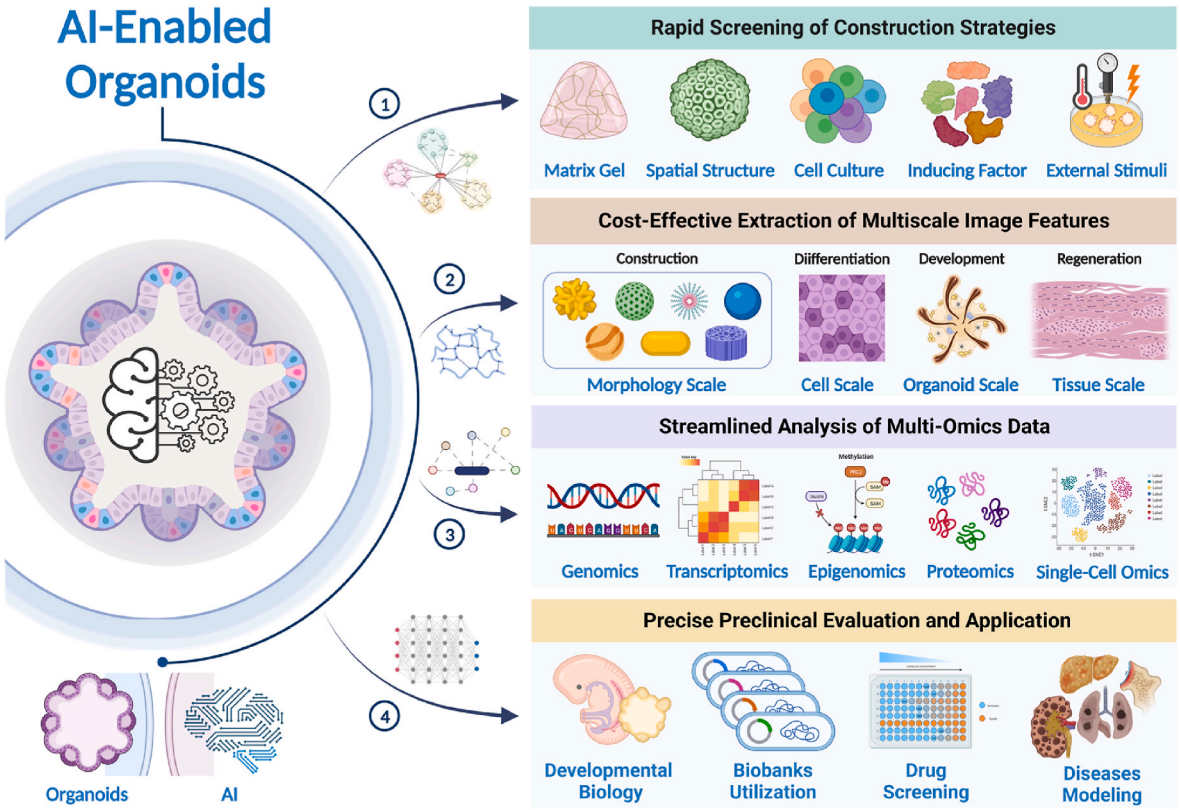

Fig. 5. Definition and content of AI-Enabled organoids.

As an auxiliary approach, the implementation of AI and machine learning methodologies is instigating the fourth paradigm shift (data-driven science) in matrix gel research, presenting new perspectives and feasible solutions for accelerating innovation in matrix gel design and development. By utilizing existing datasets with data-driven models, machine learning can automatically discern implicit patterns and extract valuable information, accounting for the inherent complexity of matrix gel mixtures and their properties. Therefore, machine learning is being utilized as a potent instrument to elucidate process-structure-property-performance relationships, identify matrix gel formation and degradation mechanisms, and support matrix gel material design and discovery, in conjunction with high-throughput experimentation and computation. The application of machine learning in matrix gel science has been explored for various types of gels, including hydrogels, aerogels, and xerogels. As machine learning models become increasingly user-friendly, it is anticipated that the applications of machine learning will continue to broaden within the matrix gel domain to facilitate data analysis and stimulate scientific discovery.

The advent of the fourth paradigm in scientific research, characterized by data-intensive scientific discovery, has ushered in unprecedented opportunities for the field of biomaterials. While we acknowledge that the data processed by AI algorithms are fundamentally derived from experimental studies, it is imperative to recognize that AI serves a role beyond mere data processing. AI is not merely a backend tool for automating data analysis; it is an enabler for a new paradigm in material design. Traditional experimental approaches often fall short in capturing the multi-dimensional interactions between variables such as chemical composition, mechanical properties, and biological responses. AI algorithms, conversely, excel in modeling these complex relationships, thereby providing a robust framework for predictive analytics and hypothesis generation. Moreover, AI algorithms can predict optimal material compositions and structures, which can subsequently be validated through experimental protocols. This creates a dynamic feedback loop, where AI continually refines and directs experimental design based on newly acquired data and insights. In summary, AI's role in biomaterials research extends beyond automation engineering and backend data processing. It acts as a catalyst for both theoretical advancements and practical applications, thereby substantiating its position as a cornerstone in the fourth paradigm of biomedical research.

Machine learning-guided personalized customization of matrix gel: In the construction strategy of organoids, the selection of matrix materials is the first and most critical step [105]. Current organoid construction is divided into scaffold-free self-organization methods and co-culture with active biomaterials. The scaffold-free self-organization method is limited by insufficient nutrient and oxygen supply, and the volume cannot exceed 500 μm, which is not suitable for widespread clinical application [106,107]. Therefore, the construction of organoids requires bioactive matrix hydrogels as support to achieve controllable tissue morphology and break through larger volume limitations. The construction of organoids generally relies on Matrigel, an animal-derived extracellular matrix, which poses several issues such as poor reproducibility, variability, and potential immunogenicity [108–116]. Synthetic/hybrid hydrogel matrices have emerged as a promising alternative owing to their relatively low cost, good mechanical properties, ease of purification, and handling [117–120]. These synthetic matrices more closely resemble the native structural and functional properties of human organs, thereby improving the quality and potential applications of the organoids [121] (Table 1). Nevertheless, the synthesis of these hydrogels can be complex due to their different chemical compositions, cross-linking mechanisms, and physical structures, requiring multiple attempts to optimize parameters for individual experiments.

Machine learning offers a powerful solution to the complex challenges inherent in designing hydrogels as biomaterials for specific applications, including organoid research. The performance of these polymers is influenced by a multitude of factors such as chemistry, structure, and biomechanical properties. Machine learning algorithms

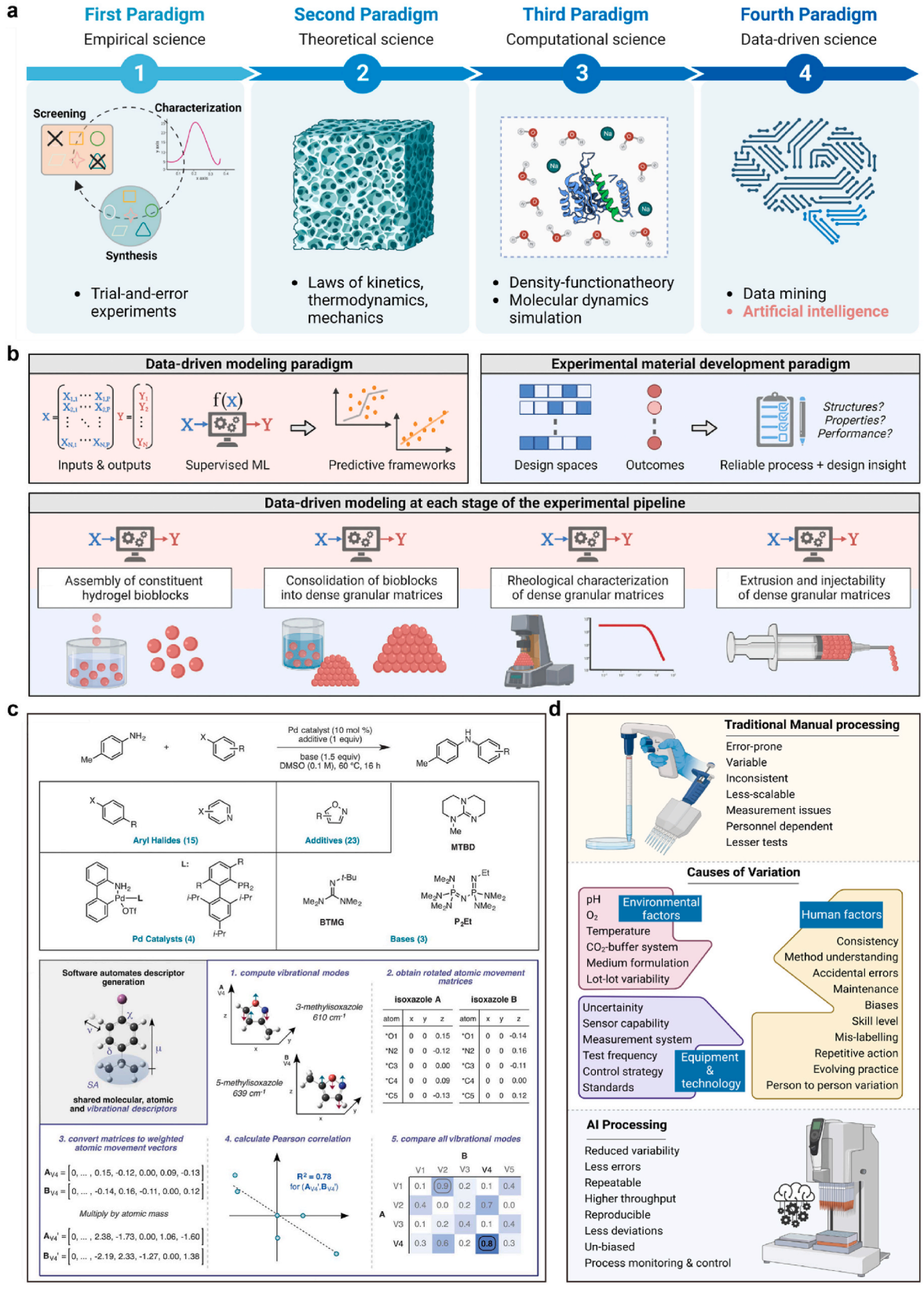

Fig. 6. Machine learning-guided rapid screening of construction strategies. (a) Four paradigms of matrix gel synesthesia: empirical, theoretical, computational, and data-driven. (b) Illustration of an integrated data-driven experimental pipeline for soft granular matrices. Copyright 2023, Cell Press. (c) Application of machine learning to reaction prediction. Copyright 2018, American Association for the Advancement of Science. (d) Comparison of manual and AI enabled strategies for screening of cell culture conditions.

Table 1
Summary of hydrogel types used for organoids engineering [121].

Hydrogels types	Major properties	Cell source	Organoid types	Applications
Natural				
Matrigel	•Biodegradability •Derived from mouse sarcoma •Promoting cell growth and self-organization • Undefined compositions • Not conducive to controlled modifications • Risks of immunogen and pathogen transfer • Poor mechanical properties	hPSCs (hiPSCs [108–116] and hESCs [108–110,112,113] mASC mASC/hASC epithelial progenitors cell hESC [122]/mESC [123]	Cerebral organoids Lung bud Gastric Colonic Kidney Liver bud Alveolar Intestinal Liver/pancreas Prostate Retinal optic cup	• Studying development of brain-region specific organoids [114] • Modeling interactions between brain regions [108] • Probing mechanisms of microcephaly from patient-derived cerebral organoid [115] • Modeling Zika virus infection and drug screening [114] • Studying syncytial virus infection [124] • Modeling intractable pulmonary fibrosis from patient derived lung bud organoids [124] • Studying gastric development process [110] • Modeling *Helicobacter pylori* infection [110] • Exploring colorectal cancer using patient-derived organoids with APC mutation [125] • Testing responses of patient-derived organoids to XAV939 and rapamycin [125] • Modeling renal disease using proband-derived iPSCs with IFT140 mutations [126] • Generating vascularized and functional liver from an iPSC-derived organ bud transplant [127] • Generating efficiently and long-term expansion of alveolar organoids [128] • Building crypt–villus structures [129] • Establishing adult liver and pancreas [130] • Generating prostate organoids [131] • Testing patient-derived tumor organoids responses to Akt inhibitor and mTOR inhibitor [131] • Dissecting retinal morphogenesis [132] and optic-cup morphogenesis [133]
Collagen	• Exhibiting structural and mechanical proper- ties reminiscent of native tissues • Enzymatically degraded • Containing cell adhesive domains • Facilitating cell growth and differentiation	hPSCs [133,134] hASCs [135]	Kidney Ventricle-like cardiac Mammary gland	• Modeling PKD cystogenesis [136] • Modeling pumping human heart chamber *in vitro* [137] • Pharmaceutical testing [137] • Generating branched structures resembling terminal ductal-lobular units (tdlus) [135]
Alginate	• Immediate gelation at mild conditions • Conducive to controlled modifications • Degradable • Finely adjustable architectures • No inherent cell instructive properties	hiPSCs [136,138] hPSCs	Brain Intestinal	• Modeling brain development [136,138] • Probing fetal alcohol spectrum disorder in iPSC-derived organoids [136,138] • Modeling HIO development resembling fetal intestinal compared with Matrigel [139]
Fibroin	• Biocompatible • Degradable • Possibility of carrier other factors	hiPSCs/kidney progenitors	Kidney	• Acting as scaffolds to develop kidney organoids with epithelial characteristics [109] • Engrafting in vivo [109]
Synthetic				
Amikagel	• Defined compositions • Functionalization with chemical modification • Tunable physiochemical properties • Nonadhesive • High mechanical stiffness	hESC	Islet	• Forming homogenous islet [117] • Generating self-organized multicellular pancreatic organoids [117]
PEG	• Cell-repellent • Promoting cell-to-cell and cell-to-ECM interactions • Tunable mechanical properties • Bearing adhesive peptide sites	hiPSCs	Cardiac	• PEG-based patterning forming confinement for organoids self-organization [118] • Studying embryonic spatial patterning early cardiac development [118] Testing drug-induced developmental toxicity [118]
Eight-arm PEG	• Defined compositions • Enabling chemical modification • Tunable physical properties • Existing adhesive peptide sites	hASC/mASC hESC Pancreas progenitors	Intestinal Neural tube Pancreas	• Supporting intestinal and other organoids generation [119] • Regulating stiffness for intestinal stem cell maintained and intestinal organoids generation [119] • Studying the discrete action of extrinsic factors Pancreas progenitors in organogenesis • Modeling neural tube development [140] • Deconstructing pancreas development under artificial niche [141]
PEG-DA	• Defined compositions • Functioned with ECM protein	hiPSCs ASC (SGSCs)	Liver Salivary glands	• An inverted colloidal crystal PEG scaffold for bioengineered liver organoids generation [111] • Modeling infection in liver organoids [111]

(*continued on next page*)

Table 1 (*continued*)

Hydrogels types	Major properties	Cell source	Organoid types	Applications
	• Tunable mechanical properties (varied mechanical stiffness) • Scalable structure			• Transplanting liver organoids in vivo to form vascularized tissue [111]] • Generating organoids with salivary gland marker and displayed$\alpha\alpha$-amylase secretion [142] • Engrafting organoids into nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice [142]
PEG-4MAL	• Defined compositions • High cytocompatibility • Well-defined structure • Incorporation of biofunction groups • In situ gelation	hPSCs	Intestinal	• Supporting generation of intestinal organoids [115] • Serving as an injection vehicle in HIO engraftment [115] • Improving colonic wound repair [115]
PLGA	• Defined compositions Biodegradability • Chemically defined copolymer • Defined architectures • Microporous • Improving cellular survival and function	hPSCs [122,124,143]	Cerebral Lung	• Promoting elongated cerebral organoids generation [143] • Modeling guided cortical development [143] • Provided a niche for host transplantation [122] • Promoting HLO maturation in vivo [122]
PAm	• Defined compositions • Enabling chemical modification • Tunable mechanical properties		Kidney	• Acting as a CAM-like substrate in kidney organoids transplanting in chick [124] • Engrafting in vivo [124]
Hybrid				
HA-Na/chitosan	• Defined compositions • Considerable tunability • Controlled physical and chemical properties	hiPSCs	Cerebral	• Generating rapidly induction of cerebral organoids [144] • Modeling adrenoleuko dystrophy disease from patient-derived organoids [144]
Fibrin/laminin	• Enzymatical degradability • Defined composites • Suitable physical support • Occurring RGD adhesion domains • Chemical functionalization	mASC/hASC	Epithelial (liver intestinal, and pancreas)	• Generating epithelial organoids [120] • Acting as a defined equivalent to ECM [120]
Matrigel/collagen I	• Similar to natural ECM • Promoting cell differentiation	hPSCs	Human blood vessel	• Generating blood vessel organoids formation [145] • Modeling diabetic vasculopathy [145]
Laminin/fibronectin/HA/collagen I	• Defined composites • Similar to natural ECM	ASC	Mammary gland	• Studying effects of Cadmium on patient-derived breast stem cell proliferation and differentiation [146]
PEG-NHS/collagen I/PAm	• Tunable mechanical stiffness	mESC	Cardiovascular	• Forming matrix rigidity-modulated cardiovascular [147]

can sift through large datasets to identify correlations between these variables and the observed performance, thereby providing valuable insights for design optimization. In the context of organoids, the matrix gel is a foundational hydrogel whose properties significantly affect stem cell activity and organoid functionality. Machine learning can be instrumental in guiding the synthesis of these matrix gels by analyzing how different polymer compositions influence stem cell behavior and organoid formation. The integration of machine learning into this design process can accelerate the development of tailored matrix gels, improve the efficiency of organoid research, and open new avenues for personalized medicine. Indeed, machine learning has been explored to investigate the formation ability of peptide hydrogels, the cell adhesion and protein adsorption profiles on polymer surfaces, the foreign body response to polymers, and the preparation of gene delivery vehicles [148]. Table 2 shows examples of applications of machine learning in synthetic hydrogels. Overall, machine learning stands as a pivotal tool in advancing the field of organoid research by optimizing the design of critical biomaterials like matrix gels.

A recent study introduces a new approach to designing soft granular matrices with predictable structures and properties for use in biomedical applications, using a modular machine learning method [149]. The authors report the assembly of hydrogel bioblocks and their application in granular matrices with emergent non-linear rheological behavior and functional extrudability (Fig. 6b). They also demonstrate the use of their modular machine learning approach to derive data-driven predictive models and design rules, making it generalizable and applicable for data-driven advancement of any complex material system.

A clear illustration of machine learning's application in hydrogel production is found in a research project that utilized a machine learning model trained on data derived from the photodegradation process of more than 900 distinct hydrogel pads [150]. This model served as an automated tool for decision-making in the creation of functional hydrogels. Significant advancements in the response properties of the hydrogels were realized through repeated model enhancements guided by Bayesian Optimization. This development not only broadened the range of material properties achievable within the chemical domain of hydrogels but also facilitated an efficient and cost-effective optimization of these properties. These research endeavors underscore the considerable potential of machine learning in the realm of hydrogel synthesis, emphasizing the advantage of merging high-throughput experimental approaches with intelligent optimization algorithms for the effective optimization of materials.

In addition to the synthesis process of matrix gels, another key aspect that holds immense importance is the prediction of their reactions. The ability to anticipate the performance of a synthetic reaction in a multi-dimensional chemical space can lead to significant advancements in the field [151]. Particularly, this can be a game-changer in scenarios where traditional experimental methods prove to be time-consuming and resource-intensive. As an illustration of this, an enlightening study took machine learning applications in material science a step further [152]. The authors utilized machine learning to predict the outcome of a specific reaction in organic chemistry (Fig. 6c). In the presented study, code was formulated to calculate and derive atomic, molecular, and vibrational characteristics for the constituents involved in a palladium-

Table 2
Examples of application of machine learning in synthetic hydrogels [148].

Input parameters	Input property	Output target property	Output assay	No. of experiments	Key results obtained
Peptides prepared via Ugi reaction of 31 monomers	Chemistry	Formation ability of peptide hydrogels	Hydrogel formation	2304	• Peptide hydrogels • Identify top 20 descriptors that determine formation of peptide hydrogels
Polyacrylate from 22 acylate monomers	Secondary-ion mass ToF-SIMS spectra or 23 molecular descriptors	Cell adhesion behaviors	Colony-formation frequency	496	• Adhesion behaviors of human embryoid body •Identify the effects of structure units on cell adhesion behaviors
Self-assembled monolayers (SAMs)	10 structure descriptors	Protein adsorption	Fibrinogen adsorption	Two datasets: 72 from single lab and 133 from multilab	• Fibrinogen adsorption behaviors on polymers • Identify the effects of terminal groups on cell adhesion behaviors
Fibroin	Molecular descriptors	Foreign body response	A composite dependent variable	144 homopolymer for screening and 400 copolymers for ML	• Foreign body response to polymers • Identify the effects of structure units on foreign body response
Polymerization of different acrylates with different amines	Chemistry	Gene delivery to cells	Cell transfection experiments	12 000	• Optimized nanoparticles • Identify properties that lead to high transfection

catalyzed Buchwald-Hartwig cross-coupling of aryl halides with 4-methylaniline. This procedure took place in the presence of an array of potential inhibitory additives. A random forest machine learning model was then used to predict the performance of the reaction and infer underlying reactivity. The significance of this work lies not only in its immediate findings but also in the broader implications for the field of organic chemistry, which has traditionally relied heavily on laborious trial-and-error experimentation.

Machine learning-guided spatial structure discerning of matrix gel: In the realm of organoids construction, discerning the spatial structure of the matrix gel is another critical aspect. This involves understanding the three-dimensional arrangement of the matrix gel, which is crucial for the successful growth and development of organoids. The spatial structure of the matrix gel can influence the behavior of cells, including their proliferation, differentiation, and migration. Therefore, accurately discerning the spatial structure of the matrix gel is essential for the optimization of organoids construction strategies.

In the context of matrix gel spatial structure discerning, machine learning can be used to analyze imaging data of the matrix gel, identify patterns in the spatial arrangement of the gel, and predict how changes in this arrangement might affect the behavior of cells within the organoids. For instance, CNNs, a type of machine learning algorithm that excels in image analysis, can be used to analyze three-dimensional imaging data of the matrix gel. The CNN can be trained to recognize different spatial arrangements of the gel and predict how these arrangements might influence cell behavior. This could help researchers optimize the spatial structure of the matrix gel to promote the growth and development of organoids. Moreover, machine learning can also be used to automate the process of spatial structure discerning. This could significantly speed up the process, allowing researchers to quickly optimize the spatial structure of the matrix gel and improve the efficiency of organoids construction. In brief, machine learning-guided spatial structure discerning of matrix gel could revolutionize the field of organoid research, providing a powerful tool for the optimization of organoids construction strategies. By harnessing the power of machine learning, researchers can gain a deeper understanding of the spatial structure of the matrix gel and how it influences the behavior of cells within organoids, paving the way for the development of more sophisticated and accurate models of human organ function and disease.

Machine learning-guided fine-tuning of cell culture conditions: Fine-tuning of cell culture conditions can significantly influence the success of organoids development. These conditions include factors such as temperature, oxygen concentration, pH, nutrient availability, and the presence of growth factors, among others. Each of these factors can have a profound impact on cell behavior, including their proliferation, differentiation, and survival. Therefore, optimizing these conditions is crucial for the successful construction of organoids. However, the traditional approach for optimizing of cell culture conditions has several limitations. The process of developing and optimizing cell culture protocols is a labor-intensive, error-prone process that involves a significant degree of trial and error. It is subject to variability and inconsistency, largely due to environmental factors, equipment and technology limitations, and human factors. This variability can result in differences in cell behavior and phenotype, which can subsequently influence experimental outcomes and the effectiveness of cell-based therapies. These issues are amplified in the context of organoids, where the production of specific cell types in large quantities is required. Variability and inconsistency in cell culture protocols can potentially affect the safety and efficacy of these cell-based treatments, making it essential to establish reliable, standardized cell culture processes.

The implementation of AI in cell culture offers a solution to these challenges. By automating the cell culture process, it is possible to reduce variability and minimize errors, leading to more consistent, repeatable results. Additionally, automation enables higher throughput, allowing for the simultaneous optimization of multiple culture conditions and the production of larger quantities of cells. The study by Kanda et al. exemplifies how this can be achieved. In their study, the investigators leveraged an integrated system of robotics and AI to fine-tune cell culture protocols and consistently generate particular cell types [153]. The AI system could characterize the cultured cells and formulating an ideal cell culture protocol based on the accumulated data, thereby eliminating the necessity for human involvement in these stages. This approach represents a significant advancement in the field. It not only improves the efficiency and accuracy of cell culture protocols but also greatly enhances their reproducibility. Such improvements could have profound implications for regenerative medicine and other biomedical applications, enabling the development of more effective, reliable cell-based treatments. The incorporation of AI in cell culture thus marks a pivotal step toward the reproducible manufacturing of organoids and organoids-derived products for regenerative treatments.

Machine learning-guided identification of active inducing factors: In the context of organoid construction, the selection and combination of various growth and inducing factors play a critical role in the growth and differentiation of organoids [154]. These factors, which

include proteins like WNTs, VEGF, and TGF-β, can significantly influence cell behavior, including their proliferation, differentiation, and survival. Therefore, identifying the optimal set of active inducing factors is crucial for the successful construction of organoids. However, the current process of identifying these factors is often inefficient and time-consuming. It typically involves extensive literature research and a series of orthogonal experiments to test different combinations of factors. This approach not only requires a significant amount of time and resources but also has a low success rate due to the complexity and variability of biological systems.

In the context of active inducing factors, machine learning can be used to analyze data from previous experiments, identify the most effective factors for promoting cell growth and organoids development, and predict how different combinations of these factors might affect the behavior of cells within the organoids. A recent study describes a novel approach to predict the fate of neural stem cells using deep learning [155]. The authors propose that deep neural network models can extract small features from large-scale datasets to reliably identify the differentiation of neural stem cells, even in the early stages of culture. This article describes the process of selecting key factors that influence neural stem cell differentiation. The authors used a combination of literature review and experimental validation to identify a set of candidate factors that were then screened using statistical analysis. The results showed that several factors, including Wnt3a and BMP4, were significantly associated with neural stem cell differentiation. In brief, the study highlights the importance of identifying key factors that influence neural stem cell differentiation and demonstrates how machine learning can be used to develop predictive models based on these factors. This method has the potential to be applied to other types of stem cells and could lead to significant advances in organoids.

Machine learning-guided assessment of external stimuli : In the field of organoid research, the role of external stimuli such as mechanical, optical, and electrical stimuli is increasingly recognized as crucial for the growth and differentiation of organoids. These stimuli can significantly influence cell behavior, including their proliferation, differentiation, and survival. Therefore, identifying the optimal type, intensity, and duration of these stimuli is a critical aspect of organoids construction. Similarly, the current process of identifying and optimizing these stimuli is often inefficient and time-consuming. It typically involves extensive literature research and a series of orthogonal experiments to test different types and combinations of stimuli. This approach not only requires a significant amount of time and resources but also has a low success rate due to the complexity and variability of biological systems.

In the context of external stimuli, machine learning can be used to analyze data from previous experiments, identify the most effective types and combinations of stimuli for promoting cell growth and organoid development, and predict how changes in these stimuli might affect the behavior of cells within the organoids. For instance, a study introduces an epidermal piezoresistive structure that utilizes deep learning-assisted data translation to accurately evaluate and assess various external stimuli [156]. The customized regression and classification model can predict the magnitude of the external force, epidermal hardness, and object shape with high accuracy. The integration of silicon piezoresistors and deep learning data processing improves the accuracy of the sensor, making it a promising tool for physiological parameter monitoring in medical and health monitoring fields. The study emphasizes the use of machine learning techniques to predict external stimuli accurately. By integrating deep learning algorithms into the sensor design, the researchers were able to develop a customized regression and classification model that can predict various parameters with high accuracy. This approach has significant implications for physiological parameter monitoring, as it provides a more accurate and convenient way to identify and optimize these stimuli in organoids research.

4.3. Cost-effective extraction of multiscale image features in AI-enabled organoids

The construction of organoids begins with the synthesis of matrix hydrogels. The morphological features of these hydrogels have a significant impact on stem cell activity within the organoids, making rapid and efficient analysis of hydrogel morphology crucial. Following this, the differentiation of stem cells is key to organoid construction, and analysis at the single-cell scale can provide predictive insights into organoid functionality. Once the organoid is formed, morphological analysis during its dynamic development becomes essential. Finally, for in vivo applications of organoids, extensive tissue slice analysis is required.

To date, the cost-effective extraction of multiscale image features from high-throughput imaging data remains a significant challenge in the field of biomedicine. Herein, image analysis of organoids is particularly difficult, as the collection of images for organoids is usually at a single focal plane, and there are significant differences in size and shape between organoids of the same tissue type and culture samples. Although cells can be genetically modified to express fluorescent proteins that facilitate image segmentation and tracking, this process undoubtedly increases experimental time and complexity and may alter the cell dynamics of the original sample. Automating this process can improve the precision and efficiency of feature extraction, which is crucial in organoids research. Machine learning can be used to automate the process of extracting features from images at various scales. Therefore, there is an urgent need to develop an automated image analysis tool using machine learning that can dynamically assess the characteristic changes during the growth and development of organoids without the need for fluorescence or transgenic labeling.

Machine learning-guided image analysis of in morphology scale: As aforementioned, the involvement of matrix gel materials is necessary in the construction of organoids, and the morphological analysis of these materials is crucial for their biological performance [157]. The morphology of the matrix gel can significantly influence the growth and development of the organoids. Traditional means often require manual identification and processing, which can be error-prone, inefficient, and subjective. Therefore, the introduction of artificial intelligence is needed.

Machine learning algorithms can be trained on large datasets of images of matrix gel materials, learning to recognize and quantify various morphological features such as porosity, fiber alignment, and fiber diameter. These algorithms can then be used to analyze new images of matrix gel materials, providing rapid and accurate morphological analysis. Moreover, machine learning algorithms can be integrated into a feedback loop, where the results of the morphological analysis are used to guide the synthesis of new matrix gel materials. This approach can lead to the development of optimized matrix gel materials for organoids construction, improving the quality and reproducibility of the organoids. In addition to improving the efficiency and accuracy of morphological analysis, machine learning can also reduce the subjectivity associated with manual analysis. By using objective, quantitative measures of morphology, machine learning can provide more consistent and reliable results, reducing the potential for bias and error. A recent study discusses a new method for analyzing the morphologies of nanoparticles using machine learning-based electron microscopy image analysis [158]. The authors explain that precise characterization of the morphological properties of nanomaterials is essential for understanding their physical and chemical properties, such as optical, electronic, and catalytic aspects. However, analyzing nanoparticles quantitatively in a statistical manner is challenging. The proposed method aims to address this challenge by using a genetic algorithm to identify the most relevant features of nanoparticle morphology and then using machine learning techniques to classify them accurately (Fig. 7a). The significance of this research lies in its potential to expand nanoparticle-related research into the statistical domain for use in big data analysis. This

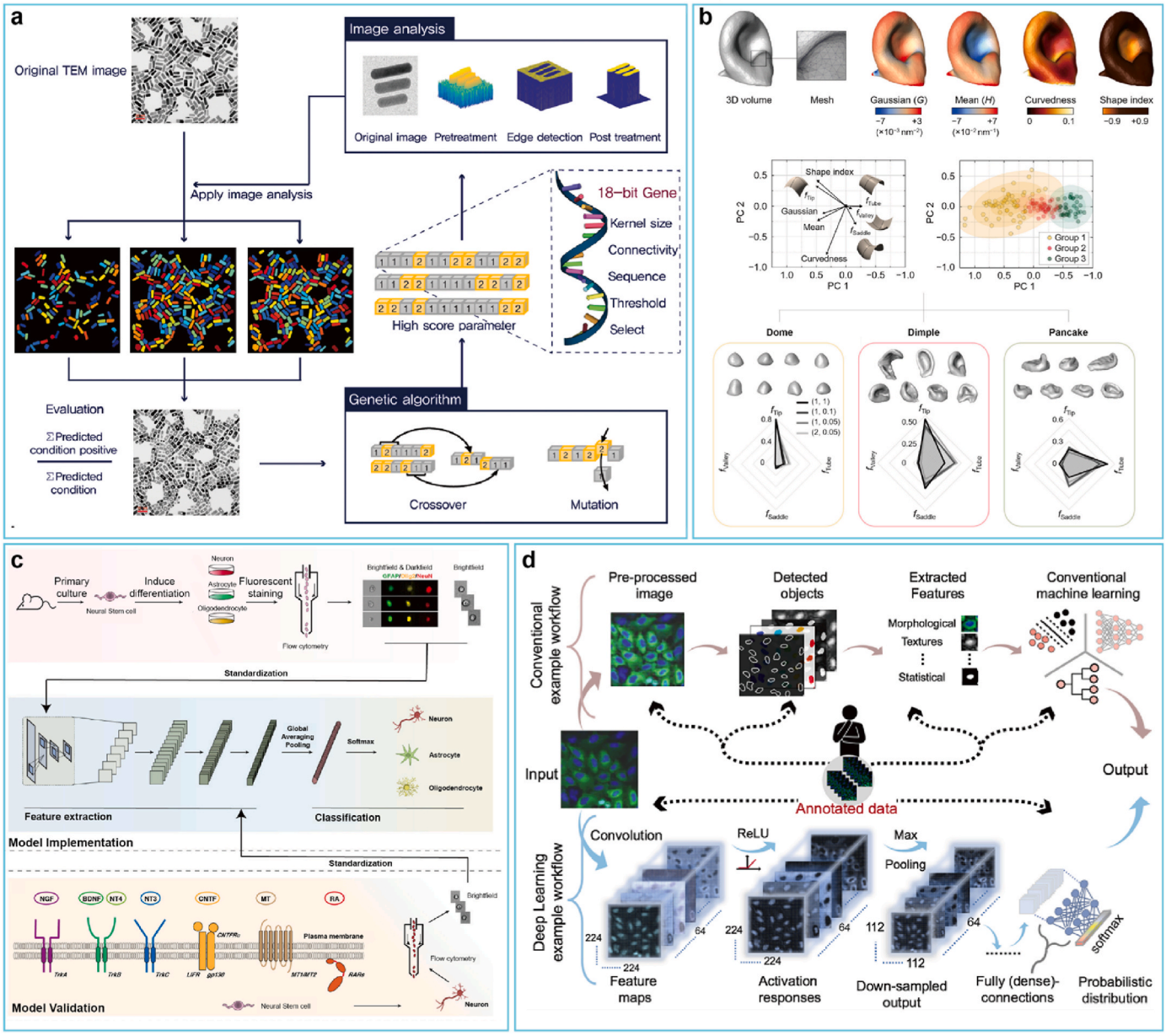

Fig. 7. Machine learning-guided image analysis of in morphology and cell scale. (a) A method for mass-throughput analysis of the morphologies of nanoparticles by applying a genetic algorithm to an image analysis technique. Copyright 2020, American Chemical Society. (b) Machine learning-based nanomorphology grouping of crumples. Copyright 2022, American Association for the Advancement of Science. (c) Deep learning-based platform for neural stem cells differentiation identification. Copyright 2021, Nature Publishing Group. (d) Overview of conventional versus deep learning workflows in image cytometry. Copyright 2019, International Society for Advancement of Cytometry.

method could become a powerful tool for researchers studying nanomaterials and their properties. Another study explores the mechanism and performance relevance of nanomorphogenesis in polyamide films (Fig. 7b). The authors use advanced techniques such as electron tomography, reaction-diffusion theory, machine learning, and liquid-phase atomic force microscopy to study the three-dimensional crumpling of polyamide membranes [159]. The goal is to inspire new strategies for diversifying material structure and functionality by exploring biological morphogenesis concepts. The authors hope that their findings will lead to the development of soft nanomaterials with improved properties and potential applications in various fields.

Machine learning-guided image analysis in cell scale: In the process of organoids functional assessment, many cell experiments are involved, generating a vast amount of image data based on optical microscopy. Cellular features such as cell count, cell morphology, and cell behavior can provide valuable insights into the functionality of the organoids. For example, changes in cell morphology can indicate cellular differentiation, while changes in cell behavior can suggest cellular response to environmental stimuli. Therefore, accurate and efficient analysis of cellular images is essential for the functional assessment of organoids. Traditional analysis methods have significant drawbacks, including time-consuming manual counting, subjective bias, and the inability to accurately quantify complex cellular features. The introduction of AI, specifically machine learning, can address these issues.

Machine learning algorithms can be trained on large datasets of cellular images, learning to recognize and quantify various cellular features. These algorithms can then be used to analyze new cellular images, providing rapid and accurate cellular analysis. This can significantly improve the efficiency of organoid assessment, reducing the time

and effort required for manual analysis. A recent study describes the use of deep learning to predict the fate of neural stem cells (NSCs) during differentiation [155]. The authors note that while NSC differentiation is critical for potential cell-based therapies for central nervous system diseases, it is complex and not yet clearly established, especially at the early stages. They hypothesize that deep learning could extract important information from large-scale datasets to create a reliable model for identifying NSC fate. The study found that their deep neural network model was able to accurately predict NSC differentiation outcomes, even at early stages of culture (Fig. 7c). The significance of this research lies in its potential to improve our understanding of NSCs differentiation and pave the way for more effective cell-based therapies for CNS diseases. Another review summarizes the application of conventional versus deep learning workflows to analysis of microscopy image data of cell samples [160]. The conventional workflow for image cytometry requires human input at each step, such as parameter tuning and feature engineering using annotated data. These steps require a significant amount of human effort and time, and may be subject to subjective factors. In contrast, the deep learning workflow only requires annotated data to automatically optimize features (Fig. 7d). Deep learning methods can automatically extract features from images without the need for manual feature design and selection. Therefore, compared to traditional methods, deep learning methods can process image cytometry data more quickly and accurately while reducing the impact of human intervention.

Machine learning-guided image analysis in organoids scale: Organoids features such as size, shape, internal structure, and the presence of specific organoid markers can provide valuable insights into the functionality and maturity of the organoids. For example, the size and shape of an organoid can indicate its growth and development, while the internal structure can suggest the organization and differentiation of cells within the organoid. Therefore, accurate and efficient analysis of organoid-scale images is essential for the functional assessment of organoids. This process often involves the generation of a large amount of image data, typically acquired through techniques such as 3D imaging or confocal microscopy. Traditional analysis methods, which often involve manual identification and quantification of organoid features, are time-consuming, prone to subjective bias, and may not fully capture the complexity of organoid structures. The current problems

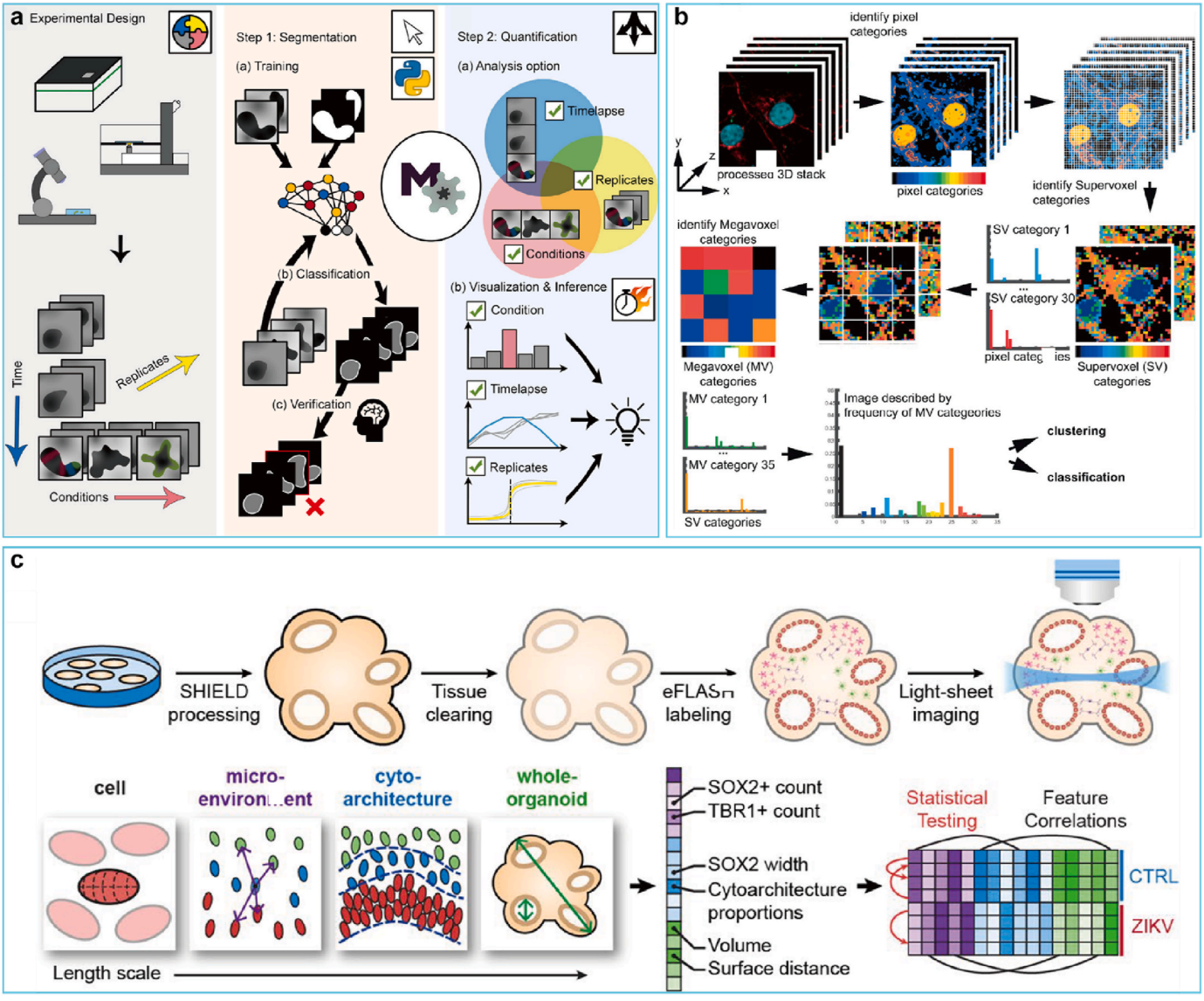

Fig. 8. Machine learning-guided image analysis of in organoids scale. (a) Workflow of MOrgAna, a Python based software that implements machine learning to segment images, quantify and visualize morphological and fluorescence information of organoids. Copyright 2021, The Company of Biologists Ltd. (b) Overview and validation of the image analysis algorithms called Phindr3D. Copyright 2021, Public Library of Science. (c) Pipeline for multiscale hyperdimensional analysis of organoids via SCOUT. Copyright 2020, Nature Publishing Group.

facing organoid image analysis are: How can the intricate structures within organoids be quantitatively described? Is it possible to conduct a large-scale analysis without compromising on the quality of phenotypic measurements? How can quantitative analysis be standardized to make organoid studies more relevant for translational medicine?

The introduction of AI, specifically machine learning, offers a promising solution to these challenges. Machine learning algorithms can be trained on large datasets of organoid-scale images, learning to recognize and quantify various organoid features. These algorithms can then be used to analyze multiple organoid-scale images, providing rapid and accurate organoid analysis. MOrgAna, a Python-based software that utilizes machine learning to analyze and segment images of organoids is reported recently [161]. The need for such a tool arises from the increasing use of organoids in biomedical research, which generates large volumes of image data that require rapid and automated analysis (Fig. 8a). MOrgAna addresses these queries by automating the analysis, thereby reducing human error and increasing the throughput; Providing a set of reliable, quantitative metrics that help in understanding organoid morphology and function; Enabling comparability across different imaging platforms, which is crucial for integrating data from multiple studies or clinical trials. Moreover, MOrgAna addresses this demand by providing an easy-to-use interface for users with little to no programming experience, while also offering customization options for advanced users. The software's versatility is demonstrated through its successful application to various *in vitro* systems imaged with different microscopes. Overall, MOrgAna represents a significant advancement in the field of organoid analysis, enabling researchers to efficiently interpret complex image data and accelerate their studies. A recent study presents a novel approach to analyzing cellular phenotypes using data-driven machine learning called Phindr3D (Fig. 8b). The researchers tackle the difficulties of determining a biologically relevant number of clusters for data set analysis and pinpointing individual organoid volumes within extensive image stacks [162]. The importance of this method is found in its quick and precise capability to scrutinize intricate biological culture systems, such as neuronal cultures and organoids, eliminating the requirement for cell segmentation. This method has the potential to greatly improve our understanding of cellular phenotypes and their role in various biological processes. Overall, this study provides valuable insights into the development of new techniques for analyzing complex biological data sets.

A significant impediment to implementing organoid-based screening studies has been the absence of stereotypic development and a shared coordinate system in organoids. To overcome this hurdle, one study introduces a state-of-the-art technology platform for 3D phenotyping of human cerebral organoids at multiple scales, which opens up unique possibilities to study human brain development and dysfunction [163]. The pipeline for single-cell and cytoarchitecture analysis of organoids using impartial techniques (SCOUT) is an early effort at comprehensive cerebral organoid characterization, facilitating a thorough 3D examination of entire organoids (Fig. 8c). Specifically, a U-Net model was trained using Keras to identify ventricles in the nuclear dye images of cerebral organoids. The revised U-Net model was trained using a mixed loss that included a weighted binary cross-entropy (WBCE) term and a Dice coefficient loss term. The automated ventricle segmentation achieved a Dice coefficient of 97.2% on the reserve test set. Utilizing SCOUT, the authors identified significant variances among experimental groups with consistent patterns among duplicates. This impartial high-throughput examination of antibody-labeled organoids represents a critical advancement in biological research, as data analysis continues to be a major obstacle to achieving organoid-based screening studies. Overall, this study enhances our understanding of human brain development and diseases by offering a fresh method to study the intricate cytoarchitectures of cerebral organoids and their potential uses in neuroscience research.

While there have been instances of software tools created for automated organoid image analysis, these platforms primarily employ conventional image processing methods, such as adaptive thresholding, to recognize organoid structures in sequences of microscope images. Despite their merits, these techniques necessitate manual adjustments for each image or are confined to bounding box detection, falling short in capturing potentially beneficial morphological information. Alterations in organoid structures, like peaks or protrusions, can unveil critical responses of organoids to external stimuli, which are likely overlooked by bounding box measurements. Based on this, there is an urgent need to develop new machine learning algorithms that can not only parse contours to label individual organoids but also accurately segment and track various cell morphologies, including osteoblasts, osteoclasts, endothelial cells, and macrophages. This will enable a more comprehensive understanding of organoid behavior, response to stimuli, and the various cell types involved in the organoid's growth and development, ultimately improving the efficiency and effectiveness of organoids research.

Machine learning-guided image analysis in tissue scale: The evaluation of tissue-level characteristics is a critical step in the realm of organoids research and development. This process often involves the generation of a large amount of image data, typically acquired through techniques such as histology or confocal microscopy. Tissue features such as cell organization, tissue architecture, and the presence of specific tissue markers can provide valuable insights into the functionality and maturity of the organoids. For example, the organization of cells into specific tissue structures can indicate organoids maturation, while the presence of specific tissue markers can suggest the successful differentiation of cells into specific tissue types. Therefore, accurate and efficient analysis of tissue-scale images is essential for the functional assessment of organoids. Traditional analysis methods, which often involve manual identification and quantification of tissue features, are time-consuming, prone to subjective bias, and may not fully capture the complexity of tissue structures. The introduction of machine learning, offers a promising solution to these challenges.

Machine learning algorithms can be trained on large datasets of tissue-scale images, learning to recognize and quantify various tissue features. These algorithms can then be used to analyze numerous tissue-scale images, providing rapid and accurate tissue analysis. This can significantly improve the efficiency of organoid assessment, reducing the time and effort required for manual analysis. Based on that, is propelled by the understanding that histological anomalies in cryosectioned tissue can obstruct quick diagnostic evaluations during surgical procedures. Although formalin-fixed and paraffin-embedded (FFPE) tissue yields superior slide quality, the method to acquire them is tedious and hence not practical for use during surgery. In response, the researchers designed a deep-learning model capable of swiftly converting the style of cryosectioned whole-slide images into that of FFPE tissue, thereby enhancing image quality (Fig. 9a). The paper elaborates on this deep-learning model and its efficacy [164]. The model is built on a generative adversarial network, which includes an attention mechanism to correct cryosection artifacts. Additionally, it employs a self-regulation constraint between the cryosectioned and FFPE images to retain clinically pertinent features. The relevance of this paper is the potential of this deep-learning model to transform quick diagnostic evaluations during surgery and elevate image quality. It could potentially aid doctors in diagnosing patients more accurately and creating a more informed basis for treatment plans.

Another study describes the development of an interpretable deep learning pipeline called im4MEC, which is designed to predict the four molecular classes in endometrial cancer using whole-slide images (Fig. 9b). The pipeline employes leverages self-supervised learning to isolate morphological attributes specific to endometrial cancer, and incorporates an attention-focused classification model for making predictions at the whole-slide-image level [165]. The goal of this pipeline is not only to accurately predict the molecular classification of endometrial cancer but also to identify morpho-molecular correlates and refine prognostication. In other words, im4MEC aims to provide a more

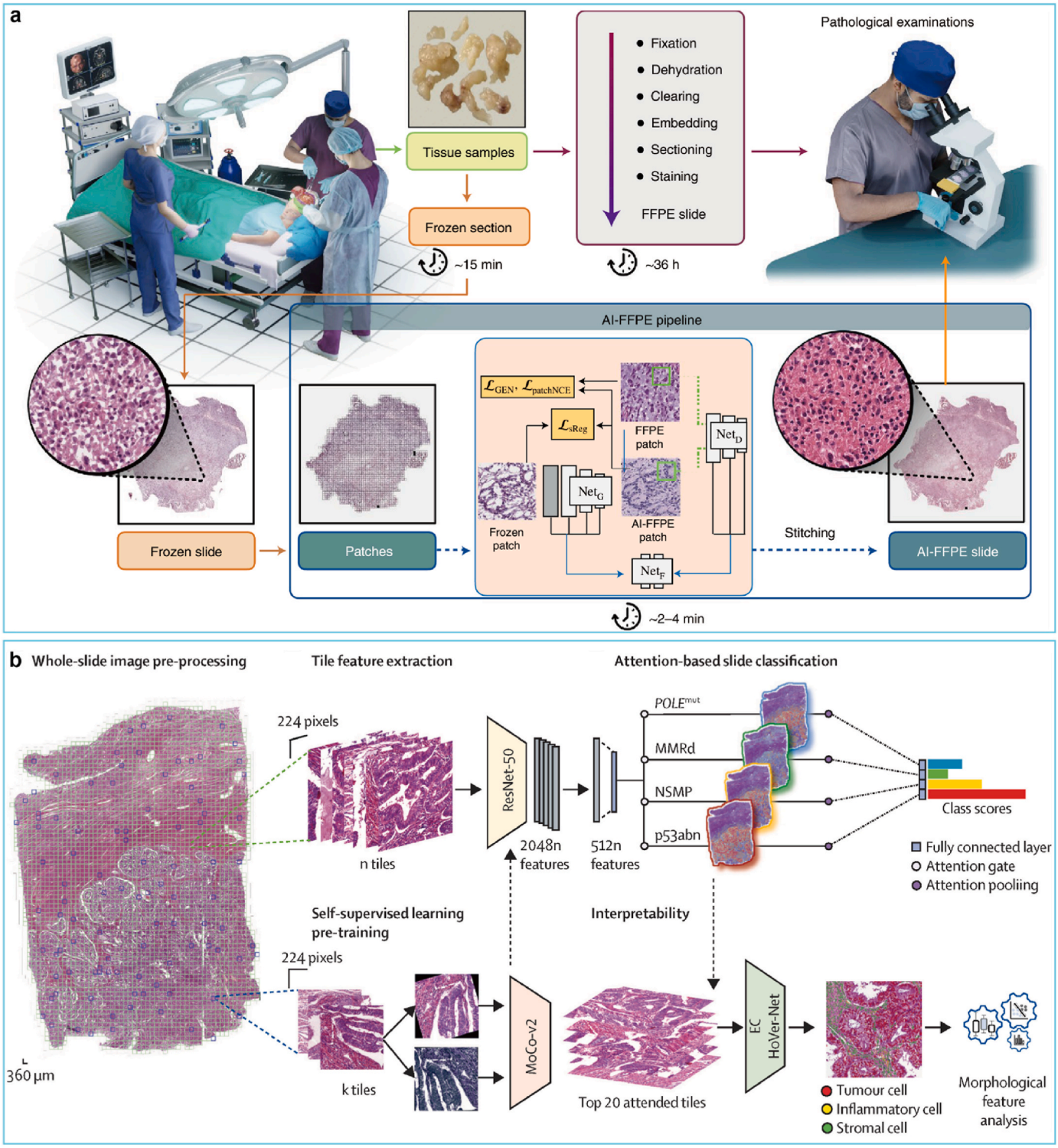

Fig. 9. Machine learning-guided image analysis in tissue scale. (a) Diagram summarizing how AI-formalin-fixed and paraffin-embedded (FFPE) method fits into the routine preparation of surgically excised specimens for histopathological evaluation. Copyright 2022, Nature Publishing Group. (b) An interpretable deep learning pipeline for whole-slide-image-based prediction of the four molecular classes in endometrial cancer (im4MEC), to identify morpho-molecular correlates, and to refine prognostication. Copyright 2022, The Lancet.

comprehensive understanding of the relationship between morphology and molecular classification in endometrial cancer, which can help improve clinical risk stratification and patient outcomes. The use of deep learning techniques in this study represents a significant advancement in the field of pathology and has important implications for personalized medicine.

4.4. Streamlined analysis of multi-omics data in AI-enabled organoids

Another challenge in organoids research is the analysis of high-throughput multi-omics data during the evaluation process. The analysis of multi-omics data, which includes genomics, transcriptomics, epigenomics, proteomics, and single-cell omics, is a complex task due to

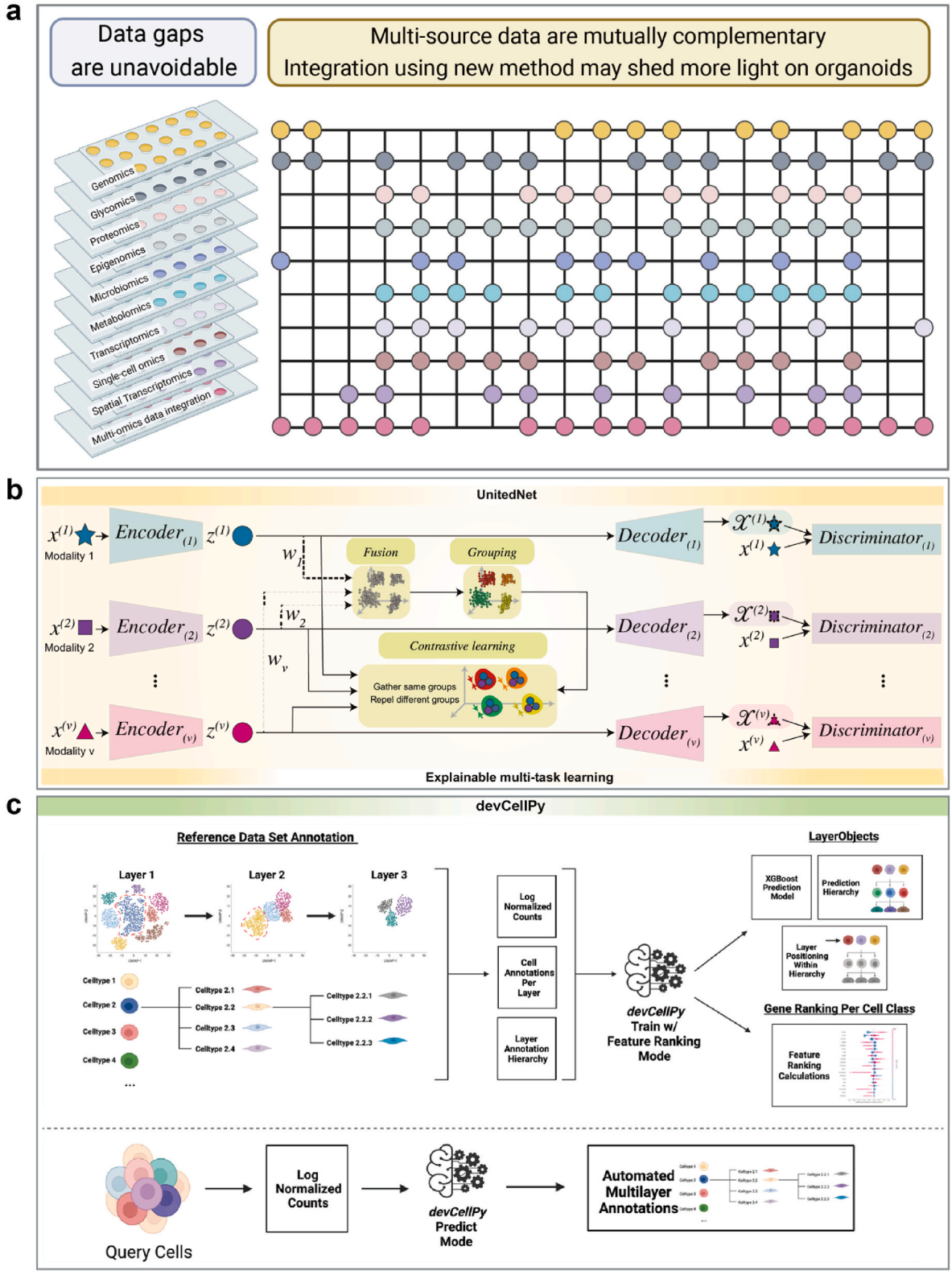

Fig. 10. Machine learning enabled analysis of multi-omics data. (a) Illustration of multi-omics data involved in organoids research. (b) Multi-task learning of multi-modality biological data by UnitedNet. Copyright 2023, Nature Publishing Group. (c) Overview of devCellPy, which is a multilayered machine learning algorithm for the hierarchical annotation of single-cell RNA-seq data. Copyright 2022, Nature Publishing Group.

the sheer volume and complexity of the data (Fig. 10a). Omics analysis has expanded to include statistical analysis and computational modeling of data from different biomolecular levels. In addition, data types have shifted from traditional structured data to unstructured, semi-structured, and heterogeneous architectures with diverse features. The relationships between omics data are more complex, involving both linear and nonlinear relationships. Traditional analytical methods exhibit distinct limitations when applied to both structured and

unstructured data. For structured data, these methods grapple with issues of scalability [166], high dimensionality [167], and data integrity [168], often necessitating computationally expensive operations or pre-processing steps that may introduce bias. Conversely, the analysis of unstructured data poses challenges due to its inherent lack of organization [169], necessitating specialized tools and expertise for effective utilization. Furthermore, the integration of structured and unstructured data remains a significant hurdle, as conventional business intelligence tools are predominantly designed for structured data [170]. These challenges underscore the imperative for advanced analytical frameworks capable of accommodating the complexities inherent in both data types.

The growth and development of organoids often involve multidimensional functional interactions among various cell types. Therefore, the analysis and processing of massive multi-omics sequencing data present significant challenges to traditional analysis methods in organoids research. AI can simplify this process by using machine learning to handle these complex datasets and extract meaningful biological insights [171]. In recent years, the rapid development of machine learning has provided a unique means for multi-omics data analysis to explore complex relationships between different omics and phenotypic targets. A team introduced UnitedNet, an interpretable multi-task deep neural network, designed to merge various tasks for the evaluation of single-cell multi-modality data (Fig. 10b). Comparative studies show that UnitedNet matches or outperforms contemporary techniques in terms of multi-modal amalgamation and inter-modal prediction [172]. Additionally, the use of interpretable machine learning techniques to analyze the trained UnitedNet enables the direct measurement of the correlation between gene expression and other modalities specific to cell types. As a result, UnitedNet offers a broader understanding of multi-modal data and could potentially reveal biological insights, including cell-specific, inter-modal feature correlations from multi-modal biological data. This could enhance our capacity to map and foresee cell states by employing multi-modal information in diverse biological systems.

A different recent research paper introduces devCellPy, a machine learning-empowered workflow for automated labeling of intricate, multilayered single-cell transcriptomic data [173]. The authors introduce an exceptionally precise and accurate instrument that facilitates automated identification of cell types across intricate annotation hierarchies (Fig. 10c). They highlight the efficacy of devCellPy by creating a mouse cardiac developmental atlas and training the tool to formulate a cardiac prediction algorithm. The authors also assert that devCellPy is ideally suited for datasets annotated in a hierarchical manner and is extraordinarily adaptable and applicable to any scRNA-seq dataset. As large-scale developmental cell atlases continue to expand, devCellPy will serve as a resource to aid in the recognition of cell types across different platforms and species, especially in well-labeled reference datasets that display complex multilayered annotation structures.

Accordingly, machine learning can achieve cross-scale and multi-modal data analysis and mining, improving the delay signal-to-noise ratio, thus obtaining organoids data with higher spatial and temporal resolution. High-content imaging combined with machine learning has been used for data mining at multicellular and organoids scales. Additionally, through neural network-based image analysis, multi-scale and multi-modal analysis and comparison can be conducted for molecular, cellular, spatial structure, and organ-level characteristics of organoids. Furthermore, during the evaluation of organoids, massive information is embedded in different modalities and scales. Machine learning can organically integrate these data, significantly reducing redundancy and achieving unexpected results.

Although machine learning and multi-omics data have been widely combined and produced many novel research results, there are still significant challenges for machine learning in multi-omics research. Current machine learning algorithms often struggle to provide biologically interpretable explanations for a given model's output, limiting the model's effectiveness in understanding underlying biological mechanisms and clinical applications. Interpreting model features requires more advanced machine learning methods (e.g., deep neural networks). Therefore, there is an urgent need to develop new machine learning algorithms that can transform existing "black boxes" into "white boxes" with biologically specific interpretability. This will allow researchers to gain more comprehensive insights into the complex molecular mechanisms underlying organoids growth and development, ultimately improving the efficiency and effectiveness of organoids research.

4.5. *Precise preclinical evaluation and application in AI-enabled organoids*

AI can also be used in the preclinical evaluation and application phase of organoids research. Predictive models and optimization algorithms can be used to evaluate the mechanisms involved in organoid intervention development, screen potential pharmaceutical agents, and construct *in vitro* disease models. This can improve the efficiency and effectiveness of this phase, which is crucial in bridging the gap between fundamental research and clinical application.

Developmental Biology: AI can analyze the complex processes involved in organoids growth and development. This can provide insights into human development and disease, and potentially guide the creation of tissues for regenerative medicine. For example, a recent research paper details the creation of a machine learning system known as brain and organoids manifold alignment (BOMA), which is designed for comparative analysis of gene expression between brains and organoids [174]. The framework uses manifold alignment to compare gene expression in organoids with developing brains, allowing for the identification of conserved and specific cell trajectories and genes across different species (Fig. 11a). The authors showcase the ability of BOMA to be scaled up by assessing it on both bulk tissue and single-cell datasets, and they also make a web tool available for widespread use in the scientific community. The significance of this work lies in its potential to improve our understanding of genomic regulations during brain development, as well as its broader applications in comparative analysis of gene expression between different types of samples. The development of BOMA and its successful application in comparing gene expression in developing brains and organoids highlights the importance of using AI to gain a deeper understanding of genomic regulations during development.

Biobanks Utilization: AI holds promise for the optimization of biobank utilization, wherein organoids from diverse individuals and conditions are stored. Biobanks, encompassing bioinformatics databases, specimen databases, and image databases, to name a few, are interconnected. The traditional analysis and extraction of data from these complex interrelations and large-scale repositories often pose significant challenges. However, AI can analyze this vast amount of data to discern patterns and correlations, potentially leading to innovative discoveries. Machine learning can play a pivotal role in automating the management and analysis of the voluminous and complex datasets generated during clinical trials, thereby streamlining the process and mitigating the risk of human error. The massive, multifaceted datasets produced by clinical trials can be onerous for human analysts to manage and analyze effectively. By automating tasks such as data entry, quality control, and statistical analysis, AI enables researchers to focus on higher-order tasks and decision-making. Furthermore, machine learning algorithms can detect patterns and trends in the data that may elude human analysts, potentially yielding novel insights and discoveries. By enhancing data management and analysis, AI holds substantial potential for augmenting the overall efficiency and effectiveness of clinical trials involving organoids.

Drug Screening: In the field of drug discovery, researchers are using AI-organoid interfaces to predict drug response in a more sophisticated and accurate manner. This involves the use of AI algorithms to analyze organoid data and identify new therapeutic targets and biomarkers. AI can analyze the complex data generated from organoids to predict drug

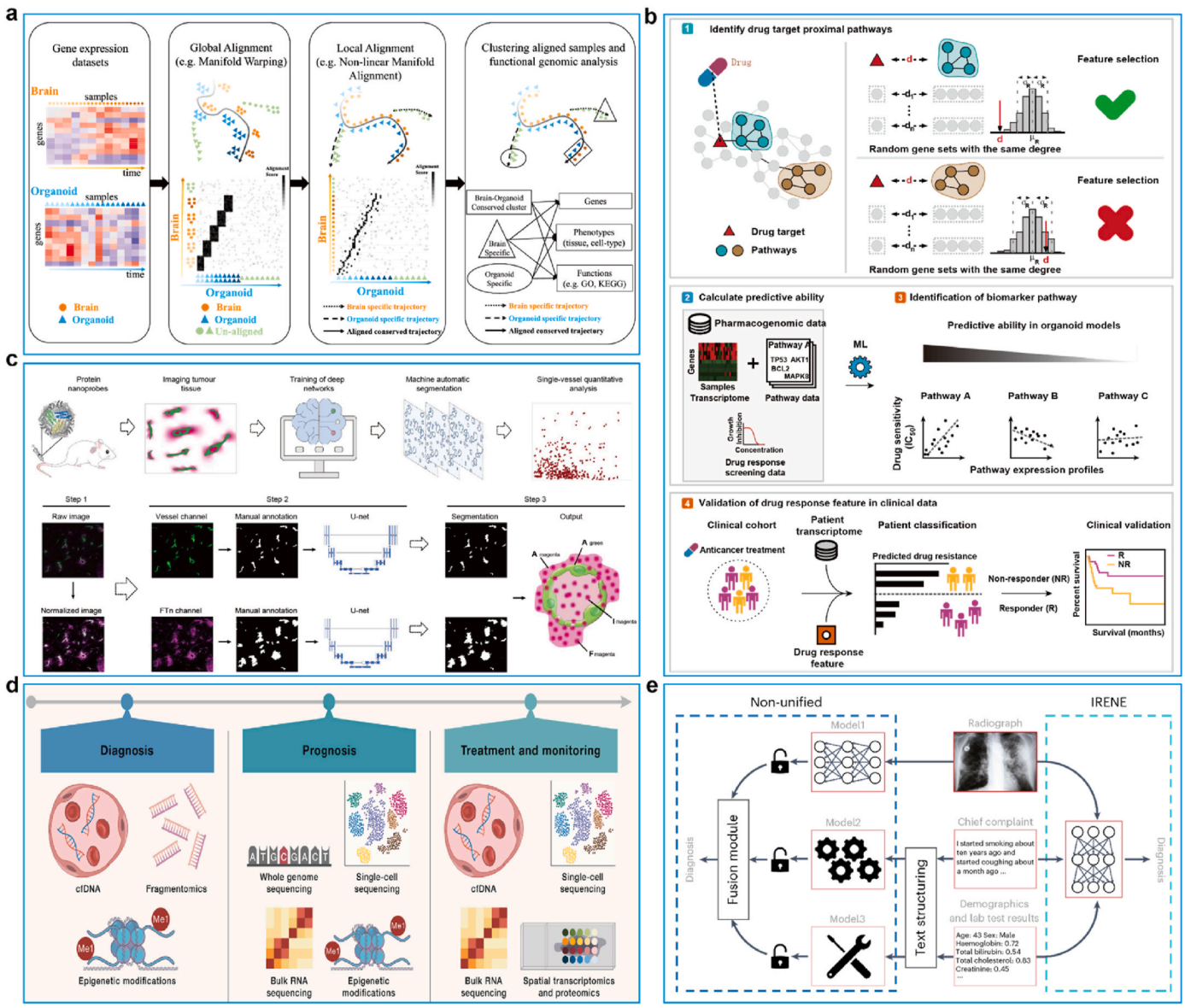

Fig. 11. Machine learning enabled precise preclinical evaluation and application of organoids. (a) Illustration of BOMA, a computational framework for comparative analyses of developmental gene expression data between brains and organoids. Copyright 2023, Cell Press. (b) Identification of biomarkers associated with drug response using a network-based machine-learning approach. Copyright 2020, Nature Publishing Group. (c) Machine learning-based single-vessel analysis method. Copyright 2023, Springer Nature. (d) Machine learning for diagnosis, prognosis, and treatment of disease models. Copyright 2023, Cell Press. (e) Contrasting the previous non-unified multimodal diagnosis paradigm with IRENE. Copyright 2023, Springer Nature.

responses. This can lead to more precise drug screening processes and the development of personalized treatments based on an individual's unique organoid responses. A study presents a new machine-learning framework for predicting anti-cancer drug efficacy in patients using organoid models [175]. The authors emphasize that the classification of cancer patients through predictive biomarkers for responses to anti-cancer drugs is crucial for enhancing treatment results. Nevertheless, present machine-learning-aided predictions for drug response frequently struggle to discover reliable translational biomarkers from pre-clinical models. To tackle this challenge, the authors have designed a network-oriented method that utilizes pharmacogenomic data obtained from three-dimensional organoid culture models to pinpoint reliable drug biomarkers (Fig. 11b). The results show that this approach accurately predicts drug responses in colorectal and bladder cancer patients and confirms them using external trans. The significance of this work lies in its potential to improve cancer treatment outcomes by identifying more accurate predictive biomarkers for anti-cancer drugs. Additionality, a study is reported on the heterogeneity of vascular permeability in tumor vasculatures and its impact on nanoparticle delivery to tumors [176]. The authors introduce an innovative approach for measuring vascular permeability by employing protein-based nanoprobes and image-segmentation-oriented machine learning (Fig. 11c). Their findings question the conventional understanding that the delivery of nanoparticles to tumors necessitates increased vascular leakiness, uncovering a broad spectrum of permeability levels across various tumors. The study has important implications for the development of more effective and targeted cancer treatments, as it suggests that personalized delivery strategies may be necessary to overcome the heterogeneity of vascular permeability in different tumors.

Disease Modeling: AI can help in creating more accurate disease models using organoids. By analyzing the organoid's response to various conditions, AI can help researchers understand the progression of diseases and evaluate potential treatments. Moreover, AI can help identify patient-specific organoid models and predict treatment response,

enabling the development of personalized treatment strategies. By utilizing patient-derived cells to generate organoids, researchers can model individual patients' diseases more accurately. AI algorithms can analyze these organoid models and determine which treatments are most likely to be effective for each patient, considering their unique genetic makeup, disease characteristics, and response patterns. This approach enables the development of targeted therapies and improves the overall efficiency of the treatment process, reducing side effects and increasing the likelihood of success. One example of machine learning's application in organoid disease modeling is its use in predicting neurotoxicity in human midbrain organoids [177]. In this instance, brain organoids, which are highly effective for researching neurodegenerative disorders such as Parkinson's disease (PD), were utilized. The research formulated an analytical approach based on machine learning, which facilitated comprehensive image-based cellular profiling and the prediction of toxicity in brain organoids exposed to the neurotoxic substance 6-hydroxydopamine. The machine learning algorithm was capable of measuring attributes like the count of dopaminergic neurons and neuronal complexity. It was also employed to improve data processing strategies and distinguish between various treatment conditions. The effectiveness of this method was confirmed using high-content imaging data derived from midbrain organoids of PD patients.

Despite these advances, the application of machine learning in organoids disease modeling is not yet widespread. This is largely due to the challenges associated with developing and managing organoids and the complexity of the diseases being modeled. While the use of machine learning in organoid disease modeling is still in the early stages, its widespread use and documented effectiveness in diagnosing, predicting, and treating various ailments lay a strong groundwork for progress in organoid disease modeling [178]. A recently published review offers a summary of the latest progress in the application of machine learning in the field of clinical oncology (Fig. 11d). The authors concentrate on machine learning technologies that are fairly advanced and either currently in use or nearing deployment in clinical environments [179]. They evaluate the application of these methods to medical imaging and molecular data gathered from liquid and solid tumor biopsies for cancer detection, prognosis, and treatment planning. They also deliberate on the significant factors when creating machine learning solutions tailored to the unique challenges presented by imaging and molecular data. In addition to discussing the current state of machine learning in clinical oncology, the authors examine the potential future applications of machine learning in disease modeling. Specifically, they explore how combining machine learning with organ-on-a-chip technology could lead to more accurate disease models that better reflect human physiology. This could have significant implications for drug discovery and personalized medicine.

A recent study presents a transformer-based representation-learning model, IRENE, which is a unified AI-based medical diagnostic model designed to make decisions by jointly learning holistic representations of medical images, unstructured chief complaint and structured clinical information for clinical diagnostics (Fig. 11e). The authors address the need for an advanced model capable of processing multimodal input in a unified manner, which includes radiographs, clinical history, and structured clinical information. By leveraging embedding layers, the model converts images and text into visual and text tokens, enabling a holistic understanding of the data [180]. The study holds significant implications for the field of clinical diagnostics, particularly in the identification of pulmonary diseases and the prediction of adverse clinical outcomes in COVID patients. The performance of the model surpasses that of image-only and non-unified multimodal diagnosis models, highlighting its effectiveness in accurately diagnosing and predicting clinical outcomes. In brief, as technology continues to advance and our understanding of organoids and disease processes improves, it is expected that machine learning will play an increasingly important role in disease modeling and the development of new treatments.

5. Conclusion and future perspectives

AI-Enabled organoids have the potential to provide even greater insights into complex biological systems of various organoids. The successful construction and stable cultivation of organoids are pivotal. AI technologies, particularly machine learning algorithms, offer promising avenues for optimizing organoid construction. Specifically, AI can optimize matrix gel design with desired physicochemical performance, automate quality control through image analysis, and dynamically monitor culture conditions. It can also analyze high-throughput omics data to feedback on various functionality information and construction parameters. This enables more efficient and higher-quality organoid construction, thereby accelerating the transition from laboratory research to clinical applications. Despite its many benefits, there are also significant challenges and limitations that must be overcome in order to fully realize the potential of this approach.

Data collection and standardization

Organoids are diverse and complex, making it difficult to collect consistent, high-quality data for AI analysis. Additionally, organoid cultures can vary in their structure and function, depending on the protocols and conditions used during their development.

Interdisciplinary collaboration

Combining AI and organoids requires collaboration between experts in computer science, biology, and other relevant fields. Effective communication and shared understanding can be challenging, as each field has its own terminology, methodologies, and theoretical frameworks.

Computational resource requirements

AI techniques, especially deep learning, can be computationally intensive. Analyzing large datasets from organoid research may require significant computational resources and specialized hardware, which can be costly and limit the accessibility of these techniques.

Model interpretability

AI models can be complex and difficult to interpret, making it challenging to understand the underlying biological processes driving their predictions. This is especially true for deep learning models, which are often described as "black boxes."

Ethical considerations

Combining AI and organoids raises ethical questions regarding the use of human-derived tissues, data privacy, and the potential for unintended consequences. Researchers must consider these issues and develop guidelines to ensure responsible research practices.

Validation and reproducibility

To ensure the reliability of AI predictions in the context of organoids, it is essential to validate the models using independent datasets. However, due to the variability in organoid cultures, reproducibility can be challenging.

Integration with existing knowledge: Integrating AI-generated insights with existing knowledge in biology, medicine, and other related fields can be challenging, especially given the rapid pace of research in these areas.

Regulatory and legal issues

As AI becomes more integrated into organoid research, there may be questions about the regulatory and legal implications, such as the ownership of intellectual property, liability for AI-generated insights, and the proper oversight of AI-driven research.

Despite these challenges, the future of AI-Enabled Organoids holds great promise. By development of AI-Enabled Organoids, researchers can gain a deeper understanding of human organ function and disease. One of the primary methods used to achieve AI-Enabled Organoids is the integration of high-throughput imaging and analysis techniques. By automating the process of capturing and analyzing large amounts of data, researchers can quickly and accurately identify changes in the morphology, gene expression, and metabolic activity of organoids over time. This information can then be used to train machine learning algorithms, which can then be used to make predictions about future developments. Another approach is the use of microfluidics and other lab-on-a-chip technologies to interface organoids with AI. These systems allow for precise control of the environment surrounding the organoids, enabling researchers to study complex biological processes and make accurate predictions about the behavior of individual cells or groups of cells. In addition, these systems can be used to perform high-throughput screens to identify new drugs or other treatments that can help to mitigate or cure disease. This can provide a powerful tool for drug discovery, disease diagnosis, and treatment development. With continued advancements in both fields, it is likely that we will see significant progress in the development of new treatments for various diseases and an improved understanding of complex biological processes. The AI-Enabled Organoids has the potential to greatly improve the way we approach medicine and biomedical engineering, and it is an exciting area of research that deserves continued attention and investment.

Ethics approval and consent to participate

The current review does not involve any experimental work on human subjects or animals, and thus does not require approval from an ethics committee. As this work solely involves the synthesis and analysis of pre-existing literature, it doesn't necessitate any form of direct involvement or consent from patients or healthy volunteers.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service, and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled, "AI-Enabled Organoids: Construction, Analysis, and Application".

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