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MATHEMATICAL MODELING OF INFECTIOUS DISEASE TRANSMISSION USING FRACTIONAL DIFFERENTIAL EQUATIONS

Aleena Khadim[1], Darshan Mal[2], Abia[*3], Muhammad Amir Ashraf[4]

[1]*Department of Statistics, University of Gujrat*
[2]*Department of Mathematics, Shah Abdul Latif University Khairpur*
[*3,4]*Department of Mathematics and Statistics, University of Agriculture Faisalabad*

[1]aleenarajpoot99@gmail.com, [2]darshan@salu.edu.pk, [*3]abiarajpoot@gmail.com [4]amirashraf2311@gmail.com

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Abstract

Mathematical modeling of infectious disease transmission has traditionally relied on classical integer-order differential equations, which assume memoryless, Markovian dynamics. However, real-world epidemiological processes exhibit non-Markovian behavior, long-range temporal dependencies, and anomalous diffusion that cannot be adequately captured by integer-order systems. This review examines the transformative role of fractional differential equations (FDEs) in epidemiological modeling, providing a comprehensive analysis of their theoretical foundations, operator taxonomy, and practical applications. We systematically classify key fractional operators including Riemann-Liouville, Caputo, Caputo-Fabrizio, Atangana-Baleanu, and fractal-fractional hybrids and evaluate their kernel properties, singularity characteristics, and suitability for modeling distinct disease transmission patterns such as waning immunity, fading behavioral memory, and multi-wave epidemic trajectories. The canonical fractional SEIR framework is presented alongside representative models for pathogens including COVID-19, Ebola, tuberculosis, hepatitis B, and childhood diseases. We further analyze qualitative properties essential for biological validity, including positivity, boundedness, existence, uniqueness, and stability of equilibrium states. The derivation of the basic reproduction number using the Next-Generation Matrix method and the formulation of fractional optimal control problems via Pontryagin's Maximum Principle are discussed. Numerical approximation schemes, particularly the Fractional Adams-Bashforth-Moulton predictor-corrector method, are reviewed. Critical methodological challenges dimensional inconsistency, operator selection ambiguity, and computational complexity are addressed, with emphasis on parameter rescaling and calibration strategies. This review demonstrates that fractional calculus provides a rigorous, flexible framework for capturing memory effects in disease transmission, enabling more accurate forecasting and informed public health interventions compared to classical integer-order models.

1. INTRODUCTION

Mathematical modeling of infectious disease transmission has historically relied on classical integer-order differential equations, a paradigm originating from the foundational compartmental frameworks established by Kermack and McKendrick. These deterministic systems partition a host population into distinct health states such as Susceptible (S), Exposed (E), Infected (I), and Recovered (R) and model transitions between compartments using continuous-time ordinary differential equations (Peter et al., 2022). Despite their widespread application in epidemiology, classical integer-order models operate under an implicit mathematical assumption: the underlying epidemiological dynamics are strictly Markovian. In an integer-order system, the future rate of change depends exclusively on the current state of the system at time t, rendering the dynamics memoryless. This framework implies that the probability of an individual transitioning out of a compartment follows an exponential distribution, asserting that historical duration within an infected or exposed state exerts no influence on future transition rates (Manivel et al., 2024) .

In real-world biological systems, pathogen transmission, host immune response, behavioral adaptation, and contact networks exhibit pronounced non-Markovian behavior, long-range temporal dependencies, and anomalous diffusion (Shaikh et al., 2020). The duration of immunity, heterogeneous incubation periods, and historical community compliance with non-pharmaceutical interventions create dynamic memory effects. To capture these hereditary characteristics, fractional calculus the branch of mathematical analysis dealing with differential and integral operators of arbitrary non-integer real or complex orders has emerged as a transformative tool in mathematical epidemiology (Alshammari et al., 2025).

The theoretical development of fractional calculus spans over three centuries, beginning with foundational inquiries by Laplace in 1812 and Lacroix in 1819, and maturing through the formalizations of Riemann, Liouville, Hadamard, and Caputo. In recent decades, the field has experienced a major shift from pure theoretical mathematics to applied biophysical modeling (Abidemi & Owolabi, 2024). The introduction of non-integer derivative operators to epidemiological frameworks allows the order of differentiation, denoted by $\alpha \in (0,1]$, to serve as an intrinsic structural parameter. Varying α alters the rate of dynamic memory decay, enabling fractional-order differential equations to fit empirical epidemiological curves with higher fidelity than integer-order models ($\alpha = 1$) (Jan et al., 2023).

The structural transition from memoryless integer-order dynamics to memory-aware fractional systems represents a shift in modeling philosophy. When integer-order assumptions are relaxed, the memory mechanism transforms state transitions from localized exponential decays into non-local integrations over past states (Srivastava et al., 2021). Depending on the selected fractional operator, this memory decay can assume power-law, exponential, or generalized Mittag-Leffler characteristics. Consequently, fractional differential equations provide a rigorous mathematical framework for analyzing, forecasting, and controlling complex infectious disease outbreaks (Chatterjee & Ahmad, 2021).

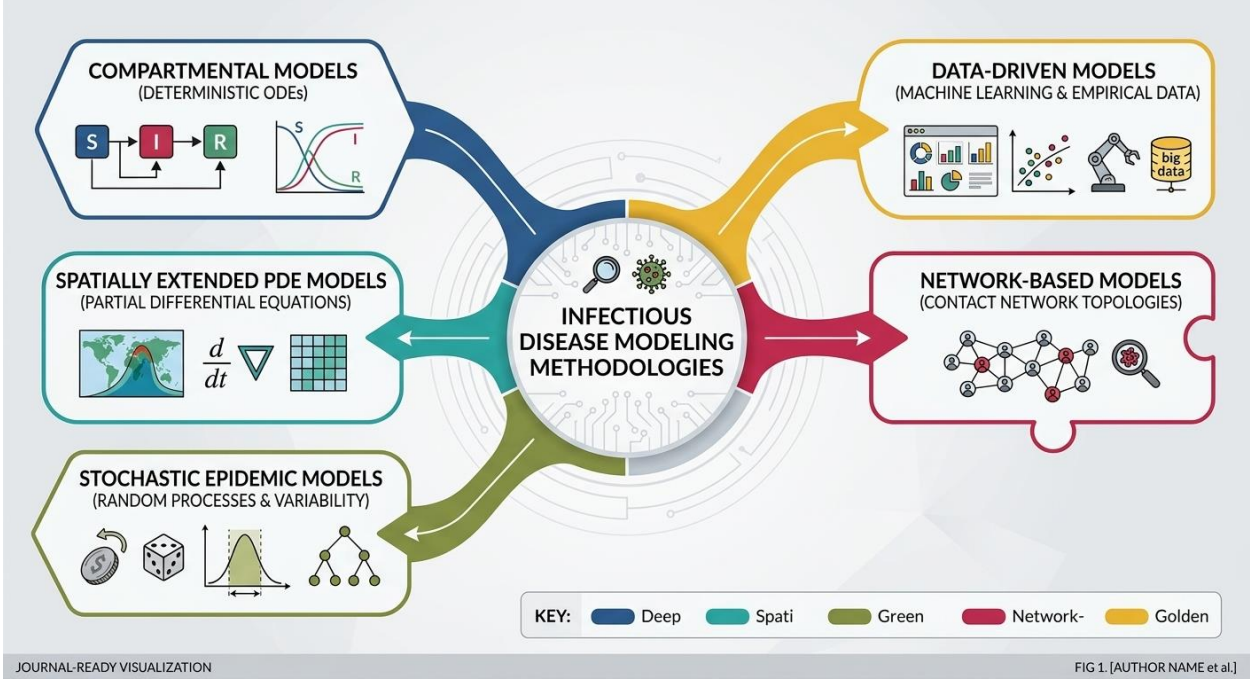


Figure 1: Taxonomical Classification and Methodological Framework of Infectious Disease Transmission Models

2. Taxonomy of Fractional Operators in Epidemiology

The choice of fractional derivative operator dictates the underlying memory mechanism embedded within an epidemiological model. Fractional operators are defined via convolution integrals involving specific kernel functions. These kernels fall broadly into two categories: singular kernels, which possess mathematical singularities at the lower boundary of integration, and non-singular kernels, which remain bounded throughout the domain (Ghosh, 2025).

2.1 Riemann-Liouville Fractional Derivative

For a continuous function $x: [a, b] \to \mathbb{R}$ and a real fractional order $\alpha > 0$ with $n = [\alpha] + 1$, the left Riemann-Liouville fractional derivative is defined as:

$$\prescriptRLaD_t^{\alpha} x(t) = \frac{1}{\Gamma(n-\alpha)} \frac{d^n}{dt^n} \int_a^t (t - \tau)^{n-\alpha-1} x(\tau) d\tau$$

where $\Gamma(\cdot)$ represents the Euler Gamma function. The associated Riemann-Liouville fractional integral is expressed as:

$$I_a^{\alpha} x(t) = \frac{1}{\Gamma(\alpha)} \int_a^t (t - \tau)^{\alpha-1} x(\tau) d\tau$$

While mathematically foundational, the Riemann-Liouville derivative presents significant limitations when applied to epidemiological initial value problems (Li et al., 2021). The derivative of a constant under the Riemann-Liouville formulation is non-zero ($\prescriptRLaD_t^{\alpha} c = \frac{ct^{-\alpha}}{\Gamma(1-\alpha)}$), and the formulation requires initial conditions specified in terms of fractional integrals at $t = a$, which lack direct physical or biological interpretation (Jumarie, 2006).

2.2 Caputo Fractional Derivative

To overcome the physical initial-condition limitation of the Riemann-Liouville derivative, Michele Caputo proposed an alternative formulation. For $\alpha \in (0,1]$ and a differentiable function $x(t)$, the Caputo fractional derivative is defined as:

$$\prescriptCaD_t^{\alpha} x(t) = \frac{1}{\Gamma(1-\alpha)} \int_a^t (t - \tau)^{-\alpha} x'(\tau) d\tau$$

The Caputo operator satisfies \ $prescriptCaD_t^{\alpha} c = 0$ for any constant c and allows initial conditions to be specified in terms of classical integer-order state values at $t = 0$ (Almeida, 2027). The kernel $(t-\tau)^{-\alpha}$ is a power-law function, which models slowly decaying, long-range memory. This property makes the Caputo operator effective for modeling disease dynamics characterized by long-term immunity loss or persistent sub-diffusive spatial dispersion (Gao et al., 2014).

2.3 Caputo-Fabrizio Fractional Derivative

In 2015, Caputo and Fabrizio introduced a fractional derivative featuring a non-singular, exponential decay kernel. For $x \in H^1(a,b)$ and $\alpha \in [0,1]$, the Caputo-Fabrizio derivative is defined as:

$$\prescriptCFaD_t^{\alpha} x(t) = \frac{M(\alpha)}{1-\alpha}\int_a^t x'(\tau)\exp\left[-\frac{\alpha}{1-\alpha}(t-\tau)\right]d\tau$$

where $M(\alpha)$ is a normalization function satisfying $M(0) = M(1) = 1$ (Baleanu et al., 2020). The associated Caputo-Fabrizio fractional integral is defined as:

$$\prescriptCFaI_t^{\alpha} x(t) = \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)}x(t) + \frac{2\alpha}{(2-\alpha)M(\alpha)}\int_a^t x(s)ds$$

The exponential kernel in the Caputo-Fabrizio operator eliminates the boundary singularity at $t = \tau$. Epidemiologically, this models systems with short-range or fading memory, where recent historical states exert an exponentially larger influence on current dynamics than distant past states (Atanacković et al., 2018).

2.4 Atangana-Baleanu Fractional Derivative

To preserve non-locality while eliminating boundary singularities, Atangana and Baleanu in 2016 introduced a fractional derivative based on the generalized Mittag-Leffler function. The Mittag-Leffler function with parameter α, defined as:

$$E_{\alpha}(z) = \sum_{k=0}^{\infty}\frac{z^k}{\Gamma(\alpha k+1)}$$

serves as the non-singular, non-local kernel (Syam & Al-Refai, 2019). In the Caputo sense (ABC), the Atangana-Baleanu fractional derivative of order $\alpha \in (0,1]$ is defined as:

$$\prescriptABCaD_t^{\alpha} x(t) = \frac{B(\alpha)}{1-\alpha}\int_a^t x'(\tau)E_{\alpha}\left[-\frac{\alpha}{1-\alpha}(t-\tau)^{\alpha}\right]d\tau$$

where $B(\alpha)$ is a normalization factor obeying $B(0) = B(1) = 1$. In the Riemann-Liouville sense (ABR), it is formulated as:

$$\prescriptABRaD_t^{\alpha} x(t) = \frac{B(\alpha)}{1-\alpha}\frac{d}{dt}\int_a^t x(\tau)E_{\alpha}\left[-\frac{\alpha}{1-\alpha}(t-\tau)^{\alpha}\right]d\tau$$

The ABC operator captures crossover phenomena transitions between power-law and exponential decay behaviors frequently observed during multi-wave epidemic trajectories (Sene & Abdelmalek, 2019).

2.5 Fractal-Fractional Hybrid Operators

Fractal-fractional operators combine fractal differentiation, which captures spatial scale self-similarity and fractal dimensions, with fractional differentiation, which models temporal memory. When applied to plant and vector-borne epidemiology, fractal-fractional operators simultaneously capture non-homogeneous spatial pathogen dispersion across complex host architectures and temporal memory in disease progression (Etemad et al., 2022).

Table 1 summarizes the mathematical and structural properties of these primary fractional derivative operators.

Table 1: Mathematical Classification and Structural Characteristics of Key Fractional Derivatives in Epidemiological Modeling

Operator	Kernel Function	Kernel Singularity	Non-Locality Property	Initial Condition Type	Primary Epidemiological Application

Riemann-Liouville (RL)	Power-Law: $(t-\tau)^{-\alpha}$	Singular at $t=\tau$	Non-Local (Infinite Memory)	Fractional Integrals (Non-Physical)	Theoretical mathematical formulations
Caputo (C)	Power-Law: $(t-\tau)^{-\alpha}$	Singular at $t=\tau$	Non-Local (Infinite Memory)	Classical Integer Values $(x(0)=x_0)$	Waning immunity, persistent sub-diffusion
Caputo-Fabrizio (CF)	Exponential: $\exp\left[-\frac{\alpha(t-\tau)}{1-\alpha}\right]$	Non-Singular	Local Memory Filter	Classical Integer Values $(x(0)=x_0)$	Short-term behavioral memory, fading intervention effects
Atangana-Baleanu (ABC)	Mittag-Leffler: $E_\alpha\left[-\frac{\alpha(t-\tau)^\alpha}{1-\alpha}\right]$	Non-Singular	Non-Local (Crossover Memory)	Classical Integer Values $(x(0)=x_0)$	Complex multi-wave epidemics, crossover transmission
Fractal-Fractional (FF)	Hybrid Convolution / Power-Law / ML	Variable / Non-Singular	Spatial-Temporal Non-Local	Classical / Spatial Dimensions	Vector-borne diseases, agricultural plant epidemics

3. Model Formulations and Compartmental Architecture

Fractional differential equations can be integrated across a wide spectrum of compartmental disease models. The system equations replace the first-order time derivative $\frac{d}{dt}$ with a fractional operator of order $\alpha \in (0,1]$ (Yang et al., 2019).

3.1 Canonical Fractional SEIR System Formulation

To illustrate the formal mathematical structure of a fractional-order system under the Caputo derivative, consider a canonical $SEIR$ epidemic model governed by the following system of non-linear fractional differential equations for $t > 0$ and $\alpha \in (0,1]$:

$$\prescriptC0D_t^\alpha S(t) = \Lambda^\alpha - \frac{\beta^\alpha S(t) I(t)}{N(t)} - \mu^\alpha S(t)$$

$$\prescriptC0D_t^\alpha I(t) = \sigma^\alpha E(t) - (\gamma^\alpha + \mu^\alpha + d^\alpha) I(t)$$

$$\prescriptC0D_t^\alpha R(t) = \gamma^\alpha I(t) - \mu^\alpha R(t)$$

Here, $N(t) = S(t) + E(t) + I(t) + R(t)$ represents the total host population size (Ghori et al., 2022). The parameters Λ^α, β^α, μ^α, σ^α, γ^α, and d^α denote the fractional recruitment rate, disease transmission rate, natural mortality rate, incubation transition rate, recovery rate, and disease-induced mortality rate, respectively. Fractional powers are attached to parameters to preserve physical dimensional consistency across fractional orders (Baleanu et al., 2006).

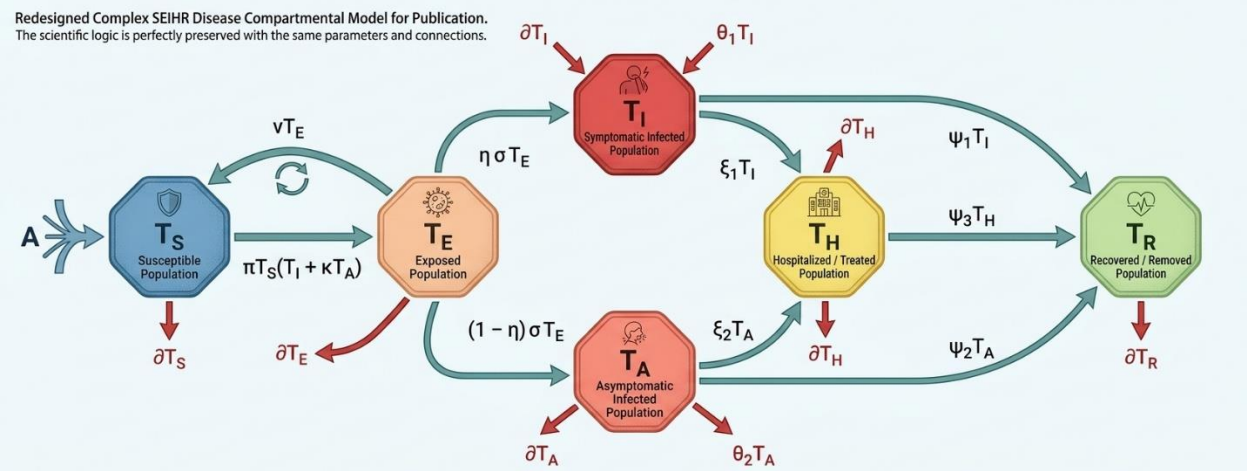


Figure 2: Dynamic Schematic and State Transition Architecture of the Fractional SEIHR Compartmental Model

Table 2: Representative Fractional Epidemiological Models Across Pathogen Typologies

Pathogen / System	Compartmental Structure	Primary Fractional Operator Used	Distinct Model Features	Key Findings / Insights
Childhood Diseases (Measles, Mumps, Rubella)	$M-S-E-I-R$	Caputo	Incorporates passive maternal immunity (M)	Dynamic fluctuations in short-incubation childhood infections are modeled more realistically.
Ebola Virus	$S-E-I-H-F-R$	Caputo	Hospitalization (H) & Post-Mortem (F) transmission	Identifies safe burial practices and rapid hospitalization as primary control drivers.
COVID-19	$S-E-Q-I_A-I_S-R$	Caputo, CF, ABC	Asymptomatic transmission (I_A), saturated incidence, quarantine (Q)	Lower fractional order α slows predicted epidemic peak, reflecting behavioral memory.
Tuberculosis (TB)	$S-E_S-E_F-I-T-R$	Caputo, ABC	Fast (E_F) & slow (E_S) latency, treatment (T), drug defiance	Treatment compliance combined with memory parameters suppresses long-term TB persistence.
Hepatitis B Virus (HBV)	$S-E-A-C-R$	Caputo, ABC	Asymptomatic carriers (A) & chronic infection (C)	Chronic carrier states act as persistent reservoirs modulated by memory fractional order.
Maize Foliar / Plant Viruses	$S-I_A-I_S-R$	Fractal-Fractional (FF)	Spatial fractal geometry + temporal fractional memory	Rogueing and replanting strategies analyzed alongside spatial canopy patchiness.

Malware / Computer Viruses	$S-L-B-R$	Caputo	Latent (L) & active infected (B) network nodes	Memory effects capture network node latency and patch dissemination delays.

4. Qualitative Properties, Positivity, and Stability Theory

To ensure that a fractional differential model provides a physically meaningful representation of infectious disease spread, the system must satisfy rigorous mathematical well-posedness criteria. These include non-negativity of solutions, positive invariance of the state space, existence and uniqueness of solutions, and asymptotic stability of equilibrium states (Friesecke & Pego, 1999).

4.1 Positive Invariance and Boundedness

Because epidemiological compartmental variables denote living populations, all state trajectories originating in the non-negative orthant $\mathbb{R}_+^n$ must remain non-negative and bounded for all $t \geq 0$. Consider the total population $N(t)$ derived from a generic fractional compartmental model (Aziz-Alaoui & Okiye, 2003). Summing the fractional differential equations yields an inequality for the total population trajectory:

$$\prescriptC0D_t^{\alpha} N(t) + \mu^{\alpha} N(t) \leq \Lambda^{\alpha}$$

Applying the Laplace transform ($\mathcal{L}\{\prescriptC0D_t^{\alpha} N(t)\} = s^{\alpha} N(s) - s^{\alpha-1} N(0)$) to both sides yields:

$$s^{\alpha} N(s) - s^{\alpha-1} N(0) + \mu^{\alpha} N(s) \leq \frac{\Lambda^{\alpha}}{s}$$

$$N(s) \leq N(0) \frac{s^{\alpha-1}}{s^{\alpha} + \mu^{\alpha}} + \frac{\Lambda^{\alpha}}{s(s^{\alpha} + \mu^{\alpha})}$$

Taking the inverse Laplace transform produces a dynamic bound governed by the single-parameter Mittag-Leffler function $E_{\alpha,1}(\cdot)$:

$$N(t) \leq \left(N(0) - \frac{\Lambda^{\alpha}}{\mu^{\alpha}} \right) E_{\alpha,1}(-\mu^{\alpha} t^{\alpha}) + \frac{\Lambda^{\alpha}}{\mu^{\alpha}}$$

Because $E_{\alpha,1}(-\mu^{\alpha} t^{\alpha})$ is a completely monotonic, non-negative function bounded by 1 for $t \geq 0$, and $\lim_{t \to \infty} E_{\alpha,1}(-\mu^{\alpha} t^{\alpha}) = 0$, the solution trajectory remains inside the biologically feasible, positively invariant domain:

$$\Omega = \left\{ (S, E, I, R) \in \mathbb{R}_+^4 : 0 \leq N(t) \leq \frac{\Lambda^{\alpha}}{\mu^{\alpha}} \right\}$$

Thus, the system is mathematically well-posed, preventing population variables from growing unbounded or taking non-physical negative values (Hennet & Tarbouriech, 1998).

4.2 Existence and Uniqueness via Fixed Point Theory

Existence and uniqueness of solutions for non-linear fractional differential equations are established using fixed point theorems in Banach spaces. The fractional system is converted into an equivalent Volterra integral equation (Granas & Dugundji, 2013). For a system governed by an ABC fractional derivative $\prescriptABC0D_t^{\alpha} x(t) = f\big(t, x(t)\big)$, integration yields:

$$x(t) = x(0) + \frac{1-\alpha}{B(\alpha)} f\big(t, x(t)\big) + \frac{\alpha}{B(\alpha)\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1} f\big(\tau, x(\tau)\big) d\tau$$

Defining a continuous operator $T: C([0,T], \mathbb{R}^n) \to C([0,T], \mathbb{R}^n)$, existence and uniqueness are proven by demonstrating that $f\big(t, x(t)\big)$ satisfies a uniform Lipschitz condition $\|f(t, x_1) - f(t, x_2)\| \leq L \|x_1 - x_2\|$. If the contraction constant $K = \left(\frac{1-\alpha}{B(\alpha)} + \frac{\alpha T^{\alpha}}{B(\alpha)\Gamma(\alpha+1)} \right) L < 1$, the Banach Fixed Point Theorem guarantees the existence of a unique solution trajectory on $[0, T]$. Alternative proofs employ the Schauder Fixed Point Theorem when contraction constraints are relaxed (Kellogg, 1976).

4.3 Basic Reproduction Number ($\mathcal{R}_0$) Derivation

The basic reproduction number, $\mathcal{R}_0$, defines the average number of secondary infections generated by a single infectious individual introduced into a completely susceptible population. In fractional order models, $\mathcal{R}_0$ is calculated using the Next-

Generation Matrix (NGM) method (Van den Driessche & Watmough, 2008).

The compartmental vector is partitioned into infected compartments $\mathcal{X} = (E, I)^T$ and uninfected compartments $\mathcal{Y} = (S, R)^T$. The rate of appearance of new infections $\mathcal{F}$ and the rate of internal compartment transitions $\mathcal{V}$ are evaluated at the Disease-Free Equilibrium (DFE), $E_0 = \left(\frac{\Lambda^\alpha}{\mu^\alpha}, 0,0,0\right)$. The Jacobian matrices $F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}\right]_{E_0}$ and $V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}\right]_{E_0}$ yield:

$$F = \begin{bmatrix} 0 & \beta^\alpha \\ 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} \sigma^\alpha + \mu^\alpha & 0 \\ -\sigma^\alpha & \gamma^\alpha + \mu^\alpha + d^\alpha \end{bmatrix}$$

The Next-Generation Matrix is constructed as $K = FV^{-1}$ (Zhao, 2017). The basic reproduction number $\mathcal{R}_0$ corresponds to the spectral radius (largest absolute eigenvalue) of K:

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{\beta^\alpha \sigma^\alpha}{(\sigma^\alpha + \mu^\alpha)(\gamma^\alpha + \mu^\alpha + d^\alpha)}$$

If $\mathcal{R}_0 < 1$, the disease-free equilibrium is stable, and the infection dies out; if $\mathcal{R}_0 > 1$, the disease persists, giving rise to a unique endemic equilibrium E^* (Van den Driessche & Watmough, 2002).

5. Numerical Schemes and Optimal Control Frameworks

Because analytical closed-form solutions for non-linear fractional differential equations rarely exist, numerical approximation algorithms and optimal control frameworks are required to simulate disease progression and evaluate public health interventions (Rao, 2009).

5.1 Numerical Approximation Algorithms

Computational algorithms for fractional equations must evaluate non-local memory integrals over long historical time domains. The Fractional Adams-Bashforth-Moulton (ABM) Predictor-Corrector Method discretizes Caputo fractional differential equations over a grid $t_j = jh$ $(j = 0,1, \dots, N)$ with step size h (Cohen, 2011). The predictor state $x_h^p(t_{n+1})$ and corrector state $x_h(t_{n+1})$ are computed as:

$$x_h^p(t_{n+1}) = x(0) + \frac{1}{\Gamma(\alpha)} \sum_{j=0}^{n} b_{j,n+1} f\left(t_j, x_h(t_j)\right)$$

$$x_h(t_{n+1}) = x(0) + \frac{h^\alpha}{\Gamma(\alpha+2)} f\left(t_{n+1}, x_h^p(t_{n+1})\right) + \frac{h^\alpha}{\Gamma(\alpha+2)} \sum_{j=0}^{n} a_{j,n+1} f\left(t_j, x_h(t_j)\right)$$

where the weights $a_{j,n+1}$ and $b_{j,n+1}$ are defined by piecewise linear interpolation polynomials.

Complementing the predictor-corrector approach, the Modified Euler's Method (MEM) approximates Caputo fractional equations using fractional weights derived from Taylor expansions, offering lower computational complexity per time step for large multi-compartment systems (Meinardus, 2012). For non-singular operators such as Caputo-Fabrizio and Atangana-Baleanu, numerical schemes combine integral transforms such as the Laplace transform or Shehu transform with iterative decomposition techniques. Methods including the Adomian Decomposition Method (ADM), Picard Iteration Method (PM), Residual Power Series Method (RPSM), and Generalized Hat Functions solve the Volterra integral forms by generating rapidly converging series solutions (Markovsky, 2012).

5.2 Optimal Control Formulations

Optimal control theory in fractional epidemiology seeks to design time-dependent intervention strategies such as vaccination rate $u_1(t)$ and treatment/isolation enforcement rate $u_2(t)$ that minimize disease burden and implementation costs (Athans & Falb, 2013). A representative objective cost functional is formulated as:

$$\min_{u_1,u_2} J(u_1, u_2) = \int_0^T \left(w_1 I(t) + w_2 E(t) + \frac{1}{2} c_1 u_1^2(t) + \frac{1}{2} c_2 u_2^2(t) \right) dt$$

subject to the fractional dynamic constraints:

$$\prescriptC0D_t^\alpha S(t) = \Lambda^\alpha - \frac{\beta^\alpha S(t) I(t)}{N(t)}(1 - u_1(t)) - \mu^\alpha S(t)$$

$$\prescriptC0D_t^{\alpha} I(t) = \sigma^{\alpha} E(t) - \left(\gamma^{\alpha} + \mu^{\alpha} + d^{\alpha} + u_2(t)\right) I(t)$$

Here, w_1, w_2 denote severity weights for infected and exposed populations, while c_1, c_2 represent relative quadratic costs associated with control efforts (Lewis et al., 2012).

Optimal control profiles (u_1^*, u_2^*) are derived using Pontryagin's Maximum Principle generalized for fractional systems. The formulation constructs a fractional Hamiltonian $\mathcal{H}$, introducing co-state variables $\lambda_i(t)$ governed by right-sided Caputo derivatives $\prescriptCtD_T^{\alpha} \lambda_i(t) = -\frac{\partial \mathcal{H}}{\partial x_i}$ with transversality boundary conditions $\lambda_i(T) = 0$. Solving the coupled forward-backward fractional system provides optimal control trajectories, demonstrating that memory effects alter the timing and duration of peak control measures compared to integer-order control strategies (Berkovitz, 2013).

6. Methodological Challenges, Dimensional Consistency, and Future Directions

Despite the analytical advances of fractional calculus in epidemiology, several methodological challenges remain, requiring rigorous parameter handling and structural justification (Wani, 2025).

6.1 Dimensional Consistency

A common theoretical issue in fractional differential modeling stems from physical dimensional inconsistency. In a classical integer-order system $\frac{dx}{dt} = f(x)$, the left-hand operator possesses a physical dimension of $[\text{time}]^{-1}$. When replacing $\frac{dx}{dt}$ with a fractional derivative $\prescriptC0D_t^{\alpha} x(t)$, the left-hand operator assumes a physical dimension of $[\text{time}]^{-\alpha}$ (Johnstone & Lu, 2009).

If the right-hand rate parameters (such as contact rate β or natural death rate μ) are kept in classical units of $[\text{time}]^{-1}$, an explicit dimensional mismatch occurs between both sides of the differential equation (Nandy et al., 2018). To preserve physical unit homogeneity, parameters must be rescaled using an auxiliary time scale parameter σ (having dimension of [time]):

$$\prescriptC0D_t^{\alpha} x(t) = \frac{1}{\sigma^{1-\alpha}} f\left(x(t)\right)$$

Alternatively, parameters must be redefined to possess fractional dimensions $[\text{time}]^{-\alpha}$ (e.g., $\beta^{\alpha}, \mu^{\alpha}$). Neglecting dimensional consistency distorts parameter values when fitting real-world data, leading to incorrect estimates of the basic reproduction number $\mathcal{R}_0$ (Ruscio et al., 2010).

6.2 Operator Selection and Biological Interpretation

The existence of multiple fractional derivative definitions (Caputo, Caputo-Fabrizio, Atangana-Baleanu, Fractal-Fractional) introduces operator selection ambiguity. Modelers must align operator mechanics with the physical characteristics of the target disease. Caputo operators are suitable for processes driven by power-law memory, such as long-term immunity waning or sub-diffusive movement (Berg & von Hippel, 1987). Caputo-Fabrizio operators fit short-term fading behavioral memory, such as temporary compliance with non-pharmaceutical interventions. Atangana-Baleanu operators effectively capture multi-wave crossover behaviors, where transmission dynamics shift between exponential growth and heavy-tailed decay (Ma et a., 2006).

6.3 Computational Complexity and Parameter Fitting

Evaluating non-local fractional memory integrals requires storing all previous trajectory states, which increases memory consumption and computational runtime for long time-series simulations. Furthermore, calibrating fractional parameters (α, β, σ) against clinical data requires robust optimization algorithms such as non-linear least squares, Markov Chain Monte Carlo (MCMC), or genetic algorithms to avoid overfitting (Goldsmith et al., 2007).

Conclusion

This review has established that fractional differential equations offer a mathematically rigorous and epidemiologically meaningful extension of classical compartmental modeling for

infectious disease transmission. By replacing integer-order derivatives with non-integer operators, FDEs introduce intrinsic memory mechanisms that capture hereditary characteristics of pathogen transmission, host immune response, and behavioral adaptation features that are fundamentally absent in memoryless Markovian frameworks. The taxonomy of fractional operators reveals that operator selection must be guided by the physical characteristics of the target disease: Caputo operators for power-law memory processes such as long-term immunity waning, Caputo-Fabrizio for short-term fading behavioral memory, and Atangana-Baleanu for multi-wave crossover phenomena. The canonical fractional SEIR system and its pathogen-specific variants demonstrate the flexibility of this framework across diverse epidemiological contexts, from COVID-19 and Ebola to tuberculosis and hepatitis B. Rigorous qualitative analysis encompassing positivity, boundedness, existence, uniqueness, and stability ensures that fractional models remain biologically valid and mathematically well-posed. The derivation of the basic reproduction number and the formulation of fractional optimal control problems provide practical tools for evaluating intervention strategies and predicting epidemic trajectories. However, critical challenges persist, including dimensional inconsistency, operator selection ambiguity, and computational complexity in evaluating non-local memory integrals. Addressing these challenges through parameter rescaling, robust calibration algorithms, and efficient numerical schemes is essential for advancing the field. Future research should prioritize the development of standardized dimensional consistency protocols, comparative studies across operator types, and integration of fractional models with real-time epidemiological data. Ultimately, fractional calculus represents not merely a mathematical refinement but a paradigm shift in epidemiological modeling one that acknowledges the deep historical dependencies inherent in disease transmission and offers a more faithful representation of complex biological reality.

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