https://doi.org/10.46344/JBINO.2026.v15i03.04

UNRAVELLING HOST IMMUNITY IN COVID-19: INSIGHTS FROM COMPUTATIONAL AND SYSTEMS MODELLING

Diasha Ghosh, Rojina Khatun, Malavika Bhattacharya*

Department of Biotechnology, Techno India University, West Bengal
EM 4, Salt Lake, Sector V, Kolkata-700091
*Corresponding Author Email: malavikab@gmail.com

ABSTRACT

Immunity plays a central part in how people respond to the virus behind the 2019 outbreak, shaping whether symptoms stay light or turn into serious lung issues or affect muscles. When the body detects pathogens like this one, early defences kick in - interferons get released, signals pass through cytokines, natural killer cells activate, and antigen-presenting cells join the effort. Yet if these systems go off track, excessive inflammation may follow, harming tissues instead of protecting them. Though designed to fight invaders fast, natural killer cells sometimes underperform during infection with this particular virus, weakening overall resistance over time. Interference from outside sources shows that adding type I or type II interferons can influence viral activity directly. What began as a single health crisis spread worldwide, driven by a pathogen known scientifically as SARS-CoV-2, leaving lasting impacts on public well-being. These point toward type I, and more so type III interferon, less likely to cause side effects, as useful tools in handling COVID-19. While $CD4^+$ helper T cells, $CD8^+$ cytotoxic T cells, and B cells drive viral elimination along with lasting protection, issues like fading antibody levels or worn-out T cells can open doors to serious illness and repeat infections. Control over most viruses relies heavily on the adaptive immune response. Antibody production, plus coordination through CD4+ and CD8+ T cells, forms its core structure. When molecules like IL-6, TNF-a, or IL-1β flood the body unchecked, they spark a cascade: rampant inflammation follows, blood vessels leak, tissues suffer - especially lung tissue - which may progress into ARDS and affect multiple organs. Though rooted in equations, simulations of immune behaviour stretch beyond basic formulas to include complex system interactions. From single-cell activity to broad physiological patterns, these tools map how bodies respond when invaded by pathogens. One such approach uses ODE-driven virus replication cycles to track infection progress over time. Instead of simplifying biological processes, some frameworks simulate individual agents acting within layered environments. Such methods reveal how local events influence overall immunity outcomes. Coagulation studies, similarly, turn to math to uncover hidden steps in clot formation pathways. By testing virtual scenarios, researchers spot previously unknown molecular reactions. These models also highlight possible points where medicines might intervene effectively. Rather than replacing experiments, they guide lab work toward more promising avenues.

Keywords: COVID-19, SARS-CoV-2, host immunity, innate immune response, adaptive immune response, interferons, cytokine storm, natural killer cells, $CD4^+$ T cells, $CD8^+$ T cells, B cells, T cell exhaustion, agent-based modelling, systems biology, immunomodulation

INTRODUCTION

Coronavirus SARS-CoV-2 causes severe respiratory illness. COVID-19 appeared in Wuhan, China, in late 2019 and spread globally by early 2020. It was declared a pandemic. The COVID-19 pandemic challenged global healthcare systems, emphasising how the body's defences shape what happens when illness strikes, triggering widespread infection alongside financial damage [1].

As the body responds to SARS-CoV-2, multiple factors shape how illness advances. Connected steps begin when the virus enters through contact made by the spike protein. Interaction between protein and ACE2, along with alternative receptors, occurs before reduced activity in the innate immune response. Using viral proteins, the response shifts. Immune detection falters once adaptation is blocked, leading to persistence

Widespread infection may occur, sometimes accompanied by severe inflammatory responses or conditions where the immune system attacks the body's own tissues. Immune responses involving multiple stages reveal why advancing research into their mechanisms remains essential. Using computer simulations to mimic how the body fights the virus and forecasts what happens during illness, offering clarity on how serious forms of COVID-19 develop [2].

To understand host immunity during COVID-19 infection, it is necessary to go beyond the. Some studies rely on testing through experiments, while others depend on math tools instead. Numbers help show patterns when real-world checks are tough. Models step in where hands-on methods cannot reach. When measurements fall short, calculations offer another path forward to measure intricate connections between the immune system and viruses - ones hard to explore within living organisms. Through modelling, scientists can explore how viruses spread, how the body fights back, and also assess how well vaccines work under different conditions. Immunity fades over time. When existing evidence about its decline merges with patterns of change seen in variants, a clearer picture emerges under varying circumstances. Because of differences in viruses along with variations among hosts, such models provide useful forecasts about how infections might spread, wave regulation, and planning treatments or community well-being initiatives [3].

Each variant of SARS-CoV-2 has its own unique replication and clearance characteristics. One key factor - often overlooked - is how the host influences both spread and impact. What matters most? The way infections move through populations is tied directly to the traits of the individual carrying them. Severity shifts depending on biological responses within that host. Patterns emerge when tracking who gets infected, yet underlying mechanisms remain tied to physiology. Understanding this helps explain differences in outcomes across groups. Some viruses spread differently. When scientists compared forms like Alpha, Delta, Epsilon, and Gamma, patterns began appearing. Each version behaved in distinct ways during outbreaks. Research indicates the Delta variant carries a greater viral load, reaching its maximum faster than others. Following symptom appearance, viral levels shift. Early phases show variation, even so. Though differences exist in how quickly viruses multiply, the overall

duration until they disappear from the body stays roughly the same across versions. This pattern holds regardless of strain; viral load usually drops quickly at first - then slows down later on. This two-stage process shows up consistently during treatment monitoring. A short phase follows, spanning several days - this reflects coordination between innate and adaptive immunity responses [4].

Over time, data gathered from long-term research has shown that people who already had certain conditions. Following a second encounter with SARS-CoV-2, the body often eliminates the virus more quickly. This pattern suggests prior exposure shapes immune responsiveness. Past infection may therefore influence how rapidly the virus is removed. Evidence points to immunity playing a part in this shortened timeline. Speedier clearance appears linked to earlier contact with the pathogen. Immunity's lasting effects help shield individuals from illness. Such defence, shaped by prior exposure, adapts over time. Like immunity from vaccines, it reduces how long an infection lasts as well as how severe it becomes. Surprisingly, certain people clear the virus more quickly over time. Often falling ill might suggest how well a person's body fights off germs, pointing toward individual differences in defence strength that are stable over time [5].

2. HOST IMMUNITY MODELS

2. 1. Network models covid 19

In the analysis of complex biological systems, particularly the immune system, it is not often the case that a single molecule or pathway is involved. All aspects of our body are interlinked – genes control proteins, proteins talk to cells, and cells talk to each other through cytokines. Network models can be used to effectively analyse the complexity of biological systems by treating these biological entities as nodes and their interactions as edges. Rather than analysing one pathway at a time, network models enable us to analyse and visualise how the immune system responds as a whole. This is particularly crucial in the case of the COVID-19 pandemic, where the SARS-CoV-2 virus sets off a chain reaction of the immune system responding in multiple ways through various pathways.

a. Protein-Protein Interaction (PPI) Networks: Protein-Protein Interaction (PPI) Networks are very important for understanding the interaction between SARS-CoV-2. Yet at the molecular scale, interactions between pathogen and person begin to unfold. Such maps emerge through methods combining computational models with lab-based observations. By comparing viral and human proteomes, researchers gain insight into interactions between viral proteins. Some viruses rely on specific proteins within human cells to invade and multiply. By examining how these components work together, researchers can pinpoint key proteins. Routes impacted by infection tend to become targets for possible medication. Among available resources, STRING stands out for interaction mapping. BioGRID offers curated protein associations across species. IntAct provides open-access data on molecular relationships. Visualisation often relies on network diagrams generated through specialised software. Cytoscape tools frequently appear when building such networks. These approaches rely on them. By examining various models, key molecular interactions can emerge as central

players behind observed effects. Understanding how COVID-19 develops helps shape precise treatments. How the disease unfolds influences medical strategies. Progress in therapy design follows clues from biological mechanisms. Clues about illness progression guide treatment choices. Medical advances rely on insights into viral behaviour. Treatment paths emerge from studying disease roots. Research into onset patterns shapes intervention methods. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might lead to severe health issues marked by excessive production of immune signalling molecules that contribute to harm in blood vessels, problems with coagulation, and worsening of lung tissue damage. The virus seems to infect various organs, mainly due to its effects on the endothelial cells along the walls of blood vessels. The genetic material of SARS-CoV-2 contains instructions for 29 proteins, yet their functions How these proteins contribute to illness - especially when blood vessels fail to function properly - remains unclear. In a recent study, the authors attempted to understand the role of 26 SARS-CoV-2. Examining how proteins produced in human cells influence endothelial function reveals distinct impacts when studied one at a time. Some proteins influenced how substances moved through cells, whereas nsp2 altered this process differently. A change in nsp5 - specifically the nsp5_c145a variant - along with nsp7, led to lower levels of CD31. This effect emerged clearly when both elements were present together. Higher levels of von Willebrand factor appear alongside elevated IL-6 gene activity, pointing to changes in blood vessel lining function. Through the construction of a protein-protein interaction map, researchers identified connections following tissue damage. Picture how these SARS-CoV-2 proteins might disrupt normal functions within the host cell endothelial pathways. Another suggestion involved how viral proteins might influence additional body parts. Tissue responses could shift when exposed to these elements. Changes in one area may trigger adjustments elsewhere. Effects were not limited to a single site. Some reactions appeared indirect. Protein activity possibly altered neighbouring functions. Impacts extended beyond initial infection zones. Because of the pandemic, tests confirmed changes in tight-junction proteins. Proteins such as cadherin-5 showed changes when exposed to nsp2, though ZO-1 responded more strongly under the influence of nsp5_c145a. Meanwhile, β-catenin levels shifted notably during contact with nsp7. Each protein reacted differently depending on the viral component present. Supporting the network's forecasts, these findings align when considered as a whole, emphasising the SARS CoV-2 proteins that are most likely to cause vascular Problems in function, revealing deeper details about how serious cases affect the blood vessel linings of COVID-19 [6].

b. Molecular Mechanisms of SARS-CoV-2 Replication:

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative

agent of COVID-19, is a positive-sense RNA virus with one of the largest RNA Some 30 kilobases of genetic code rely on an enzyme tasked with copying RNA to replicate. Reproduction occurs only if

a particular polymerase becomes active - its function tied directly to the presence of RNA. Alongside RdRp, several helper proteins play roles in handling genetic information during replication and transcription processes Together, the RTC handles mRNA synthesis while also assembling new pieces of the virus. Its dual role unfolds through coordinated steps that link genetic copying with particle formation. One function feed into the next, ensuring materials are ready when needed. This process runs without pause during active infection. Components emerge steadily as long as conditions support replication. The system operates as a continuous flow rather than separate events. Inside each cell, genetic instructions work hand in hand with newly formed proteins. Rather than acting alone, viral sequences align precisely with host machinery through tight regulatory links. While viral proteins are central to antiviral strategies, advancing their development encounters obstacles due to lingering uncertainty around underlying processes; progress has hit a pause. Recent research now explores these gaps in deeper detail. Looking inside the RTC uncovered complex structures that changed how things were understood. Though its functions seemed unclear at first, they began showing shapes never noticed earlier. Each discovery slotted together in ways nobody predicted. Attention to detail made invisible parts become visible. A clearer image took shape - more complete than old theories had shown. How SARS-CoV-2 manages its copying process in human cells holds vital clues about how it operates. Within infected cells, particular molecular encounters drive these processes. Understanding forms the foundation when building a precise computer-based simulation of virus behaviour. How hosts react influences pathogen growth within cells [7].

c. Multi-Omics and Epitranscriptomic Analyses in Modelling Host Immunity:

RNA analysis during viral attacks shows how SARS-CoV-2 changes what cells do. Because data comes from many types of biological measurements, combined methods are key to reading how hosts react. Instead of focusing on single genes, researchers watch groups of active transcripts shaped by markers such as methyl groups. When these signatures change, the pathogen may grow stronger - meanwhile, defence systems might also intensify. Standard gene tools miss subtle shifts; yet modifications in RNA, much like epigenetic signals, redirect protein creation and affect immunity. Following each piece in sequence uncovers hidden regulatory spots useful for treatment planning. From insight into these mechanisms emerge paths to block virus tactics while leaving regular cell work undisturbed [8].

3. ODE Models (Ordinary Differential Equation Models)

a. Viral Kinetics: The Ordinary Differential Equation (ODE)-based viral kinetic models are widely utilised to estimate and predict the dynamics of SARS-CoV-2 infection in the host. The models describe the vital processes of viral replication, target cell exhaustion, and immune system-mediated clearance, enabling scientists to simulate the dynamic course of viral load and immune response over time. A target cell-limited model has been widely used to describe the interactions between uninfected epithelial cells, infected cells, and free

virions with the help of rate constants for infection, replication, and clearance [9].

Early treatment cuts peak virus levels, according to simulations. These models show that drugs blocking virus entry, copying, or exit reduce both how much virus builds up and how long the infection lasts. Starting antivirals sooner slashes the total amount of virus over time - measured as AUC - and shortens shedding periods.[10].

Viral kinetic modelling is also applicable to special groups, such as immunocompromised or paediatric patients, for whom ODE models have shown that viral RNA remains for a longer period and with different rates of decay than in normal hosts. These results demonstrate the variability of infection dynamics in hosts and the relevance of model-based drug repurposing and optimisation of therapies. Taken together, viral kinetics modelling offers a quantitative basis for understanding the pathogenesis of SARS-CoV-2 and developing personalised antiviral therapies [11].

b. Innate Immune Response Modelling: When danger like SARS-CoV-2 shows up, the body's defences kick in rapidly - driven by detection systems shaping how sick someone might get. Splitting into the cell's interior after spike proteins bind ACE2 receptors, viral genetic material kicks off the cGAS-STING process. Out of this activation come interferons alongside inflammatory agents - effective at curbing infection, yet capable of damage should their presence extend beyond necessity. Though type one interferon normally slows down virus copying, it frequently loses strength in serious illness - perhaps due to inherited traits or self-directed antibodies disrupting communication lines. Left uncontrolled, the invader multiplies freely even as the immune system pushes back harder. When out of balance, the system releases a flood of cytokines - IL-6, TNF-a, IFN-γ - alongside sudden spikes in GM-CSF, triggering harm in lungs and organs alike. Though blocking IL-6 pathways may appear sound initially, outcomes hinge on rapidly changing immune cell behaviours. Instead of staying inactive, mast cells release histamine while sending out signals that worsen stress in tissues. Should basophil counts fall too soon, later issues could become significantly more severe. Flaws in core immune reactions often mirror what is observed in critical cases of COVID-19 [12].

c. Adaptive immune response Modelling: The adaptive immune response is a critical mechanism in the elimination of SARS CoV-2 infection and the development of long-term immunity. Immune protection emerges through teamwork between T and B cells, each recognising pieces of the virus to launch targeted reactions. While CD8+ T cells eliminate host cells carrying the infection, support comes from CD4+ T cells, guiding antibody creation in B cells. Those showing robust activity in T cells often experience less severe illness, clearing the pathogen quickly - a sign that cell-driven defences play a shielding role. Mathematical and computational models of adaptive immunity have been developed to predict the impact of differences in T-cell activation, antibody turnover, and memory cell persistence on disease outcomes. These models have also been used to evaluate the immune response triggered by vaccines and cross-reactivity with viral variants. Moreover, the gut microbiota has been

demonstrated to indirectly modulate adaptive immunity by influencing cytokine milieus and the maturation of immune cells. In general, the modelling of the adaptive immune network is very important for understanding immune memory, the efficiency of vaccines, and protection after infection, in addition to models of the innate immune response. The combination of both levels of understanding into one model enables a systems-level understanding of host immunity to COVID-19.

d. Cytokine Storm and Hyperinflammation Modelling: A rush of cytokines stands as one of the most serious challenges the immune system encounters in COVID-19, frequently leading to critical respiratory problems and damage in several organs. As SARS-CoV-2 establishes infection, molecules such as TNF-a, IL-6, and IFN-γ spread widely through the body without restraint, promoting widespread inflammation. Recent computer simulations indicate that TNF-a combined with IFN-γ might trigger PANoptosis - a form of aggressive cell death - shaped by signals from the JAK/STAT1/IRF1 pathway and influenced by nitric oxide concentrations. Inhibition of these cytokines or PANoptosis is protective in preclinical models. Computational and systems-level models also emphasise the role of dysregulated TGF-β signalling and imbalances in the complement and coagulation pathways in potentiating inflammation. Modelling studies suggest that imbalances in regulators such as complement factor H and C1-inhibitor can exacerbate the inflammatory cascade, while inhibition of IL-6 or coagulation enzymes can help to rebalance the immune system. Models that include mitochondrial stress also suggest that cell-free mitochondrial DNA is a strong inducer of innate immune activation.[13].

Another important cell type is the neutrophil, which is also highlighted by multi-omics modelling as a critical mechanism involving the IL-8/CXCR1/2 loop in the hyperactivation of neutrophils, the production of NETs, and immunothrombosis in more severe cases. The IL 8/CXCR1/2 loop has been demonstrated to have potential in decreasing lung inflammation and microvascular clotting. These modelling studies, therefore, help to elucidate the role of excessive cytokine signalling in tissue damage during COVID-19 and can be used to identify potential therapeutic targets for the management of hyperinflammation and the prediction of disease severity [14].

4. MULTISCALE MODELLING

The complex nature of the progression of COVID-19 in patients has emphasised the need for One way to tackle this challenge is by examining how infections spread differently from person to person. Addressing these variations becomes key moving forward, because of intricate systems, scientists now build layered simulations which include Inside cells, where viruses multiply. As they move between cells, infection extends across tissues. Immune activity follows, responding to these changes. Such systems rely on differential equations, while also incorporating randomness through stochastic methods to mimic behaviour

Some processes follow fixed patterns; others unfold unpredictably in living systems. Linking patient data with observed outcomes. Using model simulations, values like the proportion of

infected cells alongside the incubation Some studies during this time aimed to measure differences among patients. Findings derived from these approaches showed variation across individuals. Studies suggest stronger interferon responses - or environments where viruses struggle - may alter infection outcomes. Progress in tackling illness may be limited when signs show that T cells are losing function, a shift often linked to worsening condition. For moderate or severe cases, treatment could rely on just one drug. Importantly, results suggest single-drug therapy might work well enough for less serious cases. Treatment often shifts away from intensive approaches, though pairing medications still plays a key role when illness worsens. Immune recovery through T cells becomes more central under those conditions. Progression of the illness can be measured through this method, offering insights into how COVID-19 advances over time instead of merely describing symptoms, and proposes tailored options for individual treatment strategies [15].

Looking at molecules, scientists apply models across scales to grasp how things work complex structure of the SARS-CoV-2 envelope, mainly consisting of the spike, membrane, is studied. Molecular dynamics simulations reveal how M proteins behave alongside envelope proteins. These components form thread-like arrangements, helping to reinforce the viral structure - a finding aligned with newer observations. Measurements from tests feed into these models. By doing so, they deepen understanding of form while assisting prediction under stress. The search for antiviral targets. Alongside examining structures and cells, research on immunity now spans multiple scales, shaping how scientists understand the contributions of natural versus learned defences within the body Parts involved during various phases of illness. Amount of virus, signalling proteins, along with the activity of immune cells. Studies focusing on non-human primates reveal how crucial the innate immune system is during early infection stages. CD4+ T cells take part importantly after the early stage of viral control begins. What happens first involves broader immune activity, then shifts toward these specific cells stepping in later. Clearance of the virus relies on multiple factors. Antibodies targeting the spike protein contribute little. Other immune components take greater responsibility. Their involvement shapes overall effectiveness. Protection emerges through varied mechanisms. Minor contributions do not rule out function entirely. Immunity at the cellular level plays a key role in clearance, highlighting its relevance through biological defence mechanisms. Putting it all together, building tools that combine biology data across different levels has begun to shift how research moves forward vaccine plus treatment research advances when scientists combine molecular forecasting methods alongside vast Because immune simulations operate at scale, such systems evaluate how the body responds immunologically while estimating interactions across variants Together, these approaches improve forecasts of vaccine safety. Protection offered by current vaccines also gets clearer through such methods Scaling models connects tiny biological processes to real patient results in meaningful ways Together, these efforts begin to untangle how the immune system responds to COVID-19 - offering clearer insight

through combined approaches that build on one another slowly, yet steadily Creating focused treatments alongside prevention methods has advanced significantly [16].

Multiscale modelling is a powerful tool for integrating immune processes across different layers of life, from tiny signals in cells to how whole creatures fight sickness. Within an individual, Immunity modelling links internal cell activities - take cytokine signalling, for example - with how viruses operate. Immune cell movement ties into how tissues become inflamed through advanced biological functions. These responses unfold when recognition links to broader physiological activities. Higher-level mechanisms guide this interplay across affected areas. Inflammation arises alongside cellular navigation shaped by detection systems. Processes evolve as signals align within bodily networks. Immune control across the body works together with targeted responses. This allows for combined effects between focused areas. Biological mechanisms often involve intricate patterns of immunity that influence how illnesses progress [17].

When it comes to SARS-CoV-2, multiscale models connect how the virus multiplies inside cells. Activation of both innate and adaptive regulatory mechanisms shapes adaptive immunity. Such processes influence how the body responds at a fundamental level. Models can simulate how molecular-level immune signalling processes, such as interferon, activate cytokines, which fuel local damage before spreading body-wide through inflammatory pathways. Immune-related reactions, like cytokine surges or worn-out defences, emerge. When time factors mix into the picture, across different spatial levels, multiscale frameworks help anticipate variations in host immunity through integrated analysis, pinpointing major control points that influence how illnesses advance or improve [18].

5. SYSTEMS BIOLOGY MODELS

Though first seen in early 2020, system-wide biological methods soon helped unpack how SARS-CoV-2 manipulates immune function during infection. With layers of molecular data combined into predictive frameworks, scientists began tracing how each emerging variant altered its tactics to interfere with human defences. Instead of blocking interferon-driven genes - common among Alpha, Beta, Gamma, and Delta strains - the BA.1 version weakened this interference pattern noticeably. Surprisingly, changes in certain viral components, including Orf6, N protein, and Orf9b, turned out to weaken key cellular safeguards against infection. Later on, updated forms like BA.4 and BA.5 regained strong abilities to dampen frontline immune signals, revealing an ongoing shift in viral survival strategy [19].

Beyond escaping detection, broader network analyses tied the virus to faulty regulation in central inflammation controls such as NF-κB, STAT3, and IL-6, often seen behind extreme immune reactions in serious cases. MicroRNAs appear to shape inflammatory processes, with recent work pointing to their influence on cytokine levels - hinting at clinical benefits through precise network intervention [20].

Beyond that, systems immunology contributes meaningfully to understanding how SARS-CoV-2 disturbs brain-immune communication. Evidence from single-cell profiling shows heightened activity in pathways like TNF,

T-cell receptor, HIF-1, and cytokine receptors within microglial and astrocyte populations during infection. Because of this activation, nerve cell function often declines, driven by oxygen shortage and persistent inflammation after viral exposure [21].

Facing complex cross-tissue dynamics, researchers now build computational frameworks connecting immune storms, redox imbalance, clotting events, and metabolic disruption. Within these maps, reinforcing loops in interferon and cytokine signals emerge as key drivers of runaway immunity and whole-body instability. Model-based exploration uncovers candidate markers and nodes capable of curbing excessive reactions and organ damage, opening alternative routes toward tailored treatment strategies for severe cases. Putting it together, models from systems biology have clarified how host defences, virus changes, and infection dynamics interact during SARS-CoV-2 invasion. Such insights deepen knowledge about disrupted immunity while guiding new ways to treat or stop the disease [22].

6. AIM-HIS: AI-Integrated Model for Host Immune Signature:

COVID-19 remains a challenge to our understanding of the immune system response during severe infection. To address this, scientists examined over 45,000 transcriptomic datasets from different viral outbreaks and developed an immune signature involving 166 genes, using ACE2 as the initial point because it is the receptor that SARS-CoV-2 uses to gain entry into human cells. Through AI-powered analytics, they found that this gene signature was surprisingly similar across different pandemics. A reduced gene set of 20 genes was able to distinguish between mild and severe COVID-19 cases, and this led to the identification of the ViP and severe-ViP signatures. These signatures revealed an unexpected pathway: the lung epithelial cells and myeloid cells initiate an IL-15-mediated cytokine storm, while the exhaustion of epithelial and NK cells determines the severity and mortality. The results provided a clear indication of the therapeutic targets, which were confirmed in hamster infection studies using either neutralising antibodies (targeting the ACE2-virus interaction) or the antiviral drug EIDD-2801. Notably, the IL-15/IL15RA levels were significantly elevated in patients who died, and plasma IL-15 was a potential biomarker for predicting the severity [23].

In parallel to this, another research was conducted on PLpro, a viral protease that plays a vital role in replication and immune evasion. As there are no approved drugs that target PLpro, a supervised machine learning-based screening pipeline was developed, along with molecular docking, dynamics, and quantum chemical analysis. Seven potential inhibitors were identified, two of which were found to be more effective than the widely cited compound Jun12682. The work also mapped key residues in PLpro that enhance inhibitor binding, guiding future drug design [24].

In addition, progress in single-cell multi-omics has enabled deeper profiling of immune heterogeneity in COVID-19. A new interpretable deep-learning model, moETM, integrates multimodal datasets (like scRNA-seq, scATAC-seq, and CITE-seq) and reliably extracts immune signatures. When applied to COVID-19 patient samples, moETM highlighted known immune pathways and

uncovered combined multi-omics biomarkers linked to critical disease, offering both biological insights and clinical utility [25].

Table 1. Summary of Modelling Approaches for Host Immunity in COVID-19

Model Type	Core Focus	Key Features	Applications in COVID-19 Host Immunity	Tools / Methods
1. Network Models	Interaction-level immune regulation	PPI networks, cytokine networks, gene regulatory networks	Identify host proteins targeted by SARS-CoV-2, map cytokine dysregulation, and uncover endothelial injury pathways	STRING, BioGRID, IntAct, Cytoscape
2. ODE Models	Time-dependent viral and immune kinetics	Viral replication, target cell dynamics, innate & adaptive response curves	Predict viral load trajectories, simulate IFN response, T/B-cell activation, cytokine storm dynamics	Target-cell ODEs, cytokine ODEs, and immune differential equations
3. Multi-Scale Models	Linking molecular → cellular → tissue → systemic immunity	Integrates viral replication, cytokine signalling, immune activation, tissue inflammation	Predict patient heterogeneity, connect molecular events to clinical outcomes, and identify therapy combinations	Hybrid ODE–stochastic models, molecular dynamics, immunological NHP models
4. Systems Biology Models	Multi-omics-driven network reconstruction	Transcriptomics, proteomics, pathway analysis, and immune regulatory circuits	Decode immune evasion across VOCs, map cytokine storm pathways, study miRNA & neuroimmune signalling	scRNA-seq, pathway enrichment, regulatory network modelling
5. AI/ML-Integrated Immune Models (AIM-HIS)	Pattern recognition & predictive immunity	Gene signatures (ViP, severe-ViP), ML-based drug screening, multi-omics integration	Predict disease severity, identify biomarkers (IL-15), discover inhibitors (e.g., PLpro blockers), classify immune states	ML pipelines, deep learning (moETM), docking + MD simulation

DISCUSSIONS

Immunity inside the body matters more than the amount when it comes to how sick someone gets. When the first line of defence - interferons, natural killer cells, antigen-presenting cells - lags or gets blocked, trouble follows. Instead of stopping the virus fast, delays let inflammation grow unchecked. The latter response involving T cells and antibodies does work, yet strain changes and cell fatigue weaken its impact over time. Problems escalate when signals go haywire: too many cytokines, neutrophil traps, and blood clotting loops join forces. What unfolds is less about invasion, more about confusion within. Timing matters. Immune reactions unfold differently when interferon acts fast, while balanced inflammation shapes results. Instead of grouping responses together, separation reveals patterns. Later behaviour depends on these initial shifts. Models gain clarity by tracking extended immune

shifts across time. Genetic differences between people add further detail. Variants leave distinct marks on disease paths. Precision improves once such factors join simulations. Predictions grow more accurate because of it.

CONCLUSION

What you're born with, what your body learns, or how your system keeps balance - all influence how hard COVID-19 hits. Rather than focusing only on visible illness, experts study deeper processes: speed of viral spread, strength of immune counterattack, moments when signalling goes off track, differences between patient reactions. Because so many levels interact, models based on mathematics are used - these show timing, links between kinds of cells, and actions unfolding across tissues. Patterns emerge through such methods: unchecked inflammation surges, T-cells slow down, virus levels rise and fall, and clues appear about optimal treatment windows.

Immunity data, when matched with computer simulations, strengthens customised healthcare strategies - targeted interventions and sharper outbreak preparedness emerge from this mix. Progress hinges less on isolated advances, instead relying upon merging deep clinical histories with multi-level biomarkers, genetic backgrounds, and strain-specific immune responses; such integration sharpens predictions of disease course while guiding personal treatment design.

ABBREVIATIONS

COVID-19 – Coronavirus Disease 2019
SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2
ODE – Ordinary Differential Equation
AI – Artificial Intelligence
ML – Machine Learning
PPI – Protein–Protein Interaction
IFN – Interferon
T/B cells – T lymphocytes / B lymphocytes
VOCs – Variants of Concern
scRNA-seq – Single-cell RNA sequencing
mRNA – Messenger RNA
NHP – Non-Human Primates
STRING – Search Tool for the Retrieval of Interacting Genes/Proteins
BioGRID – Biological General Repository for Interaction Datasets
IntAct – Molecular Interaction Database
Cytoscape – Network Visualisation Software

ACKNOWLEDGEMENTS

We would like to express our heartfelt gratitude to the Chancellor of Techno India University.

AUTHOR CONTRIBUTIONS

Diasha Ghosh: Data Collection, Formal Analysis, Writing – Original Draft
Rojina Khatun: Resources, Writing-Editing
Malavika Bhattacharya: Conceptualisation, Supervision

REFERENCES:

1. Ochani R, Asad A, Yasmin F, Shaikh S, Khalid H, Batra S, Sohail MR, Mahmood SF, Ochani R, Hussham Arshad M, Kumar A, Surani S. COVID-19 pandemic: from origins to outcomes. A comprehensive review of viral pathogenesis, clinical manifestations, diagnostic evaluation, and management. Infez Med. 2021 Mar 1;29(1):20-36. PMID: 33664170.

2. Gusev E, Sarapultsev A, Solomatina L, Chereshnev V. SARS-CoV-2-Specific Immune Response and the Pathogenesis

of COVID-19. Int J Mol Sci. 2022 Feb 2;23(3):1716. doi: 10.3390/ijms23031716. PMID: 35163638; PMCID: PMC8835786

3. Calvetti D, Somersalo E. Post-pandemic modeling of COVID-19: Waning immunity determines recurrence frequency. Math Biosci. 2023 Nov;365:109067. doi: 10.1016/j.mbs.2023.109067. Epub 2023 Sep 13. PMID: 37708989.

4. Ribeiro RM, Choudhary MC, Deo R, Giganti MJ, Moser C, Ritz J, Greninger AL, Regan J, Flynn JP, Wohl DA, Currier JS, Eron JJ, Hughes MD, Smith DM, Chew KW, Daar ES, Perelson AS, Li JZ; ACTIV-2/A5401 Study Team. Variant-Specific Viral Kinetics in Acute COVID-19. J Infect Dis. 2023 Aug 31;228(Suppl 2):S136-S143. doi: 10.1093/infdis/jiad314. PMID: 37650233; PMCID: PMC10469346.

5. Kissler SM, Hay JA, Fauver JR, Mack C, Tai CG, Anderson DJ, Ho DD, Grubaugh ND, Grad YH. Viral kinetics of sequential SARS-CoV-2 infections. Nat Commun. 2023 Oct 5;14(1):6206. doi: 10.1038/s41467-023-41941-z. PMID: 37798265; PMCID: PMC10556125.

6. Rauti R, Shahoha M, Leichtmann-Bardoogo Y, Nasser R, Paz E, Tamir R, Miller V, Babich T, Shaked K, Ehrlich A, Ioannidis K, Nahmias Y, Sharan R, Ashery U, Maoz BM. Effect of SARS-CoV-2 proteins on vascular permeability. Elife. 2021 Oct 25;10:e69314. doi: 10.7554/eLife.69314. PMID: 34694226; PMCID: PMC8545399.

7. Malone B, Urakova N, Snijder EJ, Campbell EA. Structures and functions of coronavirus replication-transcription complexes and their relevance for SARS-CoV-2 drug design. Nat Rev Mol Cell Biol. 2022 Jan;23(1):21-39. doi: 10.1038/s41580-021-00432-z. Epub 2021 Nov 25. PMID: 34824452; PMCID: PMC8613731.

8. Wang X, Chang Z, Zhao T, Zhong W, Shi J, Wang G, Xu X. The role of post-transcriptional regulation in SARS-CoV-2 infection and pathogenicity. Front Immunol. 2023 Nov 15;14:1256574. doi: 10.3389/fimmu.2023.1256574. PMID: 38035086; PMCID: PMC10684767.

9. Dodds MG, Krishna R, Goncalves A, Rayner CR. Model-informed drug repurposing: Viral kinetic modelling to prioritize rational drug combinations for COVID-19. Br J Clin Pharmacol. 2021 Sep;87(9):3439 3450. doi: 10.1111/bcp.14486. Epub 2020 Aug 5. PMID: 32693436; PMCID: PMC8451752.

10. Caplan A, Bates KW, Brioni C, Santos A, Sabatini LM, Kaul KL, Carnethon MR, Khandekar JD, Greenland P. Clinical characteristics and viral load dynamics of COVID-19 in a mildly or moderately symptomatic outpatient sample. PLoS One. 2021 Oct 21;16(10):e0258970. doi: 10.1371/journal.pone.0258970. PMID: 34673816; PMCID: PMC8530348.

11. Moragas M, Golemba MD, Fernández MF, Palladino M, Gómez S, Borgnia D, Ruhle M, Arias A, Ruvinsky S, Bologna R, Mangano A. COVID-19 in immunocompromised children: comparison of SARS-CoV-2 viral load dynamics between the first and third waves. Braz J Microbiol. 2023 Sep;54(3):1859-1864. doi: 10.1007/s42770 023-01009-y. Epub 2023 Jun 1. PMID: 37258876; PMCID: PMC10232338.

12. Zhou Z, Zhang X, Lei X, Xiao X, Jiao T, Ma R, Dong X, Jiang Q, Wang W, Shi Y, Zheng T, Rao J, Xiang Z, Ren L, Deng T, Jiang Z, Dou Z, Wei W, Wang J. Sensing of cytoplasmic chromatin by cGAS activates innate immune response in SARS-CoV-2 infection. Signal Transduct Target Ther. 2021 Nov 3;6(1):382. doi: 10.1038/s41392-021-00800-3. PMID: 34732709; PMCID: PMC8564796.

13. Karki R, Sharma BR, Tuladhar S, Williams EP, Zalduondo L, Samir P, Zheng M, Sundaram B, Banoth B, Malireddi RKS, Schreiner P, Neale G, Vogel P, Webby R, Jonsson CB, Kanneganti TD. Synergism of TNF-α and IFN-γ Triggers Inflammatory Cell Death, Tissue Damage, and Mortality in SARS-CoV-2 Infection and Cytokine Shock Syndromes. Cell. 2021 Jan 7;184(1):149-168.e17. doi: 10.1016/j.cell.2020.11.025. Epub 2020 Nov 19. PMID: 33278357; PMCID: PMC7674074.

14. Shen WX, Luo RC, Wang JQ, Chen ZS. Features of Cytokine Storm Identified by Distinguishing Clinical Manifestations in COVID-19. Front Public Health. 2021 May 24;9:671788. doi: 10.3389/fpubh.2021.671788. PMID: 34109148; PMCID: PMC8180556.

15. Wang S, Hao M, Pan Z, Lei J, Zou X. Data-driven multi-scale mathematical modeling of SARS-CoV-2 infection reveals heterogeneity among COVID-19 patients. PLoS Comput Biol. 2021 Nov 24;17(11):e1009587. doi: 10.1371/journal.pcbi.1009587. PMID: 34818337; PMCID: PMC8654229.

16. Pezeshkian W, Grünewald F, Narykov O, Lu S, Arkhipova V, Solodovnikov A, Wassenaar TA, Marrink SJ, Korkin D. Molecular architecture and dynamics of SARS-CoV-2 envelope by integrative modeling. Structure. 2023 Apr 6;31(4):492-503.e7. doi: 10.1016/j.str.2023.02.006. Epub 2023 Mar 3. PMID: 36870335.

17. Byrne C, Schiffer JT. Ensemble modeling of SARS-CoV-2 immune dynamics in immunologically naïve rhesus macaques predicts that potent, early innate immune responses drive viral elimination. Front Immunol. 2024 Nov 7;15:1426016. doi: 10.3389/fimmu.2024.1426016. PMID: 39575237; PMCID: PMC11578959.

18. Russo G, Di Salvatore V, Sgroi G, Parasiliti Palumbo GA, Reche PA, Pappalardo F. A multi-step and multi-scale bioinformatic protocol to investigate potential SARS-CoV-2 vaccine targets. Brief Bioinform. 2022 Jan 17;23(1):bbab403. doi: 10.1093/bib/bbab403. PMID: 34607353; PMCID: PMC8500048.

19. Bouhaddou M, Reuschl AK, Polacco BJ, Thorne LG, Ummadi MR, Ye C, Rosales R, Pelin A, Batra J, Jang GM, Xu J, Moen JM, Richards AL, Zhou Y, Harjai B, Stevenson E, Rojc A, Ragazzini R, Whelan MVX, Furnon W, De Lorenzo G, Cowton V, Syed AM, Ciling A, Deutsch N, Pirak D, Dowgier G, Mesner D, Turner JL, McGovern BL, Rodriguez ML, Leiva-Rebollo R, Dunham AS, Zhong X, Eckhardt M, Fossati A, Liotta NF, Kehrer T, Cupic A, Rutkowska M, Mena I, Aslam S, Hoffert A, Foussard H, Olwal CO, Huang W, Zwaka T, Pham J, Lyons M, Donohue L, Griffin A, Nugent R, Holden K, Deans R, Aviles P, Lopez-Martin JA, Jimeno JM, Obernier K, Fabius JM, Soucheray M, Hüttenhain R, Jungreis I, Kellis M, Echeverria I, Verba K,

Bonfanti P, Beltrao P, Sharan R, Doudna JA, Martinez Sobrido L, Patel AH, Palmarini M, Miorin L, White K, Swaney DL, Garcia-Sastre A, Jolly C, Zuliani-Alvarez L, Towers GJ, Krogan NJ. SARS-CoV-2 variants evolve convergent strategies to remodel the host response. Cell. 2023 Oct 12;186(21):4597-4614.e26. doi: 10.1016/j.cell.2023.08.026. Epub 2023 Sep 21. PMID: 37738970; PMCID: PMC10604369.

20. Gasparello J, Finotti A, Gambari R. Tackling the COVID-19 "cytokine storm" with microRNA mimics directly targeting the 3'UTR of pro-inflammatory mRNAs. Med Hypotheses. 2021 Jan;146:110415. doi: 10.1016/j.mehy.2020.110415. Epub 2020 Nov 25. PMID: 33422363; PMCID: PMC7685948.

21. Lin X, Nie H, Tang R, Wang P, Jin X, Jiang Q, Han F, Chen N, Li Y. Network analysis between neuron dysfunction and neuroimmune response based on neural single-cell transcriptome of COVID-19 patients. Comput Biol Med. 2022 Nov;150:106055. doi: 10.1016/j.compbiomed.2022.106055. Epub 2022 Sep 10. PMID: 36137317; PMCID: PMC9462930.

22. Sasidharakurup H, Kumar G, Nair B, Diwakar S. Mathematical Modeling of Severe Acute Respiratory Syndrome Coronavirus 2 Infection Network with Cytokine Storm, Oxidative Stress, Thrombosis, Insulin Resistance, and Nitric Oxide Pathways. OMICS. 2021 Dec;25(12):770-781. doi: 10.1089/omi.2021.0155. Epub 2021 Nov 22. PMID: 34807729.

23. Sahoo D, Katkar GD, Khandelwal S, Behroozikhah M, Claire A, Castillo V, Tindle C, Fuller M, Taheri S, Rogers TF, Beutler N, Ramirez SI, Rawlings SA, Pretorius V, Smith DM, Burton DR, Alexander LEC, Duran J, Crotty S, Dan JM, Das S, Ghosh P. AI-guided discovery of the invariant host response to viral pandemics. EBioMedicine. 2021 Jun;68:103390. doi: 10.1016/j.ebiom.2021.103390. Epub 2021 Jun 11. PMID: 34127431; PMCID: PMC8193764.

24. Li L, Li J, Zhang Q, Huang Y, Bao Y, Tang X. Discovery of SARS-CoV-2 papain-like protease inhibitors through machine learning and molecular simulation approaches. Drug Discov Ther. 2025 Jul 4;19(3):189-199. doi: 10.5582/ddt.2025.01034. Epub 2025 Jun 27. PMID: 40571587.

25. Zhou M, Zhang H, Bai Z, Mann-Krzisnik D, Wang F, Li Y. Single-cell multi-omics topic embedding reveals cell-type-specific and COVID-19 severity-related immune signatures. Cell Rep Methods. 2023 Aug 18;3(8):100563. doi: 10.1016/j.crmeth.2023.100563. PMID: 37671028; PMCID: PMC10475851.