



Original Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Target-Mediated Drug Disposition Should Be Interpreted Together with Pharmacological Feedback

James Walker^{1*}, Olivia Harris¹, George Wilson²

¹Department of Target-Mediated Disposition and Pharmacological Feedback, Faculty of Pharmacy, University of Edinburgh, Edinburgh, United Kingdom.

²Department of Drug Disposition and Receptor Pharmacology, Faculty of Pharmacy, University of Leeds, Leeds, United Kingdom.

*Email: james.walker@ed.ac.uk

ABSTRACT

Target-mediated drug disposition (TMDD) is commonly interpreted as a pharmacokinetic consequence of saturable binding between a drug and a finite-capacity pharmacological target. That formulation is indispensable but incomplete when treatment changes the biological state that determines subsequent disposition. Target abundance can vary across tissues and individuals, target turnover can create delayed recovery, pharmacological action can deplete or expand accessible target pools, and disease improvement can alter nonspecific clearance mechanisms independently of target binding. Under these conditions, exposure, target state, pharmacodynamic response, and clearance become temporally coupled rather than directionally ordered. This Current Opinion argues that TMDD should therefore be interpreted within a longitudinal pharmacokinetic–pharmacodynamic state framework whenever the determinants of target-mediated clearance are themselves treatment responsive. Classical TMDD concepts remain necessary, but nonlinear pharmacokinetics alone cannot identify the responsible mechanism, plasma linearity does not exclude local target-mediated depletion, and good model fit does not establish mechanistic uniqueness. Evidence from monoclonal antibodies, bispecific constructs, antibody–drug conjugates, soluble-target systems, small molecules, and target-depleting therapies illustrates several distinct routes through which pharmacology can reshape subsequent disposition. A proposed interpretation framework separates measured exposure from latent target state, distinguishes target-mediated feedback from disease-mediated changes in nonspecific clearance, and treats target abundance, turnover, internalization, recycling, and competing nonlinear pathways as context-dependent state variables rather than interchangeable explanations. The clinical implication is not that every TMDD model requires additional feedback compartments, but that reciprocal biology should be considered whenever post-treatment target or disease states plausibly alter future exposure.

Keywords: Target-mediated drug disposition, Pharmacological feedback, Target turnover, Nonlinear pharmacokinetics, Time-varying clearance, Exposure–response

Received: 04 July 2026; **Revised:** 24 September 2026; **Accepted:** 28 September 2026

INTRODUCTION

Target-mediated drug disposition is usually introduced as a departure from linear pharmacokinetics caused by high-affinity interaction between a drug and a finite-capacity biological target. That description is mechanistically useful, but it is directionally asymmetric: target biology alters drug disposition, whereas the possibility that drug action subsequently alters the target or the physiological state governing clearance is often treated as a secondary complication. Evidence from therapeutic antibodies shows why that simplification can become consequential.

Time-dependent clearance can emerge during treatment and may reflect changing target burden, disease improvement, altered protein catabolism, or other post-baseline processes. When the same clinical response that is being related to exposure also changes clearance, later exposure can become partly a consequence of prior response rather than an independent driver of it [1].

This interpretive problem is especially relevant for large molecules because their disposition already integrates several mechanistically distinct pathways. Monoclonal antibodies undergo distribution, nonspecific proteolytic elimination, FcRn-mediated salvage, and—in some circumstances—target-mediated binding and internalization. The relative importance of these pathways varies with molecule, dose, target abundance, tissue distribution, and patient state [2]. TMDD should therefore not be treated as a universal explanation for every nonlinear or time-varying antibody pharmacokinetic profile.

Immune checkpoint inhibitors provide a clinically important example. Their pharmacokinetics may change over treatment as disease burden, systemic inflammatory state, body composition, and other prognostic factors evolve. Consequently, associations between higher exposure and better outcomes may partly reflect lower clearance in patients whose disease state is already improving, rather than a simple monotonic causal effect of exposure on response [3]. The problem is broader than oncology: any therapy for which pharmacology modifies the abundance, accessibility, turnover, or physiological context of its own disposition pathway creates the possibility of reciprocal PK–biology coupling.

The central argument of this article is therefore narrower than a general review of TMDD. Classical TMDD remains the necessary starting point, but its interpretation should be expanded when the target or the biological environment governing clearance evolves because of treatment. The proposed synthesis developed below separates three questions that are often conflated: whether a saturable target-mediated pathway exists, whether that pathway materially contributes to observed pharmacokinetics at the studied dose and time, and whether treatment-induced changes in target or disease state subsequently modify the pathway itself. These questions require different evidence and should not be answered from nonlinearity alone.

Classical target-mediated drug disposition

Classical TMDD models represent drug binding to a pharmacological target, formation of a drug–target complex, and subsequent turnover or elimination of the participating species. Their defining feature is not merely nonlinearity but a mechanistic coupling between drug concentration and a target system with finite capacity. Because the full system can be highly parameterized, reduced forms are frequently used. Recent mathematical analysis reinforces that the validity of these approximations depends on the underlying kinetic regime. High-affinity and lower-affinity systems can yield different limiting behaviors, and the familiar Michaelis–Menten representation is not a universal reduction of every TMDD configuration [4]. Mechanistic interpretation therefore requires attention to binding affinity, systemic clearance, target kinetics, and the assumptions under which a reduced model is derived.

Soluble-target systems illustrate why target biology cannot be represented by affinity alone. The magnitude and time course of TMDD depend on baseline target concentration, synthesis, degradation, complex turnover, and—in some cases—the ability of drug binding to alter target elimination. Recent synthesis of soluble-target antibody systems emphasizes that realistic de novo modeling requires biologically plausible parameterization rather than reuse of generic target constants across unrelated proteins [5]. A model may be mathematically identifiable under a chosen structure yet remain biologically weak if the assumed target concentration or turnover rate is inconsistent with the pharmacological system.

The topology becomes more complex for multispecific drugs. Bispecific antibodies can engage two targets sequentially or simultaneously, creating binary and ternary complexes with distinct formation and elimination kinetics. Mechanistic modeling demonstrates that dose, target abundance, binding rates, and internalization can interact non-monotonically, so increasing dose does not necessarily translate immediately into proportional formation of the pharmacologically desired ternary complex [6]. This matters for feedback interpretation because a multispecific drug may encounter several target pools whose abundances and turnover rates evolve differently over time.

Accordingly, classical TMDD should be viewed as a family of target-coupled disposition structures rather than a single canonical nonlinear clearance equation. The full mechanistic model, a quasi-equilibrium approximation, a quasi-steady-state approximation, or a Michaelis–Menten representation may each be appropriate under particular conditions. What these structures do not automatically establish is whether the target pool itself remains stationary

throughout treatment. That question becomes central once target abundance and turnover are considered explicitly.

Target abundance and turnover

The capacity of a target-mediated pathway is constrained by how much pharmacological target is available to bind drug. For small molecules, quantitative proteomic analyses have renewed attention to target abundance as a determinant of whether target binding can constitute a meaningful disposition sink. Data across several enzyme targets support the principle that sufficiently abundant targets can contribute materially to nonlinear pharmacokinetics when binding capacity is non-negligible relative to drug exposure [7]. The evidence does not justify a universal abundance threshold for TMDD, but it establishes target capacity as a measurable biological variable rather than an abstract model constant.

For membrane-bound targets, abundance is also spatial. Quantitative proteomics combined with mechanistic modeling shows that membrane-target expression can vary substantially across tissues and can influence predicted local engagement of therapeutic antibodies [8]. A high target burden in a tissue can function as a local sink, potentially reducing free drug available for deeper distribution or for engagement in another compartment. Importantly, target expression, target accessibility, receptor occupancy, and pharmacodynamic effect are not interchangeable quantities. Expression establishes potential binding capacity, whereas accessibility and local free concentration determine how much of that capacity can actually interact with drug.

Soluble targets create a different measurement problem. Protein abundance and turnover estimates derived from quantitative datasets can be incorporated into mechanistic PKPD models, as illustrated for complement C5 and PCSK9 systems [9]. Such measurements can improve biological plausibility, but they remain population- or assay-dependent inputs rather than perfect representations of an individual patient's instantaneous target state. Their uncertainty should therefore be propagated rather than concealed by precise parameter estimates.

Target turnover adds the temporal dimension. A rapidly renewed target may restore binding capacity during a dosing interval, whereas a slowly recovering target can remain suppressed after plasma drug concentrations have declined. This difference becomes important when interpreting apparent clearance, duration of response, or dose dependence. The target state at one time point can depend on the cumulative history of previous exposure, not only on the simultaneous plasma concentration.

A further boundary is that systemic pharmacokinetic linearity does not necessarily rule out target-mediated depletion at the site of action. Mechanistic simulations demonstrate that binding, dissociation, internalization, molecular size, and tissue target abundance can create substantial local depletion of large molecules even when the plasma concentration–time profile appears approximately linear [10]. The proposed interpretation is therefore that target abundance should be treated as a potentially time- and tissue-indexed state variable whenever local pharmacology matters. Plasma nonlinearity is evidence that can support TMDD, but its absence is not a sufficient exclusion criterion.

Binding, internalization, and elimination

Binding is often treated as the central determinant of TMDD, yet binding and target turnover can dominate different portions of the PKPD trajectory. A recent simultaneous TMDD–pharmacodynamic analysis of finasteride and dutasteride illustrates this distinction. Saturable interaction with 5 α -reductase contributes to nonlinear pharmacokinetics, whereas the turnover and recovery of the enzyme system influence the persistence of downstream pharmacodynamic effects [11]. The implication is not that these particular kinetics generalize to other targets, but that a target system may contain at least two separable temporal processes: the drug-binding state that influences disposition and the target-recovery state that influences later pharmacodynamics and future binding capacity.

Molecular valency further complicates this relationship. For bivalent drugs, the assumptions underlying conventional Michaelis–Menten approximations can differ from those applying to monovalent systems because multivalent binding changes complex formation and effective target engagement [12]. A reduced model that adequately describes one binding topology may therefore become misleading when applied to another. Mechanistic simplification should follow the biology rather than precede it.

Internalization is equally important because formation of a drug–target complex does not necessarily imply irreversible loss of free drug from the system. Complexes may internalize and degrade, dissociate and return drug to the extracellular space, recycle, or interact with platform-specific pathways. Antibody–drug conjugates make this especially clear. A mechanistic PBPK analysis of a CLDN18.2-targeted ADC required target-mediated

disposition alongside deconjugation and other ADC-specific elimination processes to describe clinical pharmacokinetics adequately [13]. TMDD was relevant but not sufficient.

These examples support a broader interpretive rule. Nonlinear disposition should be decomposed into mechanistically plausible parallel processes before one of them is designated as target mediated. Binding affinity, target abundance, complex internalization, molecular recycling, payload loss, transporter saturation, and nonspecific elimination can generate overlapping signatures in concentration–time data. A credible TMDD interpretation therefore depends not only on whether a nonlinear component can be fitted, but on whether the biological process assigned to that component is independently plausible.

Pharmacological modulation of target expression

The classical direction of TMDD is target to pharmacokinetics: more accessible target can create a larger binding sink and thereby alter drug disposition. Pharmacological feedback begins when the reverse direction also matters. If treatment changes the abundance or accessibility of the target, the disposition pathway encountered by later doses is no longer the same pathway encountered by the first dose.

RLYB212 provides a clear mechanistic example because administration can alter the HPA-1a-positive platelet population that participates in its disposition. Joint modeling of antibody and platelet dynamics demonstrates how drug exposure, target availability, target depletion, and subsequent disposition can become temporally interdependent [14]. The important transferable principle is not the specific platelet mechanism but the structure of the interaction: pharmacology changes the target state, and the changed target state modifies the system through which subsequent drug molecules are cleared.

A second layer arises when target-mediated loss competes with molecular salvage. Pharmacokinetic modeling of rhIL-7-hyFc incorporated both IL-7 receptor-mediated disposition and FcRn-mediated recycling, illustrating that target-driven removal and recycling can operate simultaneously [15]. The net clearance observed in plasma is therefore an aggregate outcome of opposing processes rather than a direct measurement of target-mediated elimination alone.

Dose-dependent target saturation adds another dynamic. In patients receiving the anti-EGFR antibody GC1118, a TMDD population model described nonlinear pharmacokinetics in which the apparent contribution of the target-mediated route diminished as exposure increased and the pathway approached saturation [16]. This establishes a pharmacokinetic consequence of finite target capacity, but receptor occupancy generated by a model remains different from directly observed pharmacodynamic response. Target abundance, free target, occupied target, internalized complex, and downstream response should therefore remain distinct states unless the data directly justify combining them.

The proposed synthesis is to represent pharmacological target modulation as a longitudinal state transition rather than as a static covariate. Baseline target abundance defines initial capacity. Drug reaches a tissue and binds an accessible fraction of that target. Binding, internalization, recycling, depletion, synthesis, or compensatory expression then alters the available target pool. That modified pool determines both the pharmacodynamic environment and the target-mediated component of future clearance. The framework does not require that every drug produce meaningful feedback; it requires that the possibility be tested when target biology is known or suspected to change during treatment.

This distinction is summarized visually in **Figure 1**. The figure deliberately separates measured plasma exposure from local drug availability, accessible target, occupied/internalized target, and pharmacologically altered target state so that a change in future clearance cannot be inferred directly from a single observed concentration.

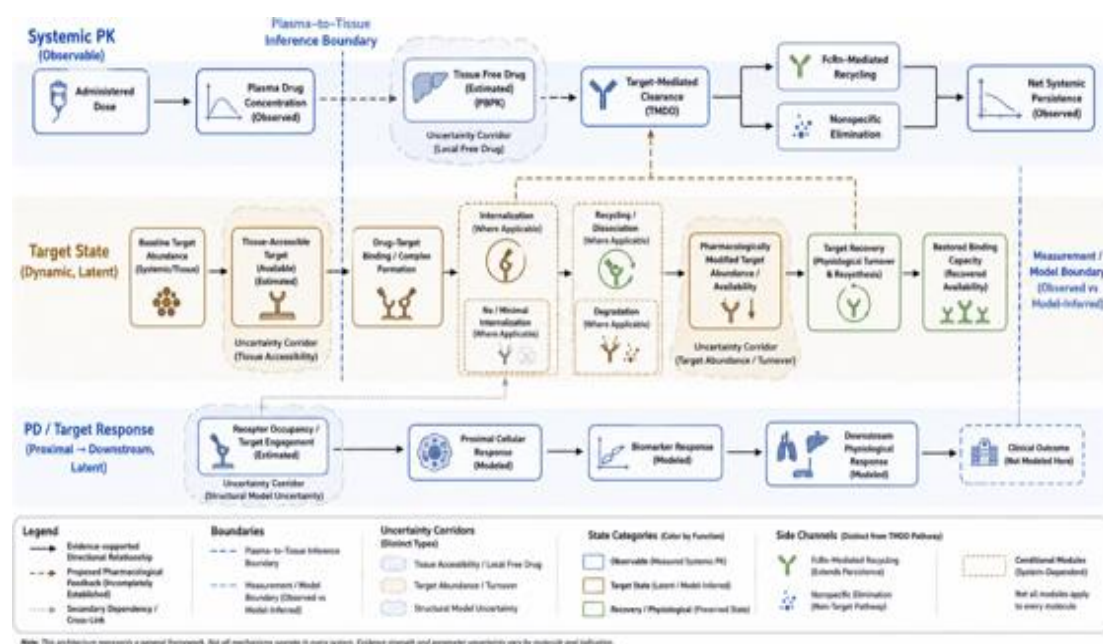


Figure 1. Longitudinal target-state remodeling separates observed exposure from the evolving biological capacity for TMDD

Disease-mediated feedback

A changing target is not the only reason clearance can evolve during treatment. Disease itself can alter physiological processes that determine drug disposition. This is particularly important for therapeutic antibodies because cachexia, systemic protein turnover, albumin dynamics, inflammatory state, and FcRn-related salvage can change concurrently with treatment response. A physiologically based analysis of durvalumab showed that longitudinal albumin behavior associated with cancer cachexia could reproduce treatment-related changes in antibody clearance without invoking target depletion as the sole mechanism [17]. This provides a critical interpretive boundary: time-varying clearance is a phenotype, not a mechanism.

A related pattern was observed with isatuximab in relapsed or refractory multiple myeloma. Population pharmacokinetic analysis identified both nonlinear target-related disposition and a linear clearance component that changed over time, while disease-associated immunoglobulin biology contributed to pharmacokinetic variability [18]. The implication is not that FcRn competition or disease burden explains every changing clearance trajectory. Rather, target-mediated and disease-mediated mechanisms can coexist, and assigning the entire time-dependent signal to one pathway can conceal clinically relevant heterogeneity.

The inferential consequence becomes most visible in exposure–response analysis. For nivolumab, post-treatment disease dynamics were associated with declining clearance, demonstrating how patients who respond well may subsequently exhibit higher measured exposure because their clearance has fallen [19]. In that situation, steady-state exposure contains information generated by the response process itself. Treating it as a purely antecedent causal determinant of outcome can exaggerate the apparent exposure–response relationship.

Temporal ordering therefore matters. Baseline exposure, early-cycle exposure, steady-state exposure, target abundance, disease burden, albumin, body composition, and other post-treatment covariates cannot be treated as interchangeable predictors. Some precede response; others may be altered by it. Clinical-trial simulations further show that randomized dose range, number of dose levels, timing of pharmacokinetic sampling, and use of earlier exposure measures can reduce the risk that time-dependent clearance generates spurious exposure–response conclusions, although they cannot remove every source of confounding [20].

The proposed framework therefore separates target-mediated feedback from disease-mediated feedback. In the former, pharmacological action changes the target system that contributes directly to drug disposition. In the latter, treatment and disease evolution change nonspecific physiological determinants of clearance. Both can alter future exposure, but their biological interpretation and clinical consequences differ. **Table 1** organizes these trajectories by temporal state rather than by mechanism name alone, because the same observed clearance decline can have different meanings depending on when it occurs, which biological variable changed first, and whether the relevant state was measured or inferred.

Table 1. Temporal states that distinguish target-linked from disease-linked changes in TMDD interpretation

State and entry conditions		Evidence through time	Transition and reassessment
Target or PD behavior	Temporal state or window / Entry condition	State-specific evidence to seek / Feedback lag or persistence / Covariate trajectory	Model assumption under test / uncertainty / TMDD interpretation consequence
Target availability reflects pretreatment biology	Temporal state or window: Pretreatment target-capacity state Entry condition: Drug has not yet materially changed target or disease physiology	State-specific evidence to seek: Baseline target abundance, disease burden, albumin or related physiological markers, early PK Feedback lag or persistence: None yet attributable to treatment Covariate trajectory: Baseline covariates only	Model assumption under test: Initial target capacity is sufficiently represented Principal uncertainty: Unmeasured tissue target and between-patient heterogeneity TMDD interpretation consequence: Establishes the initial disposition state but does not predict whether it will remain stable
Binding and internalization may begin before major disease change	Temporal state or window: Early target-engagement state Entry condition: Exposure is sufficient for measurable binding or proximal PD	State-specific evidence to seek: Early plasma PK, target measurements where available, receptor occupancy or immediate PD markers Feedback lag or persistence: Short pharmacological lag Covariate trajectory: Early target-linked covariates may move while disease markers remain relatively stable	Model assumption under test: Nonlinear clearance reflects finite target capacity Principal uncertainty: Separation of tissue binding from systemic PK TMDD interpretation consequence: Strongest window for identifying direct target-mediated contribution before extensive feedback develops
Target may be depleted, internalized, restored slowly, or otherwise redistributed	Temporal state or window: Pharmacologically remodeled target state Entry condition: Prior treatment has altered target abundance, accessibility, or recovery dynamics	State-specific evidence to seek: Serial target or proximal PD measurements plus time-resolved PK Feedback lag or persistence: Persistence determined by synthesis and turnover Covariate trajectory: Target-linked covariates change after exposure	Model assumption under test: Target pool is time varying rather than fixed Principal uncertainty: Latent target state and uncertain turnover TMDD interpretation consequence: Subsequent PK may differ because the drug has changed the capacity of its own target-mediated pathway
Target-specific changes may or may not accompany response	Temporal state or window: Disease-improvement state Entry condition: Clinical or biological disease state changes during continued therapy	State-specific evidence to seek: Longitudinal disease markers, albumin, body composition, inflammatory or protein-turnover indicators Feedback lag or persistence: Often delayed relative to initial exposure Covariate trajectory: Nonspecific physiological covariates improve or normalize	Model assumption under test: Changing clearance is not necessarily caused by target depletion Principal uncertainty: Reverse causation and competing physiological mechanisms TMDD interpretation consequence: Rising exposure or falling clearance cannot automatically be interpreted as evidence that higher exposure caused response
Target-dependent and nonspecific processes overlap	Temporal state or window: Mixed-feedback state Entry condition: Target remodeling and disease-mediated	State-specific evidence to seek: Joint PK, target, disease and physiological trajectories Feedback lag or persistence: Multiple lags with different recovery rates	Model assumption under test: One time-varying clearance term is adequate Principal uncertainty: Structural non-identifiability TMDD interpretation consequence: A descriptive model may fit well while

	physiological change occur concurrently	Covariate trajectory: Several post-baseline covariates move together	the biological source of changing clearance remains ambiguous
Target capacity can recover or diverge from earlier PD	Temporal state or window: Recovery, escape, or late-treatment state	State-specific evidence to seek: Late PK, repeat target measures, disease trajectory and recovery biomarkers	Model assumption under test: Earlier feedback parameters remain stable
	Entry condition: Target returns, disease progresses, adaptive biology emerges, or treatment is interrupted	Feedback lag or persistence: Potentially long and mechanism specific	Principal uncertainty: Sparse late sampling and changing biology
		Covariate trajectory: Covariates may reverse, plateau, or decouple	TMDD interpretation consequence: Extrapolation from early-cycle TMDD behavior may fail unless recovery and disease-state transitions are represented

Note: The temporal states are a proposed synthesis for interpretation rather than empirically validated universal categories. They should be instantiated only when corresponding longitudinal evidence exists. No Vancouver citation numbers are included in the visible table; supporting evidence is cited in the surrounding text.

Dose-dependent nonlinearity

Dose dependence is one of the most recognizable signatures of TMDD, but it is not mechanistically specific. A target-mediated pathway can dominate at low concentrations and become progressively saturated as exposure rises. At the same time, changes in target abundance may alter free and total drug concentrations differently. Iptacopan provides an instructive example: hepatic impairment was associated with changes in complement factor B and with divergence between total and unbound pharmacokinetics, illustrating that target concentration can alter the apparent exposure metric even when total plasma exposure changes little [21]. Target-bound, unbound, and total drug should therefore not be assumed to carry equivalent mechanistic information.

Other saturable processes can generate similar nonlinear signatures. For telmisartan, integration of AT1-receptor binding with OATP1B3-mediated hepatic uptake showed that nonlinear pharmacokinetics could not be assigned to TMDD alone. Transporter saturation contributed over a broad dose range, while receptor binding was more relevant in a different concentration region [22]. The general lesson is methodological: observing nonlinear exposure does not uniquely identify which saturable process produced it.

PCSK9-directed therapies illustrate how the relative importance of clearance pathways can change across the concentration range. Evolocumab exhibits saturable PCSK9-mediated elimination at concentrations where target binding materially contributes to disposition, whereas nonsaturable proteolytic elimination becomes relatively more important when the target-mediated pathway is saturated [23]. This is consistent with classical TMDD but also demonstrates why a single apparent clearance value can obscure concentration-dependent transitions between mechanisms.

Alirocumab provides a complementary modeling perspective. A large pooled population analysis successfully described pharmacokinetics using parallel linear elimination and a Michaelis–Menten approximation of a nonlinear target-mediated pathway, with PCSK9-related information contributing to interpretation of the nonlinear component [24]. Such descriptive adequacy is valuable, but it does not imply that every microscopic step of target binding, complex turnover, and receptor dynamics has been uniquely identified.

The proposed interpretation is therefore that dose-dependent nonlinearity should be treated as a mechanistic clue rather than a mechanistic verdict. Evidence for TMDD becomes stronger when nonlinear pharmacokinetics align with independently plausible target abundance, binding affinity, turnover, internalization, or receptor-occupancy behavior. It becomes weaker when competing saturable transport, distribution, protein binding, disease-dependent clearance, or formulation processes can produce a similar concentration–time signature. Most importantly for pharmacological feedback, the dose–clearance relationship observed at treatment initiation need not remain stationary if repeated therapy subsequently changes the target or the physiology governing elimination.

When PK changes the target and the target changes PK

The reciprocal character of TMDD becomes most obvious when the pharmacological target is itself altered by previous exposure. In such systems, pharmacokinetics determines how much drug reaches and occupies target, but target engagement then changes the abundance, accessibility, or composition of the target pool governing subsequent pharmacokinetics. The important quantity is therefore not simply baseline target concentration, but a

target state that evolves over time according to exposure history, synthesis, degradation, internalization, cellular trafficking, disease evolution, and pharmacodynamic action.

T-cell engagers illustrate why this state may need to contain more than one target pool. Their disposition can depend on simultaneous or sequential interactions with CD3 and a tumor-associated antigen, whose expression, accessibility, and turnover differ across tissues and species. Translational modeling indicates that accounting for target-mediated disposition can improve human pharmacokinetic prediction for several T-cell engagers compared with simple allometric scaling, although the improvement is compound dependent rather than universal [25]. For reciprocal interpretation, the key implication is that a single scalar “target concentration” may be inadequate whenever several biologically distinct binding sinks jointly determine disposition.

A related balance appears for CD47-directed antibodies. A semi-mechanistic model of IMC-002 incorporated saturable CD47-mediated disposition together with FcRn-related recycling to characterize nonlinear pharmacokinetics in patients with advanced solid tumors [26]. These processes push systemic persistence in opposite directions: target interaction can remove drug from the circulating pool, whereas recycling can protect antibody from degradation. The observed concentration–time profile is therefore an emergent result of competing biological processes rather than a direct readout of either one alone.

The proposed synthesis is to treat reciprocal TMDD as a history-dependent state problem. At time t , drug exposure depends partly on the target state inherited from earlier treatment. That exposure changes target occupancy and, in some systems, target abundance or recovery. The updated target state then contributes to the disposition of drug at $t+1$. The same logic applies whether target alteration results from receptor internalization, cellular depletion, irreversible inhibition, pharmacological downregulation, recovery after suppression, or redistribution between accessible and inaccessible pools. These mechanisms should not be collapsed biologically, but they share the mathematical consequence that the determinant of clearance is no longer stationary.

This does not imply that every repeated-dose TMDD system requires an explicit feedback model. If target abundance is stable over the clinically relevant interval, if target-mediated clearance contributes minimally at therapeutic exposure, or if sampling cannot distinguish a dynamic target process from a simpler time-varying clearance term, additional states may increase complexity without increasing inferential value. The reciprocal interpretation is warranted when target change is biologically credible, temporally consequential, and supported by observations capable of separating it from disease-mediated or nonspecific clearance changes.

Coupled TMDD–feedback models

A coupled TMDD–feedback model should begin by separating what is measured from what is inferred. Plasma concentration is commonly observed directly, whereas tissue free concentration, accessible target, receptor occupancy, internalized complex, target synthesis, and local recovery may be latent states estimated through model structure. Physiologically inspired PK–receptor-occupancy approaches demonstrate the value of this separation. Joint representation of pharmacokinetics and receptor occupancy can show that local target-mediated depletion at a site of action differs from what would be inferred from central plasma exposure or circulating receptor occupancy alone [27]. Consequently, agreement with plasma pharmacokinetics is not sufficient evidence that the model has correctly represented local target engagement.

The proposed coupled architecture contains four conceptually distinct state families. The first is the drug state, including systemic and, where justified, tissue exposure. The second is the target state, incorporating abundance, accessibility, occupancy, internalization, synthesis, degradation, and recovery only to the extent supported by data. The third is the pharmacodynamic or disease state, which may alter target biology or nonspecific clearance. The fourth is the observation state, comprising concentrations, biomarkers, target measurements, disease markers, or physiological covariates that are actually recorded. The purpose of separating these families is to prevent a measured biomarker from being treated automatically as the biological mechanism represented by a latent model state.

Feedback can then occur through several routes. Pharmacological action may reduce the available target pool and therefore decrease later target-mediated clearance. Target recovery may restore that pathway between doses. Disease improvement may reduce nonspecific antibody catabolism while leaving the target pathway unchanged. Conversely, disease progression can expand target burden or alter tissue accessibility. These routes can produce superficially similar changes in plasma clearance, which means that model structure should follow mechanistic evidence rather than the appearance of a time-varying pharmacokinetic parameter.

Parsimony remains essential. A biologically elaborate model is not automatically more informative than a simpler descriptive model. Additional target, disease, or tissue states should be introduced only when they address a

manuscript-relevant mechanistic question and when the available data provide some possibility of distinguishing their dynamics. Otherwise, feedback parameters may compensate for one another, generating a convincing fit while weakening biological interpretability.

For clinical application, model complexity should also match the intended decision. A structure used to describe nonlinear pharmacokinetics retrospectively may require less biological resolution than one used to extrapolate between doses, predict receptor occupancy at an inaccessible tissue, translate across disease states, or support individual dose adaptation. The proposed framework therefore treats model complexity as conditional on the decision horizon rather than as an intrinsic marker of mechanistic quality.

Identifiability and clinical interpretation

The largest limitation of coupled TMDD–feedback models is identifiability. Published population pharmacokinetic models of monoclonal antibodies show substantial heterogeneity in structural choices, parameterization, covariate relationships, and treatment of nonlinear clearance [28]. Different models can therefore provide acceptable descriptions of similar pharmacokinetic data while assigning the observed behavior to different biological processes. A successful fit is evidence of descriptive adequacy, not proof that the proposed microscopic mechanism is unique.

This distinction becomes especially important when several time-varying processes occur together. Declining clearance may reflect target depletion, disease improvement, reduced cachexia-associated protein catabolism, altered target accessibility, changes in endogenous ligand concentration, or combinations of these processes. If only drug concentrations are observed, several mechanistic explanations may remain observationally equivalent. Serial measurements of target, proximal pharmacodynamic markers, disease burden, albumin or other physiological variables can narrow the possibilities, but even these measurements may be imperfect proxies for the true state controlling disposition.

Clinical interpretation should therefore be graded according to evidential depth. At the first level, the data may establish an observed pharmacokinetic pattern, such as nonlinear or time-varying clearance. At the second level, model comparison may support a structural explanation, such as a saturable target-mediated component. At the third level, independent biological evidence may support a mechanistic attribution, for example documented target depletion or turnover consistent with the pharmacokinetic trajectory. At the fourth level, external or prospective evidence would be needed before claiming that the mechanistic model reliably predicts an unobserved population, individualized dose requirement, or future clinical outcome. This hierarchy is a proposed interpretive device, not a validated regulatory grading system.

Temporal ordering is equally important. Baseline covariates describe the state before meaningful treatment modification, whereas post-baseline covariates may themselves be consequences of drug exposure or response. Incorporating a treatment-responsive biomarker into a clearance model can improve fit without establishing that the biomarker causes the clearance change. Likewise, an exposure metric calculated after clearance has already responded to disease improvement cannot be interpreted in the same way as exposure measured before that change. Mechanistic claims therefore require explicit attention to which variable changed first and whether that temporal ordering is observed or inferred.

For precision dosing, the threshold should be higher still. A coupled TMDD–feedback model may be scientifically persuasive yet insufficient for patient-level dose adaptation if the relevant target or disease states are weakly observed, rapidly changing, or poorly transferable between individuals. Before such a model is used predictively, its structural assumptions, parameter uncertainty, population transportability, and performance at the actual clinical decision horizon require qualification. Retrospective recovery of observed concentrations does not by itself establish prospective dosing utility.

The clinical value of the proposed interpretation is consequently one of disciplined inference rather than mandatory mechanistic complexity. When treatment can modify the target or disease state controlling future disposition, analysts should ask whether the apparent pharmacokinetic trajectory is being treated as an independent cause, a biological consequence, or both. Where the evidence cannot distinguish these possibilities, the uncertainty should remain visible rather than being resolved by model terminology alone.

CONCLUSION

TMDD is most informative when interpreted as a biological process rather than as a synonym for nonlinear clearance. Classical target binding, complex formation, internalization, and finite-capacity elimination remain

fundamental, but their pharmacokinetic consequences can change when treatment modifies target abundance, target recovery, tissue accessibility, disease physiology, or competing clearance pathways.

The central proposal of this Current Opinion is that reciprocal pharmacology should be considered whenever the determinant of target-mediated disposition is itself treatment responsive. In such settings, exposure alters target or disease state, and the altered state can modify later exposure. Target-mediated feedback must nevertheless remain distinct from disease-mediated changes in nonspecific clearance, transporter saturation, FcRn-related recycling, and other processes capable of generating similar pharmacokinetic patterns.

A coupled interpretation is therefore justified by biology and longitudinal evidence, not by nonlinearity alone. Plasma linearity does not exclude local target-mediated depletion, while a nonlinear or time-varying plasma profile does not uniquely establish TMDD. Similarly, successful model fitting cannot substitute for mechanistic identifiability.

The practical objective is not to maximize model complexity. It is to preserve temporal direction, distinguish observed variables from latent biological states, test competing mechanisms, and match model resolution to the clinical decision being made. When those conditions are met, TMDD can be interpreted not simply as the effect of a target on drug disposition, but as one component of a dynamic pharmacological system in which drug, target, disease, and exposure may continuously reshape one another.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

REFERENCES

1. Proctor JR, Wong H. Time-dependent clearance can confound exposure-response analysis of therapeutic antibodies: A comprehensive review of the current literature. *Clin Transl Sci.* 2024;17(1):e13676. doi:10.1111/cts.13676
2. Ryman JT, Meibohm B. Pharmacokinetics of monoclonal antibodies. *CPT Pharmacometrics Syst Pharmacol.* 2017;6(9):576-88. doi:10.1002/psp4.12224
3. Centanni M, Moes DJAR, Trocóniz IF, Ciccolini J, van Hasselt JGC. Clinical pharmacokinetics and pharmacodynamics of immune checkpoint inhibitors. *Clin Pharmacokinet.* 2019;58(7):835-57. doi:10.1007/s40262-019-00748-2
4. Straube R. Target-mediated drug disposition (TMDD) revisited: High versus low-affinity approximations of the TMDD model. *CPT Pharmacometrics Syst Pharmacol.* 2025;14(7):1262-72. doi:10.1002/psp4.70048
5. Nasim A, Fairman D, Nixon E, Jagdale P, Cui Z, Mohan K, et al. TMDD modeling for antibodies directed against soluble targets: Parameter values for de novo modeling and simulation from experimental data. *Clin Pharmacol Ther.* 2026;119(6):1440-59. doi:10.1002/cpt.70255
6. Schropp J, Khot A, Shah DK, Koch G. Target-mediated drug disposition model for bispecific antibodies: Properties, approximation, and optimal dosing strategy. *CPT Pharmacometrics Syst Pharmacol.* 2019;8(3):177-87. doi:10.1002/psp4.12369
7. Xu M, Yuan X, Li P, Bach T, Zhu HJ, An G. Target abundance in pharmacological target-mediated drug disposition (TMDD) for small molecules—a proteomics approach. *AAPS J.* 2026;28(1):45. doi:10.1208/s12248-025-01182-y
8. Sepp A, Muliaditan M. Application of quantitative protein mass spectrometric data in the early predictive analysis of membrane-bound target engagement by monoclonal antibodies. *MAbs.* 2024;16(1):2324485. doi:10.1080/19420862.2024.2324485
9. Muliaditan M, Sepp A. Application of quantitative protein mass spectrometric data in the early predictive analysis of target engagement by monoclonal antibodies. *Clin Transl Sci.* 2022;15(7):1634-43. doi:10.1111/cts.13278
10. Zasedateleva T, Schaller S, de Lange ECM, de Witte WEA. Local depletion of large molecule drugs due to target binding in tissue interstitial space. *CPT Pharmacometrics Syst Pharmacol.* 2024;13(12):2068-86. doi:10.1002/psp4.13262

11. Iwaki Y, Lee W, Aoki Y, Sugiyama Y. Simultaneous target-mediated drug disposition-pharmacodynamic (TMDD-PD) modeling of finasteride and dutasteride: Impact of target binding and turnover on non-linear pharmacokinetics. *AAPS J.* 2025;28(1):32. doi:10.1208/s12248-025-01142-6
12. Straube R. Target-mediated drug disposition revisited: Michaelis-Menten approximations for bivalent drug molecules. *CPT Pharmacometrics Syst Pharmacol.* 2025;14(10):1540-43. doi:10.1002/psp4.70094
13. Zunino C, Wang S, Zhang Y, Urdy S, de Witte WEA, Declèves X, et al. Prediction of a CLDN18.2 targeted antibody drug conjugate pharmacokinetics in cancer patients using PBPK modeling and simulation. *CPT Pharmacometrics Syst Pharmacol.* 2025;14(9):1494-503. doi:10.1002/psp4.70071
14. Moc Willeford C, Shetty K, Sheridan D, Engler F. Informing pregnancy dose via target-mediated drug disposition modeling and simulations for a recombinant human monoclonal antibody. *CPT Pharmacometrics Syst Pharmacol.* 2024;13(11):2002-15. doi:10.1002/psp4.13250
15. Jeon HS, Lee SW, Jung W, Jung H, Choi D, Byun MS, et al. Dose optimization of rhIL-7-hyFc for patients with lymphopenia using a neonatal Fc receptor-mediated recycling-based and target-mediated drug disposition pharmacokinetic model. *Clin Transl Sci.* 2025;18(5):e70252. doi:10.1111/cts.70252
16. Chung TK, Lee HA, Park SI, Oh DY, Lee KW, Kim JW, et al. A target-mediated drug disposition population pharmacokinetic model of GC1118, a novel anti-EGFR antibody, in patients with solid tumors. *Clin Transl Sci.* 2021;14(3):990-1001. doi:10.1111/cts.12963
17. Proctor JR, Wong H. Albumin levels are predictive of cachexia-induced time-dependent clearance of therapeutic antibodies: A physiologically based pharmacokinetic model of durvalumab. *CPT Pharmacometrics Syst Pharmacol.* 2026;15(2):e70185. doi:10.1002/psp4.70185
18. Fau JB, El-Cheikh R, Brillac C, Koiwai K, Mace N, Campana F, et al. Drug-disease interaction and time-dependent population pharmacokinetics of isatuximab in relapsed/refractory multiple myeloma patients. *CPT Pharmacometrics Syst Pharmacol.* 2020;9(11):649-58. doi:10.1002/psp4.12561
19. Liu C, Yu J, Li H, Liu J, Xu Y, Song P, et al. Association of time-varying clearance of nivolumab with disease dynamics and its implications on exposure response analysis. *Clin Pharmacol Ther.* 2017;101(5):657-66. doi:10.1002/cpt.656
20. Proctor JR, Wong H. Clinical study design strategies to mitigate confounding effects of time-dependent clearance on dose optimization of therapeutic antibodies. *CPT Pharmacometrics Syst Pharmacol.* 2025;14(2):365-75. doi:10.1002/psp4.13280
21. Burmeister Getz E, Stein RR, Fink M, Kulmatycki K, Baltcheva I, Weis W, et al. Effect of target-mediated disposition on iptacopan clinical pharmacokinetics in participants with normal or impaired hepatic function. *Clin Pharmacol Ther.* 2025;117(5):1358-68. doi:10.1002/cpt.3559
22. Tsuchitani T, Tomaru A, Aoki Y, Ishiguro N, Tsuda Y, Sugiyama Y. Elucidating nonlinear pharmacokinetics of telmisartan: Integration of target-mediated drug disposition and OATP1B3-mediated hepatic uptake in a physiologically based model. *CPT Pharmacometrics Syst Pharmacol.* 2024;13(7):1224-37. doi:10.1002/psp4.13154
23. Kasichayanula S, Grover A, Emery MG, Gibbs MA, Somaratne R, Wasserman SM, et al. Clinical pharmacokinetics and pharmacodynamics of evolocumab, a PCSK9 inhibitor. *Clin Pharmacokinet.* 2018;57(7):769-79. doi:10.1007/s40262-017-0620-7
24. Martinez JM, Brunet A, Hurbin F, DiCioccio AT, Rauch C, Fabre D. Population pharmacokinetic analysis of alirocumab in healthy volunteers or hypercholesterolemic subjects using a Michaelis-Menten approximation of a target-mediated drug disposition model—support for a biologics license application submission: Part I. *Clin Pharmacokinet.* 2019;58(1):101-13. doi:10.1007/s40262-018-0669-y
25. Penney M, Ippolito A, Fevola E, Rata S, Brown L, Morentin Gutierrez P, et al. Predicting the pharmacokinetics of T-cell engagers as a function of target-mediated drug disposition. *Clin Transl Sci.* 2025;18(11):e70384. doi:10.1111/cts.70384
26. Jeong S, Lee SY, Kim SH, Kim HT, Yun HY, Chae JW, et al. Model-informed optimal dosing of anti-CD47 antibody using target-mediated drug disposition model. *Clin Transl Sci.* 2025;18(8):e70321. doi:10.1111/cts.70321
27. Kapitanov GI, Flowers D, Marcantonio DH, Lezon TR, Apgar JF, Hua F. A tutorial on the development of a physiologically inspired PKRO model for monoclonal antibodies. *CPT Pharmacometrics Syst Pharmacol.* 2026;15(2):e70160. doi:10.1002/psp4.70160
28. van den Berg SPH, Adolfsen PEA, Dorlo TPC, Rispens T. Does one model fit all mAbs? An evaluation of population pharmacokinetic models. *MAbs.* 2025;17(1):2512217. doi:10.1080/19420862.2025.2512217