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REVIEW ARTICLE

A comprehensive review and unified taxonomy of intelligent hybrid fractional-order models incorporated with machine learning in healthcare applications

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ABSTRACT

Fractional-order differential equations (FDEs) describe memory and hereditary effects that integer-order models cannot capture, while machine-learning (ML) methods extract patterns from large and noisy clinical data but often lack mechanistic meaning. Combining the two has become an active research direction in healthcare, yet the literature is spread across many disease areas and there is no common way to describe how the coupling is actually implemented. This review addresses that gap. Following the PRISMA 2020 guidelines, we searched PubMed and OpenAlex for journal articles published between January 2018 and March 2026 and used Scopus, Web of Science, and Google Scholar for citation searching. After screening 209 records, 43 hybrid FDE–ML studies were included. We propose a two-level taxonomy in which three coupling types (ML-informed estimation of fractional parameters; fractional physics-informed neural networks (FPINNs) and neural solvers; and fractional preprocessing of features) describe the mathematical link, and a fourth type describes the deployment layer (simulation engine and clinician-facing interface). We define a hybrid operator $\mathcal{Q}$ with an explicit domain and range that expresses every reviewed model as a composition of these components, and we illustrate it on the public UCI Dermatology dataset using repeated stratified cross-validation, baseline classifiers, and bootstrap confidence intervals. The evidence tables show that FPINNs and neural solvers dominate infectious-disease modelling, whereas oncology and cardiometabolic studies more often combine several types. Reported gains are study-specific, so we present them as representative values rather than pooled effects. We also discuss computational cost, data scarcity, uncertainty quantification, regulatory validation, and fairness. The main contribution of the work is a reproducible classification and a formal operator that can guide model selection, reporting, and validation in future hybrid fractional–ML studies in healthcare.

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1. Introduction

Motivation. Healthcare systems are under growing pressure from population ageing, the rising number of patients with complex chronic diseases, repeated epidemic outbreaks and a rapid increase in the volume of clinical data that has to be interpreted.[1–6] Mathematical models help clinicians and public-health planners reason about these problems, but the two dominant families of models have complementary weaknesses. Classical compartmental models built from integer-order ordinary differential equations give a clear picture of population dynamics, yet they assume that the rate of change depends only on the present state and therefore miss memory, delayed response and hereditary effects that are common in biology.[7–9] Data-driven ML methods extract patterns effectively, but they generalise poorly when medical datasets are small, noisy and heterogeneous, and their limited transparency makes clinical interpretation and regulatory approval difficult.[10–13]

Machine learning background. The ML side of the hybrids reviewed here rests on a small number of foundational methods. Support vector machines,[14] random forests[15] and gradient-boosted trees such as XGBoost[16] are still the most widely used tools for tabular clinical data, while deep neural networks[17] dominate imaging and signal analysis. Physics-informed neural networks (PINNs)[18] and the wider field of physics-informed machine learning[19] showed how a differential equation can be placed inside the training loss of a network, which is the key idea behind most fractional hybrids. Recent applications show how quickly these tools are moving into medicine, for example attention-guided UNet++ ensembles for brain tumour segmentation in MRI[20] and fuzzy-logic-driven ML frameworks that handle uncertain class boundaries in multi-class prediction.[21]

Fractional calculus background. Fractional calculus offers a natural way to include memory in a model,[22–25] and it has been used in many other applications.[26,27] The Caputo derivative, and related operators such as the Riemann–Liouville and Atangana–Baleanu derivatives, use non-local kernels so that the present state depends on the whole past trajectory.[28–30] The theory of fractional systems, including existence, controllability and evolution inclusions for Sobolev-type equations of order $1 < r < 2$,[31,32] gives the analytical tools needed to study such models. Fractional-order models reproduce long-term physiological and pathological patterns well,[33,34] but on their own they are not designed to learn from large raw datasets.[35,36] This gap led to the integration of modern ML with FDE systems.[37,38] The survey in[39] shows that variable-order, adaptive-order, hybrid and distributed-order systems are well suited to difficult optimisation problems in AI. One common combination uses PINNs with fractional residuals in the loss, giving hybrids that solve the equations, identify parameters and estimate uncertainty within a single stable procedure.[40–42] Another, used in,[43] calibrates the FDE system with ML: the best-performing classifier supplies initial conditions and parameters, and its class probabilities modulate the simulated trajectories, so that a single pipeline performs both static classification and dynamic progression modelling.

Existing reviews and the gap. Several reviews cover parts of this field. They survey fractional epidemic models in the life sciences,[44,45] PINNs for differential equations,[46,47] PINNs in physiological signal processing,[48] fractional-order sensing and filtering,[49] and the fractional dynamics that underlie big data and ML.[50] Others address hybrid mechanistic–ML frameworks in biomedicine,[51,52] physics-informed deep learning,[53] fractional system identification with AI,[54] distributed-order models,[55] inverse problems in rheology,[56] fractional neural networks in medical imaging,[57] glucose–insulin dynamics,[58] spectrally adapted FPINNs,[59] stability of fractional neural networks[60] and fractional-order controllers.[61] None of them, however, classifies the different ways in which FDEs and ML are coupled across clinical domains, and none gives a formal object that a reader can use to compare one hybrid with another. In addition, the uncertainty of hybrid predictions is rarely quantified, even though clinical use depends on such qualification.[62]

Novelty and contributions. This review is, to our knowledge, the first to organise intelligent hybrid FDE–ML models in healthcare around the mechanism of coupling rather than around the disease. Its contributions are as follows.

(i) A transparent PRISMA 2020 review[63] with exact search strings, database counts, duplicate removal and reasons for exclusion (Section 3).
(ii) A two-level taxonomy with three mathematical coupling types and one deployment layer, together with an explanation of why the deployment layer is treated separately (Section 6).
(iii) A rigorous definition of the hybrid operator $\mathcal{Q}$, with domain, range and input–output relation, which expresses every reviewed model as a composition of its components (Section 6).
(iv) Evidence tables and figures that summarise the 43 included studies by domain, coupling

type and reported metric, with a clear statement of which values are study-specific (Sections 4 and 5).

(v) A worked example on a public dataset, validated with repeated stratified cross-validation, baseline classifiers and bootstrap confidence intervals, with an explicit discussion of what such an example can and cannot show (Section 7).

Organisation. Section 2 recalls the fractional operators, the ML integration strategies and the role of uncertainty quantification. Section 3 describes the review method. Section 4 surveys the included hybrid models and Section 5 analyses their performance and limitations. Section 6 presents the taxonomy and the operator $\mathcal{Q}$, and Section 7 applies it to a dermatology dataset. Section 8 discusses challenges and ethical issues, Section 9 outlines future directions, and Section 10 concludes the paper.

2. Fundamental concepts of FDE and its hybrid integration with ML systems

2.1. Fractional calculus in healthcare modeling

The mathematical foundation for incorporating memory and hereditary effects into healthcare models is often provided by the Caputo fractional derivative[64,65] of order ϑ, $m-1<\vartheta<m$, $m\in\mathbb{N}$, defined as

$$ {}^{C}D_{\upsilon}^{\vartheta}h(\upsilon)=\frac{1}{\Gamma(m-\vartheta)}\int_{0}^{\upsilon}(\upsilon-s)^{m-\vartheta-1}h^{(m)}(s)\,ds, \tag{1}$$

where $m=\lceil\vartheta\rceil$; for $0<\vartheta<1$, which is the case used throughout this review, $m=1$. The Caputo operator is nonlocal because it computes the current rate of change from all past values of the function. This makes it well suited to pharmacokinetics, epidemic progression, tumour growth and neurodegenerative processes, in which previous states influence present behaviour. The main benefit of fractional-order models is their natural capacity to include the entire history of the system through the convolution-type integral kernel $(\upsilon-s)^{m-\vartheta-1}$. Because of these memory effects, FDEs are well suited to describing viscoelastic behaviour, anomalous diffusion, biological degradation and disease development. The stability of fractional systems is usually established with Lyapunov functions and fixed-point theory, which show that the memory parameter influences both the equilibrium pattern and the outbreak threshold.

2.2. Machine learning integration strategies

Fractional calculus is built into modern intelligent hybrid systems through machine-learning frameworks that solve, identify and optimise fractional-order differential equations.[66–68] The main solution method uses PINNs, which impose fractional differential equations as soft constraints in the training loss:[69–71]

$$\mathcal{L}=\mathcal{L}_{\text{data}}+\lambda\mathcal{L}_{\text{physics}}, \tag{2}$$

where $\mathcal{L}_{\text{data}}$ measures fidelity to observed clinical measurements, $\mathcal{L}_{\text{physics}}$ penalises violations of the fractional operator (commonly discretised by the L1 scheme or spectral methods) and $\lambda>0$ balances the two terms. Training with these two objectives allows the network to learn the solution while discovering unknown parameters, including the memory order ϑ.

Four principal integration strategies have emerged across the surveyed literature. The first type (ML-informed FDE parameters) uses standard machine-learning techniques, such as XGBoost and decision trees, to estimate time-varying parameters and risk scores that are then passed to a fractional differential equation solver. The second type (FPINN solvers) uses deep neural networks as universal function approximators to solve fractional systems directly while extracting ϑ from data. The third type (fractional preprocessing) enhances standard ML pipelines by extracting memory kernels and fractional features, which improve the input data for subsequent classification and regression models. The fourth type (hybrid simulation and GUI) wraps one or more of the first three types in a real-time simulation engine with a graphical user interface for clinicians. As explained in Section 6, Types 1–3 describe how the equations and the learning model are coupled, whereas Type 4 describes how the coupled model is delivered to the user. The resulting hybrid models achieve numerical stability through predictor–corrector[72] and Grünwald–Letnikov schemes and allow uncertainty quantification, which links data-based learning with physical modelling of dynamic systems.

2.3. Uncertainty quantification and the role of fuzzy numbers

A clinical prediction is only useful when its reliability is known. Two sources of uncertainty matter for hybrid FDE–ML models. Aleatoric uncertainty arises from noisy, incomplete or imprecise measurements, and epistemic uncertainty arises from limited data and from the choice of model, including

the value of the memory order ϑ.[62] Probabilistic tools such as Bayesian neural networks, deep ensembles and bootstrap resampling describe uncertainty through probability distributions. Fuzzy numbers[73] offer a complementary description that is better suited to vague or linguistically graded clinical information, for example "mild", "moderate" or "severe" histopathological grades. A triangular fuzzy number $\tilde{a} = (a_1, a_2, a_3)$ with $a_1 \le a_2 \le a_3$ has the membership function

$$\mu_{\tilde{a}}(x) = \max\Big\{\min\Big(\frac{x - a_1}{a_2 - a_1}, \frac{a_3 - x}{a_3 - a_2}\Big), 0\Big\}, \quad (3)$$

and its α-cuts $[\tilde{a}]^\alpha = [a_1 + \alpha(a_2 - a_1),\ a_3 - \alpha(a_3 - a_2)]$, $\alpha \in [0, 1]$, turn a fuzzy parameter into a family of intervals. When a parameter of the fractional system, or the order ϑ itself, is treated as a fuzzy number, solving the system for each α-cut produces a band of trajectories instead of a single curve. This band shows clinicians how far a prediction can move within the range of plausible inputs. Fuzzy logic has already been combined with ML for multi-class prediction[21] and with fractional neural networks,[60] and fuzzy aggregation operators have been used in IoT-based healthcare selection.[74] In the reviewed hybrid literature, however, uncertainty is usually reported only through point metrics such as MSE or AUC. For this reason we treat uncertainty quantification, whether probabilistic or fuzzy, as a reporting requirement in the proposed framework (Section 6), and we report confidence intervals in the worked example (Section 7).

3. Review methodology

The review follows the PRISMA 2020 statement.[63] The complete screening process is summarised in **Figure 1**, and the search strings are listed in **Table 1**.

Table 1. Search strings used in the systematic queries (title and abstract fields, 1 January 2018 to 31 March 2026)

Database	Query	Records
PubMed	("fractional order" OR "fractional-order" OR "fractional derivative" OR "fractional calculus" OR Caputo) AND ("machine learning" OR "neural network" OR "physics-informed" OR PINN OR "deep learning") AND (disease OR epidemic OR cancer OR clinical OR medical OR healthcare OR patient*)	55
OpenAlex	("fractional order" OR "fractional-order" OR Caputo) AND ("machine learning" OR "neural network" OR "physics-informed") AND (disease OR epidemic OR cancer OR clinical OR medical OR healthcare)	229
Total		284

Information sources and search. Systematic queries were run in PubMed and in OpenAlex, an open bibliographic index that covers the journals indexed by Scopus and Web of Science. The last search was run on 31 March 2026 and covered publications from 1 January 2018 to 31 March 2026. Each query combined three blocks of terms (fractional operator, learning component, and healthcare application) in the title or abstract. Scopus, Web of Science, and Google Scholar were then used for backward and forward citation searching of the included studies.

Eligibility criteria. A study was included when it (a) was a peer-reviewed journal article, (b) addressed a healthcare, epidemiological, or biomedical application, (c) used a fractional-order operator (Caputo, Caputo–Fabrizio, Atangana–Baleanu, Hattaf or a fractal–fractional operator), and (d) coupled that operator with an ML or neural component that was trained on data or used to solve the model. Studies that used only fractional calculus or only ML were excluded, as were preprints, conference papers, book chapters, editorials, and errata.

Selection process. Records from the two databases were merged and duplicates were removed by DOI and, when no DOI was available, by normalised title. Titles and abstracts were then screened against criteria (b)–(d), and the remaining reports were read in full. At the full-text stage we excluded reports that gave no quantitative validation metric, that repeated a model family already represented by a more complete study, or in which the fractional component was used only as an optimiser or for image encryption rather than as a dynamical model.

Results of the search. The database queries returned 284 records (PubMed 55, OpenAlex 229).

After removing 33 duplicates and 42 records of an ineligible type, 209 records were screened and 110 were excluded (43 without a healthcare application, 42 without a fractional operator and 25 without an ML component). Of the 99 reports assessed in full, 70 were excluded and 29 were included. Citation searching added 14 studies, so 43 hybrid FDE–ML studies were included in the synthesis (**Tables 2**–**4**). The other works cited in this paper (reviews, methodological papers, and background references) were used to frame the discussion and were not part of the evidence synthesis.

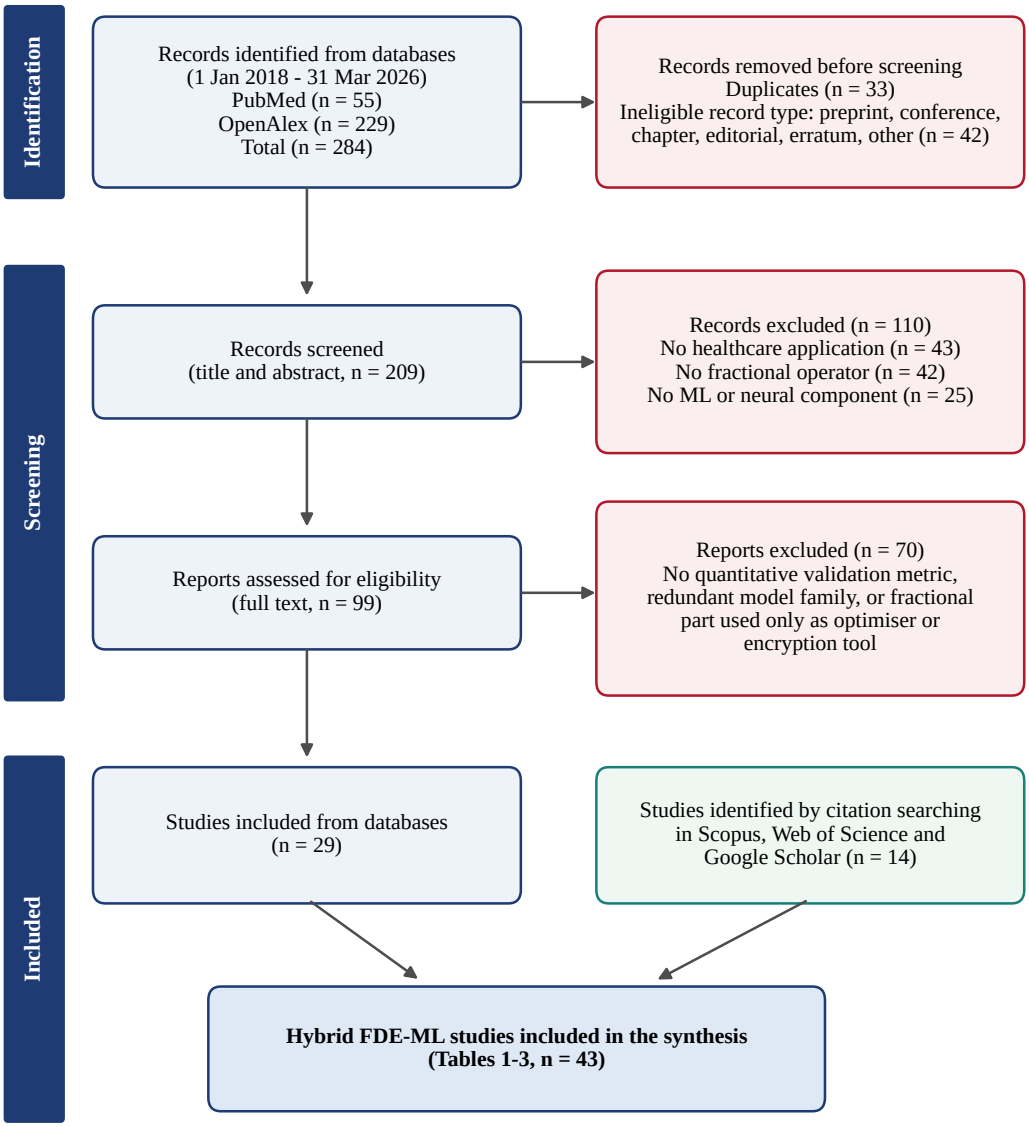


Figure 1. PRISMA 2020 flow diagram of the study selection

Quality appraisal and data extraction. Each included study was appraised on three criteria: mechanistic fidelity (whether the fractional model has an interpretable structure), clinical relevance (whether real clinical or epidemiological data were used), and reproducibility (whether data, parameters, and validation protocol are reported). The appraisal was used to describe the evidence and not to weight it. From each study we extracted the clinical domain, the fractional operator, the ML component, the coupling type, and the main reported metric.

4. Survey of Intelligent Hybrid Models

Table 4 lists representative values reported by selected included studies. They illustrate the range of results in the literature and are not a pooled estimate.

Table 2. The 43 intelligent hybrid FDE and ML studies included in the review, grouped by clinical domain

Domain	Hybrid Technique	Key Application and Results
Infectious diseases and epidemiology	PINNs for fractional SIR/SEIR models	Time-dependent parameters with superior identifiability and predictability[75]
	ANN-LMB, RF, SVM on fractional helminth model	99.8% accuracy in disease dynamics prediction[76]
	Deep Neural Networks for fractional compartmental model	Rotavirus epidemic modeling with high fidelity[77]
	LMBPNN (10 neurons, sigmoid) for Caputo fractional saturated-incidence epidemic model (SIVR compartments)	Captures vaccination/immunity effects; MSE 10^{-9} to 10^{-11} across $\rho = 0.2$–0.9; rapid convergence[78]
	Normalized Caputo-Fabrizio fractional SIRD + DNN (3 hidden layers)	Epidemic forecasting with memory effects; MSE as low as 5.6×10^{-8}, RMSE < 0.17; strong regression coefficients[79]
	Efficient ML + fractional calculus model	Early COVID-19 prediction using hybrid data-driven fractional dynamics[80]
	PINN + Caputo–Fabrizio fractional HCV model	Hepatitis C transmission (6-compartment); $R^2 \geq 0.97$ (most compartments), avg. $R^2 = 0.9621$; acute transmission drives $> 51\%$ new cases[81]
	ANN computing framework for fractional HCV model	Hepatitis C virus dynamics; accurate ANN prediction of the fractional compartments[82]
	LMB–DNN + Atangana–Baleanu–Caputo fractional rabies model	Human–dog rabies (8-compartment); MSE 10^{-8}–10^{-6}, absolute errors $< 10^{-5}$; memory effects control outbreak timing[83]
	DNN + Caputo fractional Omicron model	Omicron dynamics with vaccination/booster; high training/testing/validation accuracy via deep neural approximation[84]
	BR-DNN surrogate for fractional SITR epidemic model	Saturated-incidence SITR dynamics; low MSE validation, high-fidelity surrogate for outbreak forecasting[85]
	ANN + normalized Caputo–Fabrizio fractional SIQR model	Quarantine-inclusive epidemic; high training/validation correlation and accurate trajectory prediction[86]
	ANN + Junaid transform for fractional smoking epidemic model	Addiction/spread dynamics; high-accuracy approximation with rapid convergence[87]
	PINN for SIR epidemic with Hattaf fractional derivative	Memory-aware SIR dynamics; accurate inverse problem solving and parameter inference[88]
	PINN (spatial identity neural network) for epidemic forecasting	Enhancing epidemic forecasting with physics-informed spatial identity neural network; superior accuracy in network-based spreading[89]
	Novel fractional-order model with data-driven validation	Dynamics of complex epidemic spreading in networks; data-driven validation and high-fidelity prediction[90]

(*Cont'd...*)

Table 2. (*Continued*)

Domain	Hybrid Technique	Key Application and Results
Infectious diseases and epidemiology	Fractional-order derivatives + deep neural networks for poliomyelitis	Poliomyelitis dynamics with fractional derivatives and DNNs; accurate long-term prediction and control[91]
	PINN for COVID-19 infection and hospitalization	Physics-informed neural network modeling of COVID-19 infection and hospitalization scenarios; high-accuracy scenario forecasting[92]
	PINNs for infectious diseases during travel	Machine learning for predicting the dynamics of infectious diseases during travel through PINNs[93]
	PINNs for biological and epidemiological dynamical systems	Using PINN for modeling biological and epidemiological dynamical systems; robust performance across datasets[94]
Oncology	XGBoost + Caputo fractional differential equations	Cervical cancer prediction (AUC = 0.992, weighted MSE = 0.0042)[95]
	Levenberg–Marquardt trained DNN	Fractional-order breast cancer model[96]
	Hybrid ML-FDE framework	Multi-scale breast cancer progression modeling[97]
	Radial Basis Neural Network (RBNN) for fractional lung cancer operation model	Tumor/immune cell dynamics; minimal absolute errors vs. Runge–Kutta reference; validated by regression & error histograms[98]
	LMBPNN (18 neurons, sigmoid) for fractional lung cancer operation system	Immune/epithelial cells + oncogenes/vessels; low MSE & absolute errors; fractional orders outperform integer-order[99]
	Fractional recurrent neural network (RNN) observer	Chaotic cancer cell behavior synchronization; tumor/healthy/immune cell MSE < 0.0068; faster convergence than integer-order RNN[100]
	Fractional-order neural network for heterogeneous cancer cell propensity	Diagnostic/predictive transdifferentiability of cancer cells; robust modeling of transient biological properties[101]
	Fractional-order cancer-immune interaction model with neural analysis	Avascular T-cell/antibody dynamics; effective control mechanism and stability insights[102]
	PINN for parameter inference in tumor model	Physics-informed neural network for parameter inference in a tumor model; accurate patient-specific estimation[103]
	Hybrid bio-inspired deep learning for brain tumor classification	Hybrid bio-inspired augmented hyper-parameter deep learning model for brain tumor classification; high diagnostic accuracy[104]
	Neural fractional-order differential equation for medical image segmentation	Optimal medical image segmentation model using neural fractional-order differential equation for accurate disease detection[105]
	PINNs for patient-specific tumor microenvironment modeling	Physics-informed neural networks enable patient-specific tumor microenvironment modeling with integer- and fractional-order dynamics; precise therapy parameter identification[106]

(*Cont'd...*)

Table 2. (*Continued*)

Domain	Hybrid Technique	Key Application and Results
Cardiology, metabolic and neurology	Fractional-order + Decision Trees	Heart disease prediction with integrated GUI[107]
	Machine Learning + Fractional Calculus	Diabetes risk prediction in women[108]
	PINN	Fractional modeling of Alzheimer's disease capturing amyloid/tau memory effects[109]
	Fully Recurrent Neural Network (FRNN) + fractional-order learning	Chaotic diabetes systems (T1D/T2D/hypoglycemia); lowest RMSE (0.00024) and FIT% up to 97.13% vs. baselines[110]
	Fractional-order operator for Alzheimer's dynamics with neural integration	Long-term memory effects in neurodegeneration; enhanced predictive accuracy[111]
	AI-computing analysis of fractional COVID-19 epidemic (neurological sequelae)	Post-infection neurological modeling; high-accuracy ML-fractional hybrid predictions[112]
	PINNs for valve tissue elastic parameters	Noninvasive method for determining elastic parameters of valve tissue using PINNs; accurate cardiology application[113]
	Transfer learning on PINNs for aortic hemodynamics	Transfer learning on PINNs for tracking hemodynamics in the evolving false lumen of dissected aorta[114]
Emerging viral infections	Stochastic computing neural network (SCG) + Caputo fractional	Nipah virus (NiV) dynamics for healthcare disaster management; rapid convergence and low absolute errors[115]
	PINN for fractional SEIHDR	Epidemic inference with memory effects; high accuracy in parameter/state estimation from COVID-like data[116]
Dermatology	Hybrid FDE-ML framework	Psoriasis prediction and clinical decision support using UCI Dermatology dataset[117]

Table 3. Coupling type and key reported metric of each included study (types as defined in Section 6)

Study	Domain	Hybrid Type	Key Metric
[75]	General Epi	2	Superior identifiability
[76]	Helminth	1/3	99.83% accuracy
[77]	Rotavirus Epidemic	2	High-fidelity modeling
[78]	Infectious (Epidemic)	2	MSE 10^{-9} to 10^{-11}
[79]	Infectious (SIRD)	2	MSE 5.6×10^{-8}, RMSE < 0.17
[80]	COVID-19 Prediction	1/3	Early prediction with hybrid ML-FDE
[81]	Hepatitis C (HCV)	2	Avg. $R^2 = 0.9621$, low RMSE ($\sim$0.0095)
[83]	Rabies Epidemic	2	MSE 10^{-8}–10^{-6}, errors $< 10^{-5}$
[84]	Omicron Epidemic	2	High training/testing/validation accuracy
[85]	SITR Epidemic	2	Low MSE, high-fidelity BR-DNN surrogate
[86]	SIQR Epidemic	2	High training/validation correlation
[87]	Smoking Epidemic	2	High-accuracy ANN approximation
[88]	SIR (Hattaf) Epidemic	2	Accurate parameter inference
[89]	Epidemic Forecasting	2	Enhanced spatial forecasting accuracy
[90]	Complex Epidemic Networks	1/3	Data-driven validation with high fidelity
[91]	Poliomyelitis Dynamics	2	Accurate fractional DNN prediction
[92]	COVID-19 Scenarios	2	High-accuracy infection/hospitalization modeling
[93]	Infectious Diseases Travel	2	Superior travel-dynamics prediction via PINNs
[94]	Bio/Epidemiological Systems	2	Robust PINN modeling across datasets
[95]	Cervical Cancer	1/3/4	AUC = 0.992, with GUI integration
[96]	Breast Cancer	2	High-accuracy neural solution
[97]	Breast Cancer	1/3/4	Multi-scale prediction with hybrid dynamics
[98]	Oncology (Lung Cancer)	2	Minimal absolute errors (regression-validated)
[99]	Oncology (Lung Cancer)	2	Low MSE & absolute errors; outperforms integer-order models
[100]	Oncology (Cancer Cells)	2	Synchronization MSE < 0.0068; faster convergence
[101]	Heterogeneous Cancer Cells	2	Robust transdifferentiability prediction
[102]	Cancer-Immune Interaction	2	Effective control & stability
[103]	Tumor Model	2	Accurate parameter inference in tumors
[104]	Brain Tumor Classification	1/3	High diagnostic accuracy with hybrid DL
[105]	Medical Image Segmentation	3	Accurate disease detection via neural FDE
[106]	Tumor Microenvironment	2	Patient-specific therapy parameter identification
[107]	Heart Disease	1/4	Prediction with integrated GUI
[108]	Diabetes	1/4	Risk prediction in women
[109]	Alzheimer's	2	Physics-compliant dynamics
[110]	Diabetes (Chaotic)	2	RMSE 0.00024, FIT% up to 97.13%
[82]	Hepatitis C (HCV)	2	High-accuracy ANN prediction of HCV dynamics
[111]	Alzheimer's Dynamics	2	Enhanced long-term memory prediction
[112]	COVID Neurological Sequelae	2	High-accuracy AI-fractional predictions
[113]	Valve Tissue (Cardiology)	2	Noninvasive elastic parameter estimation
[114]	Aortic Hemodynamics	2	Transfer-learning PINN tracking accuracy
[115]	Nipah Virus	2	Low absolute errors, rapid convergence
[116]	SEIHDR Epidemic	2	High accuracy in parameter/state inference
[117]	Dermatology	1/3/4	Prediction and clinical decision support (UCI dataset)

5. Techniques, integration strategies, and performance analysis

Table 2 lists the 43 included studies and **Table 3** assigns each of them to one or more coupling types. **Table 4** collects representative metrics reported by selected studies. We stress that these values cannot be averaged. The studies use different data sets, models, metrics and validation protocols, and many of the very small errors measure the agreement between a neural surrogate and a numerical reference solution of the same fractional model rather than the agreement with clinical observations. For this reason we do not report a pooled percentage improvement. Instead, we summarise the evidence as key findings, each linked to the table or figure that supports it (**Table 5**).

The fractional order ϑ is the parameter that links all strategies. Fractional derivatives (Caputo, Caputo–Fabrizio or Atangana–Baleanu) are embedded either in the loss of a PINN or in the features passed to a conventional ML pipeline. The fractional systems themselves are solved by specialised neural solvers such as LMBPNN, RBNN and stochastic computing networks, which are trained with Levenberg–Marquardt or sequential quadratic programming. Among the studies that report such metrics, residual mean square errors stay below 0.01. Taken together, these frameworks can act as disease-progression models and,

potentially, as interpretable digital-twin components, although none of the included studies has yet demonstrated such use in a prospective clinical setting.

Table 4. Representative metrics reported in selected included studies. Each value comes from the cited study under its own data set, metric and protocol, so the values are not directly comparable and are not pooled

Metric	Reported value	Model and application	Study
MSE (neural solver vs. reference solution)	10^{-11}–10^{-9}	LMBPNN, Caputo saturated-incidence epidemic	78
MSE and RMSE	5.6×10^{-8}; < 0.17	DNN, normalised Caputo–Fabrizio SIRD	79
MSE and absolute error	10^{-8}–10^{-6}; $< 10^{-5}$	LMB–DNN, Atangana–Baleanu rabies	83
Coefficient of determination	mean $R^2 = 0.9621$	PINN, Caputo–Fabrizio hepatitis C	81
Classification accuracy	99.8%	ANN-LMB, RF, SVM, fractional helminth model	76
AUC and weighted MSE	0.992; 0.0042	XGBoost + Caputo, cervical cancer	95
Synchronisation MSE	< 0.0068	Fractional RNN observer, cancer cells	100
RMSE and FIT%	0.00024; 97.13%	Fractional FRNN, chaotic diabetes	110

5.1. Discussion of visual results

Figure 2 presents the proposed taxonomy of intelligent hybrid FDE-ML integration strategies. **Figure 3** cross-tabulates the 43 included studies by clinical domain and coupling type. It clearly shows that Type 2 dominates infectious-disease modelling, while oncology is the only domain in which all four types appear. **Figures 4** and **5** are schematic. They summarise our qualitative reading of the included studies and do not report new measurements. In this qualitative reading, Type 2 tends to give the most accurate solutions and the best robustness to noise, while Type 4 gives the most usable interface for clinicians. Type 2 and Type 4 pipelines also tend to reach a low training error in fewer epochs when the fractional physics is included in the loss. **Figure 6** presents a five-year translation plan. Its milestones run from the publication of the taxonomy, through multimodal FPINNs, Kolmogorov–Arnold Network integration and federated learning, to hospital pilot studies by 2030.

5.2. Critical analysis and limitations

The included hybrid models perform well in the settings in which they were tested, but several limitations remain. Most studies rely on synthetic data or on retrospective data sets, and very few test their models on prospective data from several centres. The computational cost of FPINNs and high-order fractional solvers is a real obstacle in clinical environments that need fast results and have limited computing resources. Most frameworks use a single data modality, whereas real clinical data combine imaging, genomics, wearable signals and electronic health records. Algorithmic bias, fairness across demographic groups and the requirements of regulators such as the FDA and EMA are rarely assessed. Standard benchmark data sets, federated learning protocols, explainable pipelines and routine uncertainty quantification are therefore needed. The taxonomy and roadmap proposed here are meant to give this future work a common structure. This review also has limitations of its own. Only two databases were searched systematically; the screening was performed by the authors without a formal inter-rater agreement statistic, and publication bias towards positive results cannot be excluded.

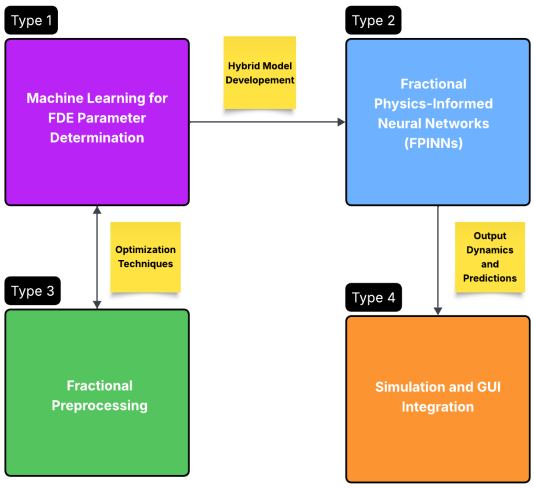


Figure 2. Proposed taxonomy of intelligent hybrid FDE-ML integrations, with the coupling layer (Types 1–3) and the deployment layer (Type 4)

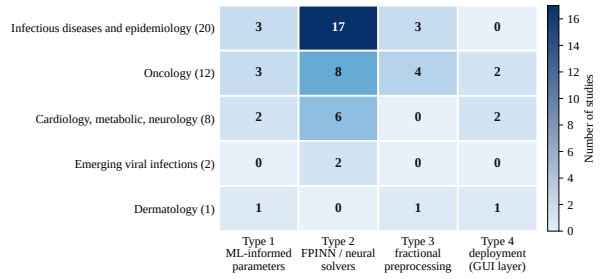


Figure 3. Number of included studies by clinical domain and coupling type (a study using several types is counted once for each type)

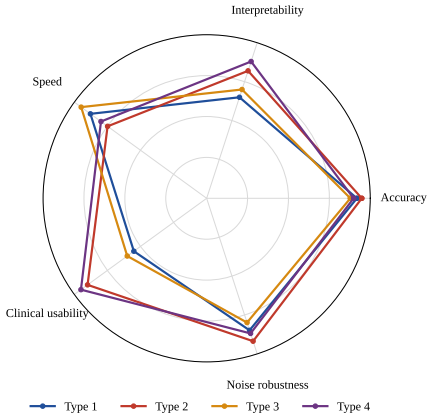


Figure 4. Schematic performance profile of the four hybrid integration types (qualitative rating from the reviewed studies, not measured values)

6. Unified taxonomy of intelligent hybrid FDE-ML integrations

This section presents a classification framework that divides intelligent hybrid models combining fractional differential equations (FDEs) with machine-learning (ML) components into four integration types. The taxonomy was derived from the studies reviewed in Sections 4 and 5, and **Figure 3** shows how those studies are distributed over it.

Why the taxonomy has two levels. Types 1–3 and Type 4 are not at the same conceptual level, and we do not treat them as if they were. Types 1–3 describe the mathematical coupling, that is, where the learning component enters the fractional model. In Type 1, it supplies the parameters; in Type 2, it supplies the solution; and in Type 3, it receives fractional features. Type 4 does not change the mathematics. It describes how a coupled model of Type 1, 2, or 3 is wrapped in a simulation engine and a user interface so that it can be used. We therefore organise the taxonomy as a *coupling layer* (Types 1–3) and a *deployment layer* (Type 4). We keep Type 4 in the classification because many healthcare hybrids are published together with such an interface, and because the deployment layer has its own requirements, including latency, usability, uncertainty display, and regulatory validation, which are not covered by the coupling layer.

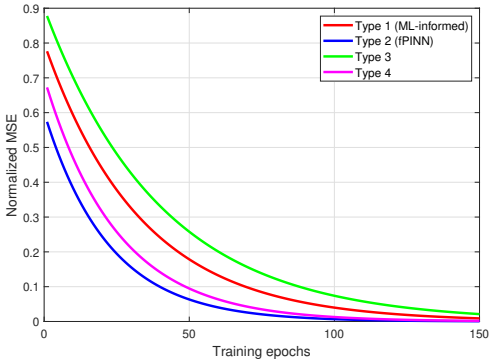


Figure 5. Schematic training behaviour of the four hybrid integration types (qualitative illustration, not measured values)

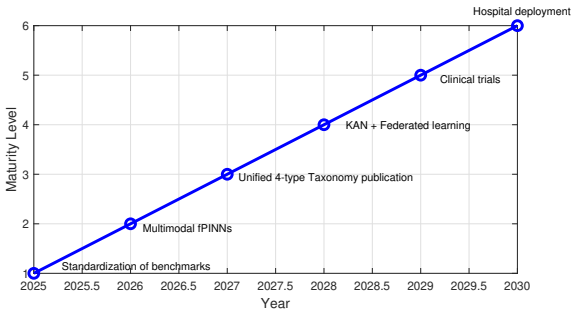


Figure 6. Five-year clinical translation roadmap

The Caputo fractional derivative **(1)** serves as the fundamental nonlocal operator in each strategy, consistent with the reviewed literature.

6.1. Type 1—ML-informed FDE parameter estimation

Standard ML regressors (such as XGBoost, neural networks, and random forests) estimate the fractional order ϑ or time-varying parameters $\boldsymbol{\theta}(\upsilon)$ from clinical data. These parameters are then passed to a standard numerical method to solve the FDEs, such as the L1 scheme, spectral methods, or the Adams–Bashforth–Moulton predictor–corrector method:[72]

$$\boldsymbol{\theta} = \mathrm{ML}(\mathbf{X}_{\mathrm{clinical}}),\ {}^{C}D_{\upsilon}^{\vartheta}\mathbf{y}(\upsilon) = \mathbf{f}\big(\mathbf{y}(\upsilon), \boldsymbol{\theta}(\upsilon), \upsilon\big). \quad (4)$$

Studies in this category often add a user interface for clinical use at a later stage, which places them in Type 4 as well.

Table 5. Key findings of the review and their implications

	Finding	Evidence	Implication
F1	FPINN and neural solvers (Type 2) are by far the most common coupling, used in 33 of the 43 studies.	**Table 3**, **Figure 3**	Methods are mature for solving known models; parameter learning from clinical data (Type 1) is less developed.
F2	Infectious diseases and epidemiology account for 20 studies, oncology for 12 and cardiometabolic and neurological disorders for 8.	**Table 2**, **Figure 3**	Dermatology and emerging viral infections are under-studied and offer room for new work.
F3	The deployment layer (Type 4) appears in only 5 studies, all of which also use Type 1, and all come from a small number of research groups.	**Table 3**	Independent replication of GUI-based systems is needed before any clinical claim.
F4	Reported neural-solver errors (MSE 10^{-11}–10^{-6}) usually measure the agreement between the network and a numerical solution of the same equations.	**Table 4**	Such errors show solver accuracy, not predictive validity on patients; both should be reported.
F5	Very few studies report confidence intervals, cross-validation details or external validation.	**Tables 2** and **4**	Uncertainty quantification and transparent validation should be standard (Section 2.3).
F6	Where sensitivity to ϑ is studied, lower orders delay epidemic peaks and slow tumour growth and chronic progression.	Studies in **Table 2**	The order ϑ acts as an interpretable memory parameter that should be estimated, not fixed.

6.2. Type 2—FPINN solvers

A deep neural network $\mathbf{u}_{\boldsymbol{w}}(\upsilon)$ with weights $\boldsymbol{w}$ acts as a universal approximator for the solution $\mathbf{y}(\upsilon)$. It is trained with a loss that combines data fidelity with the fractional physics residual:

$$\mathcal{L} = \mathcal{L}_{\text{data}} + \lambda \mathcal{L}_{\text{physics}}, \tag{5}$$

where

$$\mathcal{L}_{\text{data}} = \frac{1}{N} \sum_{i=1}^{N} \left\| \mathbf{u}_{\boldsymbol{w}}(\upsilon_i) - \mathbf{y}_{\text{obs}}(\upsilon_i) \right\|^2, \tag{6}$$

$$\mathcal{L}_{\text{physics}} = \frac{1}{M} \sum_{j=1}^{M} \left\| {}^{C}D_{\upsilon}^{\vartheta} \mathbf{u}_{\boldsymbol{w}}(\upsilon_j) - \mathbf{f}\big(\mathbf{u}_{\boldsymbol{w}}(\upsilon_j), \upsilon_j\big) \right\|^2. \tag{7}$$

Training uses optimisers such as Levenberg–Marquardt (LMB) or Adam.

6.3. Type 3—fractional preprocessing

Before the data enter ML classifiers or regressors such as SVM, ANN and RF, the raw clinical time series undergo a fractional operator transformation that produces memory-based features. This enlarges the feature set with nonlocal memory information:

$$\mathbf{X}_{\text{frac}} = \mathcal{F}^{\vartheta}(\mathbf{X}_{\text{raw}}), \qquad \hat{y} = \text{ML}(\mathbf{X}_{\text{frac}}), \tag{8}$$

where $\mathcal{F}^{\vartheta}$ denotes a fractional integral or derivative operator (Caputo, Caputo–Fabrizio, or Atangana–Baleanu) applied componentwise.

6.4. Type 4—deployment layer: Hybrid simulation and GUI integration

A model of Type 1, 2, or 3 is embedded in a real-time simulation engine whose results are shown in a graphical user interface for medical professionals. This layer turns the mathematical solver into a decision-support tool that can update patient-specific values of ϑ:

$$\text{GUI output} = \mathcal{S}\big(\text{Type 1, 2, or 3}\big), \tag{9}$$

where $\mathcal{S}$ denotes the real-time simulation wrapper.

6.5. Rigorous definition of the unifying operator $\mathcal{Q}$

We now define $\mathcal{Q}$ precisely. Fix a horizon $T > 0$, a state dimension d, p clinical features, and K outcome classes. Let

- $\mathcal{X} = \mathbb{R}^{n\times p}$ be the space of clinical feature matrices and $\mathcal{Y} = (\mathbb{R}^d)^N$ the space of state observations on a grid $0 = \upsilon_1 < \cdots < \upsilon_N \le T$;
- $\Theta \subset \mathbb{R}^q$ be a compact parameter set and $\vartheta \in (0,1)$ the fractional order;
- $\mathcal{O} = C([0,T],\mathbb{R}^d) \times C([0,T],[0,1]^K)$ be the output space (state trajectory and class-probability path).

The four components are the following maps:

(a) Type 3, the fractional feature map $\mathcal{F}^\vartheta : \mathcal{X} \to \mathcal{X}'$, which is the identity when Type 3 is absent.

(b) Type 1, a learner $g_{\boldsymbol{\phi}} : \mathcal{X}' \to \Theta \times C([0,T],[0,1]^K)$ with trainable weights $\boldsymbol{\phi}$, returning model parameters $\boldsymbol{\theta}$ and a probability path $P(\upsilon)$.

(c) Type 2, a solution map $\mathcal{S}_\vartheta : \Theta \times \mathbb{R}^d \times C([0,T],[0,1]^K) \to C([0,T],\mathbb{R}^d)$, $(\boldsymbol{\theta}, \mathbf{y}^0, P) \mapsto \mathbf{y}$, where $\mathbf{y}$ solves ${}^C D_\upsilon^\vartheta \mathbf{y} = \mathbf{f}(\mathbf{y}, \boldsymbol{\theta}, P(\upsilon), \upsilon)$ with $\mathbf{y}(0) = \mathbf{y}^0$. It is computed either by a classical scheme or by an FPINN $\mathbf{u}_{\boldsymbol{w}}$ trained with **(5)**.

(d) Type 4, a presentation map $\mathcal{R} : \mathcal{O} \to \mathcal{O} \times \mathcal{G}$, which leaves the mathematical output unchanged and attaches an interface state $\mathcal{G}$ (displayed risk, scenario controls, uncertainty band).

For data $(\mathbf{X}, \mathbf{Y}) \in \mathcal{X} \times \mathcal{Y}$, the hybrid operator is

$$\mathcal{Q}_{\vartheta,\boldsymbol{\phi},\boldsymbol{w}}(\mathbf{X}) = \Big(\mathcal{S}_\vartheta\big(g_{\boldsymbol{\phi}}(\mathcal{F}^\vartheta \mathbf{X}), \mathbf{y}^0\big),\ P_{\boldsymbol{\phi}}\Big) \in \mathcal{O}, \quad (10)$$

and its trainable quantities are fitted by

$$(\hat\vartheta, \hat{\boldsymbol{\phi}}, \hat{\boldsymbol{w}}) \in \arg\min \sum_{i=1}^{N} \omega_i \big\| \mathcal{Q}_{\vartheta,\boldsymbol{\phi},\boldsymbol{w}}(\mathbf{X})(\upsilon_i) - \mathbf{Y}_i \big\|^2 + \lambda \mathcal{L}_{\text{physics}}, \quad (11)$$

with nonnegative weights ω_i. Thus $\mathcal{Q}$ maps the domain $\mathcal{X} \times \mathcal{Y}$ (through the fitting step **(11)**) to the range $\mathcal{O}$, and the deployment map gives $\mathcal{R} \circ \mathcal{Q}$. Each reviewed model is a special case. A pure Type 1 model takes $\mathcal{F}^\vartheta = \mathrm{id}$ and a classical solver. A pure Type 2 model takes $g_{\boldsymbol{\phi}}$ constant and an FPINN solver. A pure Type 3 model omits $\mathcal{S}_\vartheta$ and returns only $P_{\boldsymbol{\phi}}$. Combined models use several non-trivial components. Well-posedness of $\mathcal{S}_\vartheta$ is required for $\mathcal{Q}$ to be well defined, and for the example of Section 7 it is guaranteed locally by **Theorem 1**. In this sense $\mathcal{Q}$ is a rigorously defined composite operator, although its properties as a whole (for example the generalisation error of the trained learner) are statistical rather than purely analytical.

This formulation makes the comparison of hybrids explicit. Two models differ exactly in the components they switch on and in how those components are trained. It also shows where uncertainty enters, namely through ϑ, $\boldsymbol{\theta}$, and P, and therefore where it should be reported.

Figure 7 shows the unified taxonomy as a single mathematical engine, with the Caputo fractional derivative as the primary nonlocal operator and the four integration types as the building blocks of $\mathcal{Q}$. **Figure 8** is a schematic polar plot. The dashed red curve marks the aspects covered by earlier reviews, and the solid blue curve marks the coverage of the present taxonomy. **Figure 9** depicts $\mathcal{Q}$ as the point where the four integration strategies meet, namely Type 1 (ML-informed parameter estimation), Type 2 (fPINN solvers), Type 3 (fractional preprocessing) and Type 4 (hybrid simulation with GUI).

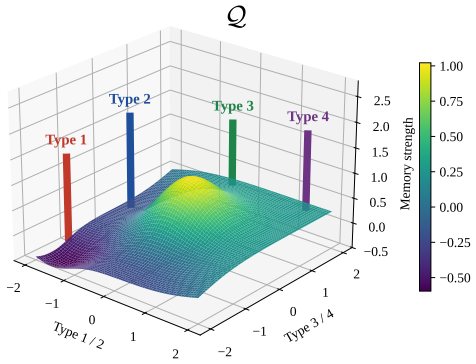


Figure 7. Unified taxonomy, with the Caputo operator and the four types composed into a single hybrid operator $\mathcal{Q}$

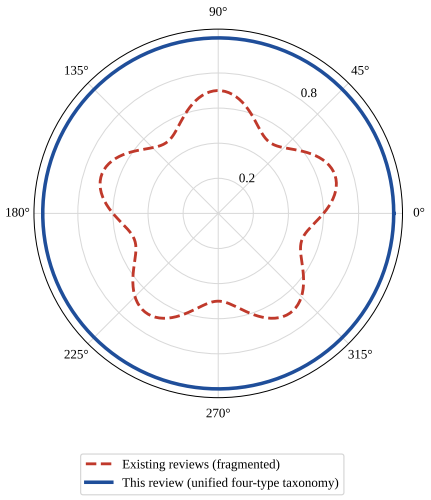


Figure 8. Schematic coverage plot, in which the four-type taxonomy covers the coupling and deployment aspects partially addressed by earlier reviews

7. Application example of the unified taxonomy

Data. We use the public UCI Dermatology data set,[118] which was also studied in.[117] It contains 366 patient records with 12 clinical and 22 histopathological attributes, graded on a 0–3 scale, together with age and one of six diagnoses. Eight records have no age and were removed, which leaves 358 records, 111 of them with psoriasis and 247 with another erythemato-squamous disease. There are no duplicate records.

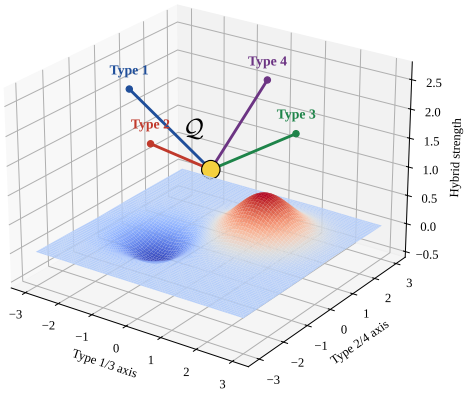


Figure 9. The unifying operator $\mathcal{Q}$ as the composition of the four integration types

Meaning of time. The data set is cross-sectional. Each patient was observed once, and there are no longitudinal measurements. The variable t below is therefore a *pseudo-time*, obtained by mapping the record index linearly onto $[0, 10]$. It is an ordering device that allows the fractional system to be fitted to the sequence of records, and it should not be read as calendar time or disease duration. Consequently, the memory captured by the Caputo operator is memory along this ordering, not a hereditary effect within an individual patient. A genuine test of hereditary effects would require longitudinal data, which we list as future work in Section 9.

Consider the fractional Caputo-type model studied in:[117]

$$\begin{cases} {}^{C}D_t^{\beta} U_1(t) = w_1 U_1(1-U_1) + k_1(U_2+U_4), \\ {}^{C}D_t^{\beta} U_2(t) = w_2 U_2(1-U_2) + k_2 P(t) + k_6 U_3, \\ {}^{C}D_t^{\beta} U_3(t) = w_3 U_3(1-U_3) + k_3 P(t) + k_7 U_4, \\ {}^{C}D_t^{\beta} U_4(t) = w_4 U_4(1-U_4) + k_4 U_1, \\ {}^{C}D_t^{\beta} U_5(t) = w_5 U_5(1-U_5) + k_5 P(t), \end{cases} \tag{12}$$

where β is the fractional order, $U = [U_1, \ldots, U_5]^{\top}$ are the normalized state variables (Age, SawToothRete, Parakeratosis, ScalpInvolvement, Scaling), and $P(t)$ is the ML (XGBoost) probability (Type 1) after fractional preprocessing (Type 3).

Interpretation of the equations. System **(12)** is a phenomenological, data-fitting model and not a mechanistic disease model. Each logistic term $w_i U_i(1-U_i)$ keeps a normalised score inside $[0, 1]$ and allows it to saturate. The coupling terms describe statistical co-variation along the pseudo-time ordering, for example between scalp involvement and age (k_4), or between the psoriasis probability $P(t)$ and the histopathological scores (k_2, k_3, k_5). Age does not grow logistically as a result of skin lesions. The first equation simply describes how the normalised age profile of the ordered records co-varies with the other scores. A mechanistic model would instead describe keratinocyte proliferation, immune-cell activity and cytokine signalling, and would require longitudinal data. We state this distinction explicitly so that the example is read as an illustration of the operator $\mathcal{Q}$, not as a biological claim.

In the notation of **(10)**, the example uses all components:

$$\mathcal{R} \circ \mathcal{Q} = \underbrace{\mathcal{R}}_{\text{Type 4: GUI}} \circ \Big(\underbrace{\mathcal{S}_{\beta}}_{\text{Type 2: solver}} \circ \underbrace{g_{\phi}}_{\text{Type 1: XGBoost}} \circ \underbrace{\mathcal{F}^{\beta}}_{\text{Type 3: preprocessing}} \Big). \tag{13}$$

Theorem 1. *Let $0 < \beta < 1$, and assume that $P \in C([0,\infty), \mathbb{R})$ is continuous and bounded, i.e., $P_{\max} = \sup_{t \geq 0} |P(t)| < \infty$. Let the growth coefficients satisfy $w_i > 0$ for $i = 1, \ldots, 5$, and let the coupling coefficients satisfy $k_j \in \mathbb{R}$ for $j = 1, \ldots, 7$. Then, for any initial condition $\mathbf{U}^0 = (U_1^0, U_2^0, U_3^0, U_4^0, U_5^0)^{\top} \in \mathbb{R}^5$, there exists $T > 0$ such that the unified fractional-order system **(12)** with $\mathbf{U}(0) = \mathbf{U}^0$ possesses a unique continuous solution $\mathbf{U} \in C([0, T], \mathbb{R}^5)$.*

Proof. Apply the Riemann–Liouville integral operator[119]

$$ {}^{RL}I_{0,t}^{\beta} y(t) = \frac{1}{\Gamma(\beta)} \int_0^t (t-s)^{\beta-1} y(s)\, ds$$

to each equation of **(12)**. Then

$$\mathbf{U}(t) = \mathbf{U}^0 + \frac{1}{\Gamma(\beta)} \int_0^t (t-s)^{\beta-1} \mathbf{f}(s, \mathbf{U}(s))\, ds, \quad t \geq 0,$$

where

$$\begin{cases} f_1(s,\mathbf{U}) = w_1U_1(1-U_1) + k_1(U_2+U_4) = w_1U_1 - w_1U_1^2 + k_1U_2 + k_1U_4, \\ f_2(s,\mathbf{U}) = w_2U_2(1-U_2) + k_2P(s) + k_6U_3 = w_2U_2 - w_2U_2^2 + k_2P(s) + k_6U_3, \\ f_3(s,\mathbf{U}) = w_3U_3(1-U_3) + k_3P(s) + k_7U_4 = w_3U_3 - w_3U_3^2 + k_3P(s) + k_7U_4, \\ f_4(s,\mathbf{U}) = w_4U_4(1-U_4) + k_4U_1 = w_4U_4 - w_4U_4^2 + k_4U_1, \\ f_5(s,\mathbf{U}) = w_5U_5(1-U_5) + k_5P(s) = w_5U_5 - w_5U_5^2 + k_5P(s). \end{cases}$$

Equip $\mathbb{R}^5$ with $\|\mathbf{U}\|_\infty = \max_{1\le i\le 5}|U_i|$, and equip $C([0,T],\mathbb{R}^5)$ with $\sup_{0\le t\le T}\|\mathbf{U}(t)\|_\infty$.

Since each f_i is quadratic in $U_1,\dots,U_5$ with coefficients continuous in s via bounded $P(s)$, we obtain $\mathbf{f}\in C([0,\infty)\times\mathbb{R}^5,\mathbb{R}^5)$.

Moreover, $\mathbf{f}$ is locally Lipschitz in $\mathbf{U}$, uniformly in s. For $M>0$, consider $\|\mathbf{U}\|_\infty \le M$ and $\|\mathbf{U}'\|_\infty \le M$. The Jacobian satisfies

$$J(s,\mathbf{U}) = \begin{pmatrix} w_1-2w_1U_1 & k_1 & 0 & k_1 & 0 \\ 0 & w_2-2w_2U_2 & k_6 & 0 & 0 \\ 0 & 0 & w_3-2w_3U_3 & k_7 & 0 \\ k_4 & 0 & 0 & w_4-2w_4U_4 & 0 \\ 0 & 0 & 0 & 0 & w_5-2w_5U_5 \end{pmatrix}.$$

Thus,

$$L(M) = \max\big\{w_1+2w_1M+2|k_1|,\ w_2+2w_2M+|k_6|,\ w_3+2w_3M+|k_7|,\ |k_4|+w_4+2w_4M,\ w_5+2w_5M\big\},$$

and, by the mean value theorem on the convex ball $\|\mathbf{U}\|_\infty \le M$, $\|\mathbf{f}(s,\mathbf{U})-\mathbf{f}(s,\mathbf{U}')\|_\infty \le L(M)\|\mathbf{U}-\mathbf{U}'\|_\infty$.

Next, bound $\|\mathbf{f}(s,\mathbf{U})\|_\infty$ on $\|\mathbf{U}\|_\infty \le M$:

$$K(M) = \max\Big\{w_1M + w_1M^2 + 2|k_1|M,\ w_2M + w_2M^2 + |k_2|P_{\max} + |k_6|M,$$
$$w_3M + w_3M^2 + |k_3|P_{\max} + |k_7|M,\ w_4M + w_4M^2 + |k_4|M,\ w_5M + w_5M^2 + |k_5|P_{\max}\Big\}.$$

Hence $\|\mathbf{f}(s,\mathbf{U})\|_\infty \le K(M)$.

Fix $\rho>0$ and set $M = \|\mathbf{U}^0\|_\infty + \rho$. Define the closed ball

$$\mathcal{B} = \Big\{\mathbf{u}\in C([0,T],\mathbb{R}^5) : \sup_{0\le t\le T}\|\mathbf{u}(t)-\mathbf{U}^0\|_\infty \le \rho\Big\}.$$

Define $\Phi : C([0,T],\mathbb{R}^5)\to C([0,T],\mathbb{R}^5)$ by

$$(\Phi\mathbf{u})(t) = \mathbf{U}^0 + \frac{1}{\Gamma(\beta)}\int_0^t (t-s)^{\beta-1}\mathbf{f}(s,\mathbf{u}(s))\,ds.$$

For $\mathbf{u}\in\mathcal{B}$, $\|\mathbf{u}(s)\|_\infty \le M$, so $\|\mathbf{f}(s,\mathbf{u}(s))\|_\infty \le K(M)$. Then

$$\|(\Phi\mathbf{u})(t)-\mathbf{U}^0\|_\infty \le \frac{K(M)t^\beta}{\Gamma(\beta+1)}.$$

Choose $T>0$ such that $\frac{K(M)T^\beta}{\Gamma(\beta+1)} \le \rho$. Thus $\Phi(\mathcal{B})\subseteq\mathcal{B}$.

For contraction, let $\mathbf{u},\mathbf{v}\in\mathcal{B}$. Then

$$\|(\Phi\mathbf{u})(t)-(\Phi\mathbf{v})(t)\|_\infty \le \frac{L(M)t^\beta}{\Gamma(\beta+1)}\sup_{0\le\sigma\le T}\|\mathbf{u}(\sigma)-\mathbf{v}(\sigma)\|_\infty.$$

Choose $T>0$ smaller if needed so that $q = L(M)T^\beta/\Gamma(\beta+1) < 1$. Therefore, Φ is a contraction on $\mathcal{B}$.

By the Banach fixed-point theorem, there exists a unique fixed point $\mathbf{U}\in\mathcal{B}\subseteq C([0,T],\mathbb{R}^5)$ that satisfies the integral equation and hence solves the original Caputo system **(12)** with $\mathbf{U}(0)=\mathbf{U}^0$.

□

Remark 1 (Scope of **Theorem 1**). *Theorem 1 concerns only the Caputo system (12) for a given continuous and bounded input P. It guarantees that the solution map $\mathcal{S}_\beta$ in (10) is well defined on $[0,T]$, which is a necessary condition for the hybrid operator to make sense. It does not cover the training of the FPINN, the fractional preprocessing, the GUI, or the statistical behaviour of the learner, and it should not be read as a mathematical validation of the whole taxonomy. Those components are assessed empirically below.*

Fitting criterion. The parameters in **Table 6** were obtained with `fmincon` by minimising the weighted mean squared error

$$\mathrm{WMSE} = \sum_{i=1}^{5}\omega_i\,\frac{1}{N}\sum_{n=1}^{N}\big(U_i(t_n)-U_i^{\mathrm{obs}}(t_n)\big)^2, \qquad \sum_{i=1}^{5}\omega_i = 1,\ \omega_i\ge 0, \tag{14}$$

and the corresponding weighted root mean squared error is $\mathrm{WRMSE} = \sqrt{\mathrm{WMSE}}$.

Table 6. Optimization results and performance of the unified hybrid model (Operator $\mathcal{Q}$)

Parameter / Metric	**Value**
w_1 (Age growth)	1.5000
w_2 (SawToothRete growth)	0.2468
w_3 (Parakeratosis growth)	0.0100
w_4 (ScalpInvolvement growth)	1.3745
w_5 (Scaling growth)	0.1112
k_1	-0.6394
k_2	-0.1009
k_3	0.1597
k_4	-0.5699
k_5	0.1565
k_6	-0.0415
k_7	0.2140
β (fractional order)	0.2000
Weighted MSE (cost, **Equation (14)**)	**0.00253926**
Weighted RMSE ($\sqrt{\text{WMSE}}$)	0.0504
Final fmincon iterations	164
Stopping criterion	Local minimum possible; constraints satisfied
Step tolerance reached	Yes (step size $< 1 \times 10^{-14}$)
Optimality tolerance	9.022×10^{-8}

Figure 10 presents the fit of the unified hybrid FDE-ML framework (Operator $\mathcal{Q}$) to the normalized dermatology dataset. The markers show the recorded values of the five state variables (Age, SawToothRete, Parakeratosis, ScalpInvolvement and Scaling), and the solid lines show the Caputo fractional-order predictions. These predictions combine ML-informed parameter estimation (Type 1), fractional preprocessing (Type 3) and the fractional solver (Type 2). The model follows the central trend of each score, while the scatter of individual records around it reflects the variation between patients that a five-state trend model cannot, and should not, reproduce.

Figure 11 shows the time evolution of the five standardized state variables of the unified fractional-order system generated by the Operator $\mathcal{Q}$. The Caputo derivative with $\beta = 0.2000$, together with the ML-derived probability $P(t)$, produces the long-memory behaviour visible in the trajectories. The trajectories summarise how the scores co-vary along the ordered records in a compact and interpretable form. As explained above, they are not a mechanistic description of psoriasis progression. The clinical graphical user interface (Type 4) of the unified hybrid FDE-ML model produces a typical "Psoriasis Likely" prediction, shown in **Figure 12**. The interface displays the ML-derived probability (Type 1) together with the Caputo fractional-order dynamics solved by the Operator $\mathcal{Q}$ ($\beta = 0.2000$) to produce a combined risk score.

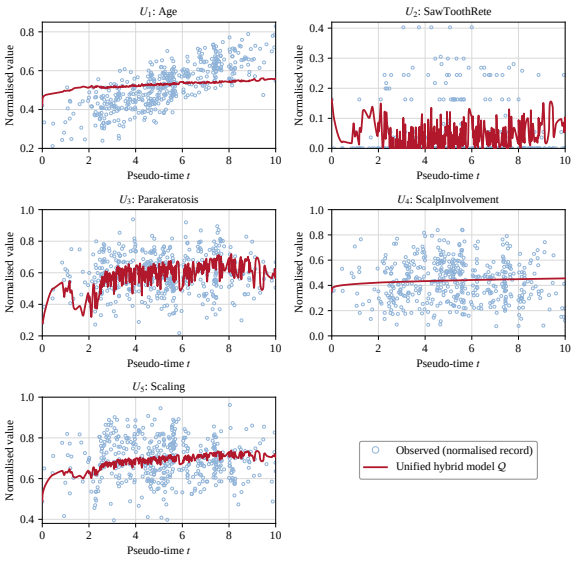


Figure 10. Model fit to the real data. Markers are the normalised records, ordered by pseudo-time, and the solid line is the fitted unified hybrid model $\mathcal{Q}$

From **Figure 13**, we see that the fmincon optimizer reached a local minimum after 164 iterations, with a final Weighted MSE of 0.00253926 (weighted RMSE 0.0504). The cost decreases steadily, which shows that the tuning procedure for $\mathcal{Q}$ converges under strict tolerance settings

(TolFun $= 10^{-14}$, StepTolerance $= 10^{-14}$). In **Figure 14**, the three-dimensional surface shows the Caputo-type memory kernel $(t-\tau)^{\beta-1}/\Gamma(\beta)$ for $\beta = 0.2000$. The kernel decays slowly along the lag axis, so distant points along the ordering still carry weight, which is the non-local behaviour that Type 3 preprocessing exploits. The β-sensitivity curve in **Figure 15** shows that small deviations from the optimal $\beta = 0.2000$ rapidly increase the Weighted MSE. This confirms that the fractional order is an important parameter of the Operator $\mathcal{Q}$ and should be estimated from the data rather than fixed in advance.

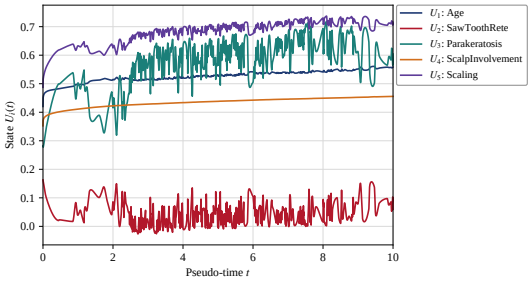


Figure 11. State variable dynamics of the fitted system **(12)** along pseudo-time

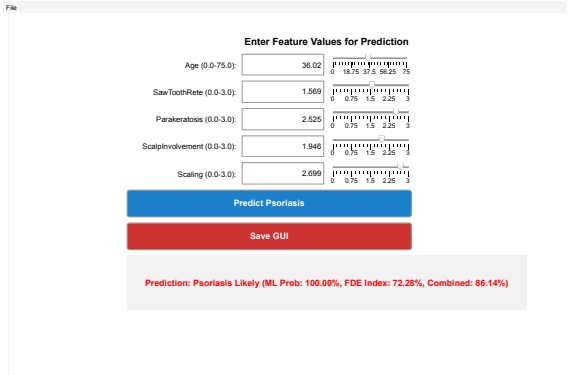


Figure 12. Likely prediction scenario shown by the Type 4 interface

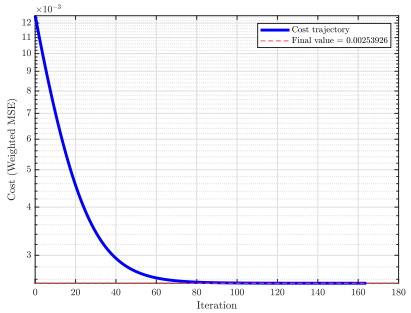


Figure 13. fmincon convergence to a local minimum (Operator $\mathcal{Q}$)

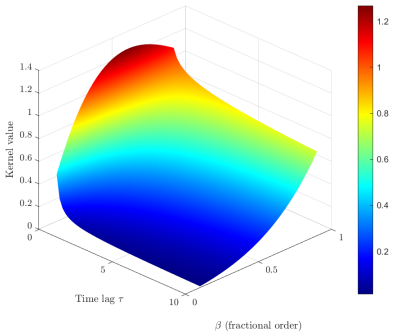


Figure 14. Memory kernel surface plot

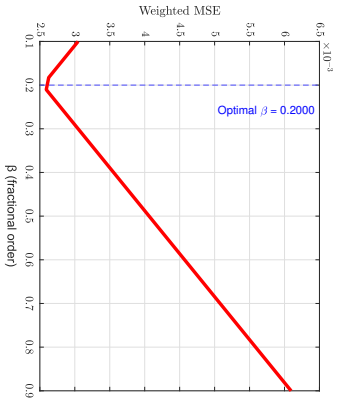


Figure 15. β-sensitivity analysis (impact on the cost)

7.1. Validation Protocol and Classification Results

To check the classification stage of $\mathcal{Q}$ for overfitting and data leakage, we re-evaluated it with an explicit protocol. The task was psoriasis versus all other diagnoses ($n = 358$; 111 positive and 247 negative records, a prevalence of 31.0%). We used five-fold stratified cross-validation repeated 10 times with different random partitions, so that every record was predicted only by models that had not seen it, and the class ratio was kept in every fold. No feature selection, scaling or tuning was done outside the training folds. The Type 1 learner (XGBoost, 200 trees of depth 3) was compared with four baselines: random forest, an RBF support vector machine, logistic regression and a depth-4 decision tree. AUC values are averaged over the 10 repetitions and reported asmean $\pm$ standard deviation (SD); 95% confidence intervals (CLs) come from 2000 bootstrap resamples of the out-of-fold predictions. Accuracy, precision, recall and F1 use a 0.5 threshold. The results are given in **Table 7** and **Figures 16** and **17**.

Table 7. Repeated stratified 5-fold cross-validation (10×5) for psoriasis versus other diagnoses on the UCI Dermatology data ($n = 358$)

Model	AUC (mean ± SD)	AUC 95% CI	Accuracy	F1	Recall
XGBoost (Type 1 component of $\mathcal{Q}$)	0.99999 ± 0.00001	0.9998–1.0000	0.9992	0.9987	1.0000
Random forest	1.00000 ± 0.00000	1.0000–1.0000	0.9997	0.9995	0.9991
SVM (RBF)	0.99999 ± 0.00001	1.0000–1.0000	0.9989	0.9982	1.0000
Logistic regression	1.00000 ± 0.00000	1.0000–1.0000	0.9989	0.9982	1.0000
Decision tree	0.9909 ± 0.0021	0.9768–0.9980	0.9905	0.9848	0.9919

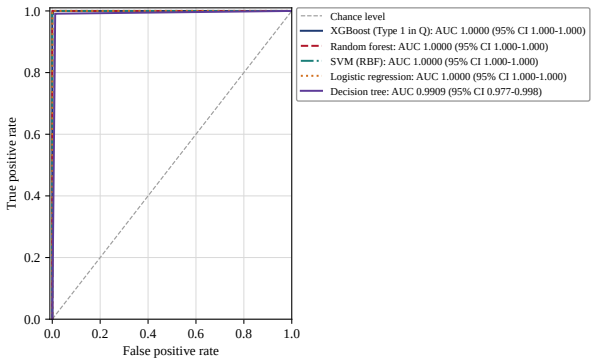


Figure 16. Out-of-fold ROC curves from stratified 5-fold cross-validation for the Type 1 learner of $\mathcal{Q}$ and four baselines

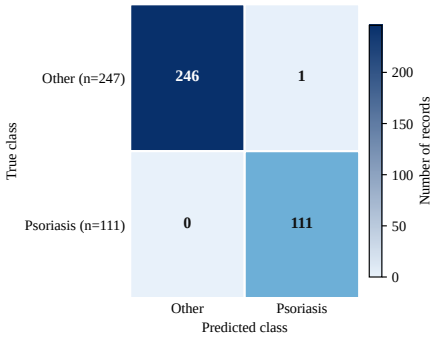


Figure 17. Confusion matrix of the pooled out-of-fold XGBoost predictions (threshold 0.5)

These results put the earlier single-split value (AUC 0.9966) in context. Under cross-validation the classification stage reaches an AUC close to 1, with only one false positive and no false negatives (**Figure 17**). Simple baselines reach essentially the same performance, however, including logistic regression. This tells us that separating psoriasis from the other five diagnoses is an easy task on this data set, because the histopathological attributes (for example clubbing of the rete ridges, thinning of the suprapapillary epidermis and Munro microabscesses) are almost diagnostic. The high AUC therefore confirms that there is no overfitting or leakage, but it does not show that the hybrid is better than the baselines at classification. The added value of $\mathcal{Q}$ in this example lies in the interpretable dynamic description and the memory parameter β, not in a gain in discrimination.

What the example shows. The example shows that the components of $\mathcal{Q}$ can be put together in one reproducible pipeline and validated with standard procedures. It gives computational feasibility and an internally validated result on a public data set. It does not establish clinical validity or usefulness at the point of care. That would require external, preferably prospective, validation on longitudinal patient data, assessment by clinicians and regulatory evaluation.

8. Challenges and ethical considerations

Hybrid fractional-order intelligent models have clear advantages, but they also face several practical and conceptual challenges. The first is computational. Fractional FPINNs and related models must evaluate non-local integral operators many times, which leads to long training times for multi-dimensional and multi-scale healthcare systems. The second is data. High-quality longitudinal data sets that would allow memory effects to be estimated are scarce. Most clinical data are collected at irregular, sparse time points, which makes it hard to identify the memory parameter ϑ and to show that long memory is really present, as the cross-sectional example in Section 7 illustrates. The third is validation. Regulators expect external and prospective validation, calibrated uncertainty and documented failure modes, and these are rarely reported in the current literature. Finally, there are ethical questions, including algorithmic bias against under-represented groups, privacy and data sovereignty, and fair access to the resulting tools. These must be considered from the design stage onwards.

9. Future directions and emerging trends

Several research directions follow from this review.[74, 120, 121] The first is multimodal fractional

PINNs connected to live data from IoT-based wearable devices. Such systems could update a patient's memory parameter ϑ continuously from vital signs, glucose measurements or cardiac signals, and would turn disease models into digital twins that can raise early alerts and suggest personalised treatment. The success of FPINNs, LMBPNN and related solvers in epidemic and cancer modelling provides a starting point for this work. The second is the combination of fractal–fractional operators with Kolmogorov–Arnold Networks (KANs). KANs learn interpretable functional representations in place of conventional multilayer perceptrons, and may give more expressive surrogates with fewer parameters while keeping the non-local memory of fractional calculus. This would ease the difficulties that high-dimensional healthcare systems create for current neural solvers. The third is federated learning, which would allow hospitals and research institutions to train shared hybrid models without moving sensitive longitudinal data, and so address the ethical and regulatory concerns raised in Section 8.

Clinical translation also needs benchmark data sets with longitudinal measurements, so that memory effects can be tested within patients and not only across records, and GUI platforms that clinicians can use and evaluate during patient care. Uncertainty should be reported routinely, either probabilistically or through fuzzy parameters and α-cut trajectory bands (Section 2.3). In the longer term, quantum-inspired solvers and variational quantum algorithms may make large simulations possible, for example of multi-scale cancer–immune interactions or national epidemic spread.[122–124] A realistic five-year plan (**Figure 6**) is to agree on evaluation standards, run external and prospective validation studies, and only then integrate validated hybrid systems into clinical decision support.

10. Conclusion

This review examined intelligent hybrid models that combine fractional-order differential equations with machine learning in healthcare. Following PRISMA 2020, we identified 43 hybrid studies from 284 database records and citation searching, and we organised them with a two-level taxonomy. Three coupling types describe the mathematical link (ML-informed parameter estimation, FPINN and neural solvers, and fractional preprocessing), and a separate deployment layer describes simulation engines and clinician-facing interfaces. We gave a rigorous definition of the hybrid operator $\mathcal{Q}$ as a composition of these components, with explicit domain and range, and showed that every reviewed model is a special case of it.

The evidence shows that neural solvers dominate the field, that infectious diseases are the most studied domain, and that very small reported errors often measure solver accuracy rather than predictive validity on patients. Reported metrics come from different data sets and protocols and should not be pooled. The worked example on the UCI Dermatology data shows that the components of $\mathcal{Q}$ can be assembled and validated in a transparent way. Its classification stage is free of leakage under repeated stratified cross-validation, but simple baselines perform equally well, so the value of the hybrid there lies in interpretability and the memory parameter, not in discrimination. The example is a phenomenological illustration on cross-sectional data and does not automatically establish clinical benefit.

Future studies should report the coupling type, the validation protocol, and the uncertainty of every prediction. They should use longitudinal and multi-centre data to test memory effects, and they should pursue external and prospective validation before any claim of clinical use is made. Multimodal FPINNs linked to wearable data, Kolmogorov–Arnold Networks, federated learning and fuzzy or probabilistic uncertainty quantification are promising directions. If they are developed with attention to fairness and data protection, hybrid FDE–ML models may become a useful part of predictive and personalised medicine.

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Conflict of interest

The authors declare that they have no competing interests.

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Writing–original draft: Muhammad Kamran
Writing–review & editing: David Amilo, Muhammad Farman, C. Ravichandran, Kottakkaran Sooppy Nisar

Availability of data

Primary data sources have been appropriately cited in the paper. The UCI Dermatology data set is publicly available at https://doi.org/10.24432/C5FK5P. The code used for the cross-validation and the figures in Section 7 is available from the corresponding author on reasonable request.

AI tools statement

All authors confirm that no AI tools were used in the preparation of this manuscript.

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