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THE GASTROINTESTINAL TRACT IS A MOVING TARGET FOR COMPUTATIONAL MODELS OF ORAL DRUG DELIVERY AND ABSORPTION

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ABSTRACT

Computational models of oral drug delivery commonly represent gastrointestinal physiology through regional averages, predefined transit compartments, or scenario-level adjustments. Such abstractions are useful, but they can obscure a central pharmaceutical reality: the gastrointestinal tract changes continuously after administration, and those changes alter the environment encountered by both the dosage form and the released drug. Transit, luminal pH, fluid availability, motility, food composition, bile-mediated solubilization, permeability, presystemic metabolism, and selected microbiome-mediated transformations do not act as independent constants. They form interacting, time-dependent processes whose consequences depend on compound properties, dosage-form behavior, administration conditions, and patient physiology. This article develops a proposed Dynamic Gastrointestinal State–Process Model that represents oral delivery as the co-evolution of regional physiological states and drug-product states. The model separates scenario initialization, segment-specific gastrointestinal trajectories, dosage-form transitions, luminal dissolution and precipitation, epithelial access, presystemic transformation, optional microbiome activity, virtual-population variability, and evidence qualification. Its central contribution is to shift computational interpretation from a fixed gastrointestinal background toward a conditional state-transition architecture in which local drug availability and systemic exposure emerge from competing and reversible processes. The proposal does not constitute a validated software platform, universal physiological representation, clinical prediction instrument, or regulatory framework. Its usefulness is conditional on compound-specific evidence, appropriate measurement resolution, qualified input distributions, identifiable mechanisms, and evaluation against both local and systemic observations. The framework may nevertheless help organize model development, sensitivity analysis, formulation comparison, food-effect assessment, and bioavailability prediction while making uncertainty and application boundaries explicit.

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Introduction

Oral drug absorption takes place within an environment whose physicochemical and biological properties change before, during, and after dosage-form transit. Gastric and intestinal pH influence ionization, apparent solubility, dissolution, precipitation propensity, and the assumptions through which absorption models translate luminal drug states into exposure. Food can further alter these conditions by changing buffering capacity, gastric residence, secretions, solubilization, viscosity, and downstream absorption processes. Consequently, a model that assigns one pH value or one fed-state multiplier to an entire gastrointestinal region may reproduce a selected observation while misrepresenting the physiological sequence that produced

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it. Food-induced and baseline changes in gastrointestinal pH alter solubility, dissolution, ionization, and the assumptions used by oral absorption models [1].

The difficulty is not simply that gastrointestinal inputs are variable; it is that they are multidimensional, spatially distributed, temporally ordered, and measured with unequal resolution. Regional fluid volumes, luminal composition, motility, transit, secretion, dosage-form position, and local disintegration may change together, yet many pharmacokinetic datasets observe only the systemic consequences of these internal events. Direct measurement technologies have shown that formulation-relevant gastrointestinal variables vary across regions, time points, and individuals [2]. A plasma concentration profile therefore represents the accumulated result of several hidden processes rather than a direct observation of dissolution, luminal concentration, epithelial uptake, or intestinal first-pass loss. This creates an identifiability problem: distinct internal mechanisms can generate similar systemic profiles, particularly when model parameters are estimated simultaneously from the same downstream observations.

Physiological heterogeneity further limits the use of a single representative gastrointestinal tract. Age, disease, food intake, sex, co-medication, altered anatomy, transporter or enzyme activity, and other contextual factors may change the determinants of oral exposure [3]. These factors also interact. A longer residence time may improve dissolution for one formulation but increase degradation or precipitation for another; increased luminal fluid may support dissolution while lowering concentration-dependent absorption; and a food-induced delay may alter the location at which release, supersaturation, or uptake occurs. The relevant modeling target is therefore not an average set of independent parameters, but a distribution of correlated physiological trajectories conditioned on the administration scenario, population, drug, and dosage form.

Physiologically based biopharmaceutics modeling can connect drug-product attributes with gastrointestinal processes and systemic pharmacokinetics, but its credibility remains dependent on parameter quality, verification, validation, and a defined context of use [4]. Reliable food-effect prediction similarly requires explicit mechanistic hypotheses, compound-specific evidence, and qualification against observations that are not merely reused for parameter fitting [5]. Building on these principles, this article proposes a Dynamic Gastrointestinal State–Process Model, abbreviated DGSPM, in which gastrointestinal regions are represented as time-indexed states and oral absorption is represented as competition among dosage-form transformation, dissolution, precipitation, transit, epithelial uptake, and presystemic loss. The proposal treats model structure, physiological heterogeneity, measurement limitations, and intended decisions as explicit components rather than residual error. Taken together, the available evidence indicates that oral absorption models must represent interacting and variable gastrointestinal conditions rather than one average physiology [1-3].

Dynamic Gastrointestinal Physiology as a Modeling Challenge

The first challenge is to distinguish physiological variability from model uncertainty. Virtual trials can vary gastric emptying, intestinal transit, fluid volumes, pH, permeability, or other inputs and thereby reveal which physiological properties materially alter predicted in vivo performance [6]. Such analyses are valuable because they expose possible drivers of variability that are difficult to isolate experimentally. However, the resulting exposure distributions are conditional on the equations, parameter ranges, correlations, and compound-specific assumptions used to construct them. A narrow output distribution does not necessarily mean that the underlying physiology is stable, and a broad distribution does not identify which representation of physiology is correct. The proposed DGSPM therefore separates variation attributed to simulated subjects from uncertainty about parameter values, measurement quality, and model form. This distinction prevents virtual heterogeneity from being interpreted as observed clinical variability without population-specific calibration.

The administered dose is also introduced into a physiological system already perturbed by the act of administration. Water volume, posture, meal timing, dosage-form size, and co-administered materials can alter the initial gastric state and the timing of subsequent transitions. Human measurements comparing different water volumes demonstrate that administered fluid volume can change gastric distension and emptying behavior rather than functioning as a trivial fixed input [7]. In the proposed model, water volume is therefore part of a scenario initializer that influences gastric volume, emptying events, dilution, and the timing of entry into the small intestine. This does not imply that one study supplies universal emptying parameters. Instead, it establishes that administration conditions belong inside the modeled physiological state and that their effects should be represented through qualified distributions or scenario-specific observations.

A second challenge is that systemic pharmacokinetics alone cannot determine where a dosage form was located, when it disintegrated, or which gastric conditions surrounded it. Magnetic resonance imaging has been used to observe dosage-form position, disintegration, gastric contents, and emptying, thereby providing constraints on internal gastrointestinal states that cannot be obtained from plasma profiles alone [8]. Such measurements can help distinguish a release delay caused by prolonged gastric residence from one caused by formulation behavior, or a variable absorption onset caused by transit from one caused by dissolution. The DGSPM consequently includes an observation layer through which imaging, aspiration, dissolution testing, motility measurements, and systemic pharmacokinetics constrain different model components. Measurement does not automatically make a mechanism identifiable, but local observations can reduce the number of mechanistically distinct explanations that remain compatible with the systemic data.

The moving-target problem continues beyond the stomach. Colonic fluid is often distributed in spatially separated pockets, while contents, motility, and transit can create discontinuous opportunities for release and absorption, particularly for delayed-release, extended-release, and locally acting products [9]. At the same time, comparative evaluations have shown that oral absorption software platforms may produce different prediction characteristics across structurally diverse low-solubility drugs,

indicating that platform output should not be treated as a universal physiological truth [10]. These observations motivate two related requirements. First, gastrointestinal states should be segment-specific and capable of representing discontinuity rather than assuming uniform luminal conditions. Second, differences arising from software structure, defaults, and numerical implementation should be examined separately from physiological variability. A dynamic model is therefore not credible merely because it is more detailed; its added states and transitions must be observable, identifiable, influential for the stated question, or explicitly retained as uncertain.

Table 1 organizes the evidence, constructs, and interpretation boundaries needed to develop dynamic gastrointestinal physiology as a modeling challenge within the article's central argument.

Table 1. Evidence domains, core questions, scientific requirements, and interpretation boundaries for Dynamic gastrointestinal physiology as a modeling challenge

Construct or Evidence Domain	Core Question	Scientific Basis	Role in the Article	Failure or Overclaiming Risk	Boundary Statement
Time-Indexed Gastrointestinal State	Which physiological properties change after administration, and on what timescale?	Gastrointestinal conditions evolve through emptying, secretion, motility, meals, regional transit, and dosage-form interaction.	Replaces static regional constants with trajectories of conditional states.	Greater temporal detail may appear inherently more accurate even when transition data are sparse.	A time-indexed representation requires evidence for transition timing and does not guarantee improved prediction.
Scenario Initialization	How do water volume, prandial state, dose, posture, and co-medication alter the starting condition?	Administration changes gastric volume, contents, emptying behavior, dilution, and subsequent regional entry.	Defines the initial state and scheduled physiological perturbations.	Treating one protocol as universally representative.	Initial conditions must be matched to the intended dosing scenario and population.
Segment-Specific Heterogeneity	Can stomach, small-intestinal regions, and colon be represented by uniform compartments?	Regional anatomy, fluid distribution, motility, surface area, secretions, and absorption capacity differ.	Supports distinct but connected regional state vectors.	Excessive compartmental detail may create poorly identifiable parameters.	Regional subdivision is justified only when it affects the modeled mechanism or decision.
Local Observation and Identifiability	Which internal states can be constrained independently of plasma pharmacokinetics?	Imaging and other local measurements can observe dosage-form location, disintegration, fluid, contents, or transit.	Links specific evidence types to the states they can inform.	Assuming that observation of one local event validates the entire process chain.	Each measurement constrains only the states and timescales it can directly or mechanistically inform.
Physiological Variability	Which differences arise among individuals, occasions, diseases, or dosing contexts?	Physiological determinants vary within and between populations and may be correlated.	Provides the biological basis for virtual-population trajectories.	Simulated variability may be mistaken for observed population representativeness.	Virtual distributions require empirical justification and population-specific calibration.
Model-Form and Implementation Uncertainty	Do alternative equations, defaults, or software structures produce different explanations?	Dissolution, precipitation, transit, permeability, and absorption can be implemented differently across platforms.	Separates structural uncertainty from biological variability.	Selecting one platform output as physiological ground truth.	Cross-platform agreement is supportive but does not establish mechanistic correctness.
Context-of-Use Qualification	What decision is the model intended to support?	Required evidence depends on whether the question concerns mechanism, formulation comparison, food effect, study design, or exposure prediction.	Restricts evaluation claims to a defined pharmaceutical question.	Generalizing success in one compound, formulation, or scenario to unrelated uses.	Credibility is decision-specific and cannot be inferred from model complexity alone.

Transit, pH, Fluid Volumes, Motility, Food, and Microbiome Variation

Food effects illustrate why gastrointestinal variables should be modeled as interacting trajectories rather than independent fed–fasted switches. A meal can change gastric pH and buffering, delay or reshape emptying, increase luminal volume and viscosity, stimulate bile secretion, alter regional motility and blood flow, and modify transporter or enzyme activity. The direction and magnitude of the resulting exposure change depend on the drug and formulation because the same physiological event may increase solubilization, delay release, promote degradation, shift an absorption window, or alter presystemic extraction. Food effects therefore emerge from interacting physiological and formulation mechanisms rather than from a single correction factor [11]. Within the DGSPM, a meal is represented as a scheduled perturbation that updates several correlated regional states over time. This representation is proposed as a mechanistic organizing principle; it does not assume that every food-related process can be independently estimated for every compound.

Fluid volume deserves separate attention because it affects multiple processes with potentially opposing consequences. More fluid can increase wetting, disintegration, dissolution capacity, and transport of released material, but it can also dilute dissolved drug, alter supersaturation, and change concentration gradients at the epithelial surface. Experimental and modeling work with oral jelly formulations indicates that the effect of intestinal fluid volume on absorption depends on membrane

permeability and dosage-form context [12]. Fluid volume should therefore not enter the model as an isolated linear modifier. It should condition the dosage-form state, luminal concentration, dissolution environment, precipitation risk, and epithelial flux. The relevant input may also be a spatial distribution rather than a single compartmental volume, especially when intestinal or colonic fluid is discontinuous. Where direct measurements are unavailable, uncertainty in fluid volume and its distribution should be propagated rather than concealed by one deterministic default.

Transit, pH, bile secretion, motility, and blood flow similarly change through the postprandial period and should be represented with temporal dependencies. Reviews of food-effect modeling show that PBPK prediction requires consideration of changing pH, gastrointestinal movement, bile secretion, blood flow, dissolution conditions, and first-pass processes [13]. The proposed architecture captures these effects through an event-driven transition engine. Gastric emptying transfers formulation and drug mass into the duodenum; regional transit moves intact, solid, dissolved, precipitated, and transformed material; pH and bile states modify dissolution and solubilization; and blood-flow or enzyme states affect the relationship between epithelial uptake and systemic appearance. These transitions are coupled rather than merely sequential. For example, delayed emptying changes not only arrival time but also the duration of gastric dissolution or degradation, while altered intestinal transit changes the time available for dissolution, precipitation, uptake, and metabolism.

Microbiome variation is conceptually different from broadly acting variables such as pH or transit because microbial effects are highly compound-specific and depend on the presence, abundance, and activity of relevant metabolic functions. Mechanistic work has demonstrated that microbial metabolism can make a separable contribution to pharmacokinetics and toxicity for susceptible compounds [14]. The DGSPM therefore treats microbiome-mediated transformation as an optional module rather than a universal correction factor. Activation would require evidence for a drug-specific microbial pathway, a relevant gastrointestinal location, substrate availability, and a plausible connection to parent-drug or metabolite exposure. In the absence of such evidence, microbiome composition alone should not be used to claim a mechanistic effect on absorption.

More generally, food changes several time-varying physiological processes whose consequences remain conditional on compound properties, formulation behavior, permeability, and the structure of the computational model [11-13].

Linking Dissolution, Precipitation, Permeability, and Metabolism

Dissolution should be modeled as a regional, time-dependent transformation rather than a formulation property that occurs independently of gastrointestinal physiology. The amount dissolved in a segment depends on the material delivered from the preceding segment, local fluid availability, pH, bile-mediated solubilization, particle properties, residence time, and removal through absorption or transit. Mechanistic deconvolution has shown that dynamic gastrointestinal fluid representation can support estimation of regional in vivo dissolution, although those estimates remain difficult to validate directly when local concentration measurements are unavailable [15]. The proposed DGSPM therefore distinguishes measured dissolution behavior, inferred regional dissolution, and model-generated dissolved mass. Agreement with systemic pharmacokinetics alone is insufficient to establish that the inferred regional dissolution trajectory is correct.

Dissolved drug is not necessarily durably available for absorption. A formulation may create transient supersaturation after gastric emptying, pH change, salt conversion, or release from a solubilizing vehicle, but the resulting state can be lost through nucleation, particle growth, precipitation, degradation, or transit. Precipitation kinetics can materially influence early oral absorption predictions and should be linked explicitly to dissolution and epithelial uptake rather than represented only through equilibrium solubility [16]. In the proposed model, supersaturated, precipitated, and redissolved material are separate mass-balanced states. Their transitions compete with permeability and transit, making the timing of precipitation as important as its eventual extent. This representation remains conditional on experimentally justified kinetic inputs and does not imply that every solid-state transition can be identified in vivo.

Weak bases make the consequences of process coupling especially visible. Gastric dissolution may generate dissolved drug under acidic conditions, but transfer into a higher-pH intestinal environment can reduce solubility and promote precipitation before absorption is complete. Bottom-up modeling of poorly soluble free weak bases indicates that gastric dissolution and local pH assumptions can materially affect predicted fraction absorbed and predictions of interactions with acid-reducing agents [17]. The DGSPM therefore transfers dissolved and undissolved mass separately during gastric emptying and recalculates their downstream states as the regional environment changes. Surface pH, bulk pH, buffering, precipitation delay, and permeability are treated as linked hypotheses whose influence must be evaluated against compound-specific evidence rather than adjusted simultaneously until a plasma profile is reproduced.

The process chain does not end when drug crosses the luminal boundary. Epithelial access may involve passive permeation, carrier-mediated uptake, efflux, regional absorption windows, and intracellular metabolism before drug reaches portal blood. The representation of intestinal blood flow and tissue segregation can alter estimates of intestinal and hepatic metabolism and thereby change the interpretation of oral availability [18]. Accordingly, the DGSPM separates luminal availability, epithelial uptake, gut-wall escape, portal delivery, and hepatic availability. This prevents low systemic exposure from being attributed automatically to incomplete dissolution or permeability when intestinal metabolism, efflux, or flow assumptions may be responsible. The full relationship is therefore a coupled competition among release, dissolution, precipitation, transit, uptake, and presystemic loss rather than a sequence of independently fitted fractions.

Table 2 organizes the evidence, constructs, and interpretation boundaries needed to develop linking dissolution, precipitation, permeability, and metabolism within the article's central argument.

Table 2. Components, relationships, uncertainties, and validation needs within Linking dissolution, precipitation, permeability, and metabolism

Component or Layer	Inputs	Core Function	Expected Output	Uncertainty or Limitation	Validation Requirement
Dosage-Form Release State	Formulation structure, disintegration behavior, release testing, regional physiological conditions	Transfers drug from intact or retained product states into dispersed or releasable material	Time- and segment-specific released and unreleased mass	In vitro release may not reflect in vivo mechanical, fluid, or motility conditions	Orthogonal in vitro testing and, where feasible, in vivo dosage-form location or disintegration evidence
Dissolution and Solubilization	Solid-state properties, particle attributes, pH, fluid volume, bile or surfactant capacity, mixing and residence time	Converts undissolved material into molecularly or colloidally available drug	Regional dissolved-drug trajectory	Local hydrodynamics, surface pH, bile composition, and effective volume may be weakly observed	Biorelevant dissolution evidence linked to relevant gastrointestinal scenarios
Supersaturation And Precipitation	Dissolved concentration, equilibrium solubility, nucleation delay, precipitation and particle-growth kinetics	Represents temporary excess dissolved drug and its conversion back to solid material	Supersaturated, precipitated, and redissolved drug states	Kinetic parameters may be method-dependent and difficult to identify from plasma data	Kinetic precipitation and redissolution experiments with sensitivity and identifiability analysis
Regional Transit Coupling	Gastric emptying, segmental residence, motility, formulation location and mass transfer	Moves intact, solid, dissolved, precipitated, and transformed states between regions	Segment-specific arrival and residence histories	Average transit values may conceal episodic transfer and interindividual variability	Time-resolved transit or imaging evidence under matched administration conditions
Epithelial Access And Permeability	Dissolved concentration near the membrane, regional surface area, passive permeability, transporters and efflux	Converts locally available drug into epithelial uptake flux	Regional absorbed amount and rate	Effective permeability may vary by region, concentration, disease state, or transporter activity	Independent permeability evidence and external evaluation across relevant doses or regions
Presystemic Transformation	Enterocyte metabolism, efflux recycling, intestinal blood flow, portal delivery and hepatic first pass	Separates epithelial uptake from drug reaching systemic circulation	Gut-wall escape, portal input, metabolites and systemic availability	Alternative flow and tissue structures may yield different inferred first-pass losses	Comparison of plausible structures using metabolism, interaction, metabolite and pharmacokinetic evidence
Observation and Identifiability Layer	Local sampling, imaging, dissolution data, plasma profiles, metabolites and perturbation studies	Determines which internal process combinations are compatible with available evidence	Constrained parameter and mechanism sets rather than one assumed mechanism	Distinct process chains can produce similar systemic profiles	Calibration with orthogonal observations and explicit structural-identifiability assessment
Coupled-Process Interpretation	Outputs from all preceding components	Evaluates competition among dissolution, precipitation, permeability, transit and metabolism	Mechanistic explanation with stated uncertainty and alternatives	A well-fitting explanation may remain nonunique	Prospective prediction under a scenario that discriminates among competing mechanisms

Architecture of the Dynamic Oral-Delivery Model

The proposed DGSPM is a modular, mass-balanced architecture designed to represent the co-evolution of gastrointestinal conditions and drug-product states. Mechanistic modeling precedents demonstrate that unreleased, undissolved, dissolved, transiting, and absorbed states can be maintained separately across gastrointestinal compartments [19]. Building on that principle, the DGSPM contains a scenario initializer, time-indexed regional physiological states, an event-driven transition engine, a dosage-form state module, a luminal transformation module, an epithelial-access module, a presystemic-transformation interface, an optional microbiome plug-in, and an observation and uncertainty layer. These components define an original proposed architecture rather than a completed software implementation. Their inclusion does not establish that all states are observable or that all associated parameters can be estimated for a given drug.

The transition engine determines when and how physiological and drug-product states change. Events include administration, meal entry, gastric emptying, secretion, regional transit, dosage-form disintegration, release, dissolution, precipitation, uptake, metabolism, and elimination from the modeled absorption domain. Finite absorption time provides a useful structural constraint because it makes the duration and termination of absorption explicit and can expose differences between model assumptions that otherwise produce similar pharmacokinetic profiles [20]. The DGSPM therefore requires defined entry and exit conditions for each regional state. Material cannot remain indefinitely available merely because a compartmental equation has no physiological stopping rule, and absorbed flux must cease when the relevant material, residence time, or absorption opportunity has been exhausted.

Architecture alone does not provide credibility. The question of interest must determine the required components, evidence resolution, parameter treatment, verification tests, and acceptable uncertainty. Best-practice discussions of physiologically based biopharmaceutics modeling emphasize a defined question, transparent inputs, uncertainty analysis, verification, and fit-for-purpose validation [21]. The DGSPM consequently uses an activation principle: a process module is included only when it is mechanistically relevant to the intended decision and supported by sufficient evidence to parameterize, constrain, or

transparently bracket it. A microbiome component, regional transporter, precipitation mechanism, or specialized formulation process should not be activated merely because the architecture can accommodate it. Unnecessary detail may increase apparent realism while reducing identifiability and reproducibility.

The model's final architectural layer connects scientific evidence to bounded claims. Reporting guidance for physiologically based biopharmaceutics models indicates that the question of interest, context of use, input evidence, modeling plan, validation strategy, and model risk should be connected explicitly [22]. The DGSPM therefore assigns provenance to parameters and structural assumptions, distinguishes calibration from external evaluation, records alternative model forms, and restricts outputs to the decision context for which the system was qualified. Its outputs may include regional trajectories, exposure distributions, mechanism comparisons, sensitivity rankings, or scenario contrasts. None is interpreted as a universal prediction score, clinical recommendation, regulatory conclusion, or proof that the unobserved internal mechanism is correct.

Figure 1 presents the dynamic gastrointestinal delivery corridor, showing how the article's key components and boundaries are connected within architecture of the dynamic oral-delivery model.

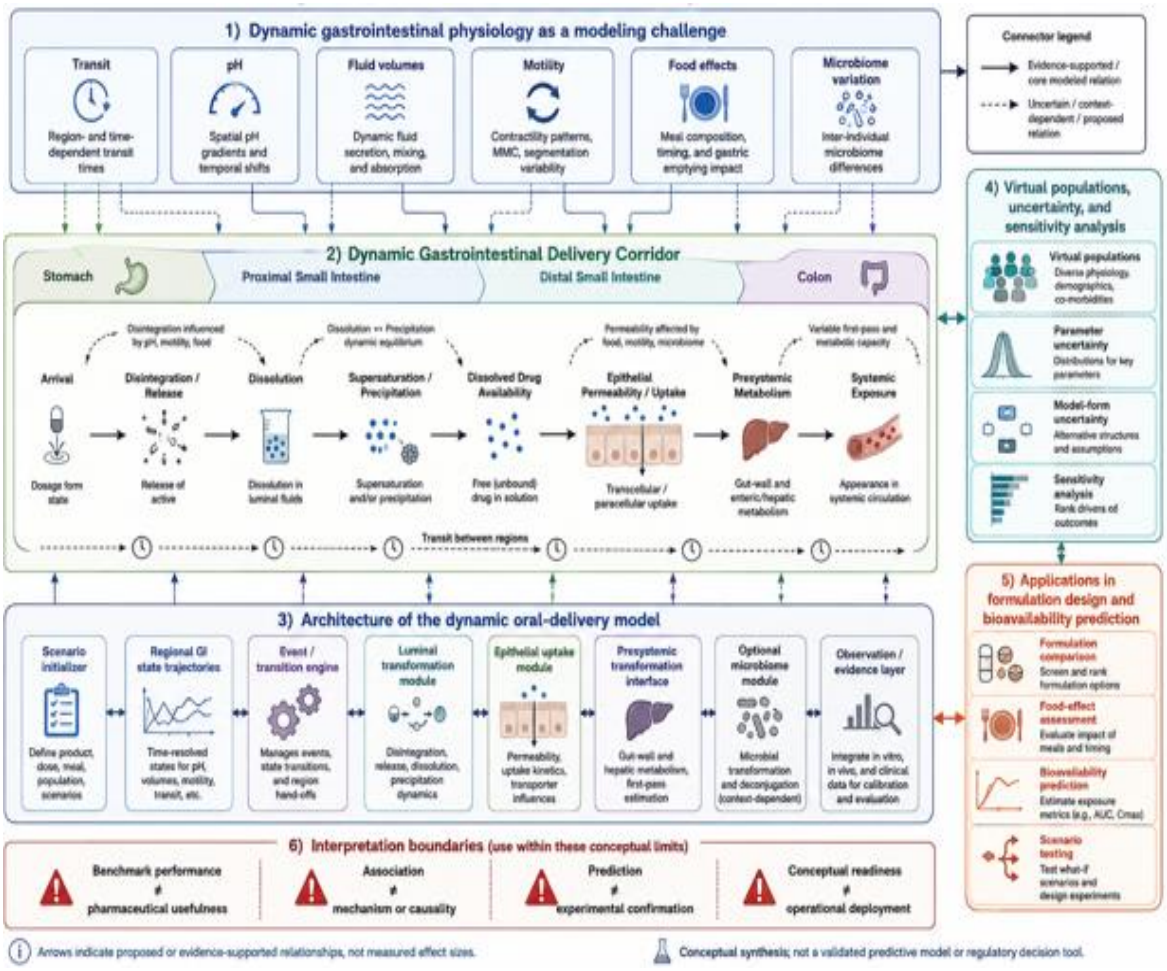

Figure 1. Dynamic Gastrointestinal Delivery Corridor.

The figure is an original conceptual synthesis that organizes the article's central contribution across dynamic gastrointestinal physiology as a modeling challenge, transit, pH, fluid volumes, motility, food, and microbiome variation, fluid volumes, microbiome variation, linking dissolution, precipitation, permeability, and metabolism, linking dissolution. Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, regulatory determination, clinical recommendation, or deployment-ready system.

Virtual Populations, Uncertainty, and Sensitivity Analysis

A dynamic oral-delivery model should generate distributions of plausible trajectories rather than rely solely on one average virtual subject. Virtual bioequivalence analyses for poorly soluble drugs require mechanistic representation of formulation behavior and physiology and cannot be inferred from a single mean concentration–time profile [23]. In the DGSPM, virtual subjects are generated from correlated distributions of pH, transit, fluid volume, motility, prandial response, permeability, enzyme activity, and other relevant parameters. Correlation is important because physiologically incompatible combinations can arise when every variable is sampled independently. These virtual subjects remain mathematical constructs. Their output

distributions cannot be described as representative of a clinical population unless the distributions, dependencies, and resulting variability have been evaluated against population-specific observations.

Sensitivity analysis should determine which uncertainties matter for the stated output and scenario rather than produce one permanent ranking of model inputs. Global sensitivity analysis can distinguish influential drug-substance, drug-product, and physiological parameters and can guide targeted evidence generation [24]. The DGSPM therefore evaluates sensitivity across multiple outputs, including regional dissolved mass, time above a supersaturation state, fraction absorbed, gut-wall escape, systemic exposure, and formulation ranking. Sensitivity may change between fasted and fed conditions, across doses, or among formulations. A variable that has little effect on mean exposure may still control tail risk or the probability of a decision reversal. Local one-at-a-time perturbations are insufficient when variables interact, when input distributions are non-linear, or when physiological parameters are correlated.

Conditional thresholds may be useful when the model is used to investigate excipients or administration conditions, but such thresholds must not be universalized. Physiologically based biopharmaceutics modeling has been used to estimate provisional no-effect ranges for excipient-related changes in gastrointestinal physiology, while explicitly retaining their dependence on the modeled drug, mechanism, and assumptions [25]. The DGSPM treats a no-effect region as an output of a defined scenario and consequence function, not an intrinsic property of an excipient, formulation, or gastrointestinal variable. The threshold must be recalculated when compound permeability, dissolution limitation, dose, population, formulation, or physiological context changes. It also requires experimental confirmation before it can support a consequential pharmaceutical claim.

Virtual bioequivalence and safe-space analyses can be informative when absorption is controlled by a defined mechanism and when the model and population assumptions have been qualified [26]. The DGSPM therefore reports four uncertainty classes separately: physiological variability, parameter uncertainty, measurement uncertainty, and model-form uncertainty. A narrow virtual-population interval is not reassuring when plausible alternative structures produce different conclusions. Likewise, wide physiological variation should not conceal poorly measured parameters or unsupported correlations. Collectively, virtual-population conclusions require qualified distributions, global sensitivity analysis, and explicitly conditional thresholds [23-25]. Decision use should proceed only when the conclusion remains sufficiently stable across plausible parameter sets, virtual populations, and structural alternatives.

Applications in Formulation Design and Bioavailability Prediction

One potential application is construction of a formulation-specific dissolution or bioequivalence safe space. Case-based work indicates that such spaces may support product-quality and formulation decisions when relevant dissolution behavior and deliberately non-bioequivalent variants are included in model qualification [27]. Within the DGSPM, a safe space is defined as a bounded set of product and physiological conditions under which a specified decision criterion is predicted to remain stable. It is not a universal dissolution specification, proof of bioequivalence, or substitute for experimental evidence. Its credibility depends on whether the model has been challenged with formulations that discriminate among dissolution, precipitation, permeability, and transit mechanisms rather than calibrated only to similar products.

A second application is comparison of formulations or multisource products through product-specific dissolution inputs linked to systemic pharmacokinetics. Modeling of oral acyclovir products illustrates that dissolution data can contribute to pharmacokinetic prediction while the result remains conditional on permeability, gastrointestinal physiology, and model calibration [28]. The DGSPM extends this logic by retaining the temporal location of dissolution and by evaluating whether differences in product behavior occur before or after the principal absorption opportunity. Two products with different dissolution profiles may produce similar exposure if permeability or transit limits absorption, while apparently similar dissolution may yield different exposure if release occurs in physiologically different regions. Formulation comparison should therefore report the controlling mechanism and uncertainty, not only the simulated exposure ratio.

Food-effect analysis provides a more demanding application because several physiological and formulation mechanisms may change simultaneously. Mechanistic modeling of selumetinib has shown that food-dependent dissolution and precipitation may need to be considered together with efflux and intestinal first-pass metabolism to explain formulation and exposure differences [29]. Under the DGSPM, fed and fasted simulations share compound properties but follow different physiological trajectories, including gastric residence, pH, fluid, bile-mediated solubilization, regional arrival, and presystemic conditions. The model can then compare competing hypotheses for an observed food effect and identify measurements capable of discriminating among them. A successful fit does not prove that the selected mechanism is causal, particularly when local gastrointestinal observations are absent.

The architecture may also support formulation selection where gastric pH, acid-reducing therapy, or dissolution performance creates development risk. Physiologically based biopharmaceutics modeling has integrated formulation dissolution and gastric pH effects to inform immediate-release formulation development and define a conditional dissolution safe space [30]. In the DGSPM, this application requires scenario-specific initial conditions, pH trajectories, formulation dissolution data, precipitation assumptions, permeability evidence, and external pharmacokinetic evaluation. The intended output is not a universally optimal formulation but a transparent comparison of alternatives under stated physiological assumptions. The most valuable result may be identification of a formulation decision that is robust, a condition under which rankings reverse, or an experiment that would reduce the uncertainty responsible for that reversal.

Table 3 organizes the evidence, constructs, and interpretation boundaries needed to develop applications in formulation design and bioavailability prediction within the article's central argument.

Table 3. Evaluation, implementation, and research priorities arising from The Gastrointestinal Tract Is a Moving Target for Computational Models of Oral

Evaluation Dimension	What Must be Tested	Suitable Evidence or Assessment	Failure Signal	Interpretive Limitation	Decision Relevance
Internal Mass Balance	Conservation across unreleased, solid, dissolved, precipitated, absorbed, transformed and exited states	Solver diagnostics, unit tests, edge-case simulations and mass-balance residuals	Unexplained gain or loss of drug mass	Internal consistency does not establish physiological validity	Minimum requirement before any formulation comparison
Temporal Fidelity	Timing of disintegration, gastric emptying, regional arrival, dissolution and absorption	Imaging, tracer studies, local measurements and time-resolved pharmacokinetics	Correct total exposure generated through incorrect event timing	Sparse observations may permit several compatible timelines	Determines whether release and absorption opportunities are aligned
Regional Process Fidelity	Plausibility of segment-specific fluid, pH, dissolution, precipitation and uptake states	Regional aspiration, imaging, capsule measurements, validated priors and mechanistic perturbations	Systemic fit masks implausible regional behavior	Local evidence is method-dependent and often incomplete	Important for modified-release, food-effect and regional-delivery questions
Process Identifiability	Distinguish dissolution, precipitation, permeability, transit and presystemic loss	Orthogonal experiments, local plus systemic observations, profile-likelihood or posterior-dependence assessment	Several mechanisms reproduce the same systemic profile	Identifiability may remain limited despite extensive calibration	Controls the strength of mechanistic claims
External Predictive Adequacy	Prediction of formulations, doses, food states, pH conditions or populations not used for fitting	Withheld or prospective scenarios with predefined evaluation criteria	Calibration performance presented as external prediction	No single error threshold applies to every context of use	Determines whether the model can support a specified development question
Uncertainty Calibration	Agreement between predicted distributions and observed variation	Predictive checks, interval coverage and population-specific calibration	Intervals are systematically narrow or miss subgroup behavior	Observed variability can include adherence and analytical effects	Required for virtual-population and tail-risk interpretation
Structural Robustness	Stability of conclusions across plausible equations and compartment structures	Alternative transit, flow, precipitation, permeability and metabolism structures	Formulation ranking reverses under an equally plausible model	Comparable calibration across structures may be difficult	Reveals when a decision depends on model form rather than evidence
Sensitivity Robustness	Stability of influential inputs across outputs and scenarios	Correlation-aware global sensitivity and scenario-stratified analysis	Rankings change without being reported or depend on arbitrary ranges	Sensitivity is conditional on distributions and output definitions	Prioritizes experiments and indicates decision fragility
Population Transportability	Relevance of physiology and parameter distributions to the intended population	External population data, subgroup checks and recalibration analysis	Average healthy-adult assumptions are transferred without evidence	Data availability does not guarantee suitability	Defines the population boundary of formulation and bioavailability claims
Decision Usefulness And Oversight	Whether simulation changes a real scientific decision with uncertainty visible	Prospective decision-impact evaluation, documented review and value-of-information analysis	Precise output is accepted without mechanism, uncertainty or human challenge	Scientific usefulness is not regulatory acceptance	Supports bounded formulation selection and study planning
Reproducibility And Provenance	Reconstruction of inputs, assumptions, versions, transformations and outputs	Independent reproduction, traceability audit and change-impact testing	Undocumented defaults or manual adjustments alter conclusions	Reproducibility alone does not demonstrate correctness	Enables review, updating and accountable reuse

Figure 2 presents the evidence, validation, and translation boundary observatory for the gastrointestinal tract is a moving target, showing how the article's key components and boundaries are connected within applications in formulation design and bioavailability prediction.

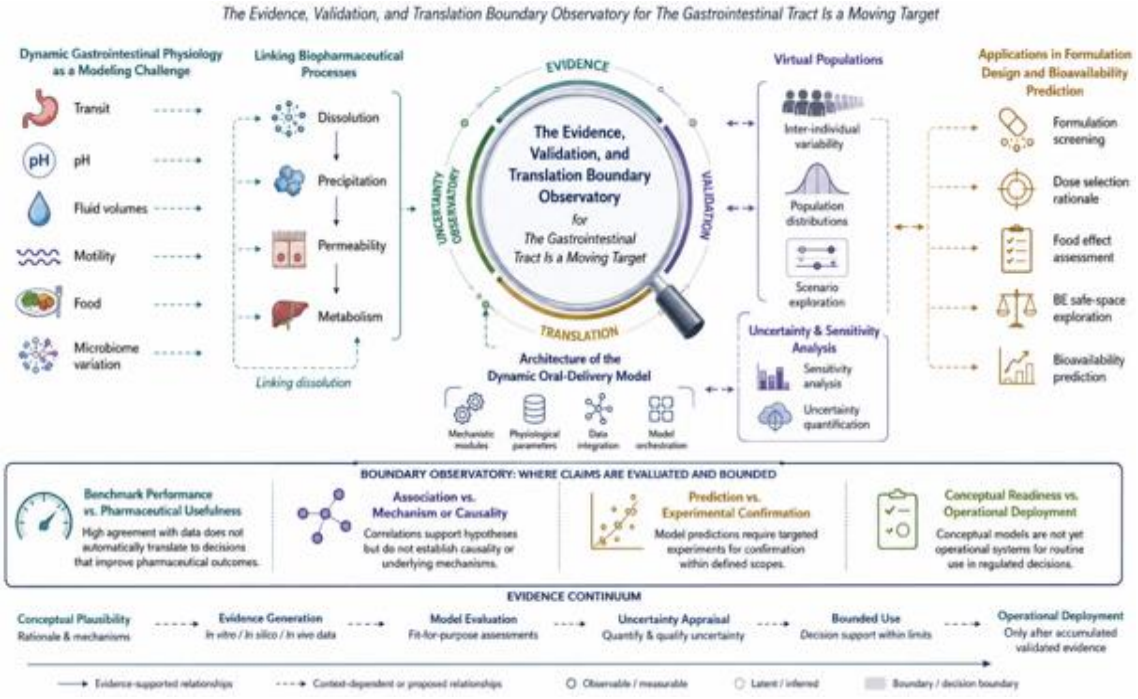

Figure 2. Evidence, Validation, and Translation Boundaries.

The figure is an original conceptual synthesis that shows how claims move from conceptual plausibility through evaluation, uncertainty assessment, and bounded pharmaceutical use. Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, regulatory determination, clinical recommendation, or deployment-ready system.

Limitations and Boundary Conditions

The DGSPM is a conceptual architecture rather than a complete representation of gastrointestinal biology. Its regional state vectors simplify continuous anatomy, heterogeneous luminal contents, mucosal microenvironments, neural regulation, mechanical forces, and adaptive physiology. Increasing the number of states does not necessarily improve inference, because additional parameters may be weakly observed, correlated, or structurally non-identifiable. The architecture should therefore be reduced when a simpler model answers the defined question with less ambiguity. It should also preserve alternative mechanisms when available evidence cannot distinguish among them. The proposal cannot establish causal mechanisms merely because its simulated trajectories are physiologically plausible or its systemic predictions agree with observations.

The supporting evidence is uneven across physiological variables, gastrointestinal regions, compounds, formulations, and populations. Time-resolved local measurements are limited, invasive methods may perturb the system being measured, and imaging or capsule-derived observations may not directly quantify the molecular states required by the model. Precipitation, permeability, metabolism, and microbiome parameters can also depend strongly on assay conditions and scaling assumptions. Microbiome functionality is particularly unsuitable as a generic population variable unless a compound-specific transformation pathway has been demonstrated. Consequently, missing evidence should remain visible as uncertainty or an inactive module rather than be replaced automatically by software defaults, literature averages, or parameters borrowed from a weakly related population.

The proposed model cannot determine regulatory acceptability, establish bioequivalence, select a clinically superior formulation, or guarantee individual exposure. Model credibility remains conditional on the stated question, context of use, input provenance, verification, and fit-for-purpose validation [21]. Transparent reporting of assumptions, model risk, calibration, external evaluation, and limitations is necessary for review but does not itself validate the model [22]. Likewise, a simulated safe space may support a bounded pharmaceutical assessment, but it cannot be generalized beyond the product, mechanism, population, and scenarios used to qualify it [27]. Human scientific judgment remains necessary wherever assumptions are uncertain or the consequences of a wrong decision are substantial.

Research Agenda and Implementation Priorities

The highest research priority is generation of time-aligned local and systemic evidence. Future studies should combine dosage-form imaging, gastric and intestinal transit measurements, regional pH and fluid characterization, formulation testing, precipitation kinetics, and pharmacokinetics under matched administration conditions. Such studies should be designed to discriminate among competing mechanisms rather than merely provide additional observations for calibration. Imaging can constrain dosage-form location and disintegration [8], while regional dissolution modeling demonstrates the value and difficulty of connecting changing luminal conditions to local drug states [15]. Prospective perturbations involving meals, water

volume, pH modification, formulation changes, or targeted process inhibitors may provide greater mechanistic information than repeated fitting of unperturbed plasma profiles.

A second priority is development of qualified virtual populations and explicit structural ensembles. Population models should preserve biologically plausible covariance among transit, pH, fluid, motility, permeability, metabolic capacity, disease, age, anatomy, and administration context. Sensitivity analysis should be global, correlation-aware, scenario-specific, and linked to identifiable decisions or experimental priorities [24]. Alternative precipitation, transit, permeability, intestinal-flow, and absorption-window structures should be compared before one mechanism is treated as explanatory. Research should also establish objective activation criteria for optional modules, particularly microbiome-mediated transformation, regional transport, and complex formulation processes. Negative results and known failure conditions should be retained as part of the model's applicability domain.

Implementation should proceed in stages rather than through immediate operational deployment. The first stage is equation-level verification, mass-balance testing, provenance capture, and stress testing under limiting conditions. The second is retrospective, context-specific qualification against local and systemic evidence, with calibration data separated from external evaluation. The third is prospective assessment of whether the model correctly predicts a discriminating formulation or physiological scenario and whether uncertainty estimates remain calibrated. Reporting structures should connect the question of interest, inputs, assumptions, validation evidence, alternative models, and model risk [22]. Only after these stages should the framework be considered for bounded decision support under documented human oversight, and even then its conclusions should remain conditional rather than universal.

Conclusion

The gastrointestinal tract is a moving target because the dosage form and drug encounter physiological conditions that change across time, region, administration context, and individual. The proposed Dynamic Gastrointestinal State–Process Model responds to this problem by representing gastrointestinal states and drug-product states as co-evolving, mass-balanced trajectories linked through transit, dissolution, precipitation, permeability, presystemic transformation, and optional compound-specific microbiome activity. It further separates physiological variability from parameter, measurement, and model-form uncertainty and restricts outputs to defined formulation and bioavailability questions. The framework is an original conceptual and methodological contribution requiring empirical qualification; it is not a validated digital replica of the gastrointestinal tract, a universal prediction platform, or a substitute for experimental, clinical, or regulatory evidence. Its principal value lies in making hidden process assumptions, competing mechanisms, uncertainty sources, and decision boundaries explicit so that oral drug-delivery models can be judged by mechanistic coherence and context-specific usefulness rather than by agreement with a single downstream profile.

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