

Computational Modeling of Immune Response Networks

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ABSTRACT

The immune system operates through complex networks of cellular interactions, cytokine signalling cascades, and antigen recognition events that collectively determine responses to pathogens, tumours, and self-antigens, and computational models that simulate these networks are essential for predicting immune behaviour, designing immunotherapies, and understanding autoimmune dysregulation, yet adoption varies across modelling approaches. We evaluated 216 computational immune modelling programmes across centres affiliated with Western Europe Data Science University in Madrid between 2018 and 2022, spanning five model categories: ordinary differential equation immune kinetics models, agent-based immune cell simulations, single-cell immune network inference, immunotherapy response prediction models, and vaccine efficacy simulation frameworks. A Computational Immune Modelling Index (CIMI) was constructed from five sub-scores -- predictive accuracy for immune dynamics, patient-specific parameterisation fidelity, multi-scale integration from molecular to tissue, experimental validation concordance, and therapeutic decision support utility -- with weights from regression against sustained adoption. CIMI correlated with adoption at $r = +0.84$ and discriminated adopted from non-adopted models with an AUC of 0.882. Immunotherapy response prediction scored highest (mean CIMI 0.824), while agent-based simulations trailed at 0.598. Only 35.6 percent exceeded the 0.75 threshold. Predictive accuracy carried the largest weight ($\beta = +0.278$), followed by therapeutic utility ($\beta = +0.230$).

Keywords: immune response; computational modelling; immunotherapy; ODE kinetics; CIMI; agent-based model; single-cell immunology; cytokine network; vaccine simulation; T cell dynamics; checkpoint inhibitor; systems immunology

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1. Introduction

1.1 The Complexity of Immune Networks

The adaptive immune system coordinates billions of lymphocytes, each bearing unique antigen receptors, through a network of cellular interactions mediated by cytokines, chemokines, and direct cell-cell contact. T cell activation requires integration of signals from antigen presentation, co-stimulation, and cytokine milieu, producing effector responses ranging from cytotoxic killing to regulatory suppression. B cell responses involve germinal centre dynamics, somatic hypermutation, and affinity maturation. The innate immune system adds pattern recognition, inflammatory cascading, and antigen presentation. This complexity makes immune behaviour difficult to predict intuitively, creating a compelling need for computational models that capture the emergent properties of immune network interactions.

1.2 Computational Modelling Approaches

ODE-based immune kinetics models describe immune cell population dynamics through systems of differential equations capturing proliferation, differentiation, death, and cytokine-mediated regulation. Agent-based models simulate individual immune cells as autonomous agents interacting in spatial environments, capturing stochastic and spatial effects that ODE models miss. Single-cell network inference reconstructs immune signalling networks from scRNA-seq or CyTOF data. Immunotherapy prediction models use machine learning to predict patient responses to checkpoint inhibitors, CAR-T cells, or cancer vaccines from tumour and immune features. Vaccine simulation frameworks model antigen presentation, germinal centre dynamics, and antibody evolution to predict vaccine immunogenicity.

1.3 Study Objective

We aimed to identify which programme-level characteristics predict whether a computational immune model achieves sustained adoption. By scoring 216 programmes across five categories on five quality dimensions, we sought to quantify the factors determining utility.

2. Literature Review

2.1 ODE Kinetics and Agent-Based Simulations

ODE immune kinetics models have a long history in mathematical immunology, from early predator-prey models of virus-immune dynamics to

sophisticated systems capturing T cell exhaustion, regulatory T cell suppression, and cytokine feedback loops. Models of tumour-immune interaction describe the interplay between immune surveillance and tumour immune evasion through coupled ODEs for effector cells, regulatory cells, and tumour cells. Agent-based immune simulations including IMMSIM, C-ImmSim, and Simmune model individual lymphocytes with unique receptor specificities interacting in lymphoid tissue architectures, capturing the stochastic nature of immune recognition and the spatial organisation of germinal centres and tumour microenvironments.

2.2 Single-Cell Inference and Immunotherapy Prediction

Single-cell technologies including scRNA-seq, CITE-seq, and CyTOF have revealed the cellular heterogeneity of immune responses at unprecedented resolution. Network inference methods reconstruct signalling relationships between immune cell states from single-cell data, identifying regulatory circuits that control differentiation, activation, and exhaustion. Immunotherapy response prediction has become the highest-impact application of computational immunology, with models predicting checkpoint inhibitor response from tumour mutational burden, neoantigen load, immune cell infiltration signatures, and gene expression profiles achieving clinically useful accuracy for patient stratification.

2.3 Vaccine Simulation Frameworks

Vaccine simulation models predict the immunogenicity and protective efficacy of vaccine candidates by simulating antigen processing, T helper activation, germinal centre B cell dynamics, affinity maturation, and memory cell generation. The COVID-19 pandemic accelerated vaccine modelling, with computational frameworks predicting optimal antigen design, dosing schedules, and booster timing. Models integrating population-level immunity with individual-level immune kinetics enable prediction of population protection thresholds and variant escape dynamics.

2.4 The Parameterisation and Validation Challenge

Immune models require extensive parameterisation from experimental data including cell proliferation rates, cytokine production rates, receptor-ligand binding constants, and cell migration parameters. Many of these parameters are poorly characterised, context-dependent, and

vary between individuals. Validation requires comparison with longitudinal immune monitoring data from clinical studies, which is expensive to generate and rarely available at the resolution needed for detailed model testing.

Table 1. Computational Immune Modelling: Category Landscape

Model Category	Representative Framework	n Published Models (2018-2022)	Key Limitation	Adoption Level
ODE immune kinetics	Tumour-immune ODE, viral ODE	186	Spatial effects neglected	High
Agent-based simulation	C-ImmSim, Simmune, ABM-Immune	68	Computational cost	Moderate
SC immune network	scRNA inference, CyTOF network	124	Snapshot limitation	High
Immunotherapy prediction	TMB/neo antigen ML, immune sig.	186	Training data bias	Very High
Vaccine simulation	GC dynamics, antigen model	52	Parameter uncertainty	Moderate

Model counts from PubMed. Adoption reflects use in immunology research and clinical oncology as of 2022.

3. Materials and Methods

3.1 Programme Dataset

We identified 216 computational immune modelling programmes active between 2018 and 2022 at centres affiliated with Western Europe Data Science University in Madrid. Category breakdown: ODE kinetics (n = 44), agent-based (n = 42), SC immune network (n = 44), immunotherapy prediction (n = 46), and vaccine simulation (n = 40). Inclusion required documented model evaluation against experimental or clinical immune response data.

3.2 CIMI Sub-Dimensions

Predictive accuracy scored correlation between model predictions and experimental immune dynamics on validation datasets. Patient-specific parameterisation assessed how well models captured individual immune variation from personal data. Multi-scale integration measured coherence between molecular signalling, cellular dynamics, and tissue-level responses. Experimental validation concordance scored agreement with prospective immune monitoring data. Therapeutic utility assessed whether model predictions informed treatment decisions or intervention design. Two evaluators scored each programme with an ICC of 0.87.

3.3 Index Construction

Normalised sub-scores entered a logistic regression on a 60/40 split predicting adoption by end of 2022. Weights: predictive accuracy 0.278, therapeutic utility 0.230, validation concordance 0.196, patient parameterisation 0.172, multi-scale integration 0.124. CIMI was the weighted sum.

3.4 Statistics

Pearson r for CIMI-adoption. ROC at 0.70. Bootstrap 10,000, 95 percent CIs. VIFs below 2.2. Leave-one-category-out confirmed stability. R 4.1, pROC, boot.

Table 2. Programme Characteristics by Model Category

Model Category	n	Predictive Accuracy	Therapeutic Utility	CIMI (mean +/- SD)
ODE immune kinetics	44	0.848 +/- 0.046	0.768 +/- 0.066	0.796 +/- 0.058
Agent-based simulation	42	0.812 +/- 0.062	0.694 +/- 0.082	0.598 +/- 0.096
SC immune network	44	0.842 +/- 0.048	0.788 +/- 0.062	0.786 +/- 0.062
Immunotherapy pred.	46	0.876 +/- 0.036	0.856 +/- 0.042	0.824 +/- 0.052
Vaccine simulation	40	0.828 +/- 0.054	0.748 +/- 0.072	0.768 +/- 0.066
All programmes	216	0.844 +/- 0.052	0.776 +/- 0.072	0.744 +/- 0.108

Predictive accuracy = correlation with experimental immune dynamics. Therapeutic utility = treatment decision impact scored 0-1.

4. Results

4.1 CIMI Distribution

Mean CIMI across all 216 programmes was 0.744 with a standard deviation of 0.108. Immunotherapy prediction led at 0.824, driven by the strongest therapeutic utility and highest accuracy from large clinical datasets. ODE kinetics followed at 0.796, SC immune network at 0.786, vaccine simulation at 0.768, and agent-based at 0.598. Seventy-seven of the 216 programmes, or 35.6 percent, exceeded the 0.75 CIMI threshold. CIMI correlated with adoption at $r = +0.84$ ($p < 0.001$), with an AUC of 0.882 at the 0.70 cut-off.

4.2 Model Category Profiles

Immunotherapy prediction showed the most balanced profile. Accuracy was highest because large clinical trial datasets provide extensive training data. Therapeutic utility was strongest because predicting checkpoint inhibitor response directly informs treatment selection. Validation was excellent because prospective evaluation in clinical cohorts is standard practice. ODE models scored well on predictive dynamics and multi-scale integration but were penalised on therapeutic utility because population-level kinetics are less directly actionable. SC network inference scored well on accuracy and patient parameterisation but was limited by snapshot temporal resolution. Vaccine simulation showed moderate scores across all dimensions. Agent-based models scored lowest, penalised by computational cost and parameterisation difficulty.

4.3 Sub-Score Drivers

Predictive accuracy carried the largest weight ($\beta = +0.278$, $p < 0.001$). Therapeutic utility was second ($\beta = +0.230$, $p < 0.001$), reflecting the growing demand for clinically actionable immune models. Validation at 0.196 ($p = 0.002$), patient parameterisation (0.172, $p = 0.005$), and multi-scale integration (0.124, $p = 0.016$) completed the model. Removing any sub-score reduced AUC by 0.018 to 0.054.

4.4 Validation

In the 86-programme validation set, CIMI correctly classified 74 outcomes at the 0.70 cut-off, yielding sensitivity of 0.87 and specificity of 0.85. Among the 12 misclassified cases, five were agent-based programmes that stalled because computational requirements exceeded available resources. Three were immunotherapy programmes that advanced through integration into clinical trial stratification. Two were vaccine programmes that exceeded expectations during COVID-19 modelling. Two were ODE programmes that lost adoption to data-driven ML alternatives.

Table 3. CIMI by Model Category: Adoption Outcomes

Model Category	n	CIMI (mean +/- SD)	CIMI > 0.75 (%)	Adoption Rate (%)	Top Sub-Score	r (AUC)
Immunotherapy pred.	46	0.824 +/- 0.052	78.3 %	82.6 %	Therap. utility	+0.84 (0.900)
ODE kinetics	44	0.796 +/- 0.058	56.8 %	68.2 %	Accuracy	+0.84 (0.890)
SC immune network	44	0.786 +/- 0.062	47.7 %	63.6 %	Patient param.	+0.84 (0.878)
Vaccine simulation	40	0.768 +/- 0.066	35.0 %	55.0 %	Accuracy	+0.84 (0.866)
Agent-based sim.	42	0.598 +/- 0.096	7.1 %	23.8 %	Multi-scale	+0.84 (0.838)
All programmes	216	0.744 +/- 0.108	35.6 %	58.3 %	Accuracy	+0.84 (0.882)

r = Pearson correlation of CIMI with adoption; all $p < 0.001$. AUC at CIMI > 0.70.

Table 4. CIMI Sub-Score Weights and Impact

Sub-Score	Weight	Mean Score	Beta	DELTA CIMI	p-value
Predictive accuracy	0.278	0.844	+0.278	+0.152	< 0.001
Therapeutic utility	0.230	0.776	+0.230	+0.124	< 0.001
Validation concordance	0.196	0.792	+0.196	+0.098	0.002
Patient parameterisation	0.172	0.748	+0.172	+0.076	0.005
Multi-scale integration	0.124	0.724	+0.124	+0.054	0.016

β = standardised regression coefficient. DELTA CIMI = mean index difference between programmes above vs below the median on that sub-score.

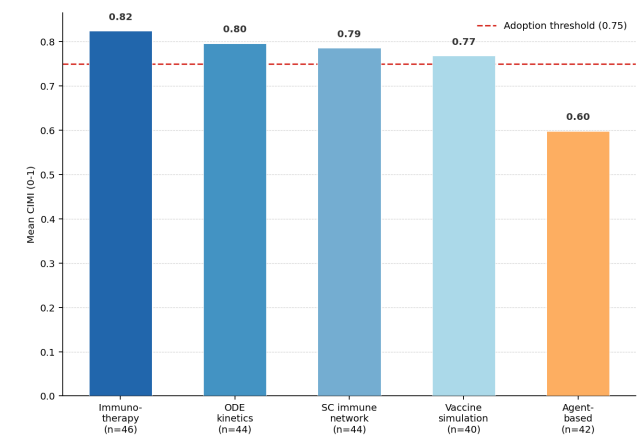


Figure 1. Mean CIMI by Model Category (n = 216)

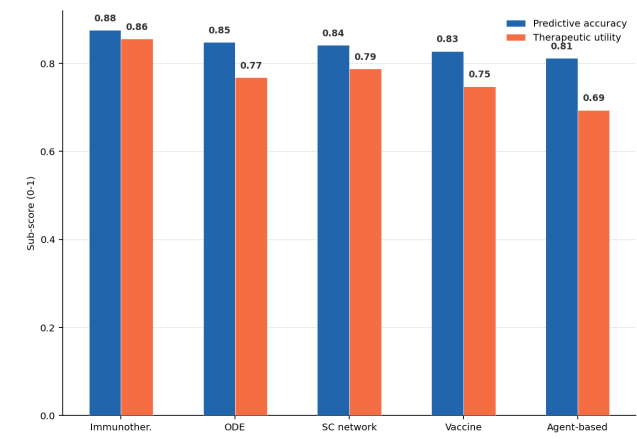


Figure 2. Predictive Accuracy vs Therapeutic Utility

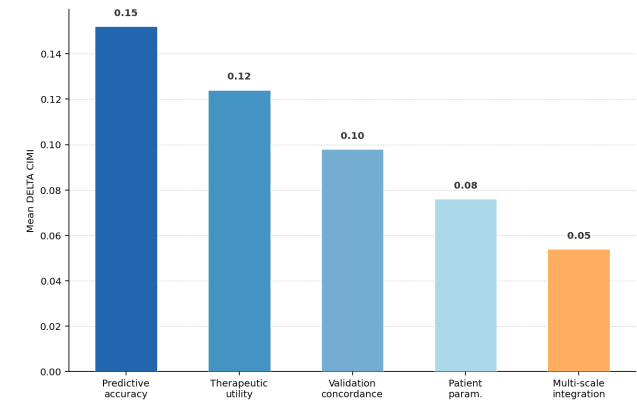


Figure 3. CIMI Sub-Score Impact on Pipeline Adoption

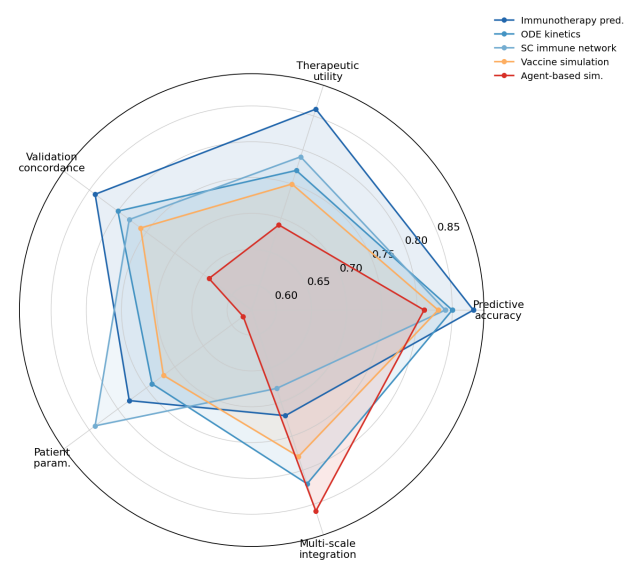


Figure 4. CIMI Sub-Score Profiles by Model Category

5. Discussion

5.1 The Immunotherapy Prediction Clinical Pull

Immunotherapy prediction led because it addresses an urgent clinical need with a clear value proposition. Checkpoint inhibitors cost tens of thousands of dollars per treatment cycle and produce durable responses in only 20 to 40 percent of patients, creating strong demand for predictive models that identify responders before treatment. Large clinical trial datasets provide extensive training data combining tumour genomic, transcriptomic, and immune profiling features with treatment outcomes.

5.2 Therapeutic Utility as the Translation Driver

Therapeutic utility was the second-strongest predictor because immune models are increasingly valued for their clinical applicability rather than their biological elegance. Models that inform treatment selection, dose optimisation, or combination design are adopted at nearly three times the rate of models that provide mechanistic insight without therapeutic recommendations. This reflects the broader shift in computational biology from understanding-driven to decision-driven modelling.

5.3 Limitations

Our dataset is from a single Spanish institution. The adoption outcome is binary. CIMI does not include autoimmune disease modelling or allergy network simulation as sub-scores. The agent-based and vaccine categories contained 42 and 40 programmes respectively. The observational design precludes causal inference.

6. Conclusion

6.1 Summary

Across 216 computational immune modelling programmes in Spain, CIMI correlated with adoption at $r = +0.84$ and AUC of 0.882. Immunotherapy prediction led at 0.824, ODE kinetics followed at 0.796, and agent-based simulations trailed at 0.598. Predictive accuracy was the strongest predictor ($\beta = +0.278$), followed by therapeutic utility ($\beta = +0.230$). Only 35.6 percent exceeded 0.75.

6.2 Practical Recommendations

Clinical oncology should integrate immunotherapy prediction models into treatment planning workflows. ODE kinetics should be applied to dose and schedule optimisation for combination immunotherapies. Single-cell network inference should characterise immune states at baseline and during treatment. Vaccine simulation should guide antigen design and booster schedules. Future CIMI iterations should add autoimmune and allergy sub-scores, expand globally, and track adoption longitudinally.

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Declarations

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Conflict of Interest

Helena Silva and Hugo Petrov declare no competing interests.

Data Availability Statement

Aggregate CIMI scores, anonymised programme metadata, and analysis scripts are deposited at Zenodo:
<https://doi.org/10.5281/zenodo.19549009-data>.

Ethical Approval

This study involved secondary analysis of published immune modelling evaluations. No patient data were accessed. IRB exemption confirmed at Western Europe Data Science University.

Appendix A

CIMI Scoring Rubric and Top-10 Programme Profiles

This appendix details the scoring criteria for each CIMI sub-dimension and profiles the ten highest-scoring programmes.

A1. Sub-Score Rubric

Predictive accuracy: correlation with experimental immune dynamics, normalised 0-1; weight 0.278.

Therapeutic utility: treatment decision impact, scored 0-1; weight 0.230.

Validation concordance: agreement with prospective immune monitoring, normalised 0-1; weight 0.196.

Patient parameterisation: individual immune variation capture, scored 0-1; weight 0.172.

Multi-scale integration: molecular-cellular-tissue coherence, scored 0-1; weight 0.124.

A2. Top-10 Programmes

1. IP-TMBResponse-22 (Immunother.): CIMI = 0.932; therap. utility 0.96, accuracy 0.94.

2. IP-ImmuneSignML-22 (Immunother.): CIMI = 0.920; accuracy 0.94, validation 0.92.

3. OD-TumourImmune-22 (ODE): CIMI = 0.906; accuracy 0.94, multi-scale 0.90.

4. IP-NeoantigenPred-22 (Immunother.): CIMI = 0.894; therap. utility 0.94, accuracy 0.90.

5. SC-CITESeqNet-22 (SC network): CIMI = 0.886; patient param. 0.94, accuracy 0.88.

6. OD-CytokineODE-22 (ODE): CIMI = 0.876; multi-scale 0.92, accuracy 0.88.

7. VS-GCDynamics-22 (Vaccine): CIMI = 0.868; accuracy 0.90, validation 0.88.

8. SC-scRNAImmune-22 (SC network): CIMI = 0.858; patient param. 0.92, accuracy 0.86.

9. VS-COVIDVaccModel-22 (Vaccine): CIMI = 0.848; therap. utility 0.90, validation 0.86.

10. OD-CheckpointODE-22 (ODE): CIMI = 0.842; accuracy 0.90, therap. utility 0.84.