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Hybrid Machine Learning-ODE Framework for Predicting COVID-19 Variants' Spread and Evaluating Public Health Interventions in the U.S

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Abstract: The COVID-19 pandemic highlighted the need for models that are both mechanistic and data-driven. In this study, we develop and analyze a hybrid machine learning–ODE framework for predicting the spread of COVID-19 variants in the United States and for assessing public health interventions. We formulate a susceptible–exposed–infectious–recovered (SEIR) model with a time-varying transmission rate $\beta(t)$ that is learned from covariates using a recurrent neural network. The covariates include mobility indices, vaccination coverage, and variant prevalence. We present basic qualitative properties of the model, derive the effective reproduction number, and describe the parameter estimation strategy. The hybrid framework reproduces the timing and relative magnitude of major epidemic waves and improves short-term forecast accuracy during periods of structural change, such as the emergence of the Delta and Omicron variants. We further show how the model can be used to simulate alternative intervention scenarios, such as increased booster coverage or changes in mobility. The proposed framework provides a concrete example of how hybrid ML–ODE models can support data-driven public health planning in the U.S.

Keywords: Hybrid Modelling, Covid-19 Variant Prediction, Public Health Intervention, SEIR Model.

INTRODUCTION

The COVID-19 pandemic reaffirmed the critical need for accurate, adaptable, and reliable epidemiological models that can capture the changing dynamics of infectious disease dissemination. Existing epidemiological techniques, particularly compartmental frameworks like the SIR and SEIR models, have long been utilized to study transmission dynamics and evaluate intervention measures. These models are based on differential equations, which characterize population transitions between epidemiological states using characteristics including transmission, recovery, and gestation rates. Mathematical approaches are useful because they enable interpretability and counterfactual analysis of interventions. At the same time, these models frequently rely on simplifying assumptions like homogenous mixing or set parameters. Such assumptions, together with the requirement for complete surveillance data, decrease their accuracy when applied to real-world and quickly changing epidemic environments (Kissler *et al.*, 2020).

Machine learning is now regarded as a powerful technique for evaluating huge, diverse datasets such as mobility data, genetic sequences, hospitalization rates, and vaccination records, yielding predictive insights without the need for explicit mechanistic assumptions. Long short-term memory (LSTM) networks, recurrent neural networks (RNNs), and ensemble learning models have all been used effectively to forecast COVID-19 in the short term, including nonlinear trends and adjusting to changing conditions (Arik *et al.*, 2020). However, ML approaches are frequently criticized for their lack of epidemiological interpretability and low generalizability in the face of structural changes, such as the appearance of new variations or the deployment of novel interventions. For example, during the formation of the Omicron variety, several ML models calibrated on Delta-era dynamics underperformed significantly because their learnt patterns failed to detect the abrupt shift in transmissibility and immune escape. Such examples underscore the need for frameworks that can adapt structurally and statistically, a gap that hybrid ML ODE models are ideally suited to address.

To address the drawbacks of these approaches, hybrid models that combine machine learning techniques with ordinary differential equation (ODE) frameworks have gained popularity in epidemiological research. These hybrid machine learning-ODE models combine the interpretability of mechanistic transmission structures with the flexibility of ML-driven parameter estimation and residual error correction. ODEs, for example, can represent essential epidemic dynamics like transmission and recovery, but ML components can dynamically predict time-varying transmission rates, immunological escape, and behavioral changes that fixed equations cannot capture (Rackauckas *et al.*, 2020). This synergy enables hybrid models to address the nonlinearities and uncertainties caused by new variants, diverse

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human behavior, and decentralized intervention programs.

Hybrid frameworks are particularly important in the context of COVID-19. They can simulate variant-induced variations in spread and rate while utilizing real-time genomic surveillance data. Furthermore, they allow the simulation of public health initiatives such as vaccination campaigns, mask mandates, and mobility limitations. Despite significant advances, obstacles persist in areas like data quality, uncertainty quantification, ethical considerations, and computing scalability. The goal of this review is to analyze the use of hybrid ML-ODE frameworks for predicting COVID-19 variant dissemination and evaluating public health interventions in the United States. We will address how these models improve on previous techniques, the methodological and data problems they encounter, and the policy implications for pandemic preparedness and response. This review, which combines findings from epidemiology, applied mathematics, and machine learning, emphasizes the relevance of hybrid models in enhancing public health resilience against COVID-19 and other emerging infectious diseases.

In this paper, we move beyond a purely narrative review of hybrid ML–ODE approaches and construct a concrete hybrid model tailored to the United States COVID-19 experience. We specify an SEIR-type system of ordinary differential equations for variant-driven transmission and embed it in a machine learning pipeline that learns a time-varying transmission rate from mobility, vaccination, and genomic surveillance data. We analyze the mathematical properties of the model, estimate its parameters from national surveillance data, and illustrate how the framework can be used both for forecasting and for evaluating public health interventions such as vaccination and mobility restrictions.

Model Formulation

We consider a homogeneous population of size Npartitioned into four main epidemiological compartments: susceptible $S(t)$, exposed $E(t)$, infectious $I(t)$, and recovered $R(t)$. The total population satisfies

$$N = S(t) + E(t) + I(t) + R(t),$$

and is assumed constant over the time horizon of interest. To account for changing transmissibility driven by emerging variants and behavioral changes, we allow the transmission rate to vary in time and denote it by $\beta(t)$.

The core SEIR dynamics are given by the system of ordinary differential equations

$$\begin{aligned}\frac{dS}{dt} &= -\beta(t)\,\frac{S(t)I(t)}{N},\\ \frac{dE}{dt} &= \beta(t)\,\frac{S(t)I(t)}{N} - \kappa E(t),\\ \frac{dI}{dt} &= \kappa E(t) - \gamma I(t),\\ \frac{dR}{dt} &= \gamma I(t),\end{aligned} \tag{1}$$

where $\kappa > 0$is the progression rate from exposed to infectious (inverse of the mean incubation period) and $\gamma > 0$is the recovery rate (inverse of the mean infectious period).

In practice, vaccination and prior immunity strongly affect susceptibility. To keep the model tractable while still allowing for such effects, we introduce an "effective susceptibility" term $S_{\text{eff}}(t) = (1 - v(t))S(t)$, where $v(t)$denotes the fraction of the susceptible population protected by vaccination or prior infection at time t. In (1), we may therefore replace $S(t)$with $S_{\text{eff}}(t)$when computing the force of infection. For clarity of exposition, we keep (1) in its simpler form and incorporate vaccination into the definition of $\beta(t)$via covariates in the machine learning component (Section 4

The model is initialized at time $t_0$with

$$S(t_0) = N - E_0 - I_0 - R_0, E(t_0) = E_0, I(t_0) = I_0, R(t_0) = R_0,$$

where E_0, I_0, and $R_0$are chosen to match early epidemic conditions. Observed reported cases are linked to the infectious compartment through

$$C_{\text{model}}(t) = \rho\,\gamma I(t),$$

where $0 < \rho \leq 1$denotes the reporting fraction.

Qualitative analysis

We summarize basic properties of system (1) under the assumption that $\beta(t)$is bounded and non-negative.

Positivity and boundedness.

Let $S(t_0), E(t_0), I(t_0), R(t_0) \geq 0$with $S(t_0) + E(t_0) + I(t_0) + R(t_0) = N$. Standard results for SEIR systems imply that solutions remain non-negative and satisfy

$$0 \leq S(t), E(t), I(t), R(t) \leq N, S(t) + E(t) + I(t) + R(t) = N$$

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for all $t \geq t_0$. Thus, the model is epidemiologically well-posed.

Basic reproduction number.

If $\beta(t) \equiv \beta_0$is constant, system (1) has a disease-free equilibrium

$$\mathcal{E}_0 = (S, E, I, R) = (N, 0,0,0).$$

The basic reproduction number $R_0$is given by

$$R_0 = \frac{\beta_0}{\gamma},$$

which represents the expected number of secondary infections generated by a single infectious individual in a fully susceptible population.

Stability of the disease-free equilibrium.

Linearization of (1) around $\mathcal{E}_0$shows that the disease-free equilibrium is locally asymptotically stable if $R_0 < 1$and unstable if $R_0 > 1$. In the time-varying case, the effective reproduction number is

$$R_{\text{eff}}(t) = \frac{\beta(t)S(t)}{\gamma N},$$

and the epidemic grows when $R_{\text{eff}}(t) > 1$and declines when $R_{\text{eff}}(t) < 1$. Tracking $R_{\text{eff}}(t)$over time provides a natural way to study the influence of emerging variants and interventions.

Machine Learning in COVID-19 Prediction

Unlike mathematical frameworks like SIR or SEIR, which are based on hypotheses about disease transmission dynamics, ML models learn directly from actual data, making them extremely adaptable to changing trends. For example, machine learning algorithms have been used to predict daily confirmed cases, hospital admissions, ICU occupancy, and fatality rates. They allow healthcare systems to plan more efficiently. In addition to population-level forecasts, machine learning has been used to predict patient-level outcomes. It can forecast the risk of severe illness progression, hospitalization, or death. These projections rely on demographic, clinical, and laboratory data. Furthermore, hybrid models that combine ML with statistical approaches have arisen to identify nonlinear patterns in data while maintaining the interpretability of classic models. Because of its diversity, machine learning has been shown to be an invaluable tool for real-time epidemic forecasting in a highly uncertain context (Yang *et al.,* 2020).

Supervised Learning and Time-Series Models (LSTMs, Transformers, Regression)

In COVID-19 forecasting, supervised learning has been one of the most extensively used ML techniques. In this framework, models are trained to predict future trends using historical input-output pairs, such as past case counts and associated future outcomes. Long Short-Term Memory (LSTM) networks and regression-based algorithms have emerged as popular supervised approaches. LSTMs, a form of recurrent neural network, are ideally adapted to handling periodic dependencies in sequential data, allowing them to learn how previous case counts influence the future over long time periods. Several studies have found that LSTMs outperform traditional time-series models like ARIMA, especially when the data contains nonlinearities or sudden shifts. In the case of more stable epidemic phases or when data availability is limited, simpler models like linear regression or ARIMA may be preferred due to their interpretability, lower processing needs, and resistance to overfitting. This emphasizes the significance of tailoring forecasting methodologies to the specific characteristics of the epidemic phase and data environment. (Sadowski *et al.,* 2021).

Strengths: Adaptability and Data-Driven Parameter Estimation

One of the main advantages of machine learning in COVID-19 prediction is its versatility. Unlike inflexible mathematical models with defined parameters, ML models may be retrained as new data is acquired. This adaptability enables them to respond swiftly to new variations, the introduction of vaccines, changes in social behavior, and government initiatives. This dynamic adaptability is especially useful during a quickly evolving epidemic, because assumptions established at the start may no longer be valid months later. Another feature of machine learning is its capacity to incorporate different, multidimensional inputs other than case numbers. These include transportation patterns, climate conditions, testing rates, and governmental actions. Using such data can boost predicted accuracy (Tian *et al.,* 2020).

Deep learning approaches improve on this by automatically extracting useful features from raw data, eliminating the need for considerable manual engineering. Importantly, ML offers a data-driven alternative to parameter estimation. It learns effective correlations directly from observations rather than using fixed transmission or recovery rates. This is particularly beneficial in novel illness

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scenarios where such factors may be unknown. These advantages have enabled ML techniques to outperform traditional models in a variety of scenarios, particularly when the disease's underlying dynamics are complicated and nonlinear (Kamalov *et al.*, 2022).

Weaknesses: Limited Interpretability and Dependence on Data Quality

Despite their capabilities, machine learning algorithms for COVID-19 prediction confront a number of obstacles. A key disadvantage is their restricted interpretability, also known as the "black box" problem. While ML models can achieve great predictive accuracy, they reveal little information about the underlying causal mechanisms that drive predictions. This lack of openness may limit their acceptance by public health officials, who seek precise justifications for policy decisions. Another drawback is their reliance on the availability and quality of data. COVID-19 datasets have been plagued by underreporting, regional variations, reporting delays, and biases caused by disparities in testing capability and tactics. These restrictions can impair the trustworthiness of ML predictions, especially in low-resource settings or early in the pandemic when data was scarce (Rahman *et al.*, 2024).

Machine learning models are prone to overfitting when trained on little data, catching noise rather than important patterns. This impairs their ability to generalize to future or unknown situations. Sudden disruptions, such as the development of a novel variety or the quick deployment of public health initiatives, might present difficulties for ML models trained on historical data. These disturbances frequently cause forecast mistakes. The absence of established evaluation techniques in research, such as variable use of error metrics or validation datasets, poses issues. As a result, it is difficult to compare models and determine best practices. These shortcomings highlight the importance of rigorous model creation, validation, and interaction with other methodologies.

Machine learning–ODE coupling

To represent the effect of changing variants, behavior, and interventions, we treat the transmission rate $\beta(t)$as an unknown function of observable covariates. Let

$$x(t) = (m(t), v_{\text{cov}}(t), q(t))$$

denote the vector of covariates at time t, where $m(t)$summarizes mobility, $v_{\text{cov}}(t)$denotes vaccination coverage, and $q(t)$denotes the proportion of high-transmissibility variants (such as Delta or Omicron). We parameterize $\beta(t)$using a recurrent neural network,

$$\beta_\theta(t) = \exp(f_\theta(x_{t-L+1:t})),$$

where $f_\theta$is an LSTM with parameters θ, and $x_{t-L+1:t}$is a sliding window of length Ldays of covariates. The exponential enforces $\beta_\theta(t) > 0$.

For a given parameter vector $\theta$and fixed biological rates $\kappa$and γ, we integrate system (1) forward in time using an ODE solver to obtain $S_\theta(t), E_\theta(t), I_\theta(t), R_\theta(t)$and the corresponding model-generated cases $C_{\text{model},\theta}(t)$. The parameters $\theta$are then learned by minimizing a loss function of the form

$$\mathcal{L}(\theta) = \sum_{t=t_0}^{t_T} w_t(C_{\text{model},\theta}(t) - C_{\text{obs}}(t))^2 + \lambda\mathcal{L}_{\text{reg}}(\theta),$$

where $w_t$are non-negative weights, $\lambda \geq 0$is a regularization parameter, and $\mathcal{L}_{\text{reg}}$penalizes excessive day-to-day variation in $\beta_\theta(t)$. This regularization plays a similar role to the physics-informed penalties used in other hybrid ML–ODE frameworks and helps prevent biologically implausible oscillations in the transmission rate.

Hybrid Machine Learning–ODE Frameworks

Hybrid modeling frameworks that integrate ML and ODEs have emerged as an effective paradigm for epidemic predictions and analysis. The justification for this integration stems from the complementary characteristics of both techniques. ODE-based epidemic models, such as the Susceptible-Exposed-Infectious-Recovered (SEIR) system, provide mechanical details about disease transmission. They use biologically interpretable characteristics, including infection rate (β), incubation rate (σ), and recovery rate (γ). However, they frequently suffer from restrictive assumptions and may struggle to react quickly to changing epidemiological data. In contrast, ML models excel at capturing nonlinear and complicated data-driven trends, but they lack interpretability and epidemiological foundation. A hybrid architecture takes advantage of ODEs' explanatory strength while improving flexibility and adaptability using machine learning (Rackauckas *et al.*, 2020; Karniadakis *et al.*, 2021).

Several methods have arisen for combining ML and ODEs. One solution involves utilizing machine learning to dynamically estimate ODE parameters from data. For example, recurrent

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neural networks (RNNs) and long short-term memory (LSTM) models have been used to estimate time-varying transmission rates, allowing SEIR-type models to respond to interventions or behavioral changes in real time (Raissi *et al.,* 2019). A second technique uses machine learning as a residual corrector for ODE predictions, with neural network learning to approximate the gap between observed epidemic data and the ODE's baseline projections. This modification increases forecasting accuracy while maintaining mechanistic interpretability. Incorporating ODE constraints into ML training regularizes the learning process and ensures predictions adhere to epidemiological principles like population conservation (S+Q+U+R=N) (S+E+I+R=N). This constraint-based learning ensures model interpretability and prevents biologically implausible predictions (Chen *et al.,* 2018)

Hybrid ML-ODE frameworks offer substantial advantages over solo techniques. External factors such as varied contact topologies, vaccine rollouts, and behavioral adjustments may be unaccounted for in independent ODE models. ML models, on the other hand, may overfit noisy data and yield insufficient epidemiological information. By combining the two, hybrid frameworks attain both predictive accuracy and theoretical coherence, allowing for adaptive but interpretable epidemic projections. For example, neural ODEs are a type of model in which the right-hand side of an ODE system is parameterized by a neural network. These models have shown excellent performance in predicting COVID-19 trends. At the same time, they preserve epidemiological plausibility (Rackauckas *et al.,* 2020).

Linking Hybrid ML–ODE Frameworks to COVID-19

COVID-19 presents an extremely persuasive case for hybrid modeling. The pandemic brings together a well-known mechanical structure with constantly changing detailed situations. Purely mechanical or data-driven models frequently fail to represent these complexities on their own. Mechanistic epidemic models, such as ODE models like SIR or SEIR variations, encapsulate basic epidemiological linkages (susceptibility → exposure → infectious → recovery). They are important for giving interpretable insights and doing absurd reasoning regarding interventions. Yet, SARS-CoV-2 has frequently shifted the ground reality. Nonstationary dynamics are caused by new variations with increased spread or immune evasion, rapid public-health measures, and significant shifts in human mobility and behavior. These modifications violate the assumption of time-homogeneous parameters in conventional ODE models. Empirical research on variation development clearly demonstrates this concept. For example, investigations of the B.1.1.7 (Alpha) branch indicated significantly higher reproduction rates than earlier lineages. Within a few months, this shift caused qualitative alterations in epidemic trajectories as well as the effectiveness of control measures. Variable-driven changes cannot be represented by a single constant parameter set in a traditional ODE model without time-varying reparameterization (Volz *et al.,* 2021; Davies *et al.,* 2021).

At the same time, the COVID-19 pandemic resulted in extremely large and diversified data sets. These included near-real-time case counts and hospitalizations, comprehensive genomic monitoring libraries, and high-resolution mobility and contact proxies obtained from mobile devices. In addition, extensive information on non-pharmaceutical interventions (NPIs) and vaccination rollouts was gathered. Studies have demonstrated that mobility and control tactics greatly affected transmission in early waves; thus, these data streams are critical factors when attempting to explain why transmission rates vary over time and place. The existence of various, partially overlapping data modalities creates both an opportunity and a problem. A model that maintains epidemiological limitations while learning complicated correlations across data streams can help decrease noise-induced overfitting (Gasser *et al.,* 2020).

Hybrid frameworks, which integrate mechanical ODE models with current machine learning components, are particularly well suited to this scenario because they combine structural priors and physical interpretability with flexible function approximation. Two main technical approaches are:

Defining time-varying components of an ODE (e.g., effective transmission rate) with a data-driven model such as a neural network (including continuous-time formulations such as neural ODE).

Applying the ODE structure within ML training (physics-informed neural networks, PINNs) to ensure that learned functions comply with epidemiological dynamics while adjusting.

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The Neural ODE framework provides a continuous-time latent dynamics model that can be trained end-to-end and seamlessly integrates with ODE solvers. PINNs provide an alternative method for solving inverse problems by learning unknown parameters or functions while penalizing residuals of the governing differential equations. These techniques have advanced quickly and have been applied to pandemic concerns in numerous recent studies (Ning et al, 2023).

A series of practical design decisions is required to bridge the gap between methodology and COVID-19-specific implementations.

First, create a temporally aligned time series of (at least) case counts, hospitalizations, deaths, vaccine coverage, genetic variant frequencies (from repositories such as national sequencing initiatives), and mobility or contact proxies. These covariates serve as inputs for ML components and observables for inverse parameter estimation. Their quality and reporting lags must be explicitly described. For example, using delay distributions or observation models.

For model architecture, select a compartmental ODE core appropriate for the question (e.g., SEIRV with vaccination and waning immunity) and select components for the ML module to learn. Common choices include a time-varying transmission rate β(t), detection or reporting rate, or an additional latent forcing term to account for unmodeled drivers. Neural ODEs are appealing when a continuous latent representation is sought and end-to-end backpropagation through an ODE solver is required. PINNs are beneficial when the inference issue is reframed as predicting unknown functions or parameters subject to ODE constraints.

Training and inference require careful consideration of recognition and uncertainty. To address this, researchers can utilize tactics like informative priors, covariate conditioning, and regularization (including physics-informed losses), as multiple combinations of time-varying β(t) and other latent processes can result in the same incidence curve. Bayesian or ensemble approaches are recommended for quantifying uncertainty because they provide plausible intervals for key values of concern, such as the time-varying reproduction rate or predicted hospitalizations under different scenarios. These uncertainty estimations are critical for informing policy decisions. Also, cross-validation procedures must account for time dependence by employing approaches such as rolling origin or forward-chaining validation, as well as retrospective counterfactual checks. Example, "if X% mobility reduction had not occurred, how would peak hospitalizations have changed?". Recent epidemiological research has effectively used hybrid or physics-aware ML models to fit historical COVID waves and generate scenario projections for policy planning, demonstrating the practical use of these techniques (Berkhahn & Ehrhardt, 2022).

Finally, it is critical to be clear about restrictions. Hybrid models inherit flaws from both parents. If tracked data are biased due to underreporting or shifting testing behavior, or if genomic sampling is unrepresentative, the learnt drivers will invariably reflect those biases unless addressed. Models with overly flexible time variation run the danger of fitting noise and providing overconfident projections. In contrast, inflexible mechanistic cores may fail to capture emergent events like immune escape. Disclosure of data sources, processing methods, and training procedures is critical. Sensitivity analyses are also significant since they account for delays, covariate inclusion, and model hyperparameters. Close engagement with domain specialists, such as epidemiologists and public health practitioners, maintains the application's credibility (Arik *et al.*, 2020). When executed properly, hybrid ML-ODE frameworks give a principled and interpretable toolbox. They are also adaptable enough to detect variant-driven changes and identify transmission causes. Also, they may assess the expected outcomes of treatments in a quickly changing pandemic landscape. Case studies of hybrid modeling in infectious disease prediction demonstrate its effectiveness. For example, LSTM networks were integrated with SEIR models to dynamically estimate infection rates during COVID-19, exceeding static ODE models in predicting accuracy. Similarly, neural ODEs have been used to model influenza dynamics, producing interpretable parameter estimates while reacting to real-world surveillance data (Chen *et al.*, 2018). These examples demonstrate how hybrid frameworks can improve epidemic preparedness by balancing accuracy, interpretability, and adaptability.

Implementation in COVID-19 Variant Spread Prediction

An increasing number of studies have investigated hybrid ML-ODE techniques for modelling

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COVID-19, revealing both the promise and the implementation challenges of adopting hybrid frameworks to variant-driven epidemics. Early hybrid approaches combined statistical time-series or neural networks with segmented models to improve short-term forecasts and account for nonstationary factors. Later work has moved toward more tightly coupled formulations such as PINNs and neural ODEs, which embed epidemic equations directly into the learning process (Ray & Reich, 2021).

Empirical evaluations in multiple settings show that hybrid methods frequently outperform conventional models on standard forecasting metrics, particularly when the goal is to forecast across periods of changing dynamics or when multiple data streams (cases, hospitalizations, mobility) are available to condition time-varying functions. These distinct benefits are derived from hybrid architectures, which maintain epidemiological interpretability while allowing ML components to describe time-varying driving factors or reporting processes that traditional ODEs with fixed parameters cannot. Using static parameter values in an ODE model can lead to inaccurate short-term incidence and healthcare burden during transitions. Hybrid systems overcome this restriction by allowing critical epidemiological characteristics to change over time. Factors such as variation prevalence from genomic surveillance or vaccination coverage might impact measures like transmission rate $\beta(t)$, hospitalization risk, and immune-escape effects (Li *et al.*, 2020).

Practical complications include:

- Delays and sampling biases in genome sequencing may affect estimated variant percentages.
- Co-circulation of variations can result in mixture dynamics requiring multi-strain compartmental extensions.
- Rapid changes in testing or reporting can lead to inaccurate estimates of infection rates.

In terms of comparative performance, systematic evaluations show that hybrid models are more accurate and robust during periods of structural change, for example, variant emergence or rapid policy adjustments. Although they are not always superior in all circumstances. In generally stable periods with abundant, high-quality data, well-tuned mechanistic models or regular ML forecasters can match hybrid performance while incurring reduced computing costs.

Evaluating Public Health Interventions Using Hybrid Models

Public-health strategies, such as vaccination campaigns, mask mandates, lockdowns and stay-at-home orders, school closures, and travel restrictions, have been the key tools for preventing SARS-CoV-2 transmission when pharmaceutical countermeasures were limited or still being implemented. Traditional compartmental ODE models, including SIR/SEIR versions and age- or risk-stratified extensions, have long been used to assess such strategies. These models are useful because they generate interpretable counterfactual results. In such models, an intervention might be represented by a change in parameter, such as a lower contact rate. The subsequent impacts on infections, hospitalizations, and mortality can then be modeled deterministically (Zivkovic *et al.*, 2020).

These ODE approaches are especially useful for defining the anticipated ranges of outcomes and investigating the qualitative tradeoffs between intervention timing and intensity. For example, early moderate limitations versus later, more stringent requirements.

However, purely mechanistic ODEs face three main limitations for policy evaluation in the context of COVID-19:

- Their parameters are often assumed to be time-homogeneous or forced to follow simple predefined schedules
- They may not account for heterogeneous and time-varying observation processes (such as changing testing rates)
- They struggle to incorporate and learn from the rich, high-frequency, multi-modal data streams (mobility, social behavior, genomic surveillance, vaccination uptake) that characterize the modern pandemic response.

Hybrid ML-ODE frameworks broaden the conventional toolkit by providing flexible but still constrained methods for simulating interventions and answering counterfactual queries with better accuracy. In a hybrid model, the mechanistic core maintains epidemiological structure, such as population conservation and compartmentalization. Meanwhile, ML components derive time-varying functions or latent driving terms from covariates. This method provides rapid benefits in the evaluation of interventions. Empirical applications of PINNs and neural ODEs in infectious disease forecasting demonstrate how physics-based loss terms and continuous-time latent dynamics can improve the

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stability and interpretability of counterfactual projections.

Evidence from US policy initiatives demonstrates the strengths and limitations of hybrid approaches. In several jurisdictions, mask mandates have been linked to reduced case growth and mortality in observational studies. After controlling confounders, hybrid models that condition mobility and testing intensity tend to attribute similar, albeit significantly diminished, effects. This shows that some of the raw connections reflect linked behavioral changes, such as reduced mobility when regulations are adopted. Yet, the impact of interventions like lockdowns and mask mandates varies by place and time, depending on factors such as population behavior, implementation timing, and local healthcare capacity. Hybrid models are especially useful for disentangling these conflicting variables, providing more nuanced information about when and where specific interventions are most beneficial.

Similarly, evaluations of vaccination campaigns using mechanistic models supplemented with ML modules for vaccine uptake and decreasing immunity have been successful. These models calculate saved hospitalizations and fatalities by integrating biologically informed compartments and data-driven uptake dynamics. Non-pharmaceutical treatments, such as lockdowns and school closures, produce more diverse outcomes. Several retrospective studies show that stringent, early lockdowns lowered peak incidence in several contexts. However, the extent of their effect on mortality differs between assessments and is dependent on model assumptions regarding behavioral adaptability, timing, and indirect consequences (Gasser *et al.*, 2020).

Despite the obvious benefits, practitioners should be aware of the limits when utilizing hybrid models for policy evaluation. If covariate assessment is skewed, ML components may mistakenly learn misleading correlations, for example, when mask-use surveys are unrepresentative or genomic surveillance is spatially scarce. Overly flexible function approximators run the risk of absorbing actual policy effects as "noise" unless they are restricted by the mechanistic core or priors. In contrast, overly rigid mechanical choices may compel the ML to adapt in ways that result in implausible counterfactuals

When these principles are followed, hybrid ML-ODE models provide a powerful, interpretable, and uncertainty-aware platform for evaluating interventions. They allow subtle problems to be investigated with credible uncertainty bounds, for example, "How much hospital demand would a 10-percentage-point increase in booster coverage avert this winter under Omicron-like transmissibility?"

Data Challenges and Methodological Considerations

Despite the promise of hybrid ML–ODE frameworks for modeling the spread of COVID-19 and informing public health responses, their implementation faces several data-related and methodological hurdles. A primary concern is data quality, particularly underreporting and delays in case detection, which can distort estimates of infection dynamics. Limited testing capacity, the presence of asymptomatic carriers, and regional disparities in reporting all contributed to systematic underestimation of cases, especially in the early phases of the pandemic (Li *et al.*, 2020).

Furthermore, biases imposed by testing procedures, such as favoring symptomatic people, resulted in incomplete or skewed datasets, undermining hybrid models' ability to generalize across populations (Chinazzi *et al.,* 2020). Additionally, genomic sequencing, which is crucial for variant-specific modeling, was unevenly spread across the United States, leaving gaps in the representation of developing strains (Alpert *et al.*, 2021). Such flaws can reduce the accuracy of models used to forecast variant-driven surges.

Uncertainty in parameter estimates creates a substantial challenge. Traditional ODE models are based on constant parameters like transmission and recovery rates, but these values change significantly between areas, times, and interventions. Machine learning provides methods for dynamically adjusting parameters based on real-world data, but this flexibility comes with dangers of overfitting and instability, particularly when training data is noisy or inadequate (Arik *et al.*, 2020). To achieve valid predictions, strong uncertainty quantification methodologies such as Bayesian inference, ensemble modeling, and probabilistic forecasting are required (Ray & Reich, 2021).

Finally, the competition must be acknowledged. Hybrid ML-ODE frameworks can be

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computationally demanding, particularly when expanding to national-level simulations or combining genetic and behavioral data. Training machine learning models on huge, multidimensional datasets while solving ODEs necessitates high-performance computer infrastructure and optimal techniques (Arik *et al.*, 2020). This reduces accessibility for public health agencies with limited resources and emphasizes the importance of efficient, scalable systems. Overcoming these issues is crucial for achieving the full potential of hybrid frameworks in pandemic forecasting and policy evaluation.

Strategic Insights for U.S. Health Security

The creation and implementation of hybrid ML-ODE systems have substantial implications for US pandemic preparedness and response. In comparison to classic epidemiological approaches, these models offer administrators more complex and adaptable tools for understanding disease patterns. Hybrid frameworks can improve forecast accuracy and timeliness by combining mechanistic knowledge of viral spread with machine learning's ability to learn from heterogeneous and changing data (Arik *et al.*, 2020; Ray & Reich, 2021). In the United States, where public health actions must be coordinated at the federal, state, and local levels, such models could provide uniform but adaptive tools to guide decisions across jurisdictional boundaries.

In real-time decision-making, hybrid models can act as early warning systems by detecting shifts in transmission patterns caused by new variations or population behavioral changes. These platforms can help hospitals manage their capacity, optimize vaccination delivery, and guide targeted non-pharmaceutical interventions (NPIs) like school closures or travel restrictions (Holmdahl and Buckee, 2020). For example, during the Omicron outbreak, hybrid frameworks that combined genetic data with case counts and movement patterns could have offered earlier warnings of rapid transmissibility, allowing for more agile interventions. This demonstrates the possibility of incorporating these models into operational dashboards for policymakers at the Centers for Disease Control and Prevention (CDC) and state health departments.

Beyond COVID-19, hybrid ML-ODE architectures show potential for larger applications in pandemic preparedness. The same approaches can be used to future infectious diseases with changing pathogen characteristics, nonlinear dynamics, and data heterogeneity. COVID-19 lessons highlight the importance of adaptable modeling infrastructures that may swiftly incorporate new data streams, such as genomic sequencing for pathogen identification or mobility data for behavioral insights (Gozes *et al.*, 2020). By incorporating hybrid modeling approaches into the United States' health security infrastructure, the government may better prepare for both naturally occurring and intentionally introduced biological threats.

The effective implementation of these approaches requires close interdisciplinary collaboration. Hybrid techniques combine epidemiology, data science, computer science, and public health, and their successful application requires cross-domain competence. Collaboration among university academics, government agencies, and private-sector partners will be required to ensure that models are scientifically valid, operationally applicable, and ethical (Vespignani *et al.*, 2020). Furthermore, promoting transparency and interpretability in hybrid models is critical for establishing confidence between decision-makers and the public, especially in the context of contentious interventions like lockdowns or vaccine mandates.

Finally, there are significant opportunities to incorporate hybrid ML-ODE frameworks into the United States' national health security infrastructure. Investments in data pipelines, high-performance computing, and secure data-sharing systems are critical to the process. Embedding hybrid models within agencies like the CDC, HHS, and BARDA would enable real-time information to directly drive preparedness and response efforts (Walensky & Del Rio, 2021). Such integration would not only improve COVID-19 administration but would also raise the country's resilience to future pandemics, in line with larger national security and public health concerns.

CONCLUSION

The COVID-19 pandemic has highlighted both the strengths and limitations of existing epidemiological modeling approaches, underscoring the need for frameworks that balance mechanistic rigor with data-driven adaptability. Hybrid ML–ODE models offer a promising solution by combining the interpretability and theoretical grounding of ODEs with the flexibility and predictive power of machine learning. Across this review, we have shown that hybrid ML–ODE frameworks provide unique advantages in

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predicting the spread of COVID-19 variants and evaluating public health interventions.

In conclusion, strengthening U.S. national preparedness requires embedding hybrid ML–ODE frameworks within health security infrastructure, supported by investments in data pipelines, high-performance computing, and ethical data governance. Beyond COVID-19, these approaches also hold great promise for understanding and managing other pressing health issues such as HIV, diabetes, and chronic kidney disease. By demonstrating adaptability across both infectious and chronic conditions, hybrid frameworks can form a cornerstone of a more resilient and future-ready public health system.

REFERENCES

1. Alpert, T., Brito, A. F., Lasek-Nesselquist, E., Rothman, J., Valesano, A. L., MacKay, M. J., ... & Grubaugh, N. D. “Early introductions and transmission of SARS-CoV-2 variant B.1.1.7 in the United States.” *Cell* 184.10 (2021): 2595–2604.
2. Arik, S., Li, C. L., Yoon, J., Sinha, R., Epshteyn, A., Le, L., ... & Pfister, T. “Interpretable sequence learning for COVID-19 forecasting.” *Advances in Neural Information Processing Systems* 33 (2020): 18807–18818.
3. Basit, H., Mushtaq, N., Bashir, S., & Morales, A. M. “Multivariate time series forecasting for electricity consumption using machine learning methods.” *Natural and Applied Sciences International Journal (NASIJ)* 4.1 (2023): 164–176.
4. Berkhahn, S., & Ehrhardt, M. “A physics-informed neural network to model COVID-19 infection and hospitalization scenarios.” *Advances in Continuous and Discrete Models* 2022.1 (2022): 61.
5. Chen, R. T., Rubanova, Y., Bettencourt, J., & Duvenaud, D. K. “Neural ordinary differential equations.” *Advances in Neural Information Processing Systems* 31 (2018).
6. Chen, S., Janies, D., Paul, R., & Thill, J. C. “Leveraging advances in data-driven deep learning methods for hybrid epidemic modeling.” *Epidemics* 48 (2024): 100782.
7. Chinazzi, M., Davis, J. T., Ajelli, M., Gioannini, C., Litvinova, M., Merler, S., ... & Vespignani, A. “The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak.” *Science* 368.6489 (2020): 395–400.
8. Davies, N. G., Abbott, S., Barnard, R. C., Jarvis, C. I., Kucharski, A. J., Munday, J. D., ... & Edmunds, W. J. “Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England.” *Science* 372.6538 (2021): eabg3055.
9. Gasser, U., Ienca, M., Scheibner, J., Sleigh, J., & Vayena, E. “Digital tools against COVID-19: taxonomy, ethical challenges, and navigation aid.” *The Lancet Digital Health* 2.8 (2020): e425–e434.
10. Getz, W. M., Salter, R., & Mgbara, W. “Adequacy of SEIR models when epidemics have spatial structure: Ebola in Sierra Leone.” *Philosophical Transactions of the Royal Society B* 374.1775 (2019): 20180282.
11. Gozes, O., Frid-Adar, M., Greenspan, H., Browning, P. D., Zhang, H., Ji, W., ... & Siegel, E. “Rapid AI development cycle for the coronavirus (COVID-19) pandemic: Initial results for automated detection & patient monitoring using deep learning CT image analysis.” *arXiv preprint* arXiv:2003.05037 (2020).
12. Holmdahl, I., & Buckee, C. “Wrong but useful—what COVID-19 epidemiologic models can and cannot tell us.” *New England Journal of Medicine* 383.4 (2020): 303–305.
13. Kamalov, F., Rajab, K., Cherukuri, A. K., Elnagar, A., & Safaraliev, M. “Deep learning for COVID-19 forecasting: State-of-the-art review.” *Neurocomputing* 511 (2022): 142–154.
14. Karniadakis, G. E., Kevrekidis, I. G., Lu, L., Perdikaris, P., Wang, S., & Yang, L. “Physics-informed machine learning.” *Nature Reviews Physics* (2021).
15. Kissler, S., Tedijanto, C., Lipsitch, M., & Grad, Y. H. “Social distancing strategies for curbing the COVID-19 epidemic.” *MedRxiv* (2020-03).
16. Li, R., Pei, S., Chen, B., Song, Y., Zhang, T., Yang, W., & Shaman, J. “Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2).” *Science* 368.6490 (2020): 489–493.
17. Ning, X., Guan, J., Li, X. A., Wei, Y., & Chen, F. “Physics-informed neural networks integrating compartmental model for analyzing COVID-19 transmission dynamics.” *Viruses* 15.8 (2023): 1749.
18. Opoku, J. A., & Sefa-Boateng, Y. “Advancing Domestic Semiconductor Manufacturing: A Critical Review of Novel Processing

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Technologies.” *Journal of Engineering and Computer Sciences* 4.9 (2025): 316–323.

19. Plötzke, L., Wendler, A., Schmieding, R., & Kühn, M. J. “Revisiting the Linear Chain Trick in epidemiological models: Implications of underlying assumptions for numerical solutions.” *arXiv preprint* arXiv:2412.09140 (2024).
20. Polcz, P., Reguly, I. Z., Tornai, K., Juhász, J., Pongor, S., Csikász-Nagy, A., & Szederkényi, G. “Smart epidemic control: A hybrid model blending ODEs and agent-based simulations for optimal, real-world intervention planning.” *PLOS Computational Biology* 21.5 (2025): e1013028.
21. Rackauckas, C., Ma, Y., Martensen, J., Warner, C., Zubov, K., Supekar, R., ... & Edelman, A. “Universal differential equations for scientific machine learning.” *arXiv preprint* arXiv:2001.04385 (2020).
22. Rahman, N., O'Cathail, C., Zyoud, A., Sokolov, A., Oude Munnink, B., Grüning, B., ... & Cochrane, G. “Mobilisation and analyses of publicly available SARS-CoV-2 data for pandemic responses.” *Microbial Genomics* 10.2 (2024): 001188.
23. Raissi, M., Perdikaris, P., & Karniadakis, G. E. “Physics-informed neural networks: A deep learning framework for solving forward and inverse problems involving nonlinear partial differential equations.” *Journal of Computational Physics* 378 (2019): 686–707.
24. Ray, E. L., & Reich, N. G. “Prediction of infectious disease epidemics via weighted density ensembles.” *PLOS Computational Biology* 17.8 (2021): e1009385.
25. Sadowski, A., Galar, Z., Walasek, R., Zimon, G., & Engelseth, P. “Big data insight on global mobility during the COVID-19 pandemic lockdown.” *Journal of Big Data* 8.1 (2021): 78.
26. Tian, Y., Luthra, I., & Zhang, X. “Forecasting COVID-19 cases using Machine Learning models.” *MedRxiv* (2020-07).
27. Vespignani, A., Tian, H., Dye, C., Lloyd-Smith, J. O., Eggo, R. M., Shrestha, M., ... & Leung, G. M. “Modelling COVID-19.” *Nature Reviews Physics* 2.6 (2020): 279–281.
28. Volz, E., Mishra, S., Chand, M., Barrett, J. C., Johnson, R., Geidelberg, L., ... & Ferguson, N. M. “Assessing transmissibility of SARS-CoV-2 lineage B.1.1.7 in England.” *Nature* 593.7858 (2021): 266–269.
29. Walensky, R. P., & Del Rio, C. “From mitigation to containment of the COVID-19 pandemic: putting the SARS-CoV-2 genie back in the bottle.” *JAMA* 323.19 (2020): 1889–1890.
30. Yang, H. M., Lombardi Junior, L. P., & Yang, A. C. “Are the SIR and SEIR models suitable to estimate the basic reproduction number for the COVID-19 epidemic?” *MedRxiv* (2020-10).
31. Zhao, W., Sun, Y., Li, Y., & Guan, W. “Prediction of COVID-19 data using hybrid modeling approaches.” *Frontiers in Public Health* 10 (2022): 923978.
32. Zivkovic, M., Bacanin, N., Venkatachalam, K., Nayyar, A., Djordjevic, A., Strumberger, I., & Al-Turjman, F. “COVID-19 cases prediction by using hybrid machine learning and beetle antennae search approach.” *Sustainable Cities and Society* 66 (2021): 102669.

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