Reviews

Artificial Intelligence in Immunoinformatics: From Multi-Omics to Precision Immunology

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The immune system is a multilayered, adaptive network whose behavior emerges across molecules, cells, tissues, and time. Contemporary immunology therefore generates high-dimensional, heterogeneous datasets that strain classical analytical assumptions. Artificial intelligence (AI), spanning machine learning and deep learning, is increasingly becoming a core paradigm for extracting structure, prediction, and actionable insight from these data.

This review summarizes how AI is transforming key steps of modern immunology, from sequencing- and repertoire-based analysis to antigen specificity and epitope prioritization for vaccine design; from single-cell and spatial profiling to inference of immune states and cell–cell communication; and from multi-omics integration to prediction and optimization of immunotherapy responses, including immune checkpoint blockade and CAR-based therapies. We compare the strengths and limitations of major model families—convolutional and recurrent networks, graph neural networks, generative models, and transformer-based architectures—highlighting how their inductive biases map to immunological questions.

We also discuss barriers to broad adoption, including data standardization and metadata quality, interpretability and uncertainty calibration, computational costs, and gaps between benchmark performance and clinical generalizability. Finally, we outline a roadmap toward interpretable and uncertainty-aware models, cross-center data sharing and benchmarking, closed-loop "dry–wet" validation with perturbation experiments, and clinically deployable pipelines for personalized immunodiagnosis and therapy.

Introduction

The immune system is a highly adaptive, multi-scale network whose function emerges from coordinated interactions among molecules, cells, tissues, and the environment. With the rapid maturation of high-throughput sequencing (NGS), single-cell and spatial omics, mass cytometry, and high-dimensional imaging, immunology has entered a data-intensive era in which genomic, transcriptomic, epigenomic, proteomic, and immune-repertoire measurements are generated at unprecedented scale and resolution[1]. However, immunological data are uniquely challenging for classical bioinformatics and statistics because they are intrinsically heterogeneous (e.g., extreme diversity of TCR/BCR sequences), dynamic across space and time, high-dimensional yet sparse (especially at single-cell resolution), and frequently multi-modal, requiring joint interpretation of molecular, cellular, and clinical layers[2, 3]. Artificial intelligence (AI), particularly deep learning – based machine learning, is increasingly adopted as a complementary paradigm because it can learn hierarchical representations from raw or minimally processed data, capture nonlinear dependencies, and support the discovery of biomarkers and interaction networks that enable both mechanistic hypotheses and translational decision-making[4, 5].

AI for Immune Repertoire Analysis

Immune repertoires—the collection of functional TCR and BCR sequences in an individual—directly reflect adaptive immune diversity and immune history and are now routinely profiled by AIRR-seq[6]. Beyond classical diversity indices, NLP-inspired models (e.g., Word2Vec and Transformer architectures) treat amino-acid sequences as "sentences" to learn embeddings that capture contextual features and enable efficient clustering, visualization, and antigen-specificity inference, often improving scalability over alignment-centric heuristics[7–9]. For clonotype assignment and evolutionary tracking, deep neural networks (e.g., CNNs and BiLSTMs) integrate V(D)J usage, CDR3 composition, and length patterns to improve clonal grouping, while GNNs enable lineage-style inference of somatic hypermutation trajectories and relatedness within graph- structured similarity spaces[10,11]. A central objective is predicting pMHC–TCR recognition: whereas earlier work relied on shallow models such as SVMs, recent deep learning frameworks (e.g., DeepTCR and TCRGP) exploit convolutional and attention mechanisms, and integrative models such as ERGO incorporate peptide sequence, MHC allele information, and TCR features to enhance generalization across alleles[12-14]. For antibodies, structure-aware deep learning tools (e.g., DeepAb and ABody-Builder) support structure prediction and downstream inference of antigen binding and function [15,16].

AI for Epitope Prediction and Vaccine Design

Epitope prediction is foundational for vaccines and immune therapies. For B-cell epitopes — often conformational — AI models trained on antibody–antigen complex resources reduce reliance on expensive structure simulations; CNN-based methods such as DeepBepi and BepiPred-3.0 support prediction from sequence and/or structural features, while generative approaches (e.g., SEGAN) extend toward antibody design with desired binding properties[17-19]. For T-cell epitopes, MHC-binding prediction has matured into practical standards: NetMHCpan and related ANN-based tools are widely used for class I/II prediction[20,21], and newer versions (e.g., NetMHC-pan-4.1) together with MHCflurry 2.0 integrate mass-spectr-

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ometry –derived eluted ligand data to improve accuracy[22,23]. In neoantigen discovery, AI-enabled pipelines typically combine somatic variant detection with personalized MHC-binding prediction and immunogenicity ranking; pVACseq provides an integrative framework for prioritization[24], while deep learning models such as DeepHLApan and EDGE move toward end-to-end prediction by leveraging larger-scale multi-omics information[25,26]. AI also accelerated rational vaccine development during COVID-19 by enabling rapid epitope screening and sequence optimization, and generative models (e.g., VAEs and GANs) increasingly propose novel immunogens under predefined constraints, with potential extensions to delivery optimization and personalized design guided by immune repertoire and HLA context [27, 28].

AI for Immune Cell Profiling and Systems Immunology

Single-cell multi-omics (scRNA-seq, CITE-seq, scATAC-seq) has made immune heterogeneity and dynamics directly observable, but also increases computational complexity. Automated annotation tools (e.g., SingleR and scPred) use reference-based machine learning classifiers to improve speed and reduce subjectivity[29,30], while Transformer-based pretraining such as scBERT treats expression profiles as structured "language," enabling accurate cell-type recognition under zero- or few-shot settings[31]. Deep generative models such as scVI and scANVI learn unified latent representations that support dimensionality reduction, batch correction, and clustering within a single probabilistic framework[32]. For trajectories and fate decisions, graph-based learning and Markov-process formulations (e.g., Palantir and CellRank) estimate transition probabilities and lineage biases[33,34], and neural ODE–inspired methods such as TrajectoryNet model continuous cellular dynamics over time[35]. Intercellular communication analysis remains central: ligand–receptor tools such as CellPhoneDB rely on curated interactions and statistics, whereas methods like NicheNet connect ligands to downstream target programs using expression and prior knowledge[36]. Spatially informed deep learning frameworks (e.g., SpaGCN and MISTY) integrate spatial transcriptomics to resolve microenvironmental communication patterns and contextual dependencies[37,38]. For multi-omics integration, approaches such as MOWGLI and MOFA+ discover shared latent factors across modalities[39,40], and GNN-based network modeling supports pathway-level reasoning under perturbation by embedding molecular interactions into learnable graph structures[41].

AI for Immunotherapy Optimization

AI is increasingly deployed to predict response, toxicity, and optimal use of immunotherapies. In radiomics and computational pathology, CNNs extract quantitative features from CT/PET and whole-slide images to infer PD-L1 status, immune infiltration patterns, and likelihood of response to immune checkpoint inhibitors; histology-derived represe- ntations of tumor-infiltrating lymphocyte spatial organization have shown predictive value beyond conventional biomar- kers[42-45]. AI also supports risk stratification for immune-related adverse events (irAEs) by integrating baseline clinical variables with immunological and microbiome features to anticipate complications such as colitis or pneumonitis, enabling earlier monitoring and intervention[46]. For CAR-T therapy, machine learning can assist CAR design by learning from sequence–function datasets to estimate affinity, activation thresholds, and off-target risk, and can additionally optimize manufacturing decisions and forecast in vivo expansion and persistence dynamics[47,48].

Challenges and Future Directions

Despite rapid progress, broad adoption is constrained by data quality and standardization, because immunological datasets are collected across platforms and centers with variable protocols, metadata completeness, and batch effects; community standards such as those promoted by AIRR remain critical for reproducibility and generalization[49]. Model interpretability and calibrated uncertainty are equally essential for mechanistic credibility and clinical safety, motivating explainable AI approaches including attention visualization, feature attribution, and counterfactual reasoning[50]. Looking ahead, the field is likely to advance through immunology-specific foundation models pretrained on large-scale repertoire and single-cell resources, iterative "dry–wet" closed-loop validation that rapidly tests AI-generated hypotheses experimentally, and individualized digital immune twins that integrate genomes, repertoires, microbiomes, and clinical history to simulate disease trajectories and optimize interventions.

Conclusion

Across immune repertoires, epitope and vaccine design, single-cell systems immunology, and immunotherapy, AI is evolving from a set of specialized tools into an enabling framework that links high-dimensional immunological measurements to predictive and mechanistic insight, with a clear path toward clinically actionable immunodiagnosis and therapy.

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